

ENHANCED DELIVERY EPINEPHRINE AND PRODRUG COMPOSITIONS

CLAIM FOR PRIORITY

This application is a continuation of U.S. Patent Application No. 17/549,219, filed on
5 December 13, 2021, which is a continuation-in-part of U.S. Patent Application No. 16/143,821,
filed on September 27, 2018, which is a continuation-in-part of U.S. Patent Application
15/791,249, filed on October 23, 2017, which is a continuation-in-part of U.S. Patent Application
15/717,859, filed September 27, 2017, which is a continuation-in-part of U.S. Patent Application
No. 15/587,364, filed May 4, 2017, issued on December 7, 2021, as U.S. Patent No. 11,191,737,
10 which claims priority under 35 U.S.C. §119(e) to U.S. Patent Application Serial No. 62/331,996,
filed on May 5, 2016, each of which is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

This invention relates to pharmaceutical compositions.

15

BACKGROUND

Active ingredients, such as drugs or pharmaceuticals, are delivered to patients in
deliberate fashion. Delivery of drugs or pharmaceuticals using film transdermally or
transmucosally can require that the drug or pharmaceutical permeate or otherwise cross a
20 biological membrane in an effective and efficient manner.

SUMMARY

In general a pharmaceutical composition can include a polymeric matrix, epinephrine in
the polymeric matrix, and an adrenergic receptor interacter. Epinephrine can be provided in the
25 form of a prodrug, such as a lipophilic prodrug, for example, dipivefrin. In certain embodiments,
the epinephrine prodrug conversion to epinephrine has a half-life in humans of less than one
minute. In certain embodiments, the pharmaceutical composition can further include a
permeation enhancer. In certain embodiments, an adrenergic receptor interacter can be an
adrenergic receptor blocker. In some embodiments, the adrenergic receptor interacter can also
30 be a flavonoid, or used in combination with a flavonoid.

In certain embodiments, the adrenergic receptor interacter can be a terpenoid, terpene or a C3-C22 alcohol or acid. The adrenergic receptor interacter can be a sesquiterpene. In certain embodiments, the adrenergic receptor interacter can include farnesol, linoleic acid, arachidonic acid, docosahexanoic acid, eicosapentanoic acid, or docosapentanoic acid, or combinations thereof.

In certain embodiments, a pharmaceutical composition can include a polymeric matrix, a pharmaceutically active component in the polymeric matrix, and an aporphine alkaloid interacter.

In other embodiments, a pharmaceutical composition can include a polymeric matrix, a pharmaceutically active component in the polymeric matrix, and a vasodilator interacter.

In certain embodiments, the pharmaceutical composition can be a film further comprising a polymeric matrix, the pharmaceutically active component being contained in the polymeric matrix.

In certain embodiments, the adrenergic receptor interacter can be a phytoextract.

In certain embodiments, the permeation enhancer can be a phytoextract.

In certain embodiments, the permeation enhancer can include a phenylpropanoid.

In certain embodiments, the pharmaceutical composition can include a fungal extract.

In certain embodiments, the pharmaceutical composition can include saturated or unsaturated alcohol.

In certain embodiments, the alcohol can be benzyl alcohol.

In some cases, the flavonoid, phytoextract, phenylpropanoid, eugenol, or fungal extract can be used as a solubilizer.

In certain embodiments, the phenylpropanoid can be eugenol. In other embodiments, the phenylpropanoid can be eugenol acetate. In certain embodiments, the phenylpropanoid can be a cinnamic acid. In other embodiments, the phenylpropanoid can be a cinnamic acid ester. In other embodiments, phenylpropanoid can be a cinnamic aldehyde.

In other embodiments, the phenylpropanoid can be a hydrocinnamic acid. In certain embodiments, the phenylpropanoid can be chavicol. In other embodiments, the phenylpropanoid can be safrole.

In certain embodiments, the phytoextract can be an essential oil extract of a clove plant. In other examples, the phytoextract can be an essential oil extract of a leaf of a clove plant.

The phytoextract can be an essential oil extract of a flower bud of a clove plant. In other embodiments, the phytoextract can be an essential oil extract of a stem of a clove plant.

In certain embodiments, the phytoextract can be synthetic. In certain embodiments, the phytoextract can include 20-95% eugenol, including 40-95% eugenol, and including 60-95% eugenol. In certain embodiments, the phytoextract can include 80-95% eugenol.

In certain embodiments, the polymer matrix can include a polymer. The polymer can include a water soluble polymer.

In certain embodiments, the polymer can be a polyethylene oxide.

In certain embodiments, the polymer can be a cellulosic polymer. In certain embodiments, the cellulosic polymer can be hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethyl cellulose and/or sodium carboxymethylcellulose.

In certain embodiments, the polymer can include hydroxypropyl methylcellulose.

In certain embodiments, the polymer can include polyethylene oxide and hydroxypropyl methylcellulose.

In certain embodiments, the polymer can include polyethylene oxide and/or polyvinyl pyrrolidone.

In certain embodiments, the polymeric matrix can include polyethylene oxide and/or a polysaccharide.

In certain embodiments, the polymeric matrix can include polyethylene oxide, hydroxypropyl methylcellulose and/or a polysaccharide.

In certain embodiments, the polymeric matrix can include polyethylene oxide, a cellulosic polymer, polysaccharide and/or polyvinylpyrrolidone.

In certain embodiments, the polymeric matrix can include at least one polymer selected from the group of: pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, ethylene oxide, propylene oxide co-polymers, collagen, albumin, poly-amino acids, polyphosphazenes, polysaccharides, chitin, chitosan, and derivatives thereof.

In certain embodiments, the pharmaceutical composition can further include a stabilizer. Stabilizers can include antioxidants, which can prevent unwanted oxidation of materials,

sequestrants, which can form chelate complexes and inactivating traces of metal ions that would otherwise act as catalysts, emulsifiers and surfactants, which can stabilize emulsions, ultraviolet stabilizers, which can protect materials from harmful effects of ultraviolet radiation, UV absorbers, chemicals absorbing ultraviolet radiation and preventing it from penetrating the composition, quenchers, which can dissipate the radiation energy as heat instead of letting it break chemical bonds, or scavengers which can eliminate free radicals formed by ultraviolet radiation.

In yet another aspect, the pharmaceutical composition has a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a mucosal delivery-enhancing agent selected from: (a) an aggregation inhibitory agent; (b) a charge-modifying agent; (c) a pH control agent; (d) a degradative enzyme inhibitory agent; (e) a mucolytic or mucus clearing agent; (f) a ciliostatic agent; (g) a membrane penetration-enhancing agent selected from: (i) a surfactant; (ii) a bile salt; (ii) a phospholipid additive, mixed micelle, liposome, or carrier; (iii) an alcohol; (iv) an enamine; (v) a nitric oxide donor compound; (vi) a long chain amphipathic molecule; (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid; (x) a cyclodextrin or beta-cyclodextrin derivative; (xi) a medium-chain fatty acid; (xii) a chelating agent; (xiii) an amino acid or salt thereof; (xiv) an N-acetylamino acid or salt thereof; (xv) an enzyme degradative to a selected membrane component; (ix) an inhibitor of fatty acid synthesis; (x) an inhibitor of cholesterol synthesis; and (xi) any combination of the membrane penetration enhancing agents recited in (i)-(x); (h) a modulatory agent of epithelial junction physiology; (i) a vasodilator agent; (j) a selective transport-enhancing agent; and (k) a stabilizing delivery vehicle, carrier, mucoadhesive, support or complex-forming species with which the compound is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the compound for enhanced mucosal delivery, wherein the formulation of the compound with the transmucosal delivery-enhancing agents provides for increased bioavailability of the compound in a blood plasma of a subject.

In general a method of making a pharmaceutical composition can include combining an adrenergic receptor interacter with a pharmaceutically active component including epinephrine or its prodrug, and forming a pharmaceutical composition including the adrenergic receptor interacter and the pharmaceutically active component.

In general, a pharmaceutical composition can be dispensed from a device. A device can include a housing that holds an amount of a pharmaceutical composition, including a polymeric matrix; a pharmaceutically active component including epinephrine in the polymeric matrix; and an adrenergic receptor interacter; and an opening that dispenses a predetermined amount, such as a predetermined dose, of the pharmaceutical composition. The device can also dispense a pharmaceutical composition including a permeation enhancer including a phenylpropanoid and/or a phytoextract.

In certain embodiments, a pharmaceutical composition can include a polymeric matrix; a pharmaceutically active component in the polymeric matrix; and an interacter that creates increased blood flow or enables a flushing of the tissue to modify transmucosal uptake of the pharmaceutically active component.

In certain embodiments, a pharmaceutical composition can include a polymeric matrix; a pharmaceutically active component in the polymeric matrix; and an interacter that has a positive or negative heat of solution which are used as aids to modify (increase or decrease) transmucosal uptake.

In other embodiments, a pharmaceutical composition includes a polymeric matrix, a pharmaceutically active component in the polymeric matrix, and an interacter, the composition contained in a multilayer film having at least one side where the edges are coterminous.

In general, a method of treating a medical condition can include administering an effective amount of a pharmaceutical composition including a polymeric matrix, pharmaceutically active component including epinephrine in the polymeric matrix, and an adrenergic receptor interacter. The epinephrine can be administered as a prodrug, such as dipivefrin. Thus, a method of treating a medical condition can include administering an effective amount of a pharmaceutical composition including a polymeric matrix, pharmaceutically active component including dipivefrin in the polymeric matrix, and an adrenergic receptor interacter. In certain embodiments, the medical condition can include hypotension, cardiac arrest, heart failure, anaphylaxis, mydriasis, asystole, pulseless electrical activity, ventricular fibrillation, pulseless ventricular tachycardia, bradycardia, arrhythmia, or asthma exacerbation.

In certain embodiments, a pharmaceutical film can include a polymeric matrix, a pharmaceutically active component including epinephrine or its prodrug contained in the polymeric matrix and an adrenergic receptor interacter. The pharmaceutical film can have a

Tmax of 5-60 minutes, and a Cmax of 0.1 ng/ml-2 ng/ml. In certain embodiments, the Tmax is 40 minutes or less and wherein the Cmax is 0.1 ng/ml or greater. In certain embodiments, the Tmax is 35 minutes or less and wherein the Cmax is 0.15 ng/ml or greater. In certain embodiments, Tmax is 30 minutes or less and wherein the Cmax is 0.2 ng/ml or greater.

5 The Cmax can be 0.1 ng/ml- 2 ng/ml, 0.15 ng/ml-25 ng/ml, 0.2 ng/ml- 1.0 ng/ml, 0.2 ng/ml -1.2 ng/ml, and 0.2 ng/ml - 1.3 ng/ml. The Cmax can be greater than 0.1 ng/ml, greater than 0.15 ng/ml, greater than 0.2 ng/ml , greater than 0.4ng/ml, greater than 0.5ng/ml, greater than 1.0ng/ml, greater than 1.2 ng/ml. The Cmax can be less than 3 ng/ml, less than 2 ng/ml and less than 1.5 ng/ml.

10 The Tmax can be 0-240 minutes, 10-60 minutes, 20-40 minutes, 12-15 minutes, and 5-10 minutes. The Tmax can be less than 25 minutes, less than 20 minutes, 15 minutes, less than 12 minutes, and less than 10 minutes.

Other aspects, embodiments, and features will be apparent from the following description, the drawings, and the claims.

15 BRIEF DESCRIPTION OF THE FIGURES

Referring to **Figure 1A**, a Franz diffusion cell 100 includes a donor compound 101, a donor chamber 102, a membrane 103, sampling port 104, receptor chamber 105, stir bar 106, and a heater/circulator 107.

20 Referring to **Figure 1B**, a pharmaceutical composition is a film 100 comprising a polymeric matrix 200, the pharmaceutically active component 300 being contained in the polymeric matrix. The film can include a permeation enhancer 400.

Referring to **Figures 2A** and **2B**, the graphs show the permeation of an active material from a composition.

25 Referring to **Figure 2A**, this graph shows average amount of active material permeated vs. time, with 8.00 mg/mL epinephrine bitartrate and 4.4 mg/mL epinephrine base solubilized.

Referring to **Figure 2B**, this graph shows average flux vs. time, with 8.00 mg/mL epinephrine bitartrate and 4.4 mg/mL epinephrine base solubilized.

30 Referring to **Figure 3**, this graph shows ex-vivo permeation of epinephrine bitartrate as a function of concentration.

Referring to **Figure 4**, this graph shows permeation of epinephrine bitartrate as a function of solution pH.

Referring to **Figure 5**, this graph shows the influence of enhancers on permeation of epinephrine, indicated as amount permeated as a function of time.

5 Referring to **Figure 6A** and **6B**, these graphs show the release of epinephrine on polymer platforms (6A) and the effect of enhancers on its release (6B), indicated as amount permeated (in μg) vs. time.

Referring to **Figure 7**, this graph shows a pharmacokinetic model in the male Yucatan, miniature swine. The study compares a 0.3 mg Epipen, a 0.12 mg Epinephrine IV and a placebo
10 film.

Referring to **Figure 8**, this graph shows the impact of no enhancer on the concentration profiles of a 40 mg epinephrine film vs 0.3 mg Epipen.

Referring to **Figure 9**, this graph shows the impact of Enhancer A (Labrasol) on the concentration profiles of a 40 mg epinephrine film vs 0.3 mg Epipen.

15 Referring to **Figure 10**, this graph shows the impact of Enhancer L (clove oil) on the concentration profiles of two 40 mg Epinephrine films (10-1-1) and (11-1-1) vs. a 0.3 mg Epipen.

Referring to **Figure 11**, this graph shows the impact of Enhancer L (clove oil) and film dimension (10-1-1 thinner, bigger film and 11-1-1 thicker, smaller film) on the concentration
20 profiles of 40 mg Epinephrine films vs. a 0.3 mg Epipen.

Referring to **Figure 12**, this graph shows the concentration profiles for varying doses of Epinephrine films in a constant matrix for Enhancer L (clove oil) vs. a 0.3 mg Epipen.

Referring to **Figure 13**, this graph shows the concentration profiles for varying doses of epinephrine films in a constant matrix for Enhancer L (clove oil) vs. a 0.3 mg Epipen.

25 Referring to **Figure 14**, this graph shows the concentration profiles for varying doses of epinephrine films in a constant matrix for Enhancer A (Labrasol) vs. a 0.3 mg Epipen.

Referring to **Figure 15**, this graph shows the impact of Farnesol and Farnesol in combination with Linoleic Acid on plasma concentration profiles of 40mg Epinephrine Films vs. a 0.3 mg Epipen.

30 Referring to **Figure 16**, this graph shows the impact of Farnesol on plasma concentration profiles of 40 mg epinephrine films vs. a 0.3 mg Epipen.

Referring to **Figure 17**, this graph shows the impact of Farnesol in combination with Linoleic Acid on plasma concentration profiles of 40 mg epinephrine films vs. a 0.3 mg Epipen.

Referring to **Figure 18**, this graph shows the impact of Farnesol and Farnesol in combination with Linoleic Acid on plasma concentration profiles of 40 mg Epinephrine Films vs. a 0.3 mg Epipen.

Referring to **Figure 19**, this graph shows the impact of Enhancer A (Labrasol) in combination with Enhancer L (clove oil) on the concentration profiles of a 40 mg Epinephrine film (also shown in Fig. 20), in logarithmic view.

Referring to **Figure 20**, this graph shows the impact of Enhancer A (Labrasol) in combination with Enhancer L (clove oil) on the concentration profiles of a 40 mg Epinephrine film vs. the average data collected from 0.3 mg Epipens.

Referring to **Figure 21**, this graph shows the impact of Enhancer A (Labrasol) in combination with Enhancer L (clove oil) on the concentration profiles of a 40 mg Epinephrine films, shown as separate animal subjects.

Referring to **Fig. 22A and Fig. 22B**, the data shows average epinephrine plasma concentration vs. time.

Referring to **Fig. 23A and Fig. 23B**, the data shows average dipivefrin plasma concentration vs. time.

Referring to **Fig. 24**, the data shows average plasma concentration of epinephrine administered as dipivefrin.

Referring to **Fig. 25**, the graph shows the conversion of dipivefrin to epinephrine.

Referring to **Fig. 26**, the data shows average average epinephrine profiles across all matrix studies.

Referring to **Fig. 27**, the data shows additional data comparing plasma concentration of dipivefrin and epinephrine.

Referring to **Fig. 28**, this graph shows an epinephrine concentration vs. time profile of a film treated with phentolamine.

DETAILED DESCRIPTION

Mucosal surfaces, such as the oral mucosa, are a convenient route for delivering drugs to the body due to the fact that they are highly vascularized and permeable, providing increased

bioavailability and rapid onset of action because it does not pass through the digestive system and thereby avoids first pass metabolism. In particular, the buccal and sublingual tissues offer advantageous sites for drug delivery because they are highly permeable regions of the oral mucosa, allowing drugs diffusing from the oral mucosa to have direct access to systemic
 5 circulation. This also offers increased convenience and therefore increased compliance in patients. For certain drugs, or pharmaceutically active components, a permeation enhancer can help to overcome the mucosal barrier and improve permeability. Permeation enhancers reversibly modulate the penetrability of the barrier layer in favor of drug absorption. Permeation enhancers facilitate transport of molecules through the epithelium. Absorption profiles and their
 10 rates can be controlled and modulated by a variety of parameters, such as but not limited to film size, drug loading, enhancer type/loading, polymer matrix release rate and mucosal residence time.

A pharmaceutical composition can be designed to deliver a pharmaceutically active component in a deliberate and tailored way. However, solubility and permeability of the
 15 pharmaceutically active component in vivo, in particular, in the mouth of a subject, can vary tremendously. A particular class of permeation enhancer can improve the uptake and bioavailability of the pharmaceutically active component in vivo. In particular, when delivered to the mouth via a film, the permeation enhancer can improve the permeability of the pharmaceutically active component through the mucosa and into the blood stream of the subject.
 20 The permeation enhancer can improve absorption rate and amount of the pharmaceutically active component by more than 5%, more than 10%, more than 20%, more than 30%, more than 40%, more than 50%, more than 60%, more than 70%, more than 80%, more than 90%, more than 100%, more than 150%, about 200% or more, or less than 200%, less than 150%, less than 100%, less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%,
 25 less than 30%, less than 20%, less than 10%, or less than 5%, or a combination of these ranges, depending on the other components in the composition.

In certain embodiments, a pharmaceutical composition has a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a mucosal delivery-enhancing agent selected from: (a) an aggregation
 30 inhibitory agent; (b) a charge-modifying agent; (c) a pH control agent; (d) a degradative enzyme inhibitory agent; (e) a mucolytic or mucus clearing agent; (f) a ciliostatic agent; (g) a membrane

penetration-enhancing agent selected from: (i) a surfactant; (ii) a bile salt; (ii) a phospholipid additive, mixed micelle, liposome, or carrier; (iii) an alcohol; (iv) an enamine; (v) an NO donor compound; (vi) a long chain amphipathic molecule; (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid; (x) a cyclodextrin or beta-cyclodextrin derivative; (xi) a medium-chain fatty acid; (xii) a chelating agent; (xiii) an amino acid or salt thereof; (xiv) an N-acetylamino acid or salt thereof; (xv) an enzyme degradative to a selected membrane component; (ix) an inhibitor of fatty acid synthesis; (x) an inhibitor of cholesterol synthesis; and (xi) any combination of the membrane penetration enhancing agents recited in (i)-(x); (h) a modulatory agent of epithelial junction physiology; (i) a vasodilator agent; (j) a selective transport-enhancing agent; and (k) a stabilizing delivery vehicle, carrier, mucoadhesive, support or complex-forming species with which the compound is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the compound for enhanced transmucosal delivery, wherein the formulation of the compound with the transmucosal delivery-enhancing agents provides for increased bioavailability of the compound in blood plasma of a subject. Penetration enhancers have been described in J. Nicolazzo, et al., *J. of Controlled Disease*, 105 (2005) 1-15, which is incorporated by reference herein.

There are many reasons why the oral mucosa might be an attractive site for the delivery of therapeutic agents into the systemic circulation. Due to the direct drainage of blood from the buccal epithelium into the internal jugular vein first-pass metabolism in the liver and intestine may be avoided. First-pass effect can be a major reason for the poor bioavailability of some compounds when administered orally. Additionally, the mucosa lining the oral cavity is easily accessible, which ensures that a dosage form can be applied to the required site and can be removed easily in the case of an emergency. However, like the skin, the buccal mucosa acts as a barrier to the absorption of xenobiotics, which can hinder the permeation of compounds across this tissue. Consequently, the identification of safe and effective penetration enhancers has become a major goal in the quest to improve oral mucosal drug delivery.

Chemical penetration enhancers are substances that control the permeation rate of a coadministered drug through a biological membrane. While extensive research has focused on obtaining an improved understanding of how penetration enhancers might alter intestinal and

transdermal permeability, far less is known about the mechanisms involved in buccal and sublingual penetration enhancement.

The buccal mucosa delineates the inside lining of the cheek as well as the area between the gums and upper and lower lips and it has an average surface area of 100 cm². The surface of the buccal mucosa consists of a stratified squamous epithelium which is separated from the underlying connective tissue (lamina propria and submucosa) by an undulating basement membrane (a continuous layer of extracellular material approximately 1–2 µm in thickness). This stratified squamous epithelium consists of differentiating layers of cells which change in size, shape, and content as they travel from the basal region to the superficial region, where the cells are shed. There are approximately 40–50 cell layers, resulting in a buccal mucosa which is 500–600 µm thick.

Structurally the sublingual mucosa is comparable to the buccal mucosa but the thickness of this epithelium is 100–200 µm. This membrane is also non-keratinised and being relatively thinner has been demonstrated to be more permeable than buccal mucosa. Blood flow to the sublingual mucosal is slower compared with the buccal mucosa and is of the order of 1.0 ml/min-cm-2.

The permeability of the buccal mucosa is greater than that of the skin, but less than that of the intestine. The differences in permeability are the result of structural differences between each of the tissues. The absence of organized lipid lamellae in the intercellular spaces of the buccal mucosa results in greater permeability of exogenous compounds, compared to keratinized epithelia of the skin; while the increased thickness and lack of tight junctions results in the buccal mucosa being less permeable than intestinal tissue.

The primary barrier properties of the buccal mucosa have been attributed to the upper one-third to one-quarter of the buccal epithelium. Researchers have learned that beyond the surface epithelium, the permeability barrier of nonkeratinized oral mucosa could also be attributed to contents extruded from the membrane-coating granules into the epithelial intercellular spaces.

The intercellular lipids of the nonkeratinized regions of the oral cavity are of a more polar nature than the lipids of the epidermis, palate, and gingiva, and this difference in the chemical nature of the lipids may contribute to the differences in permeability observed between these tissues. Consequently, it appears that it is not only the greater degree of intercellular lipid

packing in the stratum corneum of keratinized epithelia that creates a more effective barrier, but also the chemical nature of the lipids present within that barrier.

The existence of hydrophilic and lipophilic regions in the oral mucosa has led researchers to postulate the existence of two routes of drug transport through the buccal mucosa paracellular
5 (between the cells) and transcellular (across the cells).

Since drug delivery through the buccal mucosa is limited by the barrier nature of the epithelium and the area available for absorption, various enhancement strategies are required in order to deliver therapeutically relevant amounts of drug to the systemic circulation. Various methods, including the use of chemical penetration enhancers, prodrugs, and physical methods
10 may be employed to overcome the barrier properties of the buccal mucosa.

A chemical penetration enhancer, or absorption promoter, is a substance added to a pharmaceutical formulation in order to increase the membrane permeation or absorption rate of the coadministered drug, without damaging the membrane and/or causing toxicity. There have been many studies investigating the effect of chemical penetration enhancers on the delivery of
15 compounds across the skin, nasal mucosa, and intestine. In recent years, more attention has been given to the effect of these agents on the permeability of the buccal mucosa. Since permeability across the buccal mucosa is considered to be a passive diffusion process the steady state flux (Jss) should increase with increasing donor chamber concentration (CD) according to Fick's first law of diffusion.

20 Surfactants and bile salts have been shown to enhance the permeability of various compounds across the buccal mucosa, both in vitro and in vivo. The data obtained from these studies strongly suggest that the enhancement in permeability is due to an effect of the surfactants on the mucosal intercellular lipids.

Fatty acids have been shown to enhance the permeation of a number of drugs through the
25 skin, and this has been shown by differential scanning calorimetry and Fourier transform infrared spectroscopy to be related to an increase in the fluidity of intercellular lipids.

Additionally, pretreatment with ethanol has been shown to enhance the permeability of tritiated water and albumin across ventral tongue mucosa, and to enhance caffeine permeability across porcine buccal mucosa. There are also several reports of the enhancing effect of Azone®
30 on the permeability of compounds through oral mucosa. Further, chitosan, a biocompatible and

biodegradable polymer, has been shown to enhance drug delivery through various tissues, including the intestine and nasal mucosa.

Oral transmucosal drug delivery (OTDD) is the administration of pharmaceutically active agents through the oral mucosa to achieve systemic effects. Permeation pathways and predictive models for OTDD are described, e.g. in M. Sattar, Oral transmucosal drug delivery – Current status and future prospects, *Int'l. Journal of Pharmaceutics*, 47(2014) 498-506, which is incorporated by reference herein. OTDD continues to attract the attention of academic and industrial scientists. Despite limited characterization of the permeation pathways in the oral cavity compared with skin and nasal routes of delivery, recent advances in our understanding of the extent to which ionized molecules permeate the buccal epithelium, as well as the emergence of new analytical techniques to study the oral cavity, and the progressing development of in silico models predictive of buccal and sublingual permeation, prospects are encouraging.

In order to deliver broader classes of drugs across the buccal mucosa, reversible methods of reducing the barrier potential of this tissue should be employed. This requisite has fostered the study of penetration enhancers that will safely alter the permeability restrictions of the buccal mucosa. It has been shown that buccal penetration can be improved by using various classes of transmucosal and transdermal penetration enhancers such as bile salts, surfactants, fatty acids and their derivatives, chelators, cyclodextrins and chitosan. Among these chemicals used for the drug permeation enhancement, bile salts are the most common.

In vitro studies on enhancing effect of bile salts on the buccal permeation of compounds is discussed in Sevda Senel, Drug permeation enhancement via buccal route: possibilities and limitations, *Journal of Controlled Release* 72 (2001) 133–144, which is incorporated by reference herein. That article also discusses recent studies on the effects of buccal epithelial permeability of dihydroxy bile salts, sodium glycodeoxycholate (SGDC) and sodium taurodeoxycholate (TDC) and tri-hydroxy bile salts, sodium glycocholate (GC) and sodium taurocholate (TC) at 100 mM concentration including permeability changes correlated with the histological effects. Fluorescein isothiocyanate (FITC), morphine sulfate were each used as the model compound.

Chitosan has also been shown to promote absorption of small polar molecules and peptide / protein drugs through nasal mucosa in animal models and human volunteers. Other

studies have shown an enhancing effect on penetration of compounds across the intestinal mucosa and cultured Caco-2 cells.

The permeation enhancer can be a phytoextract. A phytoextract can be an essential oil or composition including essential oils extracted by distillation of the plant material. In certain circumstances, the phytoextract can include synthetic analogues of the compounds extracted from the plant material (i.e., compounds made by organic synthesis). The phytoextract can include a phenylpropanoid, for example, phenyl alanine, eugenol, eugenol acetate, a cinnamic acid, a cinnamic acid ester, a cinnamic aldehyde, a hydrocinnamic acid, chavicol, or safrole, or a combination thereof. The phytoextract can be an essential oil extract of a clove plant, for example, from the leaf, stem or flower bud of a clove plant. The clove plant can be *Syzygium aromaticum*. The phytoextract can include 20-95% eugenol, including 40-95% eugenol, including 60-95% eugenol, and for example, 80-95% eugenol. The extract can also include 5% to 15% eugenol acetate. The extract can also include caryophyllene. The extract can also include up to 2.1% α -humulen. Other volatile compounds included in lower concentrations in clove essential oil can be β -pinene, limonene, farnesol, benzaldehyde, 2-heptanone and ethyl hexanoate. Other permeation enhancers may be added to the composition to improve absorption of the drug. Suitable permeation enhancers include natural or synthetic bile salts such as sodium fusidate; glycocholate or deoxycholate and their salts; fatty acids and derivatives such as sodium laurate, oleic acid, oleyl alcohol, monoolein, and palmitoylcarnitine; chelators such as disodium EDTA, sodium citrate and sodium laurylsulfate, azone, sodium cholate, sodium 5-methoxysalicylate, sorbitan laurate, glyceryl monolaurate, octoxynonyl-9, laureth-9, polysorbates, sterols, or glycerides, such as caprylocaproyl polyoxylglycerides, e.g., Labrasol. The permeation enhancer can include phytoextract derivatives and/or monolignols. The permeation enhancer can also be a fungal extract.

Some natural products of plant origin have been known to have a vasodilatory effect. There are several mechanisms or modes by which plant-based products can evoke vasodilation. For review, see McNeill J.R. and Jurgens, T.M., Can. J. Physiol. Pharmacol. 84:803-821 (2006), which is incorporated by reference herein. Specifically, vasorelaxant effects of eugenol have been reported in a number of animal studies. See, e.g., Lahlou, S., et al., J. Cardiovasc. Pharmacol. 43:250-57 (2004), Damiani, C.E.N., et al., Vascular Pharmacol. 40:59-66 (2003), Nishijima, H., et al., Japanese J. Pharmacol. 79:327-334 (1998), and Hume W.R., J. Dent Res.

62(9):1013-15 (1983), each of which is incorporated by reference herein. Calcium channel blockade was suggested to be responsible for vascular relaxation induced by a plant essential oil, or its main constituent, eugenol. See, Interaminense L.R.L. et al., *Fundamental & Clin. Pharmacol.* 21: 497-506 (2007), which is incorporated by reference herein.

5 Fatty acids can be used as inactive ingredients in drug preparations or drug vehicles. Fatty acids can also be used as formulation ingredients due to their certain functional effects and their biocompatible nature. Fatty acid, both free and as part of complex lipids, are major metabolic fuel (storage and transport energy), essential components of all membranes and gene regulators. For review, see Rustan A.C. and Dreven, C.A., *Fatty Acids: Structures and*
 10 *Properties*, Encyclopedia of Life Sciences (2005), which is incorporated by reference herein. There are two families of essential fatty acids that are metabolized in the human body: ω -3 and ω -6 polyunsaturated fatty acids (PUFAs). If the first double bond is found between the third and the fourth carbon atom from the ω carbon, they are called ω -3 fatty acids. If the first double bond is between the sixth and seventh carbon atom, they are called ω -6 fatty acids. PUFAs are further
 15 metabolized in the body by the addition of carbon atoms and by desaturation (extraction of hydrogen). Linoleic acid, which is a ω -6 fatty acid, is metabolized to γ -linolenic acid, dihomo- γ -linolenic acid, arachidonic acid, adrenic acid, tetracosatetraenoic acid, tetracosapentaenoic acid and docosapentaenoic acid. α -linolenic acid, which is a ω -3 fatty acid is metabolized to octadecatetraenoic acid, eicosatetraenoic acid, eicosapentaenoic acid (EPA), docosapentaenoic
 20 acid, tetracosapentaenoic acid, tetracosahexaenoic acid and docosahexaenoic acid (DHA).

It has been reported that fatty acids, such as palmitic acid, oleic acid, linoleic acid and eicosapentaenoic acid, induced relaxation and hyperpolarization of porcine coronary artery smooth muscle cells via a mechanism involving activation of the Na^+K^+ -ATPase pump and the fatty acids with increasing degrees of *cis*-unsaturation had higher potencies. See, Pomposiello,
 25 S.I. et al., *Hypertension* 31:615-20 (1998), which is incorporated by reference herein. Interestingly, the pulmonary vascular response to arachidonic acid, a metabolite of linoleic acid, can be either vasoconstrictive or vasodilative, depending on the dose, animal species, the mode of arachidonic acid administration, and the tones of the pulmonary circulation. For example, arachidonic acid has been reported to cause cyclooxygenase-dependent and -independent
 30 pulmonary vasodilation. See, Feddersen, C.O. et al., *J. Appl. Physiol.* 68(5):1799-808 (1990);

and see, Spannhake, E.W., et al., J .Appl. Physiol. 44:397-495 (1978) and Wicks, T.C. et al., Circ. Res. 38:167-71 (1976), each of which is incorporated by reference herein.

Many studies have reported effects of EPA and DHA on vascular reactivity after being administered as ingestible forms. Some studies found that EPA-DHA or EPA alone suppressed the vasoconstrictive effect of norepinephrine or increased vasodilatory responses to acetylcholine in the forearm microcirculation. See, Chin, J.P.F, et al., Hypertension 21:22-8 (1993), and Tagawa, H. et al., J Cardiovasc Pharmacol 33:633-40 (1999), each of which is incorporated by reference herein. Another study found that both EPA and DHA increased systemic arterial compliance and tended to reduce pulse pressure and total vascular resistance. See, Nestel, P. et al., Am J. Clin. Nutr. 76:326-30 (2002), which is incorporated by reference herein. Meanwhile, a study found that DHA, but not EPA, enhanced vasodilator mechanisms and attenuates constrictor responses in forearm microcirculation in hyperlipidemic overweight men. See, Mori, T.A., et al., Circulation 102:1264-69 (2000), which is incorporated by reference herein. Another study found vasodilator effects of DHA on the rhythmic contractions of isolated human coronary arteries *in vitro*. See Wu, K.-T. et al., Chinese J. Physiol. 50(4):164-70 (2007), which is incorporated by reference herein.

The adrenergic receptors (or adrenoceptors) are a class of G protein-coupled receptors that are a target of catecholamines, especially norepinephrine (noradrenaline) and epinephrine (adrenaline). Epinephrine (adrenaline) interacts with both α - and β -adrenoceptors, causing vasoconstriction and vasodilation, respectively. Although α receptors are less sensitive to epinephrine, when activated, they override the vasodilation mediated by β -adrenoceptors because there are more peripheral α_1 receptors than β -adrenoceptors. The result is that high levels of circulating epinephrine cause vasoconstriction. At lower levels of circulating epinephrine, β -adrenoceptor stimulation dominates, producing vasodilation followed by decrease of peripheral vascular resistance. The α_1 -adrenoreceptor is known for smooth muscle contraction, mydriasis, vasoconstriction in the skin, mucosa and abdominal viscera and sphincter contraction of the gastrointestinal (GI) tract and urinary bladder. The α_1 -adrenergic receptors are member of the G_q protein-coupled receptor superfamily. Upon activation, a heterotrimeric G protein, G_q , activates phospholipase C (PLC). The mechanism of action involves interaction with calcium channels and changing the calcium content in a cell. For review, see Smith R. S. et al., Journal of

Neurophysiology 102(2): 1103-14 (2009), which is incorporated by reference herein. Many cells possess these receptors.

α 1-adrenergic receptors can be a main receptor for fatty acids. For example, saw palmetto extract (SPE), widely used for the treatment of benign prostatic hyperplasia (BPH), has been reported to bind α 1-adrenergic, muscarinic and 1,4-dihydropyridine (1,4-DHP) calcium channel antagonist receptors. See, Abe M., et al., Biol. Pharm. Bull. 32(4) 646-650 (2009), and Suzuki M. et al., Acta Pharmacologica Sinica 30:271-81 (2009), each of which is incorporated by reference herein. SPE includes a variety of fatty acids including lauric acid, oleic acid, myristic acid, palmitic acid and linoleic acid. Lauric acid and oleic acid can bind noncompetitively to α 1-adrenergic, muscarinic and 1,4-DHP calcium channel antagonist receptors.

In certain embodiments, a permeation enhancer can be an adrenergic receptor interacter. An adrenergic receptor interacter refers to a compound or substance that modifies and/or otherwise alters the action of an adrenergic receptor. For example, an adrenergic receptor interacter can prevent stimulation of the receptor by increasing, or decreasing their ability to bind. Such interacters can be provided in either short-acting or long-acting forms. Certain short-acting interacters can work quickly, but their effects last only a few hours. Certain long-acting interacters can take longer to work, but their effects can last longer. The interacter can be selected and/or designed based on, e.g., on one or more of the desired delivery and dose, active pharmaceutical ingredient, permeation modifier, permeation enhancer, matrix, and the condition being treated. An adrenergic receptor interacter can be an adrenergic receptor blocker. The adrenergic receptor interacter can be a terpene (e.g. volatile unsaturated hydrocarbons found in the essential oils of plants, derived from units of isoprenes) or a C3-C22 alcohol or acid, preferably a C7-C18 alcohol or acid. In certain embodiments, the adrenergic receptor interacter can include farnesol, linoleic acid, arachidonic acid, docosahexanoic acid, eicosapentanoic acid, and/or docosapentanoic acid. The acid can be a carboxylic acid, phosphoric acid, sulfuric acid, hydroxamic acid, or derivatives thereof. The derivative can be an ester or amide. For example, the adrenergic receptor interacter can be a fatty acid or fatty alcohol.

The C3-C22 alcohol or acid can be an alcohol or acid having a straight C3-C22 hydrocarbon chain, for example a C3-C22 hydrocarbon chain optionally containing at least one double bond, at least one triple bond, or at least one double bond and one triple bond; said hydrocarbon chain being optionally substituted with C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄

alkoxy, hydroxyl, halo, amino, nitro, cyano, C₃₋₅ cycloalkyl, 3-5 membered heterocycloalkyl, monocyclic aryl, 5-6 membered heteroaryl, C₁₋₄ alkylcarbonyloxy, C₁₋₄ alkyloxycarbonyl, C₁₋₄ alkylcarbonyl, or formyl; and further being optionally interrupted by -O-, -N(R^a)-, -N(R^a)-C(O)-O-, -O-C(O)-N(R^a)-, -N(R^a)-C(O)-N(R^b)-, or -O-C(O)-O-. Each of R^a and R^b, independently, is

5 hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxylalkyl, hydroxyl, or haloalkyl.

Fatty acids with a higher degree of unsaturation are effective candidates to enhance the permeation of drugs. Unsaturated fatty acids showed higher enhancement than saturated fatty acids, and the enhancement increased with the number of double bonds. See, A. Mittal, et al. Status of Fatty Acids as Skin Penetration Enhancers – A Review, *Current Drug Delivery*, 2009,

10 6, pp. 274-279, which is incorporated by reference herein. Position of double bond also affects the enhancing activity of fatty acids. Differences in the physicochemical properties of fatty acid which originate from differences in the double bond position most likely determine the efficacy of these compounds as skin penetration enhancers. Skin distribution increases as the position of the double bond is shifted towards the hydrophilic end. It has also been reported that fatty acid

15 which has a double bond at an even number position more rapidly effects the perturbation of the structure of both the stratum corneum and the dermis than a fatty acid which has double bond at an odd number position. Cis-unsaturation in the chain can tend to increase activity.

An adrenergic receptor interacter can be a terpene. Hypotensive activity of terpenes in essential oils has been reported. See, Menezes I.A. et al., *Z. Naturforsch.* 65c:652-66 (2010),

20 which is incorporated by reference herein. In certain embodiments, the permeation enhancer can be a sesquiterpene. Sesquiterpenes are a class of terpenes that consist of three isoprene units and have the empirical formula C₁₅H₂₄. Like monoterpenes, sesquiterpenes may be acyclic or contain rings, including many unique combinations. Biochemical modifications such as oxidation or rearrangement produce the related sesquiterpenoids.

An adrenergic receptor interacter can be an unsaturated fatty acid such as linoleic acid. In certain embodiments, the permeation enhancer can be farnesol. Farnesol is a 15-carbon organic compound which is an acyclic sesquiterpene alcohol, which is a natural dephosphorylated form of farnesyl pyrophosphate. Under standard conditions, it is a colorless liquid. It is hydrophobic, and thus insoluble in water, but miscible with oils. Farnesol can be

25 extracted from oils of plants such as citronella, neroli, cyclamen, and tuberose. It is an intermediate step in the biological synthesis of cholesterol from mevalonic acid in vertebrates. It

30

has a delicate floral or weak citrus-lime odor and is used in perfumes and flavors. It has been reported that farnesol selectively kills acute myeloid leukemia blasts and leukemic cell lines in preference to primary hemopoietic cells. See, Rioja A. et al., FEBS Lett 467 (2-3): 291-5 (2000), which is incorporated by reference herein. Vasoactive properties of farnesyl analogues have been reported. See, Rouillet, J.-B., et al., J. Clin. Invest., 1996, 97:2384-2390, which is incorporated by reference herein. Both Farnesol and N-acetyl-S-trans, trans-farnesyl-L-cysteine (AFC), a synthetic mimic of the carboxyl terminus of farnesylated proteins inhibited vasoconstriction in rat aortic rings.

In certain embodiments, an interacter can be an aporphine alkaloid. For example, an interacter can be a dicentrine.

In general, an interacter can also be a vasodilator or a therapeutic vasodilator. Vasodilators are drugs that open or widen blood vessels. They are typically used to treat hypertension, heart failure and angina, but can be used to treat other conditions as well, including glaucoma for example. Some vasodilators that act primarily on resistance vessels (arterial dilators) are used for hypertension, and heart failure, and angina; however, reflex cardiac stimulation makes some arterial dilators unsuitable for angina. Venous dilators are very effective for angina, and sometimes used for heart failure, but are not used as primary therapy for hypertension. Vasodilator drugs can be mixed (or balanced) vasodilators in that they dilate both arteries and veins and therefore can have wide application in hypertension, heart failure and angina. Some vasodilators, because of their mechanism of action, also have other important actions that can in some cases enhance their therapeutic utility or provide some additional therapeutic benefit. For example, some calcium channel blockers not only dilate blood vessels, but also depress cardiac mechanical and electrical function, which can enhance their antihypertensive actions and confer additional therapeutic benefit such as blocking arrhythmias.

Vasodilator drugs can be classified based on their site of action (arterial versus venous) or by mechanism of action. Some drugs primarily dilate resistance vessels (arterial dilators; e.g., hydralazine), while others primarily affect venous capacitance vessels (venous dilators; e.g., nitroglycerine). Many vasodilator drugs have mixed arterial and venous dilator properties (mixed dilators; e.g., alpha-adrenoceptor antagonists, angiotensin converting enzyme inhibitors), such as phentolamine.

It is more common, however, to classify vasodilator drugs based on their primary mechanism of action. The figure to the right depicts important mechanistic classes of vasodilator drugs. These classes of drugs, as well as other classes that produce vasodilation, include: alpha-adrenoceptor antagonists (alpha-blockers); Angiotensin converting enzyme (ACE) inhibitors;

5 Angiotensin receptor blockers (ARBs); beta₂-adrenoceptor agonists (β₂-agonists); calcium-channel blockers (CCBs); centrally acting sympatholytics; direct acting vasodilators; endothelin receptor antagonists; ganglionic blockers; nitrodilators; phosphodiesterase inhibitors; potassium-channel openers; renin inhibitors.

In general, the active or inactive components or ingredients can be substances or compounds that create an increased blood flow or flushing of the tissue to enable a modification or difference (increase or decrease) in transmucosal uptake of the API(s), and/or have a positive or negative heat of solution which are used as aids to modify (increase or decrease) transmucosal uptake.

Sequence of Permeation Enhancer(s) and Active Pharmaceutical Ingredient(s)

The arrangement, order, or sequence of penetration enhancer(s) and active pharmaceutical ingredient(s)(API(s)) delivered to the desired mucosal surface can vary in order to deliver a desired pharmacokinetic profile. For example, one can apply the permeation enhancer(s) first by a film, by swab, spray, gel, rinse or by a first layer of a film then apply the API(s) by single film, by swab, or by a second layer of a film. The sequence can be reversed or

15 modified, for example, by applying the API(s) first by film, by swab, or by a first layer of a film, and then applying the permeation enhancer(s) by a film, by swab, spray, gel, rinse or by a second layer of a film. In another embodiment, one may apply a permeation enhancer(s) by a film, and a drug by a different film. For example, the permeation enhancer(s) film positioned under a film containing the API(s), or the film containing the API(s) positioned under a film containing the

20 permeation enhancer(s), depending on the desired pharmacokinetic profile.

For example, the penetration enhancer(s) can be used as a pretreatment alone or in combination with at least one API to precondition the mucosa for further absorption of the API(s). The treatment can be followed by another treatment with neat penetration enhancer(s) to follow the at least one API mucosal application. The pretreatment can be applied as a separate

25 treatment (film, gel, solution, swab etc.) or as a layer within a multilayered film construction of one or more layers. Similarly, the pretreatment may be contained within a distinct domain of a

30

single film, designed to dissolve and release to the mucosa prior to release of the secondary domains with or without penetration enhancer(s) or API(s). The active ingredient may then be delivered from a second treatment, alone or in combination with additional penetration enhancer(s). There may also be a tertiary treatment or domain that delivers additional penetration enhancer(s) and/or at least one API(s) or prodrug(s), either at a different ratio relative to each other or relative to the overall loading of the other treatments. This allows a custom pharmacokinetic profile to be obtained. In this way, the product may have single or multiple domains, with penetration enhancer(s) and API(s) that can vary in mucosal application order, composition, concentration, or overall loading that leads to the desired absorption amounts and/or rates that achieve the intended pharmacokinetic profile and/or pharmacodynamic effect.

The film format can be oriented such that no distinct sides, or such that the film has at least one side of a multiple layer film where the edges are co-terminus (having or meeting at a shared border or limit).

The pharmaceutical composition can be a chewable or gelatin based dosage form, spray, gum, gel, cream, tablet, liquid or film. The composition can include textures, for example, at the surface, such as microneedles or micro-protrusions. Recently, the use of micron-scale needles in increasing skin permeability has been shown to significantly increase transdermal delivery, including and especially for macromolecules. Most drug delivery studies have emphasized solid microneedles, which have been shown to increase skin permeability to a broad range of molecules and nanoparticles in vitro. In vivo studies have demonstrated delivery of oligonucleotides, reduction of blood glucose level by insulin, and induction of immune responses from protein and DNA vaccines. For such studies, needle arrays have been used to pierce holes into skin to increase transport by diffusion or iontophoresis or as drug carriers that release drug into the skin from a microneedle surface coating. Hollow microneedles have also been developed and shown to microinject insulin to diabetic rats. To address practical applications of microneedles, the ratio of microneedle fracture force to skin insertion force (i.e. margin of safety) was found to be optimal for needles with small tip radius and large wall thickness. Microneedles inserted into the skin of human subjects were reported as painless. Together, these results suggest that microneedles represent a promising technology to deliver therapeutic compounds into the skin for a range of possible applications. Using the tools of the microelectronics industry, microneedles have been fabricated with a range of sizes, shapes and

materials. Microneedles can be, for example, polymeric, microscopic needles that deliver encapsulated drugs in a minimally invasive manner, but other suitable materials can be used.

Applicants have found that microneedles could be used to enhance the delivery of drugs through the oral mucosa, particularly with the claimed compositions. The microneedles create
5 micron sized pores in the oral mucosa which can enhance the delivery of drugs across the mucosa. Solid, hollow or dissolving microneedles can be fabricated out of suitable materials including, but not limited to, metal, polymer, glass and ceramics. The microfabrication process can include photolithography, silicon etching, laser cutting, metal electroplating, metal electro
10 polishing and molding. Microneedles could be solid which is used to pretreat the tissue and are removed before applying the film. The drug loaded polymer film described in this application can be used as the matrix material of the microneedles itself. These films can have microneedles or micro protrusions fabricated on their surface which will dissolve after forming microchannels in the mucosa through which drugs can permeate.

The term “film” can include films and sheets, in any shape, including rectangular, square,
15 or other desired shape. A film can be any desired thickness and size. In preferred embodiments, a film can have a thickness and size such that it can be administered to a user, for example, placed into the oral cavity of the user. A film can have a relatively thin thickness of from about 0.0025mm to about 0.250mm, or a film can have a somewhat thicker thickness of from about 0.250mm to about 1.0mm. For some films, the thickness may be even larger, i.e., greater than
20 about 1.0mm or thinner, i.e., less than about 0.0025mm. A film can be a single layer or a film can be multi-layered, including laminated or multiple cast films. A permeation enhancer and pharmaceutically active component can be combined in a single layer, each contained in separate layers, or can each be otherwise contained in discrete regions of the same dosage form. In certain embodiments, the pharmaceutically active component contained in the polymeric matrix
25 can be dispersed in the matrix. In certain embodiments, the permeation enhancer being contained in the polymeric matrix can be dispersed in the matrix.

Oral dissolving films can fall into three main classes: fast dissolving, moderate dissolving and slow dissolving. Oral dissolving films can also include a combination of any of the above categories. Fast dissolving films can dissolve in about 1 second to about 30 seconds in the
30 mouth, including more than 1 second, more than 5 seconds, more than 10 seconds, more than 20 seconds, and less than 30 seconds. Moderate dissolving films can dissolve in about 1 to about 30

minutes in the mouth including more than 1 minute, more than 5 minutes, more than 10 minutes, more than 20 minutes or less than 30 minutes, and slow dissolving films can dissolve in more than 30 minutes in the mouth. As a general trend, fast dissolving films can include (or consist of) low molecular weight hydrophilic polymers (e.g., polymers having a molecular weight
5 between about 1,000 to 9,000 daltons, or polymers having a molecular weight up to 200,000 daltons). In contrast, slow dissolving films generally include high molecular weight polymers (e.g., having a molecular weight in millions). Moderate dissolving films can tend to fall in between the fast and slow dissolving films.

It can be preferable to use films that are moderate dissolving films. Moderate dissolving
10 films can dissolve rather quickly, but also have a good level of mucoadhesion. Moderate dissolving films can also be flexible, quickly wettable, and are typically non-irritating to the user. Such moderate dissolving films can provide a quick enough dissolution rate, most desirably between about 1 minute and about 20 minutes, while providing an acceptable mucoadhesion level such that the film is not easily removable once it is placed in the oral cavity of the user.
15 This can ensure delivery of a pharmaceutically active component to a user.

A pharmaceutical composition can include one or more pharmaceutically active components. The pharmaceutically active component can be a single pharmaceutical component or a combination of pharmaceutical components. The pharmaceutically active component can be an anti-inflammatory analgesic agent, a steroidal anti-inflammatory agent, an antihistamine, a
20 local anesthetic, a bactericide, a disinfectant, a vasoconstrictor, a hemostatic, a chemotherapeutic drug, an antibiotic, a keratolytic, a cauterizing agent, an antiviral drug, an antirheumatic, an antihypertensive, a bronchodilator, an anticholinergic, an anti-anxiety drug, an antiemetic compound, a hormone, a peptide, a protein or a vaccine. The pharmaceutically active component can be the compound, pharmaceutically acceptable salt of a drug, a prodrug, a derivative, a drug
25 complex or analog of a drug. The term "prodrug" refers to a biologically inactive compound that can be metabolized in the body to produce a biologically active drug. For example, the pharmaceutically active component can be an ester of epinephrine, for example, dipivefrin. *See, e.g., J. Anderson, et al., Site of ocular hydrolysis of a prodrug, dipivefrin, and a comparison of its ocular metabolism with that of the parent compounds, epinephrine, Invest., Ophthalmol.*
30 *Vis. Sci.* July 1980. The time it takes to convert 50% of the prodrug by an enzyme or multiple

enzymes to yield neat epinephrine systemically in humans is referred to as the half-life. In certain embodiments, the half-life is less than 1 minute.

For example, when the prodrug is an ester of epinephrine, the half-life of hydrolysis of the ester to form epinephrine *in-vivo* in a human subject can be less than one minute. For example, a review of pharmacokinetic data from a study in which 12 mg of an ester of epinephrine is delivered by a sublingual film as described herein, epinephrine plasma levels clearly indicate significant systemic absorption of epinephrine, however, the requisite parent prodrug concentration was undetectable. The absence of detectable prodrug in the plasma indicates a conversion half life of the prodrug that is not able to be calculated by traditional pharmacokinetic techniques. The detection limit of the prodrug was 2 pg/ml. By inferring the time between blood sampling timepoints (5 minutes) around the observed C_{max} , it can be reasonably concluded that the half life must be less than 1 minute and is very likely to be less than 30 seconds based on the data, in order to adequately clear the requisite prodrug level before the next timepoint.

The half-life of hydrolysis of a prodrug or an ester of epinephrine *in-vivo* in a human subject should not be confused with the release or dissolution of epinephrine hydrochloride from a film into 500 mL of simulated saliva as described in Alayoubi *et al.* Pharm. Dev. Technol. 2017, 22(8), 1012-1016. Note also that the Alayoubi report did not investigate the ability of a film to deliver epinephrine *in vivo* and did not involve a prodrug or the hydrolysis of any prodrug systemically.

In some embodiments, more than one pharmaceutically active component may be included in the film. The pharmaceutically active components can be ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, amphetamines, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor

agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, 5 osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral 10 vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough 15 suppressants, mucolytics, DNA and genetic modifying drugs, diagnostic agents, imaging agents, dyes, or tracers, and combinations thereof.

For example, the pharmaceutically active component can be buprenorphine, naloxone, acetaminophen, riluzole, clobazam, Rizatriptan, propofol, methyl salicylate, monoglycol salicylate, aspirin, mefenamic acid, flufenamic acid, indomethacin, diclofenac, alclofenac, 20 diclofenac sodium, ibuprofen, ketoprofen, naproxen, pranoprofen, fenoprofen, sulindac, fenclofenac, clidanac, flurbiprofen, fentiazac, bufexamac, piroxicam, phenylbutazone, oxyphenbutazone, clofezone, pentazocine, mepirizole, tiaramide hydrochloride, hydrocortisone, predonisolone, dexarnethasone, triamcinolone acetonide, fluocinolone acetonide, hydrocortisone acetate, predonisolone acetate, methylpredonisolone, dexamethasone acetate, betamethasone, 25 betamethasone valerate, flumetasone, fluorometholone, beclomethasone dipropionate, fluocinonide, edaravone, lurasidone, esomeprazole, lumateperone, naldmedine, doxylamine, pyridoxine, diphenhydramine hydrochloride, diphenhydramine salicylate, diphenhydramine, chlorpheniramine hydrochloride, chlorpheniramine maleate isothipendyl hydrochloride, tripelennamine hydrochloride, promethazine hydrochloride, methdilazine hydrochloride 30 dibucaine hydrochloride, dibucaine, lidocaine hydrochloride, lidocaine, benzocaine, p-buthylaminobenzoic acid 2-(die-ethylamino) ethyl ester hydrochloride, procaine hydrochloride,

tetracaine, tetracaine hydrochloride, chlorprocaine hydrochloride, oxyprocaine hydrochloride, mepivacaine, cocaine hydrochloride, piperocaine hydrochloride, dyclonine, dyclonine hydrochloride, thimerosal, phenol, thymol, benzalkonium chloride, benzethonium chloride, chlorhexidine, povidone iodide, cetylpyridinium chloride, eugenol, trimethylammonium bromide, naphazoline nitrate, tetrahydrozoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tramazoline hydrochloride, thrombin, phytonadione, protamine sulfate, aminocaproic acid, tranexamic acid, carbazochrome, carbaxochrome sodium sulfanate, rutin, hesperidin, sulfamine, sulfathiazole, sulfadiazine, homosulfamine, sulfisoxazole, sulfisomidine, sulfamethizole, nitrofurazone, penicillin, meticillin, oxacillin, cefalotin, cefalordin, erythromycin, lincomycin, tetracycline, chlortetracycline, oxytetracycline, metacycline, chloramphenicol, kanamycin, streptomycin, gentamicin, bacitracin, cycloserine, salicylic acid, podophyllum resin, podolifox, cantharidin, chloroacetic acids, silver nitrate, protease inhibitors, thymidine kinase inhibitors, sugar or glycoprotein synthesis inhibitors, structural protein synthesis inhibitors, attachment and adsorption inhibitors, and nucleoside analogues such as acyclovir, penciclovir, valacyclovir, and ganciclovir, heparin, insulin, LHRH, TRH, interferons, oligonucleotides, calcitonin, octreotide, omeprazole, fluoxetine, ethinylestradiol, amiodipine, paroxetine, enalapril, lisinopril, leuprolide, pravastatin, lovastatin, norethindrone, risperidone, olanzapine, albuterol, hydrochlorothiazide, pseudoephedrine, warfarin, terazosin, cisapride, ipratropium, buspirone, methylphenidate, levothyroxine, zolpidem, levonorgestrel, glyburide, benazepril, medroxyprogesterone, clonazepam, ondansetron, losartan, quinapril, nitroglycerin, midazolam, cetirizine, doxazosin, glipizide, vaccine hepatitis B, salmeterol, sumatriptan, triamcinolone acetonide, goserelin, beclomethasone, granisetron, desogestrel, alprazolam, estradiol, nicotine, interferon beta 1A, cromolyn, fosinopril, digoxin, fluticasone, bisoprolol, calcitriol, captopril, butorphanol, clonidine, premarin, testosterone, sumatriptan, clotrimazole, bisacodyl, dextromethorphan, nitroglycerine, nafarelin, dinoprostone, nicotine, bisacodyl, goserelin, and granisetron. In certain embodiments, the pharmaceutically active component can be epinephrine, a prodrug of epinephrine a benzodiazepine such as diazepam or lorazepam or alprazolam.

Epinephrine/dipivefrin Examples

In one example, a composition including epinephrine or its salts or esters (such as dipivefrin) can have a biodelivery profile similar to that of epinephrine administered by injection, for example, using an EpiPen. Epinephrine or its prodrug can be present in an amount of from about .01 mg to about 100 mg per dosage, for example, at a 0.1 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg or 100 mg dosage, including greater than 0.1 mg, more than 5 mg, more than 20 mg, more than 30 mg, more than 40 mg, more than 50 mg, more than 60 mg, more than 70 mg, more than 80 mg, more than 90 mg, or less than 100 mg, less than 90 mg, less than 80 mg, less than 70 mg, less than 60 mg, less than 50 mg, less than 40 mg, less than 30 mg, less than 20 mg, less than 10 mg, or less than 5 mg, or any combination thereof. In another example, a composition including diazepam can have a biodelivery profile similar to that of a diazepam tablet or gel, or better.

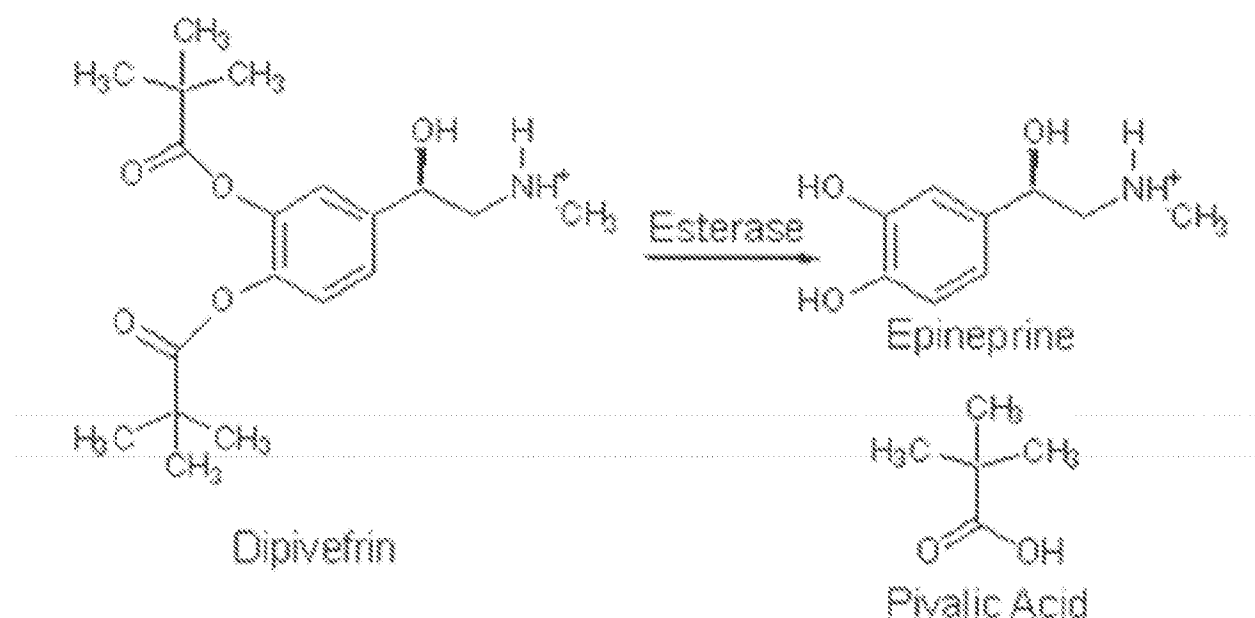
dipivefrin can be present in an amount of from about 0.5 mg to about 100 mg per dosage, for example, at a 0.5mg, 1 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg or 100 mg dosage including greater than 1 mg, more than 5 mg, more than 20 mg, more than 30 mg, more than 40 mg, more than 50 mg, more than 60 mg, more than 70 mg, more than 80 mg, more than 90 mg, or less than 100 mg, less than 90 mg, less than 80 mg, less than 70 mg, less than 60 mg, less than 50 mg, less than 40 mg, less than 30 mg, less than 20 mg, less than 10 mg, or less than 5 mg, or any combination thereof.

In another example, a composition (e.g., including epinephrine) can have a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a mucosal delivery-enhancing agent selected from: (a) an aggregation inhibitory agent; (b) a charge-modifying agent; (c) a pH control agent; (d) a degradative enzyme inhibitory agent; (e) a mucolytic or mucus clearing agent; (f) a ciliostatic agent; (g) a membrane penetration-enhancing agent selected from: (i) a surfactant; (ii) a bile salt; (ii) a phospholipid additive, mixed micelle, liposome, or carrier; (iii) an alcohol; (iv) an enamine; (v) an NO donor compound; (vi) a long chain amphipathic molecule; (vii) a hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid; (x) a cyclodextrin or beta-cyclodextrin derivative; (xi) a medium-chain fatty acid; (xii) a chelating agent; (xiii) an amino acid or salt thereof; (xiv) an N-acetyl amino acid or salt thereof; (xv) an enzyme degradative to a selected membrane component; (ix) an inhibitor of fatty acid synthesis; (x) an inhibitor of cholesterol synthesis; and (xi) any combination of the

membrane penetration enhancing agents recited in (i)-(x); (h) a modulatory agent of epithelial junction physiology; (i) a vasodilator agent; (j) a selective transport-enhancing agent; or (k) a stabilizing delivery vehicle, carrier, mucoadhesive, support or complex-forming species with which the compound is effectively combined, associated, contained, encapsulated or bound

5 resulting in stabilization of the compound for enhanced mucosal delivery, wherein the formulation of the compound with the transmucosal delivery-enhancing agents provides for increased bioavailability of the compound in a blood plasma of a subject. The formulation can include approximately the same active pharmaceutical ingredient (API): enhancer ratio as in the other examples for epinephrine.

10 Administering epinephrine as a prodrug such as dipivefrin confers certain advantages. For one, dipivefrin is lipophilic and therefore has a higher permeation through a mucosa. It also has a longer plasma half life due to higher protein binding. It is capable of sustained blood levels, and does not interact with α -receptors, therefore minimizing or eliminating unwanted or harmful vasoconstriction.



Dipivefrin can be provided as sublingual film in a similar manner as with epinephrine.

A film and/or its components can be water-soluble, water swellable or water-insoluble. The term “water-soluble” can refer to substances that are at least partially dissolvable in an aqueous solvent, including but not limited to water. The term “water-soluble” may not

20

necessarily mean that the substance is 100% dissolvable in the aqueous solvent. The term “water-insoluble” refers to substances that are not dissolvable in an aqueous solvent, including but not limited to water. A solvent can include water, or alternatively can include other solvents (preferably, polar solvents) by themselves or in combination with water.

5 The composition can include a polymeric matrix. Any desired polymeric matrix may be used, provided that it is orally dissolvable or erodible. The dosage should have enough bioadhesion to not be easily removed and it should form a gel like structure when administered. They can be moderate-dissolving in the oral cavity and particularly suitable for delivery of pharmaceutically active components, although both fast release, delayed release, controlled
10 release and sustained release compositions are also among the various embodiments contemplated.

Branched Polymers

 The pharmaceutical composition film can include dendritic polymers which can include highly branched macromolecules with various structural architectures. The dendritic polymers
15 can include dendrimers, dendronised polymers (dendrigrafted polymers), linear dendritic hybrids, multi-arm star polymers, or hyperbranched polymers.

 Hyperbranched polymers are highly branched polymers with imperfections in their structure. However they can be synthesized in a single step reaction which can be an advantage over other dendritic structures and are therefore suitable for bulk volume applications. The
20 properties of these polymers apart from their globular structure are the abundant functional groups, intramolecular cavities, low viscosity and high solubility. Dendritic polymers have been used in several drug delivery applications. See, e.g., Dendrimers as Drug Carriers: Applications in Different Routes of Drug Administration. J Pharm Sci, VOL. 97, 2008, 123-143, which is incorporated by reference herein.

25 The dendritic polymers can have internal cavities which can encapsulate drugs. The steric hindrance caused by the highly dense polymer chains might prevent the crystallization of the drugs. Thus, branched polymers can provide additional advantages in formulating crystallizable drugs in a polymer matrix.

 Examples of suitable dendritic polymers include poly(ether) based dendrons, dendrimers
30 and hyperbranched polymers, poly(ester) based dendrons, dendrimers and hyperbranched polymers, poly(thioether) based dendrons, dendrimers and hyperbranched polymers, poly(amino

acid) based dendrons dendrimers and hyperbranched polymers, poly(arylalkylene ether) based dendrons, dendrimers and hyperbranched polymers, poly(alkyleneimine) based dendrons, dendrimers and hyperbranched polymers, poly(amidoamine) based dendrons, dendrimers or hyperbranched polymers.

5 Other examples of hyperbranched polymers include poly(amines)s, polycarbonates, poly(ether ketone)s, polyurethanes, polycarbosilanes, polysiloxanes, poly(ester amine)s, poly(sulfone amine)s, poly(urea urethane)s and polyether polyols such as polyglycerols.

A film can be produced by a combination of at least one polymer and a solvent, optionally including other components. The solvent may be water, a polar organic solvent including, but not limited to, ethanol, isopropanol, acetone, or any combination thereof. In some
10 embodiments, the solvent may be a non-polar organic solvent, such as methylene chloride. The film may be prepared by utilizing a selected casting or deposition method and a controlled drying process. For example, the film may be prepared through a controlled drying processes, which include application of heat and/or radiation energy to the wet film matrix to form a visco-elastic
15 structure, thereby controlling the uniformity of content of the film. The controlled drying processes can include air alone, heat alone or heat and air together contacting the top of the film or bottom of the film or the substrate supporting the cast or deposited or extruded film or contacting more than one surface at the same time or at different times during the drying process. Some of such processes are described in more detail in U.S. Patent No. 8,765,167 and U.S.
20 Patent No. 8,652,378, which are incorporated by reference herein. Alternatively, the films may be extruded as described in U.S. Patent Publication No. 2005/0037055 A1, which is incorporated by reference herein.

A polymer included in the films may be water-soluble, water-swellaable, water-insoluble, or a combination of one or more either water-soluble, water-swellaable or water-insoluble
25 polymers. The polymer may include cellulose, cellulose derivatives or gums. Specific examples of useful water-soluble polymers include, but are not limited to, polyethylene oxide, pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid,
30 methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof. Specific examples of useful water-insoluble polymers include, but are not limited to,

ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate and combinations thereof. For higher dosages, it may be desirable to incorporate a polymer that provides a high level of viscosity as compared to lower dosages.

As used herein the phrase "water-soluble polymer" and variants thereof refer to a polymer that is at least partially soluble in water, and desirably fully or predominantly soluble in water, or absorbs water. Polymers that absorb water are often referred to as being water-swella-
5 polymers. The materials useful with the present invention may be water-soluble or water-swella-
ble at room temperature and other temperatures, such as temperatures exceeding room temperature. Moreover, the materials may be water-soluble or water-swella-
ble at pressures less
10 than atmospheric pressure. In some embodiments, films formed from such water-soluble polymers may be sufficiently water-soluble to be dissolvable upon contact with bodily fluids.

Other polymers useful for incorporation into the films include biodegradable polymers, copolymers, block polymers or combinations thereof. It is understood that the term "biodegradable" is intended to include materials that chemically degrade, as opposed to materials that physically break apart (i.e., bioerodable materials). The polymers incorporated in the films can also include a combination of biodegradable or bioerodable materials. Among the known useful polymers or polymer classes which meet the above criteria are: poly(glycolic acid) (PGA), poly(lactic acid) (PLA), polydioxanes, polyoxalates, poly(alpha-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates,
20 polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof. Additional useful polymers include, stereopolymers of L- and D-lactic acid, copolymers of bis(p-carboxyphenoxy)propane acid and sebacic acid, sebacic acid copolymers, copolymers of caprolactone, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, copolymers of polyurethane and (poly(lactic acid)), copolymers of alpha-amino
25 acids, copolymers of alpha-amino acids and caproic acid, copolymers of alpha-benzyl glutamate and polyethylene glycol, copolymers of succinate and poly(glycols), polyphosphazene, polyhydroxy-alkanoates or mixtures thereof. The polymer matrix can include one, two, three, four or more components.

Although a variety of different polymers may be used, it is desired to select polymers that provide mucoadhesive properties to the film, as well as a desired dissolution and/or
30 disintegration rate. In particular, the time period for which it is desired to maintain the film in

contact with the mucosal tissue depends on the type of pharmaceutically active component contained in the composition. Some pharmaceutically active components may only require a few minutes for delivery through the mucosal tissue, whereas other pharmaceutically active components may require up to several hours or even longer. Accordingly, in some embodiments, one or more water-soluble polymers, as described above, may be used to form the film. In other embodiments, however, it may be desirable to use combinations of water-soluble polymers and polymers that are water-swellaable, water-insoluble and/or biodegradable, as provided above. The inclusion of one or more polymers that are water-swellaable, water-insoluble and/or biodegradable may provide films with slower dissolution or disintegration rates than films formed from water-soluble polymers alone. As such, the film may adhere to the mucosal tissue for longer periods of time, such as up to several hours, which may be desirable for delivery of certain pharmaceutically active components.

Desirably, an individual film dosage of the pharmaceutical film can have a suitable thickness, and small size, which is between about 0.0625-3 inch by about 0.0625-3 inch. The film size can also be greater than 0.0625 inch, greater than 0.5 inch, greater than 1 inch, greater than 2 inches, about 3 inches, and greater than 3 inches, less than 3 inches, less than 2 inches, less than 1 inch, less than 0.5 inch, less than 0.0625 inch in at least one aspect, or greater than 0.0625 inch, greater than 0.5 inch, greater than 1 inch, greater than 2 inches, or greater than 3 inches, about 3 inches, less than 3 inches, less than 2 inches, less than 1 inch, less than 0.5 inch, less than 0.0625 inch in another aspect. The aspect ratio, including thickness, length, and width can be optimized by a person of ordinary skill in the art based on the chemical and physical properties of the polymeric matrix, the active pharmaceutical ingredient, dosage, enhancer, and other additives involved as well as the dimensions of the desired dispensing unit. The film dosage should have good adhesion when placed in the buccal cavity or in the sublingual region of the user. Further, the film dosage should disperse and dissolve at a moderate rate, most desirably dispersing within about 1 minute and dissolving within about 3 minutes. In some embodiments, the film dosage may be capable of dispersing and dissolving at a rate of between about 1 to about 30 minutes, for example, about 1 to about 20 minutes, or more than 1 minute, more than 5 minutes, more than 7 minutes, more than 10 minutes, more than 12 minutes, more than 15 minutes, more than 20 minutes, more than 30 minutes, about 30 minutes, or less than 30 minutes, less than 20 minutes, less than 15 minutes, less than 12 minutes, less than 10 minutes,

less than 7 minutes, less than 5 minutes, or less than 1 minute. Sublingual dispersion rates may be shorter than buccal dispersion rates.

For instance, in some embodiments, the films may include polyethylene oxide alone or in combination with a second polymer component. The second polymer may be another water-soluble polymer, a water-swellaable polymer, a water-insoluble polymer, a biodegradable polymer or any combination thereof. Suitable water-soluble polymers include, without limitation, any of those provided above. In some embodiments, the water-soluble polymer may include hydrophilic cellulosic polymers, such as hydroxypropyl cellulose and/or hydroxypropylmethyl cellulose. In some embodiments, one or more water-swellaable, water-insoluble and/or biodegradable polymers also may be included in the polyethylene oxide-based film. Any of the water-swellaable, water-insoluble or biodegradable polymers provided above may be employed. The second polymer component may be employed in amounts of about 0% to about 80% by weight in the polymer component, more specifically about 30% to about 70% by weight, and even more specifically about 40% to about 60% by weight, including greater than 5%, greater than 10%, greater than 15%, greater than 20%, greater than 30%, greater than 40%, greater than 50%, greater than 60%, and greater than 70%, about 70%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 20%, less than 10% or less than 5% by weight.

Additives may be included in the films. Examples of classes of additives include preservatives, antimicrobials, excipients, lubricants, buffering agents, stabilizers, blowing agents, pigments, coloring agents, fillers, bulking agents, sweetening agents, flavoring agents, fragrances, release modifiers, adjuvants, plasticizers, flow accelerators, mold release agents, polyols, granulating agents, diluents, binders, buffers, absorbents, glidants, adhesives, anti-adherents, acidulants, softeners, resins, demulcents, solvents, surfactants, emulsifiers, elastomers, anti-tacking agents, anti-static agents and mixtures thereof. These additives may be added with the pharmaceutically active component(s). As used herein, the term “stabilizer” means an excipient capable of preventing aggregation or other physical degradation, as well as chemical degradation, of the active pharmaceutical ingredient, another excipient, or the combination thereof.

Stabilizers may also be classified as antioxidants, sequestrants, pH modifiers, emulsifiers and/or surfactants, and UV stabilizers.

Antioxidants (i.e., pharmaceutically compatible compound(s) or composition(s) that decelerates, inhibits, interrupts and/or stops oxidation processes) include, in particular, the following substances: tocopherols and the esters thereof, sesamol of sesame oil, coniferyl benzoate of benzoin resin, nordihydroguaietic resin and nordihydroguaiaretic acid (NDGA),
 5 gallates (among others, methyl, ethyl, propyl, amyl, butyl, lauryl gallates), butylated hydroxyanisole (BHA/BHT, also butyl-p-cresol); ascorbic acid and salts and esters thereof (for example, acorbyl palmitate), erythorbic acid (isoascorbic acid) and salts and esters thereof, monothioglycerol, sodium formaldehyde sulfoxylate, sodium metabisulfite, sodium bisulfite, sodium sulfite, potassium metabisulfite, butylated hydroxyanisole, butylated hydroxytoluene
 10 (BHT), propionic acid. Typical antioxidants are tocopherol such as, for example, α -tocopherol and the esters thereof, butylated hydroxytoluene and butylated hydroxyanisole. The terms "tocopherol" also includes esters of tocopherol. A known tocopherol is α -tocopherol. The term " α -tocopherol" includes esters of α -tocopherol (for example, α -tocopherol acetate).

Sequestrants (i.e., any compounds which can engage in host-guest complex formation
 15 with another compound, such as the active ingredient or another excipient; also referred to as a sequestering agent) include calcium chloride, calcium disodium ethylene diamine tetra-acetate, glucono delta-lactone, sodium gluconate, potassium gluconate, sodium tripolyphosphate, sodium hexametaphosphate, and combinations thereof. Sequestrants also include cyclic oligosaccharides, such as cyclodextrins, cyclomannins (5 or more α -D-mannopyranose units
 20 linked at the 1,4 positions by α linkages), cyclogalactins (5 or more β -D-galactopyranose units linked at the 1,4 positions by β linkages), cycloaltrins (5 or more α -D-altropyranose units linked at the 1,4 positions by α linkages), and combinations thereof.

pH modifiers include acids (e.g., tartaric acid, citric acid, lactic acid, fumaric acid, phosphoric acid, ascorbic acid, acetic acid, succinic acid, adipic acid and maleic acid), acidic
 25 amino acids (e.g., glutamic acid, aspartic acid, etc.), inorganic salts (alkali metal salt, alkaline earth metal salt, ammonium salt, etc.) of such acidic substances, a salt of such acidic substance with an organic base (e.g., basic amino acid such as lysine, arginine and the like, meglumine and the like), and a solvate (e.g., hydrate) thereof. Other examples of pH modifiers include silicified microcrystalline cellulose, magnesium aluminometasilicate, calcium salts of phosphoric acid
 30 (e.g., calcium hydrogen phosphate anhydrous or hydrate, calcium, sodium or potassium carbonate or hydrogencarbonate and calcium lactate or mixtures thereof), sodium and/or calcium

salts of carboxymethyl cellulose, cross-linked carboxymethylcellulose (e.g., croscarmellose sodium and/or calcium), polacrilin potassium, sodium and or/calcium alginate, docusate sodium, magnesium calcium, aluminium or zinc stearate, magnesium palmitate and magnesium oleate, sodium stearyl fumarate, and combinations thereof.

5 Examples of emulsifiers and/or surfactants include poloxamers or pluronics, polyethylene glycols, polyethylene glycol monostearate, polysorbates, sodium lauryl sulfate, polyethoxylated and hydrogenated castor oil, alkyl polyoside, a grafted water soluble protein on a hydrophobic backbone, lecithin, glyceryl monostearate, glyceryl monostearate/polyoxyethylene stearate, ketostearyl alcohol/sodium lauryl sulfate, carbomer, phospholipids, (C₁₀-C₂₀)-alkyl and alkylene
 10 carboxylates, alkyl ether carboxylates, fatty alcohol sulfates, fatty alcohol ether sulfates, alkylamide sulfates and sulfonates, fatty acid alkylamide polyglycol ether sulfates, alkanesulfonates and hydroxyalkanesulfonates, olefinsulfonates, acyl esters of isethionates, α -sulfo fatty acid esters, alkylbenzenesulfonates, alkylphenol glycol ether sulfonates, sulfosuccinates, sulfosuccinic monoesters and diesters, fatty alcohol ether phosphates,
 15 protein/fatty acid condensation products, alkyl monoglyceride sulfates and sulfonates, alkylglyceride ether sulfonates, fatty acid methyltaurides, fatty acid sarcosinates, sulforicinoleates, and acylglutamates, quaternary ammonium salts (e.g., di-(C₁₀-C₂₄)-alkyl-dimethylammonium chloride or bromide), (C₁₀-C₂₄)-alkyl-dimethylethylammonium chloride or bromide,
 20 (C₁₀-C₂₄)-alkyl-trimethylammonium chloride or bromide (e.g., cetyltrimethylammonium chloride or bromide), (C₁₀-C₂₄)-alkyl-dimethylbenzylammonium chloride or bromide (e.g., (C₁₂-C₁₈)-alkyl-dimethylbenzylammonium chloride), N-(C₁₀-C₁₈)-alkyl-pyridinium chloride or bromide (e.g., N-(C₁₂-C₁₆)-alkyl-pyridinium chloride or bromide), N-(C₁₀-C₁₈)-alkyl-isoquinolinium chloride, bromide or monoalkyl sulfate, N-(C₁₂-C₁₈)-alkyl-polyoylaminoformylmethylpyridinium chloride, N-(C₁₂-C₁₈)-alkyl-N-methylmorpholinium
 25 chloride, bromide or monoalkyl sulfate, N-(C₁₂-C₁₈)-alkyl-N-ethylmorpholinium chloride, bromide or monoalkyl sulfate, (C₁₆-C₁₈)-alkyl-pentaoxethylammonium chloride, diisobutylphenoxyethoxyethyl dimethylbenzylammonium chloride, salts of N,N-diethylaminoethylstearylamine and -oleylamine with hydrochloric acid, acetic acid, lactic acid, citric acid, phosphoric acid, N-acylaminoethyl-N,N-diethyl-N-methylammonium chloride,
 30 bromide or monoalkyl sulfate, and N-acylaminoethyl-N,N-diethyl-N-benzylammonium chloride,

bromide or monoalkyl sulfate (in the foregoing, “acyl” standing for, e.g., stearyl or oleyl), and combinations thereof.

Examples of UV stabilizers include UV absorbers (e.g., benzophenones), UV quenchers (i.e., any compound that dissipates UV energy as heat, rather than allowing the energy to have a degradation effect), scavengers (i.e., any compound that eliminates free radicals resulting from exposure to UV radiation), and combinations thereof.

In other embodiments, stabilizers include ascorbyl palmitate, ascorbic acid, alpha tocopherol, butylated hydroxytoluene, butylated hydroxyanisole, cysteine HCl, citric acid, ethylenediamine tetra acetic acid (EDTA), methionine, sodium citrate, sodium ascorbate, sodium thiosulfate, sodium metabisulfite, sodium bisulfite, propyl gallate, glutathione, thioglycerol, singlet oxygen quenchers, hydroxyl radical scavengers, hydroperoxide removing agents, reducing agents, metal chelators, detergents, chaotropes, and combinations thereof. “Singlet oxygen quenchers” include, but are not limited to, alkyl imidazoles (e.g., histidine, L-carnosine, histamine, imidazole 4-acetic acid), indoles (e.g., tryptophan and derivatives thereof, such as N-acetyl-5-methoxytryptamine, N-acetylserotonin, 6-methoxy-1,2,3,4-tetrahydro-beta-carboline), sulfur-containing amino acids (e.g., methionine, ethionine, djenkolic acid, lanthionine, N-formyl methionine, felinine, S-allyl cysteine, S-aminoethyl-L-cysteine), phenolic compounds (e.g., tyrosine and derivatives thereof), aromatic acids (e.g., ascorbate, salicylic acid, and derivatives thereof), azide (e.g., sodium azide), tocopherol and related vitamin E derivatives, and carotene and related vitamin A derivatives. “Hydroxyl radical scavengers” include, but are not limited to azide, dimethyl sulfoxide, histidine, mannitol, sucrose, glucose, salicylate, and L-cysteine. “Hydroperoxide removing agents” include, but are not limited to catalase, pyruvate, glutathione, and glutathione peroxidases. “Reducing agents” include, but are not limited to, cysteine and mercaptoethylene. “Metal chelators” include, but are not limited to, EDTA, EGTA, o-phenanthroline, and citrate. “Detergents” include, but are not limited to, SDS and sodium lauroyl sarcosyl. “Chaotropes” include, but are not limited to guanidinium hydrochloride, isothiocyanate, urea, and formamide. As discussed herein, stabilizers can be present in 0.0001%-50% by weight, including greater than 0.0001%, greater than 0.001%, greater than 0.01%, greater than 0.1%, greater than 1%, greater than 5%, greater than 10%, greater than 20%, greater than 30%, greater than 40%, greater than 50%, less than 50%, less than 40%, less than 30%, less than 20%,

less than 10%, less than 1%, less than 0.1%, less than 0.01%, less than 0.001%, or less than 0.0001% by weight.

Useful additives can include, for example, gelatin, vegetable proteins such as sunflower protein, soybean proteins, cotton seed proteins, peanut proteins, grape seed proteins, whey proteins, whey protein isolates, blood proteins, egg proteins, acrylated proteins, water-soluble polysaccharides such as alginates, carrageenans, guar gum, agar-agar, xanthan gum, gellan gum, gum arabic and related gums (gum ghatti, gum karaya, gum tragacanth), pectin, water-soluble derivatives of cellulose: alkylcelluloses hydroxyalkylcelluloses and hydroxyalkylalkylcelluloses, such as methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose esters and hydroxyalkylcellulose esters such as cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose (HPMC); carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters such as carboxymethylcellulose and their alkali metal salts; water-soluble synthetic polymers such as polyacrylic acids and polyacrylic acid esters, polymethacrylic acids and polymethacrylic acid esters, polyvinylacetates, polyvinylalcohols, polyvinylacetatephthalates (PVAP), polyvinylpyrrolidone (PVP), PVA/vinyl acetate copolymer, and polycrotonic acids; also suitable are phthalated gelatin, gelatin succinate, crosslinked gelatin, shellac, water-soluble chemical derivatives of starch, cationically modified acrylates and methacrylates possessing, for example, a tertiary or quaternary amino group, such as the diethylaminoethyl group, which may be quaternized if desired; or other similar polymers.

The additional components can range up to about 80%, desirably about 0.005% to 50% and more desirably within the range of 1% to 20% based on the weight of all composition components, including greater than 1%, greater than 5%, greater than 10%, greater than 20%, greater than 30%, greater than 40%, greater than 50%, greater than 60%, greater than 70%, about 80%, greater than 80%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, less than 5%, about 3%, or less than 1%. Other additives can include anti-tacking, flow agents and opacifiers, such as the oxides of magnesium aluminum, silicon, titanium, etc. desirably in a concentration range of about 0.005% to about 5% by weight and desirably about 0.02% to about 2% based on the weight of all film components, including greater than 0.02%, greater than 0.2%, greater than 0.5%, greater than

1%, greater than 1.5%, greater than 2%, greater than 4%, about 5%, greater than 5%, less than 4%, less than 2%, less than 1%, less than 0.5%, less than 0.2%, or less than 0.02%.

In certain embodiments, the composition can include plasticizers, which can include polyalkylene oxides, such as polyethylene glycols, polypropylene glycols, polyethylene-
5 propylene glycols, organic plasticizers with low molecular weights, such as glycerol, glycerol monoacetate, diacetate or triacetate, triacetin, polysorbate, cetyl alcohol, propylene glycol, sugar alcohols sorbitol, sodium diethylsulfosuccinate, triethyl citrate, tributyl citrate, phytoextracts, fatty acid esters, fatty acids, oils and the like, added in concentrations ranging from about 0.1% to about 40%, and desirably ranging from about 0.5% to about 20% based on the weight of the
10 composition including greater than 0.5%, greater than 1%, greater than 1.5%, greater than 2%, greater than 4%, greater than 5%, greater than 10%, greater than 15%, about 20%, greater than 20%, less than 20%, less than 15%, less than 10%, less than 5%, less than 4%, less than 2%, less than 1%, and less than 0.5%. There may further be added compounds to improve the texture properties of the film material such as animal or vegetable fats, desirably in their hydrogenated
15 form. The composition can also include compounds to improve the textural properties of the product. Other ingredients can include binders which contribute to the ease of formation and general quality of the films. Non-limiting examples of binders include starches, natural gums, pregelatinized starches, gelatin, polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinylloxazolidone, or
20 polyvinylalcohols.

Further potential additives include solubility enhancing agents, such as substances that form inclusion compounds with active components. Such agents may be useful in improving the properties of very insoluble and/or unstable actives. In general, these substances are doughnut-shaped molecules with hydrophobic internal cavities and hydrophilic exteriors. Insoluble and/or
25 instable pharmaceutically active components may fit within the hydrophobic cavity, thereby producing an inclusion complex, which is soluble in water. Accordingly, the formation of the inclusion complex permits very insoluble and/or unstable pharmaceutically active components to be dissolved in water. A particularly desirable example of such agents are cyclodextrins, which are cyclic carbohydrates derived from starch. Other similar substances, however, are considered
30 well within the scope of the present invention.

Suitable coloring agents include food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug and cosmetic colors (Ext. D&C). These colors are dyes, their corresponding lakes, and certain natural and derived colorants. Lakes are dyes absorbed on aluminum hydroxide. Other examples of coloring agents include known azo dyes, organic or inorganic pigments, or coloring agents of natural origin. Inorganic pigments are preferred, such as the oxides of iron or titanium, these oxides, being added in concentrations ranging from about 0.001 to about 10%, and preferably about 0.5 to about 3%, including greater than 0.001%, greater than 0.01%, greater than 0.1%, greater than 0.5%, greater than 1%, greater than 2%, greater than 5%, about 10%, greater than 10%, less than 10%, less than 5%, less than 2%, less than 1%, less than 0.5%, less than 0.1%, less than 0.01%, or less than 0.001%, based on the weight of all the components.

Flavors may be chosen from natural and synthetic flavoring liquids. An illustrative list of such agents includes volatile oils, synthetic flavor oils, flavoring aromatics, oils, liquids, oleoresins or extracts derived from plants, leaves, flowers, fruits, stems and combinations thereof. A non-limiting representative list of examples includes mint oils, cocoa, and citrus oils such as lemon, orange, lime and grapefruit and fruit essences including apple, pear, peach, grape, strawberry, raspberry, cherry, plum, pineapple, apricot or other fruit flavors. Other useful flavorings include aldehydes and esters such as benzaldehyde (cherry, almond), citral i.e., aliphatic citral (lemon, lime), neral, i.e., beta-citral (lemon, lime), decanal (orange, lemon), aldehyde C-8 (citrus fruits), aldehyde C-9 (citrus fruits), aldehyde C-12 (citrus fruits), tolyl aldehyde (cherry, almond), 2,6-dimethyloctanol (green fruit), and 2-dodecenal (citrus, mandarin), combinations thereof and the like.

The sweeteners may be chosen from the following non-limiting list: glucose (corn syrup), dextrose, invert sugar, fructose, and combinations thereof, saccharin and its various salts such as the sodium salt; dipeptide based sweeteners such as aspartame, neotame, advantame; dihydrochalcone compounds, glycyrrhizin; Stevia Rebaudiana (Stevioside); chloro derivatives of sucrose such as sucralose; sugar alcohols such as sorbitol, mannitol, xylitol, and the like. Also contemplated are hydrogenated starch hydrolysates and the synthetic sweetener 3,6-dihydro-6-methyl-1,1,2,3-oxathiazin-4-one-2,2-dioxide, particularly the potassium salt (acesulfame-K), and sodium and calcium salts thereof, and natural intensive sweeteners, such as Lo Han Kuo. Other sweeteners may also be used.

Anti-foaming and/or de-foaming components may also be used with the films. These components aid in the removal of air, such as entrapped air, from the film-forming compositions. Such entrapped air may lead to non-uniform films. Simethicone is one particularly useful anti-foaming and/or de-foaming agent. The present invention, however, is not so limited and other suitable anti-foam and/or de-foaming agents may be used. Simethicone and related agents may be employed for densification purposes. More specifically, such agents may facilitate the removal of voids, air, moisture, and similar undesired components, thereby providing denser and thus more uniform films. Agents or components which perform this function can be referred to as densification or densifying agents. As described above, entrapped air or undesired components may lead to non-uniform films.

Any other optional components described in commonly assigned U.S. Patent No. 7,425,292 and U.S. Patent No. 8,765,167, referred to above, also may be included in the films described herein.

The film compositions further desirably contains a buffer so as to control the pH of the film composition. Any desired level of buffer may be incorporated into the film composition so as to provide the desired pH level encountered as the pharmaceutically active component is released from the composition. The buffer is preferably provided in an amount sufficient to control the release from the film and/or the absorption into the body of the pharmaceutically active component. In some embodiments, the buffer may include sodium citrate, citric acid, bitartrate salt and combinations thereof.

The pharmaceutical films described herein may be formed via any desired process. Suitable processes are set forth in U.S. Patent Nos. 8,652,378, 7,425,292 and 7,357,891, which are incorporated by reference herein. In one embodiment, the film dosage composition is formed by first preparing a wet composition, the wet composition including a polymeric carrier matrix and a therapeutically effective amount of a pharmaceutically active component. The wet composition is cast into a film and then sufficiently dried to form a self-supporting film composition. The wet composition may be cast into individual dosages, or it may be cast into a sheet, where the sheet is then cut into individual dosages.

The pharmaceutical composition can adhere to a mucosal surface. The present invention finds particular use in the localized treatment of body tissues, diseases, or wounds which may have moist surfaces and which are susceptible to bodily fluids, such as the mouth, the vagina,

organs, or other types of mucosal surfaces. The composition carries a pharmaceutical, and upon application and adherence to the mucosal surface, offers a layer of protection and delivers the pharmaceutical to the treatment site, the surrounding tissues, and other bodily fluids. The composition provides an appropriate residence time for effective drug delivery at the treatment site, given the control of erosion in aqueous solution or bodily fluids such as saliva, and the slow, natural erosion of the film concomitant or subsequent to the delivery.

The residence time of the composition depends on the erosion rate of the water erodable polymers used in the formulation and their respective concentrations. The erosion rate may be adjusted, for example, by mixing together components with different solubility characteristics or chemically different polymers, such as hydroxyethyl cellulose and hydroxypropyl cellulose; by using different molecular weight grades of the same polymer, such as mixing low and medium molecular weight hydroxyethyl cellulose; by using excipients or plasticizers of various lipophilic values or water solubility characteristics (including essentially insoluble components); by using water soluble organic and inorganic salts; by using crosslinking agents such as glyoxal with polymers such as hydroxyethyl cellulose for partial crosslinking; or by post-treatment irradiation or curing, which may alter the physical state of the film, including its crystallinity or phase transition, once obtained. These strategies might be employed alone or in combination in order to modify the erosion kinetics of the film. Upon application, the pharmaceutical composition film adheres to the mucosal surface and is held in place. Water absorption softens the composition, thereby diminishing the foreign body sensation. As the composition rests on the mucosal surface, delivery of the drug occurs. Residence times may be adjusted over a wide range depending upon the desired timing of the delivery of the chosen pharmaceutical and the desired lifespan of the carrier. Generally, however, the residence time is modulated between about a few seconds to about a few days. Preferably, the residence time for most pharmaceuticals is adjusted from about 5 seconds to about 24 hours. More preferably, the residence time is adjusted from about 5 seconds to about 30 minutes. In addition to providing drug delivery, once the composition adheres to the mucosal surface, it also provides protection to the treatment site, acting as an erodable bandage. Lipophilic agents can be designed to slow down erodability to decrease disintegration and dissolution.

It is also possible to adjust the kinetics of erodability of the composition by adding excipients which are sensitive to enzymes such as amylase, very soluble in water such as water

soluble organic and inorganic salts. Suitable excipients may include the sodium and potassium salts of chloride, carbonate, bicarbonate, citrate, trifluoroacetate, benzoate, phosphate, fluoride, sulfate, or tartrate. The amount added can vary depending upon how much the erosion kinetics is to be altered as well as the amount and nature of the other components in the composition.

5 Emulsifiers typically used in the water-based emulsions described above are, preferably, either obtained in situ if selected from the linoleic, palmitic, myristoleic, lauric, stearic, cetoleic or oleic acids and sodium or potassium hydroxide, or selected from the laurate, palmitate, stearate, or oleate esters of sorbitol and sorbitol anhydrides, polyoxyethylene derivatives including monooleate, monostearate, monopalmitate, monolaurate, fatty alcohols, alkyl phenols,
10 allyl ethers, alkyl aryl ethers, sorbitan monostearate, sorbitan monooleate and/or sorbitan monopalmitate.

 The amount of pharmaceutically active component to be used depends on the desired treatment strength and the composition of the layers, although preferably, the pharmaceutical component comprises from about 0.001% to about 99%, more preferably from about 0.003 to
15 about 75%, and most preferably from about 0.005% to about 50% by weight of the composition, including, more than 0.005%, more than 0.05%, more than 0.5%, more than 1%, more than 5%, more than 10%, more than 15%, more than 20%, more than 30%, about 50%, more than 50%, less than 50%, less than 30%, less than 20%, less than 15%, less than 10%, less than 5%, less than 1%, less than 0.5%, less than 0.05%, or less than 0.005%. The amounts of other components
20 may vary depending on the drug or other components but typically these components comprise no more than 50%, preferably no more than 30%, and most preferably no more than 15% by total weight of the composition.

 The thickness of the film may vary, depending on the thickness of each of the layers and the number of layers. As stated above, both the thickness and amount of layers may be adjusted
25 in order to vary the erosion kinetics. Preferably, if the composition has only two layers, the thickness ranges from 0.005 mm to 2 mm, preferably from 0.01 to 1 mm, and more preferably from 0.1 to 0.5 mm, including greater than 0.1 mm, greater than 0.2 mm, about 0.5 mm, greater than 0.5 mm, less than 0.5 mm, less than 0.2 mm, or less than 0.1 mm. The thickness of each layer may vary from 10 to 90% of the overall thickness of the layered composition, and
30 preferably varies from 30 to 60%, including greater than 10%, greater than 20%, greater than 30%, greater than 40%, greater than 50%, greater than 70%, greater than 90%, about 90%, less

than 90%, less than 70%, less than 50%, less than 40%, less than 30%, less than 20%, or less than 10%. Thus, the preferred thickness of each layer may vary from 0.01 mm to 0.9 mm, or from 0.03 to 0.5 mm.

As one skilled in the art will appreciate, when systemic delivery, e.g., transmucosal or transdermal delivery is desired, the treatment site may include any area in which the film is capable of delivery and/or maintaining a desired level of pharmaceutical in the blood, lymph, or other bodily fluid. Typically, such treatment sites include the oral, esophageal, aural, ocular, anal, nasal, and vaginal mucosal tissue, as well as, the skin. If the skin is to be employed as the treatment site, then usually larger areas of the skin wherein movement will not disrupt the adhesion of the film, such as the upper arm or thigh, are preferred.

The pharmaceutical composition can also be used as a wound dressing. By offering a physical, compatible, oxygen and moisture permeable, flexible barrier which can be washed away, the film can not only protect a wound but also deliver a pharmaceutical in order to promote healing, aseptic, scarification, to ease the pain or to improve globally the condition of the sufferer. Some of the examples given below are well suited for an application to the skin or a wound. As one skilled in the art will appreciate, the formulation might require incorporating a specific hydrophilic/hygroscopic excipient which would help in maintaining good adhesion on dry skin over an extended period of time. Another advantage of the present invention when utilized in this manner is that if one does not wish that the film be noticeable on the skin, then no dyes or colored substances need be used. If, on the other hand, one desires that the film be noticeable, a dye or colored substance may be employed.

While the pharmaceutical composition can adhere to mucosal tissues, which are wet tissues by nature, it can also be used on other surfaces such as skin or wounds. The pharmaceutical film can adhere to the skin if prior to application the skin is wet with an aqueous-based fluid such as water, saliva, wound drainage or perspiration. The film can adhere to the skin until it erodes due to contact with water by, for example, rinsing, showering, bathing or washing. The film may also be readily removed by peeling without significant damage to tissue.

A Franz diffusion cell is an in vitro skin permeation assay used in formulation development. The Franz diffusion cell apparatus (**Figure 1A**) consists of two chambers separated by a membrane of, for example, animal or human tissue. The test product is applied to the membrane via the top chamber. The bottom chamber contains fluid from which samples are taken at regular intervals

for analysis to determine the amount of active that has permeated the membrane. Referring to **Figure 1A**, a Franz diffusion cell 100 includes a donor compound 101, a donor chamber 102, a membrane 103, sampling port 104, receptor chamber 105, stir bar 106, and a heater/circulator 107.

5 Referring to **Figure 1B**, a pharmaceutical composition is a film 100 comprising a polymeric matrix 200, the pharmaceutically active component 300 being contained in the polymeric matrix. The film can include a permeation enhancer 400.

Referring to **Figures 2A** and **2B**, the graphs show the permeation of an active material from a composition. The graph shows that for the epinephrine base – solubilized in-situ vs. the
10 inherently soluble epinephrine bitartrate, no meaningful differences were observed. Epinephrine bitartrate was selected for further development based on ease of processing. Flux is derived as slope of the amount permeated as a function of time. Steady state flux is taken from the plateau of flux vs time curve multiplied by the volume of receiver media and normalized for permeation area.

15 Referring to **Figure 2A**, this graph shows average amount of active material permeated vs. time, with 8.00 mg/mL epinephrine bitartrate and 4.4 mg/mL epinephrine base solubilized.

Referring to **Figure 2B**, this graph shows average flux vs. time, with 8.00 mg/mL epinephrine bitartrate and 4.4 mg/mL epinephrine base solubilized.

Referring to **Figure 3**, this graph shows ex-vivo permeation of epinephrine bitartrate as a
20 function of concentration. The study compared concentrations of 4 mg/mL, 8 mg/mL, 16 mg/mL and 100 mg/mL. Results showed that increasing concentration resulted in increased permeation, and level of enhancement diminishes at higher loading.

Referring to **Figure 4**, this graph shows permeation of epinephrine bitartrate as a function of solution pH. Acidic conditions explored to promote stability. The results compared
25 epinephrine bitartrate pH 3 buffer and epinephrine bitartrate pH 5 buffer, and found that the epinephrine bitartrate pH 5 buffer was slightly favorable.

Referring to **Figure 5**, this graph shows the influence of enhancers on permeation of epinephrine, indicated as amount permeated as a function of time. Multiple enhancers were screened, including Labrasol, capryol 90, Plurol Oleique, Labrafil, TDM, SGDC, Gelucire 44/14
30 and clove oil. Significant impact on time to onset and steady state flux was achieved, and surprisingly enhanced permeation was achieved for clove oil and Labrasol.

Referring to **Figure 6A** and **6B**, these graphs show the release of epinephrine on polymer platforms and the effect of enhancers on its release, indicated as amount permeated (in μg) vs. time. **Figure 6A** shows the epinephrine release from different polymer platforms. **Figure 6B** shows the impact of enhancers on epinephrine release.

5 Referring to **Figure 7**, this graph shows a pharmacokinetic model in the male Yucatan, miniature swine. The study compares a 0.3 mg Epipen, a 0.12 mg Epinephrine IV and a placebo film.

Referring to **Figure 8**, this graphs shows the impact of no enhancer on the concentration profiles of a 40 mg epinephrine film vs, a 0.3 mg Epipen.

10 Referring to **Figure 9**, this graph shows the impact of Enhancer A (Labrasol) on the concentration profiles of a 40 mg epinephrine film vs, a 0.3 mg Epipen. Referring to **Figure 10**, this graph shows the impact of Enhancer L (clove oil) on the concentration profiles of two 40 mg Epinephrine films (10-1-1) and (11-1-1) vs. a 0.3 mg Epipen.

Referring to **Figure 11**, This graph shows the impact of Enhancer L(clove oil) and film dimension (10-1-1 thinner bigger film and 11-1-1 thicker smaller film) on the concentration profiles of 40 mg Epinephrine films vs. a 0.3 mg Epipen.

Referring to **Figure 12**, this graph shows the concentration profiles for varying doses of Epinephrine films in a constant matrix for Enhancer L (clove oil) vs. a 0.3 mg Epipen.

Referring to **Figure 13**, the graph shows the concentration profiles for varying doses of Epinephrine films in a constant matrix for Enhancer L (clove oil) vs. a 0.3 mg Epipen.

Referring to **Figure 14**, the graph shows the concentration profiles for varying doses of Epinephrine films in a constant matrix for Enhancer A (Labrasol) vs. a 0.3 mg Epipen.

Referring to **Figure 15**, this graph shows the impact of Farnesol and Farnesol in combination with Linoleic Acid on plasma concentration profiles of 40 mg Epinephrine Films vs. a 0.3 mg Epipen.

Referring to **Figure 16**, this graph shows the impact of Farnesol and Farnesol in combination with Linoleic Acid on plasma concentration profiles of 40 mg Epinephrine Films vs. a 0.3 mg Epipen.

Referring to **Figure 17**, this graph shows the impact of Farnesol in combination with Linoleic Acid on plasma concentration profiles of 40 mg Epinephrine Films vs. a 0.3 mg Epipen.

Referring to **Figure 18**, this graph shows the impact of Farnesol and Farnesol in combination with Linoleic Acid on plasma concentration profiles of 40 mg Epinephrine Films vs. a 0.3 mg Epipen. The following examples are provided to illustrate pharmaceutical compositions, as well as, methods of making and using, pharmaceutical compositions and devices described herein.

EXAMPLES

Example 1

Permeation Enhancers - Epinephrine

Permeation enhancement was studied using a number of permeation enhancers with Epinephrine Bitartrate 16.00 mg/mL concentration. The results show flux enhancement represented in the data below. For 100% Eugenol and 100% Clove Oil, the results showed steady state flux reached significantly earlier along with an unexpectedly heightened % flux enhancement.

Donor Solution (16.00mg/mL Epinephrine Bitartrate + enhancer)	Average Steady State Flux (ug/cm2*min)	% Flux enhancement	Permeability
			Coefficient (cm/s)
Epinephrine Bitartrate ,no enhancer	1.3173	N/A	1.37E-06
3% Clove Oil	8.2704	527.84	8.61E-06
3% Clove Oil Repeat	5.3776	308.24	5.60E-06
3% Eugenol	7.1311	441.35	7.43E-06
3% Eugenyl Acetate	1.8945	43.82	1.97E-06
3% B-Caryophyllene	3.5200	167.22	3.67E-06
0.3% Eugenol*	3.9735	201.65	4.14E-06
100% Eugenol ¹	36.8432	2696.92	3.84E-05
0.3% Clove Oil*	3.6806	179.41	3.83E-06
100% Clove Oil ¹	52.5304	3887.81	5.47E-05
3% Phenol	4.5790	247.61	4.77E-06
3% Phenol Repeat	4.1753	216.97	4.35E-06
3% Linoleic Acid	2.1788	65.40	2.27E-06
50% Clove Oil	2.5673	94.89	2.67E-06
0.3% Labrasol	3.5221	167.38	3.67E-06
3% Vanillyl Alcohol+ 6% Ethanol	1.10243	-16.31	1.15E-06
3% Safrole	2.60634	97.86	2.71E-06
3% Oleic Acid	2.06597	56.84	2.15E-06
3% Oleic Acid + 1% PEG200	2.73655	107.74	2.85E-06
3% Benzyl Alcohol	1.38455	5.11	1.44E-06

¹ steady state flux reached at much earlier time point

* 0.3% Eugenol vs 0.3% Clove -similar flux rates to one another

For these examples, clove oil was obtained from clove leaf. Similar results may be obtained from clove oil from clove bud and/or clove stem. Based on this data, similar permeability enhancement results can be expected from pharmaceutical compounds structurally similar to epinephrine.

Example 2**General Permeation Procedure – Ex vivo Permeation Study Protocol**

In one example, a permeation procedure is conducted as follows. A temperature bath is set to 37° C, and receiver media is placed in a water bath to adjust the temperature and begin degassing. A franz diffusion cell is obtained and prepared. The franz diffusion cell includes a donor compound, a donor chamber, a membrane, sampling port, receptor chamber, stir bar, and a heater/circulator. A stir bar is inserted into a franz diffusion cell. Tissue is placed over the franz diffusion cell, and it is ensured that the tissue covers the entire area with an overlap onto a glass joint. The top of a diffusion cell is placed over the tissue, and the top of the cell is clamped to the bottom. About 5 mL of receptor media is loaded into the receiver area to ensure that no air bubbles are trapped in the received portion of the cell. This ensures that all 5mL can fit into the receiver area. Stirring is begun, and temperature is allowed to equilibrate for about 20 minutes. Meanwhile, High Performance Liquid Chromatography (HPLC) vials are labelled by cell number and time point. One must then check again for air bubbles as the solution will degas during heating.

If testing films, one can perform the following next steps: (1) weigh films, punch to match diffusion area (or smaller), reweigh, record pre- and post-punching weight; (2) wet a donor area with approximately 100 µL of phosphate buffer; (3) place film on a donor surface, top with 400 µL of phosphate buffer, and start timers.

For solution studies, one can perform the following steps: (1) using a micropipette, dispense 500 µL of the solution into each donor cell, start the timers; (2) sample 200 µL at the following time points (time = 0 min, 20 min, 40 min, 60 min, 120 min, 180 min, 240 min, 300 min, 360 min), and place in labelled HPLC vials, ensure no air is trapped in the bottom of the vial by tapping the closed vials; (3) replace each sample time with 200 µL of receptor media (to maintain 5 mL); (4) When all time points completed, disassemble the cells and dispose of all materials properly.

Example 3**Ex vivo Permeation Evaluation**

An exemplary ex vivo permeation evaluation is as follows.

1. Tissue is freshly excised and shipped (e.g. overnight) at 4° C.
2. The tissue is processed and frozen at -20° C for up to three weeks prior to use.
3. The tissue is dermatomed to precise thickness.
4. Approximately 5 mL of receiving media is added to the receiving compartment. The media is selected to ensure sink conditions.
5. The tissue is placed in a franz diffusion cell, which includes a donor compound, a donor chamber, a membrane, sampling port, receptor chamber, stir bar, and a heater/circulator.
6. Approximately 0.5 mL of donor solution is applied on 8 mm circular film and wetted with 500µL PBS buffer.
7. Samples are taken from the receiving chamber at given intervals and replaced with fresh media.

Example 4

Transbuccal delivery of doxepin

The following is an exemplary permeation study on the transbuccal delivery of doxepin. The studies were conducted under a protocol approved by the Animal Experimentation Ethics Committee of the University of Barcelona (Spain) and the Committee of Animal Experimentation of the regional autonomous government of Catalonia (Spain). Female pigs 3–4-months-old were used. The porcine buccal mucosa from the cheek region was excised immediately after the pigs were sacrificed in the animal facility at Bellvitge Campus (University of Barcelona, Spain) using an overdose of sodium thiopental anesthesia. The fresh buccal tissues were transferred from the hospital to the laboratory in containers filled with Hank's solution. The remaining tissue specimens were stored at -80° C in containers with a PBS mixture containing 4% albumin and 10% DMSO as cryoprotective agents.

For the permeation studies, the porcine buccal mucosa was cut to 500 +/- 50 µm thick sheets, which contributes to the diffusional barrier (Buccal bioadhesive drug delivery — A promising option for orally less efficient drugs Sudhakar et al., *Journal of Controlled Release* 114 (2006) 15–40), using an electric dermatome (GA 630, Aesculap, Tuttlingen, Germany) and trimmed with surgical scissors in adequate pieces. The majority of the underlying connective tissue was removed with a scalpel.

Membranes were then mounted in specially designed membrane holders with a permeation orifice diameter of 9 mm (diffusion area 0.636 cm²). Using the membrane holder, each porcine buccal membrane was mounted between the donor (1.5 mL) and the receptor (6 mL) compartments with the epithelium side facing the donor chamber and the connective tissue region facing the receiver of static Franz-type diffusion cells (Vidra Foc Barcelona, Spain) avoiding bubbles formation.

Infinite dose conditions were ensured by applying 100 µL as donor solution of a saturated doxepin solution into the receptor chamber and sealed by Parafilm immediately to prevent water evaporation. Prior to conducting the experiments, the diffusion cells were incubated for 1 h in a water bath to equalize the temperature in all cells (37° +/- ° C). Each cell contained a small Teflon coated magnetic stir bar which was used to ensure that the fluid in the receptor compartment remained homogenous during the experiments.

Sink conditions were ensured in all experiments by initial testing of doxepin saturation concentration in the receptor medium. Samples (300 µL) were drawn via syringe from the center of the receptor compartment at pre-selected time intervals (0.1, 0.2, 0.3, 0.7, 1, 2, 3, 4, 5 and 6 h) for 6 h. The removed sample volume was immediately replaced with the same volume of fresh receptor medium (PBS; pH 7.4) with great care to avoid trapping air beneath the membrane.

Additional details can be found in A. Gimeno, et al. Transbuccal delivery of doxepin: Studies on permeation and histological evaluation, *International Journal of Pharmaceutics* 477 (2014), 650-654, which is incorporated by reference herein.

Example 5

Oral transmucosal delivery

Porcine oral mucosal tissue has similar histological characteristics to human oral mucosal tissue (Heaney TG, Jones RS, Histological investigation of the influence of adult porcine alveolar mucosal connective tissues on epithelial differentiation. *Arch Oral Biol* 23 (1978) 713–717; Squier CA, and Collins P, The relationship between soft tissue attachment, epithelial downgrowth and surface porosity. *Journal of Periodontal Research* 16 (1981) 434-440). Lesch et al. (The Permeability of Human Oral Mucosa and Skin to Water, *J Dent Res* 68 (9), 1345-1349, 1989) reported that the water permeability of porcine buccal mucosa was not significantly different from human buccal mucosa but the floor of the mouth was more permeable in human

tissue than in pig tissue. Comparisons between fresh porcine tissue specimens and those stored at -80° C revealed no significant effect on permeability as a result of freezing. Porcine buccal mucosal absorption has been studied for a wide range of drug molecules both in vitro and in vivo (see, e.g., Table 1 of M. Sattar, Oral transmucosal drug delivery – current status and future prospects, *International Journal of Pharmaceutics* 471 (2014) 498-506), which is incorporated by reference herein. Typically, in vitro studies involve mounting excised porcine buccal tissue in Ussing chambers, Franz cells or similar diffusion apparatus. The in vivo studies described in the literature involve the application of the drug as a solution, gel or composition to the buccal mucosa of pigs followed by plasma sampling.

Nicolazzo et al. (The Effect of Various in Vitro Conditions on the Permeability Characteristics of the Buccal Mucosa, *Journal of Pharmaceutical Sciences* 92(12) (2002) 2399-2410) investigated the effects of various in vitro conditions on the permeability of porcine buccal tissue using caffeine and oestradiol as model hydrophilic and lipophilic molecules. Drug permeation in the buccal mucosa was studied using modified Ussing chambers. Comparative permeation studies were performed through full thickness and epithelial tissues, fresh and frozen tissues. Tissue integrity was monitored by the absorption of the fluorescein isothiocyanate (FITC)-labeled dextran 20 kDa (FD20) and tissue viability was assessed using an MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) biochemical assay and histological evaluation. Permeability through the buccal epithelium was 1.8-fold greater for caffeine and 16.7-fold greater for oestradiol compared with full thickness buccal tissue. Flux values for both compounds were comparable for fresh and frozen buccal epithelium although histological evaluation demonstrated signs of cellular death in frozen tissue. The tissue appeared to remain viable for up to 12 h postmortem using the MTT viability assay which was also confirmed by histological evaluation.

Kulkarni et al. investigated the relative contributions of the epithelium and connective tissue to the barrier properties of porcine buccal tissue. In vitro permeation studies were conducted with antipyrine, buspirone, bupivacaine and caffeine as model permeants. The permeability of the model diffusants across buccal mucosa with thickness of 250, 400, 500, 600, and 700 µm was determined. A bilayer membrane model was developed to delineate the relative contribution to the barrier function of the epithelium and the connective tissue. The relative contribution of the connective tissue region as a permeability barrier significantly increased with

increasing mucosal tissue thickness. A mucosal tissue thickness of approximately 500 μm was recommended by the authors for in vitro transbuccal permeation studies as the epithelium represented the major permeability barrier for all diffusants at this thickness. The authors also investigated the effects of a number of biological and experimental variables on the permeability of the same group of model permeants in porcine buccal mucosa (Porcine buccal mucosa as in vitro model: effect of biological and experimental variables, Kulkarni et al., *J Pharm Sci.* 2010 99(3):1265-77). Significantly, higher permeability of the permeants was observed for the thinner region behind the lip (170–220 μm) compared with the thicker cheek (250–280 μm) region. Porcine buccal mucosa retained its integrity in Kreb's bicarbonate ringer solution at 4 °C for 24 h. Heat treatment to separate the epithelium from underlying connective tissue did not adversely affect its permeability and integrity characteristics compared with surgical separation.

Additional details can be found at M. Sattar, Oral transmucosal drug delivery – current status and future prospects, *International Journal of Pharmaceutics* 471 (2014) 498-506, which is incorporated by reference herein.

Example 6

Cryopreservation of buccal mucosa

Different areas of porcine buccal mucosa have different pattern of permeability, there is significantly higher permeability in the region behind the lips in comparison to cheek region, because in porcine buccal mucosa, the epithelium acts as a permeability barrier, and the thickness of the cheek epithelium is greater than that of the region behind the lips (Harris and Robinson, 1992). In exemplary permeation studies, the fresh or frozen porcine buccal mucosa from the same area was cut to 500 ± 50 μm thick sheets, which contributes to the diffusional barrier (Sudhakar et al., 2006), were obtained using an electric dermatome (model GA 630, Aesculap, Tuttlingen, Germany) and trimmed with surgical scissors in adequate pieces. All devices utilized were previously sterilized. The majority of the underlying connective tissue was removed with a scalpel. Membranes were then mounted in specially designed membrane holders with a permeation orifice diameter of 9 mm (diffusion area 0.63 cm^2). Using the membrane holder, each porcine buccal membrane was mounted between the donor (1.5 mL) and the receptor (6 mL) compartments with the epithelium facing the donor chamber and the connective tissue region facing the receiver of static Franz-type diffusion cells (Vidra Foc, Barcelona,

Spain) avoiding bubbles formation. Experiments were performed using PP, which has lipophilic characteristics ($\log P = 1.16$; n-octanol/PBS, pH 7.4), ionisable ($pK_a = 9.50$) and a MW= 259.3 g/mol, as a model drug (Modamio et al., 2000).

Infinite dose conditions were ensured by applying 300 μ L as a donor solution of a saturated solution of PP ($C_0 = 588005 \pm 5852 \mu\text{g/mL}$ at $37^\circ \pm 1^\circ\text{C}$, $n = 6$), in PBS (pH 7.4) into the receptor chamber and sealed by Parafilm immediately to prevent water evaporation.

Prior to conducting the experiments, the diffusion cells were incubated for 1 h in a water bath to equilibrate the temperature in all cells ($37^\circ \pm 1^\circ\text{C}$). Each cell contained a small Teflon coated magnetic stir bar which was used to ensure that the fluid in the receptor compartment remained homogenous during the experiments. Sink conditions were ensured in all experiments after initial testing of PP saturation concentration in the receptor medium.

Samples (300 μ L) were drawn via syringe from the center of the receptor compartment at the following time intervals: 0.25, 0.5, 1, 2, 3, 4, 5 and 6 h. The removed sample volume was immediately replaced with the same volume of fresh receptor medium (PBS; pH 7.4) with great care to avoid trapping air beneath the dermis. Cumulative amounts of the drug (μg) penetrating the unit surface area of the mucosa membrane (cm^2) were corrected for sample removal and plotted versus time (h). The diffusion experiments were carried out 27 times for the fresh and 22 times for the frozen buccal mucosa.

Additional details can be found at S. Amores, An improved cryopreservation method for porcine buccal mucosa in ex vivo drug permeation studies using Franz diffusion cells, *European Journal of Pharmaceutical Sciences* 60 (2014) 49–54.

Example 7

Permeation of quinine across sublingual mucosa sections

Since porcine and human oral membranes are similar in composition, structure and permeability measurements, porcine oral mucosa is a suitable model for human oral mucosa. Permeability across the porcine oral mucosa is not metabolically linked therefore it is not important for the tissue to be viable.

To prepare the porcine membranes, porcine floor of mouth and ventral (underside) tongue mucosa membranes were excised by blunt dissection using a scalpel. The excised mucosa were cut into approximately 1 cm squares and frozen on aluminium foil at -20°C until used (<2

weeks). For non-frozen ventral surface of porcine tongue, the mucosa was used in the permeation studies within 3 h of excision.

The permeability of the membranes to quinine was determined using all-glass Franz diffusion cells with a nominal receptor volume of 3.6mL and diffusional area of 0.2 cm². The cell flanges were greased with high performance vacuum grease and the membranes mounted between the receptor and donor compartments, with the mucosal surface uppermost. Clamps were used to hold the membranes into position before the receptor compartments were filled with degassed phosphate buffered saline (PBS), pH 7.4. Micromagnetic stirrer bars were added to the receptor compartments and the complete cells were placed in a water bath at 37°C. The membranes were equilibrated with PBS applied to the donor compartments for 20 min before being aspirated with a pipette. Aliquots of 5 µL of the quinine solution or 100 µL of the saturated solutions of Q/2-HP-β-CD complex in different vehicles were applied to each of the donor compartments. In the study to determine the effect of saliva on the permeation of quinine across the ventral surface of the tongue, 100 µL of sterile saliva was added to the donor compartments before adding 5 µL of the quinine solution.

At 2, 4, 6, 8, 10 and 12 h, the receptor phases were withdrawn from the sampling ports and aliquots of 1mL samples were transferred to HPLC autosampler vials, before being replaced with fresh PBS stored at 37°C. Apart from the studies involving Q/2-HP-β-CD saturated solutions (where an infinite dose was applied at the start of the experiments), 5 µL of the respective quinine solution was reapplied to the donor phase up to 10 h. The purpose of this was to represent a hypothetical in-use finite dosing regimen based upon an interval of 2 h between doses. At least 3 replicates were carried out for each study.

Additional details can be found at C. Ong, Permeation of quinine across sublingual mucosa, in vitro, *International Journal of Pharmaceutics* 366 (2009) 58–64.

Example 8

Ex-Vivo Initial Study – Form of the API

In this example, the permeation of Epinephrine Base was tested – solubilized in situ vs. the inherently soluble Epinephrine Bitartrate and no differences were found. Epinephrine Bitartrate was selected for further development based on ease of processing. Flux was derived as slope of the amount permeated as a function of time. Steady state flux extrapolated from the

plateau of flux vs time curve multiplied by the volume of receiver media. The graph in **Figure 2A** shows average amount permeated vs. time, with 8.00 mg/mL Epinephrine bitartrate and 4.4 mg/mL Epinephrine base solubilized. The graph in **Figure 2B** shows average flux vs. time, with 8.00 mg/mL Epinephrine bitartrate and 4.4 mg/mL Epinephrine base solubilized.

Donor Solution	Average Steady State Flux (ug/cm ² *min)
Epinephrine Base (conc 4.4mg/mL)	0.512
Epinephrine Bitartrate (conc 8.00mg/mL)	0.466

Example 9

Concentration dependence on permeation/flux

In this study, ex-vivo permeation of Epinephrine Bitartrate as a function of concentration was studied. **Figure 3** shows ex-vivo permeation of epinephrine bitartrate as a function of concentration. The study compared concentrations of 4 mg/mL, 8 mg/mL, 16 mg/mL and 100 mg/mL. Results showed that increasing concentration resulted in increased permeation, and level of enhancement diminishes at higher loading. The study compared concentrations of 4 mg/mL, 8 mg/mL, 16 mg/mL and 100 mg/mL.

Donor Solution	Average Steady State Flux (ug/cm ² *min)
Epinephrine Bitartrate (conc 4mg/mL)	0.167
Epinephrine Bitartrate (conc 8mg/mL)	0.466
Epinephrine Bitartrate (conc 16mg/mL)*	1.317
Epinephrine Bitartrate (conc 100mg/mL)	2.942

Donor Solution	Ratio of enhancement	Theoretical enhancement
Epinephrine Bitartrate (4.00mg/mL)	N/A	N/A
Epinephrine Bitartrate (8.00mg/mL)	2.8	2
Epinephrine Bitartrate (16.00mg/mL)	7.9	4
Epinephrine Bitartrate (100.00mg/mL)	17.6	25

Example 10

Influence of pH

In this example, the permeation of Epinephrine Bitartrate as a function of solution pH was studied. In this example, acidic conditions were explored for the ability to promote stability.

The results showed that pH 5 was slightly more favorable as compared to pH 3. The inherent pH of epinephrine bitartrate in solution in the concentration ranges explored is 4.5-5. No pH adjustment with buffers was required.

5 **Figure 4** shows permeation of epinephrine bitartrate as a function of solution pH. Acidic conditions were explored to promote stability. The results compared Epinephrine Bitartrate pH 3 buffer and Epinephrine Bitartrate pH 5 buffer, and found that the Epinephrine Bitartrate pH 5 buffer was slightly favorable.

Example 11

Influence of enhancers on permeation of epinephrine

10 In this example, the permeation of epinephrine to test for transmucosal delivery was studied as the amount permeated (μg) vs. time (in minutes). The following enhancers were screened for concentration effects in a solution containing 16.00 mg/mL Epinephrine. The graph on **Figure 5** demonstrates the results of these enhancers as a function of time.

Legend	Enhancer	Average Steady State Flux ($\mu\text{g}/\text{cm}^2 \cdot \text{min}$)	Percent Enhancement
No Enhancer	None	1.317	N/A
Enhancer A	3% Labrasol Caprylocaproyl polyoxyl-8 glycerides	5.208	395
Enhancer B	3% Propylene glycol monocaprylate	2.385	181
Enhancer C	3% Polyglyceryl-3 oleate	1.482	112
Enhancer D	3% Oleoyl polyoxyl-6 glycerides	0.281	21
Enhancer E	3% TDM	2.642	201
Enhancer F	3% SGDC	0.342	26
Enhancer G	3% Lauroyl polyoxyl-32 glycerides	1.641	125
Enhancer H	3% Ethanol	0.163	12
Enhancer I	6% Ethanol	0.254	19
Enhancer J	6% Labrasol Caprylocaproyl polyoxyl-8 glycerides	4.444	337
Enhancer K	6% Polyglyceryl-3 oleate	0.306	23
Enhancer L	3% clove oil	8.216	624

Enhancers were selected and designed with functionality influencing different barriers in the mucosa. While all tested enhancers did improve the amount permeated over time, clove oil

and Labrasol, in particular have shown significantly and unexpectedly high enhancement of permeation.

8.00mg/0.500mL
40mg/ strip
 no enhancer

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux (µg/cm2*min)	std dev set 2	steady state flux average
30	0	0	0	0	
45	2.5	4.33012702	0.260416667	0.4510549	1.317274
60	5.5	7.08872344	0.3125	0.3125	
120	31.33333333	26.1549868	0.672743056	0.5050226	
180	72.66666667	58.215834	1.076388889	0.8496863	
240	112.1666667	80.1878004	1.028645833	0.5733604	
300	160.1666667	103.254943	1.25	0.6036108	
360	213.3333333	131.305306	1.384548611	0.7308311	

8.00mg/0.500mL
40mg/ strip
 Labrasol

Time (min)	set 1 (A,B,C) average amount permeated (ug)	std dev set 1 amount perm	set 1 (A, B,C) average flux (µg/cm2*min)	std dev set 1	steady state flux average
0	0	0	0	0	
30	0.5	0.8660254	0.026041667	0.0451055	5.208333
45	2.666666667	0.28867513	0.225694444	0.0601407	
60	4	1.80277564	0.138888889	0.1674245	
120	28	16.3935963	0.625	0.3836177	
180	98	53.3291665	1.822916667	0.9701176	
240	238.1666667	93.0017921	3.650173611	1.136722	
300	421.1666667	115.153521	4.765625	0.6675003	
360	638.1666667	130.709921	5.651041667	0.4732495	

8.00mg/0.500mL
40mg/strip
 capryol 90

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux (µg/mL*min)	std dev set 2	steady state flux average
0	0	0	0	0	
30	0.00	0	0	0	
45	0.00	0	0	0	1.931424
60	0.00	0	0	0	
120	9.17	5.79511288	0.238715278	0.1509144	
180	38.67	16.7655401	0.768229167	0.2864583	
240	88.50	30.2654919	1.297743056	0.4018216	
300	150.67	39.6936183	1.618923611	0.3269068	
360	236.83	51.9358579	2.243923611	0.4999616	

8.00mg/0.500mL
40mg/strip
 plurol oleique

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux (µg/mL*min)	std dev set 2	steady state flux average
0	0.8	1.78885438	0	0	
30	10.80	13.325727	0.520833333	0.7186273	
45	20.90	22.1624683	1.052083333	0.9356173	1.481771
60	33.00	30.8058436	1.260416667	0.9319861	
120	90.70	68.1951245	1.502604167	1.005753	
180	157.00	107.373763	1.7265625	1.0427891	
240	239.80	140.586539	2.15625	1.2085059	
300	285.60	184.236397	1.192708333	1.484335	
360	353.60	221.81676	1.770833333	0.993644	

8.00mg/0.500mL
40mg/strip
 TDM

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux (µg/mL*min)	std dev set 2	steady state flux average
0	0.00	0.00	0.00	0.00	
20	0.00	0.00	0.00	0.00	
40	3.00	2.43	0.23	0.32	2.642144
60	8.83	4.86	0.46	0.35	
120	41.33	15.08	0.85	0.49	
180	99.75	30.17	1.52	0.79	
240	179.92	48.30	2.09	0.98	
300	276.92	72.35	2.53	1.19	
360	382.83	102.02	2.76	1.38	

8.00mg/0.500mL
40mg/strip
 SGDC

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux (µg/mL*min)	std dev set 2	steady state flux average
0	0	0	0	0	
30	0.00	0	0	0	
45	0.67	1.30384048	0.069444444	0.1261521	0.341797
60	1.58	1.94935887	0.095486111	0.1063147	
120	7.00	9.44325156	0.141059028	0.1910856	
180	16.17	22.0323626	0.238715278	0.316132	
240	28.58	37.6191441	0.323350694	0.3977149	
300	43.00	54.3927844	0.375434028	0.4112124	
360	54.83	65.7976063	0.308159722	0.3008536	

8.00mg/0.500mL
40mg/strip
 Labrafil

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux (µg/mL*min)	std dev set 2	steady state flux average
0	0.8	1.15108644	0	0	
30	1.10	1.51657509	0.015625	0.0232924	
45	1.10	1.51657509	0	0	0.28125
60	1.10	1.51657509	0	0	
120	4.00	4.89897949	0.075520833	0.0984775	
180	9.10	10.9167303	0.1328125	0.1671035	
240	15.20	18.7169709	0.158854167	0.2034753	
300	25.70	29.8487856	0.2734375	0.2910091	
360	36.80	43.3093523	0.2890625	0.3532943	

8.00mg/0.500mL
40mg/strip
 Gelucire 44/14

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux (µg/mL*min)	std dev set 2	steady state flux average
0	0	0	0	0	
20	0.33	0.89442719	0.026041667	0.0637888	
40	3.83	5.94138031	0.2734375	0.378725	1.629774
60	11.50	17.1850225	0.598958333	0.8405853	
120	41.58	48.5059275	0.783420139	0.8042794	
180	91.92	82.5124233	1.310763889	0.9525224	
240	150.17	118.949569	1.516927083	0.9914576	
300	217.50	158.792947	1.753472222	1.0756081	
360	275.33	189.967563	1.506076389	0.9083155	

8.00mg/0.500mL
40mg/strip
 clove oil

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux ($\mu\text{g}/\text{cm}^2 \cdot \text{min}$)	std dev set 2	steady state flux average
0	0	0	0	0	
20	0	0	0	0	
40	28.66666667	27.360251	2.239583333	2.1375196	8.270399
60	96.5	79.5424415	5.299479167	4.0954816	
120	389.6666667	278.072533	7.634548611	5.2070528	
180	688.6666667	451.678628	7.786458333	4.5210426	
240	1009.166667	603.252089	8.346354167	3.9590828	
300	1333.5	759.653046	8.446180556	4.1168559	
360	1644.333333	878.2762	8.094618056	3.2301203	

8.00mg/0.500mL
40mg/strip
 3% Labrasol
 +1%TDM

Time (min)	set 2 (A,B,C) average amount permeated	std dev set 2 amount perm	set 2 (D,E,F) average flux ($\mu\text{g}/\text{mL} \cdot \text{min}$)	std dev set 2	steady state flux average
0	0	0	0	0	
20	0	0	0	0	3.161892
40	1.666666667	2.88675135	0.130208333	0.2255274	
60	6.833333333	11.8356805	0.403645833	0.6991351	
120	68.83333333	92.6907942	1.614583333	2.1084505	
180	103.6666667	101.539812	0.907118056	0.3351021	
240	180	130.184484	1.987847222	0.7476876	
300	291.5	149.81572	2.903645833	0.5193664	
360	422.8333333	164.032263	3.420138889	0.5530917	

Example 12

5 Impact of enhancers on epinephrine release

Release profiles of epinephrine were studied to determine the impact of enhancers (Labrasol and clove oil) on epinephrine release. **Figure 6A** shows the epinephrine release from different polymer platforms. **Figure 6B** shows the impact of enhancers on epinephrine release. The results showed that the amount permeated leveled off after about 40 minutes to be between approximately 3250 and 4250 μg . The tested enhancers were shown not to restrict the release of epinephrine from the matrix.

Example 13**Accelerated stability**

The stabilizer loading variants were tested.

	Formulation 10	Formulation 10 with 0.25% Stabilizer	Formulation 10 with 1% Stabilizer
Time (weeks) @ 40°C/75% R.H.	EPI mg/film	EPI mg/film	EPI mg/film
0	39.3	37.9	38.3
2	35.2	36.8	34.7
4	38.2	36.8	36.2
8	37.7	35.6	35.1
12	36.1	35.4	35.1

5 **Example 14****Impact of Enhancer**

A pharmacokinetic model in the male Yucatan, miniature swine was studied. The graph on **Figure 7** shows the results of a pharmacokinetic model in the male Yucatan, miniature swine. The study compares a 0.3 mg Epipen, a 0.12 mg Epinephrine IV and a placebo.

10 The impact of no enhancer is shown in **Figure 8** on the concentration profiles of a 0.3 mg Epipen and a 40 mg Epinephrine film with no enhancer

The impact of enhancer 3% Labrasol is shown in **Figure 9**, which shows the impact of Enhancer A (Labrasol) on the concentration profiles of a 40 mg Epinephrine film vs. a 0.3 mg Epipen. **Figure 10** shows the impact of Enhancer L (clove oil) on the concentration profiles of
15 two 40 mg Epinephrine films (10-1-1) and (11-1-1) vs. a 0.3 mg Epipen.

In addition, the influence of film dimensions and impact of clove oil (3%) is also shown in **Figure 11**. This study was carried out comparing 0.30 mg EpiPen (n=4), a 40 mg Epinephrine Film (10-1-1) (n=5) and a 40 mg Epinephrine Film (11-1-1) (n=5). The concentration vs. time profiles followed sublingual or intramuscular epinephrine administration to male miniature swine.

Studies were performed to vary the ratio of epinephrine to an enhancer. These studies were also concentration vs. time profiles following sublingual or intramuscular epinephrine administration to male miniature swine. Varying the ratio of Epinephrine to clove oil (Enhancer L) produced the results shown in **Figure 12**. This study was carried out comparing 0.30 mg EpiPen (n=4), a 40 mg Epinephrine Film (12-1-1) (n=5) and a 20 mg Epinephrine Film (13-1-1) (n=5).

Example 15

A varying dose was carried out in constant matrix with enhancer Labrasol (3%) and clove oil (3%) are shown in **Figures 13** and **14** respectively. The study in **Figure 13** was carried out comparing 0.30 mg EpiPen (n=4), a 40 mg Epinephrine Film (18-1-1) (n=5) and a 30 mg Epinephrine Film (20-1-1) (n=5). The study in **Figure 14** was carried out comparing 0.30 mg EpiPen (n=4), a 40 mg Epinephrine Film (19-1-1) (n=5) and a 30 mg Epinephrine Film (21-1-1) (n=5). These studies were also concentration vs. time profiles following sublingual or intramuscular epinephrine administration to male miniature swine.

Example 16

A pharmacokinetic model in the male miniature swine was studied to determine the impact of an enhancer (farnesol) on epinephrine concentration over time. The graph on **Figure 15** shows the epinephrine plasma concentration (in ng/mL) as a function of time (in minutes) following sublingual or intramuscular administration of a farnesol permeation enhancer. This study compares a 0.3 mg EpiPen (n=3), a 30 mg Epinephrine Film 31-1-1 (n=5) and a 30 mg Epinephrine Film 32-1-1 (n=5) each Epinephrine Film being formulated with a farnesol enhancer. As shown in this figure, the 31-1-1 film demonstrates enhanced stability of epinephrine concentration starting at about 30-40 minutes until approximately 130 minutes.

The graph in **Figure 16** is taken from the same study as Figure 17, but shows exclusively the data points comparing the 0.3 mg EpiPen against the 30 mg Epinephrine Film 31-1-1 (n=5).

The graph in **Figure 17** is taken from the same study as Figure 17, but shows exclusively the data points comparing the 0.3 mg EpiPen against the 30 mg Epinephrine Film 32-1-1 (n=5).

Example 17

Referring to **Figure 18**, this graph shows a pharmacokinetic model in the male miniature swine was studied to determine the impact of an enhancer (farnesol) on epinephrine

concentration over time following sublingual or intramuscular administration. The epinephrine plasma concentration (in ng/mL) is shown as a function of time (in minutes) following sublingual or intramuscular administration of a farnesol permeation enhancer in Epinephrine films. The study compared data from three 0.3 mg Epipens against five 30 mg Epinephrine films (32-1-1). The data shows the Epinephrine films film having enhanced stability of epinephrine concentration starting at about 20-30 minutes until approximately 130 minutes.

Example 18

In one embodiment, an epinephrine pharmaceutical composition film can be made with the following formulation:

	Formulation A		
MATERIAL	WT % dry	WT % wet	mg/Strip
EPINEPHRINE bitartrate	46.40	18.56	54.56
hydroxypropylmethyl cellulose	11.54	4.61	13.57
polyvinyl pyrrolidone	27.92	11.17	32.84
Glycerol monooleate	0.58	0.23	0.68
Polyethylene Oxide	1.16	0.46	1.36
Polysorbate	0.58	0.23	0.68
Phytoextract	9.98	3.99	9.97
Stabilizer	0.12	0.05	0.14
Buffer	0.58	0.23	0.68
Artificial sweetener	1.16	0.46	1.36
Linoleic acid	0.0037	0.00	0.00
Farnesol			
Yellow # 5			
TOTAL	100.00	40.00	115.84

Example 19

An epinephrine pharmaceutical film compositions was made with the following formulation:

	Formulation B		
MATERIAL	WT % dry	WT % wet	mg/Strip
EPINEPHRINE bitartrate	46.17	18.47	54.29
Hydroxypropylmethyl cellulose	11.48	4.59	13.50
Polyvinyl pyrrolidone	27.78	11.11	32.67
Glycerol monooleate	0.58	0.23	0.68
Polyethylene Oxide	1.15	0.46	1.35
Polysorbate	0.58	0.23	0.68
Phytoextract	9.93	3.97	9.92
Stabilizer	0.12	0.05	0.14
Buffer	0.58	0.23	0.68
Artificial sweetener	1.15	0.46	1.35
Linoleic acid	0.50	0.20	0.59
Farnesol			
Yellow # 5			
TOTAL	100.00	40.00	115.85

5

Example 20

In another embodiment, pharmaceutical film compositions were made with the following formulation:

5

	Formulation C		
MATERIAL	WT % dry	WT % wet	mg/Strip
EPINEPHRINE bitartrate	46.35	18.54	54.51
Hydroxypropylmethyl cellulose	11.53	4.61	13.55
Polyvinyl pyrrolidone	27.90	11.16	32.80
Glycerol monooleate	0.58	0.23	0.68
Polyethylene oxide	1.16	0.46	1.36
Polysorbate	0.58	0.23	0.68
Phytoextract	9.97	3.99	9.96
Stabilizer	0.12	0.05	0.14
Buffer	0.58	0.23	0.68
Artificial sweetener	1.16	0.46	1.36
Linoleic acid			
Farnesol	0.10	0.04	0.06
Yellow # 5			
TOTAL	100.00	40.00	115.78

Example 21

In another embodiment, pharmaceutical film compositions were made with the following formulation:

5

	Formulation D		
MATERIAL	WT % dry	WT % wet	mg/Strip
EPINEPHRINE bitartrate	46.07	18.43	54.52
Hydroxypropylmethyl cellulose	11.46	4.58	13.56
Polyvinyl pyrrolidone	27.73	11.09	32.81
Glycerol monooleate	0.57	0.23	0.68
Polyethylene oxide	1.15	0.46	1.36
Polysorbate	0.57	0.23	0.68
Phytoextract	9.91	3.96	9.96
Stabilizer	0.11	0.05	0.14
Buffer	0.57	0.23	0.68
Artificial sweetener	1.15	0.46	1.36
Linoleic acid	0.10	0.04	0.06
Farnesol	0.50	0.20	0.29
Yellow # 5	0.10	0.04	0.06
TOTAL	100.00	40.00	116.16

Example 22

Referring to **Figure 19**, this graph shows a pharmacokinetic model (logarithmic scale) in the male miniature swine studied to determine the impact of an enhancer (6% clove oil and 6% Labrasol) on epinephrine plasma concentration over time following sublingual or intramuscular administration. The epinephrine plasma concentration (in ng/mL) is shown as a function of time

10

(in minutes) following sublingual or intramuscular administration of a farnesol permeation enhancer in Epinephrine films. The data shows the Epinephrine films film having enhanced stability of epinephrine concentration starting at just after the 10 minute time point through about 30 minutes, and until approximately 100 minutes.

5 Referring to **Figure 20**, this graph shows a pharmacokinetic model of the Epinephrine film formulation in the male miniature swine as referenced in **Figure 19** compared against the average data collected from a 0.3 mg Epipen (indicated in diamond data points). As the data indicates, the average plasma concentration for the 0.3 mg Epipen peaked between 0.5 and 1 ng/mL. By contrast, the Epinephrine film formulation peaked between 4 and 4.5 ng/mL.

10 Example 23

Referring to **Figure 21**, this graph shows a pharmacokinetic model in the male miniature swine studied to determine the impact of an enhancer (9% clove + 3% Labrasol) on epinephrine concentration over time following sublingual or intramuscular administration across 7 animal models. The general peak concentration was achieved between 10-30 minutes.

15 All references cited herein are hereby incorporated by reference herein in their entirety.

Example 23

In one embodiment, a dipivefrin pharmaceutical composition film can be made with the following formulation:

MATERIAL	WT % dry	mg/Strip
Dipivefrin	3.45	<i>3.297</i>
HPMC E15	23.22	<i>22.165</i>
PVP K90	57.57	<i>54.959</i>
GMO	0.50	<i>0.476</i>
PEO N10	0.50	<i>0.476</i>
PEG400	9.25	<i>8.830</i>
clove oil	3.00	<i>2.437</i>
sodium citrate	0.50	<i>0.476</i>
sucralose	1.00	<i>0.952</i>
labrasol	1.00	<i>0.956</i>
green #3	0.01	<i>0.010</i>
TOTAL	100.00	95.03

Example 24

In another embodiment, a dipivefrin pharmaceutical composition film can be made with the following formulation:

MATERIAL	WT % dry	mg/Strip
Dipivefrin	6.00	<i>6.602</i>
HPMC E15	21.22	<i>23.350</i>
PVP K90	51.52	<i>56.690</i>
GMO	0.50	<i>0.548</i>
PEO N10	0.50	<i>0.548</i>
PEG400	9.25	<i>10.179</i>
clove oil	3.00	<i>2.809</i>
citric acid	3.00	<i>3.301</i>
sodium citrate	2.00	<i>2.201</i>
sodium metabisulfite	1.00	<i>1.100</i>
sucralose	1.00	<i>1.097</i>
labrasol	1.00	<i>1.102</i>
green #3	0.01	<i>0.011</i>
TOTAL	100.00	109.54

Example 25

In another embodiment, a dipivefrin pharmaceutical composition film can be made with the following formulation:

MATERIAL	WT % dry	mg/Strip
Dipivefrin	10.50	<i>13.204</i>
HPMC E15	20.22	<i>25.427</i>
PVP K90	48.02	<i>60.385</i>
GMO	0.50	<i>0.627</i>
PEO N10	0.50	<i>0.627</i>
PEG400	9.25	<i>11.633</i>
clove oil	3.00	<i>3.211</i>
citric acid	3.00	<i>3.773</i>
sodium citrate	2.00	<i>2.515</i>
sodium metabisulfite	1.00	<i>1.258</i>
sucralose	1.00	<i>1.254</i>
labrasol	1.00	<i>1.259</i>
green #3	0.01	<i>0.013</i>
TOTAL	100.00	125.18

Example 26

In one study, the investigators compared the pharmacokinetics of epinephrine after Dipivefrin SL administration to other routes of administrations (Oral, SC and IV), specifically analyzing epinephrine bioavailability and conversion of dipivefrin to epinephrine.

Group	No. of Animals (Male)	Test Article	Dose Route	Target Dose Level (mg/animal)	Dipi Dose Conc. (mg/DF or mL)	Target Dose Amount (mL or DF/animal)
1	1	Placebo	SL	0	0 mg/DF	1 DF
2	5	Dipivefrin DF: Dip 16-1-1	SL	6	6 mg/DF	1 DF
3	3	Dipivefrin Solution	PO	6	0.6 mg/mL	10 mL
4	3	Dipivefrin solution (Dissolved SL Film)	PO	6	0.6 mg/mL	10 mL
5	4	Dipivefrin Solution	SC	22	22 mg/mL	1 mL
6	4	Dipivefrin Solution	IV	1	1 mg/mL	1 mL

The study compared various dose routes: sublingual (SL), per oral tablet (PO), subcutaneous (SC) and intravenous (IV). The PK Time-points (for All Groups): 0 (pre-dose), 2, 5, 10, 12, 15, 17, 20, 25, 30, 40, 60, 90 and 120 minutes and 3 hr, 4 hr, 6 hr and 8 hr post dose. An Oral Irritation assessment was performed (SL film group): Predose (0) and 24 hr postdose by Draize scoring. The dipivefrin film (DF) is an exemplary embodiment of the claimed pharmaceutical composition.

Referring to **Fig. 22A**, the data shows average epinephrine plasma concentration vs. time in 60 minutes. Referring to **Fig. 22B**, the data shows average epinephrine plasma concentration vs. time in 480 minutes. Surprisingly, the dipivefrin film showed ability to meet target C_{max} of 0.2 ng/mL- 1.5 ng/mL in less than 30 minutes. The C_{max} was shown to be 0.1 ng/mL- 2 ng/mL, 0.15 ng/mL-1.5 ng/mL, and 0.2 ng/mL- 1.0 ng/mL. The C_{max} was shown to be greater than 0.1 ng/mL, greater than 0.15 ng/mL, greater than 0.2 ng/mL, greater than 0.4 ng/mL, greater than

0.5ng/ml, greater than 0.6 ng/ml, greater than 0.7 ng/ml and less than 2 ng/ml and less than 1.5 ng/ml.

The Tmax is shown in the range of 0-480 minutes, including 10-60 minutes, 20-40 minutes, 12-15 minutes, and 5-10 minutes. The Tmax has been shown to be less than 25 minutes, less than 20 minutes, 15 minutes, less than 12 minutes, and less than 10 minutes.

Referring to **Fig. 23A**, the data shows average dipivefrin plasma concentration vs. time in 60 minutes. Referring to **Fig. 23A**, the data shows average dipivefrin plasma concentration vs. time in 480 minutes. The amount of dipivefrin is shown to decrease as epinephrine is being formed. This data shows a surprising ability of the subject film to meet a target Cmax of 0.2 ng/ml- 1.5 ng/ml and a Tmax of less than 35 minutes. The Cmax is shown to be 0.1 ng/ml- 2 ng/ml, 0.15 ng/ml-25 ng/ml, 0.2 ng/ml- 1.0 ng/ml, 0.2 ng/ml -1.2 ng/ml, and 0.2 ng/ml - 1.3 ng/ml. The Cmax has been shown to be greater than 0.1 ng/ml, greater than 0.15 ng/ml, greater than 0.2 ng/ml, greater than 0.4ng/ml, greater than 0.5ng/ml, greater than 1.0ng/ml, greater than 1.2 ng/ml, and less than 3 ng/ml, less than 2 ng/ml and less than 1.5 ng/ml. The Tmax is shown in the range of 0-480 minutes, including 10-60 minutes, 20-40 minutes, 12-15 minutes, and 5-10 minutes. The Tmax has been shown to be less than 25 minutes, less than 20 minutes, 15 minutes, less than 12 minutes, and less than 10 minutes.

Referring to **Fig. 24**, the data shows that average plasma concentration of epinephrine (dipivefrin SL 16-1-1 E) in round data points and dipivefrin (dipivefrin SL-Dip 16-1-1 D) in square data points. This shows the amount of dipivefrin decreases as epinephrine is being formed.

Referring to **Fig. 25**, the graph shows the conversion of dipivefrin to epinephrine (SC and IV groups). The dashed lines indicate dipivefrin, and the solid lines indicate epinephrine.

	EPI AUC0-t	EPI Tmax (Min)	EPI Cmax (mean, ng/ml)	DIPI AUC0-t	DIPI Tmax (Min)	DIPI Cmax (mean, ng/ml)
Placebo SL	0	0	0	0	0	0
Dipi 9%C6 mg	197.4	180	0.75	12.26	30	1.14
Dipi Solution (6mg, PO)	41.4	120	0.28	0	0	0
Dipi Film Solution (6mg, PO)	24.2	12	0.24	0	0	0
Dipi Solution (22 mg, SC)	4220.0	180 (3 rd peak)	12.5	1505	5	15
Dipi Solution (1mg, IV)	146.4	2	7.62	53.24	2	11.7
%Bioavailability- Dipi solution SC (Relative to IV)	131.0%			128.5%		

The results showed no local irritation with the Dipivefrin SL film. Half-life or hydrolysis by enzyme is reflected in the conversion rate of dipivefrin to epinephrine. In certain
5 embodiments, the half-life is less than 1 minute. In other embodiments, the half-life is so rapid
that it may be seconds or fractions of a second. In some cases, plasma assays for the prodrug may
not be feasible but are reflected in the emergence of neatepinephrine plasma levels not attributed
to endogenous epinephrine. The results also showed that dipivefrin was converted into
Epinephrine rapidly-SC administration of dipivefrin had a depot effect-had the higher and
10 prolonged epinephrine exposure compared to IV administration. The results showed that
dipivefrin IV administration had a faster onset and maximum epinephrine exposure at 2 minutes
and cleared from the system within 2 hours. The results indicate that oral administration showed
minimal epinephrine exposure compared to other routes of administration (dipivefrin

concentration was below the detection limit). In short, surprisingly, no difference was found between dipivefrin solution and dipivefrin film solution with permeation enhancers.

Example 27

In this investigation, the investigators studied the conversion of dipivefrin to epinephrine. The study adjusted three variables systemically: drug concentration, dose, and enhancer loading. The data was analyzed to identify speed to onset, Cmax, area under the plasma drug concentration-time curve (AUC) during the first 20-25 minutes.

Referring to **Fig. 26**, the data shows average average epinephrine profiles across all matrix studies. The time to initial peak average is within about 30 minutes, 25 minutes, and 20 minutes. The 6mg dipivefrin/6% clove film (dip 10-1-1) achieved the fastest average results.

	dose/clove	minutes									average
		-10	5	10	12	15	17	20	25	30	
Dip 4-1-2	3mg/3%				1	2	1			1	17.8
Dip 4-2-1	6mg/3%			2	1	1					11.75
Dip 10-1-1	6mg/6%		1	4							9
Dip 11-1-1	6mg/6%					1		2	2		21
Dip 11-2-1	9mg/6%					2			2	1	22
Dip 12-1-1	9mg/9%						1	2		1	21.75
Dip 12-2-1	12mg/9%				1	2		2			16.3
Dip 13-1-1	12mg/6%						1	2	2		21.3
Dip 14-1-1	12mg/6%						2	1	2		20.5

Referring to **Fig. 27**, the data shows additional data comparing plasma concentration of dipivefrin and epinephrine (ng/ml) vs. time in hours. A mean therapeutic window has shown to be achieved within 30 minutes or less, including individual averages in 20 minutes or less, and 15 minutes or less.

Example 28

An investigation yielded results that validate the receptor interactor antagonism needed to drive greater levels of epinephrine transmucosally. Preclinical results comparing the 30mg formulation of epinephrine sublingual firm (ESF) versus a pretreatment of a phentolamine (a reversible nonselective α -adrenergic antagonist) at the site of application 10 min prior to dosing (phen 0.10 mg/ESF). The pretreatment showed that improved plasma concentration levels within a therapeutic window of 30 minutes or less, 25 minutes or less, and 20 minutes or less.

	Tmax (min)	Cmax (ng/mL)	AUC (min*ng/mL)
Epipen	35	1.52 + 0.857	74.48 + 22.94
ESF	25	0.99 + 0.64	42.96 + 11.04
Phen 0.10 mg/ESF	25	7.68 + 3.89	161.22 + 70.24

Referring to **Fig. 28**, this graph shows the epinephrine plasma concentration vs. time profile in a follow-up study that examined the loading of phentolamine and how it influences the absorption of epinephrine. For this study, 30 mg epinephrine sublingual films (ESF) were used. The results show that the loading is dose dependent. The results are shown in the graph and summarized below:

	Tmax (min)	Cmax (ng/mL)	AUC (min*ng/mL)
Epipen	35	2.04 + 2.13	90.35 + 105.0
Phen 0.25 mg/ESF	25	1.93 + 1.02	43.18+ 57.5
Phen 0.10 mg/ESF	27.5	1.19 + 0.60	45.12 + 27.24

As shown in the graph and indicated in the above data, a therapeutic window can be seen for ESF within 30 minutes or less, 25 minutes or less, and 20 minutes or less.

Other embodiments are within the scope of the following claims.

CLAIMS

What is claimed is:

1. A pharmaceutical composition, comprising:
 - 5 a polymeric matrix;
 - pharmaceutically active component including epinephrine or its prodrug in the polymeric matrix, the prodrug having a half-life of less than one minute.
2. The pharmaceutical composition according to claim 1, further comprising an adrenergic
 - 10 receptor interacter or a permeation enhancer.
3. The pharmaceutical composition according to claim 1, wherein the composition is a film further comprising a polymeric matrix, the pharmaceutically active component being contained in the polymeric matrix.
 - 15
4. The pharmaceutical composition according to claim 2, wherein the permeation enhancer includes a phenylpropanoid.
5. The pharmaceutical composition according to claim 2, wherein the permeation enhancer
 - 20 includes farnesol or Labrasol.
6. The pharmaceutical composition according to claim 2, wherein the permeation enhancer includes linoleic acid.
7. The pharmaceutical composition according to claim 2, wherein the pharmaceutical
 - 25 composition is a film further comprising a polymeric matrix, the pharmaceutically active component being contained in the polymeric matrix.
8. The pharmaceutical composition according to claim 2, wherein the pharmaceutical
 - 30 composition is a chewable or gelatin based dosage form, spray, gum, gel, cream, tablet, liquid or film.

9. The pharmaceutical composition according to claim 4, wherein the phenylpropanoid is eugenol or eugenol acetate.

5 10. The pharmaceutical composition according to claim 4, wherein the phenylpropanoid is a cinnamic acid, cinnamic acid ester, cinnamic aldehyde or hydrocinnamic acid.

11. The pharmaceutical composition according to claim 4, wherein the phenylpropanoid is chavicol.

10

12. The pharmaceutical composition according to claim 4, wherein the phenylpropanoid is safrole.

13. The pharmaceutical composition according to claim 2, wherein the adrenergic receptor
15 interacter is a phytoextract.

14. The pharmaceutical composition according to claim 13, wherein the phytoextract further includes an essential oil extract of a clove plant.

20 15. The pharmaceutical composition according to claim 13, wherein the phytoextract further includes an essential oil extract of a leaf of a clove plant.

16. The pharmaceutical composition according to claim 13, wherein the phytoextract further includes an essential oil extract of a flower bud of a clove plant.

25

17. The pharmaceutical composition according to claim 13, wherein the phytoextract further includes an essential oil extract of a stem of a clove plant.

18. The pharmaceutical composition according to claim 13, wherein the phytoextract is
30 synthetic or biosynthetic.

19. The pharmaceutical composition according to claim 13, wherein the phytoextract further includes 40-95% eugenol.

20. The pharmaceutical composition according to claim 2, wherein the adrenergic receptor
5 interacter includes a terpenoid, terpene or a sesquiterpene.

21. The pharmaceutical composition according to claim 1, wherein the polymer matrix includes a polymer.

10 22. The pharmaceutical composition according to claim 21, wherein the polymer is a water soluble polymer.

23. The pharmaceutical composition according to claim 21, wherein the polymer includes a polyethylene oxide.

15 24. The pharmaceutical composition according to claim 21, wherein the polymer includes a cellulosic polymer is selected from the group of: hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, methylcellulose and carboxymethyl cellulose.

20 25. The pharmaceutical composition according to claim 21, wherein the polymeric matrix comprises a cellulosic polymer, polyethylene oxide and polyvinyl pyrrolidone, polyethylene oxide and a polysaccharide, polyethylene oxide, hydroxypropyl methylcellulose and a polysaccharide, or polyethylene oxide, hydroxypropyl methylcellulose, polysaccharide and
25 polyvinylpyrrolidone.

26. The pharmaceutical composition according to claim 21, wherein the polymeric matrix comprises at least one polymer selected from the group of: pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragacanth gum, guar
30 gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, pregelatinized starch, hydrogenated starch hydrolysate, water-soluble chemical

derivatives of starch, starch, gelatin, ethylene oxide-propylene oxide co-polymers, collagen, albumin, poly-amino acids, polyphosphazenes, polysaccharides, chitin, chitosan, and derivatives thereof.

5 27. The pharmaceutical composition according to claim 1, further comprising a stabilizer.

28. The pharmaceutical composition according to claim 1, wherein the polymeric matrix comprises a dendritic polymer or a hyperbranched polymer.

10 29. The pharmaceutical composition of claim 1, further comprising one or more of sodium citrate, citric acid, sodium metabisulfite, sodium bisulfite, glycerol, glycerol monoacetate, glycerol diacetate, glycerol triacetate, polysorbate, cetyl alcohol, propylene glycol sorbitan monostearate, sorbitan monooleate, sorbitan monopalmitate, sucralose, sorbitol, mannitol, or xylitol, or combinations thereof.

15

30. A method of making a pharmaceutical composition comprising:

combining an adrenergic receptor interacter with a pharmaceutically active component including epinephrine or its prodrug, the prodrug having a half-life of less than one minute, and

forming a pharmaceutical composition including the adrenergic receptor interacter and
20 the pharmaceutically active component.

ABSTRACT

Pharmaceutical compositions of epinephrine and its prodrugs are described, the prodrugs having a half-life of less than one minute, and the compositions having enhanced active component permeation properties are described.

5

Under the Paperwork Reduction Act of 1995 no persons are required to respond to a collection of information unless it displays a valid OMB control number

FEE TRANSMITTAL		Complete if known	
		Application Number	To be assigned
		Filing Date	2024-01-16
☐ Applicant asserts small entity status. See 37 CFR 1.27.		First Named Inventor	Alexander Mark Schobel
☐ Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.		Examiner Name	To be assigned
		Art Unit	To be assigned
TOTAL AMOUNT OF PAYMENT	(\$) 7,020	Practitioner Docket No.	270712/AQU-014USC5

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____☒ Deposit Account Deposit Account Number: 50-3145 Deposit Account Name: _____

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**☒ Charge any additional fee(s) or underpayment of fee(s) ☐ Credit any overpayment of fee(s)
under 37 CFR 1.16 and 1.17**WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)

Application Type	FILING FEES			SEARCH FEES			EXAMINATION FEES			Fees Paid (\$)
	U (\$)	S (\$)	M (\$)	U (\$)	S (\$)	M (\$)	U (\$)	S (\$)	M (\$)	
Utility	320	128*	64	700	280	140	800	320	160	1,820
Design	220	88	44	160	64	32	640	256	128	
Plant	220	88	44	440	176	88	660	264	132	
Reissue	320	128	64	700	280	140	2,320	928	464	
Provisional	300	120	60	0	0	0	0	0	0	

* The \$128 small entity filing fee for a utility application is further reduced to \$64 for a small entity applicant who files the application via Patent Center or EFS-Web.

2. EXCESS CLAIM FEES

Fee Description	Undiscounted Fee (\$)	Small Entity Fee (\$)	Micro Entity Fee (\$)
Each claim over 20 (including Reissues)	100	40	20
Each independent claim over 3 (including Reissues)	480	192	96
Multiple dependent claims	860	344	172
Total Claims			
30 - 20 or HP = 10 x 100 = 1,000			
HP = highest number of total claims paid for, if greater than 20.			
Indep. Claims			
2 - 3 or HP = x =			
HP = highest number of independent claims paid for, if greater than 3.			

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is \$420 (\$168 for small entity) (\$84 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee (\$)	Fee Paid (\$)
110	- 100 = 10 / 50 = 0 (round up to a whole number)	x	0	0

4. OTHER FEE(S)

Non-English specification, \$140 fee (\$56 for small entity) (\$28 for micro entity)

Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, \$400 fee (\$200 small or micro entity)

Other (e.g., late filing surcharge): Request for Prioritized Examination 4,200

SUBMITTED BY			
Signature	/Harold H. Fox, Reg. # 41,498/	Registration No. 41,498 (Attorney/Agent)	Telephone 202.844.3380
Name (Print/Type)	Harold H. Fox, PhD.		Date 2024-01-16

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0032. Public burden for this form is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.** If filing this completed form by mail, send to: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013). <https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf>

Routine uses of the information in this record may include disclosure to: 1) law enforcement, in the event that the system of records indicates a violation or potential violation of law; 2) a Federal, state, local, or international agency, in response to its request; 3) a contractor of the USPTO having need for the information in order to perform a contract; 4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record; 5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record; 6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations; 7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals; 8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)); 9) the Office of Personnel Management (OPM) for personnel research purposes; and 9) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Additional Uses

Additional USPTO uses of the information in this record may include disclosure to: 1) the International Bureau of the World Intellectual Property Organization, if the record is related to an international application filed under the Patent Cooperation Treaty; 2) the public i) after publication of the application pursuant to 35 U.S.C. 122(b), ii) after issuance of a patent pursuant to 35 U.S.C. 151, iii) if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections, or an issued patent, or iv) without publication of the application or patent under the specific circumstances provided for by 37 CFR 1.14(a)(1)(v)-(vii); and/or 3) the National Archives and Records Administration, for inspection of records.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of
Invention

ENHANCED DELIVERY EPINEPHRINE COMPOSITIONS

As the below named inventor, I hereby declare that:

This declaration
is directed to:☒

The attached application, or

☐

United States application or PCT international application number _____

filed on _____

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

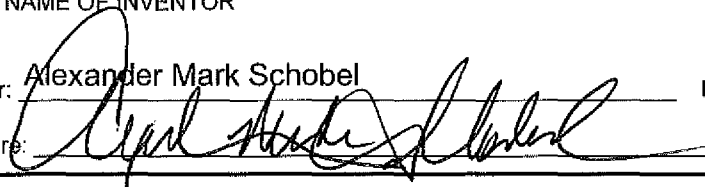
Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Alexander Mark Schobel

Date (Optional): 5/4/17

Signature:



Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN
APPLICATION DATA SHEET (37 CFR 1.76)****Title of
Invention****ENHANCED DELIVERY EPINEPHRINE COMPOSITIONS**

As the below named inventor, I hereby declare that:

This declaration
is directed to:☒

The attached application, or

☐

United States application or PCT international application number _____

filed on _____

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001
by fine or imprisonment of not more than five (5) years, or both.**WARNING:**

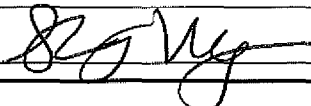
Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTORInventor: **Stephanie Marie Varjan**

Date (Optional):

05/04/17

Signature:



Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN
APPLICATION DATA SHEET (37 CFR 1.76)****Title of
Invention****ENHANCED DELIVERY EPINEPHRINE COMPOSITIONS**

As the below named inventor, I hereby declare that:

This declaration
is directed to:

The attached application, or



United States application or PCT international application number _____

filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001
by fine or imprisonment of not more than five (5) years, or both.**WARNING:**

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTORInventor: **Stephen Paul Wargacki**Date (Optional): 05/04/17Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Under the Paperwork Reduction Act of 1995 no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UTILITY PATENT APPLICATION TRANSMITTAL <i>(Only for new nonprovisional applications under 37 CFR 1.53(b))</i>	Attorney Docket No.	270712/AQU-014USC5
	First Named Inventor	Alexander Mark Schobel
	Title	ENHANCED DELIVERY EPINEPHRINE AND PRODRUG COMPOSITIONS
	Priority Mail Express® Label No.	

APPLICATION ELEMENTS <i>See MPEP chapter 600 concerning utility patent application contents.</i>	Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450
--	---

1. ☒ Fee Transmittal Form (PTO/SB/17 or equivalent) 2. ☐ Applicant asserts small entity status. See 37 CFR 1.27 3. ☐ Applicant certifies micro entity status. See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent. 4. ☒ Specification [Total Pages <u>81</u>] Both the claims and abstract must start on a new page. (See MPEP § 608.01(a) for information on the preferred arrangement) 5. ☒ Drawing(s) (35 U.S.C. 113) [Total Sheets <u>29</u>] 6. Inventor's Oath or Declaration [Total Pages <u>6</u>] (including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e)) a. ☐ Newly executed (original or copy) b. ☒ A copy from a prior application (37 CFR 1.63(d)) 7. ☒ Application Data Sheet * See note below. See 37 CFR 1.76 (PTO/AIA/14 or equivalent) 8. CD-ROM or CD-R in duplicate, large table, or Computer Program (Appendix) ☐ Landscape Table on CD 9. Nucleotide and/or Amino Acid Sequence Submission (if applicable, items a. – c. are required) a. ☐ Computer Readable Form (CRF) b. ☐ Specification Sequence Listing on: i. ☐ CD-ROM or CD-R (2 copies); or ii. ☐ Paper c. ☐ Statements verifying identity of above copies	ACCOMPANYING APPLICATION PAPERS 10. ☐ Assignment Papers (cover sheet & document(s)) Name of Assignee _____ 11. ☐ 37 CFR 3.73(c) Statement ☐ Power of Attorney (when there is an assignee) 12. ☐ English Translation Document (if applicable) 13. ☐ Information Disclosure Statement (PTO/SB/08 or PTO-1449) ☐ Copies of citations attached 14. ☐ Preliminary Amendment 15. ☐ Return Receipt Postcard (MPEP § 503) (Should be specifically itemized) 16. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed) 17. ☐ Nonpublication Request Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent. 18. ☒ Other: Request for Prioritized Examination _____ _____ _____ _____
--	--

***Note:** (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS					
☒ The address associated with Customer Number: <u>138831</u> OR ☐ Correspondence address below					
Name					
Address					
City	State	Zip Code			
Country	Telephone	Email			
Signature	/Harold H. Fox, Reg. # 41,498/		Date	2024-01-16	
Name (Print/Type)	Harold H. Fox, PhD.		Registration No. (Attorney/Agent)	41,498	

This collection of information is required by 37 CFR 1.53(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556
	Filing Date		2024-01-16
	First Named Inventor	Alexander Mark Schobel	
	Art Unit	1616	
	Examiner Name	NATHAN W SCHLIENTZ	
	Attorney Docket Number	270712/AQU-014USC5/542244	

U.S.PATENTS Remove						
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	11021437	B2	2021-06-01	Almoazen, Hassan	
	2	10149810	B2	2018-12-11	Perusse et al.	
	3	9125836	B2	2015-09-08	Nagaso et al.	
	4	7766013	B2	2010-08-03	Alexza Pharmaceuticals Inc.	
	5	10806709		2020-10-20	Fleming, Nigel Ten	
If you wish to add additional U.S. Patent citation information please click the Add button.						Add
U.S.PATENT APPLICATION PUBLICATIONS Remove						
Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20100297232	A1	2010-11-25	Myers et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	2	20110189259	A1	2011-08-04	Vasisht et al.	
	3	20110257096	A1	2011-10-20	Maggio	
	4	20110262520	A1	2011-10-27	Dormady et al.	
	5	20110262522	A1	2011-10-27	Finn et al.	
	6	20120009260	A1	2012-01-12	Schobel et al.	
	7	20120058158	A1	2012-03-08	Booles	
	8	20130085105	A1	2013-04-04	Deasy et al.	
	9	20130267585	A1	2013-10-10	Ljusberg-Wahren	
	10	20130337022	A1	2013-12-19	Pillay et al.	
	11	20140316333	A1	2014-10-23	Kwon	
	12	20170087077	A1	2017-03-30	Perusse et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	13	20170119660	A1	2017-05-04	Temtsin-Krayz et al.	
	14	20190022023	A1	2019-01-24	Schobel et al.	
	15	20170290776	A1	2017-10-12	Schobel et al.	
	16	20040265353	A1	2004-12-30	Zhang et al.	
	17	20110192863	A1	2011-08-11	Barrass et al.	
	18	20070293582	A1	2007-12-20	Hill, Malcolm	
	19	20160051494	A1	2016-02-25	GULFO, Adele	
	20	20100150986	A1	2010-06-17	Nagaso et al.	
	21	20050147653	A1	2005-07-07	Yasuda et al.	
	22	20220401456	A1	2022-12-22	Rabinowicz et al.	
	23	20140128379	A1	2014-05-08	Bergenheim et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	24	20150202148	A1	2015-07-23	Cifter et al.	
	25	20150038540	A1	2015-02-05	Zerbe et al.	
	26	20060134200	A1	2006-06-22	Vandoni et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button. [Add](#)

FOREIGN PATENT DOCUMENTS

[Remove](#)

Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1	2000027618	WO	A1	2000-05-18	Marius, Frederick		☐
	2	0024647	WO	A1	2000-05-04	Novartis AG		☐
	3	0042992	WO	A2	2000-07-27	Lavipharma Laboratories, Inc		☐
	4	2000057858	WO	A1	2000-10-05	Cima Labs Inc		☐
	5	2001003917	WO	A2	2001-01-18	Gruenenthal GmbH		☐
	6	0130288	WO	A1	2001-05-03	Anesta Corp		☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

7	2001034121	WO	A2	2001-05-17	Lohmann Therapie Syst Lts		☐
8	0143728	WO	A1	2001-06-21	Lohmann Therapie Syst Lts		☐
9	0156904	WO	A1	2001-08-09	J R Crompton Ltd		☐
10	0168452	WO	A1	2001-09-20	Stanelco Fibre Optics Ltd		☐
11	0170194	WO	A1	2001-09-27	Warner Lambert Co		☐
12	0170197	WO	A2	2001-09-27	Collaborative Technologies, Inc		☐
13	0191721	WO	A2	2001-12-06	Staley Mfg Co A E		☐
14	0205789	WO	A2	2002-01-24	Scs Skin Care Systems GmbH		☐
15	0207711	WO	A1	2002-01-31	Union Carbide Chem Plastic		☐
16	2002005820	WO	A1	2002-01-24	Lavipharma Laboratories, Inc		☐
17	2006017462	WO	A2	2006-02-16	R.p.scherer Technologies, Inc		☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

18	0243657	WO	A2	2002-06-06	Wrigley W M Jun Co		☐
19	2002064148	WO	A2	2002-08-22	Shimizu Pharmaceutical Co., Ltd		☐
20	02062315	WO	A1	2002-08-15	Pharmacia Corp		☐
21	02074238	WO	A2	2002-09-26	Lavipharma Lab Inc		☐
22	02091965	WO	A1	2002-11-21	Chalmers, Susanna		☐
23	03011259	WO	A1	2003-02-13	Wrigley W M Jun Co		☐
24	03015749	WO	A1	2003-02-27	Colgate Palmolive Co		☐
25	03030881	WO	A1	2003-04-17	Kosmos Pharma		☐
26	03030882	WO	A1	2003-04-17	Kosmos Pharma		☐
27	03030883	WO	A1	2003-04-17	Kosmos Pharma		☐
28	03043659	WO	A1	2003-05-30	Givaudan SA		☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	29	2003101357	WO	A1	2003-12-11	Univ Mississippi		☐
	30	2004009445	WO	A2	2004-01-29	Kosmos Pharma		☐
	31	2004035407	WO	A1	2004-04-29	Toppan Printing Co., Ltd		☐
	32	2004043165	WO	A1	2004-05-27	Givaudan SA		☐
	33	2004045305	WO	A2	2004-06-03	Wrigley W M Jun Co		☐
	34	2004045537	WO	A2	2004-06-03	Zengen, Inc		☐
	35	2004052335	WO	A1	2004-06-24	Monosolrx LLC		☐
	36	2004060298	WO	A2	2004-07-22	Sarnoff Corp		☐
	37	2004087084	WO	A1	2004-10-14	Procter & Gamble		☐
	38	2004113193	WO	A1	2004-12-29	Mars, Incorporated		☐
	39	2005020933	WO	A2	2005-03-10	Univ South Florida		☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	40	2005035776	WO	A2	2005-04-21	Monosol, LLC		☐
	41	2005039499	WO	A2	2005-05-06	Adhesives Research, Inc		☐
	42	2005074867	WO	A1	2005-08-18	Oreal		☐
	43	2006037425	WO	A1	2006-04-13	Lohmann Therapie Syst Lts		☐
	44	2005102287	WO	A2	2005-11-03	Duocort AB		☐
	45	2005102863	WO	A1	2005-11-03	Chaturvedi, Ashok		☐
	46	2005117905	WO	A2	2005-12-15	Zars, Inc		☐
	47	2005123074	WO	A1	2005-12-29	Boots Healthcare Int Ltd		☐
	48	2006004480	WO	A1	2006-01-12	Radi Medical Systems		☐
	49	2006031209	WO	A1	2006-03-23	Monosolrx LLC		☐
	50	2006037979	WO	A2	2006-04-13	Midatech Ltd		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556
	Filing Date		2024-01-16
	First Named Inventor	Alexander Mark Schobel	
	Art Unit	1616	
	Examiner Name	NATHAN W SCHLIENTZ	
	Attorney Docket Number	270712/AQU-014USC5/542244	

If you wish to add additional Foreign Patent Document citation information please click the Add button				Add
NON-PATENT LITERATURE DOCUMENTS				Remove
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵	
	1	PCT/US02/32575, Oct. 11, 2002.	☐	
	2	PCT/US02/32594, Oct. 11, 2002.	☐	
	3	PCT/US04/17076, May 28, 2004.	☐	
	4	PCT/US07/79357, Sep. 25, 2007.	☐	
	5	PCT/US11/36244, May 12, 2011.	☐	
	6	Bioadhesive Drug Delivery Systems (Lenaerts, V. and Gurny, R. (eds.)), Ch. 6, pp. 106-136 (1990).	☐	
	7	Blank, Z. et al., "Structural studies of organic gels by SEM", J. Material Science 9:1815-1822 (1974).	☐	
	8	CAS Presents, "Common Chemistry", http://www.commonchemistry.org.ChemicalDetail.aspx?ref=25322-68-3&terms=polyeth . . . Oct. 28, 2009.	☐	
	9	Huus et al., "Thermal Dissociation and Unfolding of Insulin", Biochemistry, 44: 11171-11177 (2005).	☐	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

10	Steiner et al., "Organic Derivatives of Alginic Acid", Industrial and Engineering Chemistry; 43(9): 2073-2077 (1951).	☐
11	Verdampfung, Kristallisation, Trocknung (Gnielinski, V. et al., (Eds.)), pp. 161-181 (Vieweg & Sohn Verlagsgesellschaft mbH 1993). (partial English translation included.).	☐
12	Giunchedi, P. and Conte, U., "Spray-drying as a preparation method of microparticulate drug delivery systems : an overview," S.T.P. Pharma. Sciences 6(4):276-290 (1995).	☐
13	Guo, J.H. and Zerbe, H., "Water Soluble Film for Oral Administration," The 24th International Symposium on Controlled Release of Bioactive Materials, pp. 227-229 (Paper No. 5001-5003) (1997).	☐
14	The Theory and Practice of Industrial Pharmacy (3rd Ed.) (Lachman, L et al. (eds.)), pp. 47-48, 51, 57, 64, 123-127, 346-369, 453-454, 461, 470, 479, 484, 491-492, 654-655 (1986).	☐
15	Physical Pharmacy (4th Ed.) (Martin, A. et al. (eds.)), pp. 423, 430-434, 453, 461, 484, 557-558, 560, 565-567 (1993).	☐
16	Introductory Polymer Chemistry (Misra, G.S. (ed.)), Ch. 6, pp. 98-118 (1993).	☐
17	Nishaoka, Y. et al., "Laser Diffraction Estimation of Particle Size Distribution of Slightly Water-Soluble Drugs Coexisting with Additives: Application to Solid Dosage Forms," Chem. Pharm. Bull. 40(6):1563-1568 (1992).	☐
18	Perumal, V.A. and Govender, T., "Investigating a New Approach to Film Casting for Enhanced Drug Content Uniformity in Polymeric Films," Drug Development and Industrial Pharmacy, 34:1034-1047 (2008).	☐
19	Remington's Pharmaceutical Sciences (17th Ed.) (Gennaro, A.R. (ed.)), Ch. 37, pp. 713-740 (1985).	☐
20	Shu, X.Z., et al., "Novel pH-sensitive citrate cross-linked chitosan film drug controlled release," Int. J. Pharmaceutics 212:19-28 (2001).	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

21	Pharmazeutische Technologie (4th Ed.), (Bauer, K.H. et al. (eds.)), pp. 94-94, 286-287 (Georg Thieme Verlag Stuttgart1993).	☐
22	Brittian, H.G., "What Is the 'Correct' Method to Use for Particle-Size Determination?," Pharmaceutical Technology 96-98 (Jul. 2001).	☐
23	"More Solutions to Sticky Problems: A Guide to Getting More From Your Brookfield Viscometer," Brookfield Engineering Laboratories, Inc. (1985).	☐
24	DeGrande, G., et al., "Specialized Oral Mucosal Drug Delivery Systems: Patches," Drugs and the Pharmaceutical Sciences (Swarbrick, J. (ed.)), Ch. 12, pp. 285-317 (1995).	☐
25	Polymer Science and Technology (Ebewele, R.O. (ed.)), pp. 1-23 (2000).	☐
26	Etzler, F.M. and Sanderson, "Partilce Size Analysis: a Comparative Study of Various Methods," Part. Part. Syst. Charact. 12: 127-224 (1995).	☐
27	Roddy, R.E., "A Controlled Trial of Nonoxynol 9 Film to Reduce Male-to-Female Transmission of Sexually Transmitted Diseases," New England J. Med. 339(8):504-510 (1998).	☐
28	Remington's Pharmaceutical Sciences (18th Ed.) (Gennaro, A.R. (ed.)), Ch. 19, pp. 296-298 (1990).	☐
29	Etzler, F.M., "Particle Size Analysis: a Comparison of Methods," Polymeric Materials: Science & Engineering 87:335-336 (2002).	☐
30	Patel, V.F. et al., "Advances in oral transmucosal drug delivery," J. Controlled Release 153:106-116 (2011).	☐
31	"Adsorption," Kirk-Othmer Encyclopedia of Chemical Technology (4th Ed.) pp. 493-494 (Wiley 1991).	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

32	"Matrix," Webster's Third New International Dictionary of the English Language Unabridged (Gove, P.B. (ed.)) (G. & C. Merriam Company 1968).	☐
33	Plastic Films (Osborn, K.R. and Jenkins, W.A. (eds.), p. 89 (1992).	☐
34	Martinez, M.N. and Amidon, G.L., "A Mechanistic Approach to Understanding the Factors Affecting Drug Absorption: A Review of Fundamentals," J. Clin. Pharmacol. 42:620-643 (2002).	☐
35	Amidon, G.L. et al., "A Theoretical Basis for a Biopharmaceutical Drug Classification: The Correlation of in Vitro Drug Product Dissolution and in Vivo Bioavailability," Pharm. Res. 12(3):413-420 (1995).	☐
36	Anders, R. and Merkle, H.P., "Evaluation of laminated muco-adhesive patches for buccal drug delivery," Int. J. Pharmaceutics 49: 231-240 (1989).	☐
37	Pharmaceutical Dosage Forms and Drug Delivery Systems (7th Ed.) (Ansel, H.C. et al. (eds.)), p. 66 (1999).	☐
38	Apicella, A. et al., "poly(ethylene oxide) (PEO) and different molecular weight PEO blends monolithic devices for drug release," Biomaterials 14(2):83-90 (1993).	☐
39	Pharmazeutische Technologie (5th Ed.) (Bauer, K.H. et al. (eds.)), pp. 208-209 (Stuttgart Jena Lubeck Ulm 1997).	☐
40	Bowser, T.J. and Wilhelm, L.R., "Modeling Simultaneous Shrinkage and Heat and Mass Transfer of a Thin. Nonporous Film During Drying," J. Food Sci. 60(4):753-757 (1995).	☐
41	Theory of pharmaceutical systems: vol. II (Carstensen, J.T. (ed.)), pp. 4-9 (1973).	☐
42	Cassidy, J. P. et al., "Controlled buccal delivery of buprenorphine," J. Controlled Release 25:21-29 (1993).	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556
	Filing Date		2024-01-16
	First Named Inventor	Alexander Mark Schobel	
	Art Unit	1616	
	Examiner Name	NATHAN W SCHLIENTZ	
	Attorney Docket Number	270712/AQU-014USC5/542244	

43	EUDRAGIT E 100, EUDRAGIT E PO, and EUDRAGIT E 12,5, Technical Information, Evonik Industries AG, (2012).	☐
44	EUDRAGIT L 100 and EUDRAGIT S 100, Technical Information, Evonik Industries AG, (2012).	☐
45	Europaisches Arzneibuch (3rd Ed.), pp. 142-143 (Deutscher Apotheker Verlag 1997).	☐
46	European Pharmacopeia (3rd Ed.), p. 134 (1997).	☐
47	Frankman, O. et al., "clinical Evaluation of C-Film, a Vaginal Contraceptive," J. Int. Med. Res. 3:292-296 (1975).	☐
48	Friend, D.R., "Polyacrylate resin microcapsules for taste masking of antibiotics," J. Microencapsulation 9(4):469-480 (1992).	☐
49	Fuller, C.S. et al., "Interactions in poly(ethylene oxide)-hydroxylpropyl methylcellulose blends," Polymer 42:9583-9592 (2001).	☐
50	Save, T. et al., "Comparative Study of Buccoadhesive Formulations and Sublingual Capsules of Nifedipine," J. Pharm. Pharmacol. 46:192-195 (1994).	☐

If you wish to add additional non-patent literature document citation information please click the Add button

Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Harold H. Fox, Reg. #41498/	Date (YYYY-MM-DD)	2024-03-18
Name/Print	Harold Fox, Ph.d.	Registration Number	41,498

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556
	Filing Date		2024-01-16
	First Named Inventor	Alexander Mark Schobel	
	Art Unit	1616	
	Examiner Name	NATHAN W SCHLIENTZ	
	Attorney Docket Number	270712-530343270712/AQU-0	

U.S.PATENTS							Remove
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	
	1						

If you wish to add additional U.S. Patent citation information please click the Add button.

Add

U.S.PATENT APPLICATION PUBLICATIONS							Remove
Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	
	1						

If you wish to add additional U.S. Published Application citation information please click the Add button.

Add

FOREIGN PATENT DOCUMENTS								Remove
Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button.

Add

NON-PATENT LITERATURE DOCUMENTS				Remove
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712-530343270712/AQU-0

1	Lahlou, Saad et al. "Cardiovascular effects of eugenol, a phenolic compound present in many plant essential oils, in normotensive rats." Journal of cardiovascular pharmacology vol. 43,2 (2004): 250-7.	☐
2	Feddersen, C O et al. "Arachidonic acid causes cyclooxygenase-dependent and -independent pulmonary vasodilation." Journal of applied physiology (Bethesda, Md.: 1985) vol. 68,5 (1990): 1799-808.	☐
3	International Search Report and Written Opinion dated Mar. 1, 2021 in International Application No. PCT/US2020/060464.	☐
4	International Search Report and Written Opinion dated Feb. 9, 2021 in International Application No. PCT/US2020/058357.	☐
5	International Search Report and Written Opinion dated Jul. 17, 2017 in International Application No. PCT/US2017/031167.	☐
6	International Search Report and Written Opinion dated Jul. 10, 2017 in International Application No. PCT/US2017/031170.	☐
7	Restriction Requirement dated Oct. 7, 2019 in U.S. Appl. No. 15/724,234.	☐
8	Non-Final Rejection dated Mar. 13, 2020 in U.S. Appl. No. 15/724,234.	☐
9	Final Rejection dated Aug. 17, 2020 in U.S. Appl. No. 15/724,234.	☐
10	Restriction Requirement dated Jun. 18, 2021 in U.S. Appl. No. 15/724,234.	☐
11	Office Action dated Jun. 1, 2021 in Brazilian Patent Application No. 112018072467-0.	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712-530343270712/AQU-0

12	Office Action dated Mar. 4, 2021 in European Application No. 17723616.3.	☐
13	First Examination Report dated Jul. 24, 2020 in Indian Application No. 201817045308.	☐
14	Non-Final Rejection dated Aug. 27, 2018 in U.S. Appl. No. 15/791,249.	☐
15	Final Rejection dated Jun. 19, 2019 in U.S. Appl. No. 15/791,249.	☐
16	Advisory Action dated Oct. 21, 2019 in U.S. Appl. No. 15/791,249.	☐
17	Non-Final Rejection dated Dec. 12, 2019 in U.S. Appl. No. 15/791,249.	☐
18	Final Rejection dated Jun. 9, 2020 in U.S. Appl. No. 15/791,249.	☐
19	Advisory Action dated Oct. 9, 2020 in U.S. Appl. No. 15/791,249.	☐
20	Non-Final Rejection dated Mar. 29, 2021 in U.S. Appl. No. 15/791,249.	☐
21	Restriction Requirement dated May 1, 2019 in U.S. Appl. No. 16/143,036.	☐
22	Non-Final Rejection dated Nov. 18, 2019 in U.S. Appl. No. 16/143,036.	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712-530343270712/AQU-0

23	Final Rejection dated May 13, 2020 in U.S. Appl. No. 16/143,036.	☐
24	Advisory Action dated Aug. 27, 2020 in U.S. Appl. No. 16/143,036.	☐
25	Non-Final Rejection dated Jan. 6, 2021 in U.S. Appl. No. 16/143,036.	☐
26	Final Rejection dated Jun. 7, 2021 in U.S. Appl. No. 16/143,036.	☐
27	Non-Final Rejection dated Nov. 4, 2020 in U.S. Appl. No. 16/143,821.	☐
28	Office Action dated Jun. 1, 2021 in Japanese Application No. 2018-558224.	☐
29	Final Rejection dated May 4, 2021 in U.S. Appl. No. 16/143,821.	☐
30	Restriction Requirement dated Feb. 19, 2020 in U.S. Appl. No. 16/143,821.	☐
31	Aqil, Mohammed et al. "Status of terpenes as skin penetration enhancers." Drug discovery today vol. 12,23-24 (2007): 1061-7.	☐
32	Office Action dated Jun. 29, 2021 in Japanese Application No. 2018-558225.	☐
33	English Translation of Office Action dated Aug. 3, 2021 in Chinese Application No. 201780037587.5	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712-530343270712/AQU-0

34	English Translation of Office Action dated Aug. 3, 2021 in Chinese Application No. 201780037588.X	☐
35	Alayoubi et al., "Development of a fast dissolving film of epinephrine hydrochloride as a potential anaphylactic treatment for pediatrics", Journal of Pharmaceutical Development and Technology, vol. 22:8, Jan. 6, 2016, pp. 1012-1016. < https://doi.org/10.3109/10837450.2015.1131715 >.	☐
36	First Examination Report dated Oct. 13, 2021 in Indian Application No. 202017016896.	☐
37	Office Action issued on July 21, 2021 in European Application No. 17723617.1	☐
38	Restriction Requirement issued on August 5, 2021 in US Application No. 16/143,678	☐
39	Notice of Allowance issued on August 20, 2021 in US Application No. 15/587,364	☐
40	Issue Notification issued on February 24, 2022 in US Application No. 15/724,234	☐
41	Hussain, Anwar et al., "Prodrug Approaches to Enhancement of Physicochemical Properties of Drugs IV: Novel Epinephrine Prodrug," Journal of Pharmaceutical Sciences (1976) Vol. 65, No. 10 pp. 1510-1512	☐
42	Non-Final Rejection issued on November 5, 2021 in US Application No. 15/724,234	☐
43	Non-Final Rejection issued on December 21, 2021 in US Application No. 16/143,036	☐
44	Final Rejection issued on June 9, 2022 in US Application No. 16/143,036	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712-530343270712/AQU-0

45	Final Rejection issued on January 13, 2022 in US Application No. 15/791,249	☐
46	Non-Final Rejection issued on March 1, 2022 in US Application No. 16/143,678	☐
47	Non-Final Rejection issued on February 4, 2022 in US Application No. 16/143,821	☐
48	English Translation of Office Action issued on January 6, 2022 in CN Application No. 201780037588.X	☐
49	English Translation of Office Action issued on January 6, 2022 in CN Application No. 201780037587.5	☐
50	English Translation of Final Rejection issued on June 30, 2022 in CN Application No. 201780037587.5	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

***EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556
	Filing Date		2024-01-16
	First Named Inventor	Alexander Mark Schobel	
	Art Unit	1616	
	Examiner Name	NATHAN W SCHLIENTZ	
	Attorney Docket Number	270712-530343270712/AQU-0	

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Harold H. Fox, Reg. #41498/	Date (YYYY-MM-DD)	2024-03-18
Name/Print	Harold Fox, Ph.d.	Registration Number	41,498

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556
	Filing Date		2024-01-16
	First Named Inventor	Alexander Mark Schobel	
	Art Unit	1616	
	Examiner Name	NATHAN W SCHLIENTZ	
	Attorney Docket Number	270712/AQU-014USC5/542244	

U.S.PATENTS							Remove
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	
	1	5766525		1998-06-16	Andersen et al.		
	2	5766620		1998-06-16	Heiber et al.		
	3	5766839		1998-06-16	Johnson et al.		
	4	5771353		1998-06-23	Eggleston et al.		
	5	5785180		1998-07-28	Dressel et al.		
	6	5792494		1998-08-11	Kanca et al.		
	7	5800832		1998-09-01	Tapolsky et al.		
	8	5806284		1998-09-15	Gifford		

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	9	5815398		1998-09-29	Dighe et al.	
	10	5822526		1998-10-13	Waskiewicz	
	11	5830437		1998-11-03	Ascione et al.	
	12	5830884		1998-11-03	Kasica et al.	
	13	5846557		1998-12-08	Eisenstadt et al.	
	14	5847023		1998-12-08	Viegas et al.	
	15	5862915		1999-01-26	Plezia et al.	
	16	5864684		1999-01-26	Nielsen	
	17	5879690		1999-03-09	Perricone	
	18	5881476		1999-03-16	Strobush et al.	
	19	5891461		1999-04-06	Jona et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	20	5891845		1999-04-06	Myers	
	21	5894930		1999-04-20	Faughey et al.	
	22	5900247		1999-05-04	Rault et al.	
	23	5906742		1999-05-25	Wang et al.	
	24	5930914		1999-08-03	Johansson et al.	
	25	5937161		1999-08-10	Mulligan et al.	
	26	5941393		1999-08-24	Wilfong, Jr.	
	27	5945651		1999-08-31	Chorosinski et al.	
	28	5948430		1999-09-07	Zerbe et al.	
	29	5955097		1999-09-21	Tapolsky et al.	
	30	5965154		1999-10-12	Haralambopoulos	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	31	5980554		1999-11-09	Lenker et al.	
	32	5992742		1999-11-30	Sullivan et al.	
	33	5995597		1999-11-30	Woltz et al.	
	34	6004996		1999-12-21	Shah et al.	
	35	6024975		2000-02-15	D'Angelo et al.	
	36	6028066		2000-02-22	Unger	
	37	6030616		2000-02-29	Waters et al.	
	38	6031895		2000-02-29	Cohn et al.	
	39	6036016		2000-03-14	Arnold	
	40	6047484		2000-04-11	Bolland et al.	
	41	6051253		2000-04-18	Zettler et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	42	6054119		2000-04-25	Hurme et al.	
	43	6064990		2000-05-16	Goldsmith	
	44	6072100		2000-06-06	Mooney et al.	
	45	6074097		2000-06-13	Hayashi et al.	
	46	6077558		2000-06-20	Euber	
	47	6090401		2000-07-18	Gowan, Jr. et al.	
	48	6099871		2000-08-08	Martinez	
	49	6103266		2000-08-15	Tapolsky et al.	
	50	6106930		2000-08-22	Ludwig	
	51	6143276		2000-11-07	Unger	
	52	6148708		2000-11-21	Pfeiffer	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	53	6152007		2000-11-28	Sato	
	54	6153210		2000-11-28	Roberts et al.	
	55	6153220		2000-11-28	Cumming et al.	
	56	6159498		2000-12-12	Tapolsky et al.	
	57	6161129		2000-12-12	Rochkind	
	58	6177066		2001-01-23	Pataut et al.	
	59	6177092		2001-01-23	Lentini et al.	
	60	6177096		2001-01-23	Zerbe et al.	
	61	6183808		2001-02-06	Grillo et al.	
	62	6197329		2001-03-06	Hermelin et al.	
	63	6203566		2001-03-20	Alanen et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	64	6219694		2001-04-17	Lazaridis et al.	
	65	6221402		2001-04-24	Itoh et al.	
	66	6227359		2001-05-08	Truluck	
	67	6230894		2001-05-15	Danville	
	68	6231957		2001-05-15	Zerbe et al.	
	69	6238700		2001-05-29	Dohner et al.	
	70	6264981		2001-07-24	Zhang et al.	
	71	6267808		2001-07-31	Grillo et al.	
	72	6268048		2001-07-31	Karaev et al.	
	73	6284264		2001-09-04	Zerbe et al.	
	74	6287595		2001-09-11	Loewy et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	75	6294206		2001-09-25	Barrett-Reis et al.	
	76	6311627		2001-11-06	Draper et al.	
	77	6338407		2002-01-15	Danville	
	78	6344088		2002-02-05	Kamikihara et al.	
	79	6374715		2002-04-23	Takatsuka	
	80	6375963		2002-04-23	Repka et al.	
	81	6391294		2002-05-21	Dettmar et al.	
	82	6394306		2002-05-28	Pawlo et al.	
	83	6395299		2002-05-28	Babich et al.	
	84	6413792		2002-07-02	Sauer et al.	
	85	6419903		2002-07-16	Xu et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	86	6419906		2002-07-16	Xu et al.	
	87	6428825		2002-08-06	Sharma et al.	
	88	6432460		2002-08-13	Zietlow et al.	
	89	6436464		2002-08-20	Euber	
	90	6454788		2002-09-24	Ashton	
	91	6467621		2002-10-22	Ishida	
	92	6468516		2002-10-22	Geria et al.	
	93	6472003		2002-10-29	Barrett-Reis et al.	
	94	6482517		2002-11-19	Anderson	
	95	6488963		2002-12-03	McGinity et al.	
	96	6495599		2002-12-17	Auestad et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	97	6503532		2003-01-07	Murty et al.	
	98	6509072		2003-01-21	Bening et al.	
	99	6534090		2003-03-18	Puthli et al.	
	100	6534092		2003-03-18	Wright	
	101	6552024		2003-04-22	Chen et al.	
	102	6562375		2003-05-13	Sako et al.	
	103	6575999		2003-06-10	Rohrig	
	104	6589576		2003-07-08	Borschel et al.	
	105	6592887		2003-07-15	Zerbe et al.	
	106	6596298		2003-07-22	Leung et al.	
	107	6596302		2003-07-22	O'Connor et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	108	6599542		2003-07-29	Abdel-Malik et al.	
	109	6610338		2003-08-26	Tang	
	110	6620440		2003-09-16	Hsia et al.	
	111	6655112		2003-12-02	Cremer et al.	
	112	6656493		2003-12-02	Dzija et al.	
	113	6660292		2003-12-09	Zerbe et al.	
	114	6667060		2003-12-23	Vandecruys et al.	
	115	6668839		2003-12-30	Williams	
	116	6708826		2004-03-23	Ginsberg et al.	
	117	6709671		2004-03-23	Zerbe et al.	
	118	6720006		2004-04-13	Hanke et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	119	6726054		2004-04-27	Fagen et al.	
	120	6730319		2004-05-04	Maeder et al.	
	121	6752824		2004-06-22	Yancy	
	122	6776157		2004-08-17	Williams et al.	
	123	6797283		2004-09-28	Edgren et al.	
	124	6800329		2004-10-05	Horstmann et al.	
	125	6824829		2004-11-30	Berry et al.	
	126	6865860		2005-03-15	Arakawa et al.	
	127	6905016		2005-06-14	Kanios et al.	
	128	6913766		2005-07-05	Krumme et al.	
	129	6929399		2005-08-16	Nokura	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	130	6929400		2005-08-16	Razeti et al.	
	131	7005142		2006-02-28	Leon et al.	
	132	7040503		2006-05-09	Leichter et al.	
	133	7067116		2006-06-27	Bess et al.	
	134	7093736		2006-08-22	Maietta et al.	
	135	7115507		2006-10-03	Kawase	
	136	7179788		2007-02-20	DeFelippis et al.	
	137	7241411		2007-07-10	Berry et al.	
	138	7357891		2008-04-15	Yang et al.	
	139	7390503		2008-06-24	Ahmed et al.	
	140	7425292		2008-09-16	Yang et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	141	7428859		2008-09-30	Fujita et al.	
	142	7484640		2009-02-03	von Falkenhausen et al.	
	143	7531191		2009-05-12	Zion et al.	
	144	7579019		2009-08-25	Tapolsky et al.	
	145	7591801		2009-09-22	Brauker et al.	
	146	7665896		2010-02-23	Higgs	
	147	7666337		2010-02-23	Yang et al.	
	148	7694617		2010-04-13	Habra et al.	
	149	7824588		2010-11-02	Yang et al.	
	150	7910031		2011-03-22	Yang et al.	
	151	8017150		2011-09-13	Yang et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

	152	8051983		2011-11-08	Simon et al.	
	153	8147866		2012-04-03	Finn et al.	
	154	8617589		2013-12-31	Fuisz et al.	
	155	8840935		2014-09-23	Haber	
	156	8936825		2015-01-20	Myers et al.	

If you wish to add additional U.S. Patent citation information please click the Add button.

Add

U.S.PATENT APPLICATION PUBLICATIONS

Remove

Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20010006677	A1	2001-07-05	McGinity et al.	
	2	20010022964	A1	2001-09-20	Leung et al.	
	3	20010046511	A1	2001-11-29	Zerbe et al.	
	4	20020006677	A1	2002-01-17	Egermeier et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	5	20020012689	A1	2002-01-31	Stillman	
	6	20020045582	A1	2002-04-18	Margolin et al.	
	7	20020098198	A1	2002-07-25	Watts et al.	
	8	20020104774	A1	2002-08-08	Hammond	
	9	20020127254	A1	2002-09-12	Fotinos et al.	
	10	20020131990	A1	2002-09-19	Barkalow et al.	
	11	20020147201	A1	2002-10-10	Chen et al.	
	12	20020170567	A1	2002-11-21	Rizzotto et al.	
	13	20020177380	A1	2002-11-28	Forman et al.	
	14	20030035841	A1	2003-02-20	Dzija et al.	
	15	20030044446	A1	2003-03-06	Moro et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	16	20030044511	A1	2003-03-06	Zerbe et al.	
	17	20030054039	A1	2003-03-20	Zyck et al.	
	18	20030068378	A1	2003-04-10	Chen et al.	
	19	20030069263	A1	2003-04-10	Breder et al.	
	20	20030072865	A1	2003-04-17	Bindels et al.	
	21	20030077315	A1	2003-04-24	Lee et al.	
	22	20030107149	A1	2003-06-12	Yang et al.	
	23	20030118649	A1	2003-06-26	Gao et al.	
	24	20030121932	A1	2003-07-03	Wajda	
	25	20030124176	A1	2003-07-03	Hsu et al.	
	26	20030140760	A1	2003-07-31	Bory	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	27	20030143195	A1	2003-07-31	Pinsker	
	28	20030147956	A1	2003-08-07	Shefer et al.	
	29	20030161926	A1	2003-08-28	Kemp et al.	
	30	20030183643	A1	2003-10-02	Fagen et al.	
	31	20030224044	A1	2003-12-04	Weibel	
	32	20040013731	A1	2004-01-22	Chen et al.	
	33	20040024003	A1	2004-02-05	Asmussen et al.	
	34	20040044367	A1	2004-03-04	Yancy	
	35	20040058457	A1	2004-03-25	Huang et al.	
	36	20040091677	A1	2004-05-13	Topolkaraev	
	37	20040096569	A1	2004-05-20	Barkalow et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	38	20040102867	A1	2004-05-27	Palanisamy et al.	
	39	20040111275	A1	2004-06-10	Kroll et al.	
	40	20040120991	A1	2004-06-24	Gardner et al.	
	41	20040136924	A1	2004-07-15	Boyd et al.	
	42	20040137458	A1	2004-07-15	Archambault et al.	
	43	20040156901	A1	2004-08-12	Thakur et al.	
	44	20040191302	A1	2004-09-30	Davidson	
	45	20040209057	A1	2004-10-21	Enlow et al.	
	46	20040219109	A1	2004-11-04	Hatch	
	47	20040241242	A1	2004-12-02	Fuisz et al.	
	48	20050003048	A1	2005-01-06	Pearce et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	49	20050011776	A1	2005-01-20	Nagel	
	50	20050019588	A1	2005-01-27	Berry et al.	
	51	20050035133	A1	2005-02-17	Gerulski et al.	
	52	20050037055	A1	2005-02-17	Yang et al.	
	53	20050042271	A1	2005-02-24	Xiong	
	54	20050048102	A1	2005-03-03	Tapolsky et al.	
	55	20050055123	A1	2005-03-10	Franz	
	56	20050089548	A1	2005-04-28	Virgalitto et al.	
	57	20050095272	A1	2005-05-05	Augello	
	58	20050115862	A1	2005-06-02	Maietta	
	59	20050118217	A1	2005-06-02	Barnhart et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	60	20050118271	A1	2005-06-02	Schliecker et al.	
	61	20050136115	A1	2005-06-23	Kulkarni et al.	
	62	20050147658	A1	2005-07-07	Tapolsky et al.	
	63	20050163714	A1	2005-07-28	Sukhishvili et al.	
	64	20050170138	A1	2005-08-04	Berry	
	65	20050191349	A1	2005-09-01	Boehm et al.	
	66	20050192309	A1	2005-09-01	Palermo et al.	
	67	20050214251	A1	2005-09-29	Pohl et al.	
	68	20050222781	A1	2005-10-06	Yue et al.	
	69	20050232977	A1	2005-10-20	Khan et al.	
	70	20050239845	A1	2005-10-27	Proehl et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	71	20050266085	A1	2005-12-01	Warner	
	72	20060023976	A1	2006-02-02	Alvater et al.	
	73	20060039958	A1	2006-02-23	Fuisz et al.	
	74	20060071057	A1	2006-04-06	Aschenbrenner et al.	
	75	20060073173	A1	2006-04-06	Banach et al.	
	76	20060073190	A1	2006-04-06	Carroll et al.	
	77	20060083786	A1	2006-04-20	Chaudhari et al.	
	78	20060093679	A1	2006-05-04	Mayer et al.	
	79	20060104910	A1	2006-05-18	Lerner	
	80	20060147493	A1	2006-07-06	Yang et al.	
	81	20060163269	A1	2006-07-27	Anderson et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	82	20060180604	A1	2006-08-17	Ginsberg et al.	
	83	20060182796	A1	2006-08-17	Wu et al.	
	84	20060189772	A1	2006-08-24	Scheibel et al.	
	85	20060198790	A1	2006-09-07	Dugger, III et al.	
	86	20060198885	A1	2006-09-07	Dharmadhikari et al.	
	87	20060210610	A1	2006-09-21	Davidson et al.	
	88	20060213348	A1	2006-09-28	Loibl	
	89	20060215941	A1	2006-09-28	Golbert	
	90	20060246141	A1	2006-11-02	Liversidge et al.	
	91	20060264448	A1	2006-11-23	Pryde	
	92	20060281775	A1	2006-12-14	Kelly, II et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	93	20060286108	A1	2006-12-21	Bell	
	94	20070027213	A1	2007-02-01	Oberegger et al.	
	95	20070045148	A1	2007-03-01	Saclier et al.	
	96	20070069416	A1	2007-03-29	Yang et al.	
	97	20070071806	A1	2007-03-29	McCarty et al.	
	98	20070087036	A1	2007-04-19	Durschlag et al.	
	99	20070098746	A1	2007-05-03	Nichols et al.	
	100	20070122455	A1	2007-05-31	Myers et al.	
	101	20070138049	A1	2007-06-21	Bitner	
	102	20070148097	A1	2007-06-28	Finn et al.	
	103	20070170196	A1	2007-07-26	Libohova et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	104	20070202163	A1	2007-08-30	Rawas-Qalaji	
	105	20070205127	A1	2007-09-06	Barndt et al.	
	106	20070231368	A1	2007-10-04	Wang et al.	
	107	20070267433	A1	2007-11-22	Fuisz et al.	
	108	20070275893	A1	2007-11-29	Quay	
	109	20070281003	A1	2007-12-06	Fuisz et al.	
	110	20070293581	A1	2007-12-20	Hill	
	111	20080044454	A1	2008-02-21	Yang et al.	
	112	20080073235	A1	2008-03-27	Harada et al.	
	113	20080075825	A1	2008-03-27	Fuisz et al.	
	114	20080081071	A1	2008-04-03	Sanghvi et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	115	20080105582	A1	2008-05-08	Ludwig et al.	
	116	20080233174	A1	2008-09-25	Myers et al.	
	117	20080242558	A1	2008-10-02	Belcher et al.	
	118	20080242736	A1	2008-10-02	Fuisz	
	119	20080254105	A1	2008-10-16	Tapolsky et al.	
	120	20080260805	A1	2008-10-23	Yang et al.	
	121	20080260809	A1	2008-10-23	Yang et al.	
	122	20080268116	A1	2008-10-30	Kring	
	123	20080290106	A1	2008-11-27	van der Klaauw et al.	
	124	20080299197	A1	2008-12-04	Tongeguzzo et al.	
	125	20080300173	A1	2008-12-04	DeFrees	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	126	20080308449	A1	2008-12-18	Intini	
	127	20090004254	A1	2009-01-01	Maibach	
	128	20090009332	A1	2009-01-08	Nunez et al.	
	129	20090014491	A1	2009-01-15	Fuisz et al.	
	130	20090029074	A1	2009-01-29	Sasine et al.	
	131	20090074333	A1	2009-03-19	Griebel et al.	
	132	20090104270	A1	2009-04-23	Myers et al.	
	133	20090146336	A1	2009-06-11	Masi	
	134	20090181075	A1	2009-07-16	Gordon et al.	
	135	20090186107	A1	2009-07-23	Haber et al.	
	136	20090192075	A1	2009-07-30	Steiner	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556	
	Filing Date		2024-01-16	
	First Named Inventor	Alexander Mark Schobel		
	Art Unit	1616		
	Examiner Name	NATHAN W SCHLIENTZ		
	Attorney Docket Number	270712/AQU-014USC5/542244		

	137	20090196907	A1	2009-08-06	Bunick et al.	
	138	20090280160	A1	2009-11-12	Monteith et al.	
	139	20090297614	A1	2009-12-03	Rademacher et al.	
	140	20100015128	A1	2010-01-21	Lee et al.	
	141	20100087470	A1	2010-04-08	Oksche et al.	
	142	20100092545	A1	2010-04-15	Yang et al.	
	143	20100178254	A1	2010-07-15	Hariharan et al.	
	144	20100221309	A1	2010-09-02	Myers et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button.

Add

FOREIGN PATENT DOCUMENTS								Remove	
Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T ⁵	
	1	2305310	EP	A1	2011-04-06	Ct De Investigacion Cooperativa En Biomateriales C			☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556	
	Filing Date		2024-01-16	
	First Named Inventor	Alexander Mark Schobel		
	Art Unit	1616		
	Examiner Name	NATHAN W SCHLIENTZ		
	Attorney Docket Number	270712/AQU-014USC5/542244		

	2	2716098	FR	A1	1995-08-18	Socoplan SA		☐
	3	1061557	GB	A	1967-03-15	Ashe Chemical Ltd		☐
	4	1154317	GB	A	1969-06-04	Russell, Higham Stanley		☐
	5	1510999	GB	A	1978-05-17	Schering, Ag		☐
	6	2166651	GB	A	1986-05-14	Elan Corp PLC		☐
	7	2193891	GB	A	1988-02-24	Sandoz Ltd		☐
	8	2447016	GB	A	2008-09-03	Reckitt Benckiser Healthcare		☐
	9	56100714	JP		2442-05-25			☐
	10	62126950	JP		2444-01-13			☐
	11	2265444	JP		2444-11-12			☐
	12	473268	JP		2445-05-24			☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	13	5147140	JP	B2	2013-02-20	Sammy Corp		☐
	14	7322812	JP		2446-03-29			☐
	15	11255247	JP		2447-04-30			☐
	16	2000159658	JP	A	2000-06-13	Lion Corp		☐
	17	2001048196	JP	A	2001-02-20	Dainippon Printing Co Ltd		☐
	18	2001225851	JP	A	2001-08-21	Okayama Taiho Pharmaceutical C		☐
	19	2001279100	JP	A	2001-10-10	Kobayashi Pharma		☐
	20	2003312688	JP	A	2003-11-06	Okayama Taiho Pharmaceutical C		☐
	21	2004222663	JP	A	2004-08-12	Ni Corportion Co Ltd		☐
	22	2006143335	JP	A	2006-06-08	Dainippon Printing Co Ltd		☐
	23	2008501019	JP	A	2008-01-17			☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	24	2008011194	JP	A	2008-01-17	Fujifilm Corp		☐
	25	2012524771	JP	A	2012-10-18			☐
	26	2014532482	JP	A	2014-12-08			☐
	27	2019519487	JP	A	2019-07-11			☐
	28	2019519488	JP	A	2019-07-11			☐
	29	1988007103	WO	A1	1988-09-22	Valmet Paper Machinery Inc		☐
	30	9105540	WO	A1	1991-05-02	Desitin Arzneimittel GmbH		☐
	31	1992012704	WO	A1	1992-08-06	Eastman Kodak Co		☐
	32	9215289	WO	A1	1992-09-17	Noven Pharmaceuticals, Inc		☐
	33	9505416	WO	A2	1995-02-23	Cygnus Therapeutic Systems		☐
	34	9518046	WO	A1	1995-07-06	Frank, Richard		☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	35	1995023596	WO	A1	1995-09-08	Boots Co PLC		☐
	36	9530601	WO	A1	1995-11-16	Sales Spa		☐
	37	9615903	WO	A1	1996-05-30	Grace W R & Co		☐
	38	9625150	WO	A1	1996-08-22	Nanosystems LLC		☐
	39	1996025638	WO	A1	1996-08-22	Johansson, Sonny		☐
	40	9731621	WO	A1	1997-09-04	Warner Lambert Co		☐
	41	9732573	WO	A1	1997-09-12	Nycomed Danmark A S		☐
	42	1997044016	WO	A1	1997-11-27	Samyang Corp		☐
	43	9810993	WO	A1	1998-03-19	Unifill Int AG		☐
	44	9817251	WO	A1	1998-04-30	Virotext Corp		☐
	45	1998014179	WO	A1	1998-04-09	Cima Labs Inc		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556	
	Filing Date		2024-01-16	
	First Named Inventor	Alexander Mark Schobel		
	Art Unit	1616		
	Examiner Name	NATHAN W SCHLIENTZ		
	Attorney Docket Number	270712/AQU-014USC5/542244		

	46	9935051	WO	A1	1999-07-15	Lohmann Therapie Syst Lts		☐
	47	9955312	WO	A2	1999-11-04	Virotex Corp		☐
	48	200002536	WO	A1	2000-01-20	Fmc Corp		☐
	49	2000002955	WO	A1	2000-01-20	Kimberly-clark Worldwide, Inc		☐
	50	0018365	WO	A2	2000-04-06	Warner Lambert Co		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
	1	U.S. Appl. No. 11/092,217, filed Mar. 29, 2005.	☐
	2	U.S. Appl. No. 11/237,525, filed Sep. 28, 2005.	☐
	3	U.S. Appl. No. 11/473,356, filed Jun. 22, 2006.	☐
	4	U.S. Appl. No. 11/517,982, filed Sep. 8, 2006.	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

5	U.S. Appl. No. 11/526,996, filed Sep. 26, 2006.	☐
6	U.S. Appl. No. 11/634,280, filed Dec. 5, 2006.	☐
7	U.S. Appl. No. 11/639,013, filed Dec. 14, 2006.	☐
8	U.S. Appl. No. 11/674,223, filed Feb. 13, 2007.	☐
9	U.S. Appl. No. 11/775,484, filed Jul. 10, 2007.	☐
10	U.S. Appl. No. 12/102,071, filed Apr. 14, 2008.	☐
11	U.S. Appl. No. 12/128,950, May 29, 2008.	☐
12	U.S. Appl. No. 12/107,389, filed Apr. 22, 2008.	☐
13	U.S. Appl. No. 12/171,692, filed Jul. 11, 2008.	☐
14	U.S. Appl. No. 12/411,505, filed Mar. 26, 2009.	☐
15	U.S. Appl. No. 12/411,835, filed Mar. 26, 2009.	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

16	U.S. Appl. No. 12/575,261, filed Oct. 7, 2009.	☐
17	U.S. Appl. No. 12/614,928, filed Nov. 9, 2009.	☐
18	U.S. Appl. No. 12/779,316, filed May 13, 2010.	☐
19	U.S. Appl. No. 13/035,328, filed Feb. 25, 2011.	☐
20	U.S. Appl. No. 13/052,655, filed Mar. 21, 2011.	☐
21	U.S. Appl. No. 13/342,614, filed Feb. 12, 2012.	☐
22	U.S. Appl. No. 13/096,996, filed Apr. 28, 2011.	☐
23	U.S. Appl. No. 13/853,237, filed Mar. 29, 2013.	☐
24	U.S. Appl. No. 13/853,223, filed Mar. 29, 2013.	☐
25	U.S. Appl. No. 13/853,253, filed Mar. 29, 2013.	☐
26	U.S. Appl. No. 13/853,276, filed Mar. 29, 2013.	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

27	U.S. Appl. No. 13/853,290, filed Mar. 29, 2013.	☐
28	U.S. Appl. No. 13/890,542, filed May 9, 2013.	☐
29	U.S. Appl. No. 13/974,376, filed Aug. 23, 2013.	☐
30	U.S. Appl. No. 13/974,389, filed Aug. 23, 2013.	☐
31	U.S. Appl. No. 13/974,401, filed Aug. 23, 2013.	☐
32	U.S. Appl. No. 13/974,413, filed Aug. 23, 2013.	☐
33	U.S. Appl. No. 14/032,588, filed Sep. 20, 2013.	☐
34	U.S. Appl. No. 14/195,362, filed Mar. 3, 2014.	☐
35	U.S. Appl. No. 14/284,019, filed May 21, 2014.	☐
36	U.S. Appl. No. 14/492,874, filed Sep. 22, 2014.	☐
37	U.S. Appl. No. 14/572,173, filed Dec. 16, 2014.	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

38	U.S. Appl. No. 14/599,803, filed Jan. 19, 2015.	☐
39	U.S. Appl. No. 14/844,810, filed Sep. 3, 2015.	☐
40	U.S. Appl. No. 14/945,181, filed Nov. 18, 2015.	☐
41	U.S. Appl. No. 14/980,836, filed Dec. 28, 2015.	☐
42	U.S. Appl. No. 15/058,056, filed Mar. 1, 2016.	☐
43	U.S. Appl. No. 15/144,191, filed May 2, 2016.	☐
44	U.S. Appl. No. 15/398,398, filed Jan. 4, 2017.	☐
45	U.S. Appl. No. 15/342,448, filed Nov. 3, 2016.	☐
46	U.S. Appl. No. 15/438,406, filed Feb. 21, 2017.	☐
47	U.S. Appl. No. 15/438,458, filed Feb. 21, 2017.	☐
48	U.S. Appl. No. 15/634,776, filed Jun. 27, 2017.	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556
	Filing Date		2024-01-16
	First Named Inventor	Alexander Mark Schobel	
	Art Unit	1616	
	Examiner Name	NATHAN W SCHLIENTZ	
	Attorney Docket Number	270712/AQU-014USC5/542244	

	49	U.S. Appl. No. 15/672,228, filed Aug. 8, 2017.	☐
	50	PCT/US02/32542, Oct. 11, 2002.	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	
*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.			
¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.			

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556
	Filing Date		2024-01-16
	First Named Inventor	Alexander Mark Schobel	
	Art Unit	1616	
	Examiner Name	NATHAN W SCHLIENTZ	
	Attorney Docket Number	270712/AQU-014USC5/542244	

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Harold H. Fox, Reg. #41498/	Date (YYYY-MM-DD)	2024-03-18
Name/Print	Harold Fox, Ph.d.	Registration Number	41,498

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556
	Filing Date		2024-01-16
	First Named Inventor	Alexander Mark Schobel	
	Art Unit	1616	
	Examiner Name	NATHAN W SCHLIENTZ	
	Attorney Docket Number	270712/AQU-014USC5/542244	

U.S.PATENTS							Remove	
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear		
	1							
If you wish to add additional U.S. Patent citation information please click the Add button.							Add	
U.S.PATENT APPLICATION PUBLICATIONS							Remove	
Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear		
	1							
If you wish to add additional U.S. Published Application citation information please click the Add button.							Add	
FOREIGN PATENT DOCUMENTS							Remove	
Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1							☐
If you wish to add additional Foreign Patent Document citation information please click the Add button								Add
NON-PATENT LITERATURE DOCUMENTS								Remove
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.						T ⁵

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

1	Engel, June V PhD, "The Benefits of Eating Fibre" http://www.diabetes.ca/common/PrintVersion.asp?ID=45493 May 11, 2005.	☐
2	Flick, E., Water-Soluble Resins—An Industrial Guide, 1991 (2nd Ed.) William Andrew Publishing/Noyes, pp. 389-392.	☐
3	Goldberg et al., "Biotechnology and Food Ingredients", Springer: 352 (1991).	☐
4	Hadvary et al., "Inhibition of pancreatic lipase in vitro by the covalent inhibitor tetrahydrolipstatin", Biochem J.; 256: 357-361 (1988).	☐
5	Ko et al., "Behavior of etrahydrolipstatin in biological model membranes and emulsions", J. of Lipid Research; 38:1544-1552 (1997).	☐
6	Kuhntreiber. In Cell Encapsulation and Therapeutics . Copyright 1999.	☐
7	Lazaridou et al.; Thermophysical properties of chitosan, chitosanstarch and chitosan-pullulan films near the glass transition; Elsevier Science Ltd.; 2002; pp. 179-190.	☐
8	Leathers, Appl. Microbiol. Biotechnol., 62: 468-473, 2003.	☐
9	Le Person, S. Le et al., "Near infrared drying of pharmaceutical thin films: experimental analysis of internal mass transport," Chemical Engineering and Processing; (1998) pp. 257-263, 37.	☐
10	Mahmood et al., "A limited sampling method for the estimation of AUC and Cmax of cabamazepine and carbamazepine epoxide folowing a single and multiple dose of a sustained-release product", BR J Clin Pharmacol; 45:241-246 (1998).	☐
11	Mix. http://www.askoxford.com/concise_oed/mixx?view=uk . Accessed Dec. 23, 2004.	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

12	Nicorete Packaging (Aug. 29, 2006).	☐
13	Oriski, S.C., "Johnson debuts cutter for new Saran film" Packaging World Oct. 1, 2004, http://www.packworld.com/view-18051 .	☐
14	Peh Kok Khiang et al., "Polymeric Films as Vehicle for Buccal Delivery: Swelling, Mechanical, and Bioadhesive Properties," J Pharm Pharmaceut Sci (1999) pp. 53-61, 2:2.	☐
15	Polyethylenglykoke, Fachgebiet Chemie, Unterthema Makromolekulare Chemie, XP-002298105 (Sep. 20, 2004).	☐
16	Repka et al., "Bioadhesive properties of hydroxypropylcellulose topical films produced by hot-melt extrusion," Journal of Controlled Release, 70: 341-351 (2001).	☐
17	Repka et al., "Influence of Vitamin E TPGS on the properties of hydrophilic films produced by hot-melt extrusion," Int. J. Pharmaceutics, 202: 63-70 (2000).	☐
18	Senel, S., et al., "Chitosan films and hydrogels of chlorhexidine gluconate for oral mucosal delivery", Int. J. Pharmaceutics, 193: pp. 197-203 (2000).	☐
19	Stella, V., et al., "Gliadin Films. I: Preparation and in vitro evaluation as a carrier for controlled drug release", Int., J. Pharmaceutics, 121: pp. 117-121 (1995).	☐
20	Sudafed & Sudafed PE, http://www.sudafed.com/products/pe_quickstrips.html (Aug. 17, 2007).	☐
21	Well—Definition of from The American Heritage College Dictionary, 3rd Ed., p. 1531 (1993).	☐
22	Bauer, K.H. et al., "Pharmazeutische Technologie", pp. 208-209 (1997).	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

23	Pinnamanemi, S. et al., "Formulation approaches for orally administered poorly soluble drugs", Pharmazie 57(5): 291-300 (2002).	☐
24	Chaumeil, J.C., "Micronization: A Method of Improving the Bioavailability of Poorly Soluble Drugs", Methods and Findings in Experimental and Clinical Pharmacology 20(3): 211-215 (1998).	☐
25	Voigt, R. et al., "Pharmaseutische Technology fur Studium und Berf", pp. 179-180 (1995).	☐
26	Nanda, A. et al., "An update on taste masking technologies for oral pharmaceuticals", Indian J Pharma Sci 64(1): 10-17 (2002).	☐
27	Bornschein, M. et al., "Micro- und Nanopartikeln als Arzneistofftragersysteme unter besonderer Berucksichtigung der Herstellungsmethoden", Die Pharmazie 44(9): 585-593 (1989).	☐
28	Cohen E. et al., "Modern Coating and Drying Technology", pp. 268-277 (1992).	☐
29	International Search Report and Written Opinion for PCT/US2018/052927, dated Dec. 19, 2018.	☐
30	Ho, N.F.H., et al., "(D) Routes of delivery: Case studies," Advanced Drug Delivery Reviews, vol. 8, No. 2-3 (Mar. 1, 1992) pp. 197-236.	☐
31	Merkle, H.P., et al., "Buccal delivery for peptide drugs," Journal of Controlled Release, vol. 21 No. 1-3 (1992).	☐
32	Wolany, Gregor, "Zur bukkalen Applikation und Absorption des Oktapeptids Octreotid," (Jan. 1, 1990).	☐
33	International Search Report and Written Opinion for PCT/US2018/053042, dated Dec. 11, 2018.	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

34	International Search Report and Written Opinion for PCT/US2018/053026, dated Dec. 14, 2018.	☐
35	Office Action mailed in European Patent Application No. 17723616.3 dated Mar. 3, 2020.	☐
36	Office action mailed in European Patent Application No. 17723617.3 dated Mar. 3, 2020.	☐
37	Nicolazzo et al. "Modification of buccal drug delivery following pretreatment with skin penetration enhancers," Journal of Pharmaceutical Sciences, vol. 93, Issue 8, 2004, pp. 2054-2063.	☐
38	Stanczak et al., "Prodrugs and Soft Drugs", Pharmacological Reports, 2006, 58, 599-613.	☐
39	Nicolazzo et al. "Assessment of the Effect of Sodium Dodecyl Sulfate on the Buccal Permeability of Caffeine and Estradiol", Journal of Pharmaceutical Sciences, vol. 93, No. 2 Feb. 2004, 431-440.	☐
40	Sudhakar et al. "Buccal bioadhesive drug delivery—A promising option for orally less efficient drugs", Journal of Controlled Release 114 (2006) 15-40.	☐
41	Van Ginkel, C.G. (1995). "Biodegradability of cationic surfactants." In: Karsa D.R., Porter M.R. (eds) Biodegradability of Surfactants, Springer, Dordrecht; pp. 1-21 (Year: 1995).	☐
42	Lu et al. (Jan. 12, 2017). "Impact of Endogenous Bile Salts on the Thermodynamics of Supersaturated Active Pharmaceutical Ingredient Solutions." Cryst. Growth Des., 17, pp. 1264-1275 (Year: 2017).	☐
43	Rogawski et al., "Diazepam buccal film for the treatment of acute seizures". Epilepsy and Behavior, Academic Press, San Diego, CA, US Vol. 101. Nov. 5, 2019.	☐
44	Health Syneos: "A Randomized, Open-Label, 2-Sequence, 3 Treatment, Crossover Study to Evaluate the Pharmacokinetics of Single Doses of Diazepam Buccal Film (DBF) (Aquestive Therapeutics) Compared With Diastat Rectal Gel (Valeant Pharmaceuticals North America) in Adult Male and Female Subjects on Concomitant Reg", May 25, 2019 (May 24, 2019).	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

45	Streubel et al., "Bimodal drug release achieved with multi-layer matrix tablets: transport mechanisms and device design", Journal of Controlled Release, Elsevier, Amsterdam, NL. vol. 69, No. 3, Dec. 3, 2000 (Dec. 3, 2000).	☐
46	Menezes, et al. "Hypotensive activity of terpenes found in essential oils." Zeitschrift fur Naturforschung. C, Journal of biosciences vol. 65,9-10 (2010): 562-6.	☐
47	Tsai, Tung-Hu et al. "Vasorelaxing alkaloids and flavonoids from Cassytha filiformis." Journal of natural products vol. 71,2 (2008): 289-91.	☐
48	Luna-Vázquez, Francisco J et al. "Vasodilator compounds derived from plants and their mechanisms of action." Molecules (Basel, Switzerland) vol. 18,5 5814-57. May 17, 2013.	☐
49	Park, Soo-Hyun et al. "The analgesic effects and mechanisms of orally administered eugenol." Archives of pharmacal research vol. 34,3 (2011): 501-7.	☐
50	Chang, Huang-Kuang et al. "Stimulatory effect of cinnamic acid analogues on alpha1A-adrenoceptors in-vitro." The Journal of pharmacy and pharmacology vol. 55,6 (2003): 833-7.	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

***EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556
	Filing Date		2024-01-16
	First Named Inventor	Alexander Mark Schobel	
	Art Unit	1616	
	Examiner Name	NATHAN W SCHLIENTZ	
	Attorney Docket Number	270712/AQU-014USC5/542244	

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Harold H. Fox, Reg. #41498/	Date (YYYY-MM-DD)	2024-03-18
Name/Print	Harold Fox, Ph.d.	Registration Number	41,498

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556
	Filing Date		2024-01-16
	First Named Inventor	Alexander Mark Schobel	
	Art Unit	1616	
	Examiner Name	NATHAN W SCHLIENTZ	
	Attorney Docket Number	270712/AQU-014USC5/542244	

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	11191737		2021-12-07	Schobel et al.	
	2	0026401		1859-12-06	Brashear et al.	
	3	0307537		1884-11-04	Foulks	
	4	0476085		1892-05-31	Smith	
	5	0492417		1893-02-28	McAlister	
	6	0503070		1893-08-08	Broadwell et al.	
	7	0596302		1897-12-28	McMahon	
	8	0688446		1901-12-10	Stempel, Jr.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	9	1110546		1914-09-15	Hewitt	
	10	1827354		1931-10-13	Cooper	
	11	2142537		1939-01-03	Tiixa	
	12	2277038		1942-03-24	Curtis	
	13	2352691		1944-07-04	Curtis	
	14	2376656		1945-05-22	Leonia	
	15	2501544		1950-03-21	Shrontz	
	16	2612165		1952-09-30	Szukerski	
	17	2980554		1961-04-18	Gentile et al.	
	18	3007848		1961-11-07	Stroop	
	19	3044338		1962-07-17	Horton et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	20	3131068		1964-04-28	Grief	
	21	3142217		1964-07-28	Busse	
	22	3189174		1965-06-15	Cormack	
	23	3237596		1966-03-01	Grass, Jr. et al.	
	24	3242959		1966-03-29	Glass	
	25	3249109		1966-05-03	Maeth et al.	
	26	3324754		1967-06-13	Peavy	
	27	3370497		1968-02-27	Busse	
	28	3419137		1968-12-31	Walck, III	
	29	3444858		1969-05-20	Russell	
	30	3451539		1969-06-24	Wysocki	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	31	3536809		1970-10-27	Applezwig	
	32	3539605		1970-11-10	Oberhofer	
	33	3551556		1970-12-29	Kliment et al.	
	34	3598122		1971-08-10	Zaffaroni	
	35	3610248		1971-10-05	Davidson	
	36	3625351		1971-12-07	Eisenberg	
	37	3632740		1972-01-04	Robinson et al.	
	38	3640741		1972-02-08	Etes	
	39	3641237		1972-02-08	Gould et al.	
	40	3650461		1972-03-21	Hutcheson	
	41	3677866		1972-07-18	Pickett et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	42	3731683		1973-05-08	Zaffaroni	
	43	3753732		1973-08-21	Boroshok	
	44	3755558		1973-08-28	Scribner	
	45	3768725		1973-10-30	Pilaro	
	46	3795527		1974-03-05	Stone et al.	
	47	3797494		1974-03-19	Zaffroni	
	48	3809220		1974-05-07	Arcudi	
	49	3809714		1974-05-07	Hussain	
	50	3814095		1974-06-04	Lubens	
	51	3825014		1974-07-23	Wroten	
	52	3835995		1974-09-17	Haines	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	53	3840657		1974-10-08	Norfleet	
	54	3892905		1975-07-01	Albert	
	55	3911099		1975-10-07	DeFoney et al.	
	56	3933245		1976-01-20	Mullen	
	57	3972995		1976-08-03	Tsuk et al.	
	58	3979839		1976-09-14	Blanie	
	59	3996934		1976-12-14	Zaffaroni	
	60	3998215		1976-12-21	Anderson et al.	
	61	4015023		1977-03-29	Lamberti et al.	
	62	4022924		1977-05-10	Mitchell et al.	
	63	4029757		1977-06-14	Mlodozieniec et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	64	4029758		1977-06-14	Mlodozeniec et al.	
	65	4031200		1977-06-21	Reif	
	66	4049848		1977-09-20	Goodale et al.	
	67	4053046		1977-10-11	Roark	
	68	4067116		1978-01-10	Bryner et al.	
	69	4105116		1978-08-08	Jones et al.	
	70	4123592		1978-10-31	Rainer et al.	
	71	4126503		1978-11-21	Gardner	
	72	4128445		1978-12-05	Sturzenegger et al.	
	73	4136145		1979-01-23	Fuchs et al.	
	74	4136162		1979-01-23	Fuchs et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	75	4139627		1979-02-13	Lane et al.	
	76	4145441		1979-03-20	Bodor	
	77	4202966		1980-05-13	Misaki et al.	
	78	4226848		1980-10-07	Nagai et al.	
	79	4249531		1981-02-10	Heller et al.	
	80	4251400		1981-02-17	Columbus	
	81	4251561		1981-02-17	Gajewski	
	82	4284194		1981-08-18	Flatau	
	83	4284534		1981-08-18	Ehrlich	
	84	4292299		1981-09-29	Suzuki et al.	
	85	4294820		1981-10-13	Keith et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	86	4302465		1981-11-24	AF Ekenstam et al.	
	87	4307075		1981-12-22	Martin	
	88	4307117		1981-12-22	Leshik	
	89	4325855		1982-04-20	Dickmann et al.	
	90	4341563		1982-07-27	Kurihara et al.	
	91	4365423		1982-12-28	Arter et al.	
	92	4373036		1983-02-08	Chang et al.	
	93	4390450		1983-06-28	Gibson et al.	
	94	4406708		1983-09-27	Hesselgren	
	95	4432975		1984-02-21	Libby	
	96	4438258		1984-03-20	Graham	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	97	4451260		1984-05-29	Mitra	
	98	4460532		1984-07-17	Cornell	
	99	4460562		1984-07-17	Keith et al.	
	100	4466973		1984-08-21	Rennie	
	101	4478658	A	1984-10-23	Wittwer, Fritz	
	102	4483846		1984-11-20	Koide et al.	
	103	4503070		1985-03-05	Eby, III	
	104	4511592		1985-04-16	Percel et al.	
	105	4515162		1985-05-07	Yamamoto et al.	
	106	4517173		1985-05-14	Kizawa et al.	
	107	4529301		1985-07-16	Rountree	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	108	4529601		1985-07-16	Broberg et al.	
	109	4529748		1985-07-16	Wienecke	
	110	4562020		1985-12-31	Hijiya et al.	
	111	4568535		1986-02-04	Loesche	
	112	4569837		1986-02-11	Suzuki et al.	
	113	4572832		1986-02-25	Kigasawa et al.	
	114	4582835		1986-04-15	Lewis et al.	
	115	4585452		1986-04-29	Sablotsky	
	116	4588592		1986-05-13	Elias	
	117	4593053		1986-06-03	Jevne et al.	
	118	4598089		1986-07-01	Hadvary et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	119	4608249		1986-08-26	Otsuka et al.	
	120	4613497		1986-09-23	Chavkin	
	121	4615697		1986-10-07	Robinson	
	122	4619701		1986-10-28	Angrick et al.	
	123	4621482		1986-11-11	Crevasse et al.	
	124	4623394		1986-11-18	Nakamura et al.	
	125	4631837		1986-12-30	Magoon	
	126	4639367		1987-01-27	Mackles	
	127	4648509		1987-03-10	Alves	
	128	4659714		1987-04-21	Watt-Smith	
	129	4661359		1987-04-28	Seaborne et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	130	4675009		1987-06-23	Hymes et al.	
	131	4695465		1987-09-22	Kigasawa et al.	
	132	4704119		1987-11-03	Shaw et al.	
	133	4705174		1987-11-10	Goglio	
	134	4712460		1987-12-15	Allen et al.	
	135	4713239		1987-12-15	Babaian et al.	
	136	4713243		1987-12-15	Schiraldi et al.	
	137	4713251		1987-12-15	Seighman	
	138	4716802		1988-01-05	O'Connor et al.	
	139	4722761		1988-02-02	Cartmell et al.	
	140	4727064		1988-02-23	Pitha	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	141	4740365		1988-04-26	Yukimatsu et al.	
	142	4748022		1988-05-31	Busciglio	
	143	4752465		1988-06-21	Mackles	
	144	4762230		1988-08-09	Croce	
	145	4764378		1988-08-16	Keith et al.	
	146	4765983		1988-08-23	Takayanagi et al.	
	147	4772470		1988-09-20	Inoue et al.	
	148	4777046		1988-10-11	Iwakura et al.	
	149	4780309		1988-10-25	Geria et al.	
	150	4781294		1988-11-01	Croce	
	151	4787517		1988-11-29	Martin	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	152	4789667		1988-12-06	Makino et al.	
	153	4802924		1989-02-07	Woznicki et al.	
	154	4828841		1989-05-09	Porter et al.	
	155	4849246		1989-07-18	Schmidt	
	156	4851394		1989-07-25	Kubodera	
	157	4860754		1989-08-29	Sharik et al.	
	158	4861632		1989-08-29	Caggiano	
	159	RE33093		1989-10-17	Schiraldi et al.	
	160	4872270		1989-10-10	Fronheiser et al.	
	161	4876092		1989-10-24	Mizobuchi et al.	
	162	4876970		1989-10-31	Bolduc	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	163	4880416		1989-11-14	Horiuchi et al.	
	164	4888354		1989-12-19	Chang et al.	
	165	4894232		1990-01-16	Reul et al.	
	166	4900552		1990-02-13	Sanvordeker et al.	
	167	4900554		1990-02-13	Yangibashi et al.	
	168	4900556		1990-02-13	Wheatley et al.	
	169	4910247		1990-03-20	Haidar et al.	
	170	4915950		1990-04-10	Miranda et al.	
	171	4925670		1990-05-15	Schmidt	
	172	4927634		1990-05-22	Sorrentino et al.	
	173	4927636		1990-05-22	Hijiya et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	174	4929447		1990-05-29	Yang	
	175	4937078		1990-06-26	Mezei et al.	
	176	4940587		1990-07-10	Jenkins et al.	
	177	4948580		1990-08-14	Browning	
	178	4958580		1990-09-25	Asaba et al.	
	179	4978531		1990-12-18	Yamazaki et al.	
	180	4980169		1990-12-25	Oppenheimer et al.	
	181	4981693		1991-01-01	Higashi et al.	
	182	4981875		1991-01-01	Leusner et al.	
	183	4993586		1991-02-19	Taulbee et al.	
	184	5023082		1991-06-11	Friedman et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	185	5023271		1991-06-11	Vigne et al.	
	186	5024701		1991-06-18	Desmarais	
	187	5025692		1991-06-25	Reynolds	
	188	5028632		1991-07-02	Fuisz	
	189	5044241		1991-09-03	Labrecque	
	190	5044761		1991-09-03	Yuhki et al.	
	191	5045445		1991-09-03	Schultz	
	192	5047244		1991-09-10	Sanvordeker et al.	
	193	5049322		1991-09-17	Devissaguet et al.	
	194	5056584		1991-10-15	Seaton	
	195	5064717		1991-11-12	Suzuki et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	196	5072842		1991-12-17	White	
	197	5078734		1992-01-07	Noble	
	198	5089307		1992-02-18	Ninomiya et al.	
	199	5100591		1992-03-31	Leclef et al.	
	200	5107734		1992-04-28	Armbruster	
	201	5116140		1992-05-26	Hirashima	
	202	5118508		1992-06-02	Kikuchi et al.	
	203	5126160		1992-06-30	Giddey et al.	
	204	5137729		1992-08-11	Kuroya et al.	
	205	5158825		1992-10-27	Altwirth	
	206	5166233		1992-11-24	Kuroya et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	207	5176705		1993-01-05	Noble	
	208	5184771		1993-02-09	Jud et al.	
	209	5186938		1993-02-16	Sablotsky et al.	
	210	5188838		1993-02-23	Deleuil et al.	
	211	5196436		1993-03-23	Smith	
	212	5229164		1993-07-20	Pins et al.	
	213	5230441		1993-07-27	Kaufman et al.	
	214	5234957		1993-08-10	Mantelle	
	215	5264024		1993-11-23	Bosvot et al.	
	216	5271940		1993-12-21	Cleary et al.	
	217	5272191		1993-12-21	Ibrahim et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	218	5273758		1993-12-28	Royce	
	219	5293699		1994-03-15	Faust et al.	
	220	5316717		1994-05-31	Koepff et al.	
	221	5325968		1994-07-05	Sowden	
	222	5328942		1994-07-12	Akhtar et al.	
	223	5344676		1994-09-06	Kim et al.	
	224	5346701		1994-09-13	Heiber et al.	
	225	5354551		1994-10-11	Schmidt	
	226	5360629		1994-11-01	Milbourn et al.	
	227	5369131		1994-11-29	Poli et al.	
	228	5375930		1994-12-27	Tani	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	229	5380529		1995-01-10	Heusser et al.	
	230	5393528		1995-02-28	Staab	
	231	5405637		1995-04-11	Martinez et al.	
	232	5407278		1995-04-18	Beer	
	233	5411945		1995-05-02	Ozaki et al.	
	234	5413792		1995-05-09	Ninomiya et al.	
	235	5422127		1995-06-06	Dube et al.	
	236	5423423		1995-06-13	Sato et al.	
	237	5433960		1995-07-18	Meyers	
	238	5451419		1995-09-19	Schwab et al.	
	239	5455043		1995-10-03	Fischel-Ghodsian	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	240	5458884		1995-10-17	Britton et al.	
	241	5462749		1995-10-31	Rencher	
	242	5472704		1995-12-05	Santus et al.	
	243	5479408		1995-12-26	Will	
	244	5489436		1996-02-06	Hoy et al.	
	245	5506046		1996-04-09	Andersen et al.	
	246	5506049		1996-04-09	Swei et al.	
	247	5518902		1996-05-21	Ozaki et al.	
	248	5529782		1996-06-25	Staab	
	249	5530861		1996-06-25	Diamant et al.	
	250	5550178		1996-08-27	Desai et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	251	5551033		1996-08-27	Foster et al.	
	252	5552152		1996-09-03	Shen	
	253	5553835		1996-09-10	Dresie et al.	
	254	5560538		1996-10-01	Sato et al.	
	255	5567237		1996-10-22	Kapp-Schwoerer et al.	
	256	5567431		1996-10-22	Vert et al.	
	257	5573783		1996-11-12	Desieno et al.	
	258	5582342		1996-12-10	Jud	
	259	5587175		1996-12-24	Viegas et al.	
	260	5588009		1996-12-24	Will	
	261	5589357		1996-12-31	Martinez et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	262	5593697		1997-01-14	Barr et al.	
	263	5595980		1997-01-21	Brode et al.	
	264	5601605		1997-02-11	Crowe et al.	
	265	5605696		1997-02-25	Eury et al.	
	266	5605698		1997-02-25	Ueno	
	267	5613779		1997-03-25	Niwa	
	268	5614212		1997-03-25	D'Angelo et al.	
	269	5620757		1997-04-15	Ninomiya et al.	
	270	5629003		1997-05-13	Horstmann et al.	
	271	5629021		1997-05-13	Wright	
	272	5633006		1997-05-27	Catania et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	273	5641093		1997-06-24	Dolin et al.	
	274	5641536		1997-06-24	Lech et al.	
	275	D380836		1997-07-08	Fitzpatrick et al.	
	276	5647431		1997-07-15	Takeshita et al.	
	277	5653993		1997-08-05	Ghanta et al.	
	278	5656296		1997-08-12	Khan et al.	
	279	5656297		1997-08-12	Bernstein et al.	
	280	5670168		1997-09-23	Baichwal et al.	
	281	5679145		1997-10-21	Andersen et al.	
	282	5681873		1997-10-28	Norton et al.	
	283	5689550		1997-11-18	Garson et al.	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit		1616
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number		270712/AQU-014USC5/542244

	284	5698181		1997-12-16	Luo	
	285	5698217		1997-12-16	Wilking	
	286	5700478		1997-12-23	Biegajski et al.	
	287	5700479		1997-12-23	Lundgren	
	288	5725648		1998-03-10	Brown et al.	
	289	5733575		1998-03-31	Mehra et al.	
	290	5738211		1998-04-14	Ichino et al.	
	291	5742905		1998-04-21	Pepe et al.	
	292	5750145		1998-05-12	Patell	
	293	5750157		1998-05-12	Grosswald et al.	
	294	5750585		1998-05-12	Park et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556	
	Filing Date		2024-01-16	
	First Named Inventor	Alexander Mark Schobel		
	Art Unit	1616		
	Examiner Name	NATHAN W SCHLIENTZ		
	Attorney Docket Number	270712/AQU-014USC5/542244		

	295	5759599		1998-06-02	Wampler et al.	
	296	5761525		1998-06-02	Williams	
	297	5764639		1998-06-09	Staples et al.	
	298	5764899		1998-06-09	Eggleston et al.	
	299	5765004		1998-06-09	Foster et al.	
	300	5766332		1998-06-16	Graves et al.	

If you wish to add additional U.S. Patent citation information please click the Add button.

Add

U.S.PATENT APPLICATION PUBLICATIONS

Remove

Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button.

Add

FOREIGN PATENT DOCUMENTS

Remove

Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T ⁵
-------------------	---------	--------------------------------------	---------------------------	------------------------	------------------	---	--	----------------

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	1	741362	AU	B2	2001-11-29	Lohmann Therapie Syst Lts		☐
	2	2274910	CA	A1	1998-06-25	Lohmann Therapie Syst Lts		☐
	3	2317491	CA	A1	1999-07-15	Lohmann Therapie Syst Lts		☐
	4	639619	CH	A5	1983-11-30	Voser, Werner		☐
	5	1118254	CN	A	1996-03-13	Bristol Myers Sqibb Company		☐
	6	1777411	CN	A	2006-05-24	Pharmaceutical Productions Inc		☐
	7	101938991	CN	A	2011-01-05	Schering Plough Healthcare		☐
	8	2746414	DE	A1	1979-04-26	Gerlach Eduard Chem Fab		☐
	9	2449865	DE	A1	1976-04-29	Schering AG		☐
	10	2432925	DE	A1	1976-01-22	Schering AG, 1000 Berlin Und 4619 Bergkamen		☐
	11	3630603	DE	A1	1988-03-10	Desitin Arzneimittel GmbH		☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	12	19646392	DE	A1	1998-05-14	Lts Lohmann Therapie- systeme GmbH, 56567 Neuwied		☐
	13	202004003781	DE	U1	2004-05-13	Klocke, Verpackungs- service Gmbh		☐
	14	0014253	EP	A2	1980-08-20	Rider, Joseph Alfred		☐
	15	0021178	EP	A1	1981-01-07	Takeda Chemical Industries, Ltd		☐
	16	0090560	EP	A2	1983-10-05	Minnesota Mining & Mfg		☐
	17	0095892	EP	A1	1983-12-07	Nippon Oil Co Ltd		☐
	18	0065370	EP	A1	1982-11-24	Smith & Nephew Ass		☐
	19	0248548	EP	A2	1987-12-09	Euro Celtique SA		☐
	20	0232877	EP	A2	1987-08-19	Zetachron, Inc		☐
	21	0241178	EP	A1	1987-10-14	Rohto Pharmaceutical Co., Ltd		☐
	22	0285568	EP	A2	1988-10-05	Warner Lambert Co		☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	23	0274431	EP	A2	1988-07-13	Medaphore Inc		☐
	24	0219762	EP	A1	1987-04-29	Desitin Arzneimittel GmbH		☐
	25	0259749	EP	A1	1988-03-16	Desitin Arzneimittel GmbH		☐
	26	0200508	EP	A2	1986-11-05	Nitto Electric Industrial Co., Ltd		☐
	27	0514691	EP	A2	1992-11-25	Euroresearch Srl		☐
	28	0273069	EP	A1	1988-07-06	Unie Colloid KK		☐
	29	0250187	EP	A2	1987-12-23	Johnson & Johnson Prod Inc		☐
	30	0452446	EP	A1	1991-10-23	Desitin Arzneimittel GmbH		☐
	31	0598606	EP	A1	1994-05-25	Johnson & Johnson Consumer Products, Inc		☐
	32	0381194	EP	A2	1990-08-08	Nitto Denko Corp		☐
	33	0440462	EP	A1	1991-08-07	Merck & Co Inc		☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	34	0636364	EP	A1	1995-02-01	Mcneil-ppc, Inc		☐
	35	0450141	EP	A1	1991-10-09	Neophore Technologies, Inc		☐
	36	0460588	EP	A1	1991-12-11	Lohmann Therapie Syst Lts		☐
	37	1143940	EP	A2	2001-10-17	Lavipharm Laboratories, Inc		☐
	38	1110546	EP	A1	2001-06-27	Johnson & Johnson Consumer Companies, Inc		☐
	39	1177788	EP	A2	2002-02-06	Laboratorios Cinfa,s.a		☐
	40	1219291	EP	A1	2002-07-03	Mcneill-ppc, Inc		☐
	41	1243523	EP	A1	2002-09-25	Amcors Flexibles France		☐
	42	0949925	EP	A2	1999-10-20	Lohmann Therapie Syst Lts		☐
	43	1504765	EP	A1	2005-02-09	Kyukyu Pharmaceutical Co., Ltd		☐
	44	1267829	EP	A1	2003-01-02	Warner Lambert Co		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556	
	Filing Date		2024-01-16	
	First Named Inventor	Alexander Mark Schobel		
	Art Unit	1616		
	Examiner Name	NATHAN W SCHLIENTZ		
	Attorney Docket Number	270712/AQU-014USC5/542244		

	45	1674078	EP	A2	2006-06-28	Mcneil-ppc, Inc		☐
	46	1852041	EP	A2	2007-11-07	Baldan, Ferdinando		☐
	47	1897543	EP	A1	2008-03-12	Euro Celtique SA		☐
	48	1591106	EP	A1	2005-11-02	Shin-etsu Chemical Co., Ltd		☐
	49	2105389	EP	A1	2009-09-30	Monosol Rx LLC		☐
	50	2253224	EP	A1	2010-11-24	Monosol Rx LLC		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

Add

NON-PATENT LITERATURE DOCUMENTS

Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
	1	Gaylor Razafimamonjison, Michel Jahiel, Thierry Duclos, Panja Ramanoelina, Fanja Fawbush, and Pascal Danthu, "Bud, leaf and stem essential oil composition of Syzygium aromaticum from Madagascar, Indonesia and Zanzibar" International Journal of Basic and Applied Sciences, 3 (3) (2014) 224-233. (Year: 2014).	☐
	2	Narayanan Gopalakrishnan, Padmanabha Pillai V Shanti and Cadavallur Subrahmanian Narayanan, "Composition of Clove (<i>Syzygium aromaticum</i>) Bud Oil Extracted Using Carbon Dioxide", Journal of the Science of Food and Agriculture, 1990, 50, 111-117. (Year: 1990).	☐
	3	S. Juglal, R. Govinden, and B. Odhav, "Spice Oils for the Control of Co-Occurring Mycotoxin-Producing Fungi", Journal of Food Protection, 65(4), 2002, 683-687. (Year: 2002).	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

4	Yiyun Cheng, Zhenhua Xu, Minglu Ma, and Tongwen Xu, "Dendrimers as Drug Carriers: Applications in Different Routes of Drug Administration", Journal of Pharmaceutical Sciences, 97(1), 2008, 123-143. (Year: 2008).	☐
5	Metin Tülü and Ali Serol Ertürk, "Dendrimers as Antibacterial Agents", A Search for Antibacterial Agents, Chapter 6, 2012, Publisher: InTech, p. 89-106. (Year: 2012).	☐
6	Nisreen Hassan, Abdul Ahad, Mushir Ali and Javed Ali, "Chemical permeation enhancers for transbuccal drug delivery", Expert Opinion Drug Delivery, 2010, 7(1), 97-112. (Year: 2010).	☐
7	Metallic Pigments in Polymers, p. 132 (Rapra Technology Limited 1999).	☐
8	White, J.G., "In Situ Determination of Delavirdine Mesylate Particle Size in Solid Oral Dosage Forms," Pharmaceutical Research 16(4):545-548 (1999).	☐
9	Yamamura, K. et al., "Oral Mucosal Adhesive Film Containing Local Anesthetics: In Vitro and Clinical Evaluation," J. Biomed. Mater. Res. (Appl. Biomater.) 43:313-317 (1998).	☐
10	Pharmazeutische Technologie: Industrielle Herstellung und Entwicklung von Arzneimitteln (Zimmermann, I. (ed.)), p. 246 (Springer-Verlag 1998).	☐
11	Modern coating technology systems for paper, film and foil (Shepherd, F. (ed.)), p. 5 (Emap Maclaren Ltd. 1995).	☐
12	"Adsorption at Solid Surfaces," Encyclopedia of Pharmaceutical Technology (Swarbrick (ed.)), pp. 73 (1988).	☐
13	Photograph of Tetracycline HCL (https://de.wikipedia.org/wiki/Tetracycline#/media/File:Tetracycline-HCL_substance_photo.jpg).	☐
14	Textbook of Polymer Science (2nd Ed.) pp. 1-22 (Wiley 1971).	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

15	Thimmashetty, J. et al., "Preparation and Evaluation of Buccal Dosage Forms of Insulin."	☐
16	Thimmashetty, J. et al., "Design and In Vivo Evaluation of Carvedilol Buccal Mucoadhesive Patches," Pak. J. Pharm. Sci. 21(3):241-248 (2008).	☐
17	Elemente des Apparatebaus, (Titz, H. (ed.)), pp. 546-669 (Springer-Verlag 1992). (includes partial English translation.).	☐
18	The United States Pharmacopeia (20th Rev.), pp. 3-4, 12, 16, 955-957, 1023, 1030-1031, 1412, 1451 (USP 1980).	☐
19	Varanda, F. et al., "Solubility of Antibiotics in Different Solvents. 1. Hydrochloride Forms of Tetracycline, Moxifloxacin, and Ciprofloxacin," Ind. Eng. Chem. Res. 45:6368-6374 (2006).	☐
20	Pharmazeutische Technologie für Studium und Beruf (Voigt, R. (ed.)), p. 65 (Ullstein Mosby 1995).	☐
21	Polymer Molecular Weights (Slade, P.E. (ed.)), p. 1-8 (Marcel Dekker, Inc. 1975).	☐
22	McNeill, J. Robert, et al., "A systematic review of mechanisms by which natural products of plant origin evoke vasodilatation," Can. J. Physiol. Pharmacol (2006) vol. 84, pp. 803-821.	☐
23	Senel, S., et al., "Drug permeation enhancement via buccal route: possibilities and limitations," Journal of Controlled Release (2001) vol. 72, pp. 133-144.	☐
24	Nicolazzo, Joseph A., et al., "Buccal penetration enhancers—How do they really work?," Journal of Controlled Release (2005) vol. 105, pp. 1-15.	☐
25	Amores, Sonia, et al., "An improved cryopreservation method for porcine buccal mucosa in ex vivo drug permeation studies using Franz diffusion cells," European Journal of Pharmaceutical Science (2014) vol. 60, pp. 49-54.	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

26	Sattar, Mohammed, et al., "Oral transmucosal drug delivery—Current status and future prospects," International Journal of Pharmaceutics (2014) vol. 471, pp. 498-506.	☐
27	Gimeno, Alvaro, et al., "Transbuccal delivery of doxepin: Studies on permeation and histological investigation," International Journal of Pharmaceutics (2014) vol. 471, pp. 650-654.	☐
28	Ong, Charlene M.Y., et al., "Permeation of quinine across sublingual mucosa, in vitro," International Journal of Pharmaceutics (2009) vol. 366, pp. 58-64.	☐
29	U.S. Pat. No. 7,357,891, 90/012,098, Ex Parte Reexamination.	☐
30	U.S. Pat. No. 7,357,891, IPR2013-00316, Inter Partes Review.	☐
31	U.S. Pat. No. 7,425,292, 90/012,097, Ex Parte Reexamination.	☐
32	U.S. Pat. No. 7,425,292, IPR2013-00315, Inter Partes Review.	☐
33	U.S. Pat. No. 7,666,337, 95/002,171, Inter Partes Reexamination.	☐
34	U.S. Pat. No. 7,824,588, 95/001,753, Inter Partes Reexamination.	☐
35	U.S. Pat. No. 7,897,080, 95/002,170, Inter Partes Reexamination.	☐
36	U.S. Pat. No. 8,017,150, IPR2016-00282, Inter Partes Review.	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

37	U.S. Pat. No. 8,603,514, IPR2016-00281, Inter Partes Review.	☐
38	U.S. Pat. No. 8,652,378, IPR2014-00794, Inter Partes Review.	☐
39	U.S. Pat. No. 8,765,167, IPR2015-00165, Inter Partes Review.	☐
40	U.S. Pat. No. 8,765,167, IPR2015-00167, Inter Partes Review.	☐
41	U.S. Pat. No. 8,765,167, IPR2015-00168, Inter Partes Review.	☐
42	U.S. Pat. No. 8,765,167, IPR2015-00169, Inter Partes Review.	☐
43	U.S. Pat. No. 8,603,514, IPR2016-01111, Inter Partes Review.	☐
44	U.S. Pat. No. 8,017,150, IPR2016-01112, Inter Partes Review.	☐
45	U.S. Pat. No. 8,603,514, IPR2017-00200, Inter Partes Review.	☐
46	U.S. Pat. No. 8,603,514, IPR2017-01557, Inter Partes Review.	☐
47	U.S. Pat. No. 8,603,514, IPR2017-01582, Inter Partes Review.	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

48	U.S. Appl. No. 10/074,272, filed Feb. 14, 2002.	☐
49	U.S. Appl. No. 10/768,809, filed Jan. 30, 2004.	☐
50	U.S. Appl. No. 10/856,176, filed May 28, 2004.	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

***EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556
	Filing Date		2024-01-16
	First Named Inventor	Alexander Mark Schobel	
	Art Unit	1616	
	Examiner Name	NATHAN W SCHLIENTZ	
	Attorney Docket Number	270712/AQU-014USC5/542244	

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Harold H. Fox, Reg. #41498/	Date (YYYY-MM-DD)	2024-03-18
Name/Print	Harold Fox, Ph.d.	Registration Number	41,498

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556
	Filing Date		2024-01-16
	First Named Inventor	Alexander Mark Schobel	
	Art Unit	1616	
	Examiner Name	NATHAN W SCHLIENTZ	
	Attorney Docket Number	270712/AQU-014USC5/542244	

U.S.PATENTS							Remove
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	
	1						

If you wish to add additional U.S. Patent citation information please click the Add button.

Add

U.S.PATENT APPLICATION PUBLICATIONS							Remove
Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	
	1						

If you wish to add additional U.S. Published Application citation information please click the Add button.

Add

FOREIGN PATENT DOCUMENTS									Remove
Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T ⁵	
	1	2006039264	WO	A1	2006-04-13	Monosolrx, LLC		☐	
	2	2006085210	WO	A1	2006-08-17	Warner Lambert Co		☐	
	3	2006133948	WO	A2	2006-12-21	Novartis AG		☐	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	4	2007015105	WO	A2	2007-02-08	Rademacher, Thomas		☐
	5	2007067494	WO	A1	2007-06-14	Monosolrx, LLC		☐
	6	2007070632	WO	A2	2007-06-21	Biodelivery Sciences International, Inc		☐
	7	2008011194	WO	A2	2008-01-24	Biodelivery Sciences International, Inc		☐
	8	2008025791	WO	A1	2008-03-06	Euro Celtique SA		☐
	9	2008036299	WO	A2	2008-03-27	Monosol Rx LLC		☐
	10	2008040534	WO	A2	2008-04-10	Labtec GmbH		☐
	11	2009044118	WO	A2	2009-04-09	Bioprogress Technology Ltd		☐
	12	2009052421	WO	A1	2009-04-23	Innozen, Inc		☐
	13	2009027625	WO	A2	2009-03-05	Eastman Kodak Co		☐
	14	2009105540	WO	A1	2009-08-27	Univ Syracuse		☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

	15	2010122355	WO	A1	2010-10-28	Londonpharma Ltd		☐
	16	2013063614	WO	A1	2013-05-02	Kwon, Sung-yun		☐
	17	2015078893	WO	A1	2015-06-04	Seppic SA		☐
	18	2017192921	WO	A1	2017-11-09	Monosol Rx, LLC		☐
	19	2017192923	WO	A1	2017-11-09	Monosol Rx, LLC		☐
	20	2019067667	WO	A1	2019-04-04	Aquestive Therapeutics, Inc		☐
	21	2019067670	WO	A1	2019-04-04	Aquestive Therapeutics, Inc		☐
	22	2014-0084176	KR	A	2014-07-04	Kwon		☐
	23	0791575	EP	A1	1997-08-27	Nakano		☐
	24	2015533155	JP	A	2015-11-19	Chin Beng Stephen Lim		☐
	25	2014057351	WO	A1	2014-04-17	Chin Beng Stephen Lim		☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number		18413556
Filing Date		2024-01-16
First Named Inventor	Alexander Mark Schobel	
Art Unit	1616	
Examiner Name	NATHAN W SCHLIENTZ	
Attorney Docket Number	270712/AQU-014USC5/542244	

26	2009084177	JP	A	2014-03-05	Hisanobu Nishikawa		☐
27	2008149440	WO	A1	2010-08-19	IIMURA YOSHIO et al.		☐
28	2004043450	JP	A	2004-02-12	Hanayo Yasuda et al.		☐
29	2006-507277	JP	A	2006-03-02	Lenaerts et al.		☐
30	2011/010732	WO	A1	2013-01-07	Kyoko Endo		☐
31	2013-530193	JP	A	2016-10-12	Ramesh Sesha		☐
32	2004/037222	WO	A2	2004-05-06	Lenaerts et al.		☐
33	2457581	EP	A1	2012-05-30	Kyoko Endo		☐
34	2012/003968	WO	A1	2012-01-12	Ramesh Sesha		☐
35	109310647	CN	A	2019-02-05	Aquistifer Medical Co Ltd		☐
36	2006-509761	JP	A	2006-03-23	Gary D. Ewing		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556	
	Filing Date		2024-01-16	
	First Named Inventor	Alexander Mark Schobel		
	Art Unit	1616		
	Examiner Name	NATHAN W SCHLIENTZ		
	Attorney Docket Number	270712/AQU-014USC5/542244		

	37	2004-131495	JP	A	2004-04-30	Naohisa Kawamura		☐
	38	2006-525370	JP	A	2006-11-09	Stephen A. Howard		☐
	39	2017023977	WO	A1	2017-02-09	Paul M. Dunman		☐
	40	2004047815	WO	A1	2004-06-10	Gary D. Ewing		☐
	41	2004026313	WO	A1	2004-04-01	Naohisa Kawamura		☐
	42	2004098567	WO	A2	2004-11-18	Stephen A. Howard		☐
	43	2015-521996	JP	A	2015-08-03	Karsten Petersson		☐
	44	2014006202	WO	A1	2014-01-09	Karsten Petersson		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

Add

NON-PATENT LITERATURE DOCUMENTS

Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
	1	Save, T. and Vankitachalam, P., "Studies on Solid Dispersions of Nifedipine," Drug Development and Industrial Pharmacy 18(15):1663-1679 (1992).	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

2	Roy, G.M., "Taste Macking in Oral Pharmaceuticals," Pharmaceutical Technology, pp. 84-99 (Apr. 1994).	☐
3	Guo, J.H. and Cookcock, K.M., "Bioadhesive Polymer Buccal Patches for Buprenorphine Controlled Delivery: Solubility Consideration," Drug Development and Industrial Pharmacy 21(7): 2013-2019 (1995).	☐
4	Mixing in the Process Industries (2nd Ed.) Harnby, N. et al. (eds.), pp. 3, 115 (Butterworth Heinemann 1997).	☐
5	Himics, R, and Pineiro, R., "The Importance of Particle Size in Liquid Coatings," Products Finishing 63(2):00329940 (1998).	☐
6	Handbook of Pharmaceutical Excipients (Rowe, R. et al. (eds.)), pp. 326, 513, 522 (2009).	☐
7	Ilango, R. et al., "In-Vitro Studies on Buccal strips of Glibenclamide using Chitosan," Indian J. Pharm. Sci. 59 (5):232-235 (1997).	☐
8	Ishikawa, T. et al., "Preparation and Evaluation of Tablets Rapidly Disintegrating in Saliva Containing Bitter-Taste-Masked Granules by the Compression Method," Chem. Pharm. Bull. 47(10):1451-1454 (1999).	☐
9	Kaya, S. and Kaya, A., "Microwave drying effects on properties of whey protein isolate edible films," J. Food Engineering, 43: 91-96 (2000).	☐
10	Al-Ghananeem et al., "Effect of pH on Sublingual Absorption of Oxycodone Hydrochloride", AAPS PharmSciTech; Article 23, 7(1) (2006) (http://www.aapspharmscitec.org).	☐
11	Bhumkar et al., "Chitosan Reduced Gold Nanoparticles as Novel Carriers for Transmucosal Delivery of Insulin", Pharmaceutical Research; 24(8): 1415-1426 (2007).	☐
12	Bowen P., "Particle Size Distribution Measurement from Millimeters to Nanometers and from Rods to Platelets", Journal of Dispersion Science and Technology; 23(5): 631-662 (2002).	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

13	Trademark Reg. No. 2,944,841—registered Apr. 26, 2005 to Reynolds Metal Co for “EZ SLIDE”.	☐
14	Hariharan et al., “Thin Film Technology, Orally Dissolving Film Strips (ODFS): The Final Evolution of Orally Dissolving Dosage Forms,” Drug Delivery Technology; 9(2): 24-29 (2009).	☐
15	Joshi et al., “Gold Nanoparticles as Carrier for Efficient Transmucosal Insulin Delivery”, Langmuir; 22: 300-305 (2006).	☐
16	Ojeda et al., “Preparation of multifunctional glyconanoparticles as a platform for potential carbohydrate-based anticancer vaccines”, Carbohydrate Research; 342: 448-459 (2007).	☐
17	U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) “Guidance for Industry—Incorporation of Physical-Chemical Identifiers into Solid Oral Dosage Form Drug Products for Anticounterfeiting” Silver Spring, MD; 1-8 (Jul. 9, 2009).	☐
18	Boo, Woong Jae, “Characterization of Thin Film Properties of Melamine Based Dendrimer Nanoparticles”, Thesis for Texas A&M University, Dec. 2003.	☐
19	“Suboxone Sublingualtableten” in: Verlag Rote Liste Service GmbH: “Rote Liste 2008” 2008, Verlag Rote Liste Service GmbH, Frankfurt/Main, XP00264986, p. 39018, the whole document.	☐
20	Transaction History for Ex Parte Reexamination Control No. 90/012,098, current as of.	☐
21	Index of Documents for Inter Partes Review Case No. IPR2013-00316, current as of Aug. 29, 2017.	☐
22	Transaction History for Ex Parte Reexamination Control No. 90/012,097, current as of Aug. 29, 2017.	☐
23	Index of Documents for Inter Partes Review Case No. IPR2013-00315, current as of Aug. 29, 2017.	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

24	Transaction History for Inter Partes Reexamination Control No. 95/002,171, current as of Aug. 29, 2017.	☐
25	Transaction History for Inter Partes Reexamination Control No. 95/001,753, current as of Aug. 29, 2017.	☐
26	Transaction History for Inter Partes Reexamination Control No. 95/002,170, current as of Aug. 29, 2017.	☐
27	Index of Documents for Inter Partes Review Case No. IPR2014-00794, current as of Aug. 29, 2017.	☐
28	Index of Documents for Inter Partes Review Case No. IPR2015-00165, current as of Aug. 29, 2017.	☐
29	Index of Documents for Inter Partes Review Case No. IPR2015-00167, current as of Aug. 29, 2017.	☐
30	Index of Documents for Inter Partes Review Case No. IPR2015-00168, current as of Aug. 29, 2017.	☐
31	Index of Documents for Inter Partes Review Case No. IPR2015-00169, current as of Aug. 29, 2017.	☐
32	Index of Documents for Inter Partes Review Case No. IPR2016-00281, current as of Aug. 29, 2017.	☐
33	Index of Documents for Inter Partes Review Case No. IPR2016-00282, current as of Aug. 29, 2017.	☐
34	Index of Documents for Inter Partes Review Case No. IPR2016-01111, current as of Aug. 29, 2017.	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

35	Index of Documents for Inter Partes Review Case No. IPR2016-01112, current as of Aug. 29, 2017.	☐
36	Index of Documents for Inter Partes Review Case No. IPR2017-00200, current as of Aug. 29, 2017.	☐
37	Index of Documents for Inter Partes Review Case No. IPR2017-01557, current as of Aug. 29, 2017.	☐
38	Index of Documents for Inter Partes Review Case No. IPR2017-01582, current as of Aug. 29, 2017.	☐
39	"Cellulose" Kirk-Othmer Concise Encyclopeida of Chemical Technology; Abridged version of the 24 Volume, NY, Wiley; 227-228 (1978-1984).	☐
40	"Excipients, Croscarmellose Sodium", Pformulate Excipients, http://www.pformulate.com/croscarmellose.htm (Sep. 29, 2002).	☐
41	Atridox(R) (Doxycycline Hyclate) Product Label.	☐
42	Barton, S. et al. "Citric Buffer Calculation", Version 1.1, Nov. 19, 2000.	☐
43	Birkhauser, "Cell Encapsulation Technology and Therapeutics" (Jan. 5, 2009).	☐
44	Bodmeier, Roland, "Evaluation of Drug-Containing Polymer Films Prepared from Aqueous Latexes", Pharmaceutical Research, vol. 6, No. 8 (1989).	☐
45	Cholewinski et al., Pharmaceutica Acta Helvetiae, 71:405-419, 1996.	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

46	Croscarmellose sodium http://www.nbent.com/crosscarmellose.htm (Mar. 29, 2005).	☐
47	Delsym Product Label (Feb. 13, 2007).	☐
48	Di Donato et al., J. Biol. Chem, 268(7): 4745-4751, 1993.	☐
49	Eiamtrakarn et al., "Gastrointestinal Mucoadhesive Path System (GI-MAPS) for oral administration of G-CSF, a model protein", Bipmaterials 23: 145-152 (2002).	☐
50	Endo and Ueda, Fabad J. Pharm. Sci., 29:27-38, 2004.	☐

If you wish to add additional non-patent literature document citation information please click the Add button

Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

***EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556
	Filing Date		2024-01-16
	First Named Inventor	Alexander Mark Schobel	
	Art Unit	1616	
	Examiner Name	NATHAN W SCHLIENTZ	
	Attorney Docket Number	270712/AQU-014USC5/542244	

CERTIFICATION STATEMENT Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s): ☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1). OR ☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2). ☐ See attached certification statement. ☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith. ☐ A certification statement is not submitted herewith. SIGNATURE A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature. <table border="1"> <tr> <td>Signature</td> <td>/Harold H. Fox, Reg. #41498/</td> <td>Date (YYYY-MM-DD)</td> <td>2024-03-18</td> </tr> <tr> <td>Name/Print</td> <td>Harold Fox, Ph.d.</td> <td>Registration Number</td> <td>41,498</td> </tr> </table> This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.				Signature	/Harold H. Fox, Reg. #41498/	Date (YYYY-MM-DD)	2024-03-18	Name/Print	Harold Fox, Ph.d.	Registration Number	41,498
Signature	/Harold H. Fox, Reg. #41498/	Date (YYYY-MM-DD)	2024-03-18								
Name/Print	Harold Fox, Ph.d.	Registration Number	41,498								

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556
	Filing Date		2024-01-16
	First Named Inventor	Alexander Mark Schobel	
	Art Unit	1616	
	Examiner Name	NATHAN W SCHLIENTZ	
	Attorney Docket Number	270712/AQU-014USC5/542244	

U.S.PATENTS							Remove	
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear		
	1							
If you wish to add additional U.S. Patent citation information please click the Add button.							Add	
U.S.PATENT APPLICATION PUBLICATIONS							Remove	
Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear		
	1							
If you wish to add additional U.S. Published Application citation information please click the Add button.							Add	
FOREIGN PATENT DOCUMENTS							Remove	
Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1							☐
If you wish to add additional Foreign Patent Document citation information please click the Add button								Add
NON-PATENT LITERATURE DOCUMENTS								Remove
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.						T ⁵

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

1	English Translation of Office Action issued on November 29, 2021 in KR Application No. 1020187035240	☐
2	English Translation of FER issued on October 7, 2021 in IN Application No. 202017016904	☐
3	English Translation of OA issued on January 26, 2022 in JP Application No. 2018-558224	☐
4	English Translation of FER issued on October 26, 2021 in IN Application No. 202017016905	☐
5	English Translation of OA issued on April 6, 2022 in IL Application No. 262751	☐
6	English Translation of OA issued on May 31, 2022 in JP Application No. 2018-558225	☐
7	Kesharwani, Payal et al. "Biomedical applications of hydrogels in drug delivery system: An update." Journal of Drug Delivery Science and Technology (2021): n. pag.	☐
8	Tangri, Pranshu et al. "ORAL MUCOADHESIVE DRUG DELIVERY SYSTEMS: A REVIEW." (2011).	☐
9	Debotton, Nir and Arik Dahan. "Applications of Polymers as Pharmaceutical Excipients in Solid Oral Dosage Forms." Medicinal Research Reviews 37 (2017): n. pag.	☐
10	English Translation of Final Rejection issued on July 20, 2022 in CN Application No. 201780037588.X	☐
11	English Translation of Final Rejection issued on July 8, 2022 in CN Application No. 201780037587.5	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

12	English Translation of OA issued on April 22, 2022 in KR Application No. 10-2018-7035236	☐
13	English Translation of OA issued on July 26, 2022 in BR Application No. BR112020005875-0	☐
14	English Translation of OA issued on August 16, 2022 in BR Application No. BR112020005948-0	☐
15	English Translation of OA issued on August 16, 2022 in BR Application No. BR112020005967-6	☐
16	English Translation of Official Hearing issued on July 15, 2022 in IN Application No. 202017016904	☐
17	Restriction Requirement issued on September 29, 2022 in US Application No. 17/086,409	☐
18	English Translation of OA issued on October 28, 2022 in JP Application No. 2020-517419	☐
19	English Translation of OA issued on October 28, 2022 in JP Application No. 2020-517586	☐
20	Non-Final Rejection issued on October 28, 2022 in US Application No. 15/791,249	☐
21	English Translation of Official Notification issued on September 28, 2022 in IL Application No. 273485	☐
22	English Translation of Official Notification issued on September 28, 2022 in IL Application No. 292487	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

23	English Translation of OA issued on November 1, 2022 in JP Application No. 2020-538776	☐
24	Final Rejection issued on November 17, 2022 in US Application No. 16/143,821	☐
25	Final Rejection issued on November 18, 2022 in US Application 16/143,678	☐
26	English Translation of Official Notification issued on October 27, 2022 in IL Application No. 273479	☐
27	English Translation of Examination Report issued on December 12, 2022 in IL Application No 273477	☐
28	Restriction Requirement issued on January 20, 2023 in US Application 17/973,345	☐
29	English Translation of Office Action issued on December 20, 2022 in CN Application 201880063175.3	☐
30	English Translation of Office Action issued on December 22, 2022 in CN Application 201880062678.9	☐
31	Notice of Allowance issued on February 27, 2023 in KR Application 10-2018-7035236	☐
32	Non-Final Rejection issued on March 2, 2023 in US Application 17/973,345	☐
33	Final Rejeciton issued on June 22, 2023 in US Application 17/973,345	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

34	Advisory Action issued on August 18, 2023 in US Application 17/973,345	☐
35	Office Action issued on December 23, 2022 in EP Application 18786579.5	☐
36	Official Notification issued on December 27, 2022 in IL Application 273479	☐
37	English Translation of Office Action issued on March 28, 2023 in JP Application 2018-558225	☐
38	English Translation of Office Action issued on January 28, 2023 in CN Application 201880062717.5	☐
39	English Translation of Office Action issued on January 13, 2023 in KR Application 10-2018-7035240	☐
40	English Translation of Rejection issued on June 30, 2023 in KR Application 10-2018-7035240	☐
41	Restriction Requirement issued on February 17, 2023 in US Application 17/098,324	☐
42	Examination Report issued on March 24, 2023 in EP Application 18786591.0	☐
43	Non-Final Rejection issued on March 2, 2023 in US Application 16/143,036	☐
44	Non-Final Rejection issued on March 3, 2023 in US Application 17/835,442	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556
	Filing Date		2024-01-16
	First Named Inventor	Alexander Mark Schobel	
	Art Unit	1616	
	Examiner Name	NATHAN W SCHLIENTZ	
	Attorney Docket Number	270712/AQU-014USC5/542244	

	45	Examination Report issued on May 24, 2023 in EP Application 20820711.8	☐
	46	Non-Final Rejection issued on March 21, 2023 in US Application 17/576,923	☐
	47	Examiner's Report issued on June 7, 2023 in CA Application 3022797	☐
	48	English Translation of Office Action issued on July 7, 2023 in KR Application 10-2020-7012106	☐
	49	English Translation of Office Action issued on July 7, 2023 in KR Application 10-2020-7012033	☐
	50	English Translation of Office Action issued on June 30, 2023 in KR Application 10-2020-7011909	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	
*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.			
¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.			

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556
	Filing Date		2024-01-16
	First Named Inventor	Alexander Mark Schobel	
	Art Unit	1616	
	Examiner Name	NATHAN W SCHLIENTZ	
	Attorney Docket Number	270712/AQU-014USC5/542244	

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Harold H. Fox, Reg. #41498/	Date (YYYY-MM-DD)	2024-03-18
Name/Print	Harold Fox, Ph.d.	Registration Number	41,498

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556
	Filing Date		2024-01-16
	First Named Inventor	Alexander Mark Schobel	
	Art Unit	1616	
	Examiner Name	NATHAN W SCHLIENTZ	
	Attorney Docket Number	270712/AQU-014USC5/542244	

U.S.PATENTS							Remove
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	
	1						

If you wish to add additional U.S. Patent citation information please click the Add button.

Add

U.S.PATENT APPLICATION PUBLICATIONS							Remove
Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	
	1						

If you wish to add additional U.S. Published Application citation information please click the Add button.

Add

FOREIGN PATENT DOCUMENTS								Remove
Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button.

Add

NON-PATENT LITERATURE DOCUMENTS				Remove
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

1	Non-Final Rejection issued on June 29, 2023 in US Application 17/086,409	☐
2	Notice of Allowance issued on June 16, 2023 in CA Application 2771089	☐
3	English Translation of Office Action issued on August 23, 2023 in CN Application 201880062678.9	☐
4	Final Rejection issued on August 1, 2023 in US Application 15/791,249	☐
5	English Translation of Office Action issued on September 11, 2023 in JP Application 2020-538776	☐
6	English Translation of Office Action issued on July 26, 2023 in JP Application 2020-517586	☐
7	Examiner's Report issued on July 20, 2023 in CA Application 3022840	☐
8	English Translation of Office Action issued on August 28, 2023 in IL Application No. 262751	☐
9	Non-Final Rejection issued on September 7, 2023 in US Application 16/143,678	☐
10	English Translation of Office Action issued on August 31, 2023 in CN Application 202080092463.9	☐
11	Rule 161(1) and 162 issued on September 5, 2023 in EP Application 22703176.2	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

12	Jung et al The Usability of Diazepam Buccal Soluble Film as an Oral Treatment in Adult Patients with Epilepsy	☐
13	Non-Final Rejection issued on October 2, 2023 in US Application 17/098,324	☐
14	English Translation of Office Action issued on October 10, 2023 in CN Application 201880063175.3	☐
15	Final Rejection issued on October 13, 2023 in US Application 17/576923	☐
16	Office Action issued on October 25, 2023 in CN Application 202080089502.X	☐
17	Hearing Notice issued on January 24, 2024 in IN Application 201817045293	☐
18	Hearing Notice issued on September 22, 2023 in IN Application 201817045293	☐
19	Non-Final Rejection issued on June 8, 2023 in US Application 17/031,207	☐
20	Notice of Allowance issued on September 29, 2023 in US Application 17/835,442	☐
21	Allowance issued on December 7, 2023 in JP Application 2020-517586	☐
22	Hearing Notice issued on October 16, 2023 in IN Application 202017016898	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

23	Notification Prior to Acceptance issued on November 28, 2023 in IL Application 273477	☐
24	Examination Report issued on September 29, 2023 in EP Application 20808609.0	☐
25	Office Action issued on December 8, 2023 in JP Application 2022-211123	☐
26	Hearing Notice issued on January 4, 2024 in IN Application 202017016905	☐
27	English Translation of Office Action issued on October 21, 2023 in KR Application 10-2023-7027814	☐
28	Final Rejection issued on November 24 in US Application 16/143,036	☐
29	English Translation of Office Action issued on February 6, 2024 in CN Application 201880062678.9	☐
30	English Translation of the Written Opinion issued on January 31, 2024 in BR Application No. 112018072467-0	☐
31	English Translation of the Written Opinion issued on January 31, 2024 in BR Application No. 112018072539-0	☐
32	English Translation of Final Rejection issued on January 16, 2024 in CN Application 201880062717.5	☐
33	Non-Final Rejection issued on February 14, 2024 in US Application 17/973,345	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

34	Examiner's Report issued on January 15, 2024 in CA Application 3076815	☐
35	Examination Report issued on February 26, 2024 in EP Application 20820711.8	☐
36	Examiner's Report issued on February 21, 2024 in CA Application 3159389	☐
37	Notification Prior to Examination issued on February 28, 2024 in IL application 311142	☐
38	Examiner's Report issued on February 22, 2024 in CA application 3076751	☐
39	Examiner's Report issued on February 28, 2024 in CA application 3159382	☐
40	Final Rejection issued on March 13, 2024 in US Application 17/031207	☐
41	Final Rejection issued on March 13, 2024 in US Application 17/031207	☐
42	Office Action issued on March 14, 2024 in CN Application 201880063175.3	☐
43	Intimation of Grant issued on March 14, 2024 in IN Application 202017016904	☐
44	Examination Report issued on March 18, 2024 in IL Application 273479	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18413556
	Filing Date		2024-01-16
	First Named Inventor	Alexander Mark Schobel	
	Art Unit	1616	
	Examiner Name	NATHAN W SCHLIENTZ	
	Attorney Docket Number	270712/AQU-014USC5/542244	

	45	Examiner's Report issued on March 18, 2024 in CA Application 3076816	☐
--	----	--	--------------------------

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

***EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18413556
Filing Date	2024-01-16
First Named Inventor	Alexander Mark Schobel
Art Unit	1616
Examiner Name	NATHAN W SCHLIENTZ
Attorney Docket Number	270712/AQU-014USC5/542244

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Harold H. Fox, Reg. \$41498/	Date (YYYY-MM-DD)	2024-03-18
Name/Print	Harold Fox, Ph.d.	Registration Number	41,498

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/413,556	01/16/2024	Alexander Mark Schobel	270712/ AQU-014USC5/542244	3757
138831	7590	08/23/2024	EXAMINER	
Honigman LLP 650 Trade Centre Way Suite 200 Kalamazoo, MI 49002			SCHLIENTZ, NATHAN W	
			ART UNIT	PAPER NUMBER
			1616	
			NOTIFICATION DATE	DELIVERY MODE
			08/23/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

THuschilt@honigman.com
hfox@honigman.com
patent@honigman.com

DETAILED ACTION

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Prioritized Examination

2. Applicant's request for Prioritized Examination under § 1.102(e)(1) (Track One) filed 16 January 2024 has been granted. Therefore, the application is **SPECIAL** and will undergo prioritized examination.

Status of the Claims

3. Claims 1-20 and 22-30 are pending in the present application.

4. It is noted that the amendment to instant claim 1 states that the pharmaceutical composition is for "oral delivery". The instant specification details the drawbacks to oral delivery and is drawn to delivery through the oral mucosa. It is believed that Applicant intended to state for oral transmucosal delivery, for delivery through the oral mucosa, or something similar.

Priority

5. The present application is a CON of 17/549,219 filed 13 December 2021, which is a CIP of 16/143,821 filed 27 September 2018, which is a CIP of 15/791,249 filed 23 October 2017, which is a CIP of 15/717,859 filed 27 September 2017, which is a CIP of 15/587,364 filed 4 May 2017, which claims benefit of 62/331,996 filed 5 May 2016.

Art Unit: 1616

6. Parent cases 16/143,821, 15/791,249, 15/717,859, 15/587,364 and 62/331,996 do not provide adequate written support for the limitation “the prodrug having a half-life of less than one minute”. The earliest filed case providing adequate written support is 17/549,219. Therefore, the effective filing date for the instant claims is 13 December 2021.

Response to Arguments

7. Applicant's arguments filed 24 July 2024 have been fully considered but they are not persuasive. Applicant asserts that the half-life is a property of the ester of epinephrine. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the relevant time, but only that the subject matter is inherent. MPEP 2112. Such is the case here. The half-life of an ester is a property of the ester, and since that ester of epinephrine was disclosed in prior applications, this feature is supported.

8. The examiner respectfully argues that the parent applications recite an ester of epinephrine or a prodrug of epinephrine, such as dipivefrin, but do not limit the genus of prodrug or ester of epinephrine to those having a half-life of less than one minute. The parent applications do not provide any basis to limit the genus of compounds to those that have the instantly claimed property. The applications recite one example of an ester and prodrug of epinephrine, dipivefrin, but that is not a sufficient disclosure to then claim any ester of epinephrine having the instantly claimed half-life.

9. As evidenced by Almoazen et al. (WO 2018/089570 A1), the genus esters of epinephrine include numerous compounds that have a half-life of one minute or more

([0023], [0028]). Almoazen et al. further teach that the half-life can increase or decrease depending on how the atom in position R4 influences the ester group ([0023]).

10. Therefore, the recitation “a prodrug of epinephrine, such as dipivefrin” is not a sufficient disclosure to show that the Applicant had adequate written support for the genus of an ester of epinephrine having a half-life of less than one minute.

Specification

11. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: the instant specification does not provide support for claim 29 recitation of “propylene glycol sorbitan monostearate”. Applicant argued that it is noted that the instant specification recites, “Emulsifiers typically used in the water-based emulsions described above are... sorbitan monostearate, sorbitan monooleate and/or sorbitan monopalmitate” (pg. 42, ln. 5-11). The instant specification also states, “In certain embodiments, the composition can include plasticizers, which can include... propylene glycol” (pg. 38, ln. 3-6). The specification does not recite the compound “propylene glycol sorbitan monostearate”.

12. It is noted that Applicant stated in their reply filed 24 July 2024 that Exhibit A was attached. However, the Exhibit does not appear in the case file. It is requested that Applicant provide a copy of the Exhibit for the file record.

Withdrawn Rejections

13. The rejection of claim 5 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, is withdrawn in view of the amendment to replace “Labrasol” with “caprylocaproyl polyoxy-8 glyceride”.

14. The rejection of claim 21 under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, is withdrawn in view of the claim being cancelled.

15. The rejection of claims 1, 3, 21-23, 26 and 29 under 35 U.S.C. 102(a)(1) as being anticipated by Keusch et al. (US 2005/0159700 A1) is withdrawn in view of the amendment to claim 1 to replace epinephrine with an ester of epinephrine. Keusch et al. do not explicitly disclose an ester of epinephrine.

16. The rejection of claims 1-20 and 22-30 under 35 U.S.C. 102(a)(1) as being clearly anticipated by Schobel et al. (US 2017/0348251 A1) is withdrawn. Schobel et al. disclose that the active compound can be a prodrug of a drug, but they do not explicitly disclose an ester of epinephrine having a half-life of less than one minute.

17. The rejection of claims 1-20, 22-27 and 29-30 under 35 U.S.C. 103 as being unpatentable over Hill (US 2007/0293581 A1) and Fuisz et al. (US 8,617,589) in view of Nicolazzo et al. (Journal of Pharmaceutical Sciences, 2004), Booles (US 2012/0293581 A1), Razafimamonjison et al. (International Journal of Basic and Applied Sciences, 2014), Gopalakrishnan et al. (Journal of the Science of Food and Agriculture, 1990), Juglal et al. (Journal of Food Protection, 2002), Quay (US 2007/0275893 A1), Schobel et al. (US 2012/0009260 A1), Myers et al. (US 8,936,825), Hassan et al. (Expert Opinion Drug Delivery, 2010) and Unger (US 6,028,066) is withdrawn in view of the argument on pages 3-4 of the Remarks filed 24 July 2024. Applicant argues that none of the references,

Art Unit: 1616

alone or in combination, teach or suggest a polymeric matrix and a pharmaceutically active component including an ester of epinephrine in the polymeric matrix, the ester having a half-life of less than one minute.

18. The rejection of claim 28 under 35 U.S.C. 103 as being unpatentable over Hill (US 2007/0293581 A1) and Fuisz et al. (US 8,617,589) in view of Nicolazzo et al. (Journal of Pharmaceutical Sciences, 2004), Booles (US 2012/0293581 A1), Razafimamonjison et al. (International Journal of Basic and Applied Sciences, 2014), Gopalakrishnan et al. (Journal of the Science of Food and Agriculture, 1990), Juglal et al. (Journal of Food Protection, 2002), Quay (US 2007/0275893 A1), Schobel et al. (US 2012/0009260 A1), Myers et al. (US 8,936,825) and Hassan et al. (Expert Opinion Drug Delivery, 2010) as applied to claims 1-27 and 29-30 above, further in view of Cheng et al. (Journal of Pharmaceutical Sciences, 2008) and Tülü et al. (A Search for Antibacterial Agents, Chapter 6, 2012) is withdrawn for the same reasons as above.

19. The provisional rejection of claim 30 under 35 U.S.C. 101 as claiming the same invention as that of claim 29 of copending Application No. 17/549,219 (reference application) is withdrawn in view of the amendment to instant claim 30.

Claim Rejections - 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention.

Art Unit: 1616

21. Claims 1-20 and 22-30 are rejected under 35 U.S.C. 102(a)(1) as being clearly anticipated by Schobel '670 (WO 2019/067670 A1).

22. It is noted that the instant claims have an effective priority date of 13 December 2021. WO 2019/067670 A1 was published 4 April 2019 and is available as prior art.

23. Regarding instant claims 1-2, Schobel '670 disclose a pharmaceutical composition comprising a polymeric matrix; a pharmaceutically active component including dipivefrin (an ester of epinephrine) in the polymeric matrix; and an adrenergic receptor interacter (Examples 23-27; Claims 1, 37, 39-46).

24. Regarding the ester having a half-life of less than one minute, Schobel '670 discloses dipivefrin, which is the same ester as disclosed in the instant specification.

25. Regarding instant claims 3 and 7, Schobel '670 disclose that the composition is a film (Examples 23-27).

26. Regarding instant claims 4-6, Schobel '670 disclose that the pharmaceutical composition further comprises a permeation enhancer, wherein the permeation enhancer includes clove oil and Labrasol (Examples 23-27). Schobel '670 further disclose that the permeation enhancer includes phenylpropanoids, farnesol and linoleic acid (Claims 4-6).

27. Regarding instant claim 8, Schobel '670 disclose that the pharmaceutical composition is a film (Examples 23-27).

28. Regarding instant claims 9-12, Schobel '670 disclose that the phenylpropanoid is eugenol, eugenol acetate, cinnamic acid, cinnamic acid ester, cinnamic aldehyde, hydrocinnamic acid, chavicol, or safrole (Claims 9-12).

29. Regarding instant claims 13-18, Schobel '670 disclose that the adrenergic receptor interacter is a phytoextract including an essential oil extract of a leaf, flower bud or stem

Art Unit: 1616

of a clove plant, or the phytoextract is synthetic or biosynthetic (Examples 23-27; Claims 13-18).

30. Regarding instant claim 19, Schobel '670 disclose that the phytoextract further includes 40-95% eugenol (Claim 19).

31. Regarding instant claim 20, Schobel '670 disclose that the adrenergic receptor interacter includes a terpenoid, terpene or a sesquiterpene (Claims 20).

32. Regarding instant claims 22-26, Schobel '670 disclose that the polymer matrix includes a polymer, including the instantly claimed polymers (Claims 21-26).

33. Regarding instant claim 27, Schobel '670 disclose that the pharmaceutical composition further comprises a stabilizer (Claim 27).

34. Regarding instant claim 28, Schobel '670 disclose that the polymeric matrix comprises a dendritic polymer or a hyperbranched polymer (Claim 28).

35. Regarding instant claim 29, Schobel '670 disclose that the pharmaceutical compositions comprise sodium citrate, citric acid, sodium metabisulfite, sodium bisulfite, glycerol, glycerol monoacetate, glycerol diacetate, glycerol triacetate, polysorbate, cetyl alcohol, propylene glycol, sorbitan monostearate, sorbitan monooleate, sorbitan monopalmitate, sucralose, sorbitol, mannitol, or xylitol (pg. 33, 35, 37-38, 41; Examples 23-27).

36. Regarding instant claim 30, Schobel '670 disclose a method of making a pharmaceutical composition comprising: combining an adrenergic receptor interacter with a pharmaceutically active component including epinephrine or its prodrug, and forming a pharmaceutical composition including the adrenergic receptor interacter and the pharmaceutically active component (Claim 29).

Art Unit: 1616

37. Claims 1, 3 and 29 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Almoazen et al. (WO 2018/089570 A1).

38. It is noted that the instant claims have an effective priority date of 13 December 2021. WO 2018/089570 A1 was published 17 May 2018 and is available as prior art.

39. Regarding instant claims 1 and 3, Almoazen et al. disclose a rapidly dissolving film comprising 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate) (i.e., dipivefrin), formulated for sublingual or buccal administration ([0028]). The rapidly dissolving film comprises a drug, a water-soluble polymer, a plasticizer, a saliva stimulating agent, a surfactant and other fillers such as sweetening agents and flavors in case of bitter taste drugs ([0029], [0032]-[0040]).

40. Regarding instant claim 29, Almoazen et al. disclose that the plasticizer includes glycerol ([0033], [0039]); the saliva stimulating agent is preferably citric acid, and the sweetening agent is xylitol ([0036]).

Double Patenting

41. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d

Art Unit: 1616

1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(I)(1) - 706.02(I)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Art Unit: 1616

42. Claims 1-20, 22-28 and 30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-25 and 27-28 of U.S. Patent No. 11,191,737. Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a pharmaceutical composition comprising a polymeric matrix, an ester of epinephrine and an adrenergic receptor interacter. The instantly claimed permeation enhancers and adrenergic receptor interacters overlap significantly with US '737, including phenylpropanoid, linoleic acid, farnesol, eugenol, eugenol acetate, cinnamic acid, cinnamic acid ester, cinnamic aldehyde, hydrocinnamic acid, chavicol, safrole, phytoextract, essential oil extract of a clove plant, a terpene, and sesquiterpene. Also, US '737 claims the same polymers as instantly claimed, as well as stabilizer. It is noted that the esters of epinephrine according to US '737 will include the instantly claimed esters having a half-life of less than one minute.

43. Claims 1-20 and 22-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-33 of U.S. Patent No. 12,233,309. Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a pharmaceutical composition comprising a polymeric matrix; a pharmaceutically active component including an ester of epinephrine in the polymeric matrix; and an adrenergic receptor interacter. US '309 recites the same adrenergic receptor interacters, polymers and a stabilizer, as the instant claims. It is noted that the esters of epinephrine according to US '309 will include the instantly claimed esters having a half-life of less than one minute.

Art Unit: 1616

44. Claims 1-20 and 22-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 2, 5-6 and 8-36 of copending Application No. 15/791,249 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a composition comprising a polymeric matrix, a pharmaceutically active component including epinephrine or its prodrug in the polymeric matrix, and an adrenergic receptor interactor or permeation enhancer. The '249 Application and the instant claims recite the same adrenergic receptor interactors and permeation enhancers, as well as the same polymers and a stabilizer. The '249 Application specifically claims that the active includes dipivefrin, which is an ester of epinephrine according to the instant claims.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

45. Claims 1-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-29, 31-40, 42-46, and 51-56 of copending Application No. 16/143,821 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a composition comprising a polymeric matrix, a pharmaceutically active component including a prodrug of epinephrine in the polymeric matrix, and an adrenergic receptor interactor or permeation enhancer. The '821 Application and the instant claims recite the same adrenergic receptor interactors and permeation enhancers, as well as the same polymers and a stabilizer. The '821 Application also specifically claims that the prodrug of epinephrine is dipivefrin.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

46. Claims 1-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-50 of copending Application No. 17/549,219 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a pharmaceutical composition comprising a polymeric matrix; a pharmaceutically active component including a prodrug of epinephrine in the polymeric matrix, the prodrug having a half-life of less than one minute; and an adrenergic receptor interacter. The '219 Application further comprises a permeation enhancer, and recites the same adrenergic receptor interacters and permeation enhancers, as well as the same polymers and a stabilizer, as the instant claims. The '219 Application also specifically claims that the prodrug is dipivefrin.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Response to Arguments

47. Applicants do not provide arguments regarding the nonstatutory double patenting rejections. Applicants state that they will address the rejections when the claims are deemed allowable. Therefore, the examiner has maintained the rejections.

Conclusion

48. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

49. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W Schlientz whose telephone number is (571)272-9924. The examiner can normally be reached on 10:00 AM to 6:00 PM, Monday through Friday.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

Art Unit: 1616

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scarlett Goon can be reached on 571-270-5241. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: <https://patentcenter.uspto.gov>. Visit <https://www.uspto.gov/patents/apply/patent-center> for more information about Patent Center and <https://www.uspto.gov/patents/docx> for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/N.W.S/

Examiner, Art Unit 1616

/Mina Haghighatian/

Primary Examiner, Art Unit 1616



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/413,556	01/16/2024	Alexander Mark Schobel	270712/ AQU-014USC5/542244	3757
138831	7590	04/29/2025	EXAMINER	
Honigman LLP 650 Trade Centre Way Suite 200 Kalamazoo, MI 49002			SCHLIENTZ, NATHAN W	
			ART UNIT	PAPER NUMBER
			1616	
			NOTIFICATION DATE	DELIVERY MODE
			04/29/2025	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

THuschilt@honigman.com
hfox@honigman.com
patent@honigman.com

Office Action Summary	Application No. 18/413,556	Applicant(s) Schobel et al.	
	Examiner Nathan W Schlientz	Art Unit 1616	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 February 2025.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 1-20 and 22-30 is/are pending in the application.
5a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 1-20 and 22-30 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some** c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date ____.
- 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date ____.
- 4) ☐ Other: ____.

DETAILED ACTION

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 21 February 2021 has been entered.

Status of the Claims

3. Claims 1-20 and 22-30 are pending in the present application. The amendment to the claims filed 21 February 2025 has been entered.

Priority

4. The present application is a CON of 17/549,219 filed 13 December 2021, which is a CIP of 16/143,821 filed 27 September 2018, which is a CIP of 15/791,249 filed 23 October 2017, which is a CIP of 15/717,859 filed 27 September 2017, which is a CIP of 15/587,364 filed 4 May 2017, which claims benefit of 62/331,996 filed 5 May 2016.

Art Unit: 1616

5. Parent cases 16/143,821, 15/791,249, 15/717,859, 15/587,364 and 62/331,996 do not provide adequate written support for the limitation “the prodrug having a half-life of less than one minute”. The earliest filed case providing adequate written support is 17/549,219. Therefore, the effective filing date for the instant claims is 13 December 2021.

Response to Arguments

6. Applicant's arguments filed 21 February 2025 have been fully considered but they are not persuasive. Applicant asserts that the half-life is a property of the ester of epinephrine. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the relevant time, but only that the subject matter is inherent. MPEP 2112. Such is the case here. The half-life of an ester is a property of the ester, and since that ester of epinephrine was disclosed in prior applications, this feature is supported.

7. The examiner respectfully argues that the parent applications recite an ester of epinephrine or a prodrug of epinephrine, such as dipivefrin, but do not limit the genus of prodrug or ester of epinephrine to those having a half-life of less than one minute. The parent applications do not provide any basis to limit the genus of compounds to those that have the instantly claimed property. The applications recite one example of an ester and prodrug of epinephrine, dipivefrin, but that is not a sufficient disclosure to then claim any ester of epinephrine having the instantly claimed half-life.

8. As evidenced by Almoazen et al. (WO 2018/089570 A1), the genus esters of epinephrine include numerous compounds that have a half-life of one minute or more

Art Unit: 1616

([0023], [0028]). Almoazen et al. further teach that the half-life can increase or decrease depending on how the atom in position R4 influences the ester group ([0023]).

9. Therefore, the recitation “a prodrug of epinephrine, such as dipivefrin” is not a sufficient disclosure to show that the Applicant had adequate written support for the genus of an ester of epinephrine having a half-life of less than one minute.

Withdrawn Rejections

10. The objection to the Specification is withdrawn in view of the amendment to claim 29 to insert a comma between propylene glycol and sorbitan monostearate.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention.

12. Claims 1-20 and 22-30 are rejected under 35 U.S.C. 102(a)(1) as being clearly anticipated by Schobel '670 (WO 2019/067670 A1).

13. It is noted that the instant claims have an effective priority date of 13 December 2021. WO 2019/067670 A1 was published 4 April 2019 and is available as prior art.

14. Regarding instant claims 1-2, Schobel '670 disclose a pharmaceutical composition comprising a polymeric matrix; a pharmaceutically active component

Art Unit: 1616

including dipivefrin (an ester of epinephrine) in the polymeric matrix; and an adrenergic receptor interacter (Examples 23-27; Claims 1, 37, 39-46).

15. Regarding the ester having a half-life of less than one minute, Schobel '670 discloses dipivefrin, which is the same ester as disclosed in the instant specification.

16. Regarding instant claims 3 and 7, Schobel '670 disclose that the composition is a film (Examples 23-27).

17. Regarding instant claims 4-6, Schobel '670 disclose that the pharmaceutical composition further comprises a permeation enhancer, wherein the permeation enhancer includes clove oil and Labrasol (Examples 23-27). Schobel '670 further disclose that the permeation enhancer includes phenylpropanoids, farnesol and linoleic acid (Claims 4-6).

18. Regarding instant claim 8, Schobel '670 disclose that the pharmaceutical composition is a film (Examples 23-27).

19. Regarding instant claims 9-12, Schobel '670 disclose that the phenylpropanoid is eugenol, eugenol acetate, cinnamic acid, cinnamic acid ester, cinnamic aldehyde, hydrocinnamic acid, chavicol, or safrole (Claims 9-12).

20. Regarding instant claims 13-18, Schobel '670 disclose that the adrenergic receptor interacter is a phytoextract including an essential oil extract of a leaf, flower bud or stem of a clove plant, or the phytoextract is synthetic or biosynthetic (Examples 23-27; Claims 13-18).

21. Regarding instant claim 19, Schobel '670 disclose that the phytoextract further includes 40-95% eugenol (Claim 19).

Art Unit: 1616

22. Regarding instant claim 20, Schobel '670 disclose that the adrenergic receptor interacter includes a terpenoid, terpene or a sesquiterpene (Claims 20).

23. Regarding instant claims 22-26, Schobel '670 disclose that the polymer matrix includes a polymer, including the instantly claimed polymers (Claims 21-26).

24. Regarding instant claim 27, Schobel '670 disclose that the pharmaceutical composition further comprises a stabilizer (Claim 27).

25. Regarding instant claim 28, Schobel '670 disclose that the polymeric matrix comprises a dendritic polymer or a hyperbranched polymer (Claim 28).

26. Regarding instant claim 29, Schobel '670 disclose that the pharmaceutical compositions comprise sodium citrate, citric acid, sodium metabisulfite, sodium bisulfite, glycerol, glycerol monoacetate, glycerol diacetate, glycerol triacetate, polysorbate, cetyl alcohol, propylene glycol, sorbitan monostearate, sorbitan monooleate, sorbitan monopalmitate, sucralose, sorbitol, mannitol, or xylitol (pg. 33, 35, 37-38, 41; Examples 23-27).

27. Regarding instant claim 30, Schobel '670 disclose a method of making a pharmaceutical composition comprising: combining an adrenergic receptor interacter with a pharmaceutically active component including epinephrine or its prodrug, and forming a pharmaceutical composition including the adrenergic receptor interacter and the pharmaceutically active component (Claim 29).

Response to Arguments

28. Applicant's arguments filed 21 February 2025 have been fully considered but they are not persuasive. Applicant asserts that the instant claims should have the

Art Unit: 1616

benefit of the priority date of May 5, 2016. Accordingly, WO 2019/067670 A1 to Schobel is not prior art.

29. As discussed above, the examiner respectfully argues that the instant claims do not have adequate written support in the priority documents to limit the scope of the instant claims to esters of epinephrine having a half-life of less than one minute. Therefore, the instant claims do not get the benefit of the earlier filed application dates.

30. Claims 1, 3 and 29 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Almoazen et al. (WO 2018/089570 A1).

31. It is noted that the instant claims have an effective priority date of 13 December 2021. WO 2018/089570 A1 was published 17 May 2018 and is available as prior art.

32. Regarding instant claims 1 and 3, Almoazen et al. disclose a rapidly dissolving film comprising 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate) (i.e., dipivefrin), formulated for sublingual or buccal administration ([0028]). The rapidly dissolving film comprises a drug, a water-soluble polymer, a plasticizer, a saliva stimulating agent, a surfactant and other fillers such as sweetening agents and flavors in case of bitter taste drugs ([0029], [0032]-[0040]).

33. Regarding instant claim 29, Almoazen et al. disclose that the plasticizer includes glycerol ([0033], [0039]); the saliva stimulating agent is preferably citric acid, and the sweetening agent is xylitol ([0036]).

Response to Arguments

34. Applicant's arguments filed 21 February 2025 have been fully considered but they are not persuasive. Applicant asserts that the instant claims should have the

Art Unit: 1616

benefit of the priority date of May 5, 2016. Accordingly, WO 2018/089570 A1

("Almoazen") is not prior art.

35. As discussed above, the examiner respectfully argues that the instant claims do not have adequate written support in the priority documents to limit the scope of the instant claims to esters of epinephrine having a half-life of less than one minute.

Therefore, the instant claims do not get the benefit of the earlier filed application dates.

Double Patenting

36. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be

Art Unit: 1616

commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

37. Claims 1-20, 22-28 and 30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-25 and 27-28 of U.S. Patent No. 11,191,737. Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a pharmaceutical composition comprising a polymeric matrix, an ester of epinephrine and an adrenergic receptor interacter. The instantly claimed permeation enhancers and adrenergic receptor interacters overlap significantly with US '737, including phenylpropanoid,

Art Unit: 1616

linoleic acid, farnesol, eugenol, eugenol acetate, cinnamic acid, cinnamic acid ester, cinnamic aldehyde, hydrocinnamic acid, chavicol, safrole, phytoextract, essential oil extract of a clove plant, a terpene, and sesquiterpene. Also, US '737 claims the same polymers as instantly claimed, as well as stabilizer. It is noted that the esters of epinephrine according to US '737 will include the instantly claimed esters having a half-life of less than one minute.

Response to Arguments

38. Applicant states that they will address these rejections when the claims are deemed allowable. Therefore, the rejection is maintained.

39. Claims 1-20 and 22-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-33 of U.S. Patent No. 12,233,309. Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a pharmaceutical composition comprising a polymeric matrix; a pharmaceutically active component including an ester of epinephrine in the polymeric matrix; and an adrenergic receptor interacter. US '309 recites the same adrenergic receptor interacters, polymers and a stabilizer, as the instant claims. It is noted that the esters of epinephrine according to US '309 will include the instantly claimed esters having a half-life of less than one minute.

Response to Arguments

40. Applicant states that they will address these rejections when the claims are deemed allowable. Therefore, the rejection is maintained.

Art Unit: 1616

41. Claims 1-20 and 22-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 2, 5-6 and 8-36 of copending Application No. 15/791,249 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a composition comprising a polymeric matrix, a pharmaceutically active component including epinephrine or its prodrug in the polymeric matrix, and an adrenergic receptor interacter or permeation enhancer. The '249 Application and the instant claims recite the same adrenergic receptor interacters and permeation enhancers, as well as the same polymers and a stabilizer. The '249 Application specifically claims that the active includes dipivefrin, which is an ester of epinephrine according to the instant claims.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Response to Arguments

42. Applicant states that they will address these rejections when the claims are deemed allowable. Therefore, the rejection is maintained.

43. Claims 1-20 and 22-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-29, 31-40, 42-46, and 51-56 of copending Application No. 16/143,821 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a composition comprising a polymeric matrix, a pharmaceutically active component including a prodrug of epinephrine in the polymeric

Art Unit: 1616

matrix, and an adrenergic receptor interacter or permeation enhancer. The '821 Application and the instant claims recite the same adrenergic receptor interacters and permeation enhancers, as well as the same polymers and a stabilizer. The '821 Application also specifically claims that the prodrug of epinephrine is dipivefrin.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Response to Arguments

44. Applicant states that they will address these rejections when the claims are deemed allowable. Therefore, the rejection is maintained.

45. Claims 1-20 and 22-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-50 of copending Application No. 17/549,219 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a pharmaceutical composition comprising a polymeric matrix; a pharmaceutically active component including a prodrug of epinephrine in the polymeric matrix, the prodrug having a half-life of less than one minute; and an adrenergic receptor interacter. The '219 Application further comprises a permeation enhancer, and recites the same adrenergic receptor interacters and permeation enhancers, as well as the same polymers and a stabilizer, as the instant claims. The '219 Application also specifically claims that the prodrug is dipivefrin.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Response to Arguments

46. Applicant states that they will address these rejections when the claims are deemed allowable. Therefore, the rejection is maintained.

Contact Information

47. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W Schlientz whose telephone number is (571)272-9924. The examiner can normally be reached on 10:00 AM to 6:00 PM, Monday through Friday.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sue Liu can be reached on (571) 272-5539. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: <https://patentcenter.uspto.gov>. Visit <https://www.uspto.gov/patents/apply/patent-center> for more information about Patent Center and <https://www.uspto.gov/patents/docx> for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197

Art Unit: 1616

(toll-free). If you would like assistance from a USPTO Customer Service

Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/N.W.S/

Examiner, Art Unit 1616

/SUE X LIU/

Supervisory Patent Examiner, Art Unit 1616