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(54) **Title**: METHOD FOR PREPARING FILMS

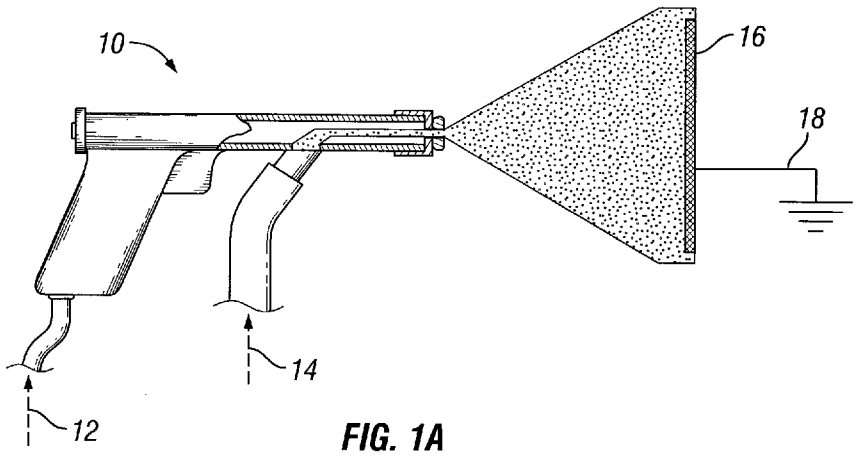


FIG. 1A

(57) **Abstract**: A process for the preparation of free films, without the use of solvent solutions or suspensions or exposure to high temperatures and shear, using electrostatic deposition or layering is disclosed. A powder or processed powder formulation is layered onto a specifically selected or treated substrate such that upon curing of the powder into a film, the film is removed from the substrate and can be handled as a free film. The free film may be used for oral, buccal, transdermal or topical delivery of an active agent or in the absence of an active agent, as a bandage or would dressing.

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Title of The Invention

Method for Preparing Films

Background of The Invention

[0001] Polymeric films have been used commonly in pharmaceutical and medical products. For oral administration, polymeric films have been used as a tablet coating or as a free film for oral, buccal or sublingual drug delivery. Polymeric films are also used for topical and transdermal drug delivery, as well as functioning as bandaids or wound dressings with or without the incorporation of active ingredients.

[0002] Free films are typically prepared by solvent casting or hot melt extrusion methods. Solvent casting techniques involve the casting of a solution or suspension to a suitable substrate and removing the solvent, whereby a film is formed on the substrate. Solvent evaporation techniques also present challenges as some materials (actives and inactives) are insoluble or unstable in aqueous or organic solvents, and there is the additional problem of removing all the organic solvent from a preparation for human or animal use. In extrusion techniques, the materials are typically exposed to high temperature and high shear for from thirty seconds to two minutes or more in order to melt the polymeric material, thus limiting the technique to actives and inactives that can withstand such temperatures and shear.

[0003] Dry powder coating processes have been developed to produce film coatings without the need for water or organic solvents. In many powder coating processes, a charged mixture of finely ground particles and polymers is sprayed by an electrostatic gun onto a grounded substrate surface and then the particle layers are cured to form a film coating on the substrate. In the coating processes, it is essential that the coating adheres tightly or permanently to the coated surface, otherwise the coating is considered a failure.

[0004] In pharmaceutical applications, powder coatings are applied to solid dosage forms such as tablets or pellets for cosmetic purposes, taste masking or in order to affect the release of the active from the dosage form, for delayed or controlled release, for example. In order for the coating to be effective, the entire tablet or pellet must be enclosed

in the coating layer so that the active ingredient(s) are not exposed to the environment, or are exposed in a controlled manner.

Summary

[0005] The present disclosure relates to free film compositions and methods of producing free films that utilize electrostatic spray technology and that provide novel compositions of free films that are free of solvent and that are produced without exposing the ingredients to high heat, high heat for long durations of time, or shear. In certain embodiments, a powder or processed powder is applied to a substrate using electrostatic charge, but the produced film does not strongly or permanently adhere to the substrate such that the film can be removed to produce an intact free film.

[0006] In certain embodiments the substrate is selected, modified or treated such that the applied and cured film does not permanently or tightly adhere. For example, the substrate itself has a non-stick coating, or can take the form of a highly polished metal. The powder is charged and applied to the grounded substrate using an electrostatic powder gun. Alternatively, the substrate can be a non-conductive, thin material that is placed into direct contact with a grounded material such that the powder is sprayed on one side of the substrate and the other side of the substrate is contacting the grounded material. This approach is a departure from the current uses of electrostatic powder guns, as those uses are intended to produce powder layers highly bound to their substrates such that a permanent or semi-permanent film coating is achieved. According to the present disclosure, energy is applied to the deposited powder layer effective to fuse the powder to form a film, which is then removed from the substrate. Appropriate fusing techniques include, but are not limited to heat, infrared (IR) or UV irradiation.

[0007] In certain embodiments, a uniform film, deposited without solvents, containing active agent, nutrient, and/or flavorant is provided. The materials can be pre-processed to prepare a uniform powder blend or milled to produce a particle size suitable for electrostatic powder layering prior to electrostatically depositing onto a non-stick conducting substrate. Appropriate granulation processes include, but are not limited to, low or high shear granulation, dry granulation, fluid bed granulation, and thermal processing techniques. High shear granulation results in the agglomeration of powders using heat or small quantities of solvent. The solvent is used to facilitate particle

engineering and uniformity, and is substantially removed by drying prior to electrostatic layering. Substantially removing the solvent is intended to convey its ordinary meaning in the art, and it is understood that in the described embodiments the solvent is removed to an appropriate or acceptable level, which can be but is not limited to, less than about 5%, less than 4%, less than 3%, less than 2% or less than about 1%. The granules can also be formed by dry granulation—such as slugging or roller compaction—followed by milling. Alternatively, the granules can be formed by thermal processing techniques such as hot melt extrusion, for example, to create an intimate mixture, promote interactions, or alter the solid state of the formulation components, including but not limited to the preparation of solid dispersions or amorphous solid dispersions. The extruded product is then milled to the appropriate particle size.

[0008] In certain aspects of the disclosure, the powder is prepared or processed as described above, or by alternate techniques known to those in the art such as spray drying, wet granulation or re-compression, and is subsequently applied to a substrate using an electrostatic powder layer technique, such as corona charging, or tribo charging. The deposited powder layer is then cured into a uniform film by heating in an oven or by UV irradiation, for example, removed from the substrate and trimmed if necessary.

[0009] In certain aspects of the disclosure, there is provided a film that contains a therapeutically active agent that is dispersed in the film as discrete particles that can themselves be processed or coated with a flavorant or sweetener (i.e., microencapsulated), such as would be desirable for bitter medicaments. A blend of the processed therapeutic particles and a film former is prepared and electrostatically applied to a non-stick conducting substrate. The film is formed by subjecting it to a radiant energy source such that the components of the therapeutic particle remain intact. The resulting film can be administered orally for rapid disintegration and the remaining therapeutic particles swallowed. Alternatively, the therapeutic particles can be deposited on a substrate followed by electrostatic deposition of the film forming composition, or prepared in the reverse order.

[00010] In another aspect of the disclosure, discrete film units are produced without the need for trimming or cutting. A thin, non-conducting stencil is placed over a conductive substrate, where the voids in the stencil are in the shape of the desired film unit.

The conductive substrate is electrically grounded and the powder formulation is electrostatically deposited such that the powder adheres to the substrate only where there is an electric potential between the powder and the substrate and is held in place due to charge coupling of the powder with the substrate. The powder is then cured into a film using radiant heat with an intensity selected such that the powder is softened and cured and the stencil material is substantially unaffected. The curing step can be performed prior to or after removing the non-conductive stencil.

[00011] In another aspect of the disclosure, a segmented multilayered film is provided. A thin, non-conducting stencil is placed over a conductive interchangeable substrate. In one embodiment, a first stencil is used to produce discrete shapes in contact with the substrate. A powder formulation is then electrostatically deposited onto the substrate and cured, forming discrete domains on the substrate areas that are exposed and this layer is then cured. The first stencil can be replaced with a stencil of a different design and a second powder electrostatically deposited on the substrate followed by a secondary curing step. This process can be repeated as desired to prepare a multitude of layered or segmented film structures. Films produced by this process can provide aesthetic or informative designs, for example, when colorants are added. Alternatively, films can be prepared containing multiple therapeutic agents, each embedded in a different location in the film.

[00012] In certain embodiments a multilayered film is produced that contains an agent for controlled release. These films provide certain advantages for pharmaceutical delivery to the skin, or to a mucosal surface, wound or surgical cavity. In certain embodiments the films include a bioadhesive component, such as a mucoadhesive polymer. Exemplary mucoadhesives include polyethylene oxide, carbomer and polycarbophil. Alternatively, a layered film can be prepared by depositing a layer of mucoadhesive powder followed by a layer of therapeutic agent and then followed by a non-adhesive impermeable polymer. Such a film will adhere to the mucosa upon application to the mucosal surface and with an impermeable backing can provide directional release of therapeutic or other agents. Films can also be produced with an adhesive layer, an absorbent layer and an impermeable layer to provide a bandage that optionally releases an active agent.

[00013] A further aspect of the disclosure is a method of forming a continuous film. In this embodiment, a substrate is continuously drawn across a conductive or grounded roll. The composition and thickness of the substrate material are selected to allow electrostatic interaction of a charged powder and the substrate. An electrostatic powder gun can be oriented in certain embodiments to apply a powder layer to the substrate immediately before the powder and web pass under a radiant heater to cure the film. Alternatively, a large conducting or grounding roller can serve to continually index the substrate material across the path of an electrostatic gun and a radiant heater.

Brief Description of the Drawings

[00014] The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present disclosure. The disclosure can be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

[00015] Fig. 1 is an example process for free film formation. Step 1 shows the electrostatic layering of the powder on the substrate; Step 2 depicts curing of the film with radiant heat; and Step 3 shows the removal of the film from the substrate.

[00016] Fig. 2 is an example powder layering configuration for free film formation using a thin non-conducting stencil, where A is a non-conducting stencil, B is a conductive substrate, C is Ground, and D is an electrostatic gun.

[00017] Fig. 3 is an example of a powder layering configuration for preparing discrete film units on a thin non-conducting removable substrate, where A is a non-conducting and releasing substrate, B is a conductor configured to contact the substrate at discrete sites, C is Ground, and D is an electrostatic gun.

[00018] Fig. 4 is an example of films prepared using interchangeable stencils. (A) is an example of a film a discrete design. (B) is a tri-layered film, in which the middle layer is discrete.

[00019] Fig. 5 is an example of continuous production using a continuous temporary substrate for the film formation process.

Detailed Description

[00020] In certain embodiments the present disclosure can be described as solvent free films that can be formed by solvent free electrospray deposition and in certain preferred embodiments are pharmaceutical, medicinal or even cosmetic films or strips for oral, buccal, sublingual or topical use by human or animal subjects.

[0001] Turning to Figs. 1A-C, a powder layering process for producing a free film as described herein is shown. Fig. 1A is the first step in which an electrospray gun 10 is connected to a negative voltage power supply 12 and to a supply of powder 14. The gun is used to spray charged powder particles onto a substrate 16 in whch the substrate is grounded 18 causing the powder to stick to the substrate through electrostatic attraction. As shown in Fig. 1B, the deposited layer of powder is cured by exposure to radiant heat 24 in a ceramic heater 20 connected to a power source 25 to produce a cured film 22 on the substrate. As described herein and shown in Fig. 1C, the substrate and powder are selected such that the free film 30 can be peeled from the substrate.

[0002] Fig. 2 is an alternate example of a powder layering powder process as shown in Fig. 1, layering configuration for free film formation using a thin non-conducting stencil, where a non-conducting stencil 32 is placed between the substrate 16 and the electrostatic spray gun 10 to create a patterned film.

[0003] Figs. 3A and B demonstrates an example of a powder layering configuration for preparing discrete film units on a thin non-conducting removable substrate. In Fig. 3A, , where an electrostatic gun 10 is used to spray powder onto a non-conducting and releasing substrate 42, that overlays a conductor 40 configured to contact the substrate at discrete sites to produce a patterned film. An example of the conductor is shown in Fig. 3B from a side view (left) and substrate face view (right).

[0004] Fig. 4 demonstrates an example of films prepared using interchangeable stencils. In Fig. 4A a discrete design can be added to a film in an alternate color or material, for example. Fig. 4B shows an example of a tri-layered film, in which the middle layer can include a discrete design 56. The design is shown in broken lines because it is hidden from the top view as shown. A cross-sectional view is shown in Fig. 4C.

[0005] Fig. 5 is an example of continuous production using a continuous temporary substrate for the film formation process. In this process a film substrate 60 is transported across a grounded roller 62 for powder deposition. The roller than moves the sprayed film

substrate past a ceramic heater to produce a cured film 64. This cured film is then contacted by a separating device 66 to free the film 64 from the substrate film 60 and produce a continuous free film.

[00021] For the purposes of the present disclosure, the terms used and described herein are meant to convey their ordinary meanings as understood by those skilled in the art unless that meaning would be contrary to the definition or context used herein.

[00022] For the purposes of the present disclosure, the term electrostatic deposition or layering, refers to the process of charging particles having a size range of less than about 1mm, or from about 100 nm to about 1mm, or between about 1 nm and 1 mm, between about 1μm and 200 μm, or between 2 μm and 250 μm, or between 2 μm and 60 μm, and impacting them onto a substrate non-stick substrate such as Teflon, stainless steel and the like such that through an electrostatic interaction they are substantially immobilized until cured. While commercially available corona powder coating guns are designed for this purpose, suitable alternative methods known to one of ordinary skill in the art can be utilized to charge and deposit the particles on a suitable substrate. Such electrostatic powder layering devices are designed for solvent-free coating applications. An example of such a device is the Vantage spray coating gun, manufactured by Nordson Corporation (Westlake, Ohio). In using these devices in coating applications, adherence of the final film to the substrate is required and release of the film from the substrate is considered a defect. In contrast, the application of electrostatic deposition techniques for the formation of free films that do not adhere to the substrate after curing provides a novel technical advance in the field.

[00023] Polymer webs that lightly adhere to surfaces and are easily removed, such as polyvinylidine chloride and polyethylene (for instance, Saran™ plastic wrap), are well known. The use of a polymer web, the exact chemistry of which is unimportant provided that it is stable during the film formation process, can facilitate the electrostatic interaction of particles and a grounded support. Furthermore, once cured, this polymer web is easily removed from the film. In environments requiring high production volumes, a polymer web material in the form of a continuous roll of material can be drawn across a conducting substrate in a continuous manner such that the electrostatic deposition produces a

continuous web of powder layered web material that can subsequently pass through a radiant heater to continuously cure the film.

[00024] A conductive substrate that resists adherence during curing can be formed by highly polishing a metal surface, which effectively reduces the contact surface area between the film and the substrate and removes any surface defects that can serve as an anchor for the film. Polishing techniques are well known and can be applied to a variety of metals. In certain embodiments, chrome or titanium nitride rollers are employed in cast film extrusion processes to transport and cool molten polymer extrudate.

[00025] Metal conductive substrates having a non-stick coating are appropriate for certain embodiments. For example, polytetrafluoroethylene (PTFE also known as Teflon®) is routinely applied to metal substrates to act as a non-stick coating. Any non-stick coating applied to a conductive substrate is potentially suitable; provided that it is stable during the film curing process and provided that the coating is sufficiently thin so that electrostatic interactions between the powder and the substrate allow demobilization of the particles for curing. As used herein, the "curing process" is intended to convey its normal meaning in the art and refers to the fusion, or melting together of particles for film formation.

[00026] In certain embodiments, including the use of film forming compositions that are particularly sticky or have a propensity to adhere to the substrate, a layer of lubricant or glidant can be applied to the substrate to disrupt direct molecular interactions between the substrate and the film formulation. Suitable materials include, but are not limited to minerals, such as talc; magnesium stearate; sodium stearyl fumarate, silicon dioxide; waxes; micronized polyols and the like.

[00027] The films of the present disclosure can be thin and quick dissolving or can be relatively thick, composed in certain embodiments of multiple layers depending on the intended use. The films can be of any appropriate thickness, for example, including but not limited to from 0.02 mm to 5 mm for oral or buccal dissolving films and from 0.25 mm to 10 mm for topical applications, for example. For those applications in which a sustained or controlled release dosage form is contained in a film, the total thickness can be from 0.05 mm to 15 mm. It is further understood that a film can be part of a multilayer composition and that the attachment of a film as described to a backing or adhesive layer, for example,

is also encompassed by the present disclosure. In the context of this disclosure, "oral use" or oral delivery of a strip is meant that the strip is manufactured to be placed in the mouth and held on the tongue, for example, and that in certain embodiments such a strip dissolves quickly when placed in the mouth of a human subject. Dissolving quickly can mean dissolving in a time period from a few second to several minutes, including but not limited to from about 10 seconds to about 10 minutes, or about 10, 20, 30, 40, or 50 seconds or about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes.

[00028] Buccal delivery refers to a product designed to be placed on the inside of the cheek. When placed under the tongue, the formulation is referred to as a sublingual delivery product. Topical delivery refers to delivery of a medicament or agent directly to the surface to be treated.

[00029] The free films of the present disclosure can include any of the inert ingredients known in the art for use in orally dissolving films, including but not limited to polymers, including water soluble, water insoluble, and water permeable polymers, plasticizers, sweetening agents, saliva stimulating agents, flavoring agents, coloring agents, stabilizers, buffers, thickeners and preservatives. The films can also include any appropriate active agent known in the art and can be produced without active agents for non-therapeutic purposes such as for breath refreshment or flavor delivery as well.

[00030] Many active agents can be included in the films, including but not limited to agents for treatment of nausea, including chemotherapy and radiotherapy induced nausea, anticholinergics, antihistamines, surfactants, stomach buffering agents, hormones, addiction treatments including opioid addiction, anesthetics, analgesics, decongestants, cough suppressants, antipyretics, antitussives, antibiotics, breath fresheners, teeth whiteners. Actives can be absent or present in any appropriate concentration, including from 0.1% to 99%, from 1% to 90%, from 5% to 85%, from 10% to 70% from 20% to 50%, or from 5% to 30%.

[00031] In certain embodiments, water-soluble polymers are used in the disclosed formulations. Such polymers can include, but are not limited to polyethylene oxide (PEO), ethylene oxide-propylene oxide co-polymers, polyethylene-polypropylene glycol (e.g. poloxamer), carbomer, polycarbophil, chitosan, polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), hydroxyalkyl celluloses such as hydroxypropyl cellulose (HPC),

hydroxyethyl cellulose, hydroxymethyl cellulose and hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, methylcellulose, hydroxyethyl methylcellulose, hydroxypropyl methylcellulose, polyacrylates such as carbomer, polyacrylamides, polymethacrylamides, polyphosphazines, polyoxazolidines, polyhydroxyalkylcarboxylic acids, alginic acid and its derivatives such as carrageenate alginates, ammonium alginate and sodium alginate, starch and starch derivatives, polysaccharides, carboxypolymethylene, polyethylene glycol, natural gums such as gum guar, gum acacia, gum tragacanth, karaya gum and gum xanthan, povidone, gelatin or the like.

[00032] In certain embodiments, as in controlled release formulations, for example, water insoluble polymers may also be used in the disclosed formulations. Such polymers can include, but are not limited to ethylene vinyl acetate, ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, cellulose acylate, cellulose diactylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate butyrate and mono-, di- and tri-cellulose acrylates, acrylic polymers, acrylic copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymers, polyacrylic acid, polymethacrylic acid, methacrylic acid aklylamine copolymer, polymethyl methacrylate, polymethacrylic acid anhydride, polymethacrylate, polyacrylamide, polymethacrylic acid anhydride and glycidyl methacrylate copolymers.

[00033] In certain embodiments, a plasticizer is also included in the disclosed formulations. Plasticizers suitable for use in the present disclosure include, but are not limited to low molecular weight polymers, oligomers, copolymers, oils, small organic molecules, low molecular weight polyols having aliphatic hydroxyls, ester-type plasticizers, glycol ethers, poly(propylene glycol), multi-block polymers, single block polymers, low molecular weight poly(ethylene glycol), citrate ester-type plasticizers, triacetin, propylene glycol, glycerol, and glycerin. Such plasticizers can also include ethylene glycol, 1,2-butylene glycol, 2,3-butylene glycol, styrene glycol, diethylene glycol, triethylene glycol, tetraethylene glycol and other poly(ethylene glycol) compounds, monopropylene glycol monoisopropyl ether, propylene glycol monoethyl ether, ethylene glycol monoethyl ether, diethylene glycol monoethyl ether, sorbitol lactate, ethyl lactate,

butyl lactate, ethyl glycolate, dibutyl sebacate, acetyltributylcitrate, triethyl citrate, acetyl triethyl citrate, tributyl citrate and allyl glycolate. l, polyethylene glycols, phthalate derivatives like dimethyl, diethyl, dibutyl phthalate, citrate derivatives tributyl, triethyl, acetyl citrate, triacetin and castor oil.

[00034] The compositions of the present disclosure can also include one or more functional excipients such as bioadhesive or mucoadhesive polymers, lubricants, thermal lubricants, antioxidants, buffering agents, alkalinizing agents, binders, diluents, sweeteners, chelating agents, colorants, flavorants, surfactants, solubilizers, wetting agents, stabilizers, hydrophilic polymers, hydrophobic polymers, waxes, lipophilic materials, absorption enhancers, preservatives, absorbents, cross-linking agents, bioadhesive polymers, retardants, pore formers, and fragrance.

[00035] Bioadhesive polymers include, but are not limited to polyethylene oxide, KLUCEL (hydroxypropylcellulose), CARBOPOL, polycarbophil, GANTREZ, Poloxamer, and combinations thereof, and others known to one of ordinary skill in the art.

[00036] Lubricants or thermal lubricants useful in the present disclosure include, but are not limited to fatty esters, glyceryl monooleate, glyceryl monostearate, wax, carnauba wax, beeswax, vitamin E succinate, and a combination thereof.

[00037] As used herein, the term "antioxidant" is intended to mean an agent that inhibits oxidation and thus is used to prevent the deterioration of preparations by oxidation due to the presence of oxygen free radicals or free metals in the composition. Such compounds include, by way of example and without limitation, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), hypophophorous acid, monothioglycerol, sodium ascorbate, sodium formaldehyde sulfoxylate and sodium metabisulfite and others known to those of ordinary skill in the art. Other suitable antioxidants include, for example, vitamin C, sodium bisulfite, vitamin E and its derivatives, propyl gallate or a sulfite derivative.

[00038] Binders suitable for use in the present disclosure include beeswax, carnauba wax, cetyl palmitate, glycerol behenate, glyceryl monostearate, glyceryl palmitostearate, glyceryl stearate, hydrogenated castor oil, microcrystalline wax, paraffin wax, stearic acid, stearic alcohol, stearate 6000 WL1644, gelucire 50/13, poloxamer 188, and polyethylene glycol (PEG) 2000, 3000, 6000, 8000, 10000 or 20000.

[00039] A buffering agent is used to resist change in pH upon dilution or addition of acid or alkali. Such compounds include, but are not limited to potassium metaphosphate, potassium phosphate, monobasic sodium acetate and sodium citrate anhydrous and dihydrate, salts of inorganic or organic acids, salts of inorganic or organic bases, and others known to those of ordinary skill in the art.

[00040] As used herein, the term "alkalizing agent" is intended to mean a compound used to provide alkaline medium for product stability. Such compounds include, but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium bicarbonate, sodium hydroxide, triethanolamine, and trolamine and others known to those of ordinary skill in the art.

[00041] Exemplary binders include: polyethylene oxide; polypropylene oxide; polyvinylpyrrolidone; polyvinylpyrrolidone-co-vinylacetate; acrylate and methacrylate copolymers; polyethylene; polycaprolactone; polyethylene-co-polypropylene; alkylcelluloses and cellulosic derivatives such as low substituted HPC (L-HPC),methylcellulose; hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and hydroxybutylcellulose; hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose; starches, pectins; PLA and PLGA, polyesters (shellac), wax such as carnauba wax, beeswax; polysaccharides such as cellulose, tragacanth, gum arabic, guar gum, and xanthan gum.

[00042] Exemplary chelating agents include EDTA and its salts, alphahydroxy acids such as citric acid, polycarboxylic acids, polyamines, derivatives thereof, and others known to those of ordinary skill in the art.

[00043] As used herein, the term "colorant" is intended to mean a compound used to impart color to solid (e.g., tablets or film) pharmaceutical preparations. Such compounds include, but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel, and ferric oxide, red, other F.D. & C. dyes and natural coloring agents such as grape skin extract, beet red powder, beta carotene, annato, carmine, turmeric, paprika, and other

materials known to one of ordinary skill in the art. The amount of coloring agent used will vary as desired.

[00044] As used herein, the term "flavorant" is intended to mean a compound used to impart a pleasant flavor and often odor to a pharmaceutical preparation. Exemplary flavoring agents or flavorants include synthetic flavor oils and flavoring aromatics and/or natural oils, extracts from plants, leaves, flowers, fruits and so forth and combinations thereof. These may also include cinnamon oil, oil of wintergreen, peppermint oils, clove oil, bay oil, anise oil, eucalyptus, thyme oil, cedar leave oil, oil of nutmeg, oil of sage, oil of bitter almonds and cassia oil. Other useful flavors include vanilla, citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences, including apple, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth. Flavors that have been found to be particularly useful include commercially available orange, grape, cherry and bubble gum flavors and mixtures thereof. The amount of flavoring may depend on a number of factors, including the organoleptic effect desired. Flavors will be present in any amount as desired by those of ordinary skill in the art.

[00045] Suitable surfactants include Polysorbate 80, sorbitan monooleate, polyoxymer, sodium lauryl sulfate or others known in the art. Soaps and synthetic detergents may be employed as surfactants. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts. Suitable detergents include cationic detergents, for example, dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl and olefin sulfonates, alkyl, olefin, ether and monoglyceride sulfates, and sulfosuccinates; nonionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene)-block-poly(oxypropylene) copolymers; and amphoteric detergents, for example, alkyl β-aminopropionates and 2-alkylimidazoline quaternary ammonium salts; and mixtures thereof.

[00046] A wetting agent is an agent that decreases the surface tension of a liquid. Wetting agents would include alcohols, glycerin, proteins, peptides water miscible solvents such as glycols, hydrophilic polymers Polysorbate 80, sorbitan monooleate, sodium lauryl sulfate, fatty acid alkali metal, ammonium, and triethanolamine salts, dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates;

anionic detergents, for example, alkyl, aryl and olefin sulfonates, alkyl, olefin, ether and monoglyceride sulfates, and sulfosuccinates; nonionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene)-block-poly(oxypropylene) copolymers; and amphoteric detergents, for example, alkyl β-aminopropionates and 2-alkylimidazoline quaternary ammonium salts; and mixtures thereof.

[00047] Solubilizers include cyclodextrins, povidone, combinations thereof, and others known to those of ordinary skill in the art.

[00048] Exemplary waxes include carnauba wax, beeswax, microcrystalline wax and others known to one of ordinary skill in the art.

[00049] Exemplary absorption enhancers include dimethyl sulfoxide, Vitamin E PGS, sodium cholate and others known to one of ordinary skill in the art.

[00050] Preservatives include compounds used to prevent the growth of microorganisms. Suitable preservatives include, by way of example and without limitation, benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal and others known to those of ordinary skill in the art.

[00051] As used herein, the term "sweetener" is intended to mean a compound used to impart sweetness to a preparation. Such compounds include, by way of example and without limitation, aspartame, sucralose, dextrose, glycerin, mannitol, saccharin sodium, sorbitol, malitol, sucrose, fructose and other such materials known to those of ordinary skill in the art.

[00052] In certain embodiments the compositions and active agents of this disclosure are administered in an "effective amount," "effective dose," or "therapeutically effective amount or dose." By an "effective" amount or a "therapeutically effective amount" or dose of a drug or pharmacologically active agent is meant a nontoxic but sufficient amount of the drug or agent to provide the desired effect. In the current disclosure, an "effective amount" is the amount of that composition or active agent that is effective to improve, ameliorate or prevent one or more symptoms of the condition being treated. The amount that is "effective" will vary from subject to subject, depending on the age and general condition of the individual, or the particular active agent. A therapeutic or effective dose or amount is determined by a physician and is often based on empirical data

obtained by administering increasing doses until the best balance of benefit vs. side effects is reached.

[00053] As used herein, the term "pharmaceutically acceptable salt" refers to non-toxic pharmaceutically acceptable salts as described (Ref. International J. Pharm., 1986, 33, 201-217; J. Pharm. Sci., 1997 (January), 86, 1, 1). Other salts well known to those in the art may, however, be useful in the preparation of compositions of the disclosure including, but are not limited to, hydrochloric, hydrobromic, hydriodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharinic or trifluoroacetic acid. Representative organic or inorganic bases include, but are not limited to, basic or cationic salts such as benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium and zinc.

[00054] It should be understood that compounds used in the art of pharmaceutical formulation generally serve a variety of functions or purposes. Thus, if a compound named herein is mentioned only once or is used to define more than one term herein, its purpose or function should not be construed as being limited solely to that named purpose(s) or function(s).

[00055] The following examples are meant to illustrate the solution of preparing films by a solvent-free process that does not depend on viscoelastic flow properties.

Example No. 1

[00056] An orally administered pharmaceutical formulation for rapid disintegration containing the active ingredient chlorphenamine maleate was prepared from the components in Table 1. Ingredient 2 was first passed through a 140-mesh sieve. Ingredients 1-3 were then blended and the resulting blend was layered by electrostatic deposition onto a conductive copper substrate using a Nordson Vantage spray coating gun. The substrate with layered powder was then cured in an infrared oven at 80°C until the film was fused. The fused film was removed from heat and allowed to cool. The film was peeled from the substrate, aided by initially separating the film from the substrate using a razor blade.

TABLE 1

Ingredient Number	Ingredient	% w/w in Film
1	Chlorphenamine Maleate	5.0
2	Polyethylene Oxide	95.0
3	FD&C Green No. 3	< 0.01

Example No. 2

[00057] An orally administered pharmaceutical formulation containing the active ingredient dextromethorphan hydrobromide was prepared according the composition in Table 2. Ingredients 1-5 are blended. A stainless steel substrate was treated with magnesium stearate and the final powder blend was then layered by electrostatic deposition onto the treated substrate using a Nordson Vantage spray coating gun. The substrate was then placed in an infrared oven at 125 °C to fuse the powder into a film. The film was allowed to cool and subsequently peeled off the substrate, aided by separating the film from the substrate using a razor blade, to produce a free film.

TABLE 2

Ingredient Number	Ingredient	% w/w in Film
1	Dextromethorphan Hydrobromide	5.0
2	Polyethylene Oxide	80.75
3	Sucralose	8.0
4	Crosscarmellose Sodium	6.0
5	FD&C Red No. 40	0.25
6	Magnesium Stearate	trace

Example No. 3

[00058] An orally administered pharmaceutical formulation containing the active ingredient albuterol sulfate was prepared according the composition in Table 3. Ingredients 1-8 are blended. A stainless steel substrate was treated with magnesium stearate and the final powder blend was then powder layered by electrostatic deposition onto the treated substrate using a Nordson Vantage spray coating gun. The substrate was then placed in an infrared oven at 125 °C to fuse the powder into a film. The film was allowed to cool and subsequently peeled off the substrate, aided by initially separating the film from the substrate using a razor blade, to produce a free film.

TABLE 3

Ingredient Number	Ingredient	% w/w in Film
1	Albuterol Sulfate	7.5
2	Polyethylene Oxide	73.89
3	Sucralose	6.0
4	Mannitol	5.0
5	Crosscarmellose Sodium	5.0
6	Polaxamer	2.5
7	FD&C Green No. 3	0.1
8	Titanium Oxide	0.01
9	Magnesium Stearate	trace

Example No. 4

[00059] A pharmaceutical formulation for topical use in the oral cavity containing the active ingredient benzocaine was prepared from the components in Table 4. Ingredients 1-2 were blended and layered by electrostatic deposition onto a conductive copper substrate using a Nordson Vantage spray coating gun. The substrate with layered powder was then cured in an infrared oven at 80°C until the film was fused. The layered substrate

was removed from the oven and again grounded to allow the electrostatic deposition of the second layer. Ingredients 3-4 were blended, passed through a sieve for deagglomeration and then layered by electrostatic deposition onto Layer 1. The bilayer film was again cured in an infrared oven at 110°C until fused. The film was allowed to cool and subsequently peeled off the substrate, aided by initially separating the film from the substrate using a razor blade, to produce a free film.

TABLE 4

Layer Number	Ingredient Number	Ingredient	% w/w in each layer
1	1	Benzocaine	10.0
	2	Polyethylene Oxide	90.0
2	3	Carbopol 974P	99.0
	4	Colloidal Silicon Dioxide	1.0

Example 5

[00060] An orally administered formulation for delivery of small quantities of the therapeutically active compound verapamil was prepared. Verapamil has low oral bioavailability because of high hepatic first-pass metabolism. A multilayer dosage form was prepared to directionally deliver the drug through a mucoadhesive layer into the oral mucosa, as it will adhere to the mucosa upon application to the mucosal surface and with an impermeable backing can provide directional release of the therapeutic agent. The dosage form consists of three parts, an ethylcellulose backing layer, a mucoadhesive layer, and an internal compartment containing the verapamil, as shown in Table 5. The multilayer dosage form was prepared by first electrostatically powder layering ingredient 1 onto a conductive substrate using a Nordson Vantage spray coating gun and was then cured in an infrared oven at 80°C until the film was fused. The layered substrate was removed from the oven and again grounded to allow the electrostatic deposition of the second layer. Ingredients 2-4 were blended and then layered by electrostatic deposition onto Layer 1. The bilayer film was again cured in an infrared oven at 80°C until fused. The bilayered

substrate was removed from the oven and again grounded to allow the electrostatic deposition of the third layer. Ingredient 5 was layered by electrostatic deposition on top of Layer 2. The trilayer film was again cured in an infrared oven at 80°C until fused. The film was allowed to cool and subsequently peeled off the substrate, aided by initially separating the film from the substrate using a razor blade, to produce a free film.

TABLE 5

Layer Number	Ingredient Number	Ingredient	% w/w in each layer
1	1	Carbopol 974P	1000
2	2	Verapamil Hydrochloride	10
	3	Polyethylene Oxide, Coagulant	75
	4	Polyethylene Oxide	15
3	5	Ethylcellulose	100

Example No. 6

[00061] A pharmaceutical formulation for transdermal administration containing the active ingredient lidocaine hydrochloride was prepared from the components in Table 6. Ingredients 1-3 were blended and layered by electrostatic deposition onto a conducted stainless steel substrate using a Nordson Vantage spray-coating gun. The substrate with layered powder was then cured in an infrared oven at 80°C until the film was fused. The layered substrate was removed from the oven and again grounded for the electrostatic layering of the second layer. Ingredient 4 was layered by electrostatic deposition onto Layer 1. The bilayer film was again cured in an infrared oven at 80°C until fused. The film was allowed to cool and was subsequently peeled off the substrate, aided by initially separating the film from the substrate using a razor blade, to produce a free film.

TABLE 6

Layer Number	Ingredient Number	Ingredient	% w/w in each layer
1	1	Lidocaine Hydrochloride	10
	2	Polyethylene Oxide, Coagulant	84
	3	Lycoat RS 720 (Starch)	6
2	4	Eudragit RL PO	100

Example No. 7

[00062] A pharmaceutical formulation for oral administration containing the active ingredient verapamil hydrochloride was prepared from the components in Table 7. Ingredients 1-3 was blended and layered by electrostatic deposition onto a grounded stainless steel substrate using a Nordson Vantage spray-coating gun. The substrate with layered powder was then cured in an infrared oven at 80°C until the film was fused. The film was allowed to cool and was subsequently peeled off the substrate, aided by initially separating the film from the substrate using a razor blade, to produce a free film.

TABLE 7

Ingredient Number	Ingredient	% w/w in Film
1	Verapamil Hydrochloride	10
2	Polyethylene Oxide Coagulant	75
3	Polyethylene Oxide	15

Example No. 8

[00063] A flavored pharmaceutical dosage form containing processed powder that can be orally administered without water was prepared. Itraconazole is known to be a

poorly soluble compound and was prepared by being first molecularly dispersed in an enteric polymer. Itraconazole was prepared by hot melt extrusion in hydroxypropyl methylcellulose acetate succinate (HPMC AS), as well as Vitamin E TPGS and triethyl citrate (TEC). Alternatively, itraconazole can be dispersed in HPMC AS using the KinetiSol® process. KinetiSol® is a fusion-based process that utilizes frictional and shear energies (no externally applied heat) to rapidly transition drug-polymer blends into a molten state with simultaneous high-intensity mixing. Hot melt extruded and KinetiSol® based compositions require milling, such as with a ball mill. The itraconazole composition was prepared according the composition in Table 8, using hot melt extrusion to produce an amorphous solid dispersion. The resulting extrudate was then milled, using a cryomill to produce a fine powder. The processed dispersion powder was blended with ingredient 5 at varying dispersion loading as shown in Tablet 8. Each final powder blend was then layered onto individual substrates, using a Nordson Vantage spray-coating gun. The films were cured in an infrared oven at 80°C until fused. The films were allowed to cool and subsequently peeled off the substrate, aided by initially separating the film from the substrate using a razor blade, to produce free films.

TABLE 8

Ingredient Number	**Material**	**Amount in Dispersion (% w/w)**	**Amount in Film (% w/w)**		
1	Itraconazole	29.41	10	20	40
2	HPMC AS	58.83			
3	Vitamin E TPGS	5.88			
4	Triethyl Citrate	5.88			
5	Polyethylene Oxide	---	90	80	60

Example No. 9

[00064] Free films were prepared using varying particle size distributions of polyethylene oxide, as shown in Table 9. Each particle size distribution was layered by

electrostatic deposition onto a conductive substrate using a Nordson Vantage spray-coating gun. Spraying was conducted for each particle size distribution for a duration of time in order to produce films with maximum thickness. The substrate with layered powder was then cured in an infrared oven at 80°C until the film was fused. The fused film was removed from heat and allowed to cool. The film was peeled from the substrate and characterized for weight, thickness, and disintegration time. Films of 2 cm x 2 cm were used for characterization. Average properties are reported below.

TABLE 9

Particle Size Distribution	**Weight (mg)**	**Thickness (mm)**	**Disintegration Time (mm:ss)**
300-600	25.33	0.147	0:30
150-300	nd	nd	1:30
90-150	49.23	0.187	1:45
63-90	nd	nd	nd
25-63	83.53	0.251	1:56

nd – not determined

Example No. 10

[00065] Same as Example No. 1, except using a non-conductive, PET stencil with a void in the shape of a shaped, discrete film.

Example No. 11

[00066] Same as Example No. 2, except using a polyvinylidene chloride polymer web in contact with a stainless steel substrate. The substrate was then placed in an infrared oven at 80 °C to fuse the powder into a film. The film was allowed to cool and subsequently the web was removed from the substrate. The film was then peeled from the polymer web to produce a free film. Alternatively, the film can be removed from polymer web at point of use.

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CLAIMS

1. A pharmaceutically acceptable composition comprising a free film containing one or more layers formed by a powder or processed powder layering onto a substrate using an electrostatic deposition technique; curing the powder to form a film; and removing the film from the substrate.

2. The pharmaceutically acceptable composition according to claim 1, wherein the film is solvent-free.

3. The method of claim 1, wherein the film thickness ranges from 0.02 mm to 15 mm.

4. The pharmaceutically acceptable composition of claim 1, wherein the film comprises of one or more of a lubricant, a thermal lubricant, an antioxidant, a buffering agent, an alkalinizing agent, a binder, a diluents, sweeteners, chelating agents, colorants, flavorants, surfactants, solubilizers, wetting agents, stabilizers, hydrophilic polymers, hydrophobic polymers, waxes, lipophilic materials, absorption enhancers, preservatives, absorbents, cross-linking agent, a bioadhesive polymer, a retardant, a pore former, and fragrance.

5. The pharmaceutically acceptable composition of claim 1, wherein the film comprises a therapeutically active agent.

6. The pharmaceutically acceptable composition of claim 5, wherein the therapeutically active agent is acetaminophen, tetracycline, penicillin, a vitamin, an antacid, a non-steroidal anti-inflammatory agent, an anesthetic, a breath freshener, or a mineral.

7. The pharmaceutically acceptable composition of claim 5, wherein the film comprises an agent for treatment of nausea, an anticholinergic, an antihistamine, a surfactant, a stomach buffering agent, a hormone, an agent for treatment of addiction, an anesthetic, an analgesic, a decongestant, a cough suppressant, an antipyretic, an antitussive, an antibiotic, a breath freshener, a teeth whitener or combinations thereof.

8. The pharmaceutically acceptable composition of claim 5, wherein the film comprises an agent effective for transdermal administration.

9. The pharmaceutically acceptable composition of claim 8, wherein the agent is scopolamine, nitroglycerin, estradiol, fentanyl, nicotine, testosterone, lidocaine, oxybutynin, methylphenidate, selegiline, rotigotine, rivastigmine, or a combination of any thereof.

10. The pharmaceutically acceptable composition of claim 5-9, wherein the film comprises from about 0.1% to 85% active agent.

11. The pharmaceutically acceptable composition of claim 5-9, wherein the film comprises from about 1% to 90% active agent.

12. The pharmaceutically acceptable composition of claim any of claims 5-9, wherein the film comprises from about 5% to 30% active agent.

13. The pharmaceutically acceptable composition of claim 1, wherein the film comprises a water-soluble polymer.

14. The pharmaceutically acceptable composition of claim 1, wherein the water soluble polymer is polyethylene oxide (PEO), ethylene oxide-propylene oxide co-polymers, polyethylene-polypropylene glycol (e.g. poloxamer), carbomer, polycarbophil, chitosan, polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, methylcellulose, hydroxyethyl methylcellulose, hydroxypropyl methylcellulose, carbomer, polyacrylamides, polymethacrylamides, polyphosphazines, polyoxazolidines, polyhydroxyalkylcarboxylic acids, alginic acid, carrageenate alginates, ammonium alginate, sodium alginate, starch and starch derivatives, polysaccharides, carboxypolymethylene, polyethylene glycol, or a natural gum.

15. The pharmaceutically acceptable composition of claim 1, wherein the film comprises a water insoluble soluble polymer.

16. The pharmaceutically acceptable composition of claim 15, wherein the water insoluble polymer is ethylene vinyl acetate, ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, cellulose acylate, cellulose diactylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate butyrate, a mono-cellulose acrylate, di- cellulose acrylate, and tri-cellulose acrylate, acrylic polymers, acrylic copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate,

aminoalkyl methacrylate copolymers, polyacrylic acid, polymethacrylic acid, methacrylic acid aklylamine copolymer, polymethyl methacrylate, polymethacrylic acid anhydride, polymethacrylate, polyacrylamide, polymethacrylic acid anhydride and glycidyl methacrylate copolymers.

17. The pharmaceutically acceptable composition of claim 1, wherein the film dissolves in the oral cavity in less than 60 seconds.

18. The pharmaceutically acceptable composition of claim 1, wherein the film dissolves in the oral cavity in less than 30 seconds.

19. The pharmaceutically acceptable composition of claim 1, wherein the film comprises of processed powder or coated particles that control the release of a therapeutically active agent for a period of from 1 hour to 5 weeks.

20. A method of preparing free films containing one or more layers formed by:

a) electrospraying a powder or processed powder onto a substrate using an electrostatic deposition technique to form a deposited layer;

b) curing the deposited layer to form a film; and

c) removing the film from the substrate.

21. The method of claim 20, wherein the substrate is selected or treated to reduce binding of the cured film to the substrate.

22. The method of claim 20, wherein the substrate is a polished conductive surface.

23 The method of claim 20, wherein the surface of the substrate wherein the substrate comprises stainless steel.

24. The method of claim 20, wherein the substrate is treated with a glidant or a lubricant effective to inhibit direct molecular interactions between the substrate and the film formulation.

25. The method of claim 24, wherein the glidant is a mineral.

26. The method of claim 25, wherein the mineral is talc or silicon dioxide.

27. The method of claim 26, wherein the lubricant is a metallic salt.

28. The method of claim 27, wherein the metallic salt is magnesium stearate.

29 The method of claim 21, wherein the substrate is treated with a wax.

30. The method of claim 21, wherein the treatment is a polyol.

31. The method of claim 30, wherein the polyol is mannitol.

32. The method of claim 21, wherein the treatment is polyethylene terephthalate (PET), polytetrafluoroethylene (PTFE), or Titanium Nitride (TiN).

33. The method of claim 20, wherein the curing step comprises heating the deposited material.

34. The method of claim 20, wherein the curing process comprises exposing the deposited material to ultraviolet radiation source.

35. A method of preparing free films containing one or more layers formed by powder or processed powder layering comprising:

a) providing a non-conductive web material substrate;

b) depositing electrosprayed powder or processed powder to a first side of the non-conductive web material while contacting the opposite side of the material with a grounded conductive material;

c) curing the deposited material to form a film; and

d) removing the film from the web material.

36. The method of claim 35, wherein the webbing is continuously transported across a conductor during the layering process and subsequently transported to a continuous heat or ultraviolet radiation source effective to cure the film.

37. The method of claim 35, wherein the web material is in contact with a conducting roller which serves to continually index the web across the path of an electrostatic gun and a heater.

38. A method of preparing a bioadhesive film comprising:

a) electrostatically layering a mucoadhesive polymer onto a substrate that is selected or treated to reduce binding of the cured film to the substrate;

b) curing the powder to form a film; and

c) removing the cured film from the substrate.

39. The method of claim 38 wherein the mucoadhesive polymer is polyethylene oxide, carbomer or polycarbophil.

40. The method in claim 38, wherein the bioadhesive film comprises one or more layers in addition to the mucoadhesive layer.

41. A topical delivery device comprising a layered film prepared by the steps of:

a) electrospray deposition of a layer of mucoadhesive powder on a substrate and curing the powder to form a first film layer;

b) electrospray deposition of a layer of active agent powder on the first film layer and curing the powder to form a second film layer; and

c) electrospray deposition of a layer of non-adhesive impermeable polymer powder on the second film layer and curing the powder to form a third film layer; wherein the device is effective for directional delivery of the active agent when the device is placed on a topical delivery site.

42. The method of claim 41, wherein the first film layer and the second film layer are combined into a single layer.

43. A method of producing a bandage device comprising a layered film comprising the steps of:

a) electrospray deposition of a layer of mucoadhesive powder on a substrate and curing the powder to form a first film layer;

b) deposition of a layer of an absorbent on the first film layer; and

c) electrospray deposition of a layer of an impermeable polymer powder on the absorbent layer and curing the powder to form a second film layer.

44. The method of claim 43 further comprising electrospray deposition of a layer of active agent powder between the first film layer and the second film layer and curing the active agent powder to form a third film layer.

45. A method of preparing a plurality of discrete pharmaceutically acceptable films comprising the steps of:

a) providing a non-conductive substrate comprising a first surface and an opposing second surface;

b) contacting the first surface of the substrate with a grounded conductive material that is shaped to contact the first surface only in discrete areas separated by areas of the first surface that are not contacted by the conductive material;

c) electrospraying powder or granules of a pharmaceutically acceptable material onto the second surface of the substrate under conditions in which the electrostatic interaction of the pharmaceutically acceptable material and the conductive material contacting the first surface of the substrate causes the

pharmaceutically acceptable material to remain on the substrate only in the discrete areas of the second surface of the substrate that are opposing the areas of the first surface that are in contact with the conductive material;

d) exposing the second surface of the substrate to radiation or heat effective to cure the pharmaceutically acceptable material remaining on the substrate to form separate sections of film; and

e) removing the separate film sections from the substrate.

46. The method of preparing a plurality of discrete pharmaceutically acceptable films of claim 45, further comprising one or more subsequent steps in which the first surface of the substrate is contacted with a second grounded conductive material shaped to contact the first surface of the substrate at different discrete areas of the first surface and repeating steps c) d) and e).

47. The method of preparing a plurality of discrete pharmaceutically acceptable films of claim 46, in which the pharmaceutically acceptable material is the same or a different material.

48. The method of preparing a plurality of discrete pharmaceutically acceptable films of claim 46, further comprising one or more subsequent steps in which the first surface of the substrate is contacted with a second grounded conductive material shaped to contact the first surface of the substrate at different discrete areas of the first surface and repeating steps c) and d) prior to step e).

49. The method of preparing a plurality of discrete pharmaceutically acceptable films of claim 48, in which the pharmaceutically acceptable material is the same or a different material.

50. A method of preparing one or more discrete pharmaceutically acceptable films comprising:

a) providing a substrate with a surface that is selected or treated to reduce binding of a cured film to the substrate

b) placing a stencil of non-conductive material over the surface of the substrate wherein the stencil comprises one or more openings in the shape of one or more desired discrete pharmaceutically acceptable films;

c) electrospraying a pharmaceutically acceptable powder or processed powder onto the surface of step b) to form a deposited layer in the one or more openings of the stencil;

d) curing the deposited layer to form one or more discrete films on the substrate; and

e) removing the one or more films from the substrate.

51. The method of preparing one or more discrete pharmaceutically acceptable films of claim 50, comprising repeating the steps of claim 46 using a different stencil.

52. The method of preparing one or more discrete pharmaceutically acceptable films of claim 51, in which the pharmaceutically acceptable material is the same or a different material.

53. The method of preparing one or more discrete pharmaceutically acceptable films of claim 52 in which at least one of the pharmaceutically acceptable materials comprises a colorant.

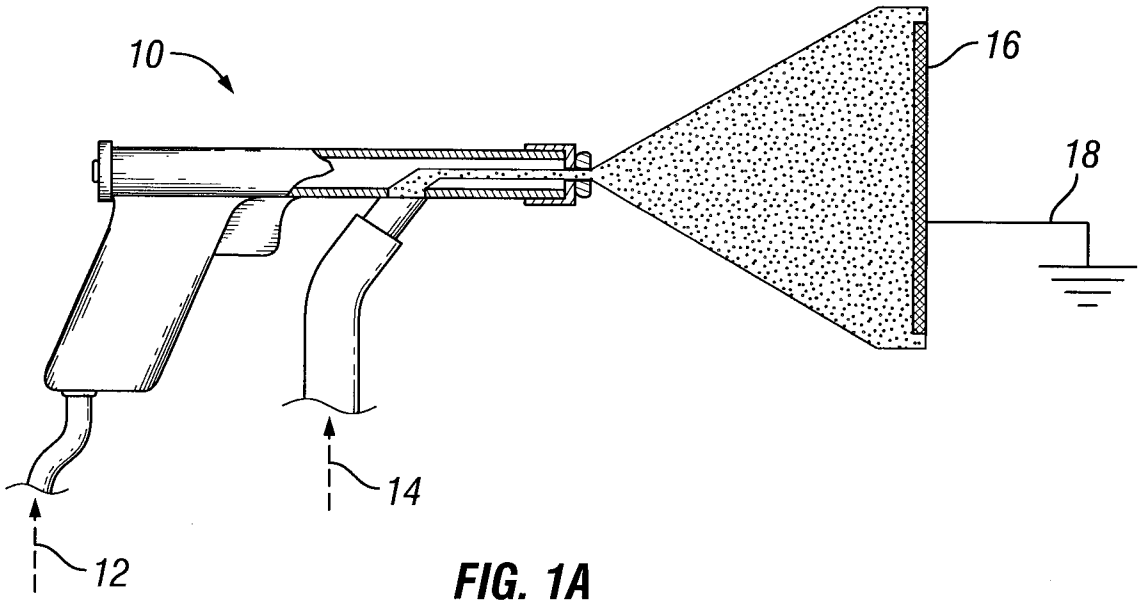


FIG. 1A

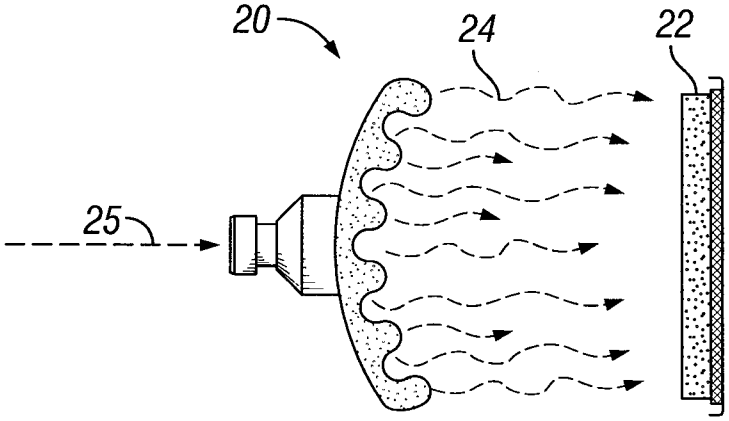


FIG. 1B

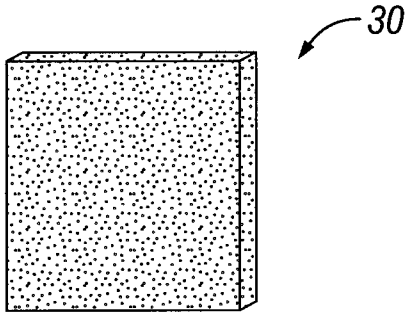


FIG. 1C

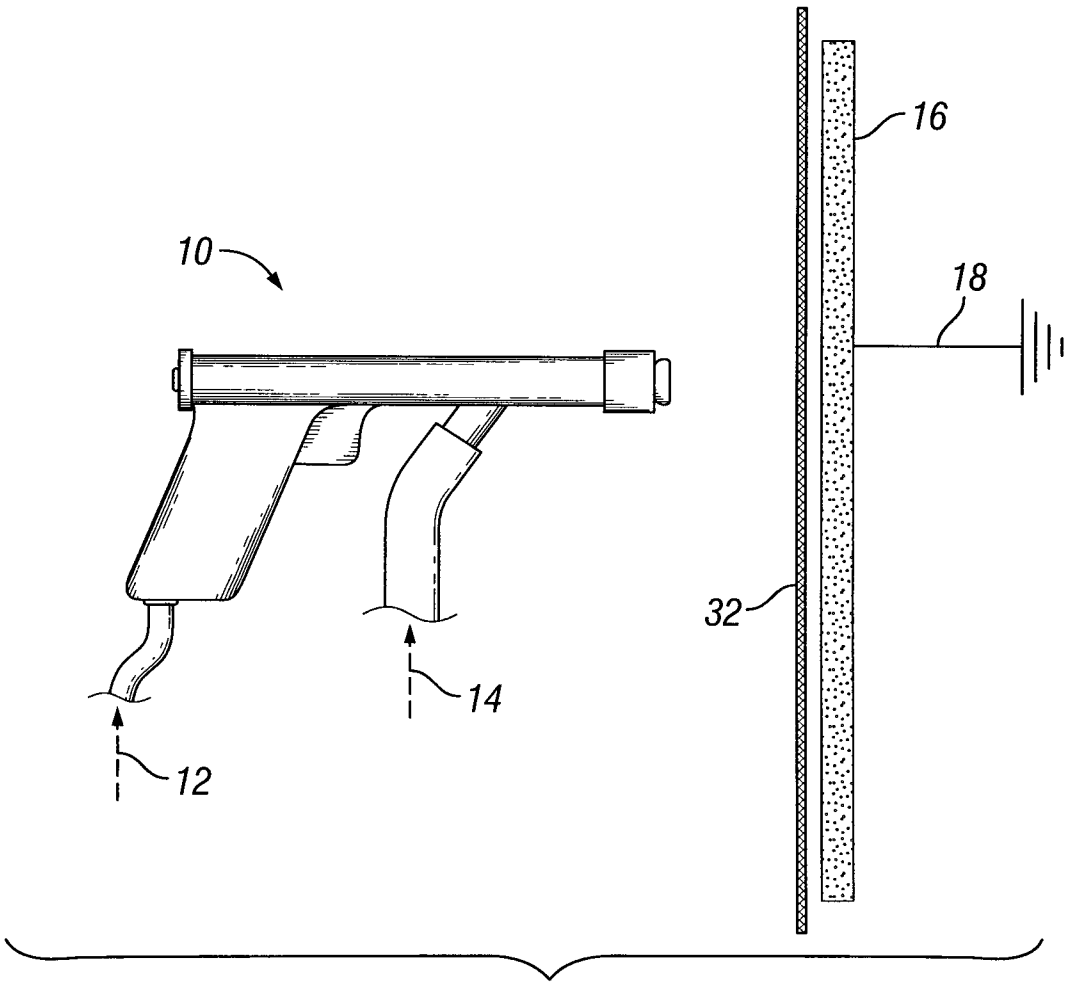


FIG. 2

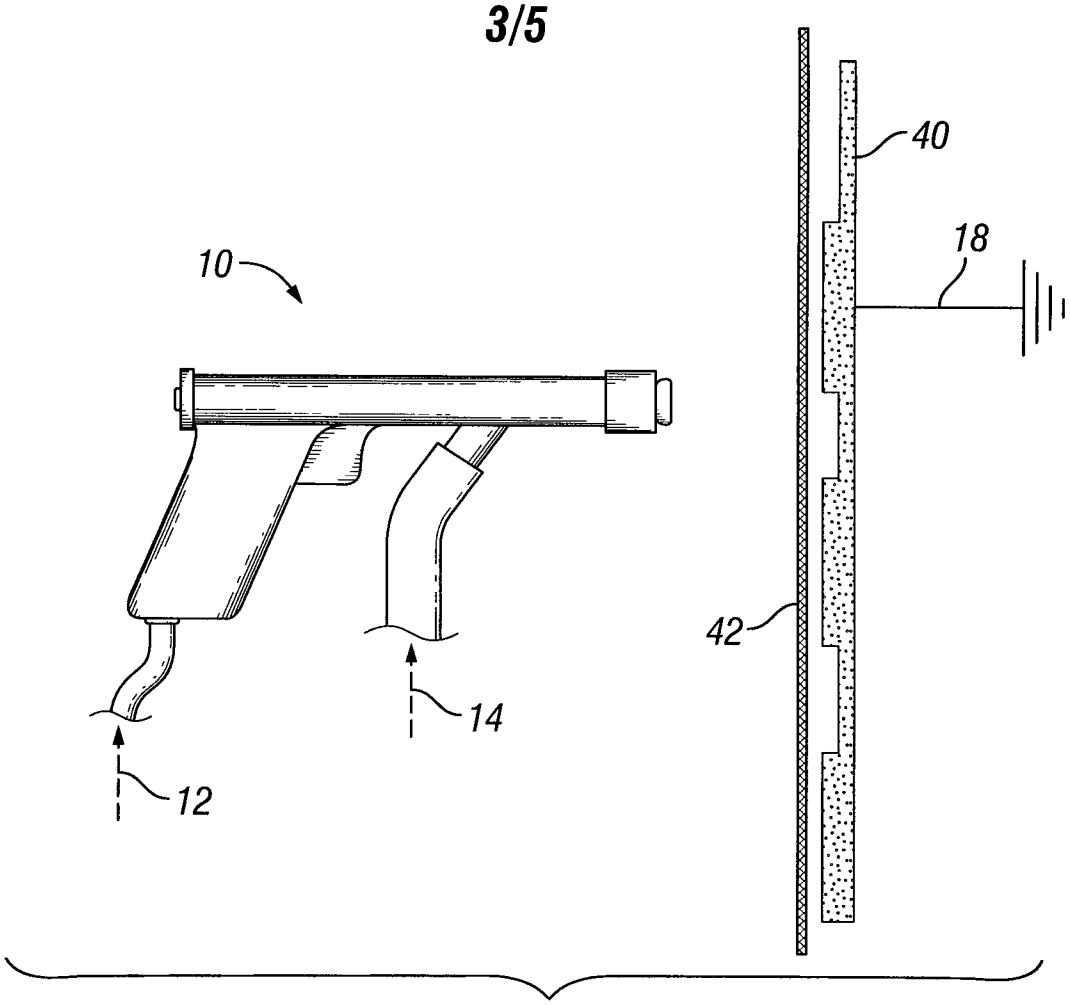


FIG. 3A

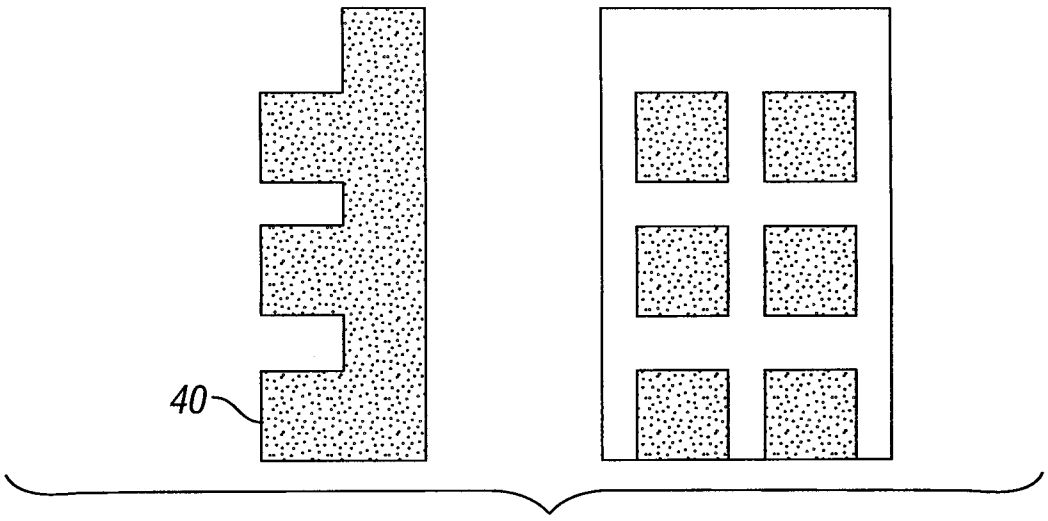


FIG. 3B

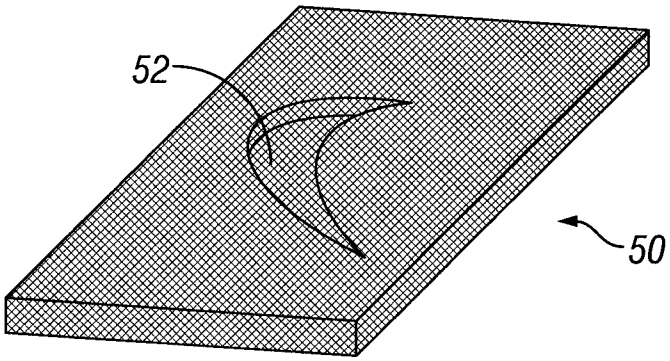


FIG. 4A

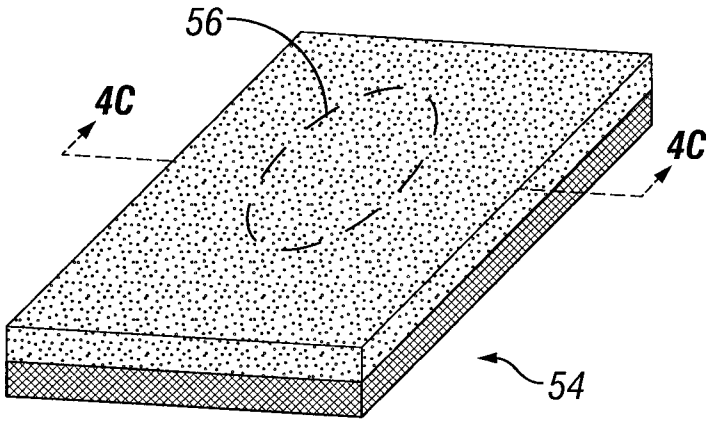


FIG. 4B

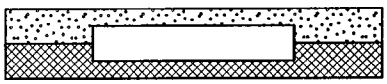


FIG. 4C

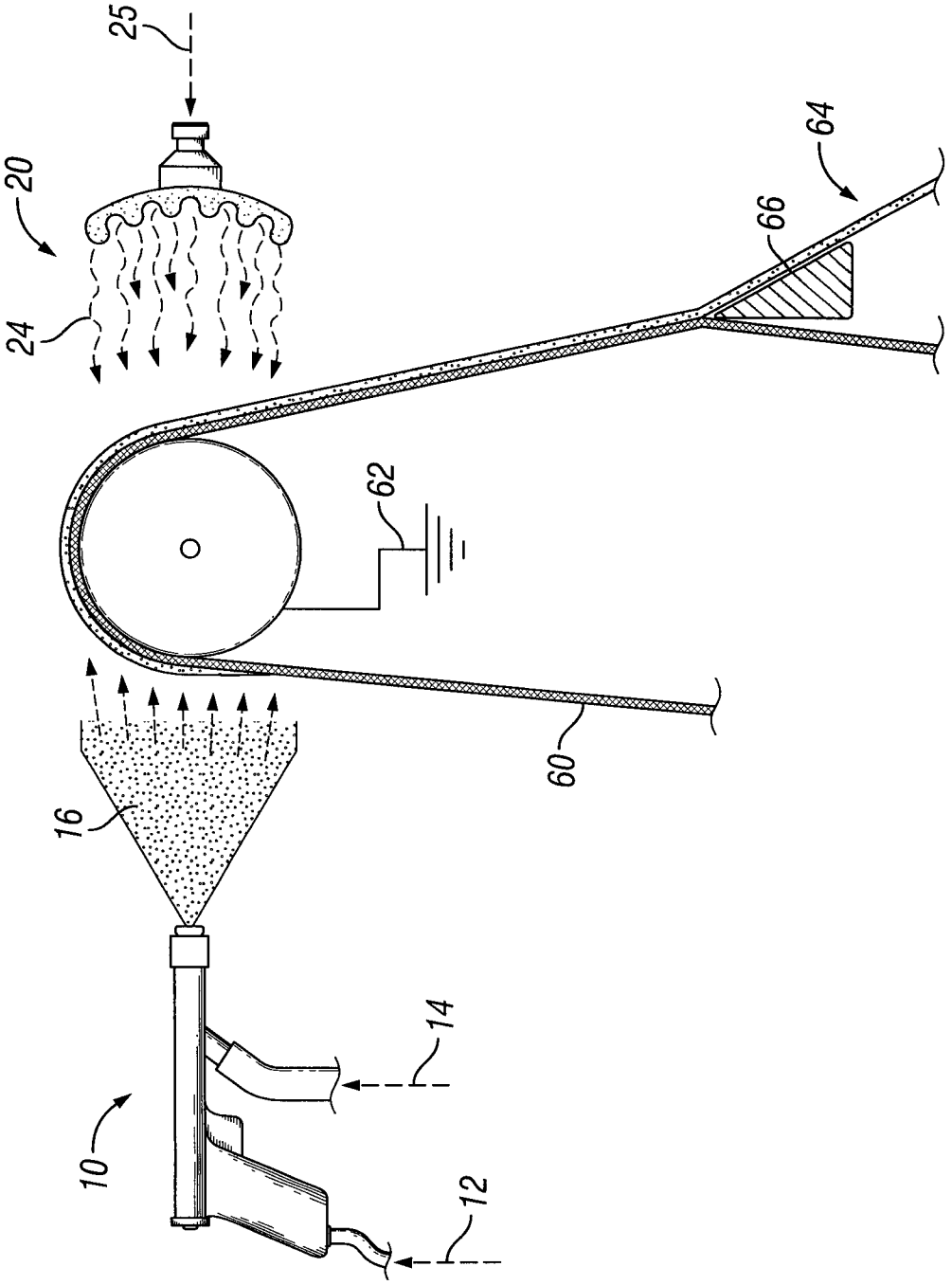


FIG. 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/13916

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/70; B05D 1/04, 1/06 (2015.01)
CPC - A61K 9/7007; B05D 1/04, 1/06
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61K 9/70; B05D 1/04, 1/06; B05B 5/025 (2015.01)
CPC: A61K 9/7007, 9/70; B05D 1/04, 1/06, 1/007, 1/045; B05B 5/025

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); ProQuest; IP.com; Google/Google Scholar; pharmaceutical, film, free, drug, medicine, therapeutical, sheet, layer, electrostatic, deposition, coat, powder, granule, cure, remove, separate, detach, peel, release, substrate, spray, transdermal, dissolve, oral, polymer, water-soluble, water-insoluble, gildant, lubricant

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 6,783,768 B1 (BROWN, SR et al.) 31 August 2004; abstract; figure 3; column 2, lines 35-38; column 3, lines 10-48; column 5, lines 50-52; column 6, lines 28-32; column 8, lines 25-28; column 10, lines 11-42; column 12, lines 24-37; column 13, lines 65-67; column 14, lines 1-67; column 15, lines 9-14; column 16, lines 1-9; claim 70	1-5, 13-15, 20-21, 32-34, 38-42 ---------- 6-9, 16-19, 22-31, 35-37, 43-53
Y	US 6,375,963 B1 (REPKA, MA et al.) 23 April 2002; column 2, lines 61-66; column 5, lines 40-44; column 6, lines 40-50; example 6	6-9, 16
Y	US 7,897,080 B2 (YANG, RK et al.) 01 March 2011; column 4, lines 41-43; column 48, lines 52-54	17-18
Y	US 2006/0099257 A1 (LANGRIDGE, JR et al.) 11 May 2006; abstract; paragraph [0021]	19
Y	US 2013/0011492 A1 (HALADA, G et al.) 10 January 2013; paragraph [0052]	22-23
Y	US 8,455,057 B2 (HEISKANEN, I et al.) 04 June 2013; abstract; column 2, lines 45-47; column 8, lines 39-43	24-28
Y	CA 1086576 A1 (SCHOLES, AB et al.) 30 September 1980; abstract; claim 17	29
Y	US 2009/0286435 A1 (BADYAL, JPS et al.) 19 November 2009; abstract; paragraph [0009]	30-31
Y	US 4,748,043 A (SEAVER, AE et al.) 31 May 1988; column 2, lines 55-63; column 4, lines 54-59; claim 14	35-37

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
02 June 2015 (02.06.2015)	06 JUL 2015
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/13916

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2009/0181074 A1 (MAKOWER, J et al.) 16 July 2009; paragraph [0081]; figure 7	43-44
Y	US 8,531,814 B2 (STONE, DK et al.) 10 September 2013; column 6, lines 18-21	45-49
Y	US 2013/0017367 A1 (RAVAGNAN, L et al.) 17 January 2013; paragraphs [0066], [0086]	50-53
A	US 6,670,038 B2 (SUN, HCS et al.) 30 December 2003; entire document	1-9, 13-53
A	WO 01/43727 A1 (PHOQUS LIMITED) 21 June 2001; entire document	1-9, 13-53
A	US 7,862,848 B2 (ZHU, J et al.) 04 January 2011; entire document	1-9, 13-53

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/13916

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

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

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

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

3. ☒ Claims Nos.: 10-12
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

Group I: Claims 1-9, 13-40 and 45-53 are directed toward making layered films by electrospraying powders on a non-conductive web material substrate while contacting the opposite side of the material with a grounded conductive material.

Group II: Claims 41-44 are directed toward a topical delivery device effective for directional delivery of an active agent that includes a layered film with an electrosprayed layer of non-adhesive impermeable polymer powder and a layer of absorbent material.

-***-Continued Within the Next Extra Sheet-***-

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

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

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

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US15/13916

-***-Continued From Box III Above: Observations where unity of invention is lacking-***-

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Group I include providing a non-conductive web material substrate; depositing electrosprayed powder or processed powder to a first side of the non-conductive web material while contacting the opposite side of the material with a grounded conductive material; and contacting the first surface of a substrate with a grounded conductive material that is shaped to contact the first surface only in discrete areas separated by areas of the first surface that are not contacted by the conductive material; electrospraying powder or granules of a pharmaceutically acceptable material onto the second surface of the substrate under conditions in which the electrostatic interaction of the pharmaceutically acceptable material and the pharmaceutically acceptable material to remain on the substrate only in the discrete areas of the second surface of the substrate that are opposing the areas of the first surface that are in contact with the conductive material; and placing a stencil of non-conductive material over the surface of the substrate wherein the stencil comprises one or more openings in the shape of one or more desired discrete pharmaceutically acceptable films, which are not present in Group II; and the special technical features of Group II include electrospray deposition of a layer of active agent powder on the first film layer and curing the powder to form a second film layer; and electrospray deposition of a layer of non-adhesive impermeable polymer powder on the second film layer and curing the powder to form a third film layer; and wherein the device is effective for directional delivery of the active agent when the device is placed on a topical delivery site; and deposition of a layer of an absorbent on the first film layer; and electrospray deposition of a layer of an impermeable polymer powder on the absorbent layer and curing the powder to form a second film layer, which are not present in Group I.

The common technical features of Groups I-II are a method of preparing a layered film containing more than one layer; including electrospray deposition of a layer of mucoadhesive powder on a substrate and curing the powder.

These common technical features are disclosed by US 6,783,768 B1 to Brown, et al. (hereinafter 'Brown'). Brown discloses a method of preparing a layered film containing more than one layer (a method of preparing a film comprising a cover coating layer over an active coating layer (more than one layer); column 3, lines 48-52; abstract); electrospray deposition of a layer of mucoadhesive powder on a substrate (electrostatically depositing a layer of PEG powder (polyethylene glycol, mucoadhesive) as the continuous phase component onto a substrate using a charge spraying device (electrospray deposition); abstract; column 10, lines 11-16; column 11, lines 13-20) and curing the powder (the powder coating is cured to form an active film; column 3, lines 34-48).

Since the common technical features are previously disclosed by Brown, these common features are not special and so Groups I-II lack unity.