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(54) **METHODS AND APPARATUS FOR THE ENHANCED DELIVERY OF PHYSIOLOGIC AGENTS TO TISSUE SURFACES**

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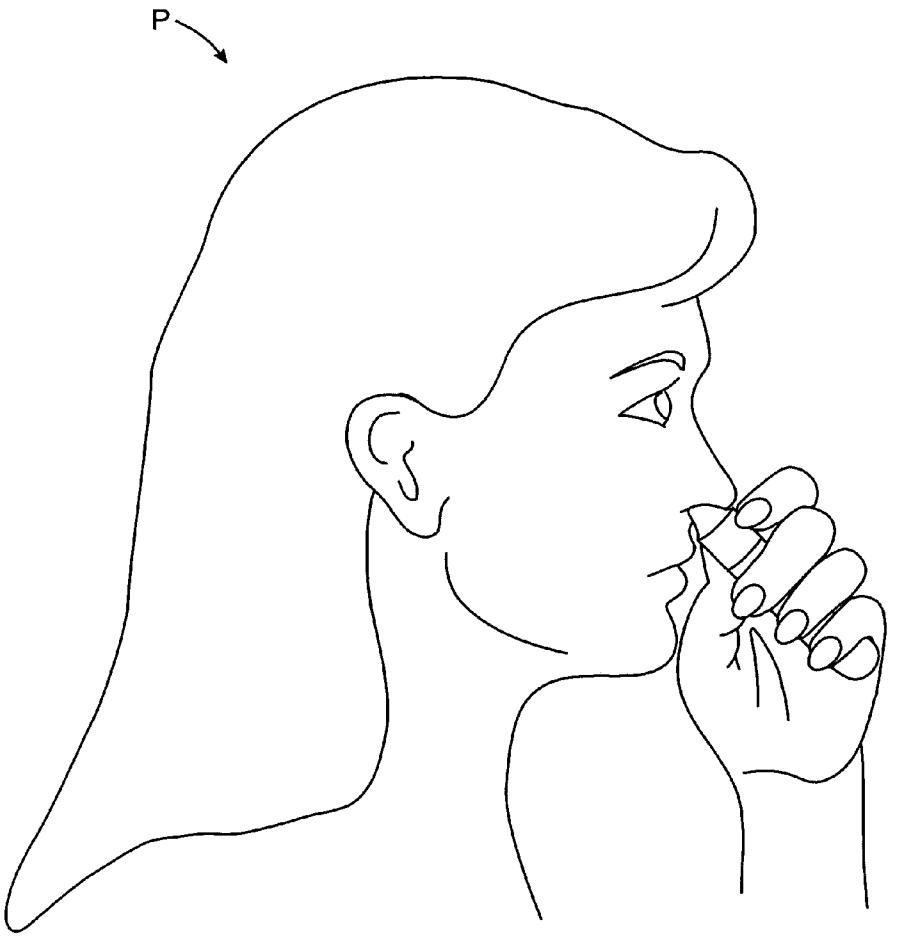
(57) **ABSTRACT**

Apparatus and methods deliver physiologically active agents in the presence of adjuvant gases. The adjuvant gases can enhance the effectiveness of the drug, lower the dosage of drug or concentration of drug necessary to achieve a therapeutic result, or both. Exemplary adjuvant gases include carbon dioxide, nitric oxide, nitrous oxide, and dilute acid gases.



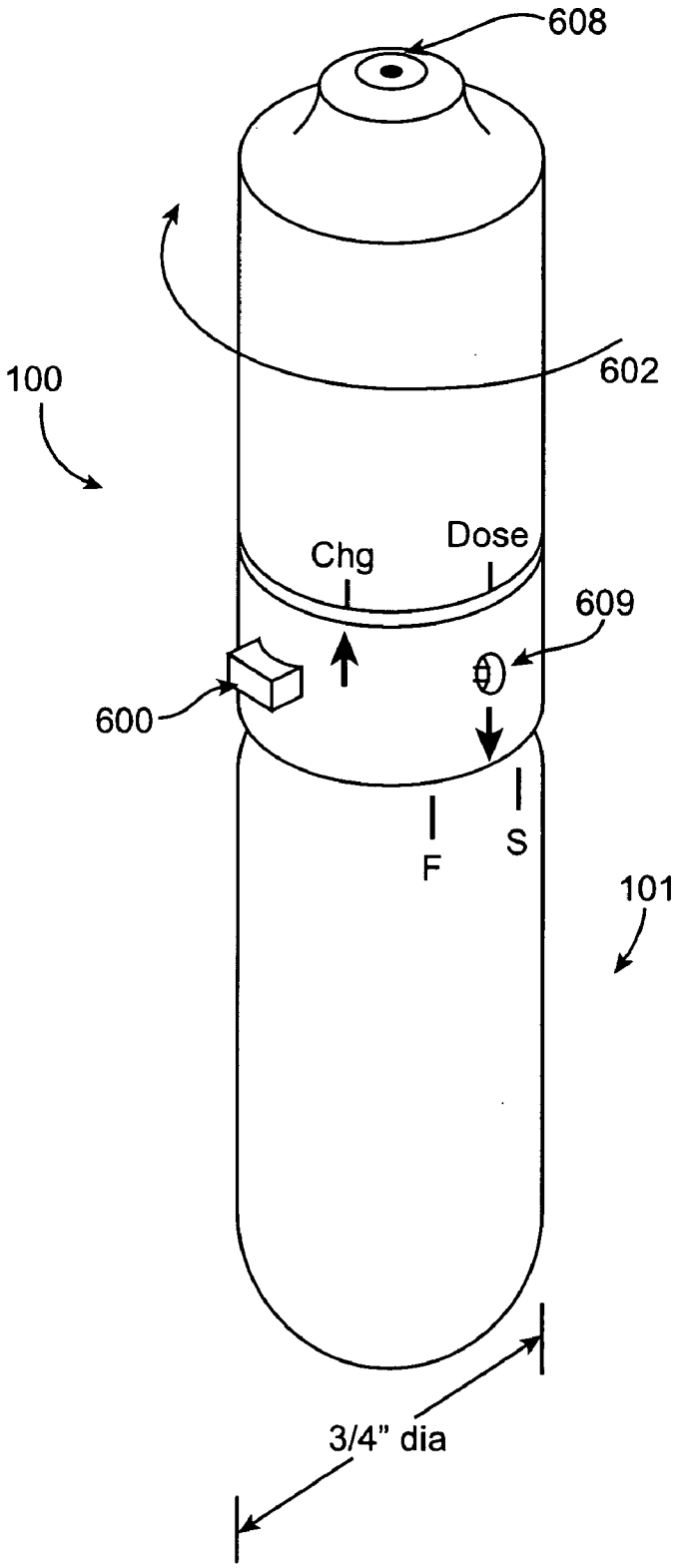


FIG. 1

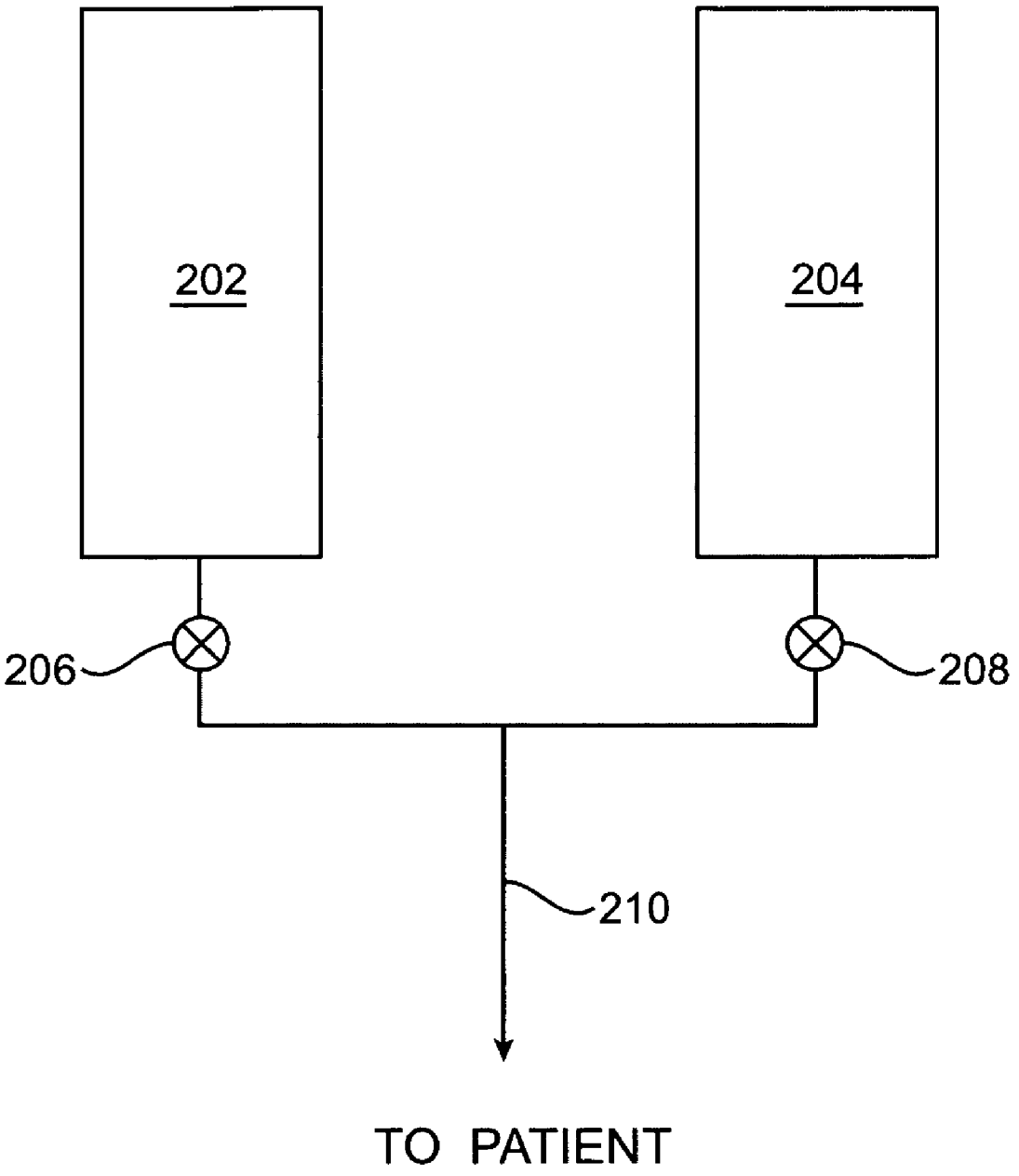


FIG. 2

FIG. 3A

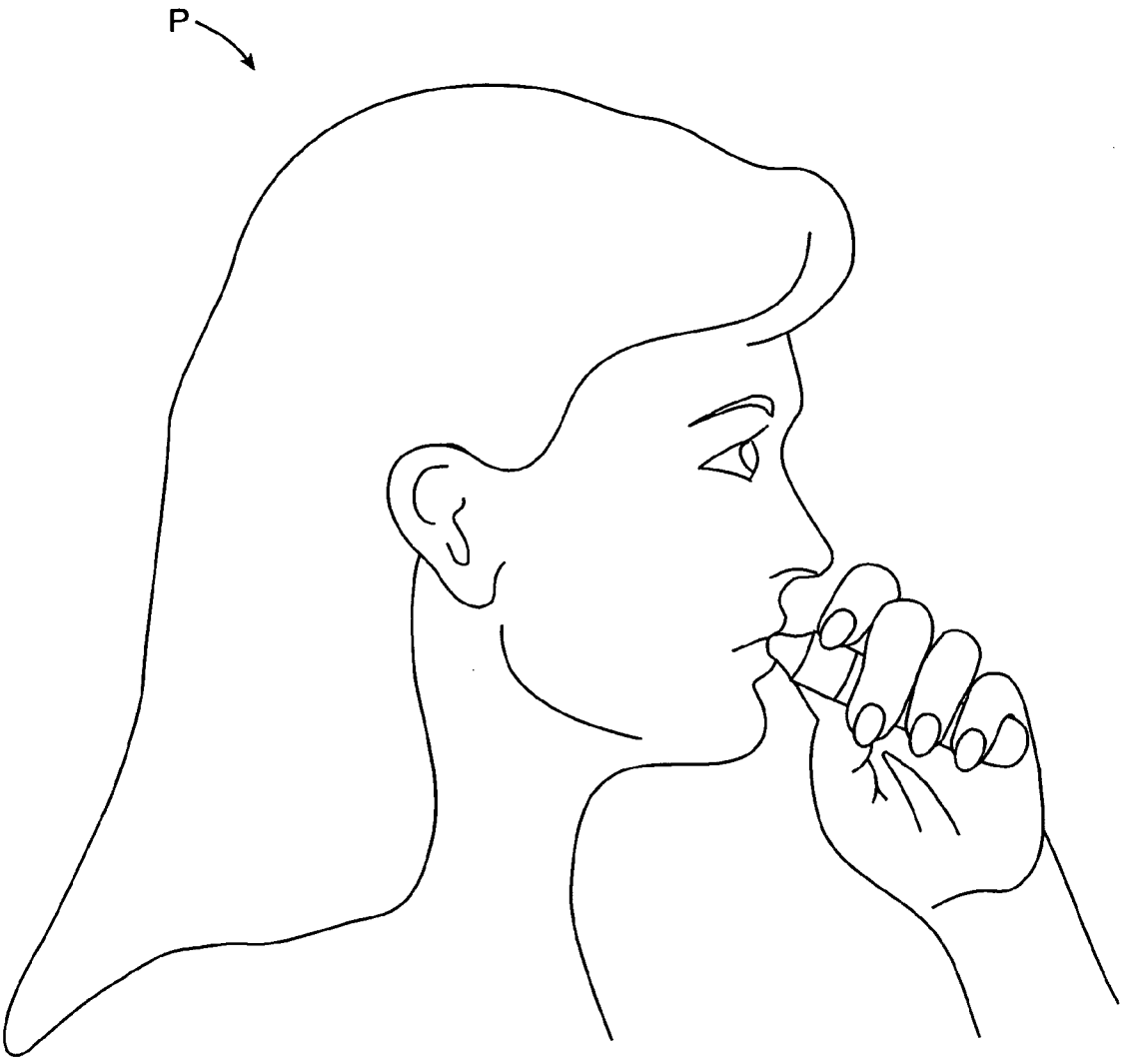


FIG. 3B

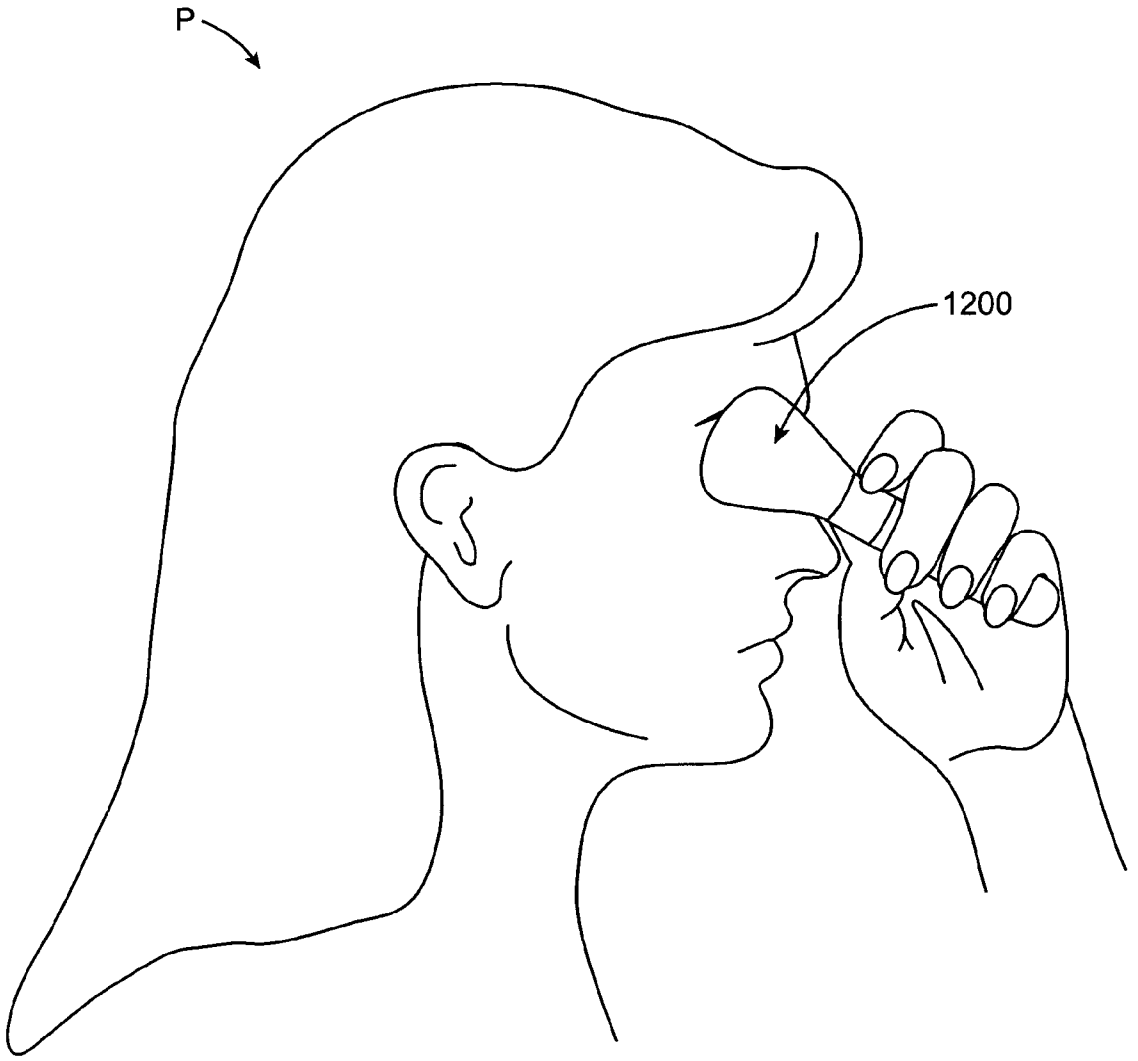


FIG. 3C

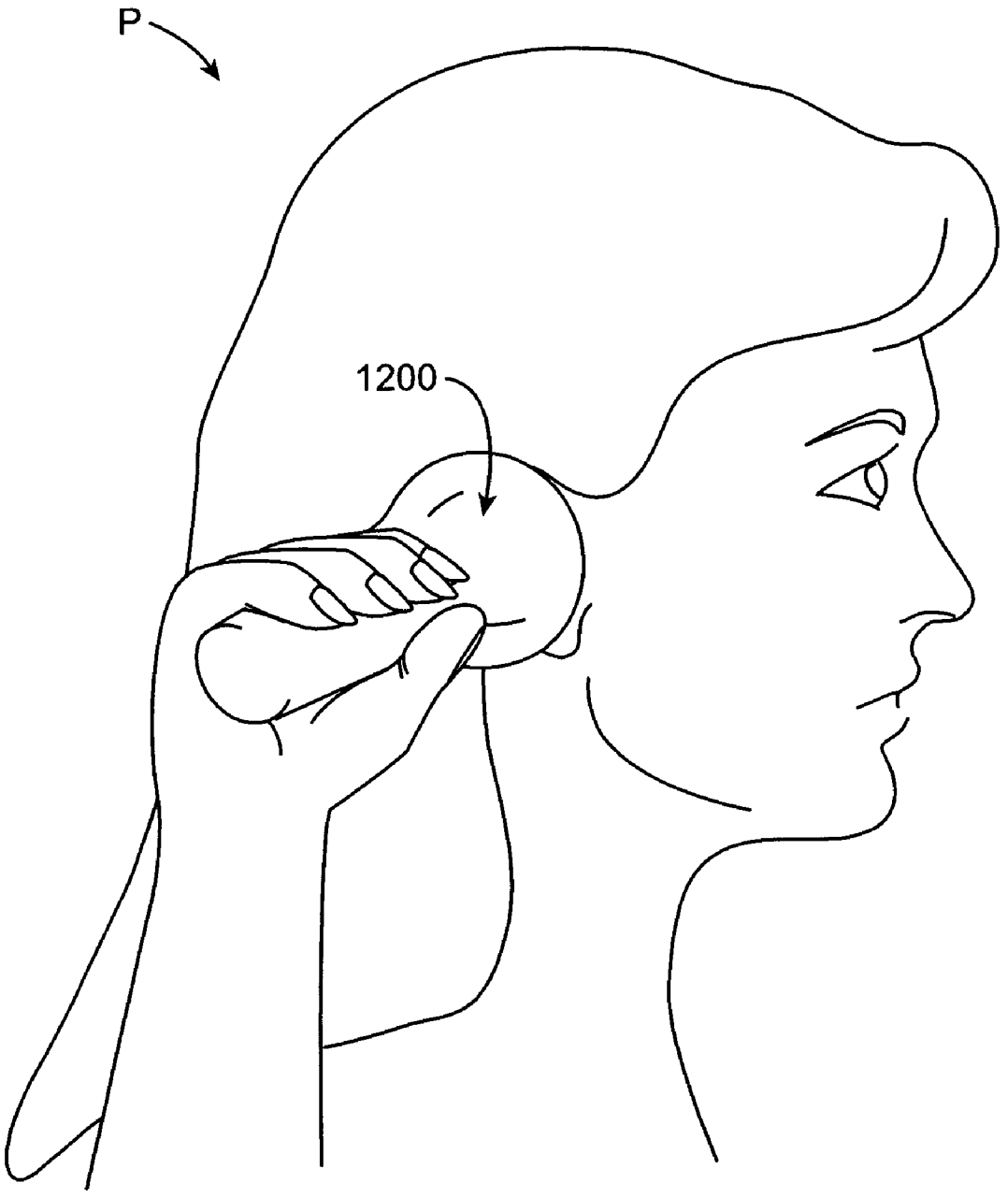


FIG. 3D

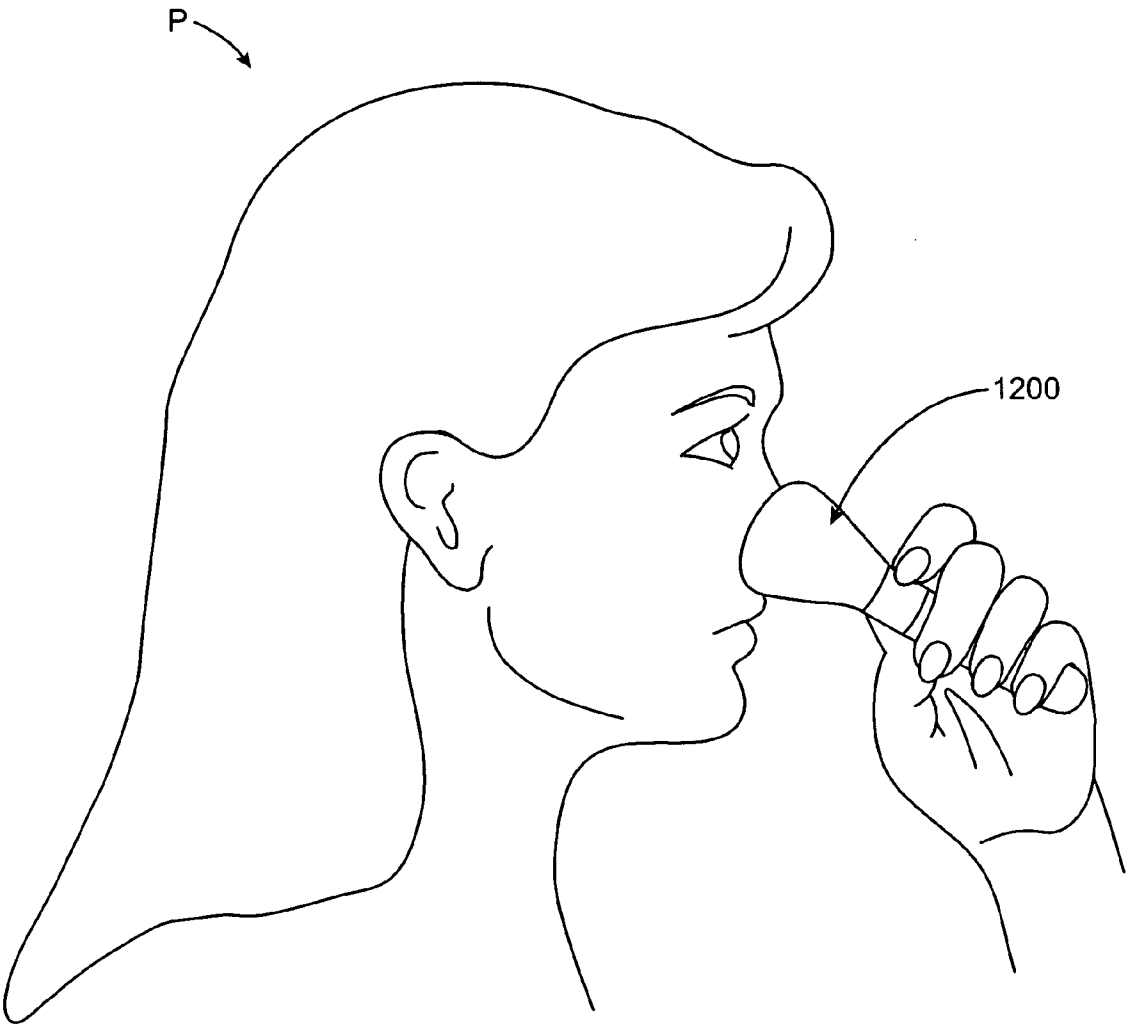


FIG. 3E

METHODS AND APPARATUS FOR THE ENHANCED DELIVERY OF PHYSIOLOGIC AGENTS TO TISSUE SURFACES

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. application Ser. No. 09/708,186 (Attorney Docket No. 020017-000310US), filed Nov. 7, 2000 (now U.S. Pat. No. _____), which claimed the benefit of U.S. Provisional Patent Application Nos. 60/164,125, filed on Nov. 8, 1999 and 60/185,495, filed on Feb. 28, 2000, each of which is incorporated by reference herein.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] The present invention relates to drug delivery. More particularly, the present invention relates to methods and apparatus for delivering physiologically active agents to mucosal and other tissue surfaces in the presence of adjuvant gases.

[0004] Drug delivery to mucosal surfaces, such as the mucosa of the nose, is well known. While in some cases drugs delivered to the nose and other mucosal surfaces are intended to have local effect, more often such transmucosal drug delivery is intended for systemic administration. In either case, penetration of the drug into or through the mucosa is limited by the ability of the particular drug to pass into or through the mucosal cell structure. Such resistance from the mucosal cell structure can result in slowing of the delivery, the need to use higher dosages of the drug, or in the case of larger molecules, the inability to deliver via a nasal or other mucosal route.

[0005] For these reasons, it would be desirable to provide improved methods and systems for transmucosal drug delivery in the nose and other organs. It would be desirable if the concentration of drug being delivered could be lowered while achieving an equivalent local or systemic physiologic effect. It would be further desirable if the activity or effective delivery of the drug could be enhanced without the need to raise the dosage or drug concentration. At least some of these objectives will be met by the invention described and claimed hereinbelow.

[0006] 2. Description of Background Art

[0007] Inhalation devices, systems and methods for delivering carbon dioxide and other gases and aerosols to patients, with and without co-delivery of a drug are described in U.S. Pat. Nos. 3,776,227; 3,513,843; 3,974,830; 4,137,914; 4,554,916; 5,262,180; 5,485,827; 5,570,683, 6,581,539; and 6,652,479. While some methods and devices provide for co-delivery of a drug and carbon dioxide or other gases, the purpose is usually not potentiation. For example, carbon dioxide may be used as a safe propellant, as shown in Wetterlin, U.S. Pat. No. 4,137,914. See also copending application Ser. Nos. 09/614,389 (Attorney Docket No. 020017-00011US); 10/666,947 (Attorney Docket No. 020017-000420US); and 10/666,562 (Attorney Docket No. 020017-000430US), the full disclosures of which are incorporated herein by reference.

[0008] Additional background art may be found in the following references: Guyton A C, Hall J E. *Textbook of Medical Physiology*. Ninth Ed., W.B. Saunders Co., Philadelphia, 1996; Tang A, Rayner M, Nadel J. "Effect of CO_2 on serotonin-induced contraction of isolated smooth muscle. *Clin Research* 20:243, 1972; Qi S, Yang Z, He B. An experiment study of reversed pulmonary hypertension with inhaled nitric oxide on smoke inhalation injury. *Chung Hua Wai Ko Tsa Chih* 35(1):56-8, January 1997; Loh E, Lankford E B, Polidori D J, Doering-Lubit E B, Hanson C W, Acker M A. Cardiovascular effects of inhaled nitric oxide in a canine model of cardiomyopathy. *Ann Thorac Surg* 67(5): 13 80-5, May 1999; Pagano D, Townend J N, Horton R, Smith C, Clutton-Brock T, Bonser R S. A comparison of inhaled nitric oxide with intravenous vasodilators in the assessment of pulmonary haemodynamics prior to cardiac transplantation. *Eur J Cardiothorac Surg* 10(12): 1120-6, 1996; and Sterling G, et al. Effect of CO2 and pH on bronchoconstriction caused by serotonin vs. acetylcholine. *J. of Appl. Physiology*, vol. 22, 1972.

BRIEF SUMMARY OF THE INVENTION

[0009] The present invention provides methods and systems for delivering physiologically active agents to tissue. The methods rely on contacting a tissue surface, typically a mucosal tissue surface, with the physiologically active agent while simultaneously and/or sequentially (either before or after) suffusing the same tissue surface with an adjuvant gas which promotes the uptake of the agent by the tissue and/or which promotes an activity of the agent. Mucosal surfaces targeted for drug delivery by the methods and apparatus of the present invention include the nasal mucosal surface, oral mucosal surfaces, ocular mucosal surfaces, auricular mucosal surfaces, and the like. The adjuvant gas may be any vasoactive, myoactive, or neuroactive gas or vapor which is capable of enhancing the efficacy of the agent being delivered and/or which is capable of reducing the dosage or concentration of agent being delivered while achieving an activity equivalent to a higher dosage and/or concentration. Preferred adjuvant gases include carbon dioxide, nitric oxide, nitrous oxide, and dilute acid gases, such as dilute hydrochloric acid, hydrofluoric acid, and the like. Particularly preferred are carbon dioxide gases having a relatively high concentration, typically greater than 10% by volume, usually greater than 20% by volume, and preferably greater than 25% by volume and often being as great as 80% by volume, 90% by volume, and in many instances being substantially pure. The adjuvant gases may be used in combinations of two or more adjuvant gases and/or may be combined with physiologically inert gases such as nitrogen, to control concentration of the active gases.

[0010] The physiologically active agent will be in a form which is capable of being delivered to the mucosal or other tissue surface, usually being in the form of a gas, vapor, liquid, mist, or powder. In certain instances, however, the drug can be in the form of a pill or other conventional solid dosage form which may be placed on the mucosal or other surface, e.g., beneath the tongue when the oral cavity is to be suffused with the adjuvant gas. Physiologically active agents which may be delivered include drugs selected from the group consisting of nitroglycerin, triptans, imidazopyridines (such as zolpidem available under the brand name Ambein®), 5-HT3 antagonists (such as ondansetron available under the brand name Zofran®), epinephrine, angiotensin II, atrophine, apomorphine, opioids, and the like.

[0011] Systems according to the present invention for delivering physiologically active substances to a mucosal surface comprise a source of an adjuvant gas and a source of the physiologically active substance, typically in fluid or other deliverable form. The systems may comprise some mechanism, structure, or the like, for delivering both the adjuvant gas and the physiologically active substance to the mucosal surface. Usually, the delivering structure will comprise a hand-held dispenser, for example where the dispenser includes a pressurized source of the adjuvant gas and a valve assembly for releasing the gas at a controlled flow rate, typically in the range from 0.5 cc/sec to 20 cc/sec in the case of high concentration of carbon dioxide. The physiologically active substance may be dissolved or suspended in the pressurized adjuvant gas for simultaneous delivery. Alternatively, the physiologically active substance may be delivered from a separate receptacle, either through the same or a different delivery path. Often, the adjuvant gas and the physiological gas, even when stored in separate receptacles, will be delivered through a common conduit and nozzle to allow for both simultaneous and sequential delivery. The exemplary adjuvant gases and physiologically active agents incorporated into these systems are the same as those set forth above with respect to the method.

[0012] The co-application of a drug with the adjuvant gas can be performed in at least three different ways. First, the drug and gas can be applied together locally by co-infusion and transmucosal co-absorption nasally, orally, and/or via the eye or ear. The form of the drug, of course, would need to be suitable for such infusion, for example, a fine powder or liquid. If the combination of the drug and gas is applied nasally or orally for local transmucosal absorption, the individual would preferably substantially inhibit passage of the drug and gas into his lungs and trachea by limiting inhalation of the gas and drug. Second, the drug and gas may be applied separately. The drug will be applied to infuse a nostril or nostrils, mouth, eye or ear or other body cavity having a mucosal surface with the gas before, during or after application of the drug.

[0013] As an example of the first method, a drug previously infused into the oral cavity, mouth, eyes, or ears by entraining with air, e.g., as an aerosol, powder, or spray, can be applied according to the present invention by entraining with CO_2, e.g., through aspiration of a drug-containing liquid or powder by CO_2. In particular, the action of drugs developed and presently used for relieving respiratory and headache symptoms may be improved by their co-infusion with CO_2, NO, or other adjuvant gases identified herein. The vasodilation which may be induced by CO_2 or NO may improve the speed and extent of absorption and distribution of the drug in the tissue in which it is co-absorbed with CO_2 or NO. This is beneficial through more rapid relief being obtained, and/or through reduction in the quantity of drug required to obtain the relief. Reduction in the required quantity of drug reduces the cost of treatment per dose and particularly reduces the side effects of such drugs, which are severe restrictions to their present use.

[0014] With respect to the second method, a particular benefit of co-application of such drugs with CO_2 or other adjuvant gases is that, in addition to the reduction of the total amount of drug required, the effect of the drug can be controlled or "modulated" in the course of its action after application. Infusion of CO_2 prior to drug application can increase the effectiveness and reduce the required quantity of the drug. Alternatively, infusion of CO_2 after application of a drug can enhance the effect of the drug at a controlled rate; i.e., if a more rapid or more intense effect of the drug is desired, CO_2 can be infused at the rate required to obtain the desired degree of enhancement. A particular advantage of such control is that the drug enhancement effect can be abruptly terminated, by ceasing CO_2 infusion, at the optimum level of beneficial drug effect that minimizes side or overdose effects. Also, since CO_2 is rapidly eliminated from the body via the bloodstream and respiration, the enhancement is reversible after CO_2 application is ceased, allowing continuous chronic adjustment of the drug effect.

[0015] An example of the beneficial regulation of the effect of a powerful drug by CO_2 inhalation or infusion is the co-application of CO_2 and nitroglycerin for the relief of acute angina and during onset of a heart attack (myocardial infarction). Nitroglycerin is a powerful vasodilator. Ordinarily persons suffering from angina or from symptoms of heart attack place a nitroglycerin tablet under their tongue (transmucosal delivery). If this is not adequate to relieve the symptoms within three minutes, another tablet is similarly ingested. After another three minutes, if relief is not obtained, this process is again repeated. If the symptoms then persist, a person should be taken immediately to a hospital for emergency treatment. Some persons are extremely sensitive to the side effects of nitroglycerin however, including severe blood pressure reduction that can result in dizziness and fainting, especially after ingesting the second tablet, at a time when good judgment and deliberate corrective action are required. A few minutes of delay can be crucial after the onset of a heart attack. With co-application, CO_2 can be infused after the first tablet to rapidly enhance and sustain its effects, possibly reducing the need for subsequent tablets. The effects of a second tablet of nitroglycerin can be initiated gradually and reversibly with CO_2 application to maintain and extend the optimum degree of pain relief without severe blood pressure reduction.

[0016] In all three methods cited only one physiologically active or other adjuvant gas is used; however, physiologically active gases may be used together, with or without drugs. For example, CO_2 has been found to relax both central and peripheral airways in asthmatic adults (Qi et al. (1997) supra). Similarly, in both in vivo and clinical tests, inhaled low dose NO has been found to be as effective as sodium nitroprusside and prostacyclin in reducing transpulmonary gradient and pulmonary vascular resistance, and is highly pulmonary vasoselective (Sterling et al., (1972) supra). NO has also been found to reverse pulmonary hypertension (Loh et al. (1999) and Pagano et al. (1996), supra). Therefore, NO and CO_2 can be co-applied to potentiate their respective actions or otherwise interact.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] **FIG. 1** illustrates an exemplary co-infusion device, illustrating the charge/dose and dose rate adjustment features.

[0018] **FIG. 2** is a schematic illustration of a delivery system incorporating separate receptacles for the adjuvant and the physiologically active agent, where the receptacles are joined through valves into a common delivery conduit.

[0019] **FIGS. 3A-3E** show application of the adjuvant gas optionally in combination with the physiologically active

agent to the nose, mouth, both nostrils, eye, and ear, using a gas dispenser according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0020] An exemplary carbon dioxide dispenser **100** comprising a carbon dioxide cartridge **101** is illustrated in **FIG. 1**. The embodiment of **FIG. 1** is described in greater detail in parent application Ser. No. 09/708,186, now U.S. Pat. No. _____, the full disclosure of which has previously been incorporated herein by reference. A user delivers a dose of carbon dioxide (optionally carrying the physiologically active agent to be delivered) by applying the top of the dispenser **608** to the user's nose or mouth and pushing a button **600** which releases an internal mechanism to allow the CO_2 to flow from the top of the dispenser **608**. The internal mechanism will lower the pressure of CO_2 in the cartridge and will control the flow rate within suitable ranges, typically from 2 to 10 cc/sec. The flow rate may be maintained for a suitable time period, typically at least 2 seconds when suffusing the nasal and sinus passages. The device is cocked by rotation as shown by arrow **602** and pushing the button **600** to deliver the dose by an automatic counter-rotation. The user may select the specific carbon dioxide flow rate by setting at a set screw through aperture **609**.

[0021] The hand-held dispenser **100** of **FIG. 1** may be used to deliver any of the adjuvant gases in accordance with the principles of the present invention. The adjuvant gases may be delivered with or without the physiologically active agent incorporated in the canister **101**. In cases where the adjuvant gas is to be delivered by itself, at some suitable concentration, the physiologically active agent will have to be delivered to the target mucosal or other tissue surface in some other manner. The physiologically active agent, for example, could be delivered by separate suffusion or infusion, by placing a liquid, powder, or the like over the tissue surface, by introducing a vapor, mist, or the like using conventional drug delivery vapor sources and misters, or the like. In some instances, such as the delivery of nitroglycerin, it would be possible to simply place a solid dosage form at the mucosal surface through which the drug is to be delivered. The adjuvant gas can be delivered before, during, and/or after any of the steps taken to deliver the physiologically active agent.

[0022] **FIG. 2** is a schematic illustration showing a system for simultaneous or sequential delivery of the adjuvant gas and physiologically active agent. The adjuvant gas is held in a separate cartridge or other container **202** while the physiologically active agent is held in a cartridge or other container **204**. Both the gas and the physiologically active agent will be in a gaseous, vapor, mist, or other flowable form which permits them to pass through associated valves **206** and **208** respectively, and thereafter through a conduit **210** which receives flow from both valves. The valves will be suitable for controlling both flow rate and pressure of the adjuvant gas and the physiologically active agent. It will be appreciated that more complex delivery systems can be provided including flow rate measurement, feedback control, temperature control, timers, and the like.

[0023] Referring now to **FIGS. 3A** to **3**E, a variety of ways for effecting mucosal infusion with the adjuvant gas, optionally combined with the physiologically active agent, are illustrated. The adjuvant gas is preferably infused at a flow rate in a range from 0.5 cc/sec-20 cc/sec, depending on the tolerance of the individual being treated. In some instances, the selected drug or other physiologically active agent can be delivered separately by suffusion, infusion, misting, the application of powder, or the like. As shown in **FIG. 3A**-B, the individual P then infuses oral and nasal mucous membranes by placing the source of low flow rate CO_2 or other appropriately physiologically active gas or vapor in or around a facial orifice, such as the mouth or nostril, while substantially inhibiting the flow of the CO_2 into the trachea and lungs by limiting inhalation of the CO_2. If the mouth is infused the gas is allowed to exit from the nostrils. Alternatively, one or both nostrils may be infused either by using the dispenser head shown in **FIG. 3B** or by use of a cup or similar device that covers both nostrils as shown in **FIG. 3E**. The gas is allowed to flow from a remaining open orifice, i.e., either the mouth, the uninfused nostril, or both as appropriate. Completely holding the breath is not necessary to substantially prevent inhalation of the CO_2. With practice, it is possible for the individual to breathe through an uninfused orifice: for example, if one nostril is infused and the gas is allowed to exit though the other nostril, it is possible for the individual to breathe through the mouth without substantial inhalation of the infused gas. The eye or eyes may also be infused using a cup as shown in **FIG. 3C** or merely by holding a hand over the eye and releasing the gas between the hand and the eye. Persons of ordinary skill in the art will appreciate that a double cup could be developed to infuse both eyes simultaneously, and similarly appropriate heads could be developed to infuse the mouth and one nostril. The ear or ears may also be infused as shown in **FIG. 3D**. Note that a similar process may be used with the first embodiment to infuse a mixture of a drug and gas into various facial orifices.

[0024] Infusion can be continued to the limit of tolerance or until the desired potentiation effect is realized. Since most individuals develop a temporary increased tolerance after extended applications or repeated applications, it may be possible and desirable to increase the duration of additional infusions after a few applications when all applications occur within a short time of each other, i.e., approximately 1 to 20 minutes between each application.

[0025] While the above is a complete description of the preferred embodiments of the invention, various alternatives, modifications, and equivalents may be used. Therefore, the above description should not be taken as limiting the scope of the invention which is defined by the appended claims.

What is claimed is:

1. A method for delivering physiologically active agents to tissue, said method comprising:

contacting a tissue surface with a physiologically active agent; and

suffusing the tissue surface with an adjuvant gas which promotes uptake of the agent by the tissue or vascular circulation and/or which promotes an activity of the agent.

2. A method as in claim 1, wherein at least a portion of the adjuvant gas is suffused simultaneously with contacting of at least a portion of the agent.

3. A method as in claim 1, wherein at least a portion of the adjuvant gas is suffused prior to contacting the agent.

4. A method as in claim 1, wherein at least a portion of the agent is suffused prior to contacting the adjuvant gas.

5. A method as in any one of claims 1 to 4, wherein contacting comprises placing a solid, powder, or liquid form of the agent on or over the tissue surface.

6. A method as in any one of claims 1 to 4, wherein contacting comprises suffusing the physiologically active agent in a gaseous, vapor, mist, or powder form.

7. A method as in any one of claims 1 to 4, wherein the adjuvant gas is selected from the group consisting of carbon dioxide, nitric oxide, nitrous oxide, and dilute acid gases.

8. A method as in any one of claims 1 to 4, wherein the physiologically active agent comprises at least one drug selected from the group consisting of nitroglycerin, triptans, imidazopyridines, 5-HT3 antagonists, epinephrine, angiotensin II, atrophine, apomorphine, and opioids.

9. A method as in any one of claims 1 to 4, wherein the tissue surface comprises a mucosal surface.

10. A method as in claim 4, wherein the mucosal surface is a nasal surface, an oral surface, an ocular tissue surface, or an auricular tissue surface.

11. A system for infusing a mucosal surface with a physiologically active substance, said system comprising:

a source of an adjuvant gas;

a source of the physiologically active substance in a fluid form; and

means for delivering both the adjuvant gas and the physiologically active substance to the mucosal surface.

12. A system as in claim 11, wherein the delivering means comprises a hand-held dispenser.

13. A system as in claim 12, wherein the hand-held dispenser comprises a receptacle of pressurized adjuvant gas and a valve assembly for releasing the gas at a controlled flow rate in the range from 0.5 cc/sec to 20 cc/sec.

14. A system as in claim 13, wherein the physiologically active substance is dissolved or suspended in the pressurized adjuvant gas.

15. A system as in claim 11, wherein the source of adjuvant gas comprises a first receptacle and the source of physiologically active substance comprises a second receptacle.

16. A system as in claim 15, wherein the means for delivering both the adjuvant gas and the physiologically active substance comprises a common conduit and nozzle for delivering the gas and substance simultaneously.

17. A system as in any one of claims 11 to 16, wherein the source of adjuvant gas comprises a gas selected from the group consisting of carbon dioxide, nitric oxide, nitrous oxide, and dilute acid gases.

18. A system as in claim 17, wherein the physiologically active agent comprises at least one drug selected from the group consisting of nitroglycerin, triptans, imidazopyridines, 5-HT3 antagonists, epinephrine, angiotensin II, atrophine, apomorphine, and opioids.

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