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Radicacion : 00048974 00/00031 Folios: 162
Fecha (AMD): 2000-09-01 17:20:38
Tramite : 002 PATENTES D 1 REGISTRO/ 444 REPUESTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

TRAMITE:002 - EVENTO:001 - ACTUACION:444

Referencia : Expediente No. 00.048.974

Solicitante : **INHALE THERAPEUTIC SYSTEMS, INC**

Asunto : Solicitud de patente para: **SISTEMAS Y METODOS PARA AEROSOLIZAR FORMULACIONES FARMACÉUTICAS**

Fecha de la solicitud : 29 de junio de 2000

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al auto número 2278, notificado por estado del 27 de julio de 2000.

2. Mediante el auto número 2278 se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por ese Despacho sobre la presente solicitud de patente. Atiendo a las observaciones de la manera siguiente:

2.1. <u>En la descripción.</u> Presento junto con este escrito nuevas páginas 8, 15, 38, 45, 68, 78 y 88 correspondientes a la descripción en las cuales se han modificado algunas unidades que no se encontraban en el Sistema Internacional.

RESPUESTA AUTO No. 2278 DEL ESTADO DEL DIA 27 de Julio, 2000

2.2. <u>En las reivindicaciones.</u> Presento junto con este escrito nuevas páginas 114, 118, 124 y 126 correspondientes al capítulo reivindicatorio en el cual se han hecho conversiones de algunas unidades que no se encontraban en el Sistema Internacional.

2.3. <u>Arte Final.</u> Adjunto a este memorial presento los artes finales de acuerdo con lo requerido.

2.4. <u>Dibujos.</u> Presento junto con este escrito los dibujos formales de las figuras 1 a 89 a que se hace referencia en la descripción y de acuerdo con lo solicitado por su Despacho.

2.5. <u>Copias Certificadas.</u> Presento con este escrito copias certificadas de las solicitudes de patente estadounidenses números 60/141.793 del 30 de junio de 1999 y 60/198.060 del 18 de abril de 2000, junto con sus respectivas traducciones simples de sus reivindicaciones y carátula, en las cuales se basa la reivindicación de la prioridad.

3. Puesto que se han atendido a cabalidad las observaciones hechas por ese Despacho sobre la presente

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solicitud de patente, atentamente solicito que se continúe su tramitación.

Bogotá, 01 SET. 2000
Señora Jefe,

EMILIO FERRERO
T.P.A. No. 31.929

COLO 09101-801-011-5
RCB-88

umbral de vacío. En un aspecto, el umbral de vacío de accionamiento de la válvula se encuentra en el rango de aproximadamente 1960 Pa hasta aproximadamente 5880 Pa.

En un aspecto particular la válvula se configura para estar dispuesta dentro del receptáculo. De esta manera, la válvula puede ser convenientemente manufacturada junto con el receptáculo.

De acuerdo con otro aspecto, la invención proporciona dispositivos y métodos para regular el flujo de gases respiratorios que proporcionan un flujo de aire consistente, independiente del índice respiratorio del usuario. En otro aspecto, el sistema incluye un sistema de regulación para regular el flujo de gases respiratorios a través de la vía de aire después de que la válvula se ha abierto. La combinación de la regulación del flujo con la válvula de umbral de acuerdo con la presente invención da como resultado dispositivos y métodos para suministrar aerosol que son efectivos en el suministro de una formulación aerosolizada al pulmón profundo.

Aún en otra modalidad, la invención proporciona un receptáculo que comprende un cuerpo de receptáculo que define una cavidad que está incluida por una tapa de acceso penetrable. El receptáculo incluye demás una válvula de umbral que está acoplada al cuerpo del receptáculo. En un aspecto, la válvula de umbral se configura para abrirse cuando se experimenta un vacío de al menos aproximadamente 3920 Pa.

De acuerdo con otro aspecto, la invención también puede utilizar una variedad de técnicas para asegurar las posiciones adecuadas de la boca del usuario sobre la pieza de boca durante el uso de un dispositivo de aerosolización. Por ejemplo, se puede incluir un guarda labio sobre la pieza de boca para permitirle al usuario ubicar sus labios de manera adyacente al guarda labio. Como otro ejemplo, la pieza de boca puede incluir muescas u otras marcas. Alternativamente, se pueden proporcionar uno o más huecos en el lado de la pieza de boca. Estos huecos se pueden cubrir por los labios con el fin de crear un vacío suficiente para operar el dispositivo. Como ejemplo adicional, la pieza de boca puede tener un perfil circular a elíptico. La porción elíptica se debe

pulmones del paciente después de que se ha alcanzado el umbral de vacío. Al permitir abruptamente el flujo de gases respiratorios solo cuando se ha aplicado suficiente vacío por el usuario, un relativamente alto índice de flujo se logra para proporcionar la corriente de gas con suficiente energía. Una manera de lograr tal proceso es ubicar una restricción, válvula, u otro mecanismo de bloqueo en el camino del paciente para evitar que los gases respiratorios entren a los pulmones del paciente cuando el paciente intenta inhalar. La restricción o válvula puede entonces ser rápidamente removida o abierta para permitirle a los gases respiratorios fluir a los pulmones. De esta manera, se puede instruir un paciente para inhalar hasta que se logra el umbral de vacío de accionamiento. El umbral de vacío de accionamiento se puede configurar de tal forma que produzca suficiente energía en la corriente de gases resultantes cuando los gases se les permite fluir a los pulmones del paciente. Preferiblemente, el vacío de umbral está en el rango de aproximadamente 1960 Pa a aproximadamente 5880 Pa de tal manera que la corriente de gas resultante tenga suficiente energía para extraer y desaglomerar la formulación farmacéutica. Más preferiblemente, el vacío de umbral es de al menos 5880 Pa una variedad de

un orificio con un tamaño de acuerdo al índice de flujo de inhalación natural del paciente.

Los dispositivos de acuerdo con la presente invención pueden comprender sendas de flujo en serie o en paralelo. En cada caso, puede ser deseable mantener un índice de flujo constante, predeterminado para una gran población de pacientes. Para construcciones en serie, como se describe en la figura 4, se prefiere que las relaciones de resistencia de flujo/vacío sea sustancialmente lineal. Para construcciones en paralelo, como se muestra en la figura 70 por ejemplo, es preferible proporcionar una relación de resistencia de flujo - vacío que sea altamente lineal.

En relación ahora a la figura 4 se describirá un sistema y este utiliza una serie de construcciones para accionar un medicamento en polvo de un receptáculo 12 que usa los gases respiratorios respirados en un paciente. El sistema 10 comprende una válvula umbral 14 que se puede configurar para abrirse cuando el vacío dentro de una línea 16 corriente debajo de la válvula de umbral 14 experimenta un vacío de 1960-5880 Pa, preferiblemente mayor de aproximadamente 3920 Pa. También acoplado a

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Una amplia variedad de válvulas de umbral se pueden utilizar para evitar que el flujo de gases llegue a los pulmones del paciente hasta que el paciente ha producido un vacío suficiente necesario para extraer el polvo del receptáculo. Tales válvulas se pueden configurar para evitar cualquier flujo de gases hasta que el vacío producido por el paciente cumpla o exceda la presión de accionamiento de umbral de la válvula. Después de que la válvula se abre, se proporciona una resistencia de flujo mínima pro la válvula. Una vez que la válvula para, la válvula se puede configurar para reestablecer su posición de inicio anterior.

Mostrado en la figura 27, se presenta un diagrama esquemático de un sistema de válvula 300 que tiene un válvula de umbral 302 que se puede configurar para romperse a una presión en el rango de aproximadamente 1960 Pa hasta aproximadamente 5880 Pa. Y más preferiblemente al menos aproximadamente 4900 Pa, para permitir el flujo de gas a través del dispositivo de aerosolización en la dirección indicada por las flechas. De esta manera, el índice de flujo relativamente alto se puede lograr durante una corta duración en el inicio de

La figura 41 ilustra esquemáticamente una modalidad del regulador de flujo 460. El regulador 460 se puede configurar para limitar el flujo de gases para que sea menor de aproximadamente 15 l/min, y más preferiblemente menor de aproximadamente 10 l/min. El regulador 460 se puede configurar de tal forma que la resistencia al flujo sea pequeña a un vacío pequeño y se incremente con el vacío generado pro el usuario. Convenientemente, el regulador 460 se puede ubicar en una senda de flujo que es paralela al receptáculo que contiene el polvo. En tal caso el regulador de flujo puede proporcionar una resistencia al sistema al flujo R que varía desde aproximadamente 9,8 $(Pa)^{1/2}$/litros estándar por minuto (SLM) hasta la resistencia de la celda de flujo de receptáculo. Alternativamente, el controlador de flujo se puede ubicar en serie con los receptáculos. En tal caso, la resistencia del sistema R puede variar desde la resistencia de la celda de flujo de receptáculo hasta una resistencia mayor de 98 $(Pa)^{1/2}$/SLM.

Mostrado en las figuras 42-59 se encuentran varios tipos de reguladores de flujo que se pueden utilizar en dispositivos de aerosolización para regular el flujo de gas después que el receptáculo sea abierto. Por ejemplo,

aproximadamente 500 ml aire inhalado, la droga ha viajado pasando el espacio anatómico muerto.

Para proporcionar tal característica, varios temporizadores o integradores de flujo podrían ser incorporados opcionalmente en los dispositivos de aerosolización de la invención. Tales integradores de flujo tienen uno o más miembros en movimiento que se mueven con base en el volumen de flujo a través del dispositivo. De esta manera, cuando el volumen inicial (regulado) se ha inhalado, el miembro se ha movido suficientemente par abrir otro canal de gas para permitir el flujo de gas creciente. Por ejemplo, el integrador de flujo puede ser una aleta de hojuela aérea hecha de una película tal como una película de polímero que tiene un grosor entre 0,0127 y 0,0508 centímetros y tiene preferiblemente un comportamiento viscoelástico u otro dependiendo del tiempo. El flujo de aire sobre la aleta de hojuela aérea induce el levantamiento aerodinámico. La aleta de hojuela aérea se puede configurar para permitir el acceso de una senda de flujo paralelo después que un volumen predeterminado de aire fluye sobre la aleta.

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4. Un método según la reivindicación 2, en donde la velocidad es menor que 8 l/min y el tiempo está en el rango entre 0,5 segundos y 5 segundos.

5. Un método según la reivindicación 2, en donde cierta velocidad permite un volumen inhalado que está en el rango entre 125 ml a 1,25 l.

6. Un método según la reivindicación 1, en donde la etapa para impedir el flujo comprende adicionalmente colocar una válvula dentro de un trayecto de aire que va hacia los pulmones y abrir la válvula para permitir que los gases respiratorios fluyan hacia los pulmones.

7. Un método según la reivindicación 6, que comprende adicionalmente abrir la válvula cuando un vacío de actuación umbral causado por la inhalación intentada se excede.

8. Un método según la reivindicación 7, en donde el vacío de actuación umbral está en un rango entre 1960 Pa a cerca de 5880 Pa.

dispositivo de inhalación hacia fuera del dispositivo y dentro del tracto respiratorio de una paciente; y

Permitir un segundo volumen de gases respiratorios para que fluya a los pulmones.

19. Un método según la reivindicación 18 en donde el flujo de gases respiratorios se impide por medio de suministrar el dispositivo con una válvula entre dichas aberturas.

20. Un método según la reivindicación 19 en donde el flujo de gases respiratorios es permitido por la abertura de dicha válvula cuando un vacío de actuación umbral se excede por la inhalación indentada.

21. Un método según la reivindicación 20 en donde dicho vacío está entre 1960 a 5880 Pa.

22. Un método según la reivindicación 18 en donde dicho primer volumen predeterminado de gases

miembro elastomérico y en donde el miembro de halado compredne una bola.

41. Un dispositivo según la reivindicación 26, en donde le vacío de actuación umbral de la válvula está en el rango entre 1960 Pa a 5880 Pa.

42. Un dispositivo según la reivindicación 26, que comprende adicionalmente un mecanismo de desaglomeración dispuesto aguas abajo del trayecto de aire del receptáculo para desaglomerar la formulación farmacéutica extraída.

43. Un dispositivo según la reivindicación 26, en donde la válvula está adaptada para estar dispuesta dentro del receptáculo.

44. Un sistema de aerosolización comprende:

Un receptáculo que comprende una cámara que tiene una formulación farmacéutica y una válvula umbral;

Una caja que define un trayecto de aire; y

48. Un receptáculo comprende:

Un cuerpo de receptáculo que define una cavidad encerrada por una tapa de acceso penetrable y

Una válvula de umbral acoplada al cuerpo de receptáculo.

49. Un receptáculo según la reivindicación 48, en donde la válvula de umbral está configurada para abrir cuando se experimenta un vacío de por lo menos 3920 Pa.

50. Un dispositivo de aerosolización, que comprende:

Una caja que tiene una pieza de boca;

Un mecanismo de aerosolización dispuesto en la caja, en donde el mecanismo de aerosolización está adaptado para aerosolizar un medicamento en polvo cuando un usuario inhala desde la pieza de boca; y

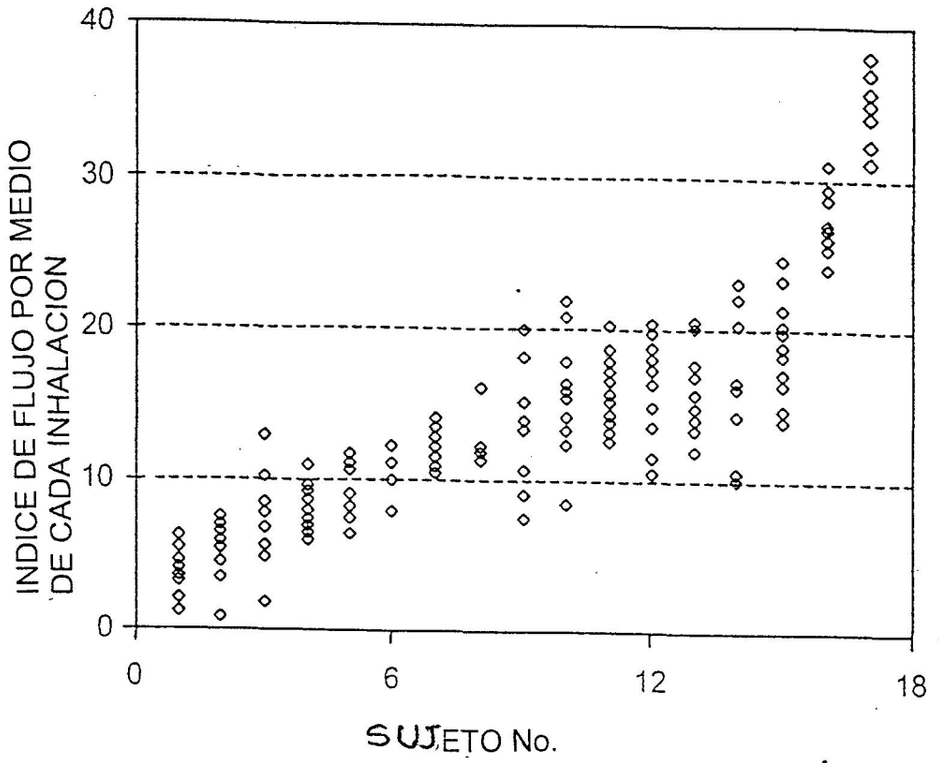

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INDICE DE FLUJO POR MEDIO DE CADA INHALACION
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SUJETO No.

FIG. 1

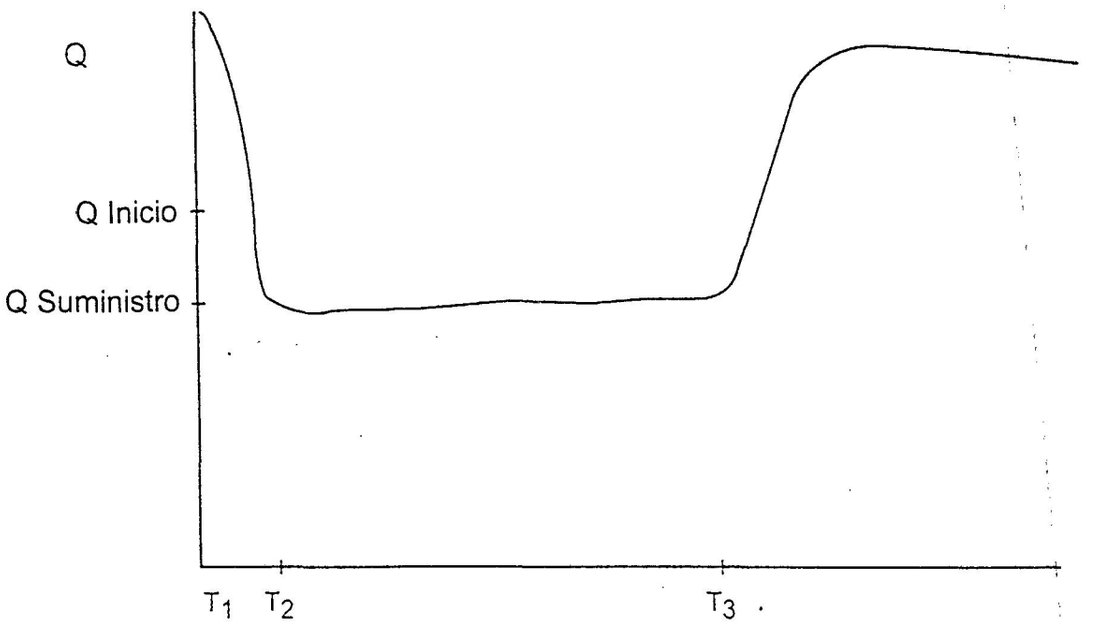


FIG. 2

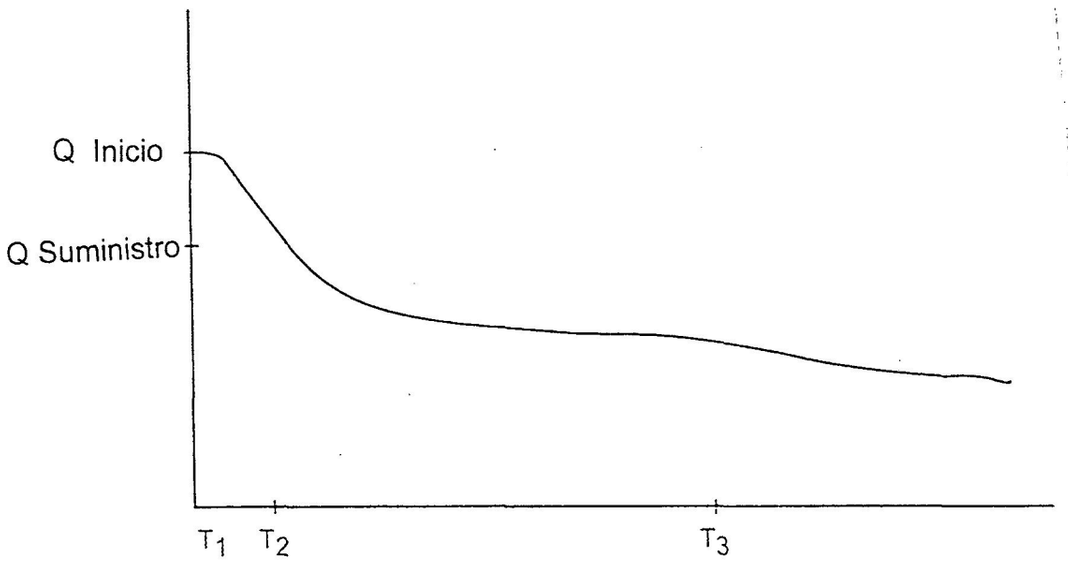


FIG. 3

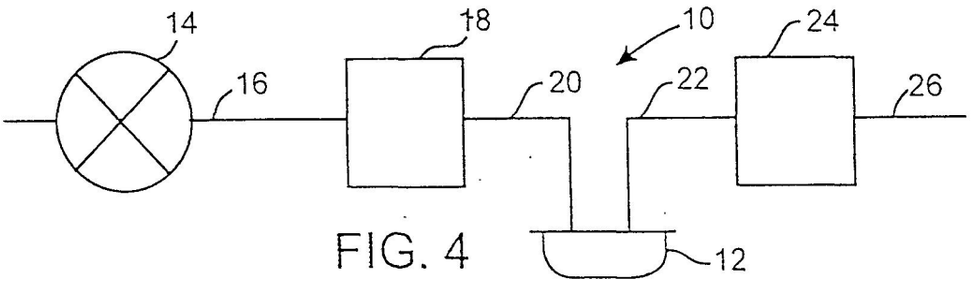


FIG. 4

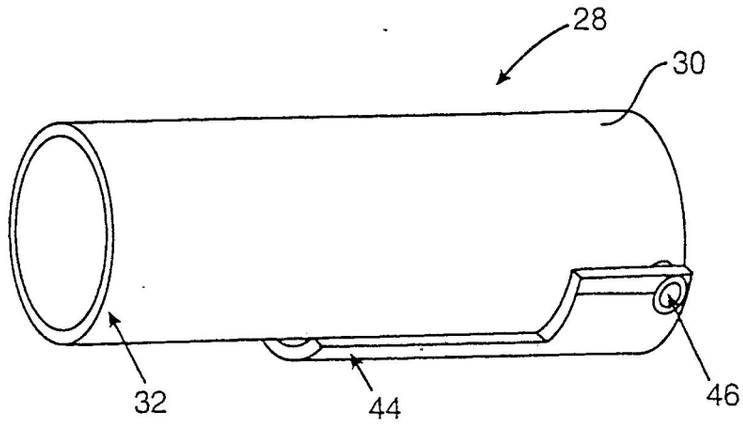


FIG. 5

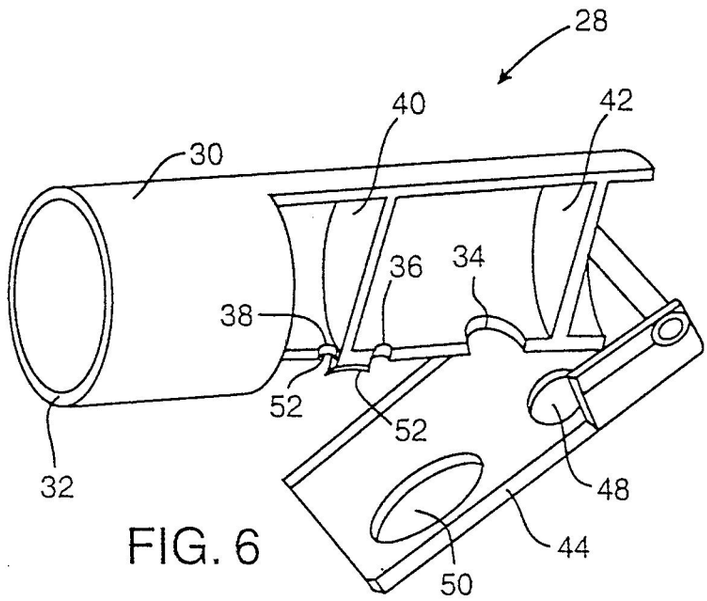


FIG. 6

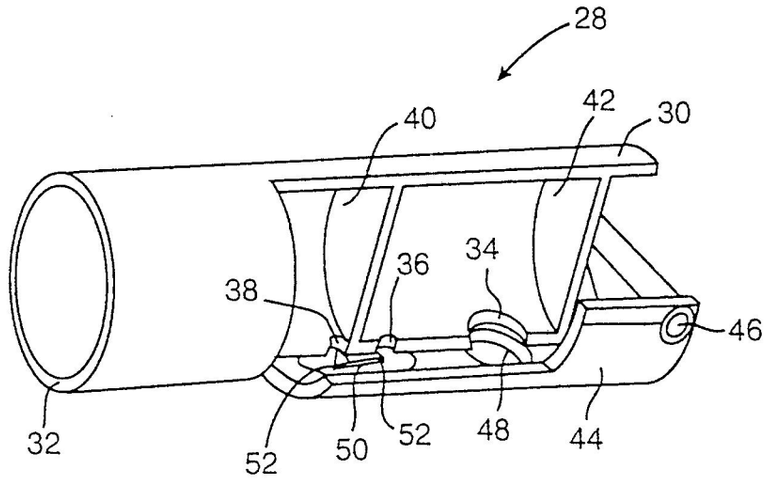


FIG. 7

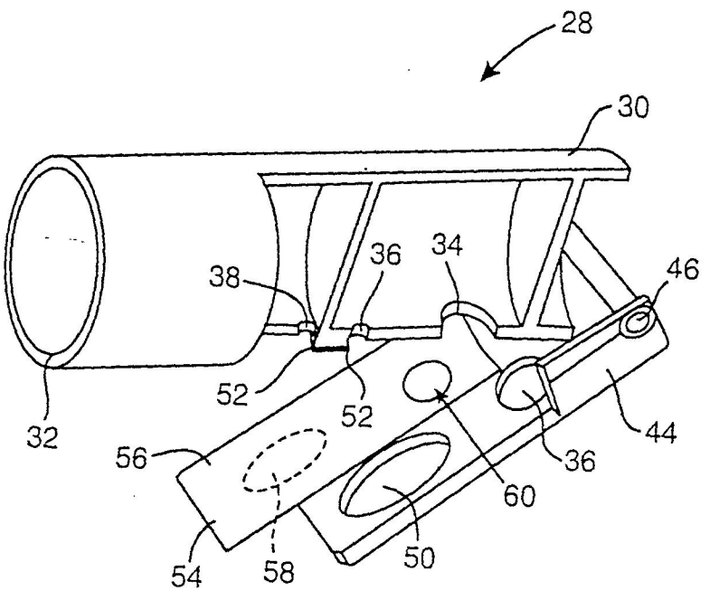

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FIG. 8

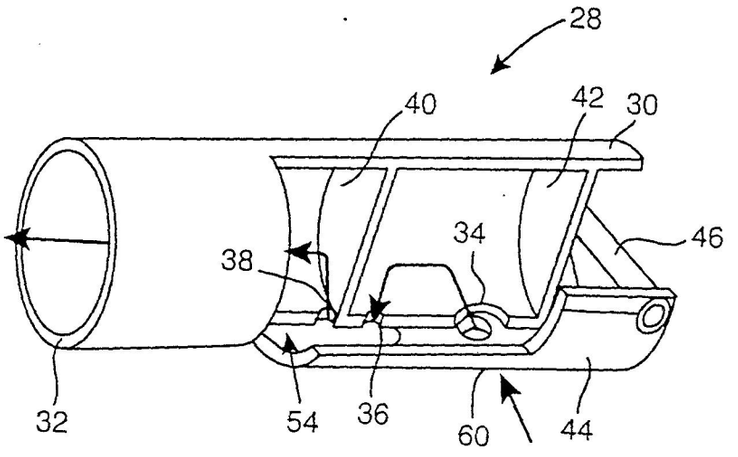

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FIG. 9

FIG. 10

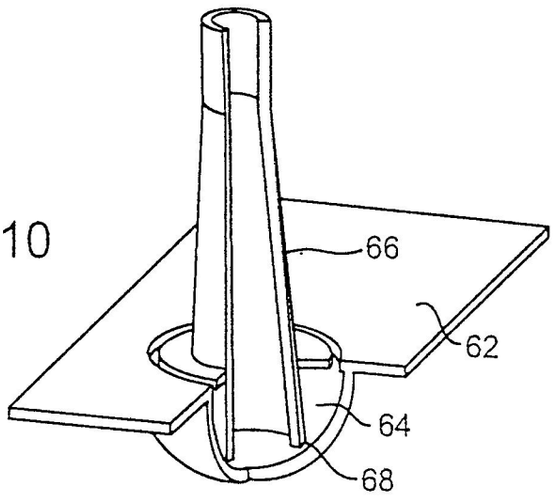
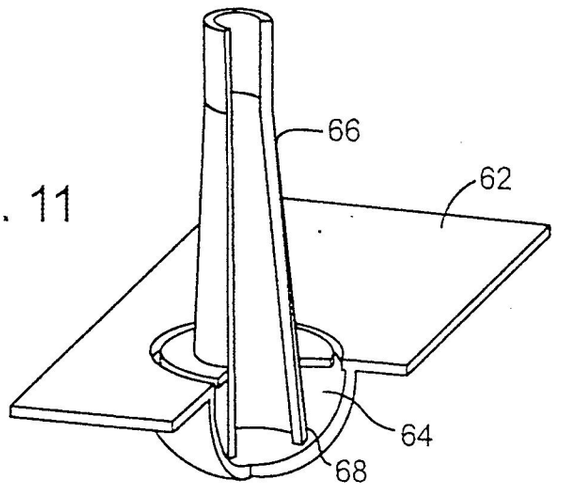


FIG. 11



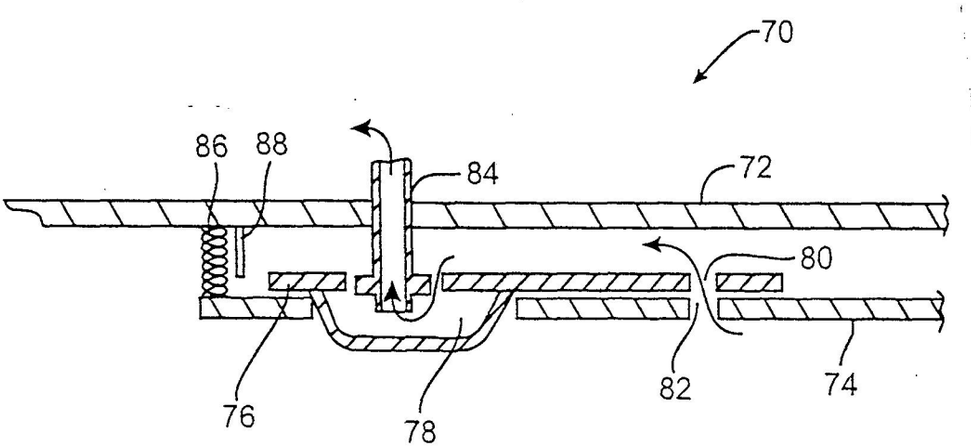


FIG. 12

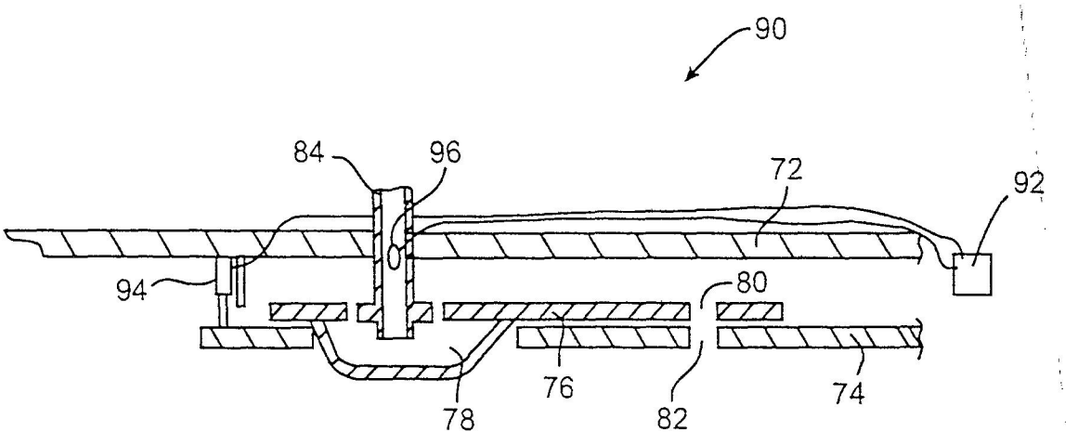


FIG. 13

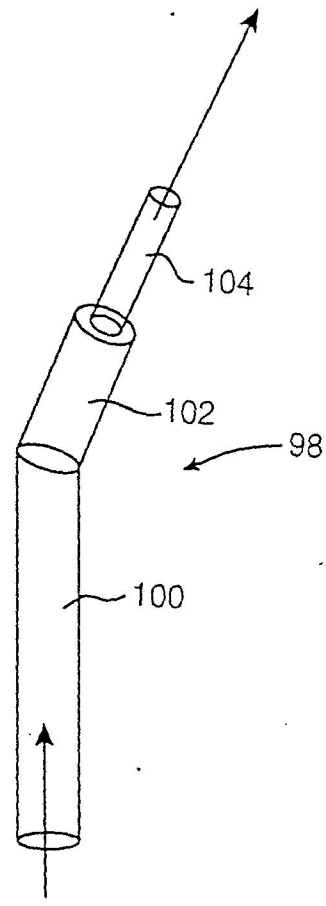


FIG. 14

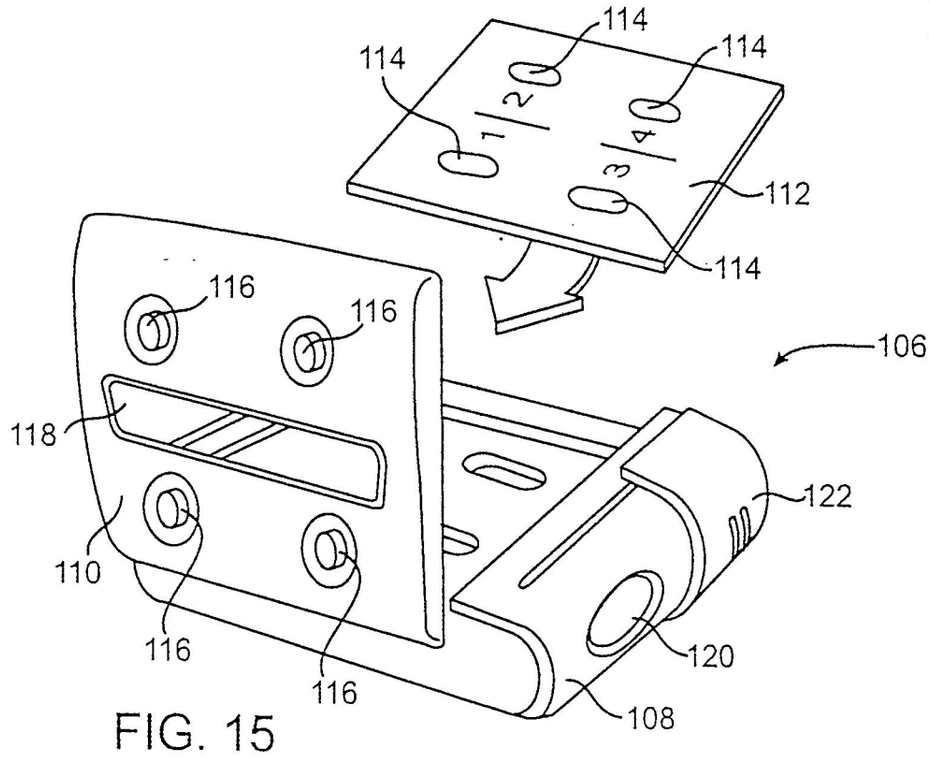


FIG. 15

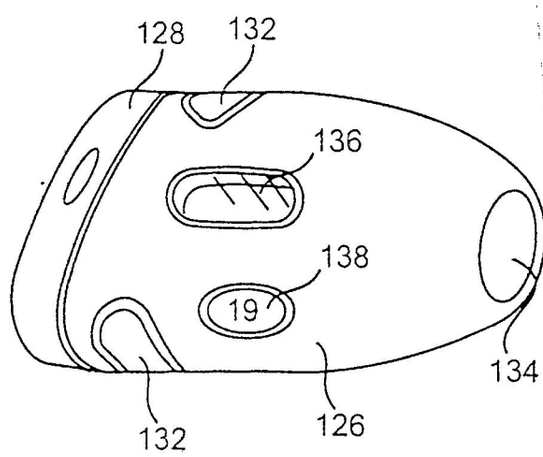


FIG. 16A

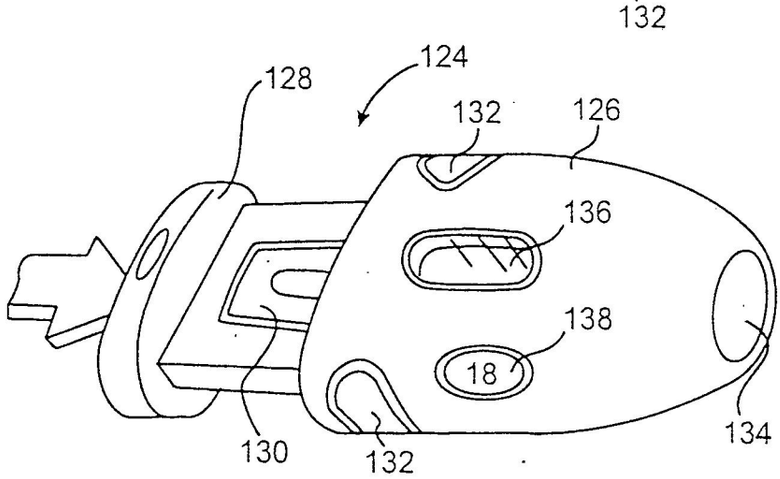


FIG. 16

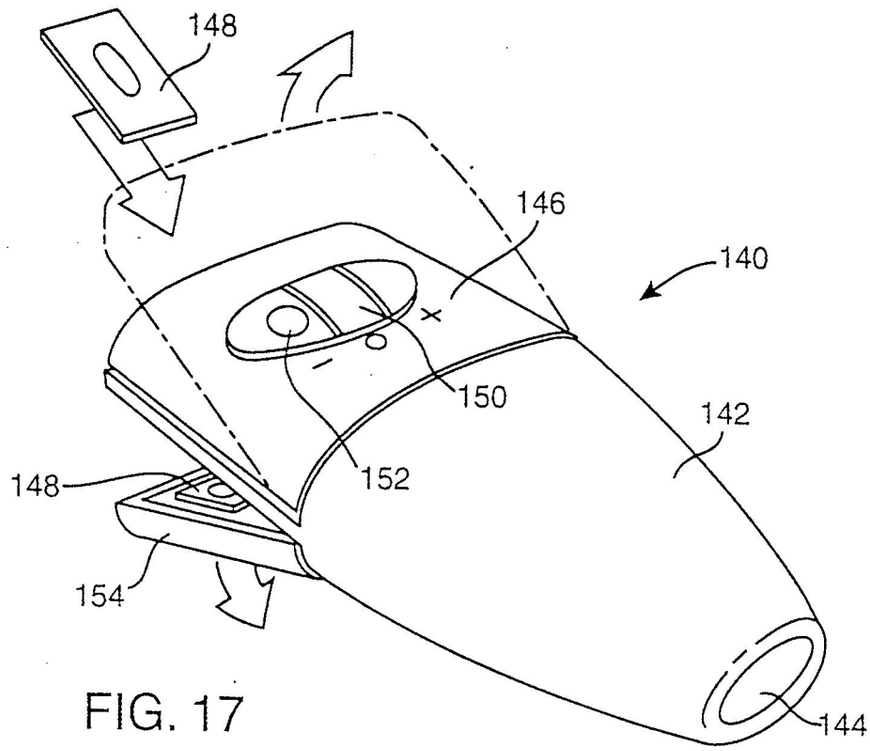

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FIG. 17

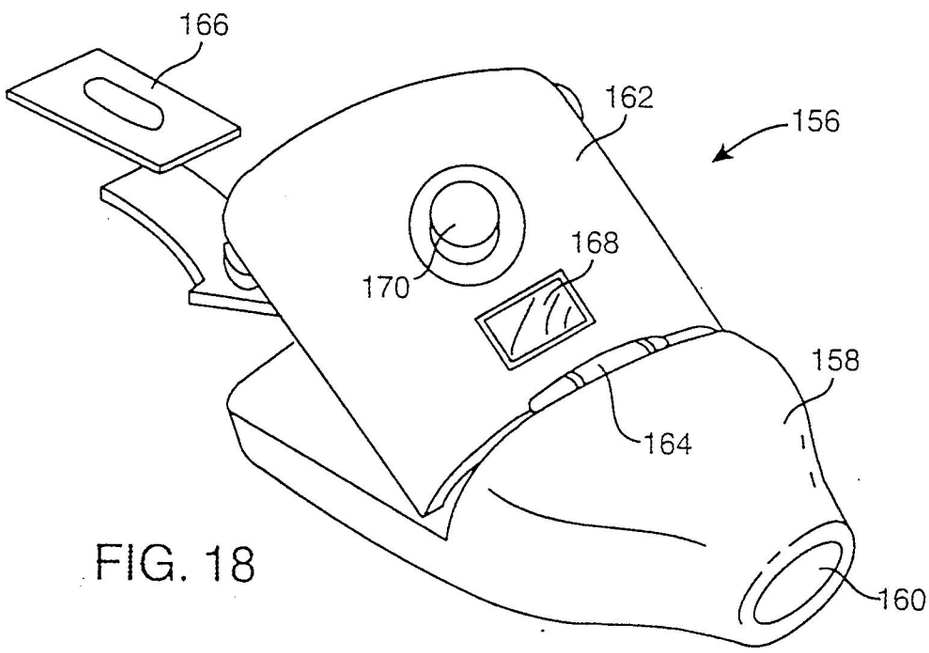

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FIG. 18

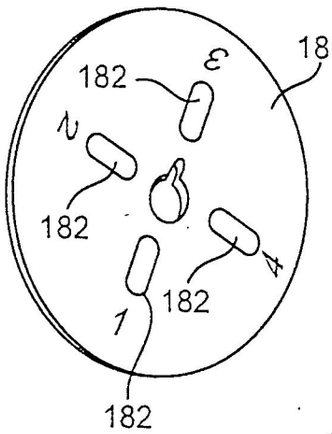


FIG. 19A

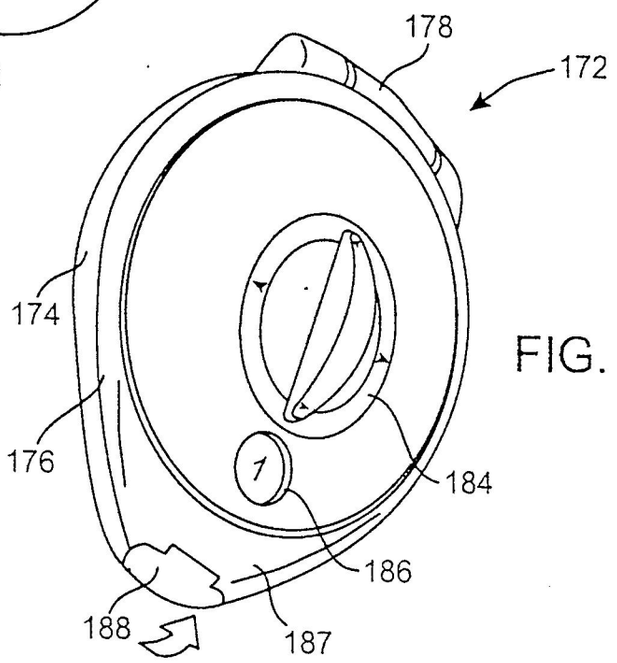


FIG. 19

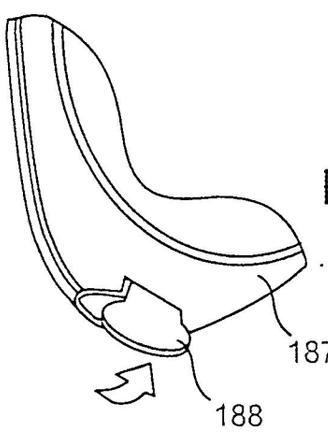


FIG. 19B

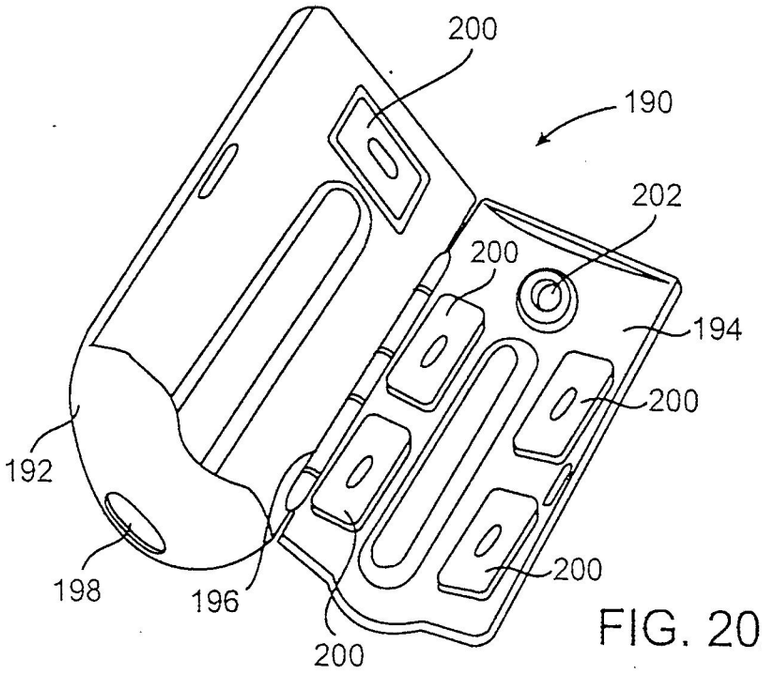


FIG. 20A

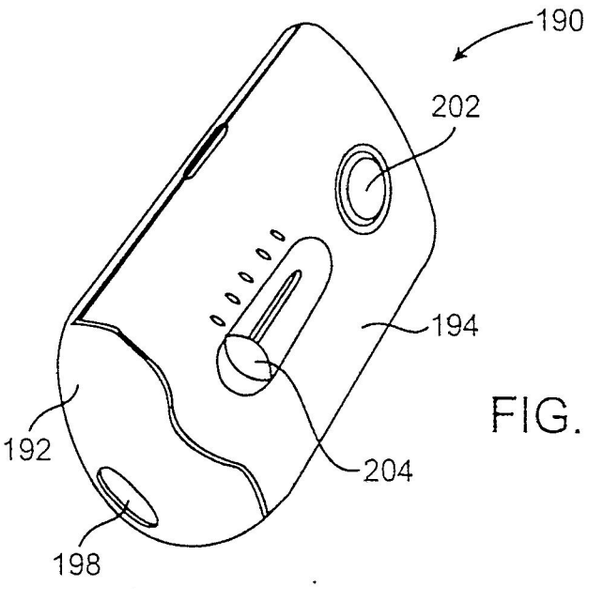


FIG. 20

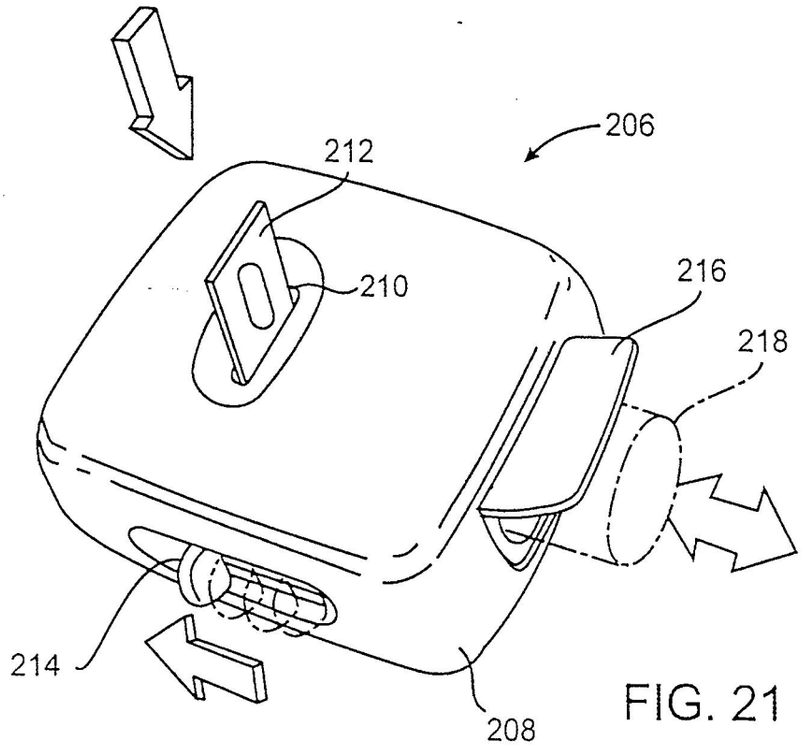


FIG. 21

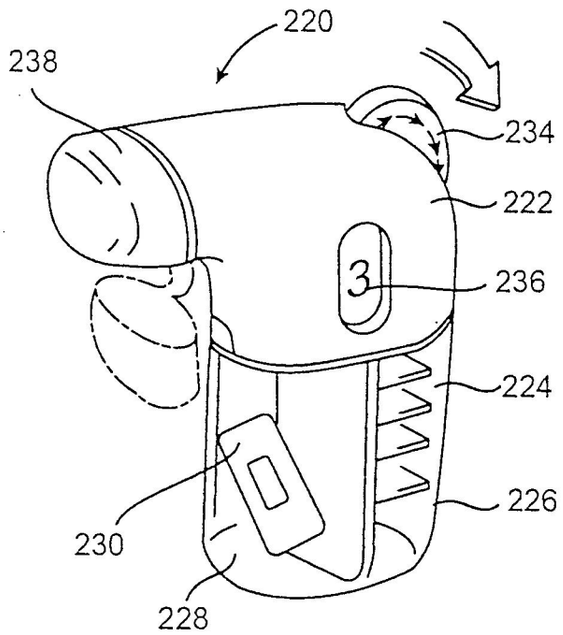


FIG. 22

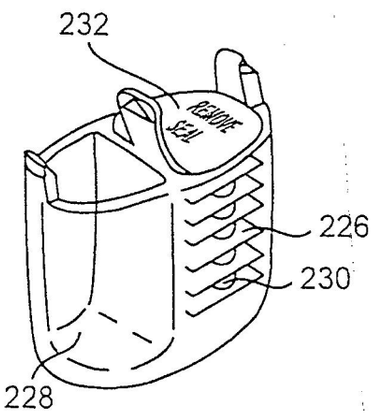


FIG. 22A

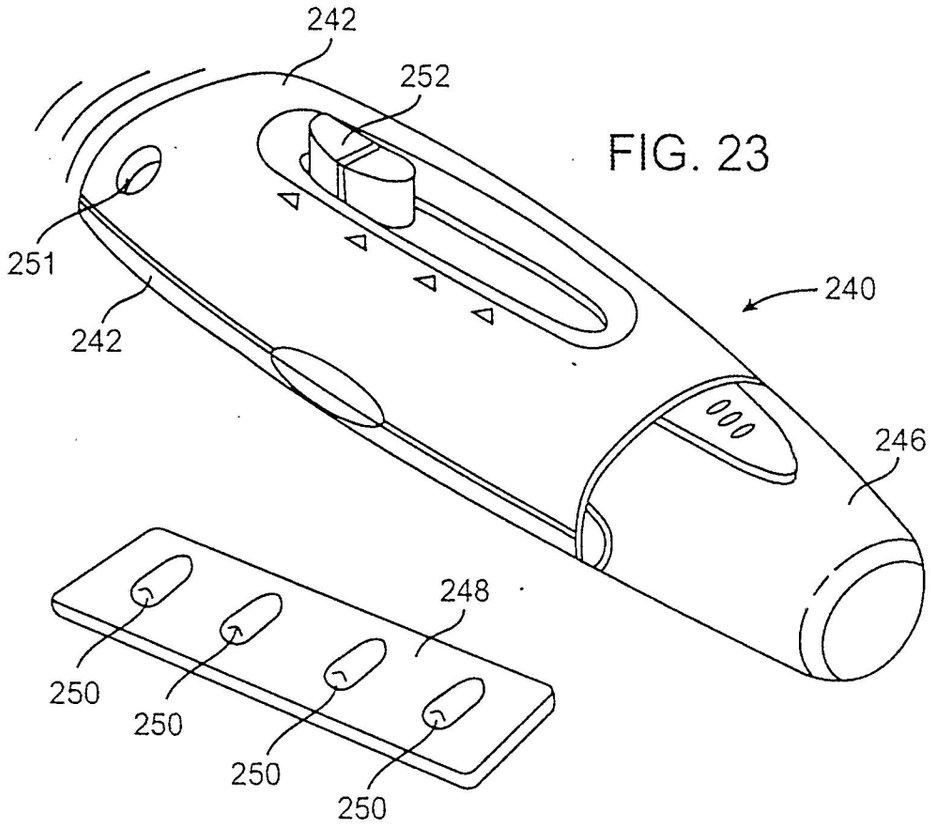


FIG. 23

FIG. 24

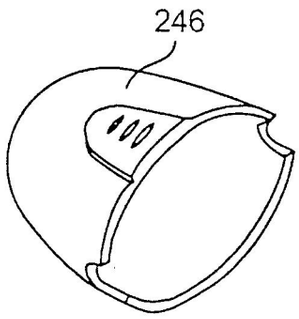


FIG. 23A

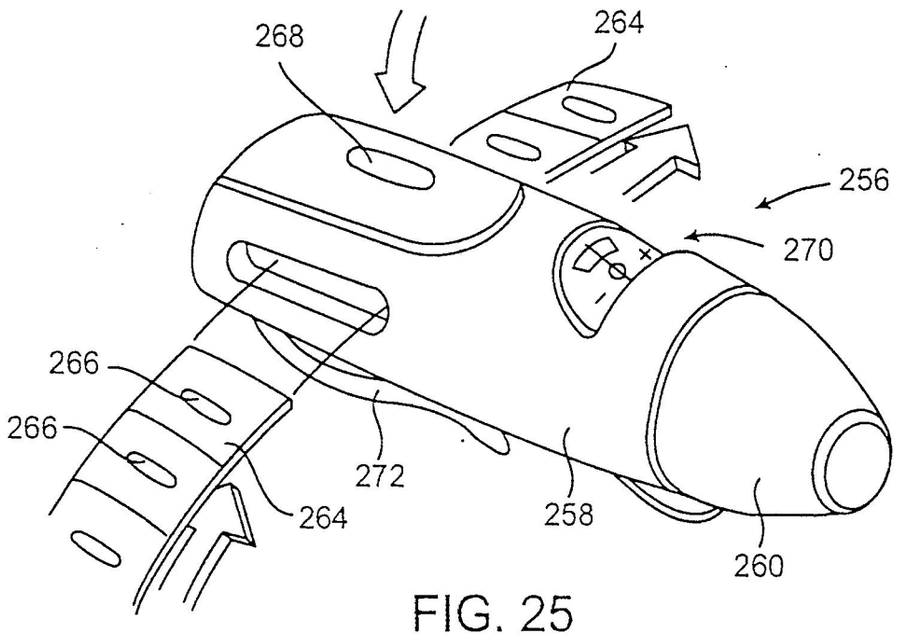

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FIG. 25

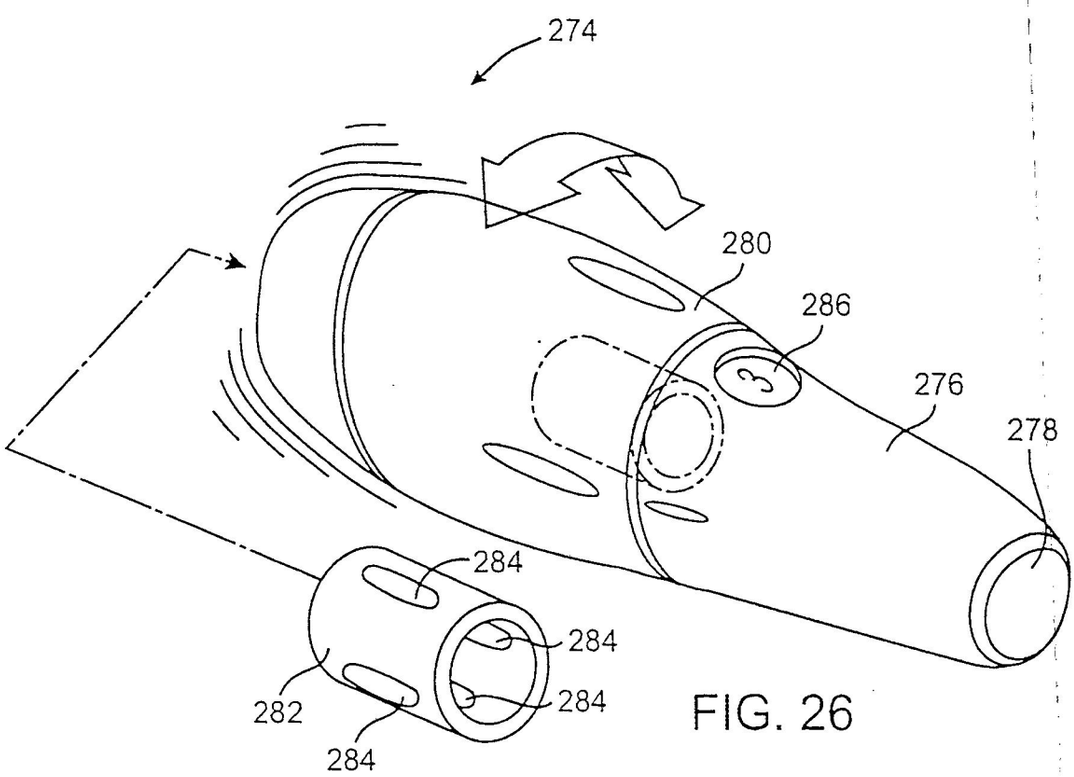

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FIG. 26

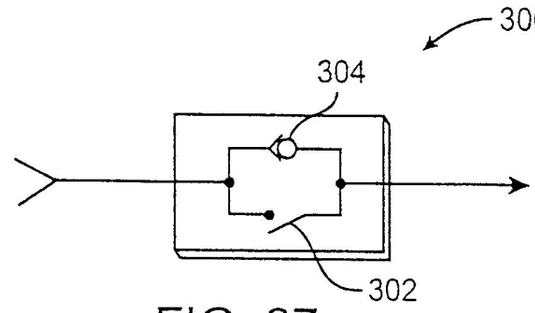


FIG. 27

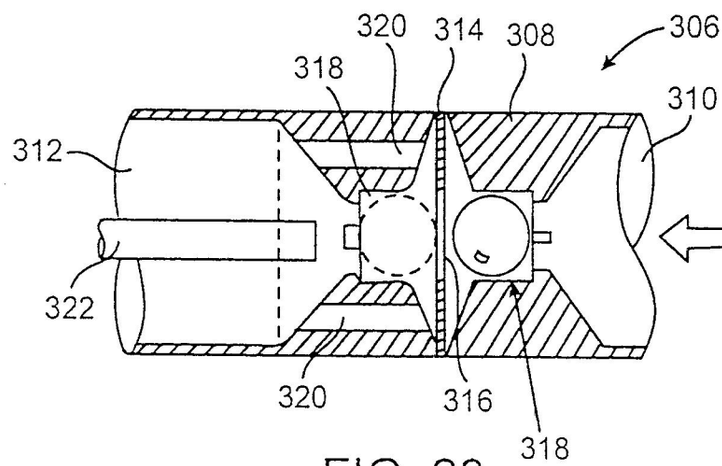


FIG. 28

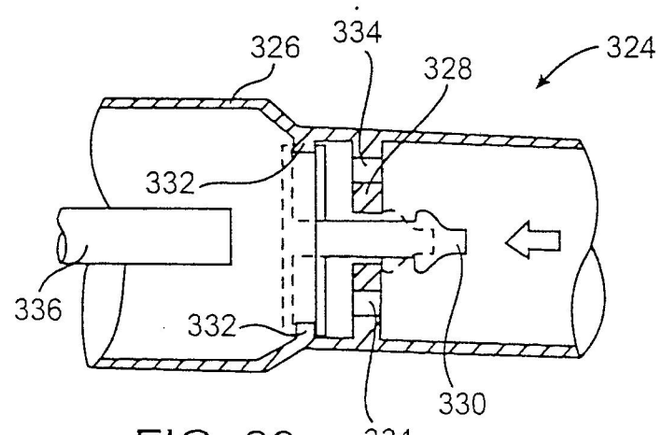


FIG. 29

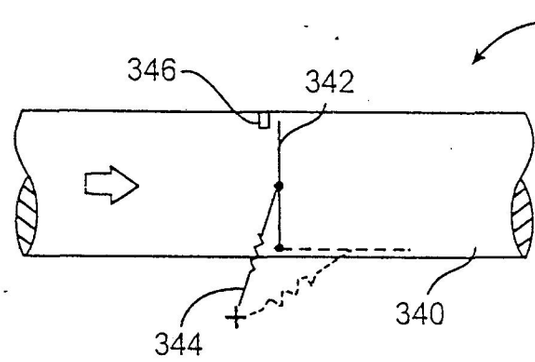


FIG. 30

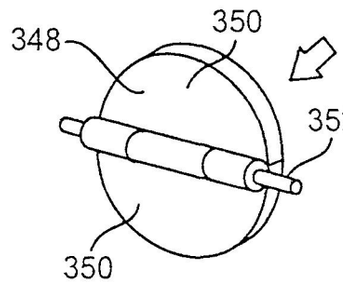


FIG. 31A

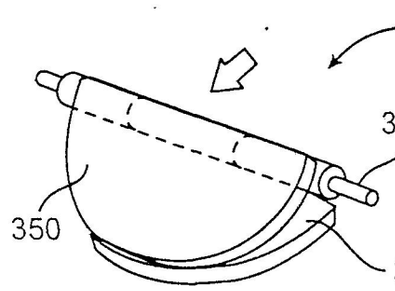


FIG. 31B

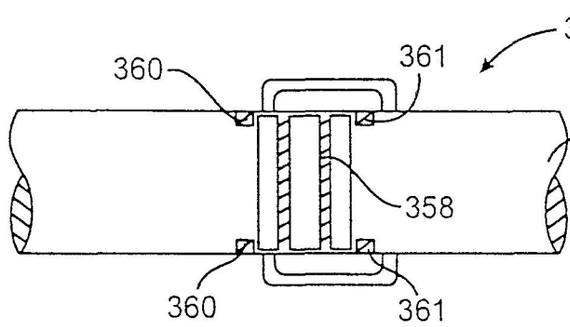


FIG. 32

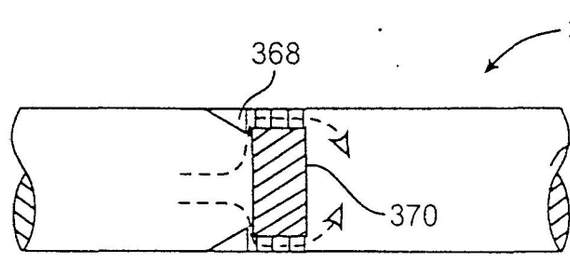


FIG. 33

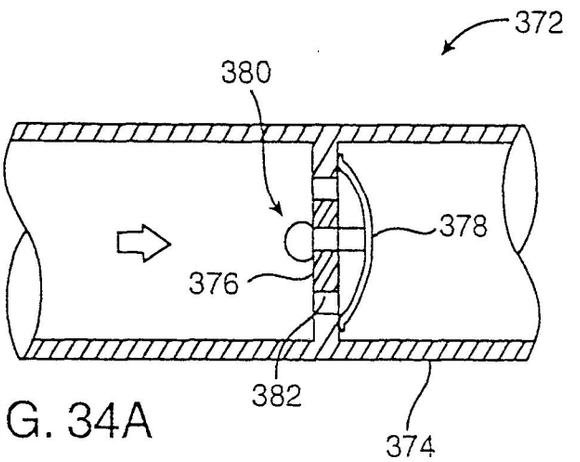


FIG. 34A

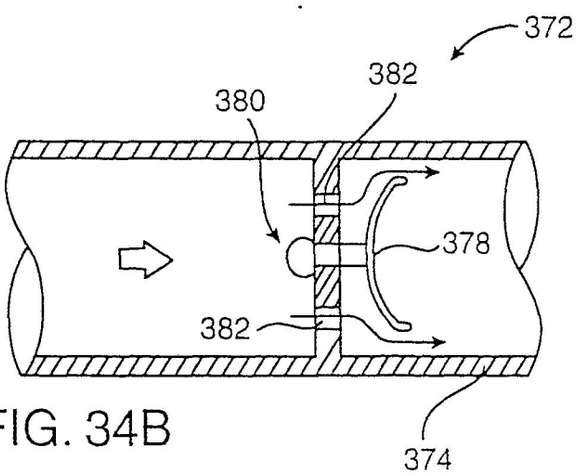


FIG. 34B

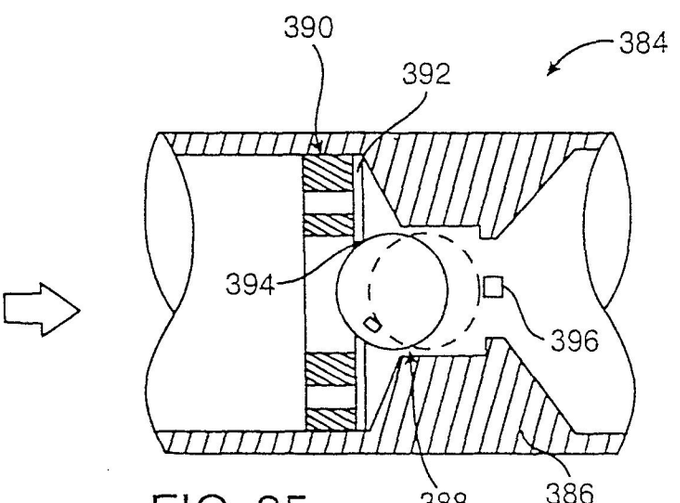


FIG. 35

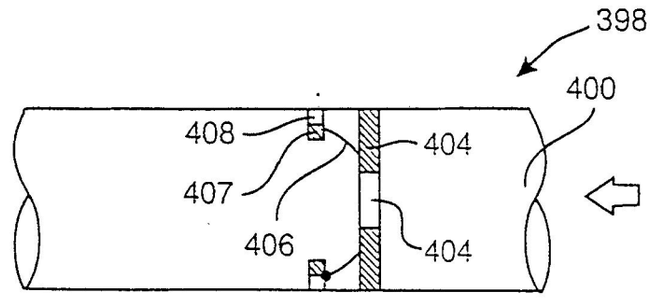


FIG. 36A

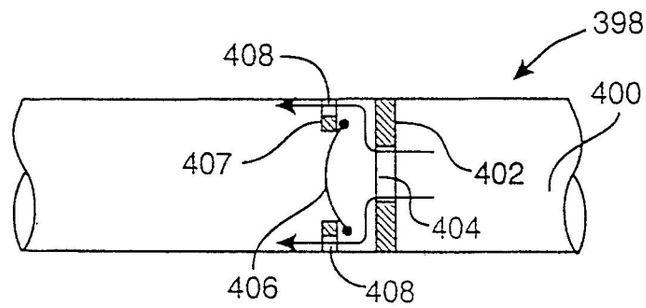


FIG. 36B

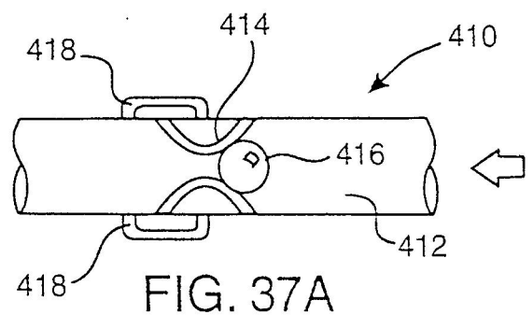


FIG. 37A

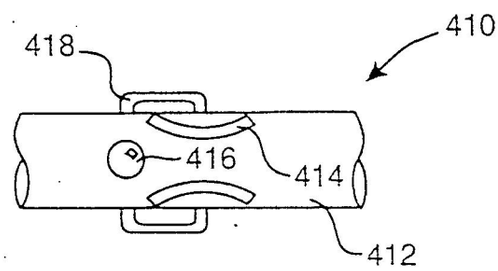


FIG. 37B

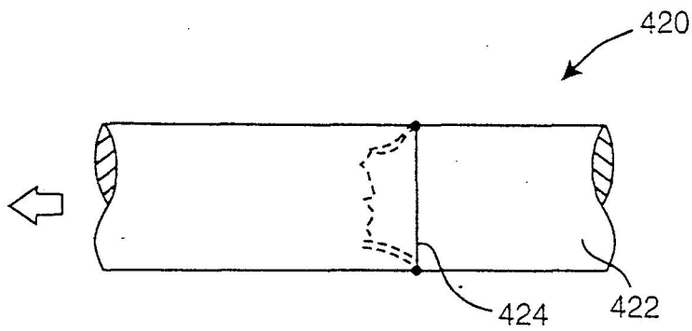


FIG. 38

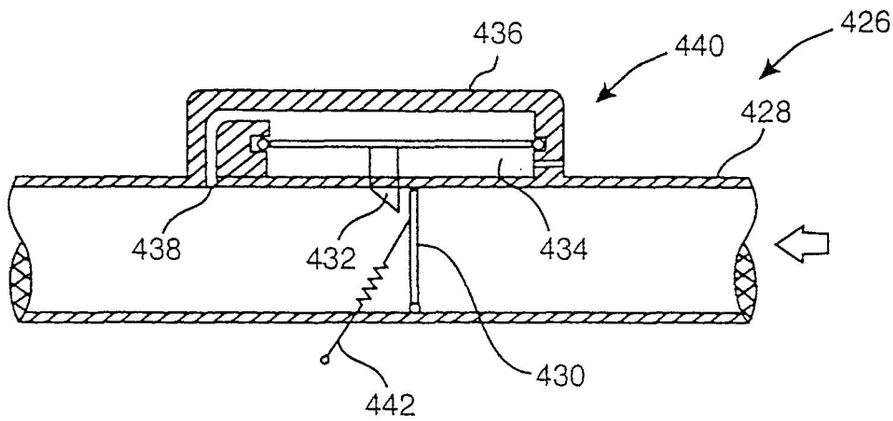


FIG. 39

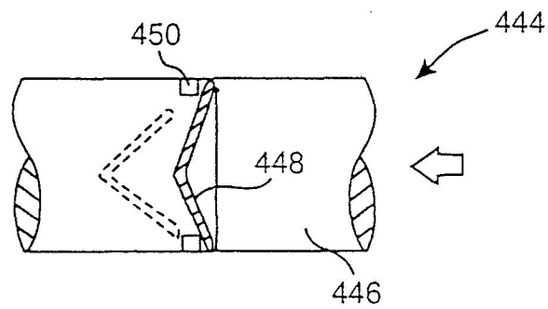


FIG. 40

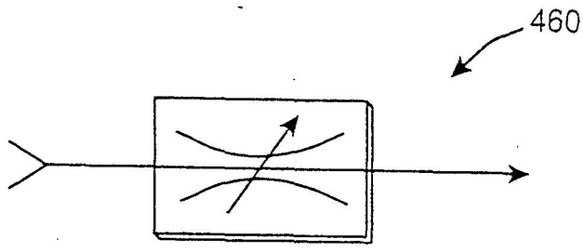


FIG. 41

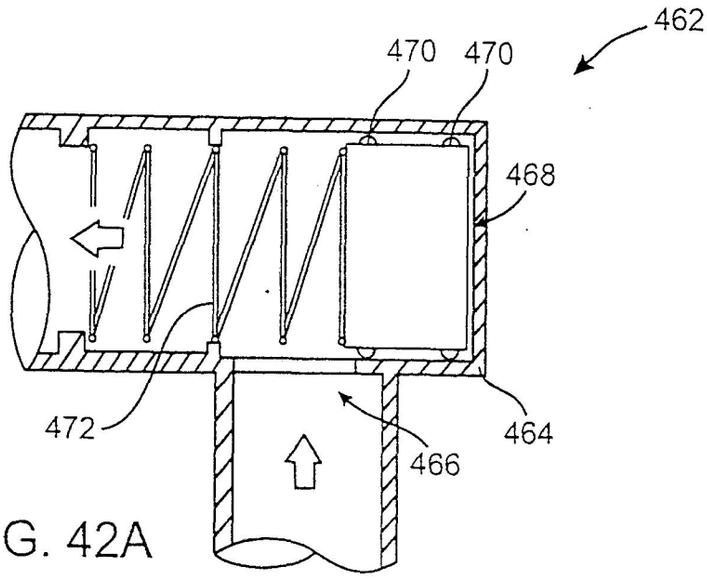


FIG. 42A

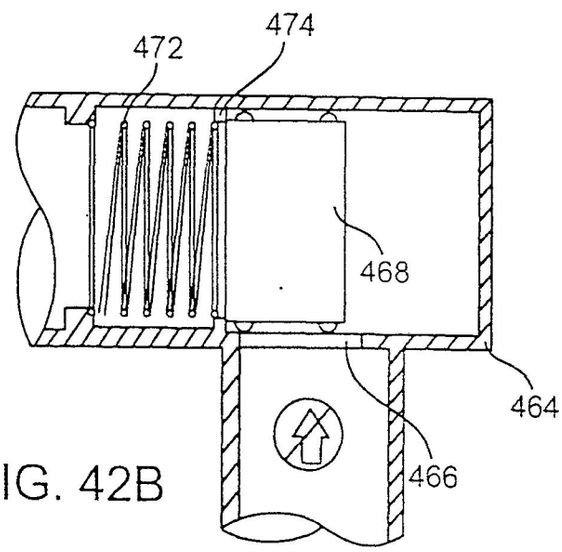


FIG. 42B

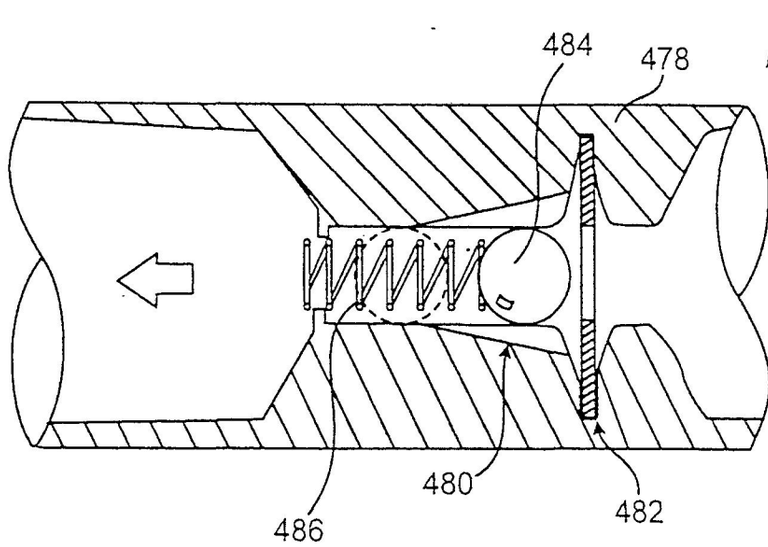


FIG. 43

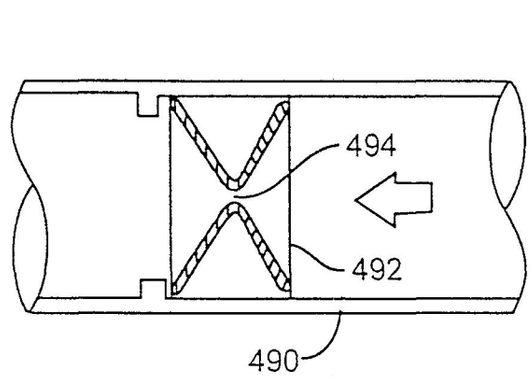


FIG. 44A

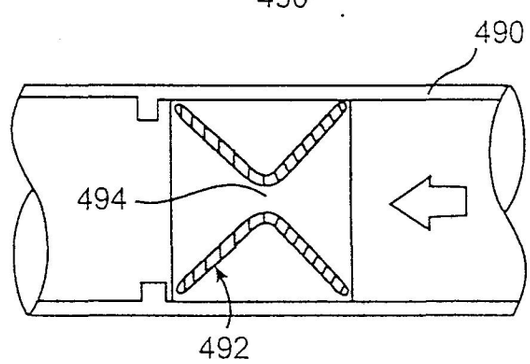


FIG. 44B

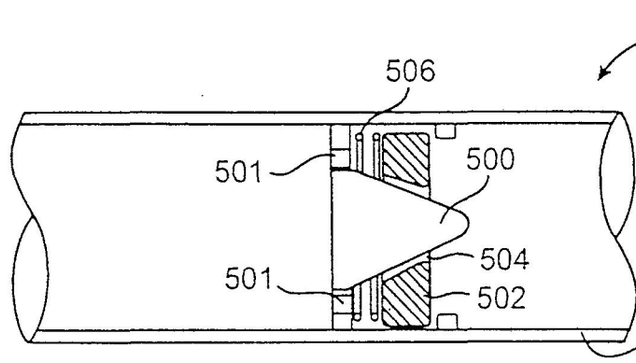


FIG. 45

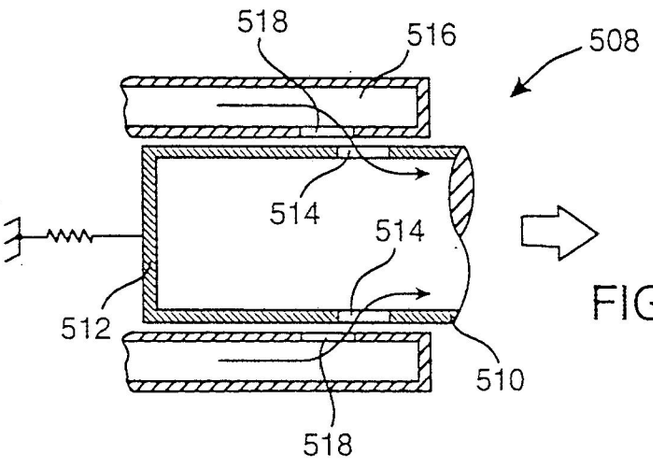


FIG. 46

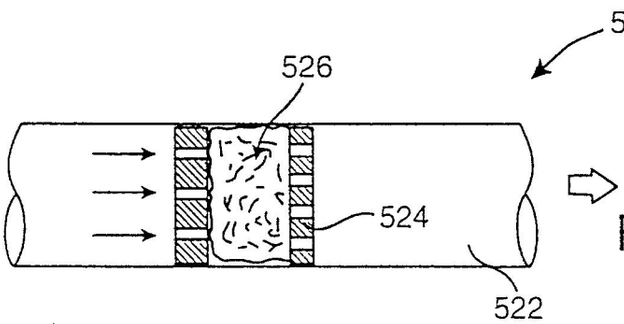


FIG. 47

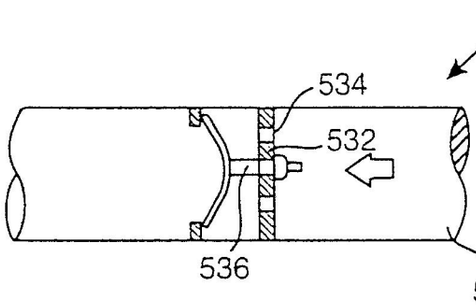


FIG. 48

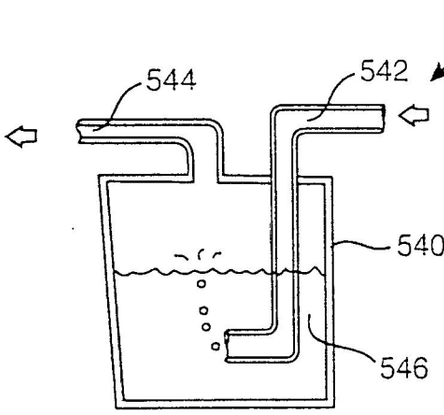


FIG. 49

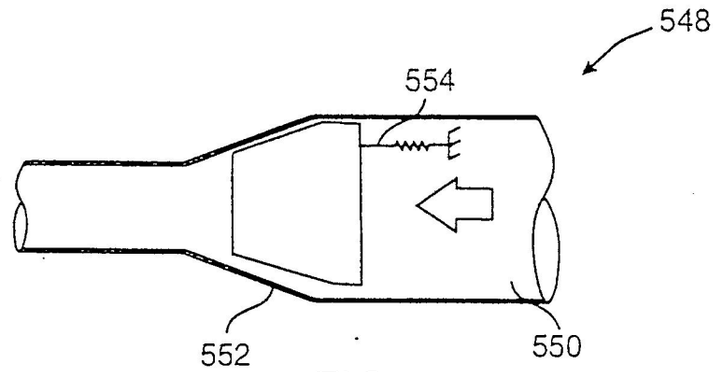


FIG. 50

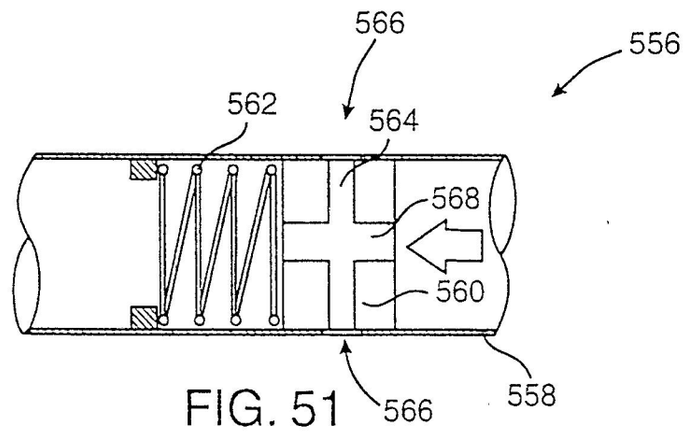


FIG. 51

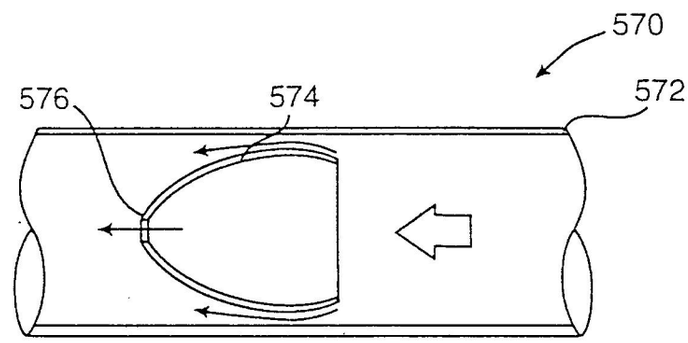


FIG. 52

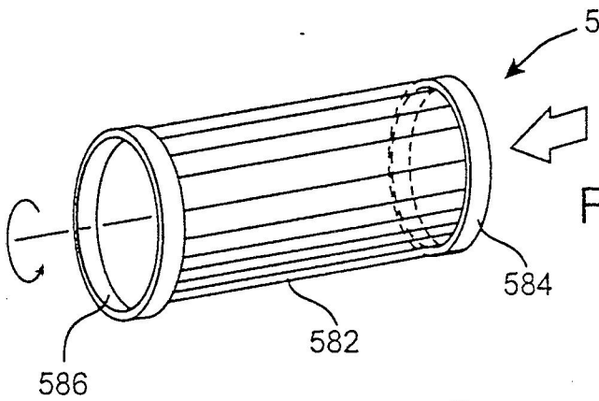


FIG. 53A

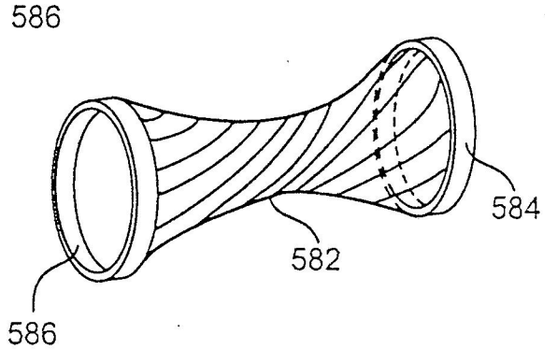


FIG. 53B

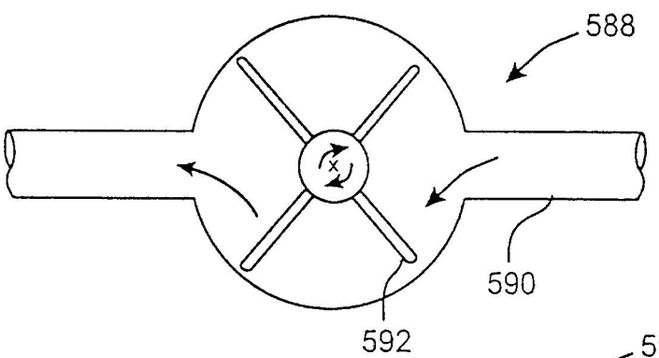


FIG. 54

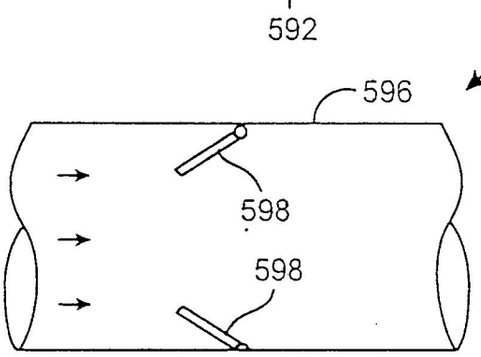


FIG. 55A

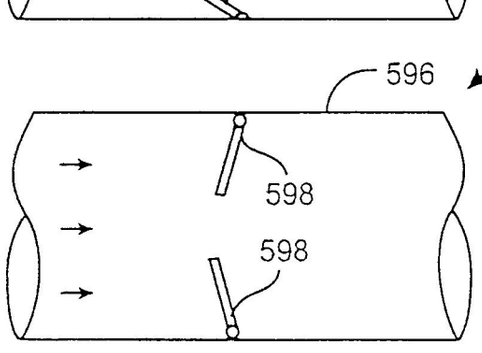


FIG. 55B

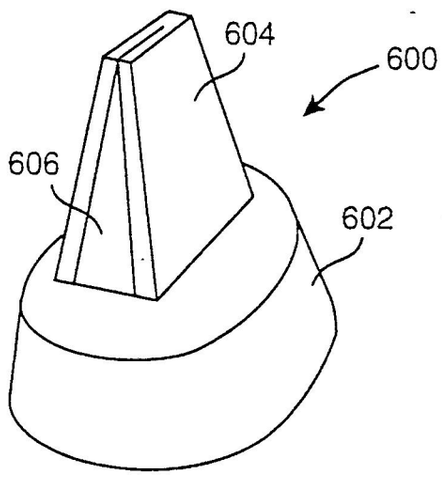


FIG. 56A

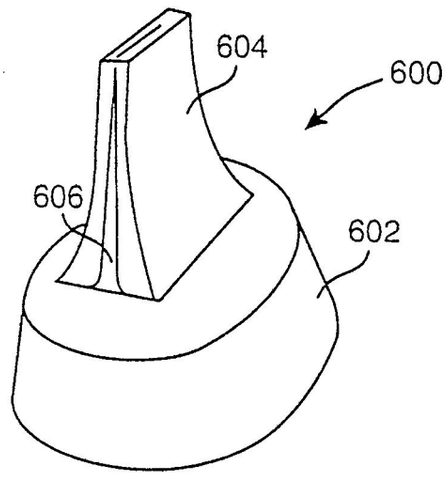


FIG. 56B

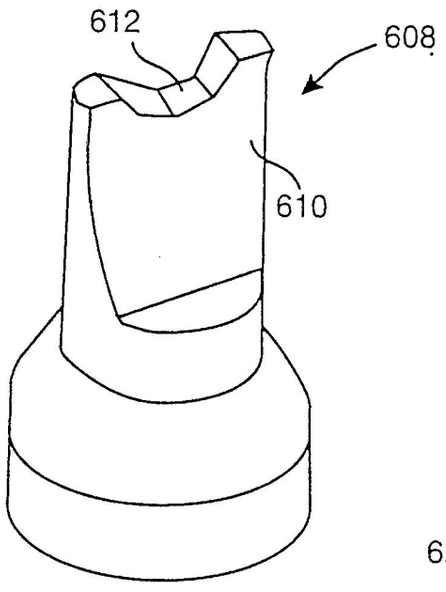


FIG. 57

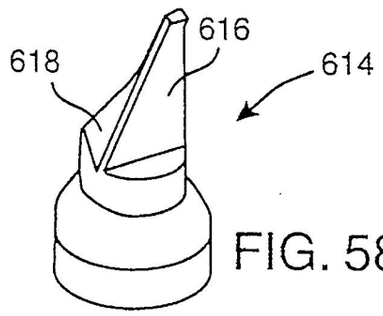


FIG. 58

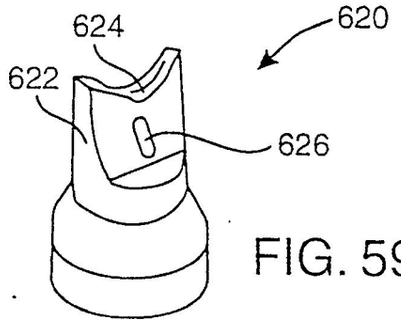


FIG. 59

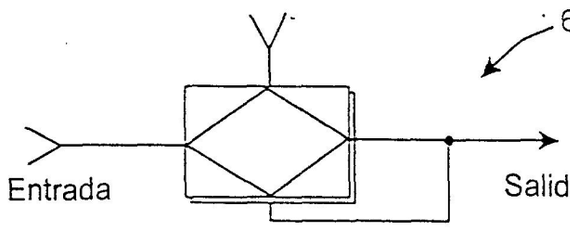


FIG. 60

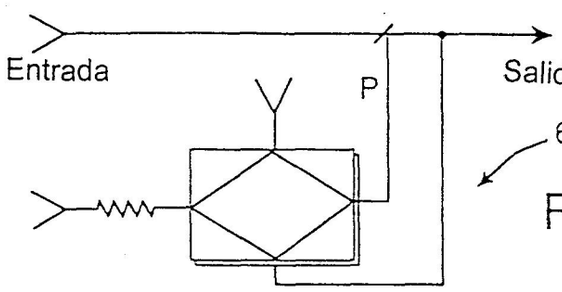


FIG. 61

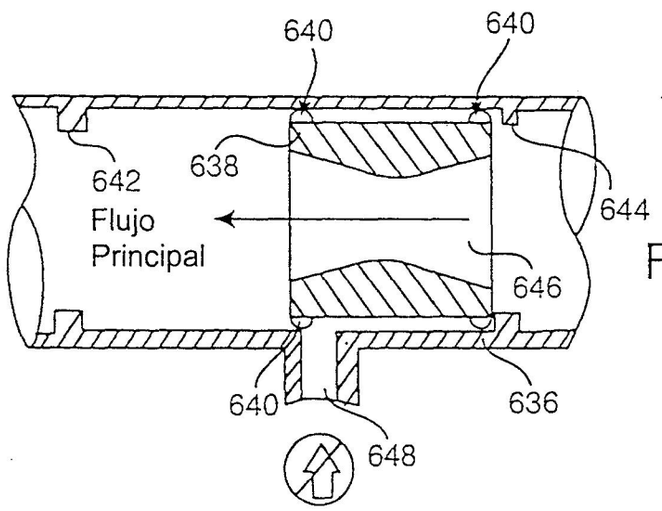


FIG. 62A

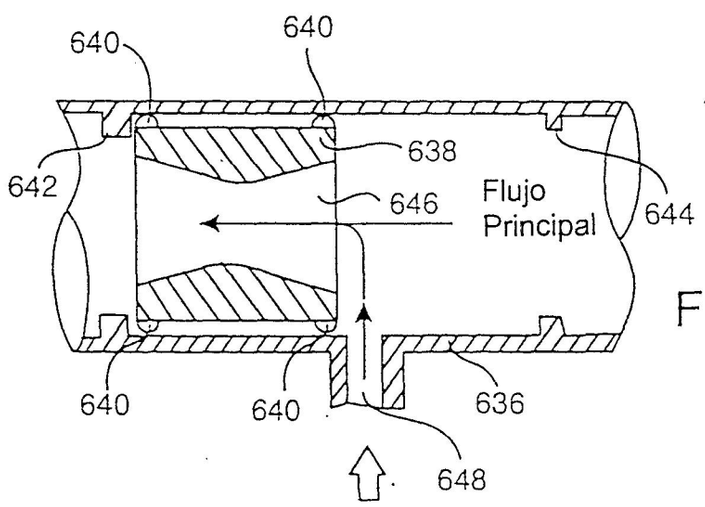


FIG. 62B

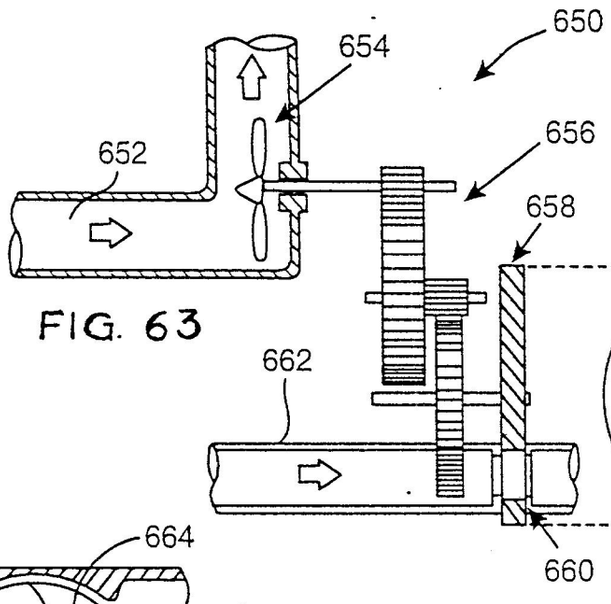


FIG. 63

FIG. 64

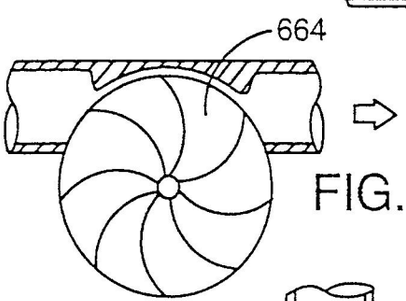


FIG. 65

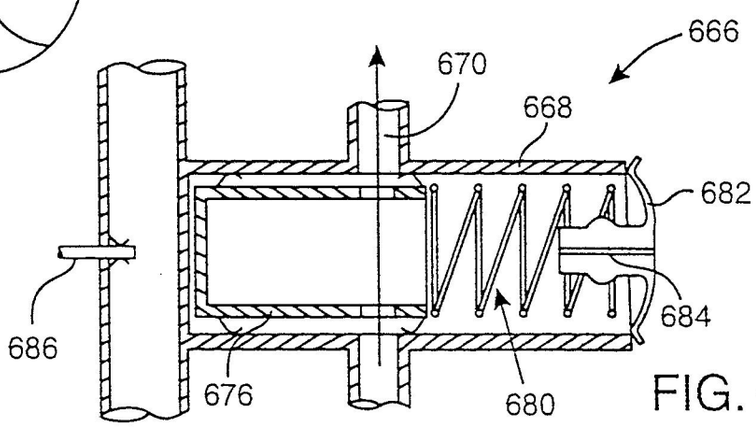


FIG. 66A

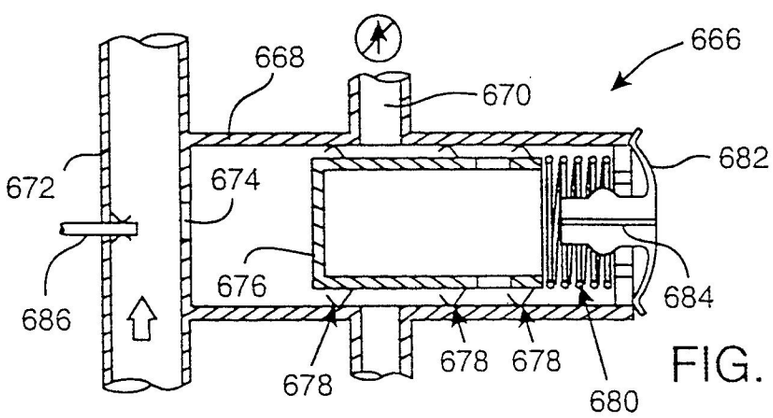


FIG. 66B

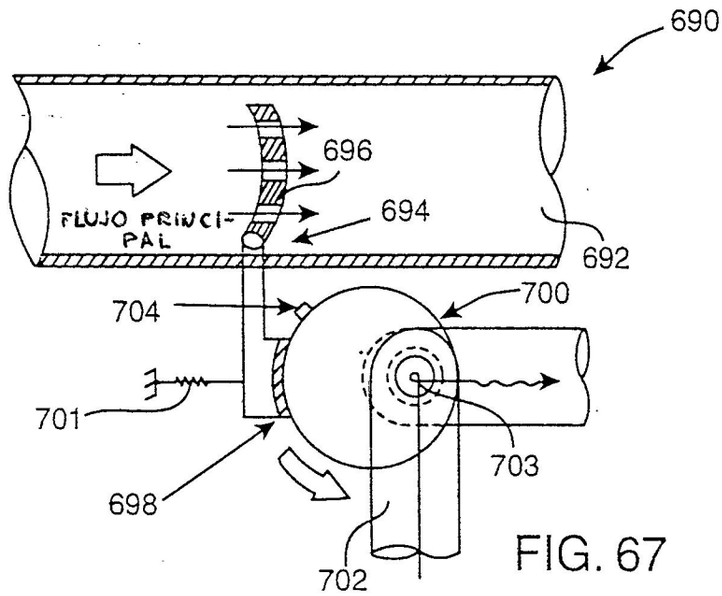

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FIG. 67

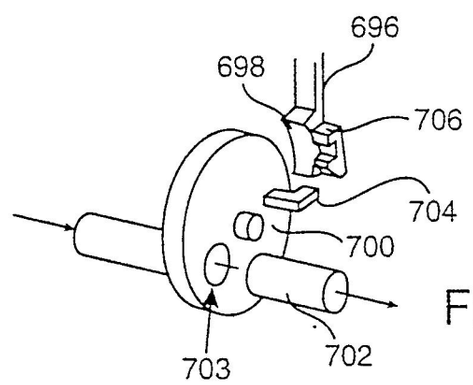

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FIG. 68

FIG. 69

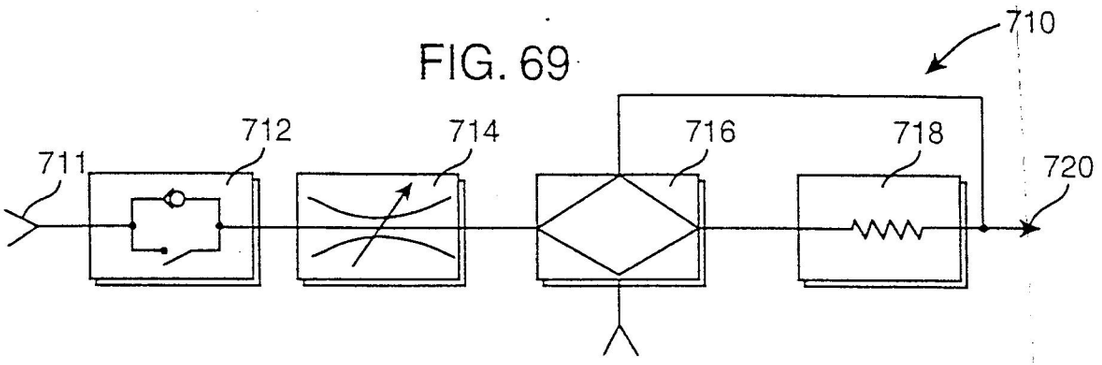


FIG. 70

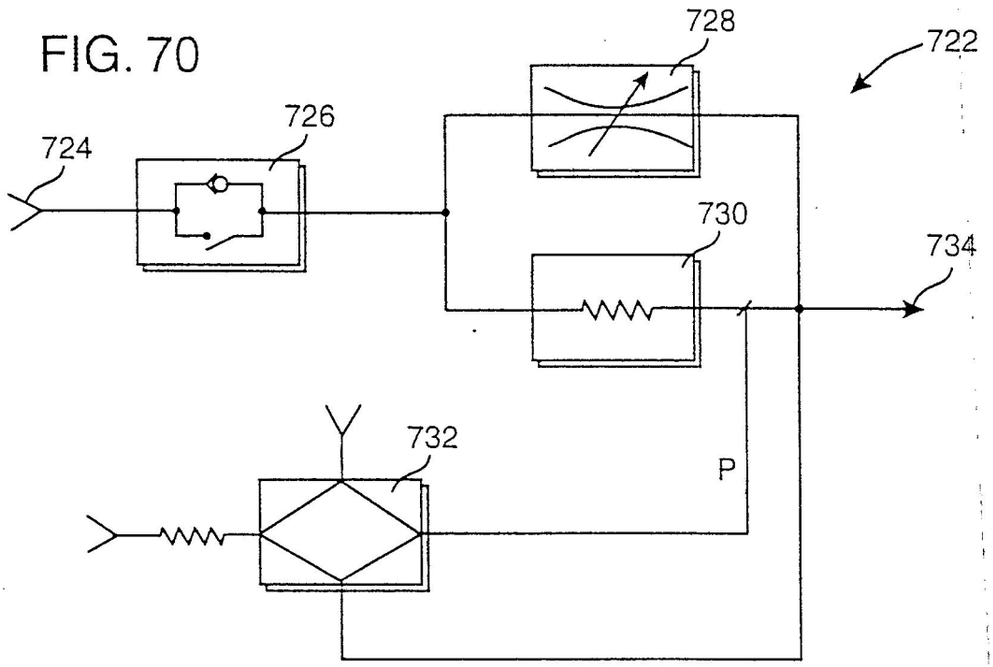
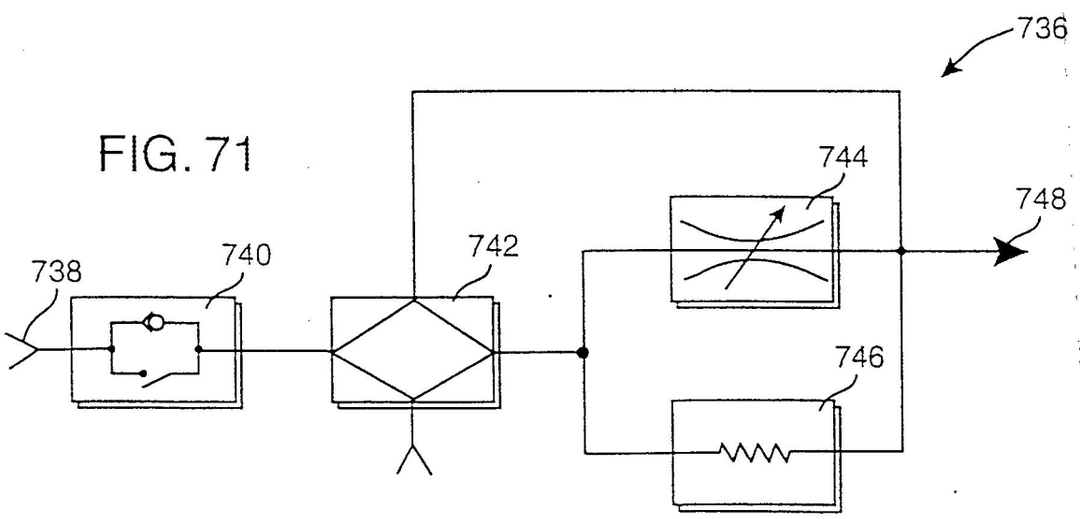


FIG. 71



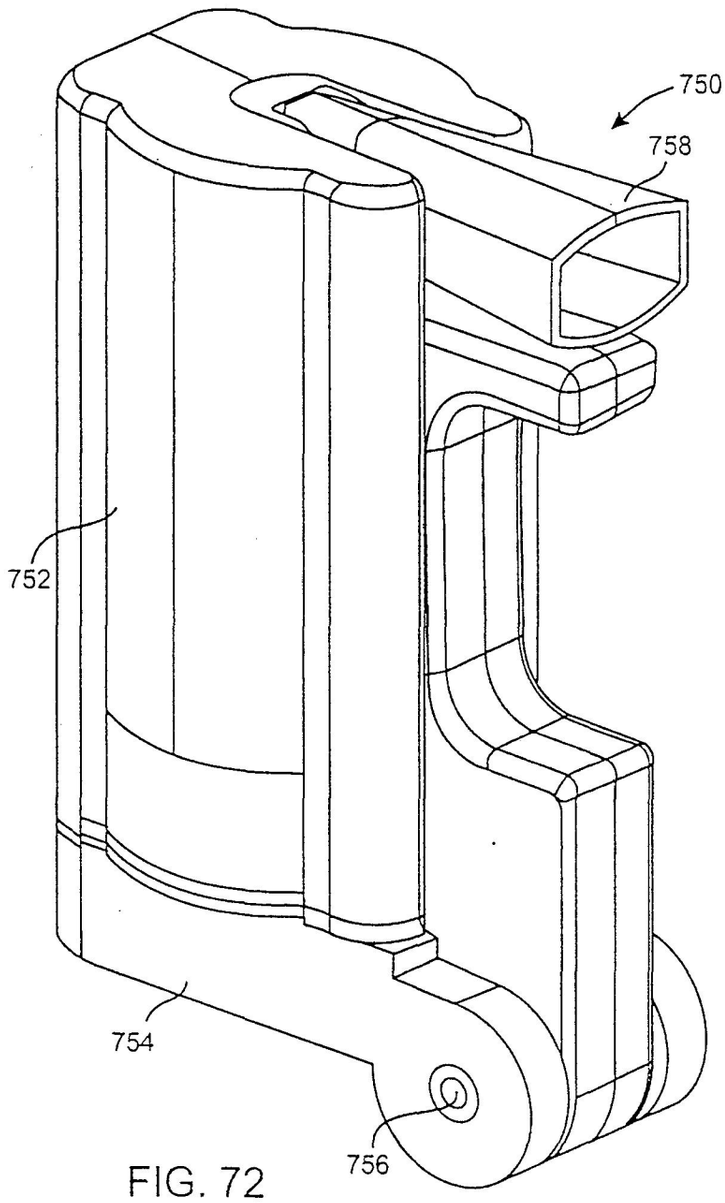


FIG. 72

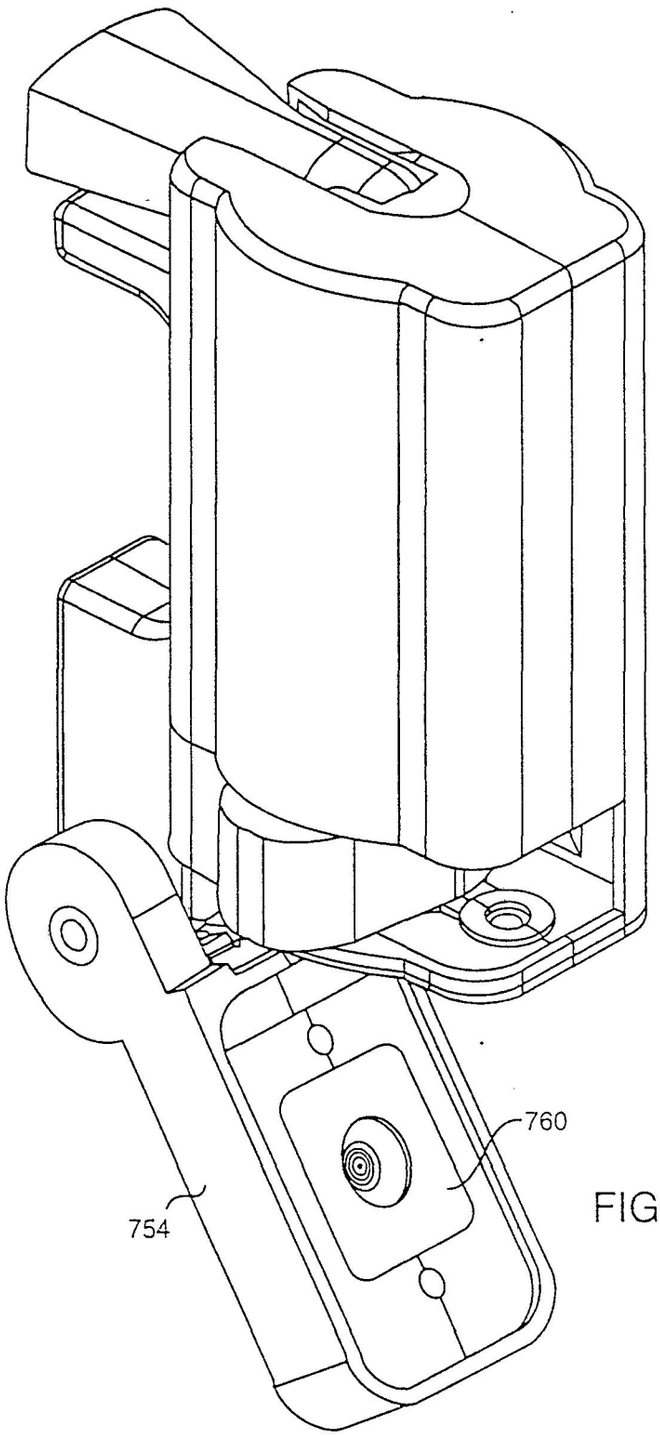


FIG. 73

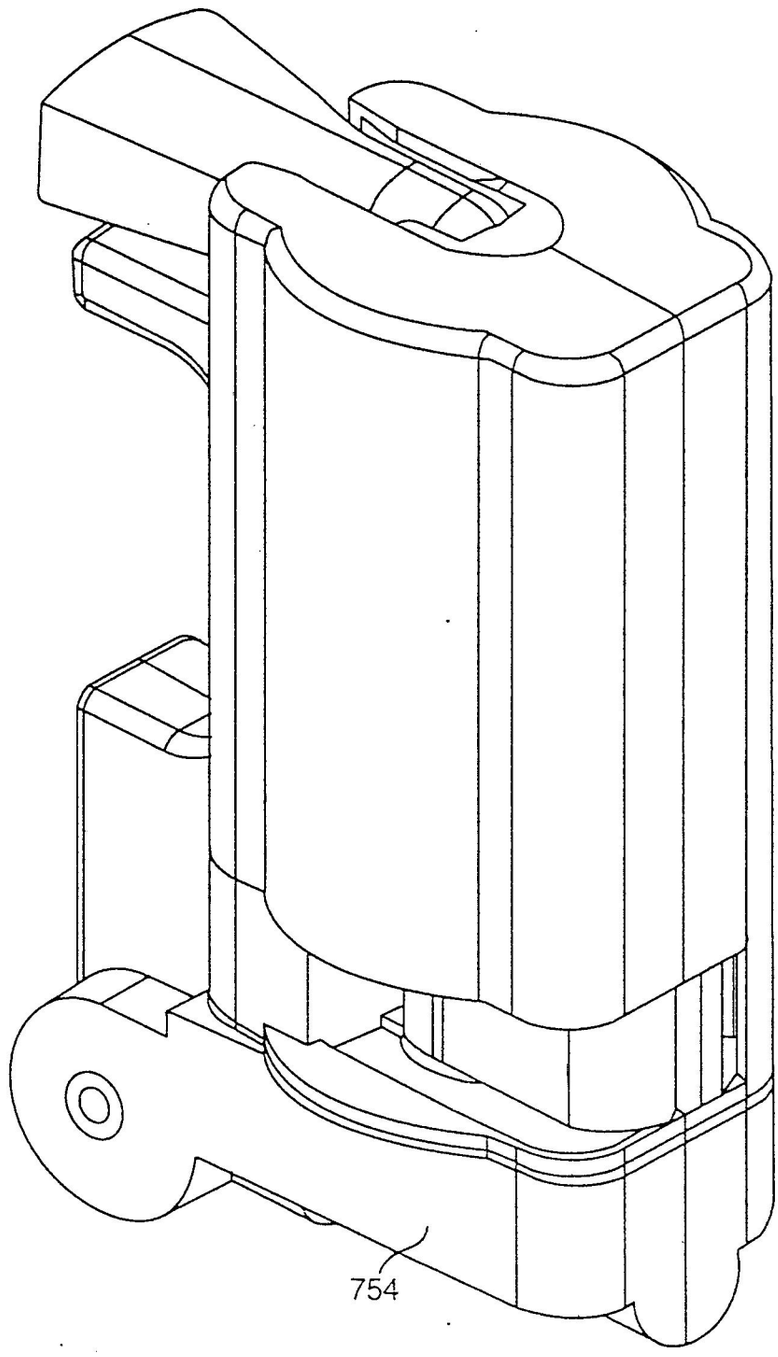


FIG. 74

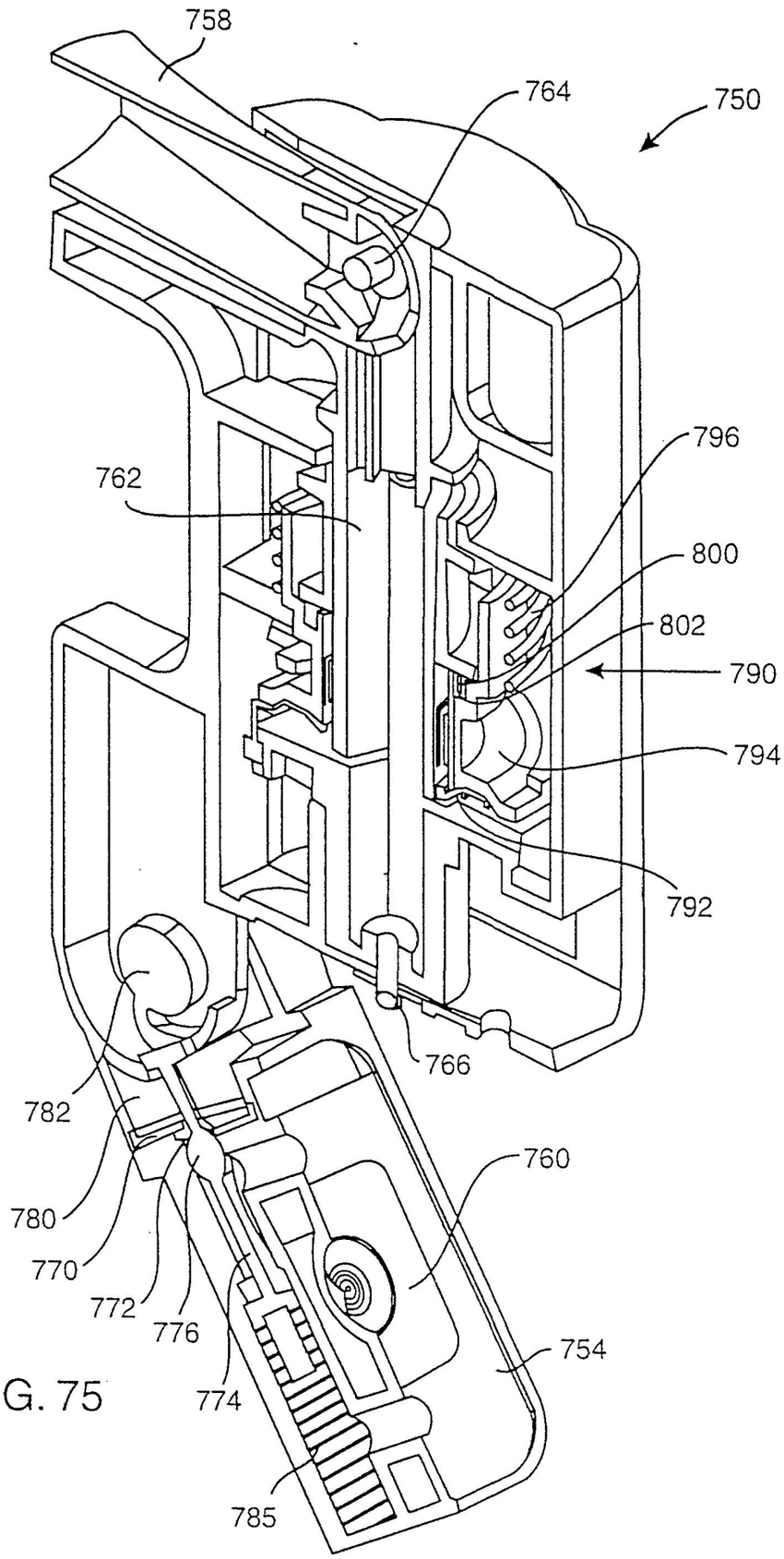

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FIG. 75

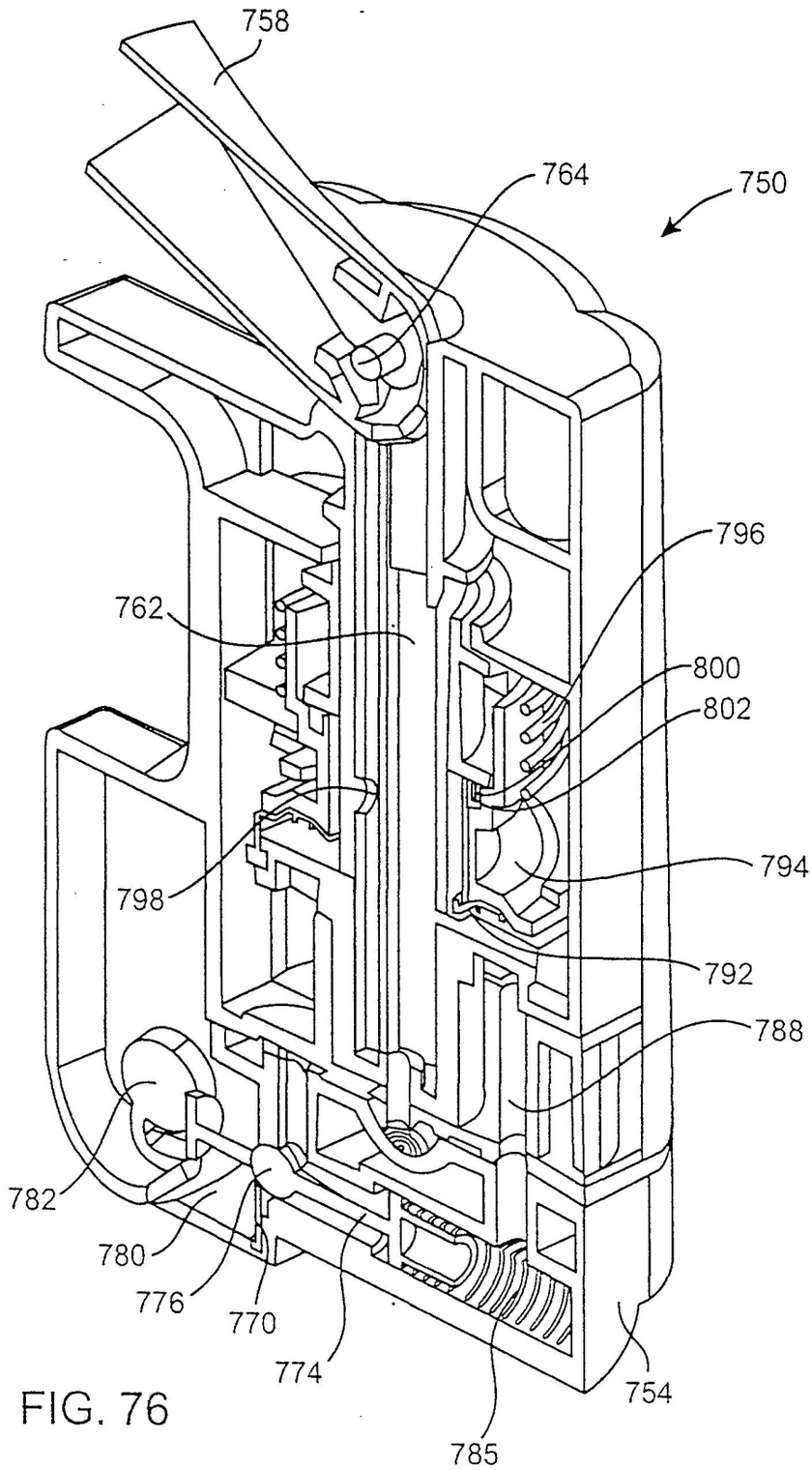

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FIG. 76

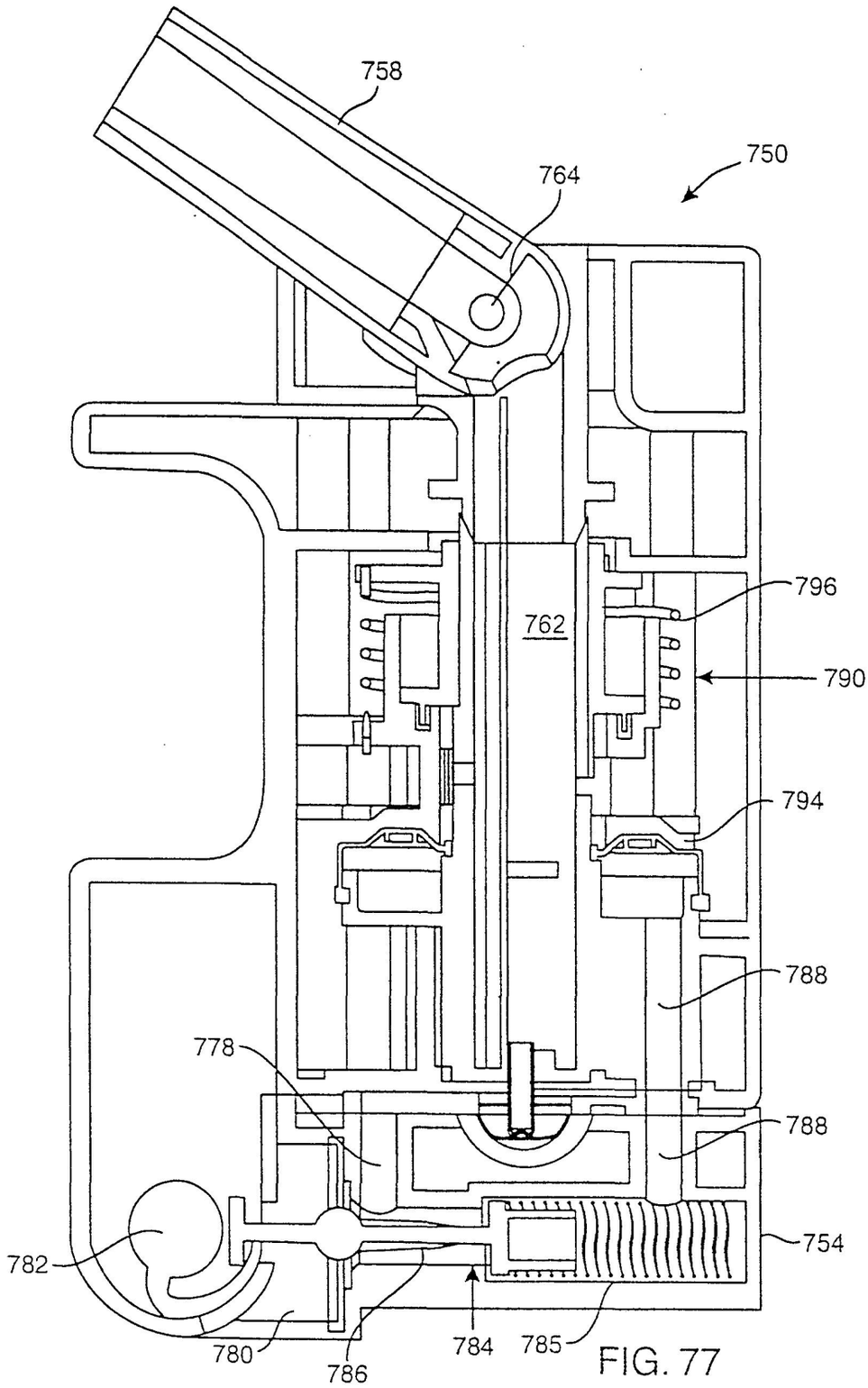


FIG. 77

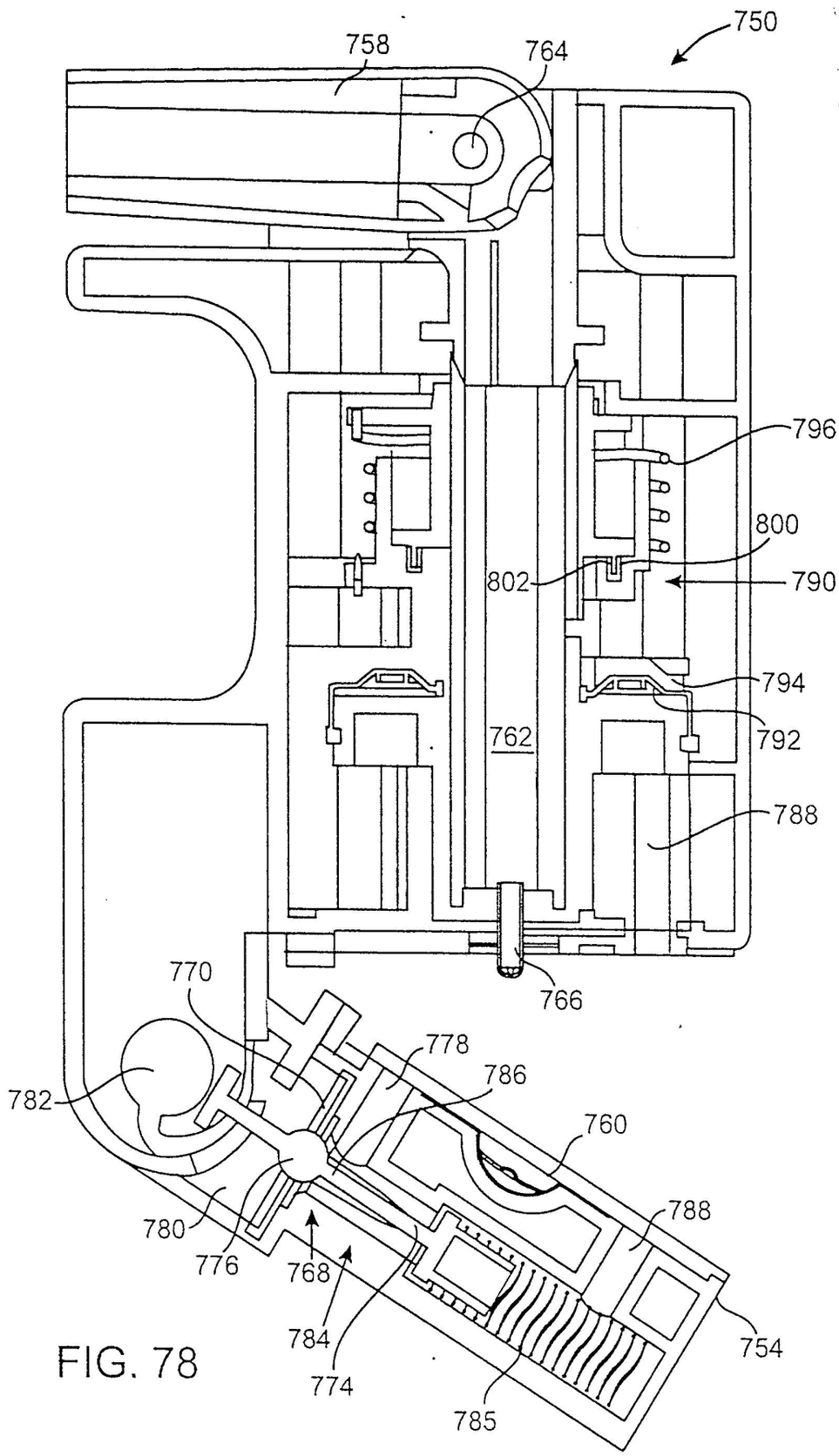

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FIG. 78

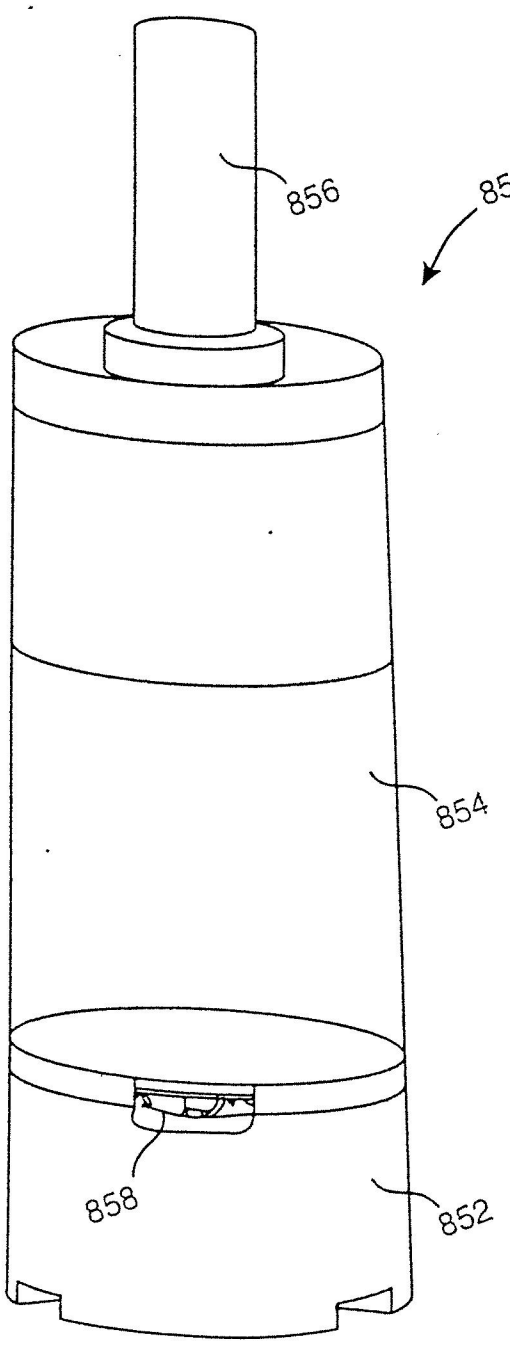


FIG. 79

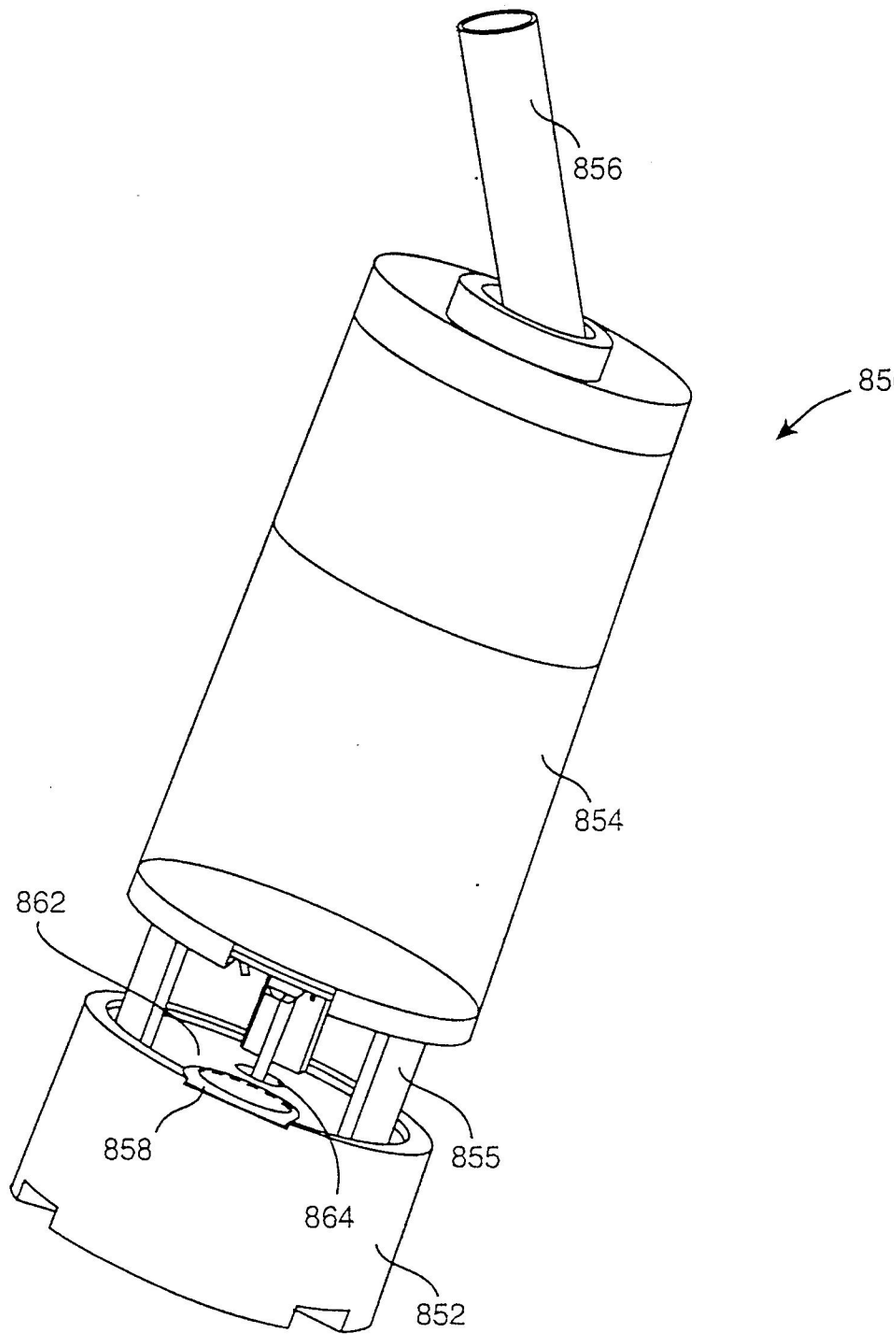


FIG. 80

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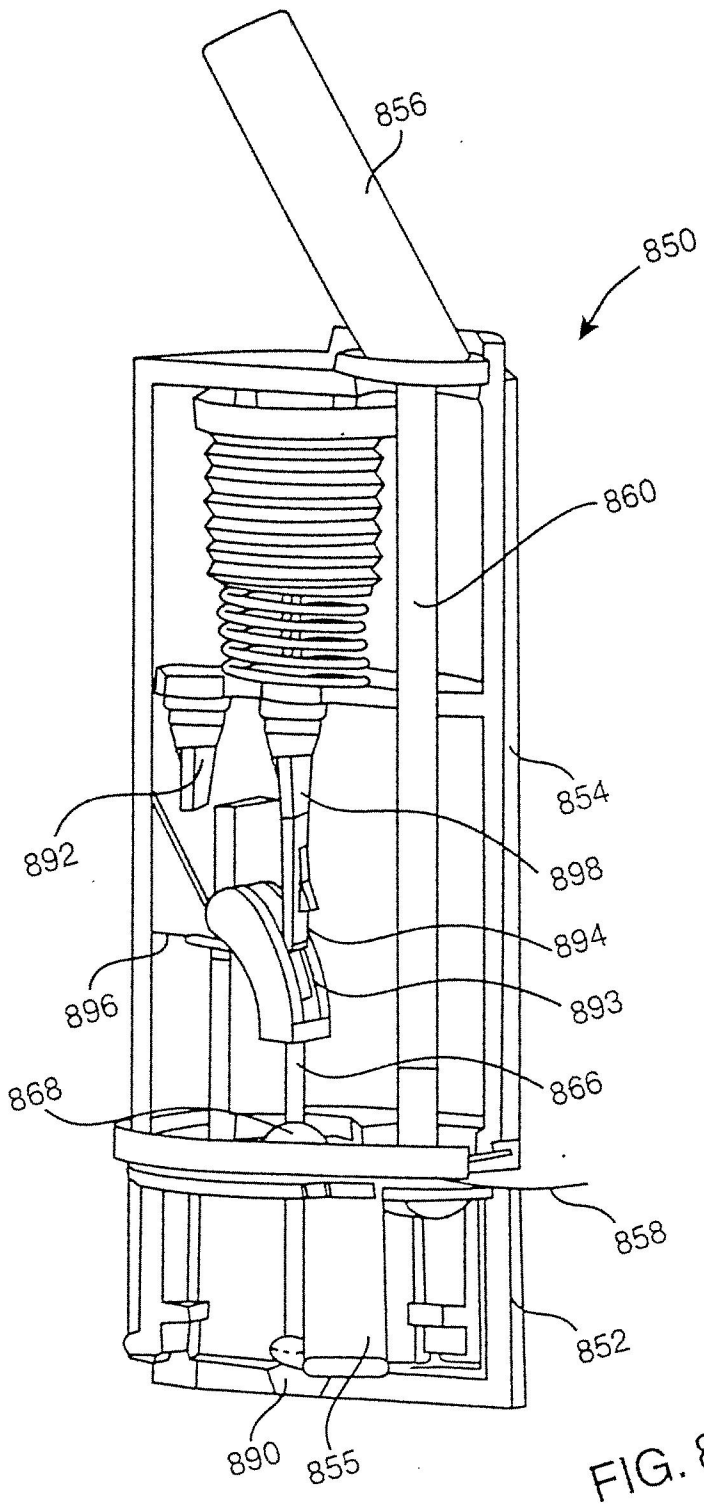


FIG. 81

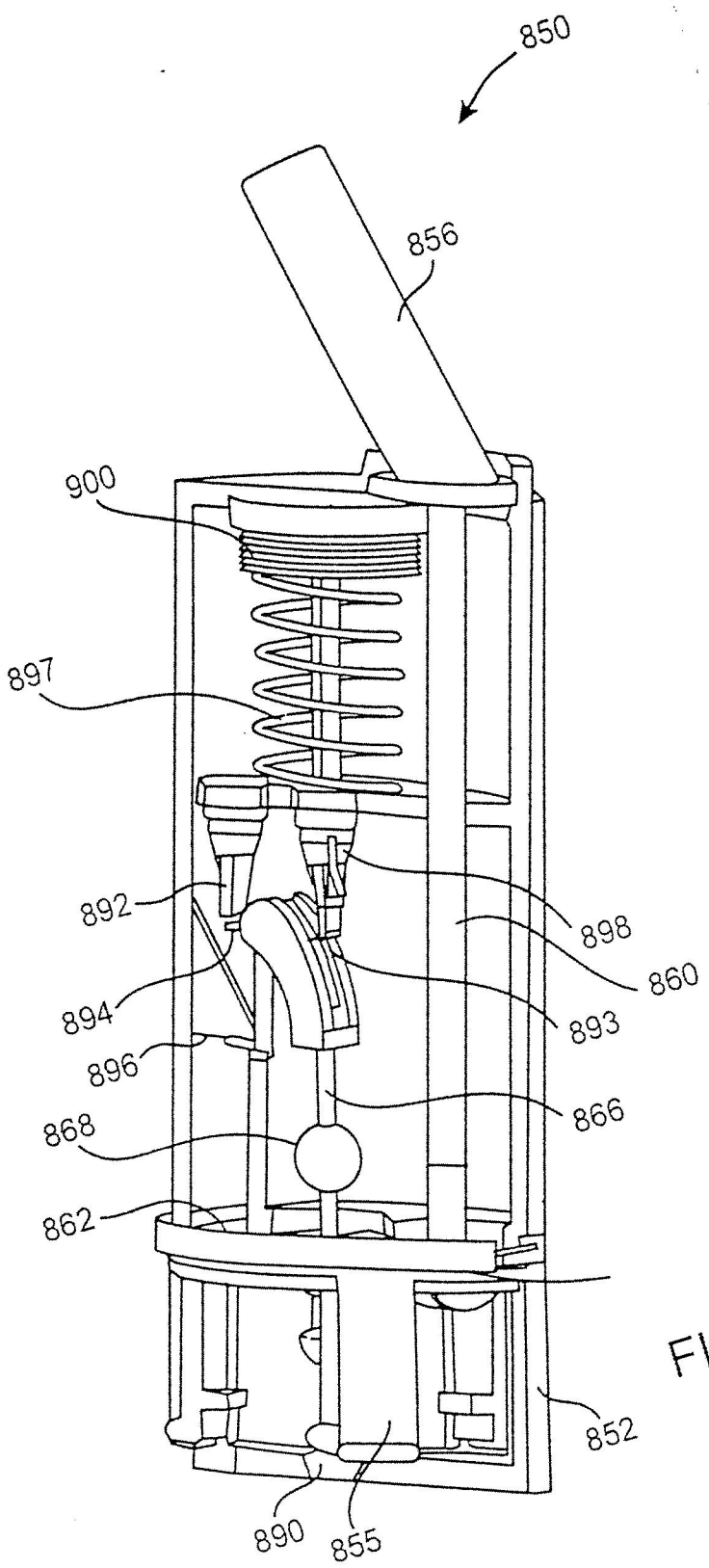


FIG. 82

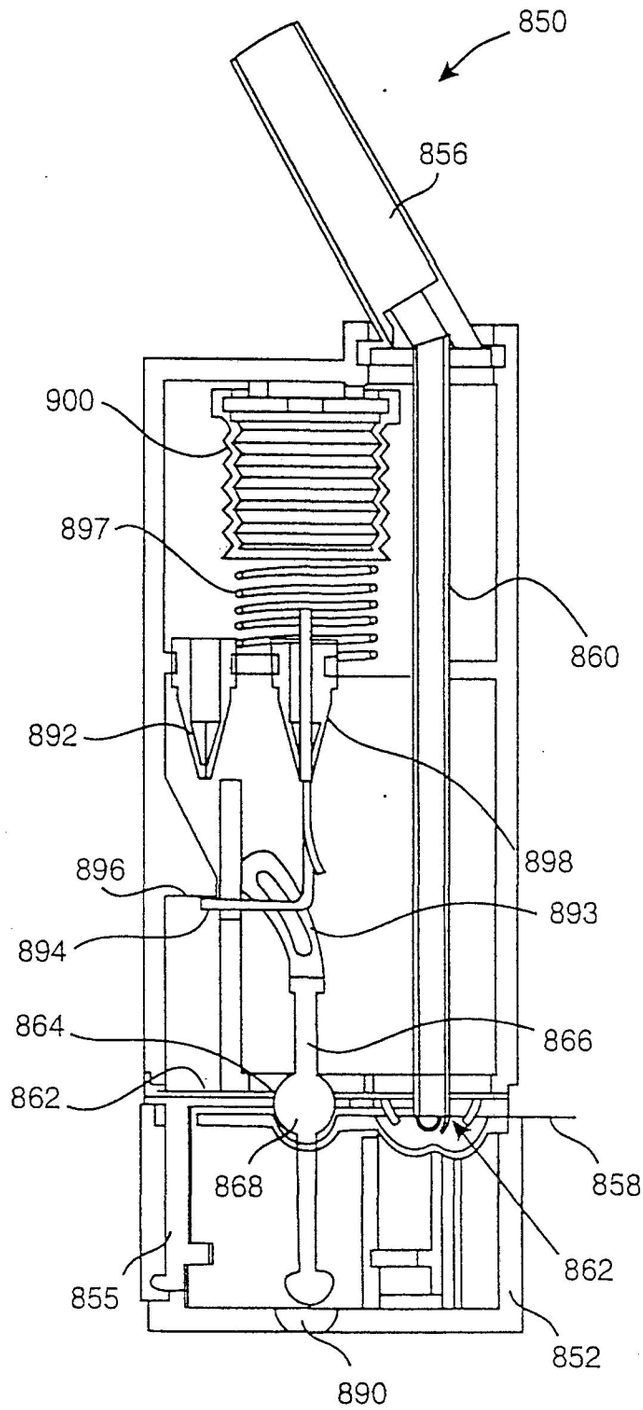

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FIG. 83

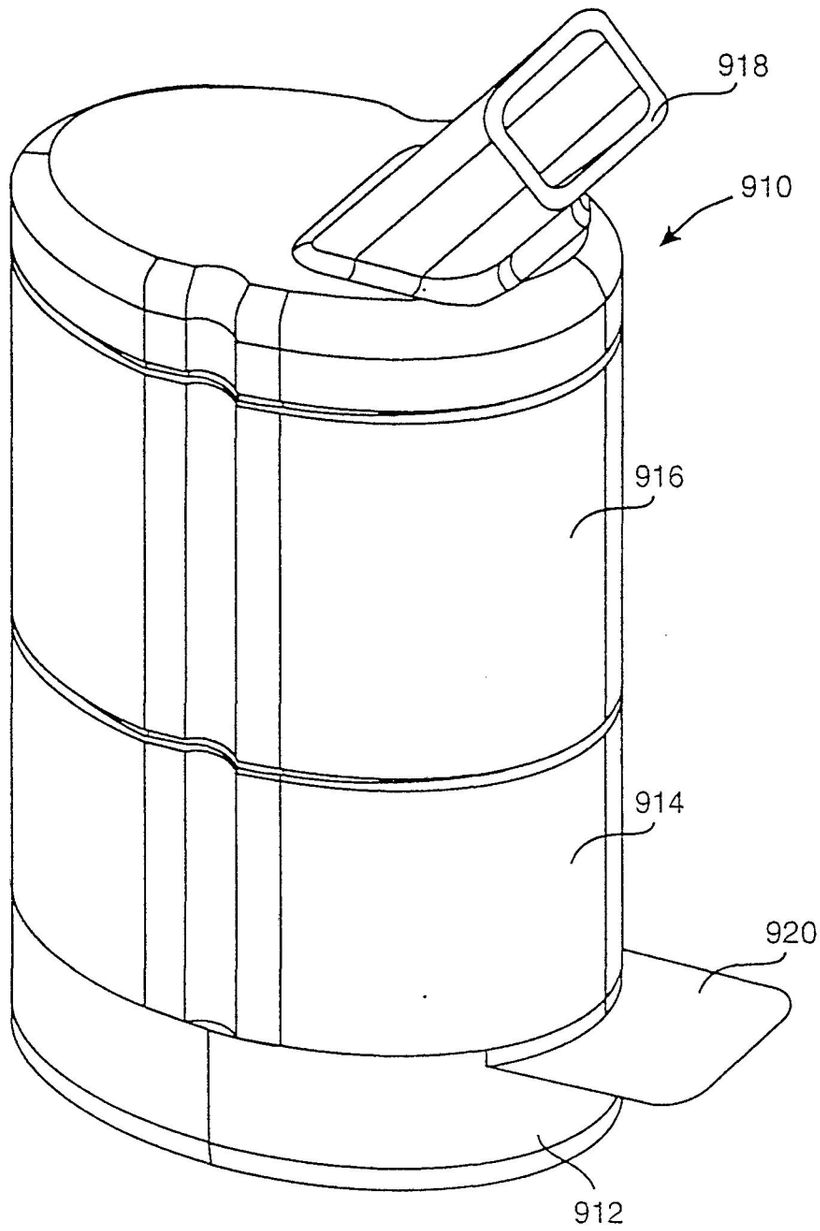


FIG. 84

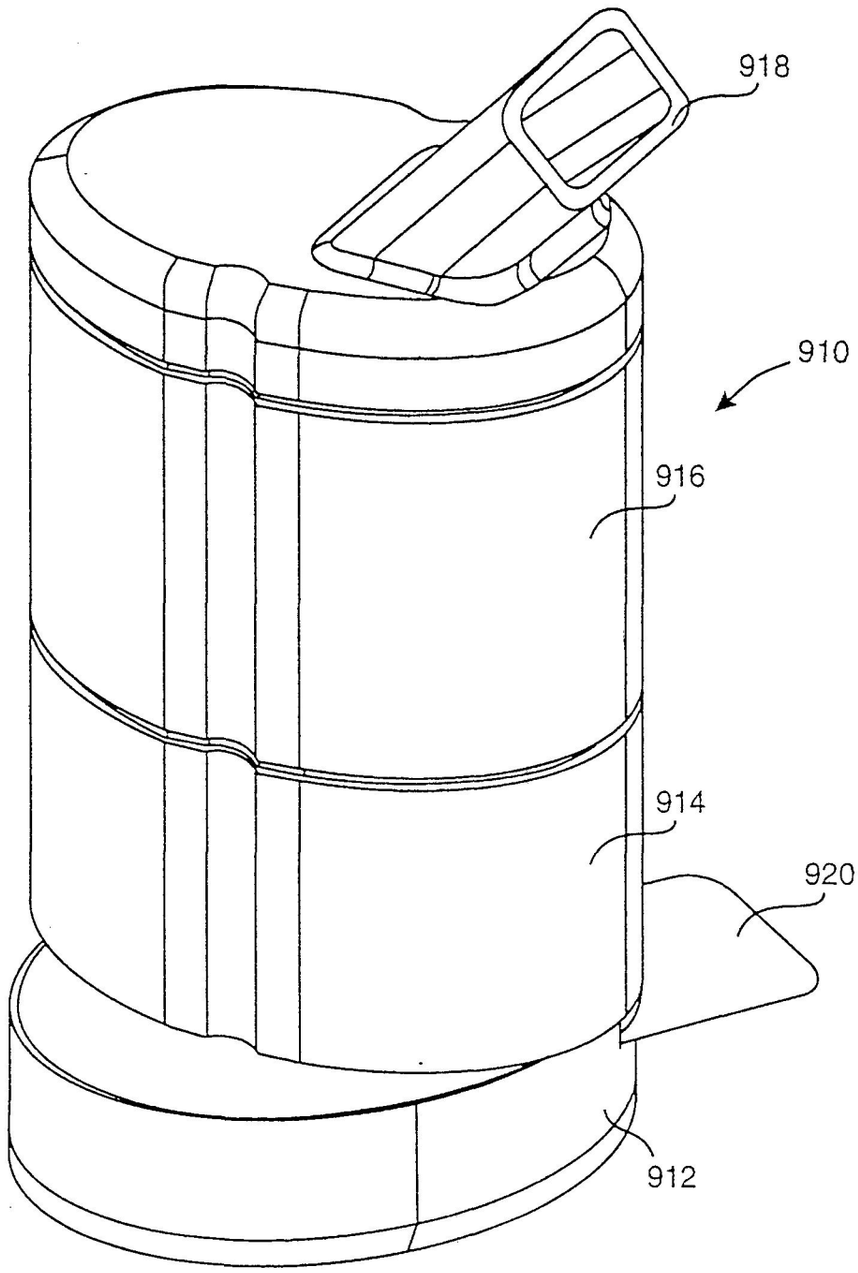


FIG. 85

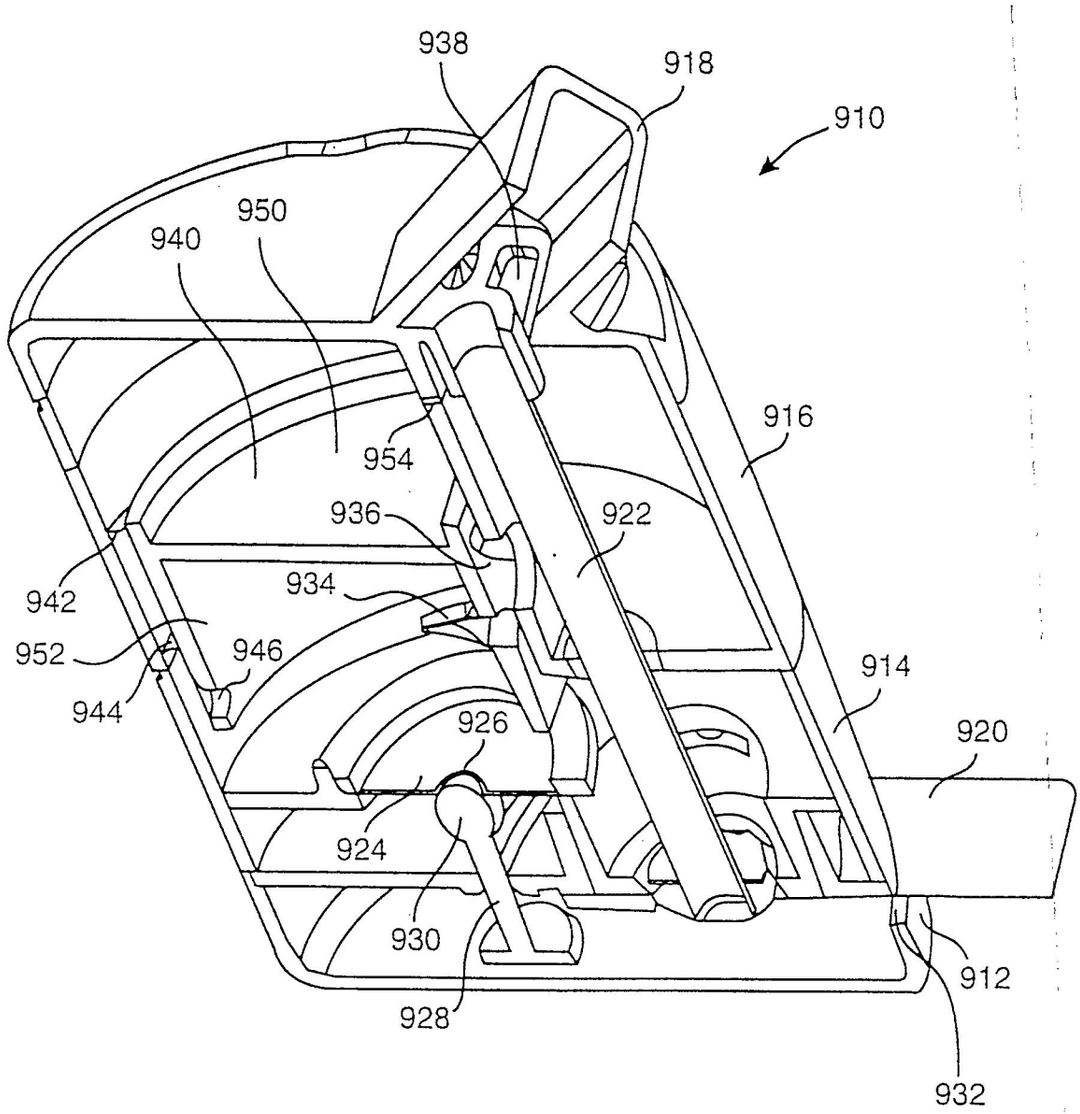

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FIG. 86

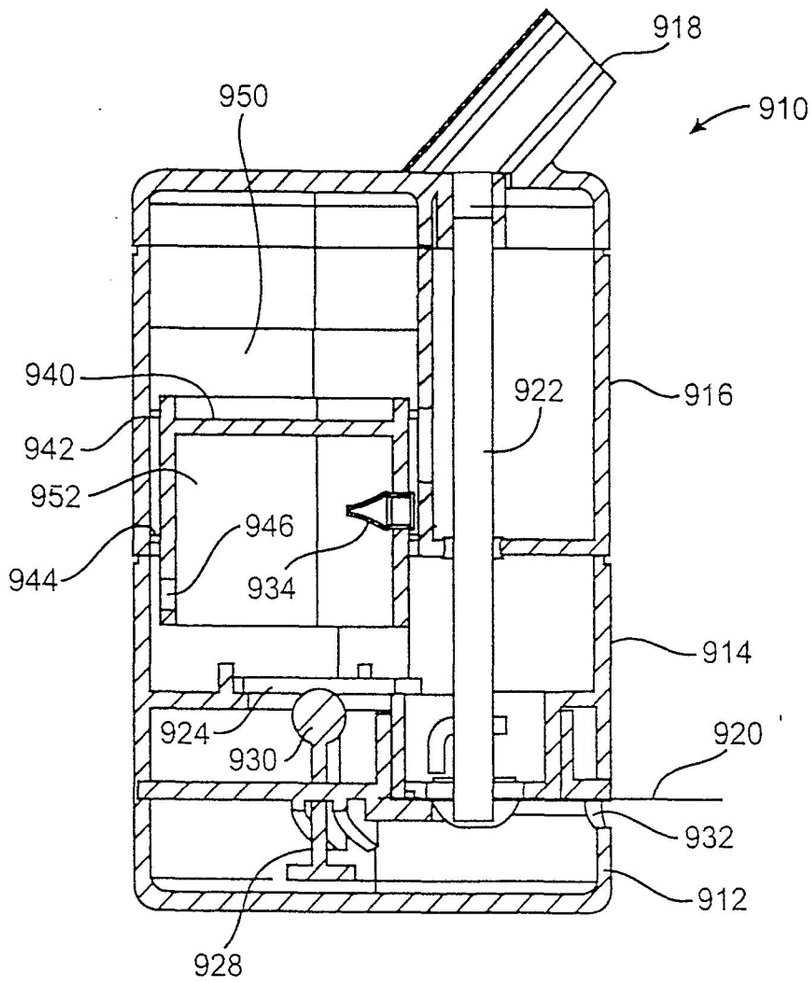

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FIG. 87

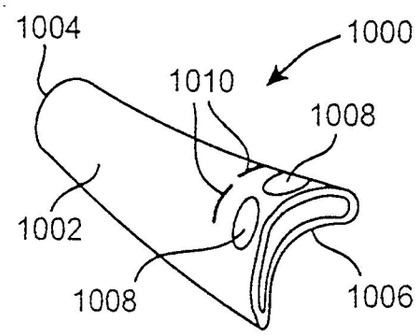

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FIG. 88

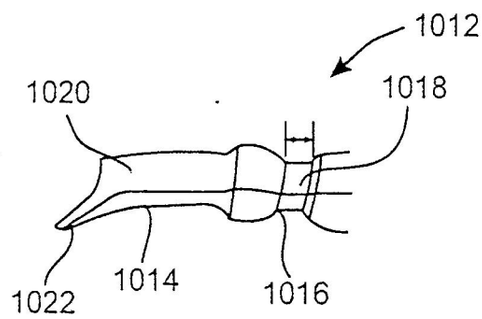
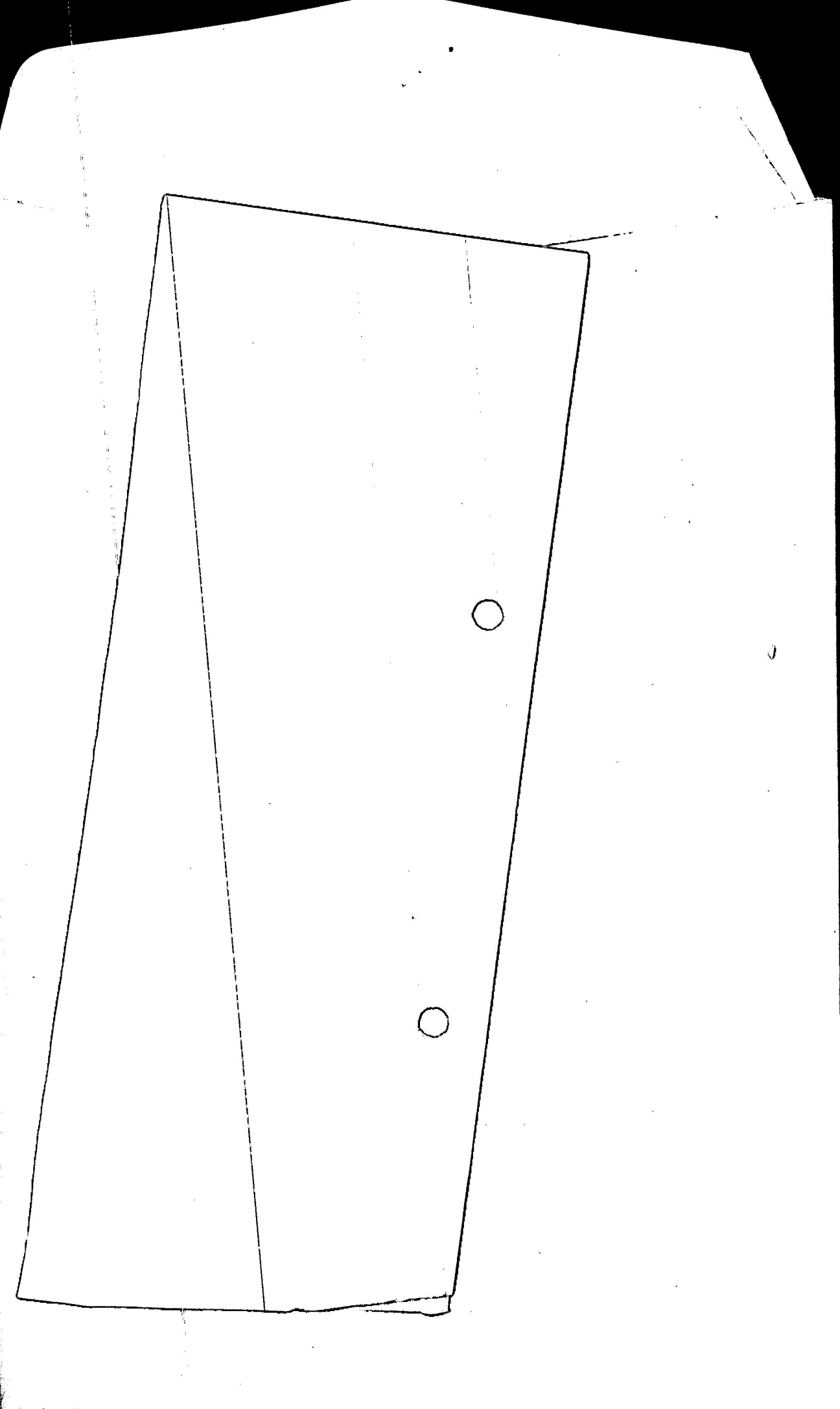

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FIG. 89

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Arte final
Expediente No. 00.048.974
INHALE THERAPEUTIC SYSTEMS, INC.



PA 283722

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

August 14, 2000

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APPLICATION NUMBER: ***60/141,793***
FILING DATE: ***June 30, 1999***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

N. WILLIAMS
Certifying Officer

jc658 U.S. PTO
06/30/99

PROVISIONAL APPLICATION

Attorney Docket No. 15225-004700US

"Express Mail" Label No. EJ786710131US
Date of Deposit: June 30, 1999

I hereby certify that this is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above, addressed to:

Assistant Commissioner for Patents
Box Provisional Patent Application
Washington, D.C. 20231

By: Janet Byrne

jc541 U.S. PTO
60/141793
06/30/99

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BOX PROVISIONAL PATENT APPLICATION
Washington, D.C. 20231
Sir:

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Paboojian	Steve		Menlo Park, California
Tuttle	Derrick	J.	San Mateo, California
Smith	Adrian	E.	Belmont, California
Rasmussen	Dennis	R.	Santa Clara, California
Bakshi	Aneesh		Belmont, California
Clark	Andrew		Half Moon Bay, California

Title: SYSTEMS AND METHODS FOR AEROSOLIZING PHARMACEUTICAL FORMULATIONS

Enclosed are:
[X] 26 pages of the specification (including description and claims).
[X] 14 sheet(s) of [ ] formal [X] informal drawing(s).
[X] Abstract.
[ ] A verified statement to establish small entity status under 37 CFR 1.9 and CFR 1.27.
[ ] The invention was made by or under a contract with the following agency of the United States Government:
_____ under Government contract number _____
[ ]

Please charge Deposit Account No. 20-1430 as follows:

[X] Filing fee $ $150.00
[X] Any additional fees associated with this paper or during the pendency of this application.

2 extra copies of this sheet are enclosed.

Respectfully submitted,

TOWNSEND and TOWNSEND and CREW LLP

Darin J. Gibby
Reg. No. 38,464
Attorneys for Applicant

Customer No. 20350

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DE 7001468 v1

SYSTEMS AND METHODS FOR AEROSOLIZING PHARMACEUTICAL FORMULATIONS

BACKGROUND OF THE INVENTION

This invention relates generally to the field of drug delivery, and in particular to the delivery of pharmaceutical formulations to the lungs. More specifically, the invention relates to the aerosolization of pharmaceutical formulations using energy created by patient inhalation.

Effective drug delivery to a patient is a critical aspect of any successful drug therapy, and a variety of drug delivery techniques have been proposed. For example, one convenient method is the oral delivery of pills, capsules, elixirs and the like. However, oral delivery can in some cases be undesirable in that many drugs are degraded in the digestive tract before they can be absorbed. Another technique is subcutaneous injection. One disadvantage to this approach is low patient acceptance. Other alternative routes of administration that have been proposed include transdermal, intranasal, intrarectal, intravaginal and pulmonary delivery.

Of particular interest to the invention are pulmonary delivery techniques which rely on the inhalation of a pharmaceutical formulation by the patient so that the active drug within the dispersion can reach the distal (alveolar) regions of the lung. A variety of aerosolization systems have been proposed to disperse pharmaceutical formulations. For example, U.S. Patent Nos. 5,785,049 and 5,740,794, the disclosures of which are herein incorporated by reference, describe exemplary powder dispersion devices which utilize a compressed gas to aerosolize a powder. Other types of aerosolization systems include MDI's (which typically have a drug that is stored in a propellant), nebulizers (which aerosolize liquids using compressed gas, usually air), and the like.

Another technique which is of interest to the invention is the use of inspired gases to disperse the pharmaceutical formulation. In this way, the patient is able to provide the energy needed to aerosolize the formulation by the patient's own inhalation. This insures that aerosol generation and inhalation are properly synchronized. Utilization of the patient's inspired gases can be challenging in several respects. For example, for some pharmaceutical formulations, such as insulin, it may be desirable to

limit the inhalation flow rate within certain limits. For example, PCT/US99/04654, filed March 11, 1999, provides for the pulmonary delivery of insulin at rates less than 17 liters per minute. As another example, copending U.S. Patent Application Serial No. 60/103,702 describes pulmonary delivery techniques where a high flow resistance is provided for an initial period followed by a period of lower flow resistance. The complete disclosures of all the above references are herein incorporated by reference.

Another challenge in utilizing the patient's inspired gases is that the inspiration flow rate can drastically vary between individuals. For instance, as shown in Fig. 1, a random sample of 17 individuals which were measured twice a week for four weeks produced flow rates ranging from about 5 liters per minute to about 35 liters per minute. Such variability may affect the ability of the formulation to be dispersed within a gas stream, the ability to deagglomerate a powdered formulation, and/or the ability of the aerosolized formulation to adequately reach the deep lung.

Hence, this invention is related to techniques for regulating the flow of inspired gases that may be utilized when dispersing a pharmaceutical formulation. In one aspect, the invention is related to techniques to enhance the ability of a formulation to be dispersed within a gas stream produced by patient inhalation, to enhance the ability to deagglomerate a powdered formulation, and to enhance the ability of the aerosolized formulation to adequately reach the deep lung.

SUMMARY OF THE INVENTION

The invention provides exemplary systems and methods that utilize the flow of respiratory gases produced by a patient to aerosolize a pharmaceutical formulation. In one particular aspect of the invention, the invention is able to extract a powdered pharmaceutical formulation from a receptacle, deagglomerate the formulation and deliver the formulation to the lungs using a wide range of patient inhalation flow rates.

In one particular embodiment, a method is provided for aerosolizing a pharmaceutical formulation. According to the method, respiratory gases are prevented from flowing to the lungs when attempting to inhale. The respiratory gases are then abruptly permitted to flow to the lungs. The flow of respiratory gases is utilized to extract a pharmaceutical formulation from a receptacle and to place the pharmaceutical formulation within the flow of respiratory gases to form an aerosol.

By initially preventing respiratory gases from flowing to the lungs when attempting to inhale, the method provides a way to ensure that the resulting gas stream has sufficient energy to extract the pharmaceutical formulation from the receptacle. In one aspect, the flow of respiratory gases may initially be prevented from flowing to the lungs by placing a valve within an airway leading to the lungs and opening the valve to permit the flow of respiratory gases. In a particular aspect, the valve is opened when a threshold actuating vacuum caused by the attempted inhalation is exceeded. In this way, when the valve is opened, the resulting gas stream has sufficient energy to extract and aerosolize the pharmaceutical formulation.

In still another aspect, the method provides for limiting the flow of respiratory gases to a rate that is less than a certain rate for a certain time. For example, the flow rate may be limited to a rate that is less than about 15 liters per minute for a time in the range from about 0.5 second to about 5 seconds, corresponding to a volume in the range from about 125 mL to about 1.25 L. Regulation of the flow rate is advantageous in that it may increase systemic bioavailability of the active agent of certain pharmaceutical formulations via absorption in the deep lung as described generally in PCT Application No. PCT/U.S. 99/04654, filed March 3, 1999 and in copending U.S. Application Serial No. 60/103,702, previously incorporated by reference.

A variety of techniques may be employed to limit or regulate the flow of respiratory gases. For example, feedback may be provided to the user when an excessive flow rate is produced to permit a user to adjust their inhalation rate. Examples of feedback which may be provided include audio feedback, including a whistle, visual feedback, such as indicator lights or a level meter, tactile feedback, such as vibration, and the like. As another alternative, the flow of respiratory gases may be controlled by regulating the size of an airway leading to the lungs. After the flow rate has been limited for the desired amount of time or inhaled volume, the size of the airway may be increased to provide for an increased flow rate. In this way, the user may comfortably inhale without substantial resistance in order to fill the user's lungs with respiratory gases and carry the pharmaceutical formulation into the deep lung.

In another aspect of the method, the pharmaceutical formulation comprises a powdered medicament. The flow of respiratory gases is used to deagglomerate the powder once extracted from the receptacle. Optionally, various structures may be placed into the airway to assist in the deagglomeration process.

In another embodiment, the invention provides an aerosolization device that comprises a housing defining an airway, and a coupling mechanism to couple a receptacle containing a pharmaceutical formulation to the airway. The device further includes a valve to prevent respiratory gases from flowing through the airway until a threshold actuating vacuum is exceeded. At such a time, the valve opens to permit respiratory gases to flow through the airway and to extract the pharmaceutical formulation from the receptacle to form an aerosol.

In one aspect, the device further includes a regulation system to regulate the flow of respiratory gases through the airway to a certain rate. For example, the regulation system may be configured to limit the flow to a rate that is less than about 15 liters per minute for a certain time or a certain inspired volume.

In one particular aspect, the regulation system may comprise a feedback mechanism to provide information on the rate of flow of the respiratory gases. For example, the feedback mechanism may comprise a whistle that is in communication with the airway and produces a whistling sound when the maximum flow rate is exceeded. In another alternative, the regulation system may comprise a restriction mechanism to limit the size of the airway. Conveniently, the restriction mechanism may be adjustable to vary the rate of flow of respiratory gases through the airway. Optionally, a control system may be provided to adjust the restriction mechanism. In one aspect, the control system is configured to limit the flow to a certain rate for a certain time or a certain inspired volume and then to adjust the restriction mechanism to permit an increased flow of respiratory gases through the airway. In this manner, the flow rate of respiratory gases may be regulated to limit the flow to a certain rate for a certain time to facilitate proper delivery of the pharmaceutical formulation to the lungs. The control system may then be employed to adjust the restriction mechanism so that the user can comfortably fill their lungs with respiratory gases to deliver the pharmaceutical formulation to the deep lung. Use of the control system is advantageous in that the device may be used with numerous users that have different inhalation flow rates, with the device regulating the flow of respiratory gases so that the pharmaceutical formulation is properly delivered to the lungs.

In another aspect, the threshold actuating vacuum of the valve is in the range from about 20 cm H_20 to about 60 cm H_20. In still another aspect, the device further comprises a deagglomeration mechanism disposed in the airway downstream of the receptacle to deagglomerate the extracted pharmaceutical formulation. In one

particular aspect, the valve is configured to be disposed within the receptacle. In this way, the valve may conveniently be manufactured along with the receptacle.

In another embodiment, the invention provides an aerosolization system that comprises a receptacle having a chamber for holding a pharmaceutical formulation and a threshold valve. The system also includes a housing defining an airway, and a coupling mechanism to position the valve across the airway and to place the pharmaceutical formulation in fluid communication with the airway. Further, the threshold valve is configured to open when a threshold actuating vacuum is exceeded to permit respiratory gases to flow through the airway and extract the pharmaceutical formulation from the chamber to form an aerosol.

In one particular aspect, the pharmaceutical formulation comprises a powdered or liquid medicament. In another aspect, the system includes a regulation system to regulate the flow of respiratory gases through the airway after the valve has been opened.

In still yet another embodiment, the invention provides a receptacle that comprises a receptacle body defining a cavity that is enclosed by a penetrable access lid. The receptacle further includes a threshold valve that is coupled to the receptacle body. In one aspect, the threshold valve is configured to open when experiencing a vacuum of at least about 40 cm H_2O.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph illustrating the average inspiration flow rate for 17 individuals that were measured twice a week for four weeks.

Fig. 2 is a graph illustrating the regulation of a patient's inspiration flow rate over time according to the invention.

Fig. 3. is a graph illustrating the regulation of another patient's inspiration flow rate over time according to the invention.

Fig. 4 is a schematic view of one system that may be utilized to extract a pharmaceutical formulation from a receptacle, deagglomerate the formulation and to place the formulation within the flow of respiratory gases to form an aerosol according to the invention.

Fig. 5 is a perspective view of an aerosolization device according to the invention.

Fig. 6 is a partial cutaway view of the aerosolization device of Fig. 5 shown in an open or loading position.

Fig. 7 illustrates the aerosolization device of Fig. 6 in a closed or operating position according to the invention.

Fig. 8 illustrates the aerosolization device of Fig. 6 when inserting a receptacle according to the invention.

Fig. 9 illustrates the aerosolization device of Fig. 8 when the receptacle has been inserted, when the device has been moved to the closed or operating position, and when respiratory gases are flowed through the device.

Fig. 10 is a partial cutaway perspective view of a receptacle and a convergent nozzle through which a pharmaceutical formulation may be extracted according to the invention.

Fig. 11 illustrates the receptacle and nozzle of Fig. 10, with the nozzle being moved further away from a bottom end of the receptacle to increase the rate of flow of respiratory gases through the nozzle according to the invention.

Fig. 12 is a schematic, cross-sectional side view of an aerosolization system having a spring to regulate the flow of respiratory gases through the system according to the invention.

Fig. 13 is a schematic, cross-sectional view of an aerosolization system having a flow regulation system to regulate the flow of respiratory gases through the aerosolization system according to the invention.

Fig. 14 illustrates one embodiment of a nozzle that may be employed to deagglomerate a pharmaceutical formulation according to the invention.

Fig. 15 is a perspective view of one embodiment of an aerosolization device according to the invention.

Fig. 16 is a perspective view of another embodiment of an aerosolization device according to the invention.

Fig. 16A illustrates a cover of the aerosolization device of Fig. 16.

Fig. 17 is a perspective view of still another embodiment of an aerosolization device according to the invention illustrating the use of a flow rate feedback device.

Fig. 18 illustrates still yet another embodiment of an aerosolization device according to the invention.

Fig. 19 illustrates one particular embodiment of an aerosolization device according the invention.

Fig. 19A illustrates a disk having multiple receptacles that may be inserted into the aerosolization device of Fig. 19.

Fig. 19B illustrates a front end of the aerosolization device of Fig. 19.

Fig. 20 illustrates another embodiment of an aerosolization device according the invention.

Fig. 20A illustrates the aerosolization device of Fig. 20 showing a lid moved to an open position.

Fig. 21 is a perspective view of yet another embodiment of an aerosolization device according to the invention.

Fig. 22 illustrates one particular embodiment of an aerosolization device according the invention capable of holding multiple drug patents.

Fig. 22A illustrates a clip for use with the aerosolization device of Fig. 22.

Fig. 23 illustrates yet another alternative embodiment of an aerosolization device according the invention.

Fig. 23A illustrates a mouthpiece cover of the aerosolization device of Fig. 23.

Fig. 24 illustrates a strip of receptacles that may be utilized within the aerosolization device of Fig. 23.

Fig. 25 illustrates still another alternative embodiment of an aerosolization device according to the invention.

Fig. 26 illustrates one embodiment of an aerosolization device according to the invention.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

The invention provides systems and methods for aerosolizing pharmaceutical formulations using the flow of respiratory gases produced by a patient. The pharmaceutical formulations that may be aerosolized include powdered medicaments, liquid solutions or suspensions, and the like, and may include an active agent.

"Active agent" as described herein includes an agent, drug, compound, composition of matter or mixture thereof which provides some pharmacologic, often beneficial, effect. This includes foods, food supplements, nutrients, drugs, vaccines,

vitamins, and other beneficial agents. As used herein, the terms further include any physiologically or pharmacologically active substance that produces a localized or systemic effect in a patient. The active agent that can be delivered includes antibiotics, antiviral agents, anepileptics, analgesics, anti-inflammatory agents and bronchodilators, and viruses and may be inorganic and organic compounds, including, without limitation, drugs which act on the peripheral nerves, adrenergic receptors, cholinergic receptors, the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulatory system, synaptic sites, neuroeffector junctional sites, endocrine and hormone systems, the immunological system, the reproductive system, the skeletal system, autacoid systems, the alimentary and excretory systems, the histamine system and the central nervous system. Suitable agents may be selected from, for example, polysaccharides, steroids, hypnotics and sedatives, psychic energizers, tranquilizers, anticonvulsants, muscle relaxants, antiparkinson agents, analgesics, anti-inflammatories, muscle contractants, antimicrobials, antimalarials, hormonal agents including contraceptives, sympathomimetics, polypeptides, and proteins capable of eliciting physiological effects, diuretics, lipid regulating agents, antiandrogenic agents, antiparasitics, neoplastics, antineoplastics, hypoglycemics, nutritional agents and supplements, growth supplements, fats, antienteritis agents, electrolytes, vaccines and diagnostic agents.

Examples of active agents useful in this invention include but are not limited to insulin, calcitonin, erythropoietin (EPO), Factor VIII, Factor IX, ceredase, cerezyme, cyclosporine, granulocyte colony stimulating factor (GCSF), alpha-1 proteinase inhibitor, elcatonin, granulocyte macrophage colony stimulating factor (GMCSF), growth hormone, human growth hormone (HGH), growth hormone releasing hormone (GHRH), heparin, low molecular weight heparin (LMWH), interferon alpha, interferon beta, interferon gamma, interleukin-2, luteinizing hormone releasing hormone (LHRH) , somatostatin, somatostatin analogs including octreotide, vasopressin analog, follicle stimulating hormone (FSH), insulin-like growth factor, insulintropin, interleukin-1 receptor antagonist, interleukin-3, interleukin-4, interleukin-6, macrophage colony stimulating factor (M-CSF), nerve growth factor, parathyroid hormone (PTH), thymosin alpha 1, IIb/IIIa inhibitor, alpha-1 antitrypsin, respiratory syncytial virus antibody, cystic fibrosis transmembrane regulator (CFTR) gene, deoxyribonuclease (Dnase), bactericidal/permeability increasing protein (BPI), anti-CMV antibody, interleukin-1 receptor, 13-cis retinoic acid, pentamidine isethionate, albuterol sulfate, metaproterenol sulfate, beclomethasone dipropionate, triamcinolone acetamide, budesonide acetonide,

ipratropium bromide, flunisolide, fluticasone, cromolyn sodium, ergotamine tartrate and the analogues, agonists and antagonists of the above. Active agents may further comprise nucleic acids, present as bare nucleic acid molecules, viral vectors, associated viral particles, nucleic acids associated or incorporated within lipids or a lipid-containing material, plasmid DNA or RNA or other nucleic acid construction of a type suitable for transfection or transformation of cells, particularly cells of the alveolar regions of the lungs. The active agents may be in various forms, such as soluble and insoluble charged or uncharged molecules, components of molecular complexes or pharmacologically acceptable salts. The active agents may be naturally occurring molecules or they may be recombinantly produced, or they may be analogs of the naturally occurring or recombinantly produced active agents with one or more amino acids added or deleted. Further, the active agent may comprise live attenuated or killed viruses suitable for use as vaccines.

"Mass median diameter" or "MMD" is a measure of mean particle size, since the powders of the invention are generally polydisperse (i.e., consist of a range of particle sizes). MMD values as reported herein are determined by centrifugal sedimentation, although any number of commonly employed techniques can be used for measuring mean particle size.

"Mass median aerodynamic diameter" or "MMAD" is a measure of the aerodynamic size of a dispersed particle. The aerodynamic diameter is used to describe an aerosolized powder in terms of its settling behavior, and is the diameter of a unit density sphere having the same settling velocity, generally in air, as the particle. The aerodynamic diameter encompasses particle shape, density and physical size of a particle. As used herein, MMAD refers to the midpoint or median of the aerodynamic particle size distribution of an aerosolized powder determined by cascade impaction.

The amount of active agent in the powdered formulation will be that amount necessary to deliver a therapeutically effective amount of the active agent to achieve the desired result. In practice, this will vary widely depending upon the particular agent, the severity of the condition, and the desired therapeutic effect. However, pulmonary delivery is generally practical for active agents that must be delivered in doses of from 0.001 mg/day to 100 mg/day, preferably 0.01 mg/day to 50 mg/day.

Powdered formulations suitable for use in the present invention include dry powders and particles suspended or dissolved within a propellant. The powdered

formulations have a particle size selected to permit penetration into the alveoli of the lungs, that is, preferably 10 μm mass median diameter (MMD), preferably less than 7.5 μm, and most preferably less than 5 μm, and usually being in the range of 0.1 μm to 5 μm in diameter. The delivered dose efficiency (DDE) of these powders is >30%, usually >40%, preferably >50% and often >60% and the aerosol particle size distribution is about 1.0 - 5.0 μm mass median aerodynamic diameter (MMAD), usually 1.5 - 4.5 μm MMAD and preferably 1.5 - 4.0 μm MMAD. These dry powders have a moisture content below about 10% by weight, usually below about 5% by weight, and preferably below about 3% by weight. Such powders are described in WO 95/24183 and WO 96/32149, which are incorporated by reference herein.

In some embodiments, the flow of respiratory gases produced by the patient is employed to extract the pharmaceutical formulation from a receptacle, to deagglomerate the pharmaceutical formulation and deliver the pharmaceutical formulation to the patient's lungs. One particular advantage of the invention is the ability to perform such functions independent of the patient's natural inhalation flow rate. Hence, in one aspect of the invention, the inhaled respiratory gases are controlled so that they remain within an acceptable range of flow rates to adequately deliver the pharmaceutical formulation to the lungs.

In another aspect, the invention is configured to regulate the flow of inspired gases so that the gases have sufficient energy to extract the pharmaceutical formulation from a receptacle, deagglomerate the formulation, and deliver it to the patient's lungs. In some cases, the invention is further configured to maintain the inhalation flow rate below a maximum level for at least a certain time or inhaled volume when initially delivering the drug. In this way, the aerosolized formulation will flow at an acceptable flow rate to enhance its ability to traverse the patient's airway and enter into the lungs. After initial delivery of the pharmaceutical formulation to the lungs, some embodiments of the invention may be configured to permit the patient to breath at a normal inspiration flow rate to fill the patient's lungs with respiratory gases and to further deliver the pharmaceutical formulation to the deep lung.

To aerosolize the pharmaceutical formulation, the flow of respiratory gases preferably contains sufficient energy to extract the pharmaceutical formulation from the receptacle. To ensure that the respiratory gases contain sufficient energy, the invention may be configured to prevent respiratory gases from flowing to the patient's lungs when

the patient attempts to inhale. Abruptly, the respiratory gases may then be permitted to flow to the patient's lungs after a threshold vacuum has been reached. By abruptly permitting the flow of respiratory gases only when sufficient vacuum has been applied by the user, a relatively high rate of flow is achieved to provide the gas stream with sufficient energy. One way to accomplish such a process is by placing a restriction, valve, or other blocking mechanism in the patient's airway to prevent respiratory gases from entering the patient's lungs when the patient attempts to inhale. The restriction or valve may then be rapidly removed or opened to permit respiratory gases to flow to the lungs. Hence, a patient may be instructed to inhale until a threshold actuating vacuum is overcome. The threshold actuating vacuum may be configured such that it will produce sufficient energy in the resulting gas stream when the gases are allowed to flow to the patient's lungs. Preferably, the threshold vacuum is in the range from about 20 cm H_20 to about 60 cm H_20 so that the resulting gas stream will have sufficient energy to extract and deagglomerate the pharmaceutical formulation.

Once the respiratory gases are allowed to flow to the lungs, the flow rate of the respiratory gases (in some cases) may need to be controlled or regulated so that the gases do not exceed a maximum flow rate during delivery of the pharmaceutical formulation to the lungs. Typically, the flow rate of respiratory gases may be regulated to be less than about 15 liters per minute for a time in the range from about 0.5 seconds to about 5 seconds, corresponding to an inhaled volume in the range from about 125 mL to about 1.25 L, to permit the aerosolized formulation to pass through the patient's airway and enter into the lungs. For example, as previously illustrated in connection with Fig. 1, some patients have a natural inhalation rate that exceeds a desired maximum flow rate.

For breathers that naturally breath above the maximum desired flow rate, the invention provides for the slowing of the flow rate during the time when the aerosolized formulation is being delivered to the lungs. This is illustrated graphically in Fig. 2. At time T_1, the patient is inhaling causing respiratory gases to flow to the patient's lungs. At time T_1, the flow rate is well above a starting flow rate, Q_{START}, which is desirable for initially extracting the pharmaceutical formulation from the receptacle as previously described. Hence, a threshold valve or other flow prevention mechanism may not be needed for such breathers. Shortly after time T_1 is time T_2, where the flow rate has been regulated to be below a $Q_{DELIVERY}$ flow rate. The flow rate is maintained below the $Q_{DELIVERY}$ rate from time T_2 to time T_3, where the aerosolized formulation is being delivered to the patient's lungs. After time T_3, the regulation of the gas flow is ceased

and the patient is permitted to inhale at their regular flow rate to fill their lungs with respiratory gases that serve to further deliver the pharmaceutical formulation to the deep lung.

Fig. 3 graphically illustrates an example of where the patient has a natural inhalation flow rate that is below $Q_{DELIVERY}$. As shown in Fig. 3, by preventing the flow of respiratory gases during patient inhalation, and then abruptly permitting the flow of respiratory gases, the starting flow rate at time T_1, is at Q_{START}. In this way, sufficient energy is provided to extract the formulation from the receptacle. After the patient continues to inhale, the flow rate rapidly falls below the $Q_{DELIVERY}$ flow rate because the patient's natural inhalation flow rate is less than the $Q_{DELIVERY}$ flow rate. Hence, after time T_1, the patient's inhalation flow rate does not need to be regulated, thereby permitting the patient to inhale at a comfortable level.

A variety of schemes and techniques may be provided to regulate the inhalation flow rate to be below the $Q_{DELIVERY}$ flow rate from time T_2 to time T_3. As one example, the patient may be provided with various types of feedback to permit the patient to self-regulate their inhalation flow rate. For instance, an aerosolization device may be provided with a whistle that creates a whistling sound when the patient's flow rate exceeds the $Q_{DELIVERY}$ flow rate. Other types of feedback that may be utilized include visual feedback, tactile feedback, auditory feedback, and the like. Optionally, a controller may be provided with a timing mechanism to indicate to the user when time T_3 has elapsed so that the user may finish their inhalation at a comfortable level.

As another example, the patient's inhalation flow rate may be regulated by restricting or impeding the respiratory gases being inhaled. For example, the size of the airway may be varied to control the rate of flow of inspired gases. The manner of regulation may be either manual, semi-automated, or automated. For example, the user may manually adjust the size of the airway or place a restriction in the airway to control the rate of flow. Alternatively, the size of the airway may be adjusted based on the patient's own inhalation as described in greater detail hereinafter. In still another example, an automated system with one or more flow sensors may be provided to regulate the size of the airway to regulate the flow of respiratory gases.

One particular advantage of restricting the flow of respiratory gases to control the inhalation flow rate is that a relatively high pressure drop may be created. Because power is generally proportional to both the pressure drop and flow rate, the flow

rate may be kept low while still providing sufficient energy to aerosolize the formulation and to deliver the formulation to the patient's lungs.

As another alternative, the flow of respiratory gases may be regulated by placing an orifice or other restriction member into the patient's airway that is made for use with a specific patient. In this way, an aerosolization device may be tailored to a specific patient simply by utilizing an orifice sized according to the patient's natural inhalation flow rate.

A variety of threshold valves may also be employed to prevent respiratory gases from reaching the patient's lungs until a threshold inhalation vacuum is obtained. For example, the threshold valve may comprise a flexible membrane that is disposed across the airway and is configured to flex when the threshold vacuum is met or exceeded. Alternatively, the threshold valve may comprise a scored membrane that is configured to tear or burst once the threshold vacuum is met or exceeded. Other types of threshold valves include bi-stable mechanisms, diaphragms, and the like.

In one particular aspect of the invention, the threshold valve may be incorporated into a receptacle that also holds the pharmaceutical formulation. In this way, each time a new receptacle is inserted into an aerosolization device, the device is provided with a new threshold valve. This is particularly advantageous when the threshold valve comprises a membrane that is configured to tear or burst after the threshold vacuum is met or exceeded.

The receptacles of the invention may conveniently be configured to have a penetrable access lid that is penetrated by one or more pointed structures when the aerosolization device is operated. Examples of such receptacles are described in U.S. Patent Nos. 5,740,754 and 5,785,049, the complete disclosures of which are herein incorporated by reference.

The invention may utilize various deagglomeration mechanisms to deagglomerate the pharmaceutical formulation once it is extracted from the receptacle. For example, the flow path for the gases may experience one or more changes in direction to cause the pharmaceutical formulation to engage the walls of the flow path to deagglomerate the formulation. The flow path may also include various contractions or restrictions that may cause the pharmaceutical formulation to engage the walls of the flow path to deagglomerate the formulation. As another example, the flow path may include one or more obtrusions or obstacles that serve to engage the pharmaceutical formulation as it passes through the flow path.

as device 28, will be described. Shown in Fig. 10 is a receptacle 62 having a chamber 64 that is typically filled with a pharmaceutical formulation (not shown). In Fig. 10, a penetrating tube 66 has already penetrated the lid over chamber 64, and a distal end 68 of tube 66 is disposed within chamber 64. In Fig. 10, distal end 68 of tube 66 is positioned near the bottom of chamber 64. In this way, the airway between distal end 68 and the bottom of chamber 64 is reduced in size to restrict the respiratory gases flowing into chamber 64 and out penetrating tube 66. As shown in Fig. 11, distal end 68 is moved vertically upward so that it is further distanced from the bottom end of chamber 64. In this way, the flow rate of respiratory gases may be increased.

A variety of techniques may be employed to adjust the distance between distal end 68 and the bottom of chamber 64. For example, one technique is to employ the use of a suction force created by patient inhalation. More specifically, as the patient begins to inhale, the vacuum source created within tube 68 by the inhalation will tend to move the bottom end of chamber 64 toward distal end 68. Various mechanisms may then be employed to control the distance between distal end 68 and the bottom end of chamber 64. For example, a variety of biasing mechanisms may be included to control the relative movement between receptacle 62 and penetrating tube 66. Automated mechanisms, such as solenoids, pistons, and the like may also be employed. Further, various manual techniques may also be used, including utilization of the user's hands or fingers.

One feature of penetrating tube 66 is that it forms a convergent nozzle that serves as a deagglomerator for the power contained within chamber 64. More specifically, as the patient inhales to extract the powder from chamber 64, the convergent flow path created by penetrating tube 66 tends to deagglomerate the powder to facilitate its aerosolization and deposition within the lung.

Referring now to Fig. 12, an embodiment of an aerosolization device 70 will be described to illustrate one technique for regulating the flow of respiratory gases through the device. For convenience of illustration, only a portion of device 70 is illustrated, it being appreciated that other components may be utilized to complete the device. Aerosolization device 70 comprises a housing 72 and a receptacle carrier 74. Receptacle carrier 74 may be configured to be movable relative to housing 72 for convenient loading and unloading of a receptacle 76. Receptacle 76 includes a chamber 78 and a threshold valve 80 that may be constructed to be similar to other embodiments described herein. Receptacle carrier 74 includes an opening 82 that is aligned with valve

80 to permit respiratory gases to flow through valve 80 once opened. Coupled to housing 72 is a penetrating tube 84 that penetrates receptacle 76 to provide access to chamber 78 in a manner similar to that described with the previous embodiments. In this manner, when a patient inhales from device 70, threshold valve 80 opens when the threshold vacuum is overcome. Respiratory gases then flow through chamber 78 and out penetrating tube 84 as illustrated by the arrows.

Device 70 further includes a spring 86 disposed between housing 72 and receptacle carrier 74. Once valve 80 is opened, the vacuum within penetrating tube 84 causes the bottom end of chamber 78 to be drawn toward penetrating tube 84. The spring constant of spring 86 may be selected to control the distance between the bottom end of chamber 78 and penetrating tube 84 to regulate the gas flow through the device. In some cases, it may be desirable to select the spring constant of spring 86 based on the average inhalation flow rate produced by the patient. In this way, device 70 may be tailored to a particular patient. Device 70 further includes a pin 88 that maintains the spacing between the bottom of chamber 78 and penetrating tube 84 to a certain distance. In this way, chamber 78 will not completely be drawn against penetrating tube 84.

Referring now to Fig. 13, an aerosolization device 90 will be described. Device 90 may be constructed from elements similar to that previously described in connection with aerosolization device 70. Hence, for convenience of discussion, similar elements used for aerosolization device 90 will be referred to with the same reference numerals used to describe device 70 and will not be described further. Aerosolization device 90 differs from aerosolization device 70 in that it employs an electronic controller 92 to control the distance between penetrating tube 84 and the bottom end of chamber 78. Controller 92 is electronically coupled to a solenoid 94 that may be extended or retracted to control the spacing between penetrating tube 84 and chamber 78. Optionally, a flow control sensor 96 may be disposed anywhere within the airway of device 90 to sense the rate of flow through the device. When controller 92 receives a signal from sensor 96, it may send a signal to solenoid 94 to adjust the spacing to thereby regulate the flow rate. One advantage of using controller 92 is that it may also include a timing circuit so that solenoid 94 may be fully extended after a certain amount of time. In this way, once the aerosolized formulation has reached the patient's lungs, solenoid 94 may be fully extended to permit the user to comfortably inhale without substantial resistance to fill their lungs with respiratory gases.

Referring now to Fig. 14, another embodiment of a nozzle 98 that may be placed downstream of a receptacle will be described. Nozzle 98 comprises a tubular structure 100 having a bent section 102 and a contracted section 104. As the pharmaceutical formulation is extracted from the receptacle, it passes through tubular structure 100 as indicated by the arrows. The change in the direction caused by bent section 102 causes the agglomerated powder to engage the walls of structure 100 to assist in its deagglomeration. When reaching contracted section 104, the powder is further agitated and the flow is increased to further deagglomerate the powder. Although shown with one bent section followed by a contracted section, it will be appreciated that various other tubular structures may be provided with various arrangements of direction changes and/or constrictions to facilitate deagglomeration of the powder.

Referring now to Figs. 15-26, various embodiments of aerosolization devices will be described. Although not shown, the aerosolization devices of Figs. 15-26 will typically include a penetrating tube with one or more penetrating structures to pierce the lid of a receptacle similar to the embodiments previously described. These devices may also include threshold valves and regulation systems for regulating the flow of respiratory gases to the patient's lungs in a manner similar to that described with previous embodiments. Further, it will be appreciated that the components of the various devices of Figs. 15-26 may be shared, substituted and/or interchanged with each other.

First referring to Fig. 15, one embodiment of an aerosolization device 106 will be described. Device 106 comprises a housing 108 having a lid 110. Lid 110 is movable to an open position to receive a sheet 112 of receptacles 114. Lid 110 includes various buttons 116 that may be pressed to puncture an associated receptacle 114 prior to inhalation. Conveniently, lid 110 includes a window 118 to indicate that sheet 112 is loaded and may also show a date and type of medication printed on sheet 112. Housing 108 further includes a mouthpiece 120 and a slidable cover 122 that may be slid over mouthpiece 120 when not in use.

When a patient is ready to receive a treatment, the patient slides cover 122 to expose mouthpiece 120. One of buttons 116 is then pressed and the user inhales while their mouth is over mouthpiece 120. Once all of buttons 116 have been pressed, sheet 112 may be replaced with a new sheet of receptacles.

Fig. 16 illustrates an aerosolization device 124 that comprises a cover 126 (see also Fig. 16A) and a drawer 128 that is slidable within cover 126 as indicated by the arrow. Drawer 128 is configured to hold a receptacle 130. As shown in Fig. 16A, when

drawer 128 is closed, receptacle 130 is held within cover 126. Conveniently, the chamber of receptacle 130 may be configured to be pierced when drawer 128 is closed. Various press buttons 132 may be provided to allow drawer 128 to be retracted following use. Cover 126 further includes a mouthpiece 134 and a window to indicate that receptacle 130 is loaded, along with showing a date and type of medication. Optionally, a counter 138 may be provided to show the cumulative number of uses for the device.

Fig. 17 illustrates an aerosolization device 140 comprising a housing 142 having a mouthpiece 144 and a lid 146. Lid 146 is movable between an open position and a closed position as illustrated in phantom line. When lid 146 is opened, a receptacle 148 may be placed within housing 142. When lid 146 is closed, receptacle 148 is pierced and device 140 is ready for operation. Conveniently, lid 146 may include a raised window 150 containing a ball 152. The region behind window 150 may be placed in communication with the airflow path, thereby causing ball 152 to move within the region depending on the rate of flow of respiratory gases through device 140. Conveniently, plus and minus signs may be used to provide the patient with visual feedback on the rate of flow through the device. In this way, the patient may adjust their inhalation rate based on the visual feedback. Optionally, device 140 may include a storage compartment 154 for holding extra receptacles 148.

Fig. 18 illustrates a device 156 comprising a housing 158 having a mouthpiece 160 and a lid 162. A hinge 164 is employed to pivotally couple lid 162 to housing 158. Lid 162 is movable between an open position and a closed position. When in the open position, a receptacle 166 may be loaded into housing 158. Lid 162 is then closed, with receptacle 166 being visible through a window 168. Lid 162 includes a press button 170 which is pushed to pierce receptacle 166 prior to use.

Fig. 19 illustrates an aerosolization device 172 comprising a housing 174 and a door 176 that is coupled to housing 174 by a hinge 178. Insertable into device 172 is a disk 180 having multiple receptacles 182 as illustrated in Fig. 19A. Conveniently, each of the receptacles may be numbered as illustrated in Fig. 19A. Door 176 includes a dial 184 that is rotatable to rotate disk 180 within device 172. Door 176 also includes a window 186 to view the receptacle that has been pierced by rotating dial 184. When ready to receive a treatment, the user places their mouth over a nose 187 of device 172 and begins to inhale. The patient's inhalation opens a lid 188 to permit the aerosolized formulation to enter into the patient's lungs. To receive another treatment, the user

simply dials dial 184 to the next receptacle which is pierced, making device 172 ready for operation.

Referring now to Figs. 20 and 20A, an alternative aerosolization device 190 will be described. Device 190 comprises a housing 192 and a lid 194 that is coupled to housing 192 by a hinge 196. Device 190 further includes a mouthpiece 198 through which the patient inhales. As shown in Fig. 20A, device 190 is in an open position where a receptacle 200 is placed in a loaded position. Lid 194 may then be closed to the position illustrated in Fig. 20. Lid 194 includes a press button 202 that is pressed to pierce receptacle 200 so that the pharmaceutical formulation may be extracted. Lid 194 also includes a timer 204 that is manually set by having the user pull timer 204 toward button 202 prior to operation. The user then begins to inhale from mouthpiece 198 to aerosolize the pharmaceutical formulation. Preferably, the user inhales until timer 204 expires. As shown in Fig. 20A, lid 194 may include multiple storage locations for storing additional receptacles 200.

Fig. 21 illustrates an aerosolization device 206 comprising a housing 208 having a slot 210 for receiving a receptacle 212. Device 206 further includes a cocking device 214 that is cocked to cause receptacle 212 to be pierced. Device 206 further includes a trap door 216 and an extendable mouthpiece 218 (shown in phantom line). When cocking device 214 is cocked to pierce receptacle 212, trap door 216 is also opened and mouthpiece 218 is extended.

Referring now to Fig. 22, another aerosolization device 220 will be described. Device 220 comprises a housing 222 and a clip 224 that may be coupled to housing 222. As best shown in Fig. 22A, clip 224 includes a storage region 226 and a waste region 228. Storage region 226 includes multiple receptacles 230 that may be loaded into housing 222 as described hereinafter. Once a receptacle has been used, it is ejected into waste region 228. Conveniently, a removable seal 232 may be disposed over storage region 226. Use of clip 224 is advantageous in that replacement clips, having a fresh supply of receptacles, may easily be coupled to housing 222, making device 220 a multi-use device.

As best shown in Fig. 22, housing device 220 further includes a rotatable dial 234 that is rotated to advance one of the receptacles 230 from storage region 226 and into housing 222. When placed within housing 222, receptacle 230 is pierced. Further, housing 222 includes a counter 236 to display how many receptacles remain unpierced.

A tethered mouthpiece cover 238 is coupled to housing 222 and is removed prior to inhalation.

Hence, to use device 220, the user simply rotates dial 234 to advance and pierce the next receptacle. Cover 238 is removed and the patient inhales to aerosolize the pharmaceutical formulation and deposit the formulation within the patient's lungs. When ready for a next dosage, dial 234 is again dialed causing the used receptacle to be ejected into waste region 228 and advancing another receptacle. When all receptacles have been used, clip 224 is removed and placed with a replacement clip.

Fig. 23 illustrates an aerosolization device 240 comprising a housing 242 and a lid 244 pivotally coupled to housing 242. A removable mouthpiece cover 246 is also provided (see also Fig. 23A). Cover 246 is removed prior to inhalation by the patient. Device 240 is configured to hold a strip 248 of receptacles 250 (as shown in Fig. 24). Once strip 248 is within housing 242, a slide 252 may be moved to indicate the desired receptacle that is to be pierced. Slide 252 may then be depressed to pierce the selected receptacle. Optionally, slide 252 may be coupled to plumbing within device 240 so that the plumbing is moved to the appropriate receptacle along with slide 252. Device 240 may also include a whistle 254 that produces an audible signal when the user inhales in excess of a maximum inhalation flow rate. The user may simply inhale at a slower flow rate until whistle 254 ceases producing a whistling sound.

Fig. 25 illustrates an aerosolization device 256 comprising a housing 258 and a mouthpiece cover 260 that is tethered to housing 258. Cover 260 is removed prior to use. Housing 258 further includes a slot 262 that extends through housing 258. In this way, a continuous strip 264 of receptacles 266 may be fed through slot 262. Alternatively, strip 264 may be separated into segments so that an individual receptacle may be fed into slot 262. Housing 258 includes a button 268 that may be depressed to pierce the loaded receptacle.

When the patient begins to inhale, their flow rate is monitored by a gas gauge 270. In this way, the user is provided with visual feedback to assist them in inhaling at the proper flow rate. Optionally, housing 258 may include a clip 272 to permit device 258 to be carried on the pocket like a pen.

Fig. 26 illustrates an aerosolization device 274 comprising a housing 276 having a mouthpiece 278 and a rotatable body 280 that is rotatable relative to housing 276. Device 274 is configured to receive a receptacle pack 282 at a back end of device 274. Receptacle pack 282 includes multiple receptacles 284 that may be pierced when

ready for use. Although receptacle pack 282 is shown as being cylindrical in geometry, it will be appreciated that other geometries may be employed, including square shaped tubes.

Once receptacle pack 282 is inserted into device 274, rotatable body 280 is rotated to advance one of the receptacles to an engaging position where the receptacle is pierced. Conveniently, housing 276 includes a counter 286 to display the remaining number of receptacles. If the patient inhales at an excessive flow rate, housing 276 is configured to vibrate to provide the user with feedback so that they may adjust their inhalation flow rate.

The invention has now been described in detail for purposes of clarity of understanding. However, it will be appreciated that certain changes and modifications may be practiced within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A method for aerosolizing a pharmaceutical formulation, the method comprising:

preventing respiratory gases from flowing to the lungs when attempting to inhale, and then abruptly permitting respiratory gases to flow to the lungs; and

using the flow of respiratory gases to extract a pharmaceutical formulation from a receptacle and to place the pharmaceutical formulation within the flow of respiratory gases to form an aerosol.

2. A method as in claim 1, further comprising limiting the flow of respiratory gases to a rate that is less than a certain rate for a certain time.

3 A method as in claim 2, wherein the rate is less than about 15 L/min and the time is in the range from about 0.5 seconds to about 5 seconds.

4. A method as in claim 2, wherein the rate is less than about 8 L/min and the time is in the range from about 0.5 seconds to about 5 seconds.

5. A method as in claim 2, wherein the certain rate permits an inhaled volume that is in the range from about 125 mL to about 1.25L.

6. A method as in claim 1, wherein the flow preventing step further comprises placing a valve within an airway leading to the lungs and opening the valve to permit respiratory gases to flow to the lungs.

7. A method as in claim 6, further comprising opening the valve when a threshold actuating vacuum caused by the attempted inhalation is exceeded.

8. A method as in claim 7, wherein the threshold actuating vacuum is in a range from about 20 cm H_20 to about 60 cm H_20.

9. A method as in claim 2, wherein the flow limiting step comprises providing feedback when an excessive flow rate is produced to permit a user to adjust their inhalation rate.

10. A method as in claim 2, wherein the flow limiting step comprises regulating the size of an airway leading to the lungs.

11. A method as in claim 10, further comprising regulating the size of the airway to permit an increased flow rate after the certain time has lapsed.

12. A method as in claim 1, wherein the pharmaceutical formulation comprises a powdered medicament, and further comprising using the flow of respiratory gases to deagglomerate the extracted powder.

13. An aerosolization device, comprising:

a housing defining an airway;

a coupling mechanism adapted to couple a receptacle containing a pharmaceutical formulation to the airway; and

a valve to prevent respiratory gases from flowing through the airway until a threshold actuating vacuum is exceeded at which time the valve opens to permit respiratory gases to flow through the airway and to extract the pharmaceutical formulation from the receptacle to form an aerosol.

14. A device as in claim 13, further comprising a regulation system to regulate the flow of respiratory gases through the airway to a certain rate.

15. A device as in claim 14, wherein the regulation system is configured to limit the flow to a rate that is less than about 15L/min for a certain time or a certain inhaled volume.

16. A device as in claim 14, wherein the regulation system comprises a feedback mechanism to provide information on the rate of flow of the respiratory gases.

17. device as in claim 16, wherein the feedback mechanism comprises a whistle in communication with the airway.

18. A device as in claim 14, wherein the regulation system comprises a restrictive member disposed in the airway, the restrictive member defining an orifice sized to limit the flow of respiratory gases through the airway.

19. A device as in claim 14, wherein the regulation system comprises a restriction mechanism to limit the size of the airway.

20. A device as in claim 19, wherein the restriction mechanism is adjustable to vary the rate of flow of respiratory gases through the airway.

21. A device as in claim 20, wherein the regulation system further comprises a control system to adjust the restriction mechanism.

22 A device as in claim 21, wherein the control system is configured to limit the flow to the certain rate for a certain time or inhaled volume and then to adjust the restriction mechanism to permit an increased flow of respiratory gases through the airway.

23 A device as in claim 13, wherein the threshold actuating vacuum of the valve is in a range from about 20 cm H_20 to about 60 cm H_20.

24. A device as in claim 13, further comprising a deagglomeration mechanism disposed in the airway downstream of the receptacle to deagglomerate the extracted pharmaceutical formulation.

25 A device as in claim 13, wherein the valve is adapted to be disposed within the receptacle.

26. An aerosolization system comprising:

a receptacle comprising a chamber having a pharmaceutical formulation and a threshold valve;

a housing defining an airway; and

a coupling mechanism to position the valve across the airway and to place the pharmaceutical formulation in fluid communication with the airway;

wherein the threshold valve is configured to open when a threshold actuating vacuum is exceeded to permit respiratory gases to flow through the airway and extract the pharmaceutical formulation from the chamber to form an aerosol.

27. A system as in claim 26, wherein the pharmaceutical formulation comprises a powdered medicament.

28. A system as in claim 26, further comprising a regulation system to regulate the flow of respiratory gases through the airway.

29 A receptacle comprising:

a receptacle body defining a cavity enclosed by a penetrable access lid; and

a threshold valve coupled to the receptacle body.

30. A receptacle as in claim 29, wherein the threshold valve is configured to open when experiencing a vacuum of at least about 40 cm H_2O.

SYSTEMS AND METHODS FOR AEROSOLIZING PHARMACEUTICAL FORMULATIONS

ABSTRACT OF THE DISCLOSURE

Systems and methods are provided for aerosolizing a pharmaceutical formulation. According to one method, respiratory gases are prevented from flowing to the lungs when attempting to inhale. Then, respiratory gases are abruptly permitted to flow to the lungs. The flow of respiratory gases is then used to extract a pharmaceutical formulation from a receptacle and to place the pharmaceutical formulation within the flow of respiratory gases to form an aerosol.

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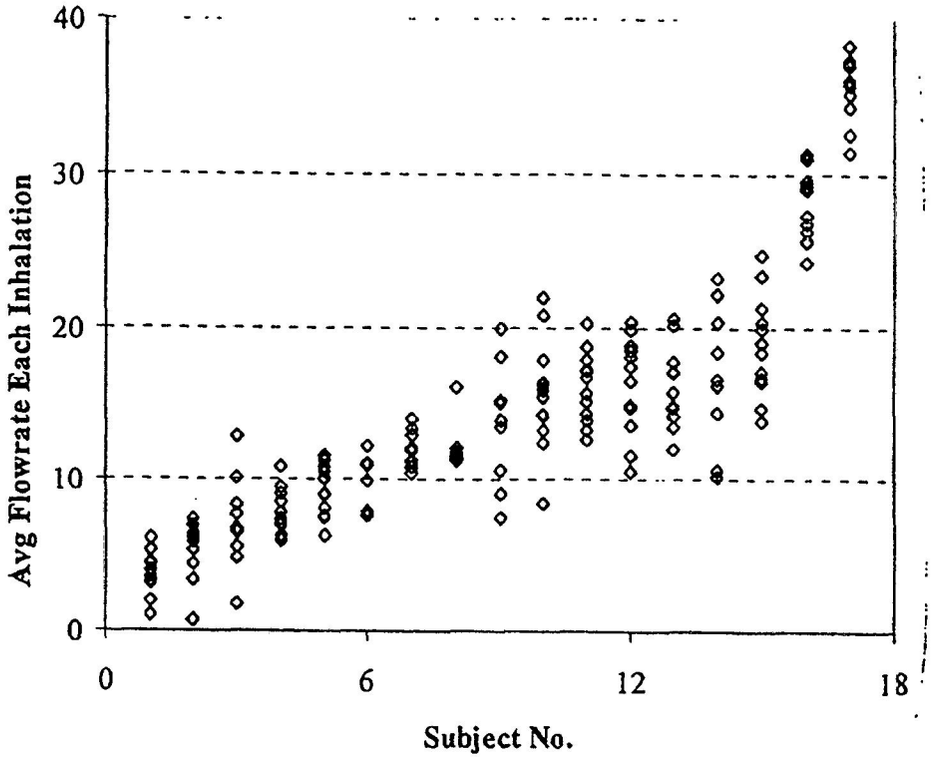


FIG. 1

FIG. 2

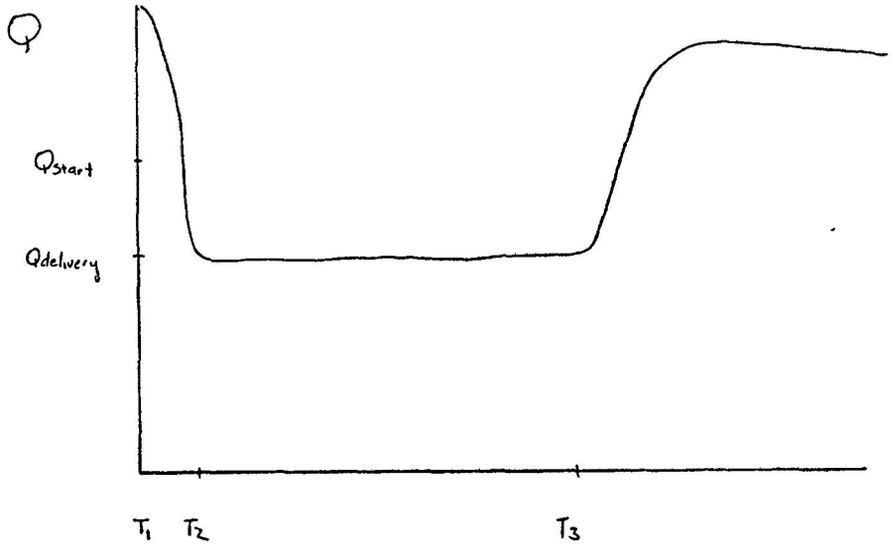


FIG. 3

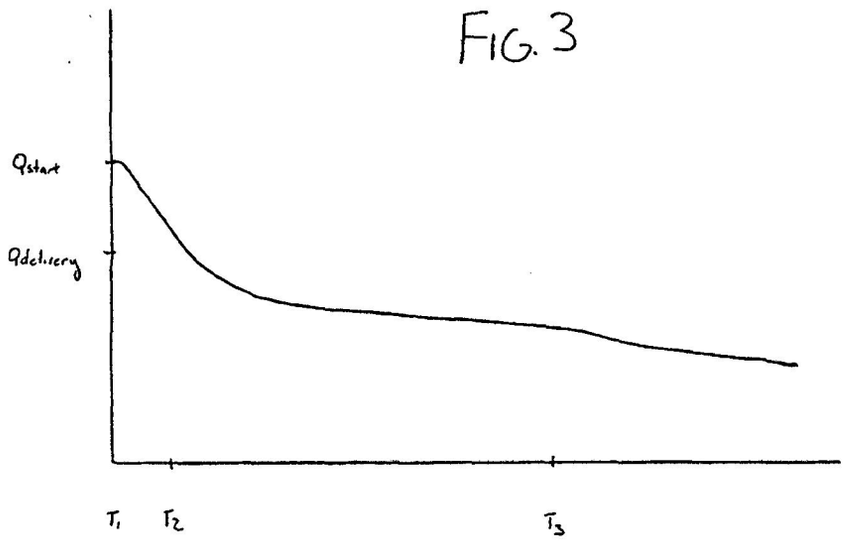


FIG. 4

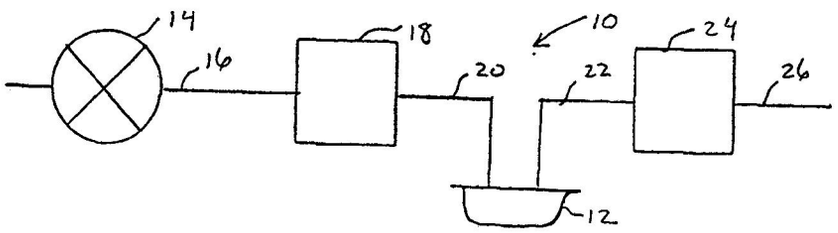


FIG.5

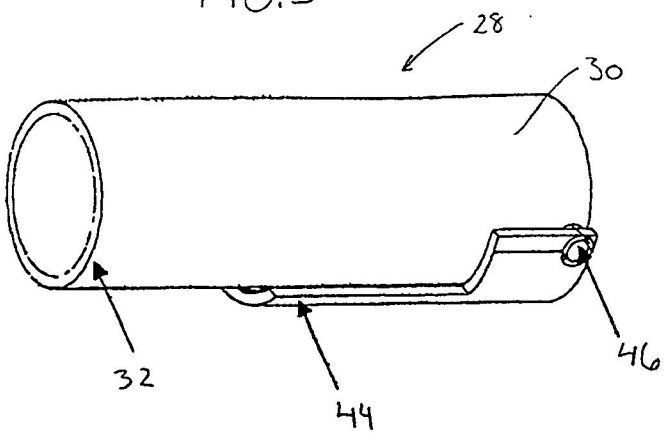


FIG.6

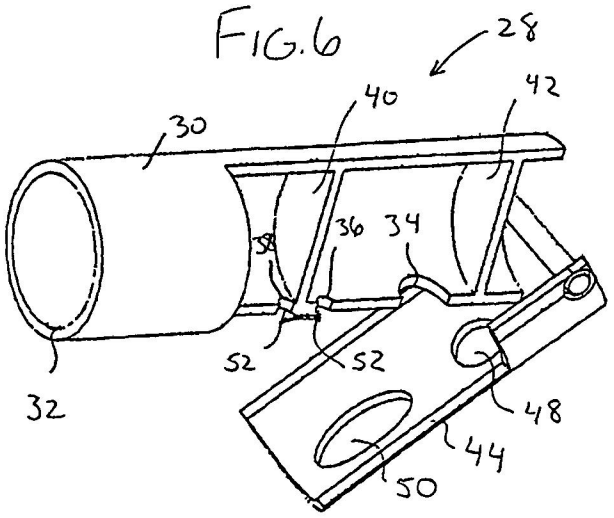


FIG.7

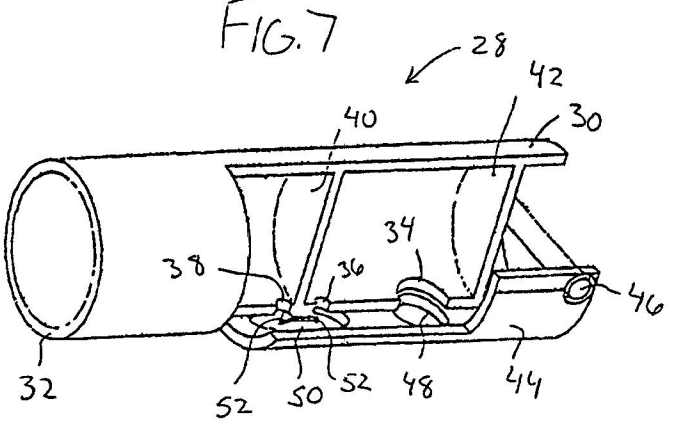


FIG. 8

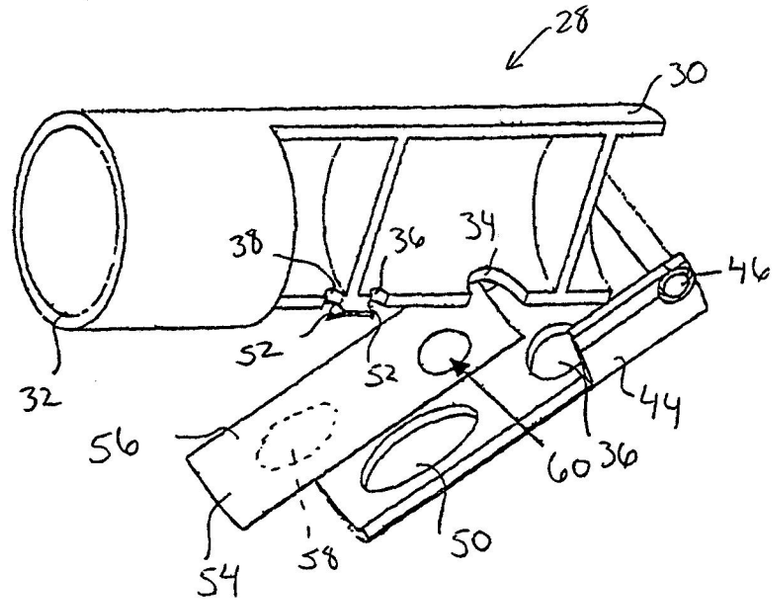

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FIG. 9

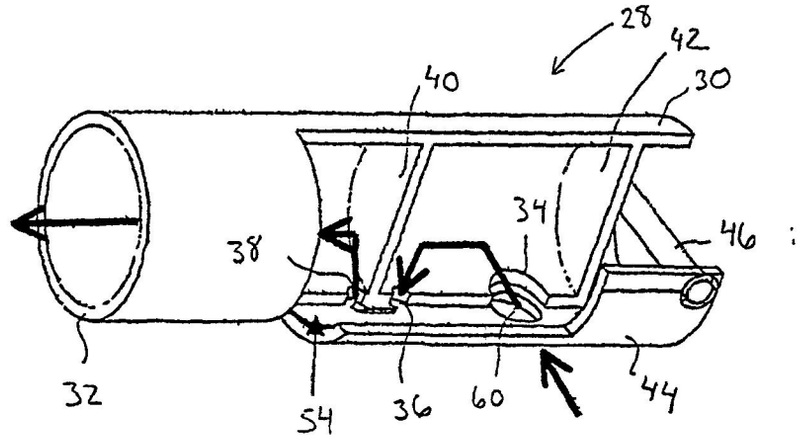

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FIG. 10

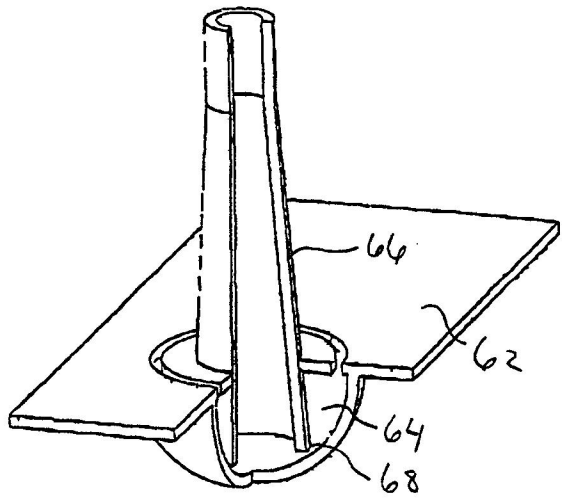


FIG. 11

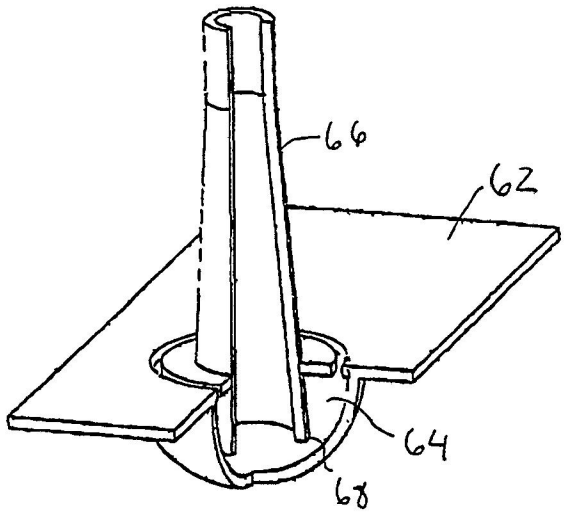


FIG. 12

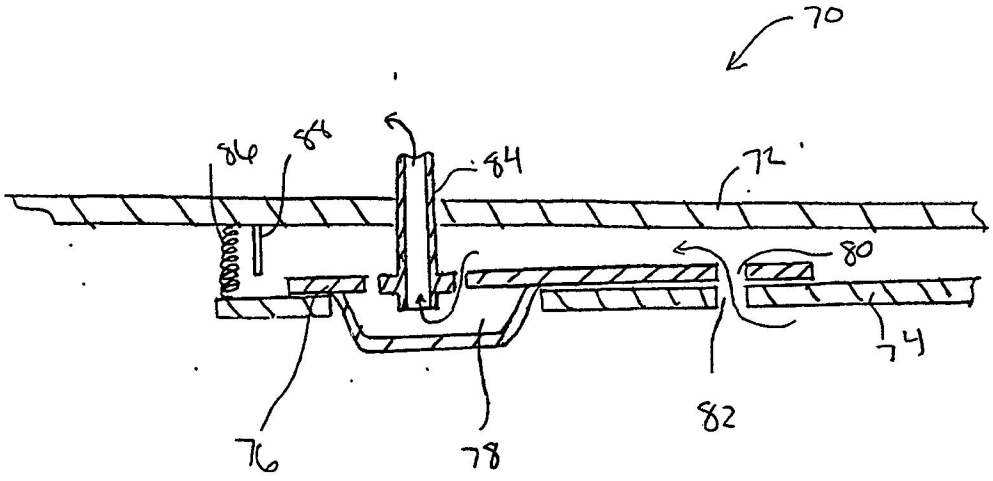
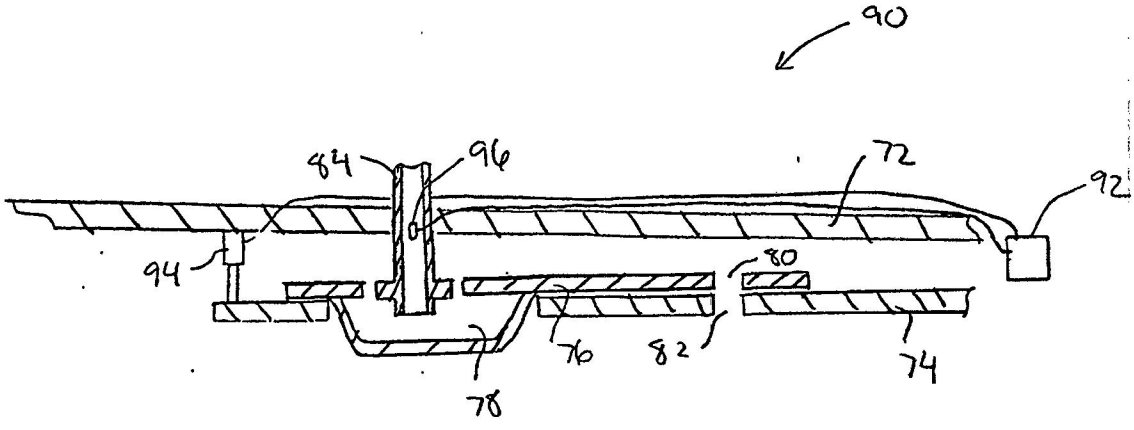


FIG. 13



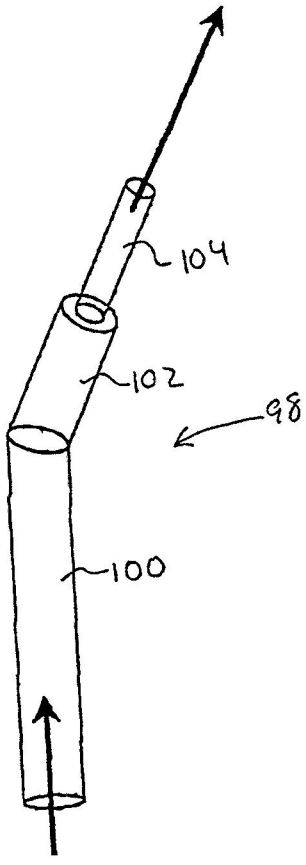


FIG. 14

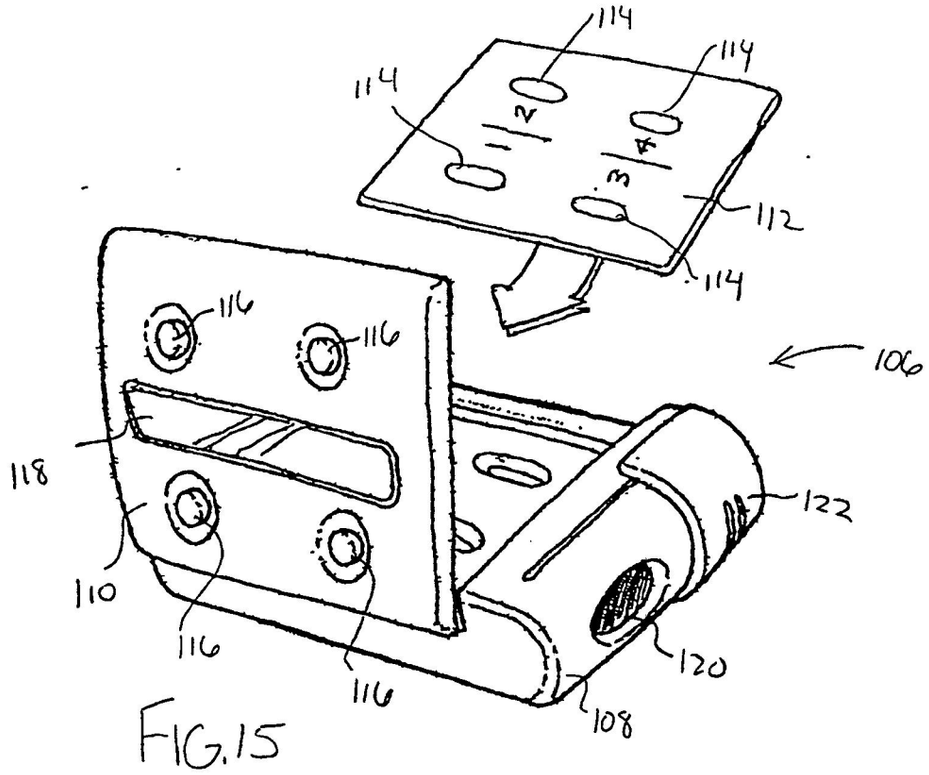


FIG.15

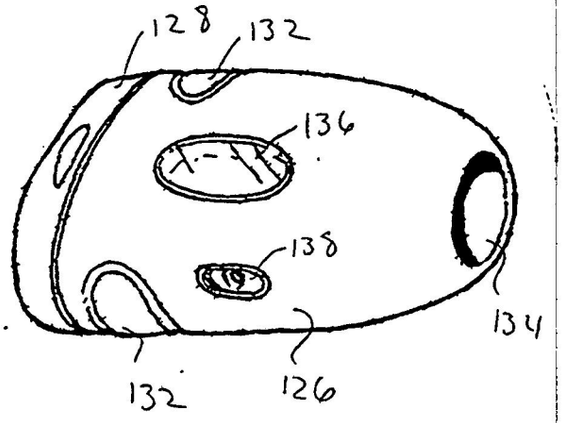


FIG.16A

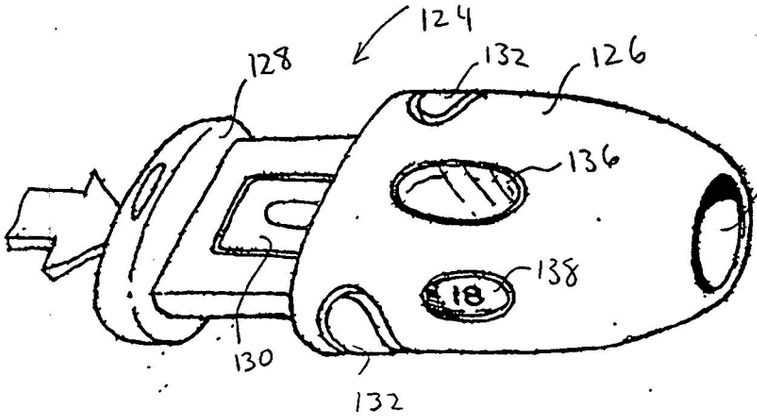


FIG.16

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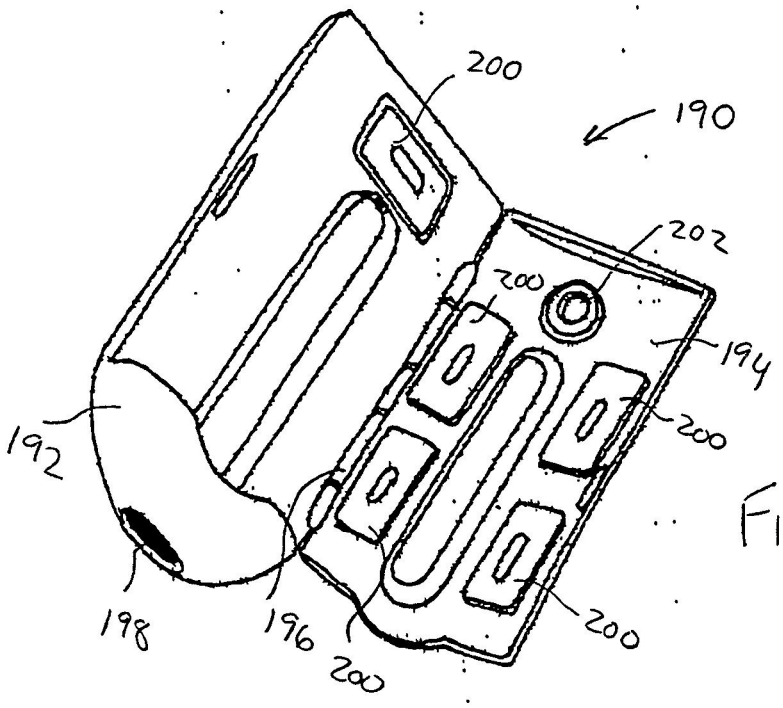


FIG. 20A

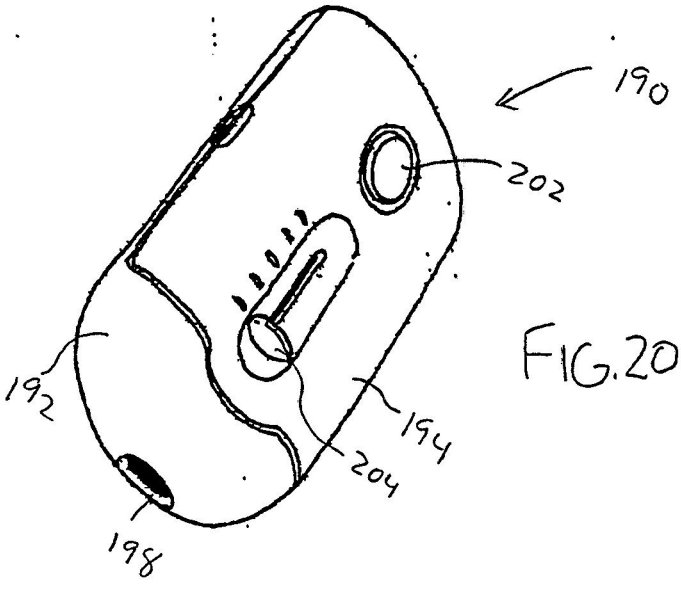


FIG. 20

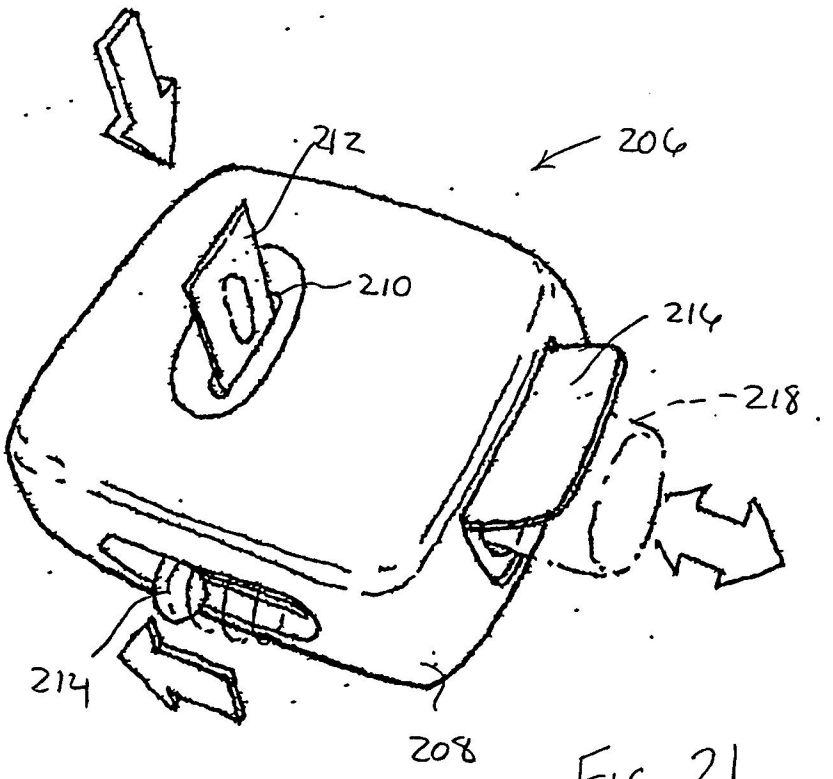


FIG. 21

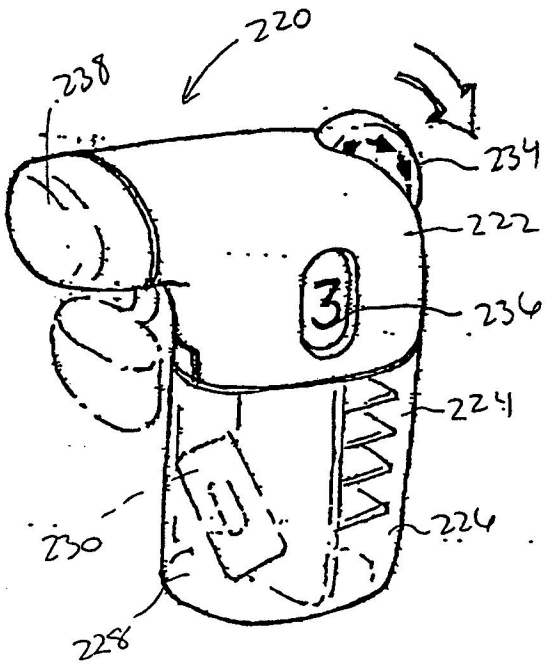


FIG. 22

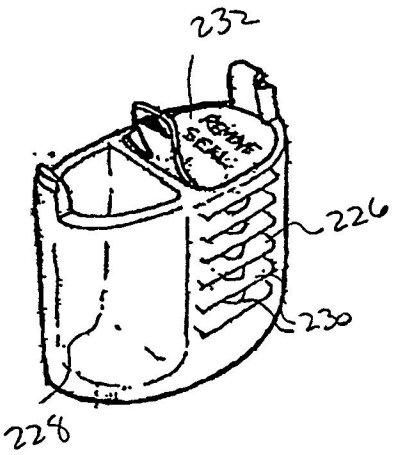


FIG. 22A

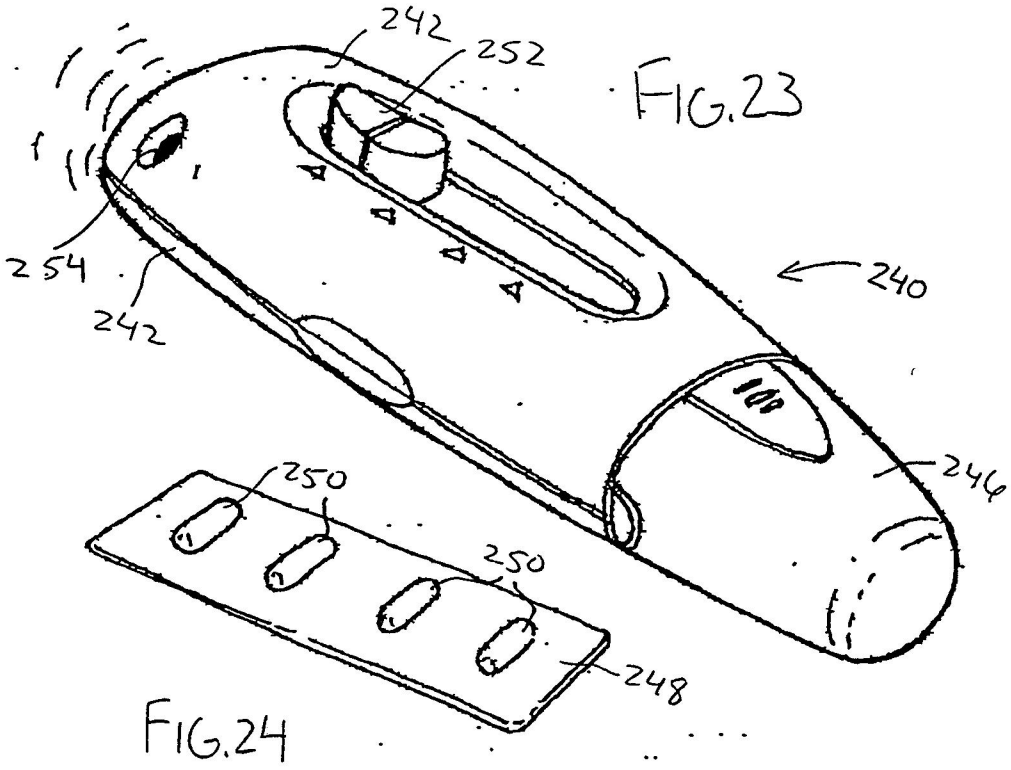


FIG.23

FIG.24

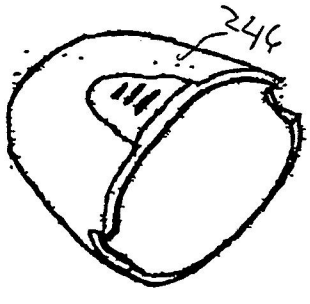


FIG.23A

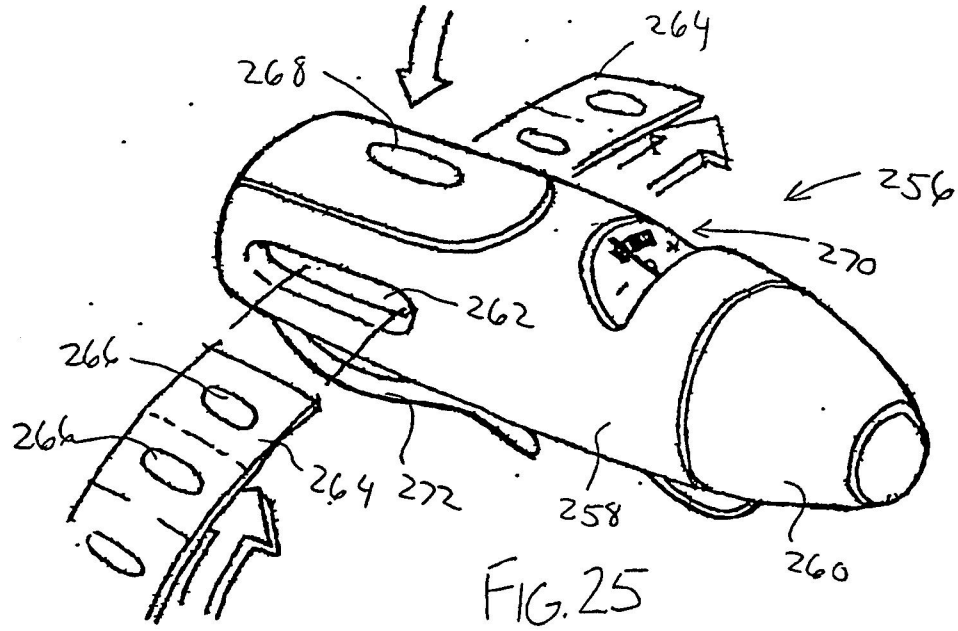

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FIG. 25

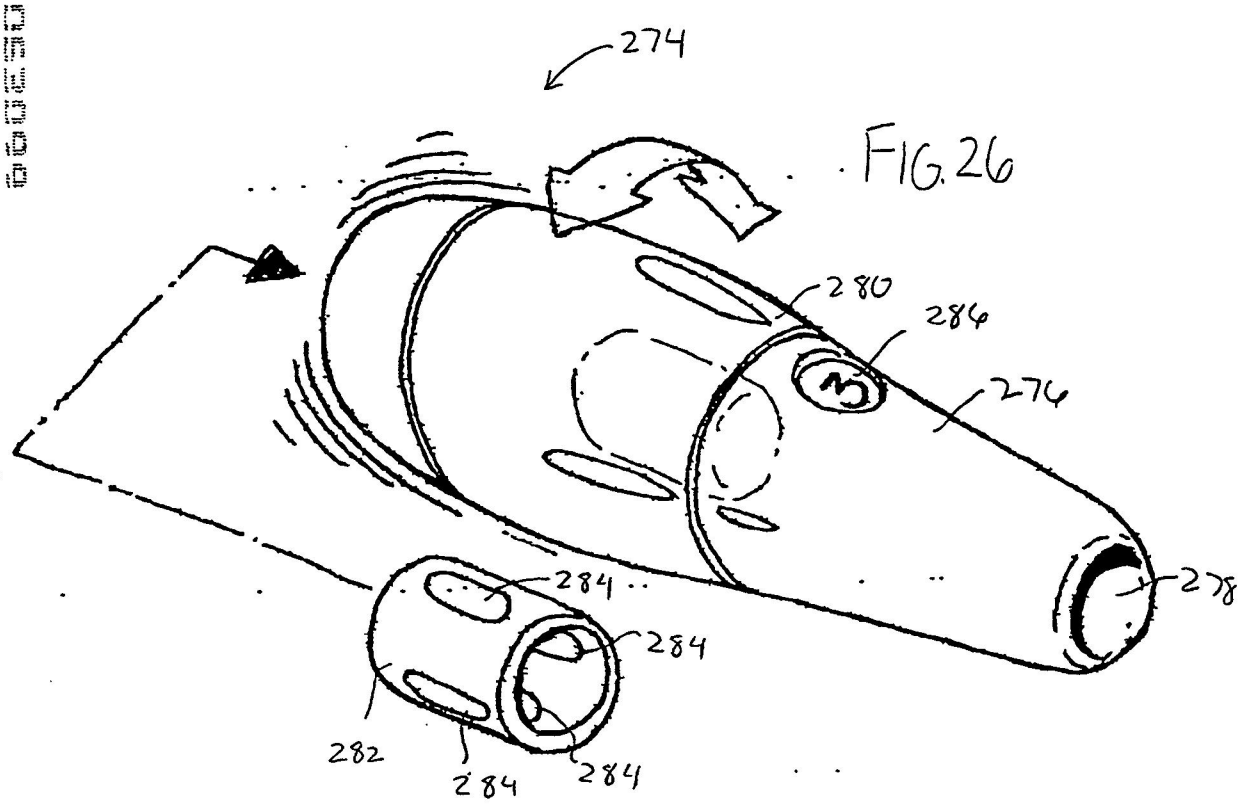

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FIG. 26

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TRADUCCION : Se traduce la carátula y las reivindicaciones anexas a una copia de la solicitud de patente estadounidense No. 60/141.793, escrita en inglés. Para el invento denominado: Sistemas y métodos para aerosolizar formulaciones farmacéuticas.

LOS ESTADOS UNIDOS DE AMÉRICA
A TODOS AQUELLOS A QUIENES LA PRESENTE CONCIERNE
DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Patentes y Marcas de los Estados Unidos

14 de Agosto de 2000

LA PRESENTE ES PARA CERTIFICAR QUE LA ANEXA A ESTA ES UNA COPIA FIEL DE LOS REGISTROS DE LA OFICINA DE LAS PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE IDENTIFICADA MAS ADELANTE QUE SATISFACEN LOS REQUISITOS PARA QUE SE OTORGUE UNA FECHA DE PRIORIDAD BAJO 35 USC 111.

SOLICITUD NÚMERO : 60/141.793
FECHA DE PRESENTACIÓN : 30 de Junio de 1999

Por la Autoridad del
COMISIONADO DE PATENTES Y MARCAS

(RUBRICA)

_____

Funcionario Certificador.

SELLO EN RELIEVE

REIVINDICACIONES

1. Método para aerosolizar una formulación farmacéutica, el método comprende:

Evitar que fluyan gases respiratorios a los pulmones cuando se intenta inhalar y luego abruptamente permitir que los gases respiratorios fluyan a los pulmones; y

Utilizar el flujo de los gases respiratorios para extraer una formulación farmacéutica de un receptáculo y ubicar la formulación farmacéutica dentro del flujo de los gases respiratorios para formar un aerosol.

2. Un método según la reivindicación 1, que comprende además limitar el flujo de gases respiratorios a un índice que sea menor que cierto índice durante un cierto tiempo.

3. Un método según la reivindicación 2, en donde el índice es menor de aproximadamente 15L/min y el tiempo está en el rango de aproximadamente 0,5 segundos a aproximadamente 5 segundos.

4. Un método como en la reivindicación 2, en donde el índice es menor de aproximadamente 8L/min y el tiempo está en el rango de aproximadamente 0,5 segundos a aproximadamente 5 segundos.

5. Un método como en la reivindicación 2, en donde el cierto índice permite un volumen inhalado que está en el rango de aproximadamente 125mL a aproximadamente 1,25L.

6. Un método según la reivindicación 1, en donde en la etapa de evitar el flujo comprende además ubicar una válvula dentro de una vía aérea que conduce a los pulmones y a oír la válvula para permitir que los gases respiratorios fluyan a los pulmones.

7. El método según la reivindicación 6, que comprende además abrir la válvula cuando se excede el umbral de vacío de accionamiento originado por el intento de inhalación.

8. Un método según la reivindicación 7, en donde el umbral de vacío de accionamiento está en el rango de aproximadamente 20 cm de H_2O a aproximadamente 60 cm de H_2O.

9. Un método según la reivindicación 2, en donde la etapa de limitar el flujo comprende proporcionar retroalimentación cuando se produce un índice de flujo excesivo para permitirle al usuario ajustar su índice de inhalación.

10. Un método según la reivindicación 2, en donde la etapa de limitar el flujo comprende regular el tamaño de una vía aérea que conduzca a los pulmones.

11. Un método según la reivindicación 10, que comprende además regular el tamaño de la vía aérea para permitir un índice de flujo creciente después que ha pasado cierto tiempo.

12. Un método según la reivindicación 1, en donde la formulación farmacéutica comprende un medicamento en polvo, y comprende además el uso del flujo de los gases respiratorios para desaglomerar el polvo extraído.

13. Un dispositivo de aerosolización que comprende:

una carcasa que define una vía aérea;

Un mecanismo de acoplamiento adaptado para acoplar un receptáculo que contiene una formulación farmacéutica a la vía aérea; y

Una válvula para evitar que los gases respiratorios fluyan a través de la vía aérea hasta que se excede el umbral de vacío de accionamiento en cuyo momento la válvula se abre para permitirle a los gases respiratorios fluir a través de la vía aérea y extraer la formulación farmacéutica del receptáculo para formar un aerosol.

14. Un dispositivo según la reivindicación 13, que comprende además un sistema de regulación para regular el flujo de gases respiratorios a través de la vía aérea a un cierto índice.

15. Un dispositivo según la reivindicación 14, en donde el sistema de regulación se configura para limitar el flujo a un índice que es menor de aproximadamente 15L/min. Durante un cierto tiempo o un cierto volumen inhalado.

16. Un dispositivo según la reivindicación 14, en donde el sistema de regulación comprende un mecanismo de retroalimentación para proporcionar información sobre el índice de flujo de los gases respiratorios.

17. Dispositivo según la reivindicación 16, en donde el mecanismo de retroalimentación comprende un pito en comunicación con la vía aérea.

18. Un dispositivo según la reivindicación 14, en donde el sistema de regulación comprende un miembro restrictivo dispuesto en la vía aérea, el miembro restrictivo define un orificio de cierto tamaño para limitar el flujo de gases respiratorios a través de la vía aérea.

19. Un dispositivo según la reivindicación 14, en donde el sistema de regulación comprende un mecanismo de restricción para limitar el tamaño de la vía aérea.

20. Un dispositivo según la reivindicación 19, en donde el mecanismo de restricción es ajustable para variar el índice de flujo de los gases respiratorios a través de la vía aérea.

21. Un dispositivo según la reivindicación 20, en donde el sistema de regulación comprende además un sistema de control para ajustar el logaritmo de restricción.

22. Un dispositivo según la reivindicación 21, en donde el sistema de control se configura para limitar el flujo a un cierto índice durante un cierto tiempo o un volumen inhalado y luego ajustar el mecanismo de restricción para permitir un flujo creciente de gases respiratorios a través de la vía aérea.

23. Un dispositivo según la reivindicación 13, en donde el umbral de vacío de accionamiento de la válvula está en un rango de aproximadamente 20 cm de H_2O a aproximadamente 60 cm de H_2O.

24. Un dispositivo según la reivindicación 13, que comprende además un mecanismo de desaglomeración dispuesto en la vía aérea corriente abajo del receptáculo para desaglomerar la formulación farmacéutica extraída.

25. Un dispositivo según la reivindicación 3, donde la válvula se adapta a estar dispuesta dentro del receptáculo.

26. Un sistema de aerosolización que comprende:

Un receptáculo que comprende una cámara que tiene una formulación farmacéutica y una válvula de umbral;

Una carcasa que define una vía aérea; y

Un mecanismo de acoplamiento para ubicar la válvula a través de la vía aérea y ubicar la formación farmacéutica para encontrar comunicación con la vía aérea;

En donde la válvula de umbral se configura para abrirse cuando el umbral de vacío se accede al umbral de vacío de accionamiento para permitirle a los gases respiratorios fluir a través de la vía aérea y extraer la formulación farmacéutica de la cámara para formar un aerosol.

27. Un sistema según la reivindicación 26, en donde la formulación farmacéutica comprende un medicamento en polvo.

28. Un sistema según la reivindicación 26, que comprende además un sistema de regulación para regular el flujo de gases respiratorios a través de la vía aérea.

29. Un receptáculo que comprende:

Un cuerpo de receptáculo que define una actividad incluida en un a tapa de acceso penetrable; y

Una válvula de umbral acoplada al cuerpo del receptáculo.

30. Un receptáculo según la reivindicación 29, en donde la válvula de umbral se configura para abrirse cuando se experimenta un vacío de al menos 40 cm de H_2O.

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PA 284195

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

August 02, 2000

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APPLICATION NUMBER: *60/198,060*
FILING DATE: *April 18, 2000*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

L. Edelen

L. EDELEN
Certifying Officer

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4-19-00 A/PROV 302

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jc780 U.S. PTO 04/18/00

jc675 U.S. PTO 60/198060 04/18/00

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

INVENTOR(S)		
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STEVE	PABOOJIAN	Menlo Park, CA
DERRICK J.	TUTTLE	San Mateo, CA

[X] *Additional inventors are being named on the* 1 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (280 characters max)

SYSTEMS AND METHODS FOR AEROSOLIZING PHARMACEUTICAL FORMULATIONS

CORRESPONDENCE ADDRESS

Direct all correspondence to:

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ENCLOSED APPLICATION PARTS (check all *that apply*)

[X] Specification Number of *Pages* 27 [ ] Small Entity Statement

[X] Drawing(s) Number of *Sheets* 14 [X] Other (specify) Postcard

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

[ ] A check or money order is enclosed to cover the filing fees

[X] The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 500348

FILING FEE AMOUNT ($): 150.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

[X] No.

[ ] Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE Michael J. Rafa

TYPED or PRINTED NAME Michael J. Rafa

TELEPHONE 650-631-3100

Date 04/18/00

REGISTRATION NO. *(if appropriate)* 38,740

Docket Number: 0047.PRO2

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C., 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C., 20231.

PROVISIONAL APPLICATION COVER SHEET
Additional Page

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Docket Number	0047.PRO2	Type a plus sign (+) inside this box →	+

INVENTOR(S)/APPLICANT(S)

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DENNIS R.	RASMUSSEN	Santa Clara, CA
ANEESH	BAKSHI	Belmont, CA
ANDREW	CLARK	Half Moon Bay, CA

Number 1 of 1

Practitioner's Docket No. 0047.PRO2 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Carlos Schuler et al.
Application No.: Unassigned Group No.: Unknown
Filed: Herewith Examiner: Unassigned
For: SYSTEMS AND METHODS FOR AEROSOLIZING PHARMACEUTICAL FORMULATIONS

Assistant Commissioner for Patents
Washington, D.C. 20231

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"Express Mail" label number EK470227991US
Date of Deposit 04/18/2000

I hereby state that the following *attached* paper or fee

Provisional Application Cover Sheet (2 pages)
Specification, Claims, Abstract (27 pages)
Drawings (14 pages)

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10, on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Kathy E. Honnert

Kathy E Honnert

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Attorney Docket No.: 15225-004700.01

PROVISIONAL

PATENT APPLICATION

SYSTEMS AND METHODS FOR AEROSOLIZING PHARMACEUTICAL FORMULATIONS

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SYSTEMS AND METHODS FOR AEROSOLIZING PHARMACEUTICAL FORMULATIONS

BACKGROUND OF THE INVENTION

This invention relates generally to the field of drug delivery, and in particular to the delivery of pharmaceutical formulations to the lungs. More specifically, the invention relates to the aerosolization of pharmaceutical formulations using energy created by patient inhalation.

Effective drug delivery to a patient is a critical aspect of any successful drug therapy, and a variety of drug delivery techniques have been proposed. For example, one convenient method is the oral delivery of pills, capsules, elixirs and the like. However, oral delivery can in some cases be undesirable in that many drugs are degraded in the digestive tract before they can be absorbed. Another technique is subcutaneous injection. One disadvantage to this approach is low patient acceptance. Other alternative routes of administration that have been proposed include transdermal, intranasal, intrarectal, intravaginal and pulmonary delivery.

Of particular interest to the invention are pulmonary delivery techniques which rely on the inhalation of a pharmaceutical formulation by the patient so that the active drug within the dispersion can reach the distal (alveolar) regions of the lung. A variety of aerosolization systems have been proposed to disperse pharmaceutical formulations. For example, U.S. Patent Nos. 5,785,049 and 5,740,794, the disclosures of which are herein incorporated by reference, describe exemplary powder dispersion devices which utilize a compressed gas to aerosolize a powder. Other types of aerosolization systems include MDI's (which typically have a drug that is stored in a propellant), nebulizers (which aerosolize liquids using compressed gas, usually air), and the like.

Another technique which is of interest to the invention is the use of inspired gases to disperse the pharmaceutical formulation. In this way, the patient is able to provide the energy needed to aerosolize the formulation by the patient's own inhalation. This insures that aerosol generation and inhalation are properly synchronized. Utilization of the patient's inspired gases can be challenging in several respects. For example, for some pharmaceutical formulations, such as insulin, it may be desirable to

limit the inhalation flow rate within certain limits. For example, PCT/US99/04654, filed March 11, 1999, provides for the pulmonary delivery of insulin at rates less than 17 liters per minute. As another example, copending U.S. Patent Application Serial No. 60/103,702 describes pulmonary delivery techniques where a high flow resistance is provided for an initial period followed by a period of lower flow resistance. The complete disclosures of all the above references are herein incorporated by reference.

Another challenge in utilizing the patient's inspired gases is that the inspiration flow rate can drastically vary between individuals. For instance, as shown in Fig. 1, a random sample of 17 individuals which were measured twice a week for four weeks produced flow rates ranging from about 5 liters per minute to about 35 liters per minute. Such variability may affect the ability of the formulation to be dispersed within a gas stream, the ability to deagglomerate a powdered formulation, and/or the ability of the aerosolized formulation to adequately reach the deep lung.

Hence, this invention is related to techniques for regulating the flow of inspired gases that may be utilized when dispersing a pharmaceutical formulation. In one aspect, the invention is related to techniques to enhance the ability of a formulation to be dispersed within a gas stream produced by patient inhalation, to enhance the ability to deagglomerate a powdered formulation, and to enhance the ability of the aerosolized formulation to adequately reach the deep lung.

SUMMARY OF THE INVENTION

The invention provides exemplary systems and methods that utilize the flow of respiratory gases produced by a patient to aerosolize a pharmaceutical formulation. In one particular aspect of the invention, the invention is able to extract a powdered pharmaceutical formulation from a receptacle, deagglomerate the formulation and deliver the formulation to the lungs using a wide range of patient inhalation flow rates.

In one particular embodiment, a method is provided for aerosolizing a pharmaceutical formulation. According to the method, respiratory gases are prevented from flowing to the lungs when attempting to inhale. The respiratory gases are then abruptly permitted to flow to the lungs. The flow of respiratory gases is utilized to extract a pharmaceutical formulation from a receptacle and to place the pharmaceutical formulation within the flow of respiratory gases to form an aerosol.

By initially preventing respiratory gases from flowing to the lungs when attempting to inhale, the method provides a way to ensure that the resulting gas stream has sufficient energy to extract the pharmaceutical formulation from the receptacle. In one aspect, the flow of respiratory gases may initially be prevented from flowing to the lungs by placing a valve within an airway leading to the lungs and opening the valve to permit the flow of respiratory gases. In a particular aspect, the valve is opened when a threshold actuating vacuum caused by the attempted inhalation is exceeded. In this way, when the valve is opened, the resulting gas stream has sufficient energy to extract and aerosolize the pharmaceutical formulation.

In still another aspect, the method provides for limiting the flow of respiratory gases to a rate that is less than a certain rate for a certain time. For example, the flow rate may be limited to a rate that is less than about 15 liters per minute for a time in the range from about 0.5 second to about 5 seconds, corresponding to a volume in the range from about 125 mL to about 1.25 L. Regulation of the flow rate is advantageous in that it may increase systemic bioavailability of the active agent of certain pharmaceutical formulations via absorption in the deep lung as described generally in PCT Application No. PCT/U.S. 99/04654, filed March 3, 1999 and in copending U.S. Application Serial No. 60/103,702, previously incorporated by reference.

A variety of techniques may be employed to limit or regulate the flow of respiratory gases. For example, feedback may be provided to the user when an excessive flow rate is produced to permit a user to adjust their inhalation rate. Examples of feedback which may be provided include audio feedback, including a whistle, visual feedback, such as indicator lights or a level meter, tactile feedback, such as vibration, and the like. As another alternative, the flow of respiratory gases may be controlled by regulating the size of an airway leading to the lungs. After the flow rate has been limited for the desired amount of time or inhaled volume, the size of the airway may be increased to provide for an increased flow rate. In this way, the user may comfortably inhale without substantial resistance in order to fill the user's lungs with respiratory gases and carry the pharmaceutical formulation into the deep lung.

In another aspect of the method, the pharmaceutical formulation comprises a powdered medicament. The flow of respiratory gases is used to deagglomerate the powder once extracted from the receptacle. Optionally, various structures may be placed into the airway to assist in the deagglomeration process.

particular aspect, the valve is configured to be disposed within the receptacle. In this way, the valve may conveniently be manufactured along with the receptacle.

In another embodiment, the invention provides an aerosolization system that comprises a receptacle having a chamber for holding a pharmaceutical formulation and a threshold valve. The system also includes a housing defining an airway, and a coupling mechanism to position the valve across the airway and to place the pharmaceutical formulation in fluid communication with the airway. Further, the threshold valve is configured to open when a threshold actuating vacuum is exceeded to permit respiratory gases to flow through the airway and extract the pharmaceutical formulation from the chamber to form an aerosol.

In one particular aspect, the pharmaceutical formulation comprises a powdered or liquid medicament. In another aspect, the system includes a regulation system to regulate the flow of respiratory gases through the airway after the valve has been opened.

In still yet another embodiment, the invention provides a receptacle that comprises a receptacle body defining a cavity that is enclosed by a penetrable access lid. The receptacle further includes a threshold valve that is coupled to the receptacle body. In one aspect, the threshold valve is configured to open when experiencing a vacuum of at least about 40 cm H_2O.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph illustrating the average inspiration flow rate for 17 individuals that were measured twice a week for four weeks.

Fig. 2 is a graph illustrating the regulation of a patient's inspiration flow rate over time according to the invention.

Fig. 3. is a graph illustrating the regulation of another patient's inspiration flow rate over time according to the invention.

Fig. 4 is a schematic view of one system that may be utilized to extract a pharmaceutical formulation from a receptacle, deagglomerate the formulation and to place the formulation within the flow of respiratory gases to form an aerosol according to the invention.

Fig. 5 is a perspective view of an aerosolization device according to the invention.

Fig. 6 is a partial cutaway view of the aerosolization device of Fig. 5 shown in an open or loading position.

Fig. 7 illustrates the aerosolization device of Fig. 6 in a closed or operating position according to the invention.

Fig. 8 illustrates the aerosolization device of Fig. 6 when inserting a receptacle according to the invention.

Fig. 9 illustrates the aerosolization device of Fig. 8 when the receptacle has been inserted, when the device has been moved to the closed or operating position, and when respiratory gases are flowed through the device.

Fig. 10 is a partial cutaway perspective view of a receptacle and a convergent nozzle through which a pharmaceutical formulation may be extracted according to the invention.

Fig. 11 illustrates the receptacle and nozzle of Fig. 10, with the nozzle being moved further away from a bottom end of the receptacle to increase the rate of flow of respiratory gases through the nozzle according to the invention.

Fig. 12 is a schematic, cross-sectional side view of an aerosolization system having a spring to regulate the flow of respiratory gases through the system according to the invention.

Fig. 13 is a schematic, cross-sectional view of an aerosolization system having a flow regulation system to regulate the flow of respiratory gases through the aerosolization system according to the invention.

Fig. 14 illustrates one embodiment of a nozzle that may be employed to deagglomerate a pharmaceutical formulation according to the invention.

Fig. 15 is a perspective view of one embodiment of an aerosolization device according to the invention.

Fig. 16 is a perspective view of another embodiment of an aerosolization device according to the invention.

Fig. 16A illustrates a cover of the aerosolization device of Fig. 16.

Fig. 17 is a perspective view of still another embodiment of an aerosolization device according to the invention illustrating the use of a flow rate feedback device.

Fig. 18 illustrates still yet another embodiment of an aerosolization device according to the invention.

Fig. 19 illustrates one particular embodiment of an aerosolization device according the invention.

Fig. 19A illustrates a disk having multiple receptacles that may be inserted into the aerosolization device of Fig. 19.

Fig. 19B illustrates a front end of the aerosolization device of Fig. 19.

Fig. 20 illustrates another embodiment of an aerosolization device according the invention.

Fig. 20A illustrates the aerosolization device of Fig. 20 showing a lid moved to an open position.

Fig. 21 is a perspective view of yet another embodiment of an aerosolization device according to the invention.

Fig. 22 illustrates one particular embodiment of an aerosolization device according the invention capable of holding multiple drug patents.

Fig. 22A illustrates a clip for use with the aerosolization device of Fig. 22.

Fig. 23 illustrates yet another alternative embodiment of an aerosolization device according the invention.

Fig. 23A illustrates a mouthpiece cover of the aerosolization device of Fig. 23.

Fig. 24 illustrates a strip of receptacles that may be utilized within the aerosolization device of Fig. 23.

Fig. 25 illustrates still another alternative embodiment of an aerosolization device according to the invention.

Fig. 26 illustrates one embodiment of an aerosolization device according to the invention.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

The invention provides systems and methods for aerosolizing pharmaceutical formulations using the flow of respiratory gases produced by a patient. The pharmaceutical formulations that may be aerosolized include powdered medicaments, liquid solutions or suspensions, and the like, and may include an active agent.

"Active agent" as described herein includes an agent, drug, compound, composition of matter or mixture thereof which provides some pharmacologic, often beneficial, effect. This includes foods, food supplements, nutrients, drugs, vaccines,

vitamins, and other beneficial agents. As used herein, the terms further include any physiologically or pharmacologically active substance that produces a localized or systemic effect in a patient. The active agent that can be delivered includes antibiotics, antiviral agents, anepileptics, analgesics, anti-inflammatory agents and bronchodilators, and viruses and may be inorganic and organic compounds, including, without limitation, drugs which act on the peripheral nerves, adrenergic receptors, cholinergic receptors, the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulatory system, synaptic sites, neuroeffector junctional sites, endocrine and hormone systems, the immunological system, the reproductive system, the skeletal system, autacoid systems, the alimentary and excretory systems, the histamine system and the central nervous system. Suitable agents may be selected from, for example, polysaccharides, steroids, hypnotics and sedatives, psychic energizers, tranquilizers, anticonvulsants, muscle relaxants, antiparkinson agents, analgesics, anti-inflammatories, muscle contractants, antimicrobials, antimalarials, hormonal agents including contraceptives, sympathomimetics, polypeptides, and proteins capable of eliciting physiological effects, diuretics, lipid regulating agents, antiandrogenic agents, antiparasitics, neoplastics, antineoplastics, hypoglycemics, nutritional agents and supplements, growth supplements, fats, antienteritis agents, electrolytes, vaccines and diagnostic agents.

Examples of active agents useful in this invention include but are not limited to insulin, calcitonin, erythropoietin (EPO), Factor VIII, Factor IX, ceredase, cerezyme, cyclosporine, granulocyte colony stimulating factor (GCSF), alpha-1 proteinase inhibitor, elcatonin, granulocyte macrophage colony stimulating factor (GMCSF), growth hormone, human growth hormone (HGH), growth hormone releasing hormone (GHRH), heparin, low molecular weight heparin (LMWH), interferon alpha, interferon beta, interferon gamma, interleukin-2, luteinizing hormone releasing hormone (LHRH) , somatostatin, somatostatin analogs including octreotide, vasopressin analog, follicle stimulating hormone (FSH), insulin-like growth factor, insulintropin, interleukin-1 receptor antagonist, interleukin-3, interleukin-4, interleukin-6, macrophage colony stimulating factor (M-CSF), nerve growth factor, parathyroid hormone (PTH), thymosin alpha 1, IIb/IIIa inhibitor, alpha-1 antitrypsin, respiratory syncytial virus antibody, cystic fibrosis transmembrane regulator (CFTR) gene, deoxyribonuclease (Dnase), bactericidal/permeability increasing protein (BPI), anti-CMV antibody, interleukin-1 receptor, 13-cis retinoic acid, pentamidine isethionate, albuterol sulfate, metaproterenol sulfate, beclomethasone dipropionate, triamcinolone acetamide, budesonide acetonide,

ipratropium bromide, flunisolide, fluticasone, cromolyn sodium, ergotamine tartrate and the analogues, agonists and antagonists of the above. Active agents may further comprise nucleic acids, present as bare nucleic acid molecules, viral vectors, associated viral particles, nucleic acids associated or incorporated within lipids or a lipid-containing material, plasmid DNA or RNA or other nucleic acid construction of a type suitable for transfection or transformation of cells, particularly cells of the alveolar regions of the lungs. The active agents may be in various forms, such as soluble and insoluble charged or uncharged molecules, components of molecular complexes or pharmacologically acceptable salts. The active agents may be naturally occurring molecules or they may be recombinantly produced, or they may be analogs of the naturally occurring or recombinantly produced active agents with one or more amino acids added or deleted. Further, the active agent may comprise live attenuated or killed viruses suitable for use as vaccines.

"Mass median diameter" or "MMD" is a measure of mean particle size, since the powders of the invention are generally polydisperse (i.e., consist of a range of particle sizes). MMD values as reported herein are determined by centrifugal sedimentation, although any number of commonly employed techniques can be used for measuring mean particle size.

"Mass median aerodynamic diameter" or "MMAD" is a measure of the aerodynamic size of a dispersed particle. The aerodynamic diameter is used to describe an aerosolized powder in terms of its settling behavior, and is the diameter of a unit density sphere having the same settling velocity, generally in air, as the particle. The aerodynamic diameter encompasses particle shape, density and physical size of a particle. As used herein, MMAD refers to the midpoint or median of the aerodynamic particle size distribution of an aerosolized powder determined by cascade impaction.

The amount of active agent in the powdered formulation will be that amount necessary to deliver a therapeutically effective amount of the active agent to achieve the desired result. In practice, this will vary widely depending upon the particular agent, the severity of the condition, and the desired therapeutic effect. However, pulmonary delivery is generally practical for active agents that must be delivered in doses of from 0.001 mg/day to 100 mg/day, preferably 0.01 mg/day to 50 mg/day.

Powdered formulations suitable for use in the present invention include dry powders and particles suspended or dissolved within a propellant. The powdered

formulations have a particle size selected to permit penetration into the alveoli of the lungs, that is, preferably 10 μm mass median diameter (MMD), preferably less than 7.5 μm, and most preferably less than 5 μm, and usually being in the range of 0.1 μm to 5 μm in diameter. The delivered dose efficiency (DDE) of these powders is >30%, usually >40%, preferably >50% and often >60% and the aerosol particle size distribution is about 1.0 - 5.0 μm mass median aerodynamic diameter (MMAD), usually 1.5 - 4.5 μm MMAD and preferably 1.5 - 4.0 μm MMAD. These dry powders have a moisture content below about 10% by weight, usually below about 5% by weight, and preferably below about 3% by weight. Such powders are described in WO 95/24183 and WO 96/32149, which are incorporated by reference herein.

In some embodiments, the flow of respiratory gases produced by the patient is employed to extract the pharmaceutical formulation from a receptacle, to deagglomerate the pharmaceutical formulation and deliver the pharmaceutical formulation to the patient's lungs. One particular advantage of the invention is the ability to perform such functions independent of the patient's natural inhalation flow rate. Hence, in one aspect of the invention, the inhaled respiratory gases are controlled so that they remain within an acceptable range of flow rates to adequately deliver the pharmaceutical formulation to the lungs.

In another aspect, the invention is configured to regulate the flow of inspired gases so that the gases have sufficient energy to extract the pharmaceutical formulation from a receptacle, deagglomerate the formulation, and deliver it to the patient's lungs. In some cases, the invention is further configured to maintain the inhalation flow rate below a maximum level for at least a certain time or inhaled volume when initially delivering the drug. In this way, the aerosolized formulation will flow at an acceptable flow rate to enhance its ability to traverse the patient's airway and enter into the lungs. After initial delivery of the pharmaceutical formulation to the lungs, some embodiments of the invention may be configured to permit the patient to breath at a normal inspiration flow rate to fill the patient's lungs with respiratory gases and to further deliver the pharmaceutical formulation to the deep lung.

To aerosolize the pharmaceutical formulation, the flow of respiratory gases preferably contains sufficient energy to extract the pharmaceutical formulation from the receptacle. To ensure that the respiratory gases contain sufficient energy, the invention may be configured to prevent respiratory gases from flowing to the patient's lungs when

the patient attempts to inhale. Abruptly, the respiratory gases may then be permitted to flow to the patient's lungs after a threshold vacuum has been reached. By abruptly permitting the flow of respiratory gases only when sufficient vacuum has been applied by the user, a relatively high rate of flow is achieved to provide the gas stream with sufficient energy. One way to accomplish such a process is by placing a restriction, valve, or other blocking mechanism in the patient's airway to prevent respiratory gases from entering the patient's lungs when the patient attempts to inhale. The restriction or valve may then be rapidly removed or opened to permit respiratory gases to flow to the lungs. Hence, a patient may be instructed to inhale until a threshold actuating vacuum is overcome. The threshold actuating vacuum may be configured such that it will produce sufficient energy in the resulting gas stream when the gases are allowed to flow to the patient's lungs. Preferably, the threshold vacuum is in the range from about 20 cm H_20 to about 60 cm H_20 so that the resulting gas stream will have sufficient energy to extract and deagglomerate the pharmaceutical formulation.

Once the respiratory gases are allowed to flow to the lungs, the flow rate of the respiratory gases (in some cases) may need to be controlled or regulated so that the gases do not exceed a maximum flow rate during delivery of the pharmaceutical formulation to the lungs. Typically, the flow rate of respiratory gases may be regulated to be less than about 15 liters per minute for a time in the range from about 0.5 seconds to about 5 seconds, corresponding to an inhaled volume in the range from about 125 mL to about 1.25 L, to permit the aerosolized formulation to pass through the patient's airway and enter into the lungs. For example, as previously illustrated in connection with Fig. 1, some patients have a natural inhalation rate that exceeds a desired maximum flow rate.

For breathers that naturally breath above the maximum desired flow rate, the invention provides for the slowing of the flow rate during the time when the aerosolized formulation is being delivered to the lungs. This is illustrated graphically in Fig. 2. At time T_1, the patient is inhaling causing respiratory gases to flow to the patient's lungs. At time T_1, the flow rate is well above a starting flow rate, Q_{START}, which is desirable for initially extracting the pharmaceutical formulation from the receptacle as previously described. Hence, a threshold valve or other flow prevention mechanism may not be needed for such breathers. Shortly after time T_1 is time T_2, where the flow rate has been regulated to be below a $Q_{DELIVERY}$ flow rate. The flow rate is maintained below the $Q_{DELIVERY}$ rate from time T_2 to time T_3, where the aerosolized formulation is being delivered to the patient's lungs. After time T_3, the regulation of the gas flow is ceased

and the patient is permitted to inhale at their regular flow rate to fill their lungs with respiratory gases that serve to further deliver the pharmaceutical formulation to the deep lung.

Fig. 3 graphically illustrates an example of where the patient has a natural inhalation flow rate that is below $Q_{DELIVERY}$. As shown in Fig. 3, by preventing the flow of respiratory gases during patient inhalation, and then abruptly permitting the flow of respiratory gases, the starting flow rate at time T_1, is at Q_{START}. In this way, sufficient energy is provided to extract the formulation from the receptacle. After the patient continues to inhale, the flow rate rapidly falls below the $Q_{DELIVERY}$ flow rate because the patient's natural inhalation flow rate is less than the $Q_{DELIVERY}$ flow rate. Hence, after time T_1, the patient's inhalation flow rate does not need to be regulated, thereby permitting the patient to inhale at a comfortable level.

A variety of schemes and techniques may be provided to regulate the inhalation flow rate to be below the $Q_{DELIVERY}$ flow rate from time T_2 to time T_3. As one example, the patient may be provided with various types of feedback to permit the patient to self-regulate their inhalation flow rate. For instance, an aerosolization device may be provided with a whistle that creates a whistling sound when the patient's flow rate exceeds the $Q_{DELIVERY}$ flow rate. Other types of feedback that may be utilized include visual feedback, tactile feedback, auditory feedback, and the like. Optionally, a controller may be provided with a timing mechanism to indicate to the user when time T_3 has elapsed so that the user may finish their inhalation at a comfortable level.

As another example, the patient's inhalation flow rate may be regulated by restricting or impeding the respiratory gases being inhaled. For example, the size of the airway may be varied to control the rate of flow of inspired gases. The manner of regulation may be either manual, semi-automated, or automated. For example, the user may manually adjust the size of the airway or place a restriction in the airway to control the rate of flow. Alternatively, the size of the airway may be adjusted based on the patient's own inhalation as described in greater detail hereinafter. In still another example, an automated system with one or more flow sensors may be provided to regulate the size of the airway to regulate the flow of respiratory gases.

One particular advantage of restricting the flow of respiratory gases to control the inhalation flow rate is that a relatively high pressure drop may be created. Because power is generally proportional to both the pressure drop and flow rate, the flow

rate may be kept low while still providing sufficient energy to aerosolize the formulation and to deliver the formulation to the patient's lungs.

As another alternative, the flow of respiratory gases may be regulated by placing an orifice or other restriction member into the patient's airway that is made for use with a specific patient. In this way, an aerosolization device may be tailored to a specific patient simply by utilizing an orifice sized according to the patient's natural inhalation flow rate.

A variety of threshold valves may also be employed to prevent respiratory gases from reaching the patient's lungs until a threshold inhalation vacuum is obtained. For example, the threshold valve may comprise a flexible membrane that is disposed across the airway and is configured to flex to provide means for altered air flow when the threshold vacuum is met or exceeded. Alternatively, the threshold valve may comprise a scored membrane that is configured to tear or burst once the threshold vacuum is met or exceeded. Other types of threshold valves include bi-stable mechanisms, diaphragms, and the like. Threshold valves suitable for use in the devices of the present invention are disclosed in U.S. Patent Nos. 4,991,745, 5,033,655, 5,213,236, 5,339,995, 5,377,877, 5,409,144, and 5,439,143, for example, which are hereby incorporated in their entirety by reference.

In one particular aspect of the invention, the threshold valve may be incorporated into a receptacle that also holds the pharmaceutical formulation. In this way, each time a new receptacle is inserted into an aerosolization device, the device is provided with a new threshold valve. This is particularly advantageous when the threshold valve comprises a membrane that is configured to tear or burst after the threshold vacuum is met or exceeded.

The receptacles of the invention may conveniently be configured to have a penetrable access lid that is penetrated by one or more pointed structures when the aerosolization device is operated. Examples of such receptacles are described in U.S. Patent Nos. 5,740,754 and 5,785,049, the complete disclosures of which are herein incorporated by reference.

The invention may utilize various deagglomeration mechanisms to deagglomerate the pharmaceutical formulation once it is extracted from the receptacle. For example, the flow path for the gases may experience one or more changes in direction to cause the pharmaceutical formulation to engage the walls of the flow path to deagglomerate the formulation. The flow path may also include various contractions or

restrictions that may cause the pharmaceutical formulation to engage the walls of the flow path to deagglomerate the formulation. As another example, the flow path may include one or more obtrusions or obstacles that serve to engage the pharmaceutical formulation as it passes through the flow path.

Referring now to Fig. 4, a system 10 for extracting a powdered medicament from a receptacle 12 using a patient's inspired respiratory gases will be described. System 10 comprises a threshold valve 14 that may be configured to open when the vacuum within a line 16 downstream of threshold valve 14 experiences a vacuum of greater than about 40 cm H_20. Also coupled to line 16 is a regulation system 18 that regulates the flow of respiratory gases through system 10. As one example, regulation system 18 may include a restriction mechanism that may be employed to control the internal size of line 16 and thereby regulate the flow of respiratory gases through line 16. Conveniently, regulation system 18 may include a control system that adjusts the restriction mechanism. The control system may be either manually operated or operated in an automated manner using a controller. For example, gas flow sensors may be disposed in system 10 and coupled to the controller to determine the rate of flow of respiratory gases through the system. Using this information, the controller may be employed to control the degree of restriction of line 16. Although regulation system 18 is shown upstream of receptacle 12, it will be appreciated that regulation system 18 may be provided in other locations, including downstream of receptacle 22 and upstream of threshold valve 14.

Regulation system 18 is coupled to receptacle 12 by a line 20. Exiting receptacle 12 is a line 22 that is in communication with a deagglomeration mechanism 24. In this way, powder extracted from receptacle 12 may be deagglomerated before leaving system 10 and passing into the patient's lungs. Exiting deagglomeration mechanism 24 is a line 26 that may be coupled to a mouthpiece (not shown) from which the patient inhales. Hence, with system 10, a patient may receive a dose of an aerosolized medicament by inhaling from the mouthpiece until the patient produces a vacuum sufficient to open threshold valve 14. When threshold 14 opens, the powdered medicament is extracted from receptacle 12 and passes through deagglomeration mechanism 24. At the same time, regulation system 18 controls the flow of respiratory gases within an acceptable rate so that the aerosolized medicament may properly pass into the patient's lungs. After a certain amount of time, the regulation system 18 may be

configured to cease operating so that the patient may inhale at a comfortable rate to fill the lungs with respiratory gases and to move the delivered medicament to the deep lung.

Referring now to Fig. 5, an exemplary embodiment of an aerosolization device 28 will be described. Device 28 comprises a generally cylindrical housing 30 having a mouthpiece 32 at one end. Housing 30 further includes openings 34, 36 and 38 which define a flow path for respiratory gases as described in greater detail hereinafter. Conveniently, a divider 40 is provided between openings 36 and 38 to permit the flow of respiratory gases to pass temporarily outside of housing 30. Similarly, a divider 42 is provided to facilitate the introduction of respiratory gases into housing 30 through opening 34 (see Fig. 6).

Pivotally coupled to housing 30 is a receptacle carrier 44. Conveniently, a pin 46 is employed to pivotally couple carrier 44 to housing 30. In this way, carrier 44 may be moved to an open position as shown in Fig. 6 to permit a receptacle to be loaded into device 28. Carrier 44 may then be moved to a closed or operating position as shown in Fig. 7. As best shown in Figs. 6 and 7, carrier 44 includes an opening 48 that is aligned with opening 34 when carrier 44 is moved to the closed position. Carrier 44 further includes another opening 50 that is positioned below two penetrating tabs 52 on housing 30.

As best shown in Fig. 8, once carrier 44 is moved to the open position, a receptacle 54 may be inserted into device 28. Receptacle 54 comprises a receptacle body 56 having a chamber 58 (shown in phantom line) which holds the powdered medicament. Receptacle body 56 is configured so that the portion above chamber 58 is penetrable by tabs 52 as described in greater detail hereinafter. Disposed in receptacle body 56 is a threshold valve 60 that comprises a membrane that is configured to rupture or tear at a specified threshold vacuum.

Receptacle 54 is inserted into device 28 so that threshold valve 60 is aligned with opening 36. Also, chamber 58 rests within opening 50. Once receptacle 54 is inserted onto carrier 44, carrier 44 is moved to the closed or operating position as illustrated in Fig. 9. When in the closed position, threshold valve 60 is aligned with opening 34. Further, tabs 52 penetrate body 56 over chamber 58 and peel back the lid to provide a pair of openings that provide access to the powder contained within chamber 58. Once carrier 44 is moved to the closed position, a user may place his mouth over mouthpiece 32 and attempt to inhale. The flow of respiratory gases through device 28 is prevented until the user creates sufficient vacuum to open threshold valve 60. At this

point, respiratory gases are abruptly permitted to flow through opening 34, through opening 36, through chamber 58, through opening 38 and out mouthpiece 32 as illustrated by the arrows.

Turning now to Figs. 10 and 11, an example of one technique that may be employed to regulate the flow of respiratory gases through an aerosolization device, such as device 28, will be described. Shown in Fig. 10 is a receptacle 62 having a chamber 64 that is typically filled with a pharmaceutical formulation (not shown). In Fig. 10, a penetrating tube 66 has already penetrated the lid over chamber 64, and a distal end 68 of tube 66 is disposed within chamber 64. In Fig. 10, distal end 68 of tube 66 is positioned near the bottom of chamber 64. In this way, the airway between distal end 68 and the bottom of chamber 64 is reduced in size to restrict the respiratory gases flowing into chamber 64 and out penetrating tube 66. As shown in Fig. 11, distal end 68 is moved vertically upward so that it is further distanced from the bottom end of chamber 64. In this way, the flow rate of respiratory gases may be increased.

A variety of techniques may be employed to adjust the distance between distal end 68 and the bottom of chamber 64. For example, one technique is to employ the use of a suction force created by patient inhalation. More specifically, as the patient begins to inhale, the vacuum source created within tube 68 by the inhalation will tend to move the bottom end of chamber 64 toward distal end 68. Various mechanisms may then be employed to control the distance between distal end 68 and the bottom end of chamber 64. For example, a variety of biasing mechanisms may be included to control the relative movement between receptacle 62 and penetrating tube 66. Automated mechanisms, such as solenoids, pistons, and the like may also be employed. Further, various manual techniques may also be used, including utilization of the user's hands or fingers.

One feature of penetrating tube 66 is that it forms a convergent nozzle that serves as a deagglomerator for the power contained within chamber 64. More specifically, as the patient inhales to extract the powder from chamber 64, the convergent flow path created by penetrating tube 66 tends to deagglomerate the powder to facilitate its aerosolization and deposition within the lung.

Referring now to Fig. 12, an embodiment of an aerosolization device 70 will be described to illustrate one technique for regulating the flow of respiratory gases through the device. For convenience of illustration, only a portion of device 70 is illustrated, it being appreciated that other components may be utilized to complete the

device. Aerosolization device 70 comprises a housing 72 and a receptacle carrier 74. Receptacle carrier 74 may be configured to be movable relative to housing 72 for convenient loading and unloading of a receptacle 76. Receptacle 76 includes a chamber 78 and a threshold valve 80 that may be constructed to be similar to other embodiments described herein. Receptacle carrier 74 includes an opening 82 that is aligned with valve 80 to permit respiratory gases to flow through valve 80 once opened. Coupled to housing 72 is a penetrating tube 84 that penetrates receptacle 76 to provide access to chamber 78 in a manner similar to that described with the previous embodiments. In this manner, when a patient inhales from device 70, threshold valve 80 opens when the threshold vacuum is overcome. Respiratory gases then flow through chamber 78 and out penetrating tube 84 as illustrated by the arrows.

Device 70 further includes a spring 86 disposed between housing 72 and receptacle carrier 74. Once valve 80 is opened, the vacuum within penetrating tube 84 causes the bottom end of chamber 78 to be drawn toward penetrating tube 84. The spring constant of spring 86 may be selected to control the distance between the bottom end of chamber 78 and penetrating tube 84 to regulate the gas flow through the device. In some cases, it may be desirable to select the spring constant of spring 86 based on the average inhalation flow rate produced by the patient. In this way, device 70 may be tailored to a particular patient. Device 70 further includes a pin 88 that maintains the spacing between the bottom of chamber 78 and penetrating tube 84 to a certain distance. In this way, chamber 78 will not completely be drawn against penetrating tube 84.

Referring now to Fig. 13, an aerosolization device 90 will be described. Device 90 may be constructed from elements similar to that previously described in connection with aerosolization device 70. Hence, for convenience of discussion, similar elements used for aerosolization device 90 will be referred to with the same reference numerals used to describe device 70 and will not be described further. Aerosolization device 90 differs from aerosolization device 70 in that it employs an electronic controller 92 to control the distance between penetrating tube 84 and the bottom end of chamber 78. Controller 92 is electronically coupled to a solenoid 94 that may be extended or retracted to control the spacing between penetrating tube 84 and chamber 78. Optionally, a flow control sensor 96 may be disposed anywhere within the airway of device 90 to sense the rate of flow through the device. When controller 92 receives a signal from sensor 96, it may send a signal to solenoid 94 to adjust the spacing to thereby regulate the flow rate. One advantage of using controller 92 is that it may also include a timing circuit so that

solenoid 94 may be fully extended after a certain amount of time. In this way, once the aerosolized formulation has reached the patient's lungs, solenoid 94 may be fully extended to permit the user to comfortably inhale without substantial resistance to fill their lungs with respiratory gases.

Referring now to Fig. 14, another embodiment of a nozzle 98 that may be placed downstream of a receptacle will be described. Nozzle 98 comprises a tubular structure 100 having a bent section 102 and a contracted section 104. As the pharmaceutical formulation is extracted from the receptacle, it passes through tubular structure 100 as indicated by the arrows. The change in the direction caused by bent section 102 causes the agglomerated powder to engage the walls of structure 100 to assist in its deagglomeration. When reaching contracted section 104, the powder is further agitated and the flow is increased to further deagglomerate the powder. Although shown with one bent section followed by a contracted section, it will be appreciated that various other tubular structures may be provided with various arrangements of direction changes and/or constrictions to facilitate deagglomeration of the powder.

Referring now to Figs. 15-26, various embodiments of aerosolization devices will be described. Although not shown, the aerosolization devices of Figs. 15-26 will typically include a penetrating tube with one or more penetrating structures to pierce the lid of a receptacle similar to the embodiments previously described. These devices may also include threshold valves and regulation systems for regulating the flow of respiratory gases to the patient's lungs in a manner similar to that described with previous embodiments. Further, it will be appreciated that the components of the various devices of Figs. 15-26 may be shared, substituted and/or interchanged with each other.

First referring to Fig. 15, one embodiment of an aerosolization device 106 will be described. Device 106 comprises a housing 108 having a lid 110. Lid 110 is movable to an open position to receive a sheet 112 of receptacles 114. Lid 110 includes various buttons 116 that may be pressed to puncture an associated receptacle 114 prior to inhalation. Conveniently, lid 110 includes a window 118 to indicate that sheet 112 is loaded and may also show a date and type of medication printed on sheet 112. Housing 108 further includes a mouthpiece 120 and a slidable cover 122 that may be slid over mouthpiece 120 when not in use.

When a patient is ready to receive a treatment, the patient slides cover 122 to expose mouthpiece 120. One of buttons 116 is then pressed and the user inhales while

their mouth is over mouthpiece 120. Once all of buttons 116 have been pressed, sheet 112 may be replaced with a new sheet of receptacles.

Fig. 16 illustrates an aerosolization device 124 that comprises a cover 126 (see also Fig. 16A) and a drawer 128 that is slidable within cover 126 as indicated by the arrow. Drawer 128 is configured to hold a receptacle 130. As shown in Fig. 16A, when drawer 128 is closed, receptacle 130 is held within cover 126. Conveniently, the chamber of receptacle 130 may be configured to be pierced when drawer 128 is closed. Various press buttons 132 may be provided to allow drawer 128 to be retracted following use. Cover 126 further includes a mouthpiece 134 and a window to indicate that receptacle 130 is loaded, along with showing a date and type of medication. Optionally, a counter 138 may be provided to show the cumulative number of uses for the device.

Fig. 17 illustrates an aerosolization device 140 comprising a housing 142 having a mouthpiece 144 and a lid 146. Lid 146 is movable between an open position and a closed position as illustrated in phantom line. When lid 146 is opened, a receptacle 148 may be placed within housing 142. When lid 146 is closed, receptacle 148 is pierced and device 140 is ready for operation. Conveniently, lid 146 may include a raised window 150 containing a ball 152. The region behind window 150 may be placed in communication with the airflow path, thereby causing ball 152 to move within the region depending on the rate of flow of respiratory gases through device 140. Conveniently, plus and minus signs may be used to provide the patient with visual feedback on the rate of flow through the device. In this way, the patient may adjust their inhalation rate based on the visual feedback. Optionally, device 140 may include a storage compartment 154 for holding extra receptacles 148.

Fig. 18 illustrates a device 156 comprising a housing 158 having a mouthpiece 160 and a lid 162. A hinge 164 is employed to pivotally couple lid 162 to housing 158. Lid 162 is movable between an open position and a closed position. When in the open position, a receptacle 166 may be loaded into housing 158. Lid 162 is then closed, with receptacle 166 being visible through a window 168. Lid 162 includes a press button 170 which is pushed to pierce receptacle 166 prior to use.

Fig. 19 illustrates an aerosolization device 172 comprising a housing 174 and a door 176 that is coupled to housing 174 by a hinge 178. Insertable into device 172 is a disk 180 having multiple receptacles 182 as illustrated in Fig. 19A. Conveniently, each of the receptacles may be numbered as illustrated in Fig. 19A. Door 176 includes a dial 184 that is rotatable to rotate disk 180 within device 172. Door 176 also includes a

window 186 to view the receptacle that has been pierced by rotating dial 184. When ready to receive a treatment, the user places their mouth over a nose 187 of device 172 and begins to inhale. The patient's inhalation opens a lid 188 to permit the aerosolized formulation to enter into the patient's lungs. To receive another treatment, the user simply dials dial 184 to the next receptacle which is pierced, making device 172 ready for operation.

Referring now to Figs. 20 and 20A, an alternative aerosolization device 190 will be described. Device 190 comprises a housing 192 and a lid 194 that is coupled to housing 192 by a hinge 196. Device 190 further includes a mouthpiece 198 through which the patient inhales. As shown in Fig. 20A, device 190 is in an open position where a receptacle 200 is placed in a loaded position. Lid 194 may then be closed to the position illustrated in Fig. 20. Lid 194 includes a press button 202 that is pressed to pierce receptacle 200 so that the pharmaceutical formulation may be extracted. Lid 194 also includes a timer 204 that is manually set by having the user pull timer 204 toward button 202 prior to operation. The user then begins to inhale from mouthpiece 198 to aerosolize the pharmaceutical formulation. Preferably, the user inhales until timer 204 expires. As shown in Fig. 20A, lid 194 may include multiple storage locations for storing additional receptacles 200.

Fig. 21 illustrates an aerosolization device 206 comprising a housing 208 having a slot 210 for receiving a receptacle 212. Device 206 further includes a cocking device 214 that is cocked to cause receptacle 212 to be pierced. Device 206 further includes a trap door 216 and an extendable mouthpiece 218 (shown in phantom line). When cocking device 214 is cocked to pierce receptacle 212, trap door 216 is also opened and mouthpiece 218 is extended.

Referring now to Fig. 22, another aerosolization device 220 will be described. Device 220 comprises a housing 222 and a clip 224 that may be coupled to housing 222. As best shown in Fig. 22A, clip 224 includes a storage region 226 and a waste region 228. Storage region 226 includes multiple receptacles 230 that may be loaded into housing 222 as described hereinafter. Once a receptacle has been used, it is ejected into waste region 228. Conveniently, a removable seal 232 may be disposed over storage region 226. Use of clip 224 is advantageous in that replacement clips, having a fresh supply of receptacles, may easily be coupled to housing 222, making device 220 a multi-use device.

As best shown in Fig. 22, housing device 220 further includes a rotatable dial 234 that is rotated to advance one of the receptacles 230 from storage region 226 and into housing 222. When placed within housing 222, receptacle 230 is pierced. Further, housing 222 includes a counter 236 to display how many receptacles remain unpierced. A tethered mouthpiece cover 238 is coupled to housing 222 and is removed prior to inhalation.

Hence, to use device 220, the user simply rotates dial 234 to advance and pierce the next receptacle. Cover 238 is removed and the patient inhales to aerosolize the pharmaceutical formulation and deposit the formulation within the patient's lungs. When ready for a next dosage, dial 234 is again dialed causing the used receptacle to be ejected into waste region 228 and advancing another receptacle. When all receptacles have been used, clip 224 is removed and placed with a replacement clip.

Fig. 23 illustrates an aerosolization device 240 comprising a housing 242 and a lid 244 pivotally coupled to housing 242. A removable mouthpiece cover 246 is also provided (see also Fig. 23A). Cover 246 is removed prior to inhalation by the patient. Device 240 is configured to hold a strip 248 of receptacles 250 (as shown in Fig. 24). Once strip 248 is within housing 242, a slide 252 may be moved to indicate the desired receptacle that is to be pierced. Slide 252 may then be depressed to pierce the selected receptacle. Optionally, slide 252 may be coupled to plumbing within device 240 so that the plumbing is moved to the appropriate receptacle along with slide 252. Device 240 may also include a whistle 254 that produces an audible signal when the user inhales in excess of a maximum inhalation flow rate. The user may simply inhale at a slower flow rate until whistle 254 ceases producing a whistling sound.

Fig. 25 illustrates an aerosolization device 256 comprising a housing 258 and a mouthpiece cover 260 that is tethered to housing 258. Cover 260 is removed prior to use. Housing 258 further includes a slot 262 that extends through housing 258. In this way, a continuous strip 264 of receptacles 266 may be fed through slot 262. Alternatively, strip 264 may be separated into segments so that an individual receptacle may be fed into slot 262. Housing 258 includes a button 268 that may be depressed to pierce the loaded receptacle.

When the patient begins to inhale, their flow rate is monitored by a gas gauge 270. In this way, the user is provided with visual feedback to assist them in inhaling at the proper flow rate. Optionally, housing 258 may include a clip 272 to permit device 258 to be carried on the pocket like a pen.

Fig. 26 illustrates an aerosolization device 274 comprising a housing 276 having a mouthpiece 278 and a rotatable body 280 that is rotatable relative to housing 276. Device 274 is configured to receive a receptacle pack 282 at a back end of device 274. Receptacle pack 282 includes multiple receptacles 284 that may be pierced when ready for use. Although receptacle pack 282 is shown as being cylindrical in geometry, it will be appreciated that other geometries may be employed, including square shaped tubes.

Once receptacle pack 282 is inserted into device 274, rotatable body 280 is rotated to advance one of the receptacles to an engaging position where the receptacle is pierced. Conveniently, housing 276 includes a counter 286 to display the remaining number of receptacles. If the patient inhales at an excessive flow rate, housing 276 is configured to vibrate to provide the user with feedback so that they may adjust their inhalation flow rate.

The invention has now been described in detail for purposes of clarity of understanding. However, it will be appreciated that certain changes and modifications may be practiced within the scope of the appended claims.

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WHAT IS CLAIMED IS:

1. A method for aerosolizing a pharmaceutical formulation, the method comprising:

preventing respiratory gases from flowing to the lungs when attempting to inhale, and then abruptly permitting respiratory gases to flow to the lungs; and

using the flow of respiratory gases to extract a pharmaceutical formulation from a receptacle and to place the pharmaceutical formulation within the flow of respiratory gases to form an aerosol.

2. A method as in claim 1, further comprising limiting the flow of respiratory gases to a rate that is less than a certain rate for a certain time.

3 A method as in claim 2, wherein the rate is less than about 15 L/min and the time is in the range from about 0.5 seconds to about 5 seconds.

4. A method as in claim 2, wherein the rate is less than about 8 L/min and the time is in the range from about 0.5 seconds to about 5 seconds.

5. A method as in claim 2, wherein the certain rate permits an inhaled volume that is in the range from about 125 mL to about 1.25L

6. A method as in claim 1, wherein the flow preventing step further comprises placing a valve within an airway leading to the lungs and opening the valve to permit respiratory gases to flow to the lungs.

7. A method as in claim 6, further comprising opening the valve when a threshold actuating vacuum caused by the attempted inhalation is exceeded.

8. A method as in claim 7, wherein the threshold actuating vacuum is in a range from about 20 cm H_20 to about 60 cm H_20.

9. A method as in claim 2, wherein the flow limiting step comprises providing feedback when an excessive flow rate is produced to permit a user to adjust their inhalation rate.

10. A method as in claim 2, wherein the flow limiting step comprises regulating the size of an airway leading to the lungs.

11. A method as in claim 10, further comprising regulating the size of the airway to permit an increased flow rate after the certain time has lapsed.

12. A method as in claim 1, wherein the pharmaceutical formulation comprises a powdered medicament, and further comprising using the flow of respiratory gases to deagglomerate the extracted powder.

13. An aerosolization device, comprising:

a housing defining an airway;

a coupling mechanism adapted to couple a receptacle containing a pharmaceutical formulation to the airway; and

a valve to prevent respiratory gases from flowing through the airway until a threshold actuating vacuum is exceeded at which time the valve opens to permit respiratory gases to flow through the airway and to extract the pharmaceutical formulation from the receptacle to form an aerosol.

14. A device as in claim 13, further comprising a regulation system to regulate the flow of respiratory gases through the airway to a certain rate.

15. A device as in claim 14, wherein the regulation system is configured to limit the flow to a rate that is less than about 15L/min for a certain time or a certain inhaled volume.

16. A device as in claim 14, wherein the regulation system comprises a feedback mechanism to provide information on the rate of flow of the respiratory gases.

17. A device as in claim 16, wherein the feedback mechanism comprises a whistle in communication with the airway.

18. A device as in claim 14, wherein the regulation system comprises a restrictive member disposed in the airway, the restrictive member defining an orifice sized to limit the flow of respiratory gases through the airway.

19. A device as in claim 14, wherein the regulation system comprises a restriction mechanism to limit the size of the airway.

20. A device as in claim 19, wherein the restriction mechanism is adjustable to vary the rate of flow of respiratory gases through the airway.

21. A device as in claim 20, wherein the regulation system further comprises a control system to adjust the restriction mechanism.

22 A device as in claim 21, wherein the control system is configured to limit the flow to the certain rate for a certain time or inhaled volume and then to adjust the restriction mechanism to permit an increased flow of respiratory gases through the airway.

23 A device as in claim 13, wherein the threshold actuating vacuum of the valve is in a range from about 20 cm H_20 to about 60 cm H_20.

24. A device as in claim 13, further comprising a deagglomeration mechanism disposed in the airway downstream of the receptacle to deagglomerate the extracted pharmaceutical formulation.

25 A device as in claim 13, wherein the valve is adapted to be disposed within the receptacle.

26. An aerosolization system comprising:

a receptacle comprising a chamber having a pharmaceutical formulation and a threshold valve;

a housing defining an airway; and

a coupling mechanism to position the valve across the airway and to place the pharmaceutical formulation in fluid communication with the airway;

wherein the threshold valve is configured to open when a threshold actuating vacuum is exceeded to permit respiratory gases to flow through the airway and extract the pharmaceutical formulation from the chamber to form an aerosol.

27. A system as in claim 26, wherein the pharmaceutical formulation comprises a powdered medicament.

28. A system as in claim 26, further comprising a regulation system to regulate the flow of respiratory gases through the airway.

29 A receptacle comprising:

a receptacle body defining a cavity enclosed by a penetrable access lid; and

a threshold valve coupled to the receptacle body.

30. A receptacle as in claim 29, wherein the threshold valve is configured to open when experiencing a vacuum of at least about 40 cm H_20.

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SYSTEMS AND METHODS FOR AEROSOLIZING PHARMACEUTICAL FORMULATIONS

ABSTRACT OF THE DISCLOSURE

Systems and methods are provided for aerosolizing a pharmaceutical formulation. According to one method, respiratory gases are prevented from flowing to the lungs when attempting to inhale. Then, respiratory gases are abruptly permitted to flow to the lungs. The flow of respiratory gases is then used to extract a pharmaceutical formulation from a receptacle and to place the pharmaceutical formulation within the flow of respiratory gases to form an aerosol.

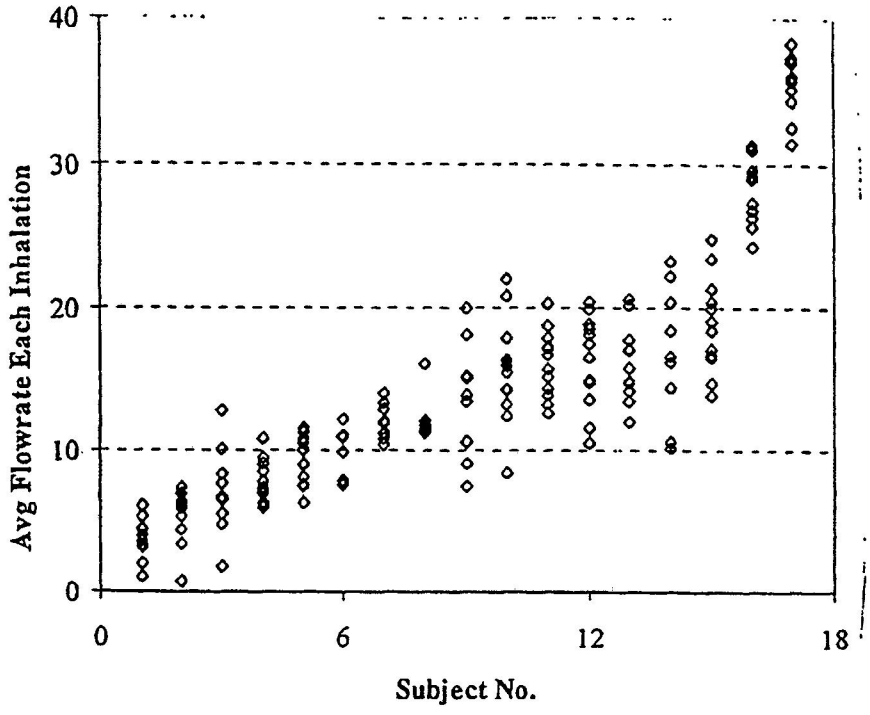


FIG.1

FIG. 2

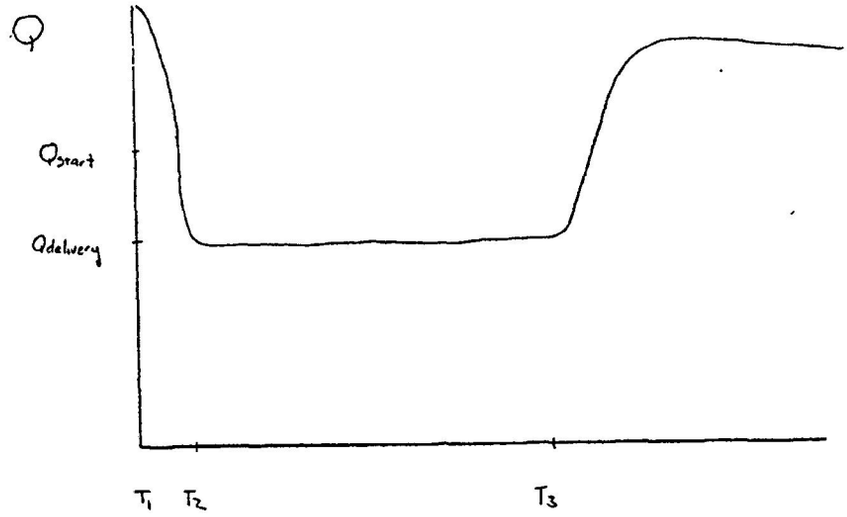


FIG. 3

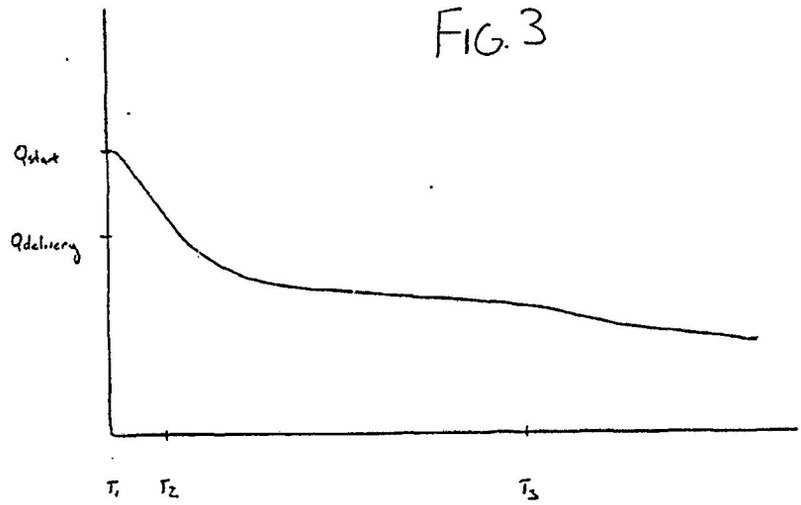
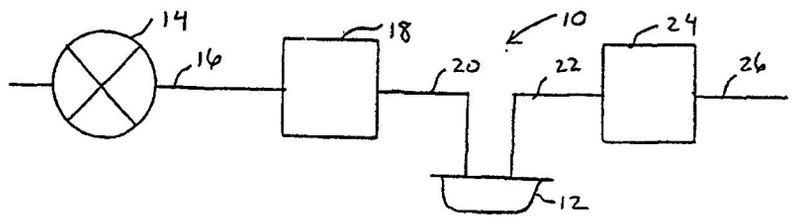


FIG. 4



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FIG. 5

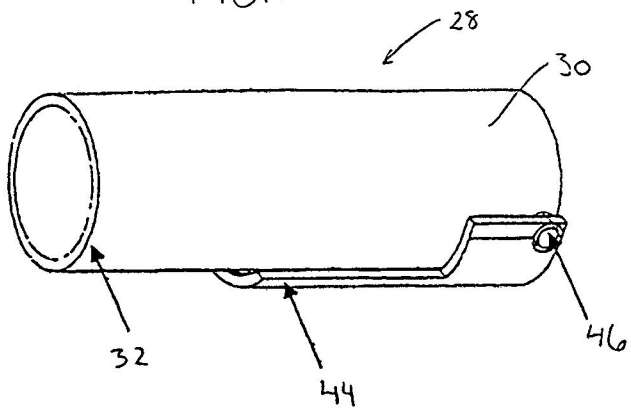


FIG. 6

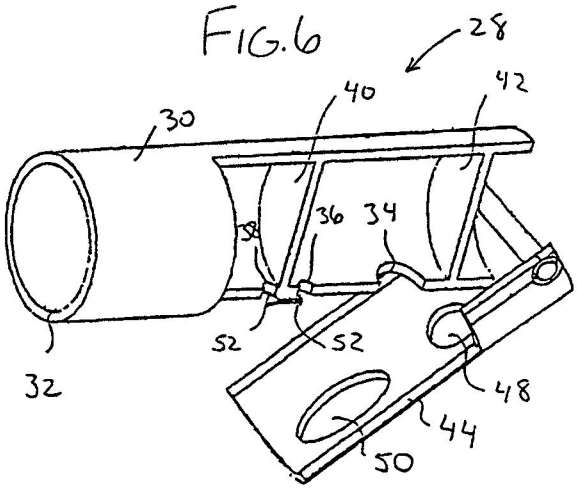
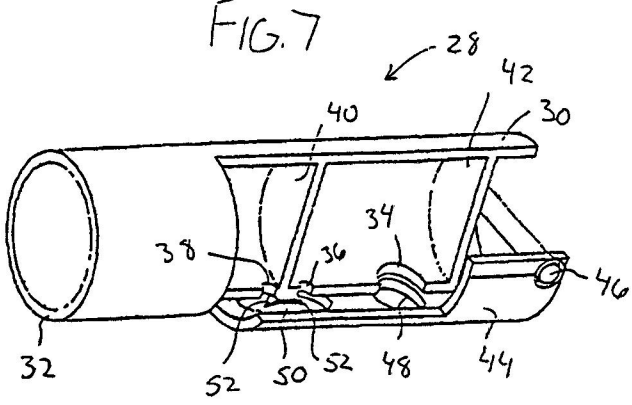


FIG. 7



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FIG. 8

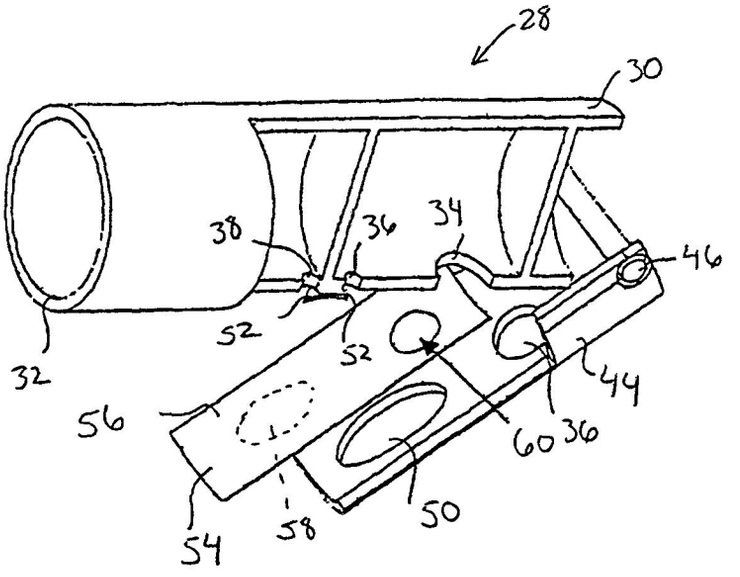


FIG. 9

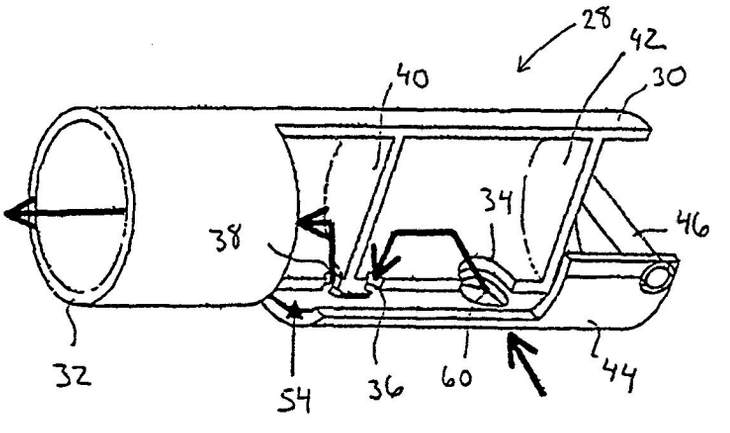


FIG. 10

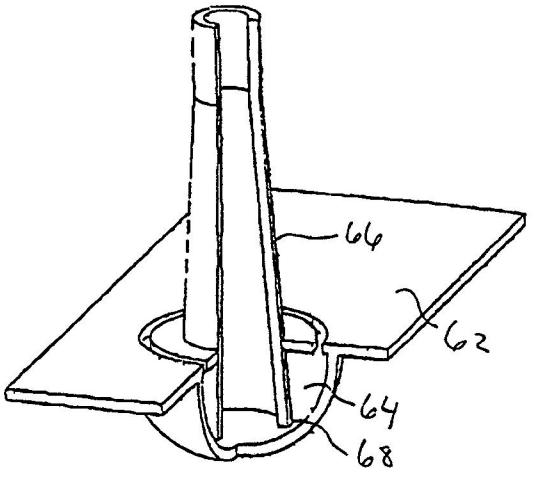


FIG. 11

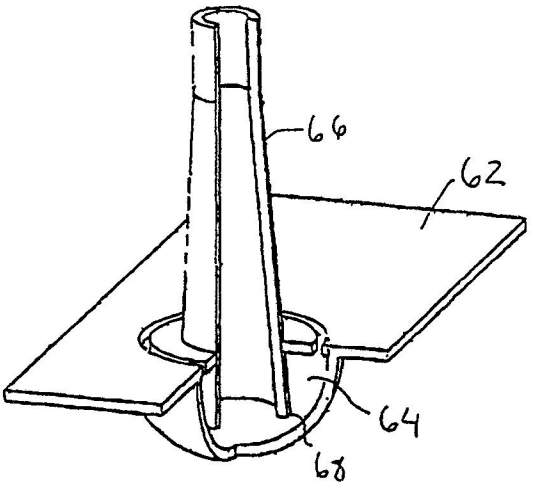


FIG. 12

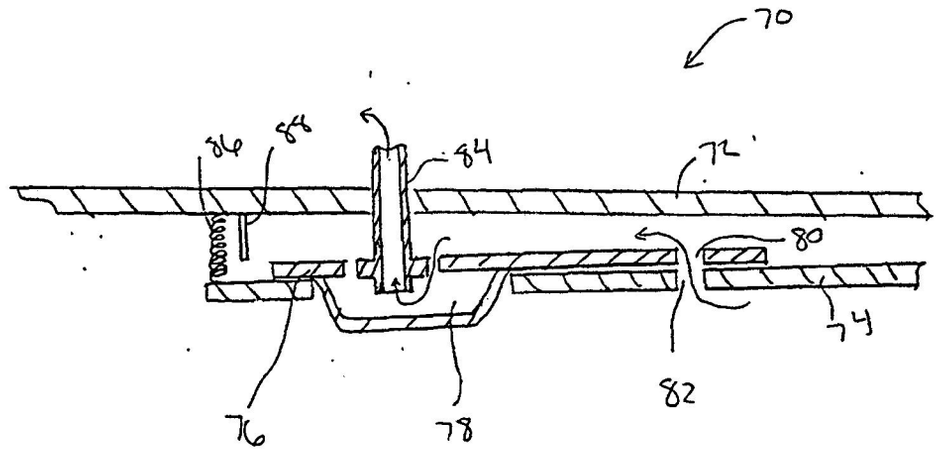
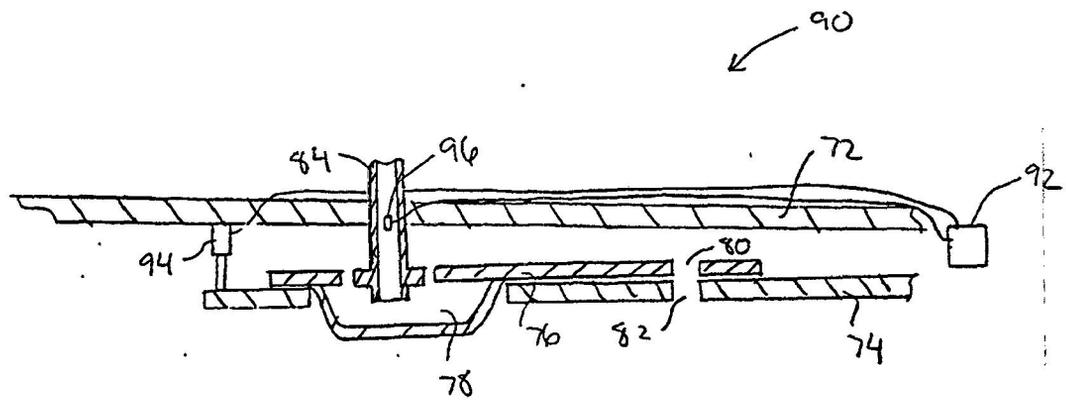


FIG. 13



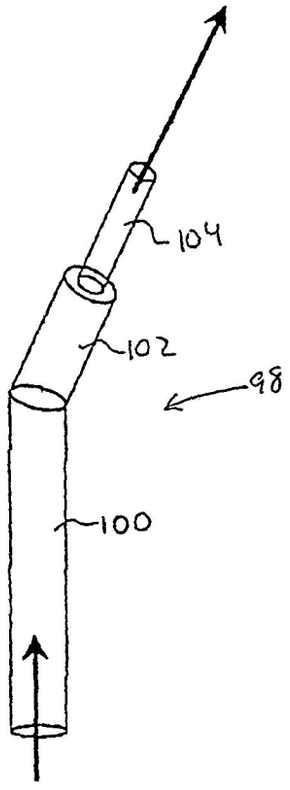


FIG. 14

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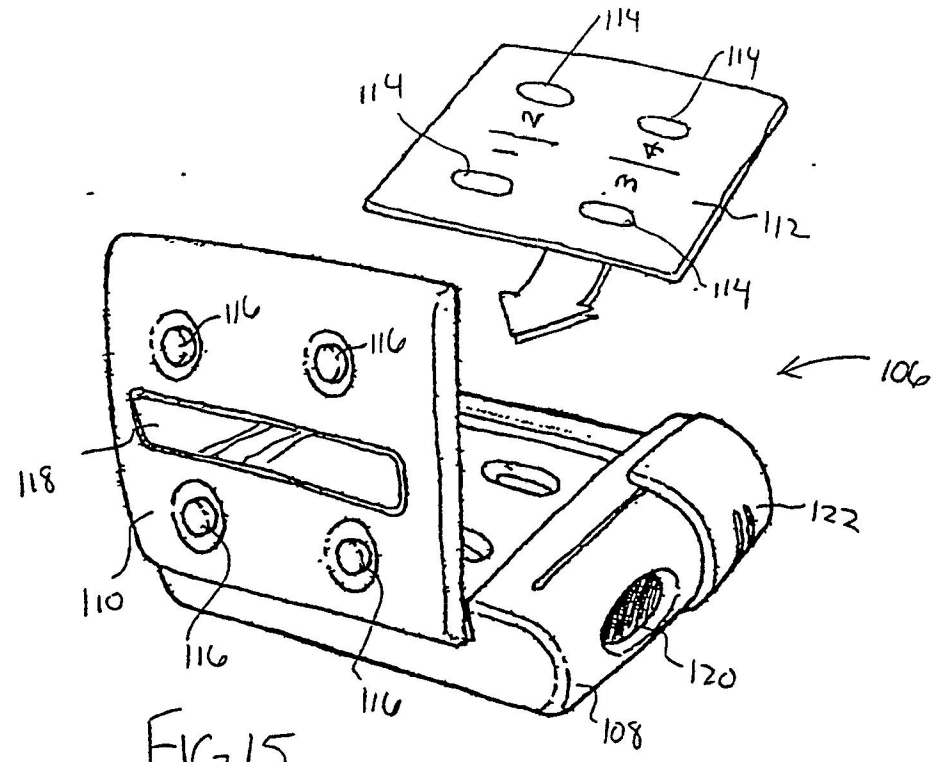


FIG.15

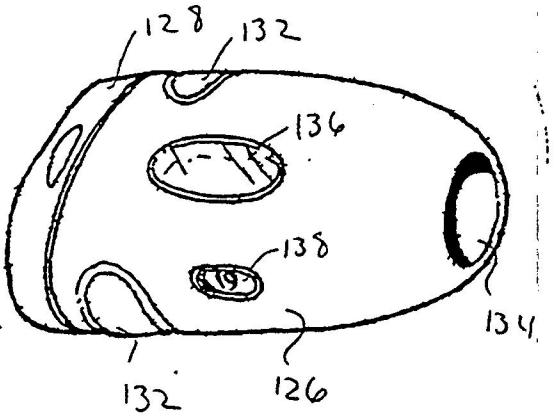


FIG.16A

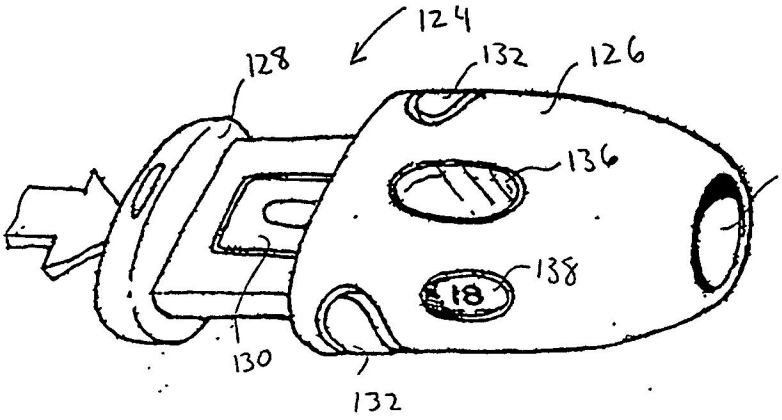


FIG.16

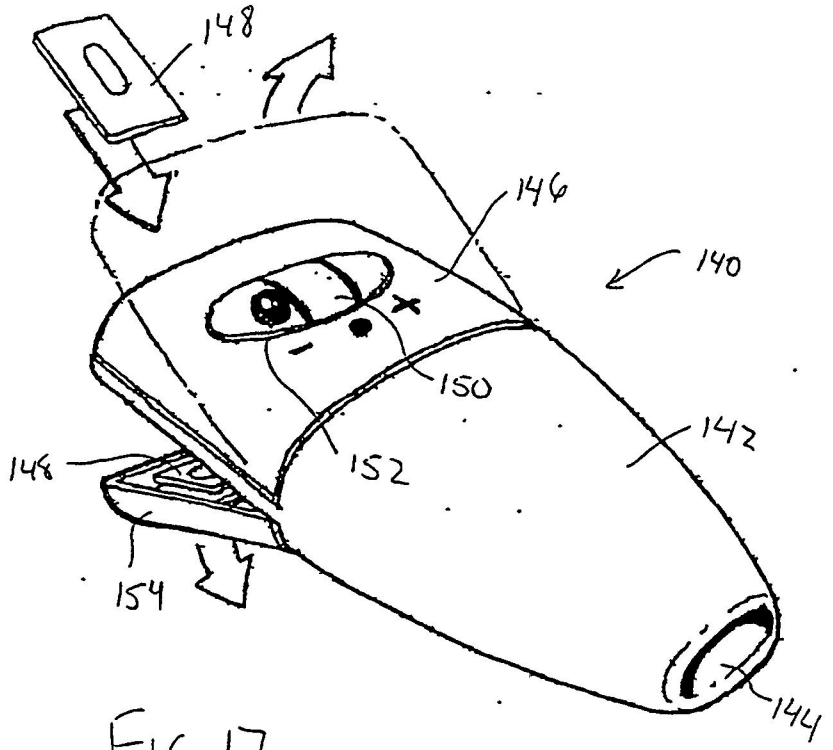

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FIG. 17

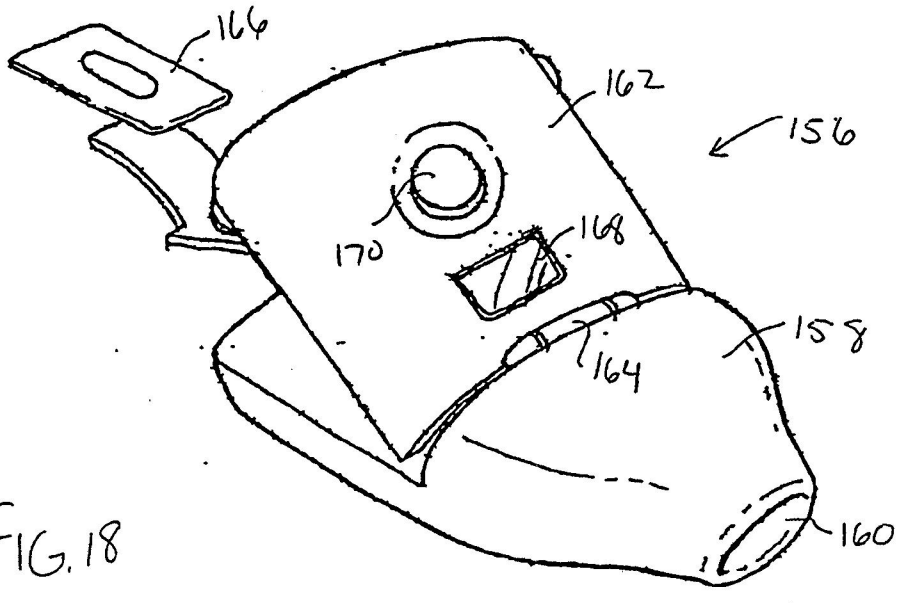

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FIG. 18

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FIG. 19B

FIG. 19

FIG. 19A

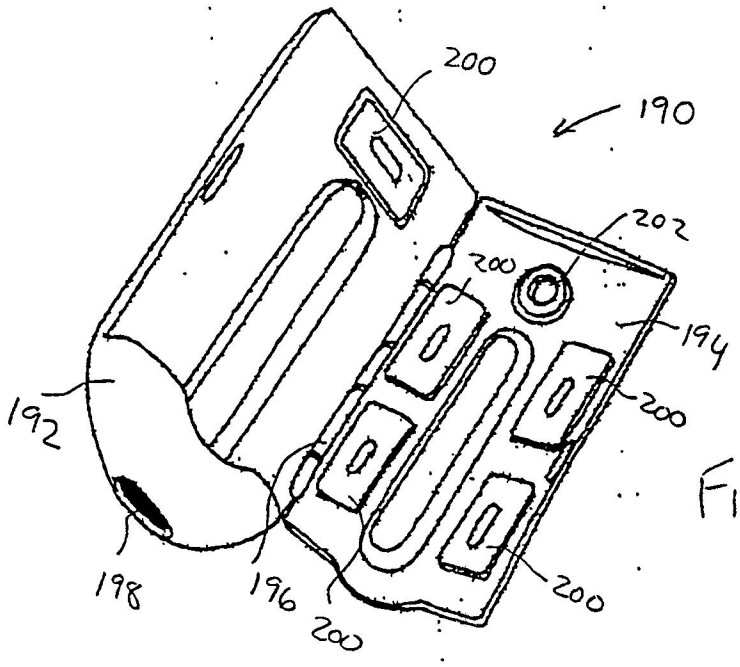


FIG. 20A

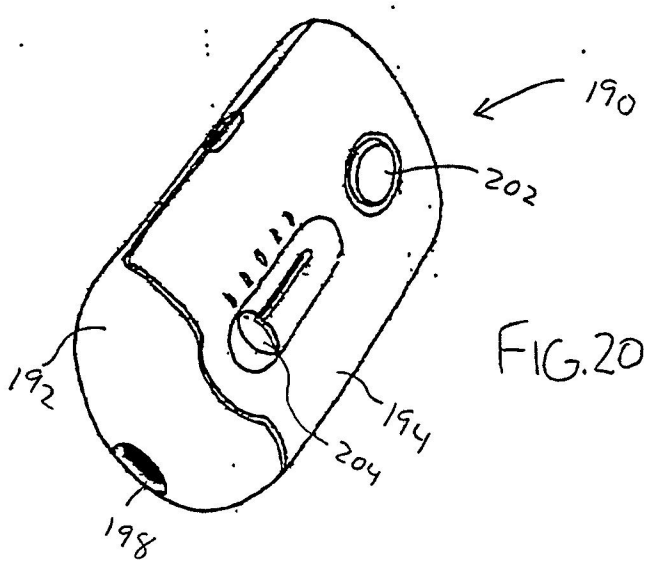


FIG. 20

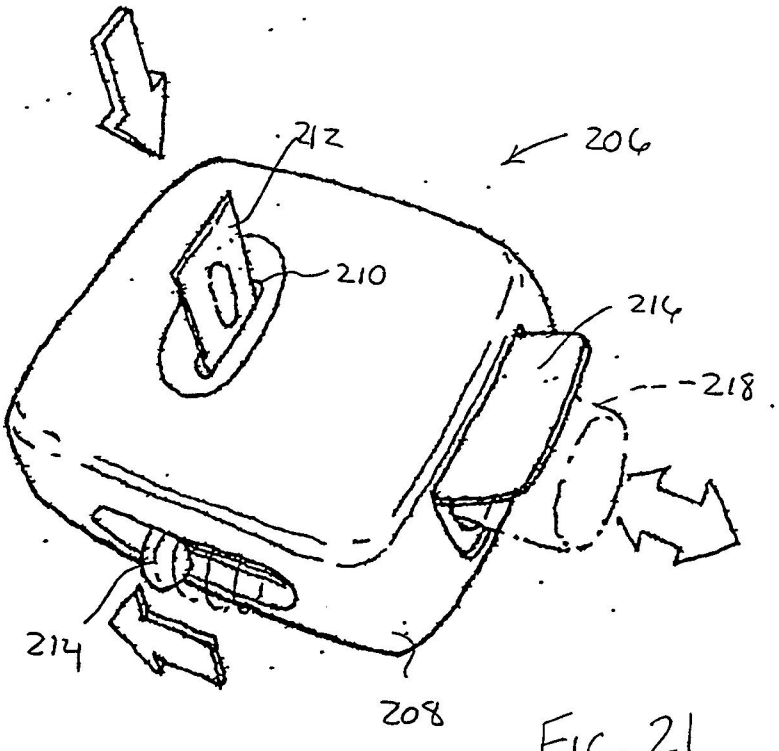


FIG. 21

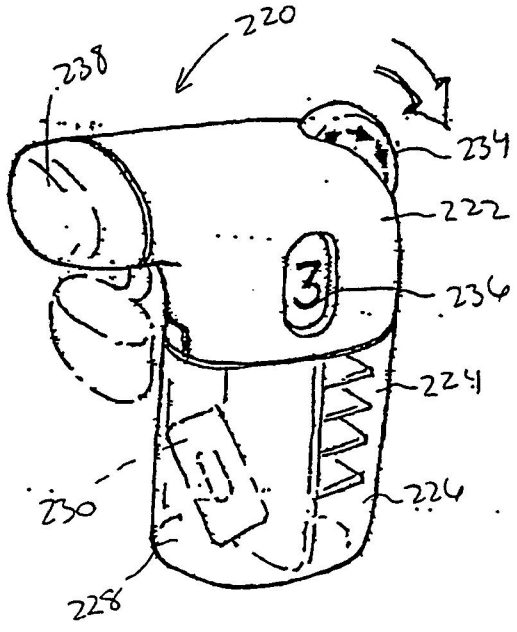


FIG. 22

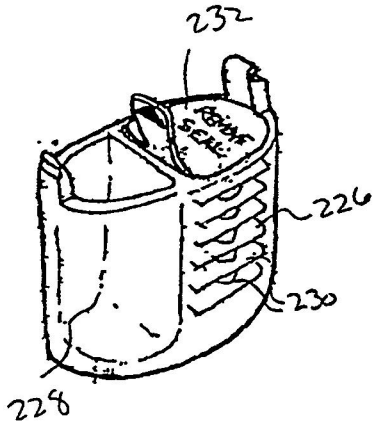


FIG 22A

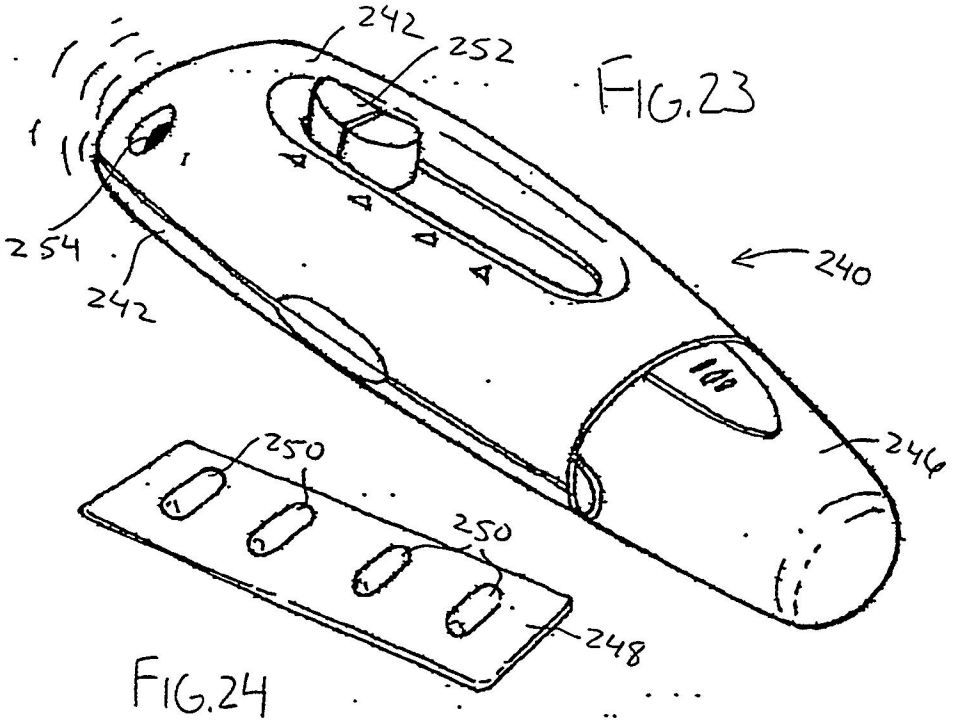


FIG.23

FIG.24

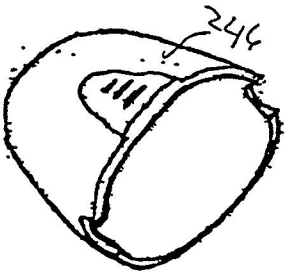


FIG.23A

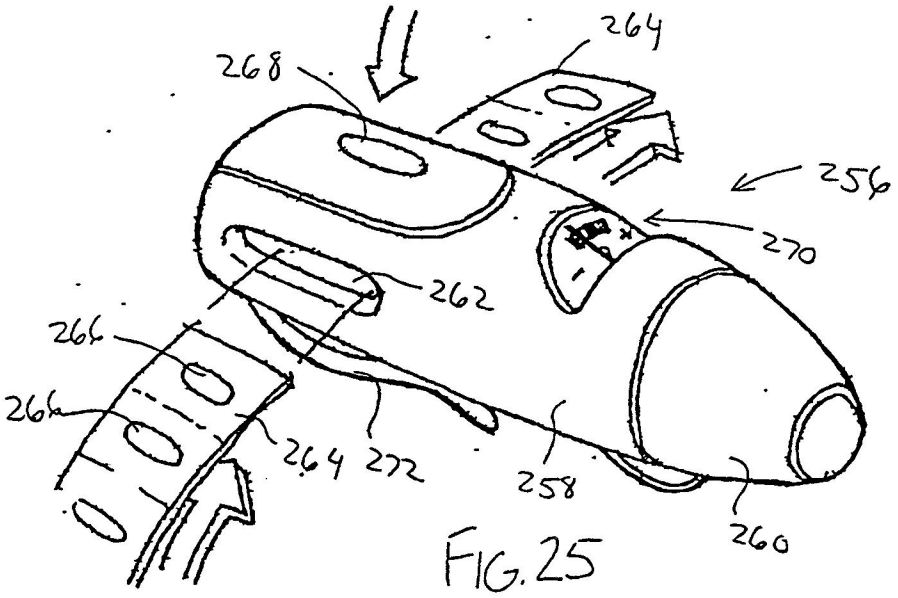

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FIG. 25

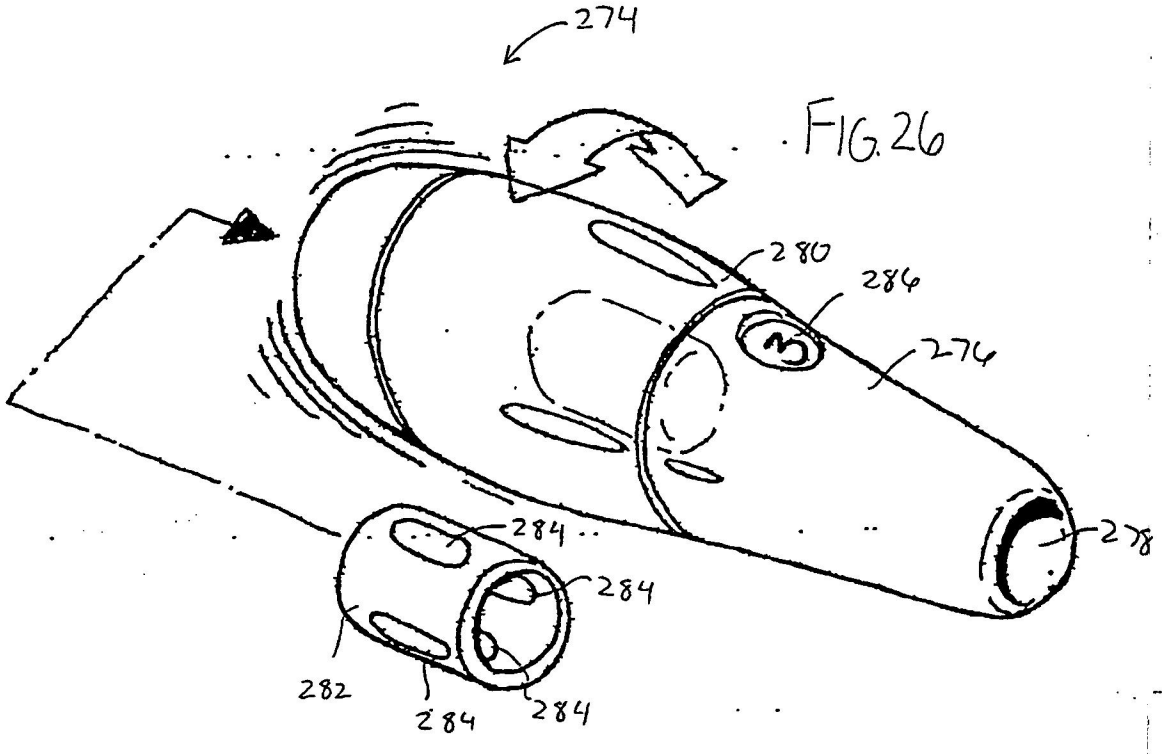

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FIG. 26

TRADUCCION : Se traduce la carátula y las reivindicaciones anexas a una copia de la solicitud de patente estadounidense No. 60/198.060, escrita en inglés. Para el invento denominado: Sistemas y métodos para aerosolizar formulaciones farmacéuticas.

LOS ESTADOS UNIDOS DE AMÉRICA
A TODOS AQUELLOS A QUIENES LA PRESENTE CONCIERNE
DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Patentes y Marcas de los Estados Unidos

2 de Agosto de 2000

LA PRESENTE ES PARA CERTIFICAR QUE LA ANEXA A ESTA ES UNA COPIA FIEL DE LOS REGISTROS DE LA OFICINA DE LAS PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE IDENTIFICADA MAS ADELANTE QUE SATISFACEN LOS REQUISITOS PARA QUE SE OTORGUE UNA FECHA DE PRIORIDAD BAJO 35 USC 111.

SOLICITUD NÚMERO : 60/198.060
FECHA DE PRESENTACIÓN : 18 de Abril de 2000

Por la Autoridad del
COMISIONADO DE PATENTES Y MARCAS

(RUBRICA)

_____

Funcionario Certificador.

SELLO EN RELIEVE

REIVINDICACIONES

1. Método para aerosolizar una formulación farmacéutica, el método comprende:

Evitar que fluyan gases respiratorios a los pulmones cuando se intenta inhalar y luego abruptamente permitir que los gases respiratorios fluyan a los pulmones; y

Utilizar el flujo de los gases respiratorios para extraer una formulación farmacéutica de un receptáculo y ubicar la formulación farmacéutica dentro del flujo de los gases respiratorios para formar un aerosol.

2. Un método según la reivindicación 1, que comprende además limitar el flujo de gases respiratorios a un índice que sea menor que cierto índice durante un cierto tiempo.

3. Un método según la reivindicación 2, en donde el índice es menor de aproximadamente 15L/min y el tiempo está en el rango de aproximadamente 0,5 segundos a aproximadamente 5 segundos.

4. Un método como en la reivindicación 2, en donde el índice es menor de aproximadamente 8L/min y el tiempo está en el rango de aproximadamente 0,5 segundos a aproximadamente 5 segundos.

5. Un método como en la reivindicación 2, en donde el cierto índice permite un volumen inhalado que está en el rango de aproximadamente 125mL a aproximadamente 1,25L.

6. Un método según la reivindicación 1, en donde en la etapa de evitar el flujo comprende además ubicar una válvula dentro de una vía aérea que conduce a los pulmones y a oír la válvula para permitir que los gases respiratorios fluyan a los pulmones.

7. El método según la reivindicación 6, que comprende además abrir la válvula cuando se excede el umbral de vacío de accionamiento originado por el intento de inhalación.

8. Un método según la reivindicación 7, en donde el umbral de vacío de accionamiento está en el rango de aproximadamente 20 cm de H_2O a aproximadamente 60 cm de H_2O.

9. Un método según la reivindicación 2, en donde la etapa de limitar el flujo comprende proporcionar retroalimentación cuando se produce un índice de flujo excesivo para permitirle al usuario ajustar su índice de inhalación.

10. Un método según la reivindicación 2, en donde la etapa de limitar el flujo comprende regular el tamaño de una vía aérea que conduzca a los pulmones.

11. Un método según la reivindicación 10, que comprende además regular el tamaño de la vía aérea para permitir un índice de flujo creciente después que ha pasado cierto tiempo.

12. Un método según la reivindicación 1, en donde la formulación farmacéutica comprende un medicamento en polvo, y comprende además el uso del flujo de los gases respiratorios para desaglomerar el polvo extraído.

13. Un dispositivo de aerosolización que comprende:

una carcasa que define una vía aérea;

Un mecanismo de acoplamiento adaptado para acoplar un receptáculo que contiene una formulación farmacéutica a la vía aérea; y

Una válvula para evitar que los gases respiratorios fluyan a través de la vía aérea hasta que se excede el umbral de vacío de accionamiento en cuyo momento la válvula se abre para permitirle a los gases respiratorios fluir a través de la vía aérea y extraer la formulación farmacéutica del receptáculo para formar un aerosol.

14. Un dispositivo según la reivindicación 13, que comprende además un sistema de regulación para regular el flujo de gases respiratorios a través de la vía aérea a un cierto índice.

15. Un dispositivo según la reivindicación 14, en donde el sistema de regulación se configura para limitar el flujo a un índice que es menor de aproximadamente 15L/min. Durante un cierto tiempo o un cierto volumen inhalado.

16. Un dispositivo según la reivindicación 14, en donde el sistema de regulación comprende un mecanismo de retroalimentación para proporcionar información sobre el índice de flujo de los gases respiratorios.

17. Dispositivo según la reivindicación 16, en donde el mecanismo de retroalimentación comprende un pito en comunicación con la vía aérea.

18. Un dispositivo según la reivindicación 14, en donde el sistema de regulación comprende un miembro restrictivo dispuesto en la vía aérea, el miembro restrictivo define un orificio de cierto tamaño para limitar el flujo de gases respiratorios a través de la vía aérea.

19. Un dispositivo según la reivindicación 14, en donde el sistema de regulación comprende un mecanismo de restricción para limitar el tamaño de la vía aérea.

20. Un dispositivo según la reivindicación 19, en donde el mecanismo de restricción es ajustable para variar el índice de flujo de los gases respiratorios a través de la vía aérea.

21. Un dispositivo según la reivindicación 20, en donde el sistema de regulación comprende además un sistema de control para ajustar el logaritmo de restricción.

22. Un dispositivo según la reivindicación 21, en donde el sistema de control se configura para limitar el flujo a un cierto índice durante un cierto tiempo o un volumen inhalado y luego ajustar el mecanismo de restricción para permitir un flujo creciente de gases respiratorios a través de la vía aérea.

23. Un dispositivo según la reivindicación 13, en donde el umbral de vacío de accionamiento de la válvula está en un rango de aproximadamente 20 cm de H_2O a aproximadamente 60 cm de H_2O.

24. Un dispositivo según la reivindicación 13, que comprende además un mecanismo de desaglomeración dispuesto en la vía aérea corriente abajo del receptáculo para desaglomerar la formulación farmacéutica extraída.

25. Un dispositivo según la reivindicación 3, donde la válvula se adapta a estar dispuesta dentro del receptáculo.

26. Un sistema de aerosolización que comprende:

Un receptáculo que comprende una cámara que tiene una formulación farmacéutica y una válvula de umbral;

Una carcasa que define una vía aérea; y

Un mecanismo de acoplamiento para ubicar la válvula a través de la vía aérea y ubicar la formación farmacéutica para encontrar comunicación con la vía aérea;

En donde la válvula de umbral se configura para abrirse cuando el umbral de vacío se accede al umbral de vacío de accionamiento para permitirle a los gases respiratorios fluir a través de la vía aérea y extraer la formulación farmacéutica de la cámara para formar un aerosol.

27. Un sistema según la reivindicación 26, en donde la formulación farmacéutica comprende un medicamento en polvo.

28. Un sistema según la reivindicación 26, que comprende además un sistema de regulación para regular el flujo de gases respiratorios a través de la vía aérea.

29. Un receptáculo que comprende:

Un cuerpo de receptáculo que define una actividad incluida en un a tapa de acceso penetrable; y

Una válvula de umbral acoplada al cuerpo del receptáculo.

30. Un receptáculo según la reivindicación 29, en donde la válvula de umbral se configura para abrirse cuando se experimenta un vacío de al menos 40 cm de H_2O.

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Industria y Comercio
SUPERINTENDENCIA

2do. EXAMEN DE FORMA PATENTE DE INVENCION

Folio 358

Radicación no 00-48974

Concepto Técnico no **1894**
Clasificación Internacional de Patentes: B05B 001/00

Practicado el examen de acuerdo a lo establecido en el Art. 38 de la Decisión 486 se determinó que esta solicitud de **Patente de Invención:**

SI [✓] NO [ ] Contiene un resumen de la invención (Art.26-e).

SI [✓] NO [ ] Contiene el título o nombre de la invención (Art.27-d).

SI [✓] NO [ ] Contiene la descripción de la invención (Art.26-b).

SI [✓] NO [ ] NO ES APLICABLE [ ] Contiene los dibujos necesarios para comprender la invención (Art.26-d)

SI [✓] NO [ ] Contiene una o más reivindicaciones. (Art.26-c).

SI [ ] NO [ ] NO ES APLICABLE [✓] Han sido desarrollados los productos y/o procedimientos a partir de recursos genéticos o de sus productos derivados de los que cualquiera de los Países Miembros es país de origen. (Art. 26- h).

SI [ ] NO [ ] NO ES APLICABLE [✓] Los productos y/o procedimientos han sido obtenidos o desarrollados a partir de los conocimientos tradicionales de las comunidades indígenas, afroamericanas, o locales de los países miembros, de acuerdo a lo establecido en la Decisión 391 y sus modificaciones y reglamentaciones vigentes.(Art.26-i).

SI [ ] NO [✓] La invención se refiere a un producto relativo a un material biológico. (Art.26-J).

SI [✓] NO [ ] NO ES APLICABLE [ ] La prioridad coincide con la materia reivindicada.

SI [✓] NO [ ] CUMPLE LOS REQUISITOS TÉCNICOS

OBSERVACIONES Y OTROS: SI [ ] NO [ ] ver hoja(s) anexa(s)

- CAMBIO FOLIOS 9, 16, 39, 46, 69, 79 y 89 CAPITULO DESCRIPTIVO, POR NUEVOS FOLIOS 196 - 202
- CAMBIO FOLIOS 115, 119, 125, 127 CAPITULO REIVINDICATORIO, POR NUEVOS FOLIOS 203 - 206
- NUEVOS DIBUJOS, FOLIOS: 207 - 252
-

EXAMINADOR TÉCNICO
202051

Bogotá D. C., diciembre 20 de 2002

Industria y Comercio
SUPERINTENDENCIA

354

Folio 359

416.
2003/01/20

2020
Bogotá DC

Doctor(a)
EMILIO FERRERO
Apoderado(a)

REFERENCIA:	Radicación No.	00-48974
	Trámite	002
	Evento	001
	Actuación	416
	Oficio No.	0093
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486 de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la misma Decisión.

Cúmplase
Dado en Bogotá DC, 20 ENE. 2003

CLARA CASTELLANOS DE JAIMES
Jefe (E) de la División de Nuevas Creaciones

202051