(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 May 2022 (19.05.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/104059 A1

(51) International Patent Classification:
A61K 9/00 (2006.01) *A61P 25/34* (2006.01)
A61K 31/465 (2006.01)

(21) International Application Number:
PCT/US2021/059140

(22) International Filing Date:
12 November 2021 (12.11.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

63/114,181	16 November 2020 (16.11.2020)	US
63/114,194	16 November 2020 (16.11.2020)	US
63/147,453	09 February 2021 (09.02.2021)	US
17225738	08 April 2021 (08.04.2021)	US
63/172,343	08 April 2021 (08.04.2021)	US
63/172,362	08 April 2021 (08.04.2021)	US
63/172,368	08 April 2021 (08.04.2021)	US
63/172,386	08 April 2021 (08.04.2021)	US
63/180,193	27 April 2021 (27.04.2021)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2022/104059 A1

(54) Title: RAPIDLY INFUSING COMPOSITIONS AND METHODS

(57) Abstract: A rapidly infusing composition that includes (a) a pharmaceutically acceptable binder and/or excipient system containing gelatin and mannitol, and (b) active therapeutic ingredient (ATI). Preferred rapidly infusing compositions are those formulated with nicotine or a derivative/analog thereof as the ATI. A method of administering an ATI such as nicotine or a derivative/analog thereof, to a subject is also disclosed. The subject is administered the rapidly infusing composition via the oral mucosa, for example, to reduce the subject's usage of more harmful nicotine delivery methods and/or nicotine withdrawal symptoms.

TITLE

RAPIDLY INFUSING COMPOSITIONS AND METHODS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Patent Application No. 17/225,738 filed April 08, 2021, which claims priority to U.S. Provisional Application No. 63/114,194 filed November 16, 2020; U.S. Provisional Application No. 63/114,181 filed November 16, 2020; U.S. Provisional Application No. 63/147,453 filed February 09, 2021; U.S. Provisional Application No. 63/172,343 filed April 08, 2021; U.S. Provisional Application No. 63/172,362 filed April 08, 2021; U.S. Provisional Application No. 63/172,386 filed April 08, 2021; U.S. Provisional Application No. 63/172,368 filed April 08, 2021; and U.S. Provisional Application No. 63/180,193 filed April 27, 2021; which are each incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

TECHNICAL FIELD

The present disclosure relates to a rapidly infusing composition for oral mucosal uptake, in particular, for administration of nicotine. Specifically, rapidly infusing compositions formulated with nicotine or a derivative/analog thereof as the active therapeutic ingredient (ATI), useful as a nicotine substitute for reducing a subject's usage of more harmful nicotine delivery methods and/or nicotine withdrawal symptoms.

DESCRIPTION OF THE RELATED ART

The "background" description provided herein is for the purpose of generally presenting the context of the disclosure. Work of the presently named inventors, to the extent it is described in this background section, as well as aspects of the description which may not

otherwise qualify as prior art at the time of filing, are neither expressly or impliedly admitted as prior art against the present invention.

Nicotine is the principal pharmacologically active component of tobacco. Users of tobacco products use them primarily for the experience they receive from nicotine, either in the form of tobacco smoke, chewing tobacco, or oral tobacco pouches. Smoking tobacco, such as with cigarettes, cigars, and pipes, is the most common method of consuming tobacco and adsorbing nicotine. However, smoking tobacco is associated with health hazards which are not necessarily related to the administration of nicotine itself. For example, there are over 4,000 toxic substances formed or released during the combustion of tobacco in cigarettes, such as carcinogenic nitrosamines, carbon monoxide, acrolein, and tar products, many of which are carcinogenic or associated with other disease states such as cardiovascular and pulmonary diseases.

Despite these known health risks, it is difficult for tobacco users to quit smoking, as nicotine is a strongly addictive substance that presents user's with potent nicotine withdrawal symptoms such as anxiety, irritability, nausea, fatigue, depression, insomnia, etc. As a result, there has been great interest in alternative means of administering nicotine without the toxic substances associated with the combustion of tobacco, that satisfies a user's nicotine dependence to facilitate reduction of or cessation from smoking.

Yet, nicotine replacement therapies often fail due to inadequate nicotine uptake and receptor saturation. Smoking a cigarette provides an almost immediate adsorption of nicotine into the smoker's blood which quickly reaches the brain. Here, the peak levels of nicotine allows binding to the nicotinic acetylcholine receptors (nAChRs) at around 90% saturation (Brody AL, Mandelkern MA, London ED, et al. Cigarette Smoking Saturates Brain α4β2 Nicotinic Acetylcholine Receptors. *Arch Gen Psychiatry.* 2006;63(8):907–914 — incorporated herein by reference in its entirety) which activates these receptors to release

dopamine, giving the smoker rapid satisfaction. Nicotine also appears to induce the release of endogenous opioids that activate opioid pathways in the reward system. These pharmacological actions are thought to be largely responsible for the strongly reinforcing effects of nicotine. The rapid delivery of nicotine and near immediate satisfying of nicotine cravings provided by peak receptor saturation from smoking tobacco has proven difficult to emulate using other nicotine administration modes.

For example, nicotine gum, nicotine lozenges, nicotine transdermal patches, as well as oral non-tobacco-based nicotine pouches (e.g., ZYN® products from Swedish Match or VELO™ products from Reynolds Vapor Company) are capable of providing a rather high steady state nicotine blood concentration, but they do not provide the rapid adsorption and peak nicotine levels obtained from smoking tobacco. As a result of nicotine release profiles being too slow, and in many cases nicotine release being incomplete (delivering only a fraction of the available nicotine to the user), many smokers find such products to be less satisfying, and thus an unacceptable alternative to smoking tobacco.

In addition to providing immediate relief from nicotine cravings, successful therapies for smoking cessation should also reduce the behavioral pattern associated with smoking (i.e., should be habit breaking). Many nicotine replacement therapies, including tobacco-smoke free inhalers (e.g., electronic cigarettes), smokeless tobacco products (e.g., chewing tobacco, snuff, and snus), oral non-tobacco-based nicotine pouches (e.g., ZYN® products from Swedish Match or VELO™ products from Reynolds Vapor Company), etc., are unsuccessful in facilitating the reduction of or cessation of nicotine product use, because these therapies replace one habit (i.e., smoking cigarettes) with another habit (e.g., smoking electronic cigarettes, dipping, snusing, etc.).

Further, many nicotine administration methods currently available to nicotine users are unhygienic, a problem exacerbated during the times of COVID-19 where personal

hygiene and sanitation are under intense scrutiny. For example, smokeless tobacco products (e.g., chewing tobacco, snuff, and snus), oral non-tobacco-based nicotine pouches, and nicotine gums each require a user to remove spent tobacco matter, pouches, or wads of gum base from their mouth after completion.

SUMMARY OF THE INVENTION

In view of the forgoing, there exists a need for new nicotine replacement therapies that do not advance or sustain behavioral habits such as those accompanying smoking tobacco, are sanitary and discreet, and that are capable of rapidly infusing nicotine into the user's bloodstream at high peak levels for receptor saturation and immediate relief of nicotine withdrawal symptoms.

Accordingly, it is an object of the present invention to provide novel rapidly infusing compositions formulated with nicotine or a suitable derivative/analog thereof that meet the above criteria.

It is another object of the present invention to provide novel processes for manufacturing the rapidly infusing composition.

It is another object of the present invention to provide novel methods of administering nicotine to a subject.

It is another object of the present invention to provide novel methods of reducing a subject's usage of more harmful nicotine delivery methods.

It is another object of the present invention to provide novel methods of reducing nicotine withdrawal symptoms in a subject.

It is another object of the present invention to provide novel methods to increase the quiet enjoyment of administering nicotine in a subject.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery of its Rapid Infusion Technology™ (RITe) platform through which nicotine or related derivatives/analogs can be administered via the oral mucosae, for rapid delivery of nicotine or a derivative/analog and immediate relief of nicotine withdrawal symptoms, and doing so without advancing or sustaining a behavioral pattern.

Thus, the present invention provides:

(1) A rapidly infusing composition, comprising:

a pharmaceutically acceptable binder and/or excipient system comprising gelatin and mannitol, and

nicotine.

(2) The rapidly infusing composition of (1), which is lyophilized.

(3) The rapidly infusing composition of (1) or (2), which has a disintegration time of approximately 1 to 30 seconds in deionized water maintained at 37° C ± 2° C.

(4) The rapidly infusing composition of any one of (1) to (3), which has a disintegration time of approximately 1 to 5 seconds in deionized water maintained at 37° C ± 2° C.

(5) The rapidly infusing composition of any one of (1) to (4), wherein the gelatin is present in the rapidly infusing composition in an amount of 10 to 35 wt.%, based on a total weight of the rapidly infusing composition on a dry basis.

(6) The rapidly infusing composition of any one of (1) to (5), wherein the gelatin is mammalian gelatin.

(7) The rapidly infusing composition of (6), wherein the mammalian gelatin is bovine gelatin.

(8) The rapidly infusing composition of any one of (1) to (7), wherein the mannitol is present in the rapidly infusing composition in an amount of 5 to 35 wt.%, based on a total weight of the rapidly infusing composition on a dry basis.

(9) The rapidly infusing composition of any one of (1) to (8), wherein the nicotine is present in the rapidly infusing composition in an amount of 0.1 to 25 wt.%, based on a total weight of the rapidly infusing composition on a dry basis.

(10) The rapidly infusing composition of any one of (1) to (9), wherein the nicotine is provided in the form of a nicotine salt or a nicotine complex.

(11) The rapidly infusing composition of (10), wherein the nicotine is provided in the form of the nicotine complex.

(12) The rapidly infusing composition of (10) or (11), wherein the nicotine complex is a nicotine cation exchange resin complex.

(13) The rapidly infusing composition of (12), wherein the nicotine cation exchange resin complex is nicotine polacrilex.

(14) The rapidly infusing composition of any one of (1) to (13), wherein the nicotine has a purity between 95 and 100% by weight on a basis of nicotine free base.

(15) The rapidly infusing composition of any one of (1) to (14), which is formulated with a solid form of nicotine.

(16) The rapidly infusing composition of any one of (1) to (15), wherein the rapidly infusing composition further comprises at least one selected from the group consisting of a sweetener, a flavorant, and a colorant.

(17) The rapidly infusing composition of (16), wherein the rapidly infusing composition comprises the flavorant, and the flavorant comprises a mixture of orange flavor and peppermint flavor.

(18) The rapidly infusing composition of (16) or (17), wherein the rapidly infusing composition comprises the sweetener, and the sweetener comprises a mixture of sucralose and acesulfame-K.

(19) A process for manufacturing the rapidly infusing composition of any one of (1) to (18), comprising:

dissolving gelatin and mannitol in water to form a solution;

adding the nicotine to the solution to form a drug product suspension; and

lyophilizing the drug product suspension to remove water and form the rapidly infusing composition.

(20) A method of administering nicotine to a subject, comprising administering to the subject in need thereof, via the oral mucosa, a therapeutically effective amount of the rapidly infusing composition of any one of (1) to (18).

(21) The method of (20), wherein the rapidly infusing composition is administered buccally to the subject via the buccal mucosa.

(22) The method of (20) or (21), wherein the therapeutically effective amount of the rapidly infusing composition is that which provides from 0.1 to 10 mg of nicotine per dose.

(23) The method of any one of (20) to (22), wherein the rapidly infusing composition is administered to the subject 1 to 10 times per day.

(24) The method of any one of (20) to (23), wherein the subject is a human.

(25) A method of reducing a subject's usage of more harmful nicotine delivery methods, comprising administering to the subject in need thereof, via the oral mucosa, a therapeutically effective amount of the rapidly infusing composition of any one of (1) to (18).

(26) The method of (25), wherein the rapidly infusing composition is administered buccally to the subject via the buccal mucosa.

(27) The method of (25) or (26), wherein the therapeutically effective amount of the rapidly infusing composition is that which provides from 0.1 to 10 mg of nicotine per dose.

(28) The method of any one of (25) to (27), wherein the rapidly infusing composition is administered to the subject 1 to 10 times per day.

(29) The method of any one of (25) to (28), wherein the subject is a human.

(30) A method of reducing nicotine withdrawal symptoms in a subject, comprising administering to the subject in need thereof, via the oral mucosa, a therapeutically effective amount of the rapidly infusing composition of any one of (1) to (18).

(31) The method of (30), wherein the rapidly infusing composition is administered buccally to the subject via the buccal mucosa.

(32) The method of (30) or (31), wherein the therapeutically effective amount of the rapidly infusing composition is that which provides from 0.1 to 10 mg of nicotine per dose.

(33) The method of any one of (30) to (32), wherein the rapidly infusing composition is administered to the subject 1 to 10 times per day.

(34) The method of any one of (30) to (33), wherein the subject is a human.

The foregoing paragraphs have been provided by way of general introduction, and are not intended to limit the scope of the following claims. The described embodiments, together with further advantages, will be best understood by reference to the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

In the following description, it is understood that other embodiments may be utilized and structural and operational changes may be made without departure from the scope of the present embodiments disclosed herein.

Definitions

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof where such isomers exist. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are within the scope of the disclosure. Many geometric isomers of C=C double bonds, C=N double bonds, ring systems, and the like can also be present, and all such stable isomers are contemplated in the present disclosure. Cis- and trans- (or E- and Z-) geometric isomers, when present, may be isolated as a mixture of isomers or as separated isomeric forms. Compounds referenced in the disclosure can be isolated in optically active or racemic forms. Optically active forms may be prepared by resolution of racemic forms or by synthesis from optically active starting materials. All processes used to prepare these compounds and intermediates made therein are considered to be part of the present disclosure. When enantiomeric or diastereomeric products are prepared, they may be separated by conventional methods, for example, by chromatography, fractional crystallization, or through the use of a chiral agent. Depending on the process conditions, the end products referenced in the present disclosure are obtained either in free (neutral) or salt form. Both the free form and the salts of these end products are within the scope of the disclosure. If so desired, one form of a compound may be converted into another form. A free base or acid may be converted into a salt; a salt may be converted into the free compound or another salt; a mixture of isomeric

compounds may be separated into the individual isomers. Compounds referenced in the present disclosure, free form and salts thereof, may exist in multiple tautomeric forms, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that all tautomeric forms, insofar as they may exist, are included within the disclosure. Further, a given chemical formula or name shall encompass all conformers, rotamers, or conformational isomers thereof where such isomers exist. Different conformations can have different energies, can usually interconvert, and are very rarely isolatable. There are some molecules that can be isolated in several conformations. For example, atropisomers are isomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. It should be understood that all conformers, rotamers, or conformational isomer forms, insofar as they may exist, are included within the present disclosure.

As used herein, the term "solvate" refers to a physical association of a referenced compound with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances, the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The solvent molecules in the solvate may be present in a regular arrangement and/or a non-ordered arrangement. The solvate may comprise either a stoichiometric or nonstoichiometric amount of the solvent molecules. Solvate encompasses both solution phase and isolable solvates. Exemplary solvent molecules which may form the solvate include, but are not limited to, water, methanol, ethanol, *n*-propanol, isopropanol, *n*-butanol, isobutanol, tert-butanol, ethyl acetate and other lower alkanols, glycerin, acetone, dichloromethane (DCM), dimethyl sulfoxide (DMSO), dimethyl acetate (DMA), dimethylformamide (DMF), isopropyl ether, acetonitrile, toluene, *N*-methylpyrrolidone

(NMP), tetrahydrofuran (THF), tetrahydropyran, other cyclic mono-, di- and tri-ethers, polyalkylene glycols (e.g., polyethylene glycol, polypropylene glycol, propylene glycol), and mixtures thereof in suitable proportions. Exemplary solvates include, but are not limited to, hydrates, ethanolates, methanolates, isopropanolates and mixtures thereof. Methods of solvation are generally known to those of ordinary skill in the art.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salt" refers to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids and phenols. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic, and the like. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting

the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non- aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Company, Easton, Pa. (1990)—which is incorporated herein by reference in its entirety.

When referencing a particular composition/material, the phrase "consists essentially of", means that the particular composition/material may include minor amounts of impurities so long as those impurities do not affect the basic and novel property of the invention—the ability to provide immediate relief of nicotine withdrawal symptoms.

As used herein, the terms "optional" or "optionally" means that the subsequently described event(s) can or cannot occur or the subsequently described component(s) may or may not be present (e.g., 0 wt.%).

The terms "administer", "administering", "administration", and the like, as used herein, refer to the methods that may be used to enable delivery of the active therapeutic ingredient (ATI) to the desired site of biological action. Routes or modes of administration are as set forth herein. In this context, the terms "treat", "treatment", and the like refers to the reduction or amelioration of severity of symptoms of the condition being treated; reduction of duration of symptoms of the condition being treated; reduction, inhibition, slowing, or arresting of the progression of symptoms associated with the condition; reduction of frequency of symptoms of the condition being treated; elimination of symptoms and/or underlying cause of the condition; prevention of the occurrence of symptoms of the condition; and/or causing regression of the condition.

The term "subject" and "user" are used interchangeably. As used herein, they refer to any subject for whom or which administration or therapy is desired. In most embodiments, the subject is a human.

The term "Rapid Infusion Technology™ (RITe) platform" or "rapidly infusing composition" as used herein means a solid dosage form containing medicinal substances that disintegrates rapidly in the oral cavity (when contacted with saliva) with no need for chewing or drinking/swallowing liquids (e.g., water, liquid carriers, saliva, etc.) to ingest these medicinal substances, with an *in-vitro* disintegration time of 30 second or less according to the United States Pharmacopeia (USP) <701> Disintegration Test performed in deionized water maintained at 37° C ± 2°. The disclosed rapidly infusing compositions are thus a different dosage form than, for example, a chewable tablet, a lozenge intended to be dissolved slowly in the mouth, or a tablet that should be swallowed whole with food or liquid.

The dosage amount and treatment duration are dependent on factors, such as bioavailability of a drug, administration mode, toxicity of a drug, gender, age, lifestyle, body weight, the use of other drugs and dietary supplements, the disease stage, tolerance and resistance of the body to the administered drug, etc., and then determined and adjusted accordingly. The terms "effective amount", "therapeutically effective amount", or "therapeutically effective dose" refer to a sufficient amount of an active therapeutic ingredient (ATI) being administered which provides the desired therapeutic or physiological effect or outcome, for example, the amount of ATI sufficient for relieving to some extent one or more nicotine withdrawal symptoms associated with smoking cessation. The result can be a reduction and/or alleviation of the signs or symptoms of a condition, or any other desired alteration of a biological system. Undesirable effects, e.g. side effects, are sometimes manifested along with the desired therapeutic effect; hence, a practitioner balances the potential benefits against the potential risks in determining what is an appropriate "effective

amount". The exact amount required will vary from subject to subject, depending on the age and general condition of the subject, mode of administration, and the like. An appropriate "effective amount" in any individual case may be determined by one of ordinary skill in the art using only routine experimentation, for example through the use of dose escalation studies.

As used herein, "active" nicotine refers to nicotine free base.

As used herein, "more harmful nicotine delivery methods" refers to nicotine delivery methods using tobacco products—including tobacco combustion products (e.g., cigarettes) and smokeless tobacco products (e.g., chewing tobacco, snuff, and snus)—as well as tobacco-smoke free inhalers (e.g., electronic cigarettes).

Rapid Infusion Technology™ (RITe) Platform

The present disclosure provides a therapeutic formulation presented in the form of a rapidly infusing composition which is suitable for administration of active therapeutic ingredients (ATIs) such as nicotine via a non-gastric mucosal surface. As described in more detail below, the novel RITe™ platform allows ATIs such as nicotine to be presented in unit dosage form for accurate dosing, rapid adsorption and onset of therapeutic effect, and in an easy-to-take format that does not mimic, and hence reinforce, the repetitive actions associated with other more harmful nicotine delivery methods. For example, the rapidly infusing composition may be presented in tablet form and packaged in individual blister units.

In particular, the RITe™ platform enables oral mucosal administration of ATIs in a solid dosage form directly into systemic circulation via the sublingual mucosa or the buccal mucosa. Administration may be carried out by simply placing the rapidly infusing composition directly in the buccal cavity (between the cheek and gum) or over the sublingual mucous gland (under the ventral surface of the tongue).

Preferred rapidly infusing compositions are those which are lyophilized products formulated for rapid infusion when placed in such an oral environment for rapid release of the ATI. The rapidly infusing compositions of the present disclosure may have a disintegration time of from approximately 1 second to 30 seconds or less, preferably 25 seconds or less, preferably 20 seconds or less, preferably 15 seconds or less, preferably 10 seconds or less, preferably 5 seconds or less, preferably 3 seconds or less, according to the United States Pharmacopeia (USP) <701> Disintegration Test performed in deionized water maintained at 37° C ± 2°. In particular, preferred rapidly infusing compositions are those formulated for oral disintegration in 5 seconds or less, preferably 4 seconds or less, preferably 3 seconds or less, preferably 2 seconds or less, preferably in approximately 1 second, according to the United States Pharmacopeia (USP) <701> Disintegration Test performed in deionized water maintained at 37° C ± 2°. A disintegration profile no higher than the above-mentioned upper limit provides a discrete amount of ATI to the user within a short time frame—a 'bolus' of ATI which is rapidly absorbed through intimate contact with the oral mucosae—providing high peak serum levels of ATIs and short onset times to therapeutic relief. For example, when formulated with nicotine as the ATI, administration of the rapidly infusing composition disclosed herein may provide peak levels of nicotine sufficient to achieve binding to the nicotinic acetylcholine receptors (nAChRs) at 50% saturation or more, preferably 55% saturation or more, preferably 60% saturation or more, preferably 65% saturation or more, preferably 70% saturation or more, preferably 75% saturation or more, preferably 80% saturation or more, preferably 85% saturation or more, preferably 90% saturation or more, preferably 95% saturation or more, and up to 96% saturation, preferably up to 97% saturation, preferably up to 98% saturation, preferably up to 99% saturation.

As a result of the rapid disintegration profile, direct introduction of the ATI into systemic circulation through the sublingual mucosa or the buccal mucosa, and ultimately high

peak serum levels of ATI, the rapidly infusing compositions disclosed herein provide a rapid onset of therapeutic effect. For example, the rapidly infusing composition formulated with nicotine may provide the desired effect (e.g., relief from nicotine withdrawal symptoms), in under 15 minutes, preferably under 10 minutes, preferably under 5 minutes, preferably under 4 minutes, preferably under 3 minutes, preferably under 2 minutes, preferably under 1 minute, preferably under 45 seconds, preferably under 30 seconds, preferably under 20 seconds, preferably under 10 seconds, preferably approximately 5 seconds. Such short onset times are comparable to those achieved through smoking tobacco, and are superior to those which can be obtained with traditional nicotine replacement therapies such as nicotine lozenges made through compression tabletting, gums, patches, nicotine oral pouches, and the like.

Another particular advantage of the disclosed rapidly infusing compositions is that administration is not habit inducing. For example, unlike other routes for administering nicotine such as smoking, chewing, dipping, snusing, sucking, etc., all of which are designed to be habitually performed by the user over sustained periods of time, the rapidly infusing compositions of the present disclosure are instead designed to be placed in the buccal cavity or over the sublingual gland for disintegration in a matter of seconds without mastication, deglutition, or any other neuromuscular activity. This “take it and it’s gone” administration route is not associated with a habit-forming activity, which is particularly advantageous to those who desire to break a smoking habit.

Yet another particular advantage of the “take it and it’s gone” administration of the rapidly infusing composition disclosed herein is that administration is sanitary and discreet, with no need to remove a spent nicotine product from the mouth upon completion—a fundamental step required when using smokeless tobacco products (must remove spent tobacco mass or spent tobacco pouch), oral non-tobacco-based nicotine pouches (must remove spent nicotine pouch), and nicotine gums (must remove spent wad of gum base). As a

result, there may be less embarrassment or stigma associated with the use of the rapidly infusing compositions and increased quiet enjoyment of administering nicotine, which may be attractive to a wider user base, compared to other products such as nicotine pouches.

Yet another advantage of the RITe™ platform is that it enables effective taste masking of bitter-tasting ATIs such as nicotine. Two main strategies contribute to the taste masking success of the present disclosure. First, any issues related to bitter taste are fundamentally mitigated by the short oral residence times provided by the rapid disintegration profile described heretofore. One "takes it and it's gone." Second, when formulated with a flavorant, a robust mixture of flavors will hit the tongue at essentially the same time—the bitter flavor of the ATI still hits the tongue, but the perception of the flavor is canceled or mitigated by the simultaneous arrival of other flavors. Even then, the robust mixture of flavors will quickly subside as the composition is rapidly absorbed through the oral mucosa.

The rapidly infusing composition also provides for reliable avoidance of first pass metabolism owing to its rapid disintegration profile coupled to the direct introduction of the ATI into systemic circulation through the sublingual mucosa or the buccal mucosa. The short residence time spent in the oral cavity reduces the tendency for enteral oral administration through voluntary or involuntary swallowing, and as a result, high levels of bioavailability may be achieved. The rapidly infusing composition thus presents ATIs such as nicotine in a highly bioavailable dosage form for maximum therapeutic effects. For example, nicotine administered via the RITe™ platform herein may have a bioavailability of at least 50%, preferably at least 55%, preferably at least 60%, preferably at least 65%, preferably at least 70%, preferably at least 75%, preferably at least 80%, preferably at least 85%, preferably at least 90%, and up to 99%, preferably up to 98%, preferably up to 96%, preferably up to 95%, preferably up to 92%. Such bioavailability is an improvement over other nicotine product types, with specific mention being made to nicotine gums, lozenges, and pouches, in part

because considerable nicotine is swallowed with subsequent first-pass metabolism owing to long oral residency times using such nicotine products.

The rapidly infusing composition herein generally contains (a) a pharmaceutically acceptable binder and/or excipient system that includes gelatin and a sugar alcohol e.g., mannitol, and optionally one or more of a sweetener, a flavorant, and a colorant; and (b) an active therapeutic ingredient such as nicotine or a pharmaceutically acceptable derivative/analog or solvate thereof.

Pharmaceutically acceptable carrier and/or excipient system

Carriers and/or excipients are ingredients which do not provide a therapeutic effect themselves, but which are designed to interact with, and enhance the properties of, the active therapeutic ingredient. In particular, carriers and/or excipients may act as a vehicle for transporting the active therapeutic ingredient from one organ, or portion of the body, to another organ, or portion of the body. The selection of appropriate carrier/excipient ingredients may impact the solubility, distribution, release profile/kinetics, absorption, serum stability, therapeutic onset time, and ultimately the efficacy of the ATI, as well as the shelf-life, dosage forms, and processability of the drug product. Each ingredient in the pharmaceutically acceptable carrier and/or excipient system must be “pharmaceutically acceptable” in the sense of being compatible with the other ingredients of the rapidly infusing composition and not injurious to the subject.

In light of the above, particular preference is given herein to pharmaceutically acceptable carrier and/or excipient systems which include gelatin and a sugar alcohol (e.g., mannitol).

Gelatin is to be included in the pharmaceutically acceptable carrier and/or excipient system in order to effect matrix formation in the lyophilized product, i.e., gelatin may act

primarily as a matrix former. During manufacture of the rapidly infusing composition, lyophilization from an aqueous suspension results in the removal of water thereby leaving behind a gelatin matrix/scaffolding upon which the ATI can be evenly dispersed or suspended. It has been found that gelatin has a propensity to establish a stable matrix in lyophilized form, yet allow for rapid disintegration when brought into contact with the aqueous oral environment, thereby providing efficient transfer of the ATI from the hydrophilic vehicle to the oral mucosa. In this regard, mammalian gelatins such as bovine gelatin and porcine gelatin are preferred, with bovine gelatin being particularly preferred. In some embodiments, the rapidly infusing composition does not contain fish gelatin.

The amount of gelatin used may be varied. Generally, gelatin may be present in the rapidly infusing composition in an amount of at least 10 wt.%, preferably at least 12 wt.%, preferably at least 14 wt.%, preferably at least 16 wt.%, preferably at least 18 wt.%, preferably at least 20 wt.%, preferably at least 22 wt.%, and up to 35 wt.%, preferably up to 32 wt.%, preferably up to 30 wt.%, preferably up to 28 wt.%, preferably up to 26 wt.%, preferably up to 24 wt.%, based on a total weight of the rapidly infusing composition on a dry basis.

The pharmaceutically acceptable carrier and/or excipient system is also formulated with one or more sugar alcohols, which may act primarily as a bulking agent. Examples of sugar alcohols include, but are not limited to, erythritol, xylitol, sorbitol, maltitol, mannitol, lactitol, and glycerin, which may be used singly or in combinations. Advantage can also be taken of the effect of certain sugar alcohols in terms of taste (sweetness and coolness due to endothermal heat of solution), as well as their ability to aid/speed tablet disintegration. In this regard, particular preference is given to mannitol.

The sugar alcohol, preferably mannitol, may be present in the rapidly infusing composition in any amount which provides the desired bulking/taste/disintegration effects.

Generally, this amount will range from at least 5 wt.%, preferably at least 10 wt.%, preferably at least 12 wt.%, preferably at least 14 wt.%, preferably at least 16 wt.%, preferably at least 18 wt.%, and up to 35 wt.%, preferably up to 30 wt.%, preferably up to 28 wt.%, preferably up to 26 wt.%, preferably up to 24 wt.%, preferably up to 22 wt.%, preferably up to 20 wt.%, based on a total weight of the rapidly infusing composition on a dry basis.

In some embodiments, a weight ratio of gelatin to sugar alcohol ranges from 1:3, preferably from 1:2, preferably from 1:1, preferably from 1.1:1, and up to 3:1, preferably up to 2:1, preferably up to 1.5:1, preferably up to 1.2:1.

The pharmaceutically acceptable carrier and/or excipient system may also optionally include one or more of a sweetener, a flavorant, and a colorant.

The sweetener may be used in any amount which provides the desired sweetening effect, generally in amount of 0 to 10 wt.%, for example in an amount of up to 8 wt.%, preferably up to 6 wt.%, preferably up to 5 wt.%, preferably up to 4.5 wt.%, preferably up to 4 wt.%, preferably up to 3.5 wt.%, preferably up to 3 wt.%, preferably up to 2.5 wt.%, preferably up to 2 wt.%, preferably up to 1.5 wt.%, preferably up to 1 wt.%, based on a total weight of the rapidly infusing composition on a dry basis. Suitable examples of sweeteners include, but are not limited to, aspartame, saccharin (as sodium, potassium or calcium saccharin), cyclamate (as a sodium, potassium or calcium salt), sucralose, acesulfame-K, thaumatin, neohisperidin, dihydrochalcone, ammoniated glycyrrhizin, dextrose, maltodextrin, fructose, levulose, sucrose, glucose, isomalt, which may be used singly or in combinations, with particular preference given to sucralose and acesulfame-K, more preferably a mixture of sucralose and acesulfame-K.

It is to be readily appreciated by those of ordinary skill in the art that one or more flavorants may be optionally included in the rapidly infusing composition to mask any unpleasant taste imparted by certain ingredients (e.g., an unpleasant tasting ATI) or to

otherwise impart an acceptable taste profile to the composition, and the composition is not limited to any particular flavor. However, flavorants suitable with the present invention require trial and error in order to achieve desired effectiveness. Suitable flavorants include, but are not limited to, oil of wintergreen, oil of peppermint, oil of spearmint, oil of sassafras, oil of clove, cinnamon, anethole, menthol, thymol, eugenol, eucalyptol, lemon, lime, lemon-lime, orange, and other such flavor compounds to add fruit notes (e.g., citrus, cherry etc.), spice notes, etc., to the composition. The flavorants may be constitutionally composed of aldehydes, ketones, esters, acids, alcohols (including both aliphatic and aromatic alcohols), as well as mixtures thereof. Specific mention is made to orange flavor, peppermint flavor, or a mixture thereof, which works particularly well with nicotine as the ATI. The flavorant may be used in any amount which provides the desired flavor, generally in an amount of 0 to 10 wt.%, for example in an amount of up to 8 wt.%, preferably up to 6 wt.%, preferably up to 5 wt.%, preferably up to 4 wt.%, preferably up to 3 wt.%, preferably up to 2 wt.%, preferably up to 1.5 wt.%, preferably up to 1 wt.%, preferably up to 0.5 wt.%, preferably up to 0.1 wt.%, based on a total weight of the rapidly infusing composition on a dry basis.

In some embodiments, the rapidly infusing compositions are formulated without a flavorant. Such non-flavored rapidly infusing compositions may be preferred in areas where sales of flavored nicotine products are banned, or will be subject to bans in the future. Even in these instances, user compliance (e.g., in terms of temporary abstinence from swallowing, which is often triggered when a subject is presented with foul-tasting oral medications) with non-flavored rapidly infusing compositions may be satisfactory, as any issues related to foul taste are minimized with the short oral residence times provided by the rapid disintegration profile described heretofore. However, the rapidly infusing compositions described here provide a safer alternative to other nicotine delivery methods such as e-cigarettes which are

subject to flavoring bans. Owing to improved safety, the rapidly infusing compositions may be formulated with a variety of palatable flavors without similar restrictions.

Likewise, the rapidly infusing composition may be colored or tinted through the optional use of one or more colorants. Suitable colorants are those approved by appropriate regulatory bodies such as the FDA and those listed in the European Food and Pharmaceutical Directives and include both pigments and dyes such as FD&C and D&C dyes, with specific mention being made to FD&C Yellow #5 and FD&C Red #40, which together produce an orange hue.

In addition to gelatin and a sugar alcohol (e.g., mannitol), and optionally one or more of a sweetener, a flavorant, and a colorant, the pharmaceutically acceptable carrier and/or excipient system may optionally include one or more other pharmaceutically acceptable carriers and/or excipients known to those of ordinary skill in art, in art appropriate levels. Examples of which include, but are not limited to,

- fillers or extenders such as starches (e.g., corn starch and potato starch), sugars (e.g., lactose or milk sugar, maltose, fructose, glucose, trehalose, sucrose), dextrates, dextrin, polydextrose, high molecular weight polyethylene glycols, silicic acid, aluminum monostearate, polyesters, polycarbonates, and polyanhydrides;
- binders, such as cellulose, and its derivatives, (e.g., carboxymethyl cellulose, sodium carboxymethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl methyl cellulose, methyl cellulose, ethyl cellulose, cellulose acetate, and microcrystalline cellulose), alginates (e.g., sodium alginate), polyvinyl pyrrolidone, powdered tragacanth, malt, acacia (gum arabic), carbomer, carrageenan, chitosan, copovidone, cyclodextrins, guar gum,

inulin, pectin, polycarbophil or a salt thereof, polyvinyl alcohol, pullulan, and xanthan gum;

- disintegrating agents, such as agar-agar, calcium carbonate, tapioca starch, alginic acid, certain silicates, sodium carbonate, sodium starch glycolate, and cross-linked sodium carboxymethyl cellulose;
- surfactants/absorption accelerators/wetting agents/emulsifying agents/solubilizers, including any of the anionic, cationic, nonionic, zwitterionic, amphoteric and betaine variety, such as polyalkylene oxide copolymers (e.g., poloxamer), sodium lauryl sulfate, sodium dodecyl benzene sulfonate, sodium docusate, sodium lauryl sulfoacetate, alkali metal or ammonium salts of lauroyl sarcosinate, myristoyl sarcosinate, palmitoyl sarcosinate, stearoyl sarcosinate and oleoyl sarcosinate, cetyl alcohol, glycerol monostearate, polyoxyethylene sorbitol, fatty acid esters of sorbitan, polysorbates (polyalkolyated fatty acid esters of sorbitan) (e.g., polyoxyethylene sorbitan monostearate, monoisostearate and monolaurate), polyethylene oxide condensates of alkyl phenols, cocoamidopropyl betaine, lauramidopropyl betaine, palmityl betaine, glyceryl monooleate, glyceryl monostearate, fatty alcohols (e.g., cetostearyl and cetyl alcohol), medium chain triglycerides, polyethoxylated castor oil, polyethoxylated alkyl ethers (e.g., ethoxylated isostearyl alcohols), polyethylene glycols (Macrogols), polyoxyethylene stearates, anionic and nonionic emulsifying waxes, propylene glycol, and propylene glycol alginates;
- absorbents, such as kaolin and bentonite clay;
- lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, zinc stearate, sodium stearate, stearic acid, ethyl oleate, and ethyl laurate;

- controlled release agents such as cross-linked polyvinyl pyrrolidone (crospovidone);
- opacifying agents such as titanium dioxide;
- buffering agents, including alkaline buffering agents, such as sodium hydroxide, sodium citrate, magnesium hydroxide, aluminum hydroxide, sodium carbonate, sodium bicarbonate, potassium phosphate, potassium carbonate, and potassium bicarbonate;
- diluents/tableting agents such as dicalcium phosphate;
- antioxidants, including (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, and sodium sulphite, (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, and alpha-tocopherol; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), tartaric acid, and phosphoric acid;
- antibacterial and antifungal agents, such as paraben, chlorobutanol, phenol, sorbic acid;
- as well as other non-toxic compatible substances employed in pharmaceutical formulations, such as liposomes, and micelle forming agents;
- including mixtures thereof.

Preferred rapidly infusing compositions are those which contain less than 1 wt.%, preferably less than 0.5 wt.%, preferably less than 0.1 wt.%, preferably less than 0.05 wt.%, preferably less than 0.001 wt.%, preferably 0 wt.%, of other pharmaceutically acceptable carriers and/or excipients, such as those listed above, in particular buffering agents and/or surfactants. In preferred embodiments, the rapidly infusing compositions are formulated without buffering agents, specifically alkaline buffering agents such as sodium hydroxide,

sodium carbonate, sodium bicarbonate, potassium phosphate, potassium carbonate, and potassium bicarbonate, which are traditionally required for nicotine oral pouches, nicotine lozenges, or other compressed tablet forms (*see*, e.g., US8940772—incorporated herein by reference in its entirety). In preferred embodiments, the rapidly infusing compositions are formulated without surfactants/absorption accelerators/wetting agents/emulsifying agents/solubilizers. In preferred embodiments, the rapidly infusing compositions are formulated without cellulose or derivatives thereof, such as microcrystalline cellulose.

Also preferred are rapidly infusing compositions which do not contain inert diluents, aqueous carriers, or non-aqueous carriers commonly used in the art for manufacture of liquid dosage forms for oral administration, such as emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. Examples of inert diluents, aqueous or non-aqueous carriers, etc. which are preferably excluded herein may include, but are not limited to, water or other solvents, solubilizing agents, and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, glycerol, polyethylene glycol, propylene glycol, 1,3-butylene glycol, oils (whether synthetic, semi-synthetic, or naturally occurring, such as long chain triglycerides, mixed glycerides, and free fatty acids, in particular, cottonseed oil, groundnut oil, corn oil, germ, olive oil, castor oil, sesame oil, borage oil, coconut oil, soybean oil, safflower oil, sunflower oil, palm oil, peanut oil, peppermint oil, poppy seed oil, canola oil, hydrogenated soybean oil, hydrogenated vegetable oils, glyceryl distearate, behenic acid, caprylyic/capric glycerides, lauric acid, linoleic acid, linolenic acid, myristic acid, palmitic acid, palmitoleic acid, palmitostearic acid, ricinoleic acid, stearic acid, soy fatty acids, oleic acid, glyceryl esters of fatty acids such as glyceryl behenate, glyceryl isostearate, glyceryl laurate, glyceryl palmitate, glyceryl palmitostearate, glyceryl ricinoleate, glyceryl oleate, glyceryl stearate), tetrahydrofuryl alcohol, fatty acid

esters of sorbitan, organic esters such as ethyl oleate, and mixtures thereof, with specific mention being made to ethyl alcohol and sesame oil.

Active therapeutic ingredient (ATI)

The amount of active therapeutic ingredient (ATI) which can be combined with the pharmaceutically acceptable carrier and/or excipient system to produce the rapidly infusing composition may vary depending upon the subject, and other factors. The amount of ATI which can be combined with the pharmaceutically acceptable carrier and/or excipient system to produce a single dosage form will generally be that amount which produces a therapeutic effect (e.g., relief from nicotine withdrawal symptoms). Generally, this amount will range from 0.1 to 25 wt.% of ATI (e.g., nicotine—active), for example, at least 0.1 wt.%, preferably at least 0.5 wt.%, preferably at least 1 wt.%, preferably at least 2 wt.%, preferably at least 3 wt.%, preferably at least 4 wt.%, preferably at least 5 wt.%, preferably at least 6 wt.%, preferably at least 7 wt.%, preferably at least 8 wt.%, preferably at least 9 wt.%, preferably at least 10 wt.%, and up to 25 wt.%, preferably up to 24 wt.%, preferably up to 23 wt.%, preferably up to 22 wt.%, preferably up to 21 wt.%, preferably up to 20 wt.%, preferably up to 19 wt.%, preferably up to 18 wt.%, preferably up to 17 wt.%, preferably up to 16 wt.%, preferably up to 15 wt.%, preferably up to 14 wt.%, preferably up to 13 wt.%, preferably up to 12 wt.%, preferably up to 11 wt.%, of the ATI, based on a total weight of the rapidly infusing composition on a dry basis.

In terms of unit dose, the rapidly infusing composition is generally formulated with 0.1 to 10 mg of ATI per unit (e.g. tablet), for example at least 0.1 mg, preferably at least 0.2 mg, preferably at least 0.4 mg, preferably at least 0.6 mg, preferably at least 0.8 mg, preferably at least 1 mg, preferably at least 1.2 mg, preferably at least 1.4 mg, preferably at least 1.6 mg, preferably at least 1.8 mg, preferably at least 2 mg, and up to 10 mg, preferably

up to 9 mg, preferably up to 8 mg, preferably up to 7 mg, preferably up to 6.5 mg, preferably up to 6 mg, preferably up to 5.5 mg, preferably up to 5 mg, preferably up to 4.5 mg, preferably up to 4 mg of ATI per unit (e.g., tablet).

In preferred embodiments, the rapidly infusing composition is formulated with, as the active therapeutic ingredient, nicotine. When the rapidly infusing compositions are formulated with nicotine, the above weight percentages and unit dosages are with respect to the active nicotine content (nicotine free base).

Nicotine useful herein may be synthetic nicotine or nicotine obtained from natural sources (e.g., *Nicotiana* plant species such as *Nicotiana tabacum*) that is unbound from plant material, i.e., naturally-occurring nicotine which is at least partially purified and not contained within a plant structure such as a tobacco leaf. Preferably, the rapidly infusing composition is formulated with nicotine that has been extracted and purified from natural sources, such as nicotine extracted from a *Nicotiana* species (e.g., tobacco). The nicotine can be purified by distillation or other suitable methods known by those of ordinary skill in the art.

Whether synthetic or obtained from natural sources, the nicotine used herein is preferably substantially pure or virtually pure, for example, having a purity of at least 95 wt.%, preferably at least 96 wt.%, preferably at least 97 wt.%, preferably at least 98 wt.%, preferably at least 99 wt.%., and up to 99.1 wt.%, preferably up to 99.2 wt.%, preferably up to 99.3 wt.%, preferably up to 99.4 wt.%, preferably up to 99.5 wt.%, preferably up to 99.6 wt.% , preferably up to 99.7 wt.%, preferably up to 99.8 wt.%, preferably up to 99.9 wt.%, preferably up to 100 wt.%. The percent purity of nicotine refers to the percent of nicotine by mass relative to a total weight of nicotine containing material—the nicotine containing material being the sum of nicotine plus any additional impurities which may be present, such as those impurities originating from the biomass from which the nicotine is obtained (e.g., *Nicotiana* species) or encountered during manufacture. Also, the nicotine purity described

herein is calculated by weight on a basis of nicotine free base. Therefore, the purity of nicotine with respect to a nicotine salt or a nicotine complex (*vide infra*) is determined on a basis of nicotine free base, prior to salt formation or complex formation—i.e., the acid/counter ion content of the nicotine salt, or the polymeric/oligomeric material content of the nicotine complex, is not measured in the nicotine purity analysis. For example, a nicotine complex formed through complexation of a 99 wt.% pure nicotine material (99 wt.% nicotine free base + 1 wt.% of impurities) with a polymer resin would be considered herein to have a nicotine 'purity' of 99 wt.% even though the polymer resin would contribute significantly to constitution of the nicotine complex. Purity of nicotine is determined using USP assay procedures, which may and often do, result in 'purity' over 100% as a result of inherent errors in the analysis (such as the case for nicotine purity determinations in nicotine polymer resin complexes which may inaccurately count weight contributions from the polymer resin to a certain degree). For example, particular mention is made of USP assay results of between 98 wt.% - 101 wt.%. For clarity purposes, applicants consider any USP assay result greater than 100% to be effectively 100% purity within the measurement accuracy of the assay.

Examples of potential impurities, such as those originating from the biomass from which the nicotine is obtained (e.g., tobacco plant) or encountered during manufacture, include, but are not limited to,

- tobacco related alkaloids such as cotinine, myosmine, anabasine, β-nicotyrine, anatabine, nornicotine, nicotine-*N*-oxide, isonicotine, neonicotine, N'-methyl anabasine, N'-methyl anatabine, N'-methylmyosmine, nornicotyrine, 2,3'-bipyridyl, and metanicotine;
- plant matter such as tobacco leaf;
- polyphenols such as rutin and quercetin;
- biopolymers such as cellulose, lignin, pectin, starch, and hemicellulose;

- sugars such as sucrose, glucose, fructose,
- polyacids acids such as malic acid, oxalic acid, and citric acid;
- pesticides such as alachlor, clomazone, metolachlor, napropamide, pebulate, pendimethalin, sethoxydim, sulfentrazone and aldicarb;
- residual solvents such as 1,4-dioxane, 2-butanol, 2-ethoxyethanol, 1,2-dichloroethane, acetone, acetonitrile, benzene, butane, cumene, cyclohexane, chloroform, ethanol, ethyl acetate, ethyl benzene, ethylene oxide, ethylene glycol, ethyl ether, heptane, isopropanol, methanol, methylene chloride, hexanes, isopropyl acetate, pentanes, propane, toluene, tetrahydrofuran, trichloroethene, and xylenes;
- microbials;
- heavy metals such as arsenic, cadmium, lead, chromium, and nickel;
- as well as mixtures thereof.

In some embodiments, the rapidly infusing composition is formulated with a form of nicotine which contains less than 1 wt.%, preferably less than 0.5 wt.%, preferably less than 0.1 wt.%, preferably less than 0.05 wt.%, preferably less than 0.001 wt.%, preferably 0 wt.% of the above listed impurities, based on a total weight of the nicotine material. In some embodiments, the rapidly infusing composition is formulated with a form of nicotine which contains no impurity, such as those listed above, in an amount above the limits of detection (LOD) and/or limits of quantification (LOQ) for the technique/instrumentation being used to make such a determination. The purity of nicotine may be determined by methods known to those of ordinary skill in the art, for example, one or more of liquid chromatography such as high performance liquid chromatography (HPLC), liquid chromatography-mass spectrometry (LCMS), and liquid chromatography with tandem mass spectrometry (LCMSMS); gas chromatography such as headspace gas chromatography with flame ionization detection (HS-

GC-FID), gas chromatography mass spectrometry (GC/MS), and headspace gas chromatography-mass spectrometry (HSGCMS); inductively coupled plasma-mass spectrometry (ICP-MS); and polymerase chain reaction (PCR).

To formulate the rapidly infusing compositions, nicotine may be provided in a variety of forms, such as nicotine free base, a nicotine salt, a nicotine complex, mixtures thereof, solvates thereof, or any other suitable form which is capable of releasing biologically active nicotine to provide the desired pharmacological action.

In some embodiments, nicotine may be provided in the form of a nicotine salt. A single nicotine salt, or a mixture of nicotine salts may be provided in the rapidly infusing composition. Any acid which provides a pharmaceutically acceptable salt with nicotine may be used. Preferred nicotine salts are those resulting from complete ionization of nicotine and the acid. The nicotine salts may be formed from reaction of nicotine with an inorganic acid or an organic acid, for example in a 1:1 to 3:1, or 2:1 molar ratio of acid to nicotine. The nicotine salts may be prepared under any conditions and using any techniques sufficient to form the salt, which are generally known to those skilled in the art, for example, US4830028, US9738622, US10556880—each incorporated herein by reference in its entirety.

Examples of inorganic acids useful for forming the nicotine salts herein, include, but are not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, sulfuric acid, bisulfate salts such as sodium bisulfate, sulfamic acid, phosphoric acid, and dihydrogen phosphate salts such as monosodium phosphate.

Examples of types of organic acids useful for forming the nicotine salts herein, include, but are not limited to, aromatic acids (e.g., benzoic acids and substituted benzoic acids, naphthoic acids, etc.), hydroxyacids, heterocyclic acids, terpenoid acids, sugar acids (e.g., pectic acids), amino acids, aliphatic acids and cycloaliphatic acids, dicarboxylic acids, keto acids, and sulfonic acids, with monocarboxylic acids being preferred. Suitable examples

of organic acids include, but are not limited to, formic, acetic, propionic, isobutyric, butyric, alpha-methylbutyric, isovaleric, beta-methylvaleric, maleic, glutamic, benzoic, 2-acetoxybenzoic, 3,5-dihydroxybenzoic acid, 2,3-dihydroxybenzoic, 4-acetamidobenzoic, gentisic, salicylic, sulfanilic, mucic, caproic, pamoic, 2-furoic, phenylacetic, heptanoic, octanoic, nonanoic, malic, citric, lactic, oxalic, malonic, glycolic, succinic, ascorbic, gluconic, tartaric, bitartaric, fumaric, pyruvic acids, levulinic, camphoric, benzenesulfonic, toluenesulfonic, methanesulfonic, ethanesulfonic, ethane disulfonic acid, and isethionic acids, as well as fatty acids (e.g., those having carbon chains of C_8 to C_{20}) such as stearic acid. Other useful organic compounds which exhibit an acid character and which form salts with nicotine may also be used, including phenolics such as guaiacol, vanillin, protocatechuic aldehyde, and the like.

Specific examples of nicotine salts suitable for use in the disclosed rapidly infusing compositions include, but are not limited to, nicotine acetate, nicotine monotartrate, nicotine bitartrate, nicotine hydrochloride, nicotine dihydrochloride, nicotine sulfate, and nicotine salicylate.

In preferred embodiments, nicotine may be provided in the form of a nicotine complex, where nicotine free base has been bound to (ionically bound to), adsorbed to, absorbed into, or enclosed into a polymeric or oligomeric material, such as a starch, an alginate, a cyclodextrin (e.g., β-cyclodextrin), a cellulose, a polymer resin, or a combination thereof, with particular preference given to a polymer resin. While the amount of nicotine (active) contained in the nicotine complex may vary, preferred nicotine complexes are those with a nicotine (active) content of at least 5 wt.%, preferably at least 10 wt.%, preferably at least 15 wt.%, preferably at least 20 wt.% and up to 60 wt.%, preferably up to 50 wt.%, preferably up to 45 wt.%, preferably up to 40 wt.%, preferably up to 35 wt.%, preferably up to 30 wt.%, preferably up to 25 wt.%, based on a total amount of the nicotine complex. The

amount of nicotine complex used to formulate the rapidly infusing compositions may be that amount which provides the desired active content of nicotine (as ATI) as described heretofore.

Preferred nicotine complexes are nicotine polymer resin complexes, preferably those formed from complexation of nicotine with a cation exchange resin (thereby forming a nicotine cation exchange resin complex). Suitable cation exchange resins are those which are strongly acidic, weakly acidic, or of intermediate acidity, due to the presence of acidic functionality, and are capable of forming an ionic complex with nicotine which is stable and water insoluble. Once administered, the release of nicotine from the nicotine cation exchange resin complex occurs through an ionic exchange process with counter ions available or that become available through dissolution in the oral cavity. This results in the release of free nicotine from the water insoluble polymer resin complexes, which is then ready for absorption through the oral mucosa.

Cation exchange resins suitable for forming nicotine cation exchange resin complexes are generally those resins bearing acidic groups such as carboxylic acids, sulfonic acids, phosphonic acids, phosphonous acids, iminodiacetic acids, and/or phenolic groups. While the cation exchange resin can additionally possess anionic groups, the resin should nonetheless be overall acidic in nature for ionic complexation with nicotine. Useful cation exchange resins may include, but are not limited to, methacrylic acid type polymers, acrylic acid type polymers, and polystyrene type polymers with sulfonic acid and/or phosphonic acid functional groups. Particular preference is given herein to cation exchange resins where the acidic groups are bound to cross-linked polymers, such as those addition polymers formed from polymerization of acidic monomers (e.g., acid functionalized styrene, methacrylic acid, and/or acrylic acid) with a crosslinking agent such as divinylbenzene. Other cation exchange resins are known, such as cross-linked phenolic resins, and other resins described in US3901248—incorporated herein by reference in its entirety, which may also be used to form

the nicotine cation exchange resin complexes. A particularly preferred example of a nicotine cation exchange resin complex is nicotine polacrilex. Polacrilex (e.g., sold as AMBERLITE IRP64 from Dupont) is a weak carboxylic acid cross-linked polymer resin prepared from polymerization of methacrylic acid and divinylbenzene.

The rapidly infusing compositions may be formulated with a combination of forms of nicotine, for example a combination of a nicotine salt and a nicotine complex can be employed.

Preferred rapidly infusing compositions are those in which nicotine is provided in a form that is a solid, for example, as a nicotine salt and/or a nicotine complex. Without being bound by theory, it is believed that during the manufacture of the rapidly infusing composition, when the nicotine is presented in solid form, lyophilization from a drug product suspension generates a structured and robust matrix of gelatin as the water is removed via sublimation, and an even distribution of the solid form of nicotine throughout the gelatin matrix. Such a structured assembly of nicotine in solid form (e.g., nicotine salt and/or a nicotine complex) suspended within a gelatin matrix is believed to afford the rapidly infusing composition with rapid disintegration properties and efficient transfer of nicotine from the hydrophilic vehicle to the mucous membrane of the buccal cavity, or the ventral surface under the tongue, upon administration.

On the contrary, when the rapidly infusing composition is formulated with an oil form of nicotine (e.g., nicotine free base) during manufacture, lyophilization is instead performed from an o/w emulsion, which may produce a matrix of gelatin which is relatively unstable, disordered, and more prone to collapse back into an oil or semi-solid state. The resulting composition tends to be less shelf stable, and can be characterized by increased disintegration times, and modest delivery/uptake of the nicotine into systemic circulation reflected in longer onset times and overall less efficacy against nicotine withdrawal symptoms.

In preferred embodiments, the rapidly infusing composition comprises, consists essentially of, or consists of gelatin, mannitol, sweetener, flavorant, and a nicotine cation exchange resin complex (e.g., nicotine polacrilex). Nicotine cation exchange resin complexes, such as nicotine polacrilex, increase mucosal uptake as compared to nicotine salts, such as nicotine bitartate. This aids to achieve both the rapid uptake and efficient delivery of nicotine necessary to mimic the kinetics of cigarettes.

Also contemplated for use as an active therapeutic ingredient are derivatives/analogs of nicotine that retain the desired pharmacological activity of nicotine, such as the ability to stimulate dopamine release, that can be used for example in the treatment of nicotine withdrawal symptoms and/or as an agent to help cessation of more harmful nicotine delivery methods, including but not limited to smoking. Derivatives/analogs that retain substantially the same activity as nicotine, or more preferably exhibit improved activity, may be produced according to standard principles of medicinal chemistry, which are well known in the art. Such derivatives/analogs may exhibit a lesser degree of activity than nicotine, so long as they retain sufficient activity to be therapeutically effective. Derivatives/analogs may exhibit improvements in other properties that are desirable in active therapeutic agents such as, for example, improved solubility, reduced toxicity, enhanced uptake, increased bioavailability, etc. Contemplated nicotine derivatives/analogs include, but are not limited to, nornicotine compounds (e.g., US5776957); lower N-alkyl analogs/derivatives of nicotine (e.g., US4965074); fluorinated or cyanonated nicotine compounds (e.g., US5278176); unsaturated nicotine or anabasine compounds (e.g., US5276043); pyridylalklypiperidines or pyridylalkylpyrolidines (e.g., US5214060); gamma-nicotine compounds (e.g., US5242934); alpha-nicotine compounds (e.g., US5232933); pyrrolidine substituted nicotine compounds (e.g., US4442292); pyridine substituted nicotine compounds (e.g., US4321387), as well as other compounds that can be used to treat habit disorders of the brain reward system, such as

lobelia alkaloids (e.g., lobeline, lobelanine, and lobelanidine) and those compounds disclosed in US5223497 and US4966916— each incorporated herein by reference in its entirety.

It is contemplated that nicotine or derivatives/analogs of nicotine may be useful in combination. It is also contemplated that nicotine or derivatives/analogs of nicotine may be useful in combination with current Standards of Care for cessation of more harmful nicotine delivery methods as well as any that evolve over the foreseeable future. Specific dosages and dosing regimens would be based on physicians' evolving knowledge and the general skill in the art.

In some preferred embodiments, nicotine or a derivative/analog thereof is the only active therapeutic ingredient in the rapidly infusing composition. In some preferred embodiments, nicotine is the only active therapeutic ingredient in the rapidly infusing composition. In some preferred embodiments, a nicotine derivative/analog is the only active therapeutic ingredient in the rapidly infusing composition.

Process for manufacturing the rapidly infusing composition

Manufacturing of the rapidly infusing compositions may be accomplished using the RITe™ platform including generally by i) dissolving gelatin and mannitol and any other optional component of the pharmaceutically acceptable carrier and/or excipient system in water to form a solution, ii) adding the nicotine or analog to the solution and optionally micronizing with a homogenizer to form a drug product suspension, and iii) lyophilizing the drug product suspension to remove water and form the rapidly infusing composition.

One exemplary process is presented below, although it should be understood that numerous modifications and variations are possible, and the rapidly infusing composition may be produced using processes or techniques otherwise than as specifically described.

Purified water, gelatin, and sugar alcohol (e.g., mannitol) may be charged to a mixer, for example a pot equipped with an overhead stirrer, and heated (e.g., 40 to 80 °C) with agitation until complete solvation. Any desired sweetener (e.g., a mixture of sucralose and acesulfame-K) may then be added and allowed to dissolve.

Upon cooling, for example to 20 to 35 °C, the solution may next be transferred to a homogenizer, and the ATI (e.g., nicotine in the form of nicotine polacrilex) may be subsequently charged and dispersed using the homogenizer, with optional micronization of the ATI, to form a drug product suspension. Any desired flavorant and colorant may be added at this point with continued mixing. The drug product suspension may be transferred to a second mixer whilst maintaining a cooled temperature (e.g., 20 to 35 °C).

In a blistering machine equipped with a dosing system, blister pockets may next be filled with the drug product suspension until achieving a target dose weight, followed by freezing in a suitable cryochamber. The blister trays may be transferred from the cryochamber to a suitable refrigerated storage cabinet (e.g., at a temperature below 0 °C) to keep the product frozen prior to lyophilization. Then, the frozen blisters may be loaded into a lyophilizer and subject to lyophilization to sublimate the water and form the rapidly infusing compositions. Finally, when the lyophilization cycle is deemed complete, final sealing (e.g., heat sealing of blister lidding) may be performed to provide the rapidly infusing compositions in single dose units in individual blister units.

Therapeutic applications and methods

The present disclosure relates generally to methods of administering nicotine or a pharmaceutically acceptable derivative/analog thereof to a subject in need thereof, whereby the nicotine or derivative/analog thereof is administered via the rapidly infusing composition of the present disclosure, in one or more of its embodiments. The methods may be performed

in order to provide a desired nicotine effect, to reduce a user's usage of more harmful nicotine delivery methods, to reduce a user's tobacco usage, to reduce a user's (non-tobacco) nicotine usage, to treat a user's nicotine withdrawal symptoms, and/or to reduce (and eventually overcome) a user's dependence on nicotine-containing products, or for any other purpose where nicotine administration may be desirable. In preferred embodiments, the subject is a human.

In some embodiments, the methods herein are intended to provide a user with a healthier alternative to smoking tobacco.

In preferred embodiments, the methods herein are used to manage a subject's nicotine withdrawal symptoms over the course of a nicotine cessation routine to aid the subject in quitting tobacco use or use of a non-tobacco-based nicotine product. The rapidly infusing compositions of the present disclosure are particularly useful as a tobacco replacement or as a means to reduce and/or stop tobacco use. The rapidly infusing compositions of the present disclosure may be used as a total replacement of tobacco or other non-tobacco-based nicotine product (e.g., electronic cigarettes). Alternatively, the rapidly infusing compositions of the present disclosure may be used as a partial replacement of tobacco or other non-tobacco-based nicotine product (e.g., electronic cigarettes), and may be used concurrently with tobacco or other non-tobacco-based nicotine product as part of a nicotine reduction program. For example, the rapidly infusing compositions are able to provide a user with rapid, on-the-spot relief from nicotine withdrawal symptoms as needed during the course of a smoking cessation routine involving a nicotine patch or some other smoking cessation therapy.

Upon being administered buccally (between the cheek and gum) or sublingually (under the ventral surface of the tongue), the rapidly infusing composition preferably disintegrates in 5 seconds or less, preferably 4 seconds or less, preferably 3 seconds or less, preferably 2 seconds or less, preferably about 1 second.

Owing to the rapid disintegration profile of the rapidly infusing composition and the direct introduction of ATI (e.g., nicotine) into systemic circulation through the sublingual mucosa or the buccal mucosa, the methods described herein are particularly advantageous in terms of their ability to rapidly deliver nicotine or a derivative/analog thereof into the user's bloodstream at high peak levels for receptor saturation and immediate relief of nicotine withdrawal symptoms, rivaling the onset times for pharmacological response provided by smoking tobacco. Administration of nicotine or related derivatives/analogs via the RITe™ platform herein via the oral mucosae may provide such ATIs to the user at peak venous plasma levels of up to 50 ng/mL, for example at least 1 ng/mL, preferably at least 5 ng/mL, preferably at least 10 ng/mL, preferably at least 15 ng/mL, preferably at least 20 ng/mL, preferably at least 25 ng/mL, and up to 50 ng/mL, preferably up to 45 ng/mL, preferably up to 40 ng/mL, preferably up to 35 ng/mL, preferably up to 30 ng/mL, which results in binding to the nicotinic acetylcholine receptors (nAChRs) at 50% saturation or more, preferably 55% saturation or more, preferably 60% saturation or more, preferably 65% saturation or more, preferably 70% saturation or more, preferably 75% saturation or more, preferably 80% saturation or more, preferably 85% saturation or more, preferably 90% saturation or more, preferably 95% saturation or more, and up to 96% saturation, preferably up to 97% saturation, preferably up to 98% saturation, preferably up to 99% saturation. As a result, the methods herein are particularly well-suited as a replacement to smoking tobacco or those seeking an aid to help them quit smoking.

With respect to administration, the rapidly infusing composition is preferably administered to the subject via one or more of the oral mucosae, preferably via the buccal mucosa (buccally) or the sublingual mucosa (sublingually). Advantages of oral mucosal delivery include the ease of administration, the ability to bypass first pass metabolic processes thereby enabling higher bioavailability than through enteral delivery via the

gastrointestinal tract, and extensive drug absorption and rapid onset of therapeutic action due to either a large surface area in the case of sublingual administration or high-levels of vascularization in the case of buccal administration.

Administration may be carried out by simply placing the rapidly infusing composition directly in the buccal cavity (between the cheek and gum) or over the sublingual mucous gland (under the ventral surface of the tongue). While the sublingual mucosa has a large surface area and extremely good permeability, the blood supply (blood flow) is lesser than that of the buccal cavity. Furthermore, sublingual administration tends to stimulate the flow of saliva more than buccal administration, and the increased saliva production may make it more difficult for users to avoid swallowing. Any amount of ATI (e.g., nicotine) that is swallowed would be subject to first pass metabolism and thus overall lower bioavailability. Swallowing further results in greater variability in the effective amount of dosing, as a result of, including but not limited to, the variability in the amount swallowed and the greater user variability of bioavailability through first-pass metabolism for the amount swallowed. Therefore, in preferred embodiments, the rapidly infusing composition is administered buccally (through the buccal mucosa). The rapid disintegration of the rapidly infusing composition, approximately in 1-5 seconds in preferred embodiments, and buccal administration together combine to provide optimal dosing control by limiting the residence time in the oral cavity and ensuring that the vast majority of the nicotine or derivative/analog thereof is absorbed through the buccal mucosa.

Another particular advantage of the disclosed methods is that buccal/sublingual administration is not habit inducing when the compositions, as here, disintegrate in a matter of seconds. For example, unlike other routes for administering nicotine such as smoking, chewing, dipping, snusing, sucking, etc., all of which are designed to be habitually performed by the user over prolonged periods of time, the rapidly infusing compositions of the present

disclosure are instead designed to be placed in the buccal cavity or over the sublingual gland for disintegration in a matter of seconds without mastication, deglutition, or any other neuromuscular activity. This ability to administer ATIs such as nicotine in an easy-to-take format which is itself not associated with a habit-forming activity is particularly advantageous to those who desire to break a tobacco-related habit such as smoking. As such, administration is intended to be mainly performed by the subject (psycho-stimulant self-administration), but may be carried out by someone other than the subject, for example, a healthcare provider, family member, etc.

The actual amount of ATI administered to the subject may be varied so as to achieve the desired therapeutic response for a particular subject, composition, and mode of administration, without being toxic to the subject. The selected amount of ATI administered to the subject will depend upon a variety of factors including the activity of the ATI employed, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds, and/or materials used in combination with the rapidly infusing composition, the age, sex, weight, condition, general health, the prior medical history of the subject, the subjects tolerance to stimulants such as nicotine, as well as like factors well known in the medical arts.

One having ordinary skill in the art can readily determine and prescribe the therapeutically effective amount of the rapidly infusing composition required to provide the required amount of ATI. For example, dosing of the ATI (e.g., nicotine) could commence at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. In general, a suitable dose of the ATI will be that amount which is the lowest dose effective to produce a therapeutic effect, which will generally depend upon the factors described above. Typically, when the ATI is nicotine

or a derivative/analog thereof, the therapeutically effective amount of the rapidly infusing composition is that which provides nicotine or a derivative/analog thereof in a range from at least 0.1 mg, preferably at least 0.2 mg, preferably at least 0.4 mg, preferably at least 0.6 mg, preferably at least 0.8 mg, preferably at least 1 mg, preferably at least 1.2 mg, preferably at least 1.4 mg, preferably at least 1.6 mg, preferably at least 1.8 mg, preferably at least 2 mg, and up to 10 mg, preferably up to 9 mg, preferably up to 8 mg, preferably up to 7 mg, preferably up to 6.5 mg, preferably up to 6 mg, preferably up to 5.5 mg, preferably up to 5 mg, preferably up to 4.5 mg, preferably up to 4 mg per dose. In preferred embodiments, the rapidly infusing composition is administered to the subject to provide 2 to 4 mg of nicotine or derivative/analog thereof per dose (dosing event).

Relative to subject body weight, the therapeutically effective amount of the rapidly infusing composition is that which provides nicotine or a derivative/analog thereof to the subject in an amount of at least 0.01 mg/kg, preferably at least 0.015 mg/kg, preferably at least 0.02 mg/kg, preferably at least 0.025 mg/kg, preferably at least 0.03 mg/kg, preferably at least 0.035 mg/kg, preferably at least 0.04 mg/kg, preferably at least 0.045 mg/kg, preferably at least 0.05 mg/kg, and up to 0.15 mg/kg, preferably up to 0.13 mg/kg, preferably up to 0.11 mg/kg, preferably up to 0.1 mg/kg, preferably up to 0.09 mg/kg, preferably up to 0.08 mg/kg, preferably up to 0.07 mg/kg, preferably up to 0.06 mg/kg, per dose.

In order to achieve the above described therapeutically effective amount per dose, the methods herein may involve administering one, or more than one, unit of the rapidly infusing composition per dose (dosing event). For example, in circumstances where each unit of the rapidly infusing composition contains 2 mg of ATI (e.g., nicotine), and it has been determined that the subject requires a therapeutically effective amount of 4 mg of ATI per dose, then the subject may be given two (2) units (e.g., tablets) to achieve the desired therapeutically effective amount of 4 mg ATI per dose. Accordingly, depending on the unit

dose of ATI in each unit of the rapidly infusing composition, the therapeutically effective amount of ATI prescribed, etc., 1, 2, 3, 4, 5, or more units (e.g., tablets) may be administered to the subject per dose. Accordingly, the phrases "administering to the subject in need thereof, via the oral mucosa, a therapeutically effective amount of the rapidly infusing composition", "the rapidly infusing composition is administered", etc., are intended herein to include administration of a single unit (e.g., tablet), or multiple units (e.g., tablets), to the subject in order to provide a therapeutically effective amount of ATI, e.g., nicotine. While it may be possible to administer partial (e.g., half) tablets to the subject, for practical reasons, it is preferred that one or more whole tablets are administered to the subject.

In many instances, a user may take the rapidly infusing composition of the present disclosure intermittently in response to an acute nicotine craving. Thus in some embodiments, the rapidly infusing composition may be administered simply 'as needed'.

In other embodiments, the subject may be prescribed a dosage regimen that involves multiple, separate dosing events at appropriate time intervals throughout the day. In any case, the subject may be administered a therapeutically effective amount of the rapidly infusing composition 1 time, 2 times, 3 times, 4 times, 5 times, 6 times, 7 times, 8 times, 9 times, 10 times, or even more times, optionally at appropriate intervals, throughout the day. The rapidly infusing composition may also be administered on an hourly dosing schedule (q), for example, administration may take place every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 hours, as appropriate. Administration may be performed multiple times a day, on consecutive days or otherwise, to achieve desired results (e.g., relief from nicotine withdrawal symptoms). For example, the subject may be administered a therapeutically effective dose of the rapidly infusing composition, at least 1 time per day and up to 30 times per day, for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9

days, 10 days, 11 days, 12 days, 13 days, 14 days, or more, such as weeks, months, or even years.

Preferred dosing regimens for smoking cessation are those involving a consistent dosing amount and schedule, with particularly preferred dosing schedules involving a gradual increase in time intervals between doses over the course of a multi-week program. For example, a subject may take buccally or sublingually a therapeutically effective dose of the rapidly infusing composition every 1 to 2 hours during an initial phase of a multi-week program, for example, for the first 1 to 6 weeks. The subject may also be provided instructions to take a minimum amount of the rapidly infusing composition in order to improve their chances of quitting smoking, such as to take a minimum of 9 doses (e.g., tablets) of the rapidly infusing composition daily during this initial phase. A subject may then take buccally or sublingually a therapeutically effective dose of the rapidly infusing composition every 2 to 4 hours during an intermediate phase of the multi-week program, for example, for weeks 7 to 9. Finally, a subject may take buccally or sublingually a therapeutically effective dose of the rapidly infusing composition every 4 to 8 hours during a final phase of the multi-week program, for example, for weeks 10 to 12.

In some embodiments, the rapidly infusing compositions may be administered (e.g., self-administered) at both predetermined intervals as well as intermittently throughout the day to assist with craving relief. In one example, the subject may be provided with instructions to take a second dose (e.g., tablet) of the rapidly infusing composition for strong/frequent nicotine cravings within 1 hour from onset of craving symptoms, in addition to a consistent dosing schedule of a multi-week program, such as that described above.

The subject may also receive different dosages of nicotine or derivative/analog thereof commensurate with their pre-existing nicotine tolerance. For example, a user who smokes less than 25 cigarettes per day may initiate a multi-week smoking cessation program with the

rapidly infusing composition having a relatively low single dose, such as 2 mg of nicotine per dose, while a user who smokes 25 or more cigarettes per day may initiate the multi-week smoking cessation program with the rapidly infusing composition having a higher dose, such as 4 mg of nicotine per dose. Upon completion of a multi-week smoking cessation program, the user may then optionally initiate another program cycle using a lower dose of ATI than the program just completed (e.g., first program using 4 mg nicotine, second program using 2 mg nicotine, etc.), until desired results, such as completely quitting smoking, are achieved.

When the ATI is nicotine, the maximum daily dosage of nicotine is preferably no more than 100 mg, preferably no more than 90 mg, preferably no more than 80 mg, preferably no more than 70 mg, preferably no more than 60 mg, preferably no more than 50 mg, preferably no more than 40 mg, preferably no more than 30 mg, preferably no more than 20 mg, preferably no more than 15 mg, preferably no more than 10 mg of nicotine per day.

The RITe™ platform herein may be used as a stand-alone therapeutic agent for administering nicotine or derivative/analog thereof, or may be used in combination therapy—wherein the rapidly infusing composition is used in combination with another nicotine-containing product, or one or more other active therapeutic agents. The combination therapy may be applied to treat nicotine withdrawal symptoms or a combination of nicotine withdrawal symptoms and a different condition such as anxiety.

In some embodiments, the RITe™ platform of the present disclosure is administered in combination with one or more other nicotine-containing products, such as a smoking tobacco product (e.g., cigarettes, cigars, and pipes), nicotine gum, a nicotine patch, a smokeless tobacco product (e.g., chewing tobacco, snuff, and snus), a non-tobacco-based nicotine pouch, a tobacco-smoke free inhaler (e.g., electronic cigarettes), nicotine lozenges, nicotine aerosols, etc. For example, a nicotine patch may be used to supplement a smoking cessation program using the rapidly infusing compositions described herein, or vice versa.

In some embodiments, the RITe™ platform of the present disclosure is administered in combination with one or more other active therapeutic agents for co-treatment of nicotine withdrawal symptoms and a condition other than nicotine withdrawal, with specific mention being made to depression, anxiety, irritation of the respiratory tract, hypertension, dyspnea, inflammation, chronic sputum production, nausea, acid reflux, heartburn, and indigestion. Examples of such other active therapeutic ingredients which may be co-administered with the rapidly infusing compositions of the present disclosure include, but are not limited to, antidepressants and anxiolytics, such as selective serotonin reuptake inhibitors (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline), serotonin and norepinephrine reuptake inhibitors (e.g., duloxetine and venlafaxine), norepinephrine and dopamine reuptake inhibitors (e.g., bupropion), tetracyclic antidepressants (e.g., mirtazapine), combined reuptake inhibitors and receptor blockers (e.g., trazodone, nefazodone, maprotiline), tricyclic antidepressants (e.g., amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline and trimipramine), monoamine oxidase inhibitors (e.g., phenelzine, tranylcypromine, isocarboxazid, selegiline), benzodiazepines (e.g., lorazepam, clonazepam, alprazolam, and diazepam), serotonin 1A receptor agonists (e.g., buspirone, aripiprazole, quetiapine, tandospirone, and bifeprunox), and beta-adrenergic receptor blockers (e.g., propranolol); expectorants such as glycerol iodination products (e.g., domiodol and organidin) and purinergic receptor agonists (e.g., uridine triphosphate and adenosine triphosphate); anti-hypertensive agents including diuretics, beta-blockers, ACE inhibitors, angiotensin II receptor blockers, calcium channel blockers, alpha blockers, alpha-2 receptor agonists, and combined alpha and beta-blockers, with specific mention being made to amiloride; bronchodilators such as β_2-adrenergic agonists (e.g., salbutamol and terbutaline), anticholinergics, and theophylline; anti-inflammatory agents such as oxicams, salicylates, acetic acid derivatives, fenamates, propionic acid derivatives, pyrazoles/pyrazolones, coxibs,

and sulfonanilides; mucolytics (e.g. n-acetylcysteine, ambroxol, bromhexine, carbocisteine, erdosteine, and mecysteine); anti-nausea agents (e.g., ondansetron); and antacids (e.g., magnesium oxide).

Combination therapy is intended to embrace administration of these therapies/products in a sequential manner, that is, wherein the rapidly infusing composition and one or more other therapies/products are administered at a different time, as well as administration of these therapies/products, or at least two of the therapies/products, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject multiple, single dosage forms for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, transdermal routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, the rapidly infusing composition formulated with nicotine or a derivative/analog thereof may be administered via buccal administration while a separate dosage form of nicotine, for example a nicotine patch, may be administered transdermally. Alternatively, for example, the therapeutic agent(s) may be administered buccally. Combination therapy also can embrace the administration of the rapidly infusing composition in further combination with other non-drug therapies (e.g., supplemental oxygen). Where the combination therapy further comprises a non-drug treatment, the non-drug treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agent(s) and non-drug treatment is achieved.

The examples below are intended to further illustrate the materials and methods of the present disclosure, and are not intended to limit the scope of the claims.

Where a numerical limit or range is stated herein, the endpoints are included. Also, all values and subranges within a numerical limit or range are specifically included as if explicitly written out.

As used herein the words “a” and “an” and the like carry the meaning of “one or more.”

The present disclosure also contemplates other embodiments “comprising”, “consisting of” and “consisting essentially of”, the embodiments or elements presented herein, whether explicitly set forth or not.

All patents and other references mentioned above are incorporated in full herein by this reference, the same as if set forth at length.

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that, within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

EXAMPLES

Rapidly Infusing Composition

Ingredients

The ingredients that were used to make the rapidly infusing composition are given in Table 1. USP = United States Pharmacopeia. EP = European Pharmacopoeia. NF = National Formulary.

Table 1. Ingredients

Ingredient	Primary Function	Specification
Gelatin	Matrix former	USP/EP/NF
Mannitol	Bulking agent	USP/EP
Orange flavor	Flavorant	Non-compendial
Peppermint flavor	Flavorant	Non-compendial
Nicotine Polacrilex (20 wt.% active nicotine)	ATI	USP/NF
Sucralose	Sweetener	USP/NF
Acesulfame-K	Sweetener	USP/NF
Purified water	Vehicle	USP/EP

Example rapidly infusing compositions were made using the formulations given in Tables 2 and 3. The amount of each component is expressed in terms of weight percentage relative to a total weight (100%). The weight percentage of each component in the drug product suspension is on a wet basis (prior to removal of water). The weight percentage of each component in the rapidly infusing composition is on a dry basis (after removal of water).

Table 2. Example 1 rapidly infusing composition

	Drug product suspension	Rapidly Infusing Composition	
Ingredient	**% wt./wt. (wet)**	**wt./unit (dry)**	**% wt./wt. (dry)**
Gelatin	3.5	10.5 mg	31
Mannitol	3	9 mg	26
Orange flavor	0.4	1.2 mg	3.5
Peppermint flavor	0.4	1.2 mg	3.5
Nicotine Polacrilex (active)	3.3	10 mg (2.0 mg)	29 (5.8)
Sucralose	0.4	1.2 mg	3.5
Acesulfame-K	0.4	1.2 mg	3.5
Purified water	88.6	Removed during manufacture	Removed during manufacture
Total	100.0	--	100.0

Table 3. Example 2 rapidly infusing composition

	Drug product suspension	Rapidly Infusing Composition	
Ingredient	**% wt./wt. (wet)**	**wt./unit (dry)**	**% wt./wt. (dry)**
Gelatin	3.5	10.5 mg	24
Mannitol	3	9 mg	20
Orange flavor	0.4	1.2 mg	2.7
Peppermint flavor	0.4	1.2 mg	2.7
Nicotine Polacrilex (active)	6.6	20 mg (4.0 mg)	45.2 (9.0)
Sucralose	0.4	1.2 mg	2.7
Acesulfame-K	0.4	1.2 mg	2.7
Purified water	85.3	Removed during manufacture	Removed during manufacture
Total	100.0	--	100.0

Methods of making the rapidly infusing composition

- Purified water was charged to a pot and mixed using an overhead stirrer as an agitating device.
- With agitation, the requisite amount of gelatin and mannitol were dispersed, and the mixture was heated until the excipients were dissolved.
- Once dissolved, the sweeteners sucralose and acesulfame-K were added and allowed to dissolve.
- The solution was cooled to 30 °C, moved to an overhead homogenizer, and then the requisite amount of nicotine polacrilex was charged and dispersed using the homogenizer to create a drug product suspension.
- The requisite amount of orange and peppermint flavor were charged and mixed for 10 minutes.
- The resulting drug product suspension was transferred to a second overhead mixer and maintained at a temperature of 30 °C for the ensuing dosing operation.
- In a blistering machine equipped with a dosing system, blister pockets were filled with a target dose weight of 300.0 mg of the drug product suspension.
- The product was frozen in a suitable cryochamber and then the blister trays were transferred from the cryochamber to a suitable refrigerated storage cabinet (temperature below 0 °C) prior to lyophilizing to keep the product frozen.
- The frozen blisters were loaded from the refrigerated storage cabinet into lyophilizers and the product was lyophilized (water was sublimated) to form the rapidly infusing compositions.
- When the lyophilizing cycle was completed, the rapidly infusing compositions were transferred from the lyophilizers to the blistering machine where the blister trays were heat sealed with lidding material. The resulting tablets are flat-topped circular units

approximately 15 mm in diameter with a convex bottom packaged in individual blister units (*see* also U.S. Provisional Application No. 63/114,181, filed November 16, 2020— incorporated herein by reference in its entirety).

- The following tests were performed:
    - A seal integrity test was performed at -0.5 Bar for 30 seconds, 1-minute soak time
    - Visual inspection was performed
    - Dry weight testing was performed

CLAIMS

1. A rapidly infused composition, comprising:

a pharmaceutically acceptable binder and/or excipient system comprising gelatin and mannitol, and

nicotine.

2. The rapidly infusing composition of claim 1, which is lyophilized.

3. The rapidly infusing composition of claim 1, which has a disintegration time of approximately 1 to 30 seconds in deionized water maintained at 37° C ± 2° C.

4. The rapidly infusing composition of claim 1, which has a disintegration time of approximately 1 to 5 seconds in deionized water maintained at 37° C ± 2° C.

5. The rapidly infusing composition of claim 1, wherein the gelatin is present in the rapidly infusing composition in an amount of 10 to 35 wt.%, based on a total weight of the rapidly infusing composition on a dry basis.

6. The rapidly infusing composition of claim 1, wherein the gelatin is mammalian gelatin.

7. The rapidly infusing composition of claim 6, wherein the mammalian gelatin is bovine gelatin.

8. The rapidly infusing composition of claim 1, wherein the mannitol is present in the rapidly infusing composition in an amount of 5 to 35 wt.%, based on a total weight of the rapidly infusing composition on a dry basis.

9. The rapidly infusing composition of claim 1, wherein the nicotine is present in the rapidly infusing composition in an amount of 0.1 to 25 wt.%, based on a total weight of the rapidly infusing composition on a dry basis.

10. The rapidly infusing composition of claim 1, wherein the nicotine is provided in the form of a nicotine salt or a nicotine complex.

11. The rapidly infusing composition of claim 10, wherein the nicotine is provided in the form of the nicotine complex.

12. The rapidly infusing composition of claim 11, wherein the nicotine complex is a nicotine cation exchange resin complex.

13. The rapidly infusing composition of claim 12, wherein the nicotine cation exchange resin complex is nicotine polacrilex.

14. The rapidly infusing composition of claim 1, wherein the nicotine has a purity between 95 and 100 % by weight on a basis of nicotine free base.

15. The rapidly infusing composition of claim 1, which is formulated with a solid form of nicotine.

16. The rapidly infusing composition of claim 1, wherein the rapidly infusing composition further comprises at least one selected from the group consisting of a sweetener, a flavorant, and a colorant.

17. The rapidly infusing composition of claim 16, wherein the rapidly infusing composition comprises the flavorant, and the flavorant comprises a mixture of orange flavor and peppermint flavor.

18. The rapidly infusing composition of claim 16, wherein the rapidly infusing composition comprises the sweetener, and the sweetener comprises a mixture of sucralose and acesulfame-K.

19. A process for manufacturing the rapidly infusing composition of claim 1, comprising:

dissolving gelatin and mannitol in water to form a solution;

adding the nicotine to the solution to form a drug product suspension; and

lyophilizing the drug product suspension to remove water and form the rapidly infusing composition.

20. A method of administering nicotine to a subject, comprising administering to the subject in need thereof, via the oral mucosa, a therapeutically effective amount of the rapidly infusing composition of claim 1.

21. The method of claim 20, wherein the rapidly infusing composition is administered buccally to the subject via the buccal mucosa.

22. The method of claim 20, wherein the therapeutically effective amount of the rapidly infusing composition is that which provides from 0.1 to 10 mg of nicotine per dose.

23. The method of claim 20, wherein the rapidly infusing composition is administered to the subject 1 to 10 times per day.

24. The method of claim 20, wherein the subject is a human.

25. A method of reducing a subject's usage of more harmful nicotine delivery methods, comprising administering to the subject in need thereof, via the oral mucosa, a therapeutically effective amount of the rapidly infusing composition of claim 1.

26. The method of claim 25, wherein the rapidly infusing composition is administered buccally to the subject via the buccal mucosa.

27. The method of claim 25, wherein the therapeutically effective amount of the rapidly infusing composition is that which provides from 0.1 to 10 mg of nicotine per dose.

28. The method of claim 25, wherein the rapidly infusing composition is administered to the subject 1 to 10 times per day.

29. The method of claim 25, wherein the subject is a human.

30. A method of reducing nicotine withdrawal symptoms in a subject, comprising administering to the subject in need thereof, via the oral mucosa, a therapeutically effective amount of the rapidly infusing composition of claim 1.

31. The method of claim 30, wherein the rapidly infusing composition is administered buccally to the subject via the buccal mucosa.

32. The method of claim 30, wherein the therapeutically effective amount of the rapidly infusing composition is that which provides from 0.1 to 10 mg of nicotine per dose.

33. The method of claim 30, wherein the rapidly infusing composition is administered to the subject 1 to 10 times per day.

34. The method of claim 30, wherein the subject is a human.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/059140

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 9/00; A61K 31/465; A61P 25/34 (2022.01)
CPC - A61K 9/0056; A61K 31/465; A61P 25/34 (2022.02)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
see Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
see Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/0298090 A1 (CHEN et al) 27 December 2007 (27.12.2007) entire document	1, 8-10, 15-17
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Y		2-7, 11-14, 18
Y	US 2015/0133504 A1 (NEW MARKET PHARMACEUTICALS) 14 May 2015 (14.05.2015) entire document	2-7
Y	US 2011/0268809 A1 (BRINKLEY et al) 03 November 2011 (03.11.2011) entire document	11-14, 18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 February 2022	MAR 10 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Harry Kim Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/059140

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet(s)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos..

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-18

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/059140

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I: claims 1-18 are drawn to rapidly infused compositions.

Group II: claim 19 is drawn to processes for manufacturing the rapidly infusing composition.

Group III: claims 20-34 are drawn to methods of administering nicotine to a subject, methods of reducing a subject's usage of more harmful nicotine delivery methods, and methods of reducing nicotine withdrawal symptoms in a subject.

The inventions listed in Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I, rapidly infused compositions, are not present in Groups II or III; the special technical features of Group II, manufacturing the rapidly infusing composition, are not present in Groups I or III, the special technical features of Group III, methods of administering nicotine to a subject, methods of reducing a subject's usage of more harmful nicotine delivery methods, and methods of reducing nicotine withdrawal symptoms in a subject, are not present in Groups I or II.

Additionally, even if Groups I-III were considered to share the technical features of a rapidly infused composition, comprising: a pharmaceutically acceptable binder and/or excipient system comprising gelatin and mannitol, and nicotine, these shared technical features do not represent a contribution over the prior art as disclosed by US 2007/0298090 A1 to Chen et al.

US 2007/0298090 A1 to Chen et al. disclose a rapidly infused composition (Para. [0052], rapidly dissolving nicotine-containing dosage form; Para. [0011]), comprising: a pharmaceutically acceptable binder and/or excipient system comprising gelatin (Para. [0058], the hydrocolloid(s) may be water-soluble and non-gelling polypeptides or proteins exemplified by gelatin) and mannitol (Para. [0034], mannitol), and nicotine (Para. [0052], rapidly dissolving nicotine-containing dosage form).

The inventions listed in Groups I-III therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.