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(54) Title: METHOD AND SYSTEM FOR MANUFACTURING ORAL SOLUBLE FILMS, COMPOSITIONS OF ORAL SOLUBLE FILMS, ORAL SOLUBLE FILMS MADE BY THEREBY, AND METHODS OF USE THEREOF

(57) Abstract: An oral soluble film contains at least one active agent. Alternatively, a multi-layered film includes a plurality of layers, at least one at least one of the plurality of layers being an oral soluble film layer containing at least one active agent. The oral soluble film may be made, e.g., by a method comprising providing a well of a predetermined size; depositing a film forming composition in the well; metering a predetermined amount of an active agent composition in the well separately from the film forming composition, the active agent composition being different than the film forming composition, the film forming composition and the active agent composition forming a single layer in the well; and drying the single layer in the well to form the oral soluble film containing the at least one active agent. In some embodiments, a film made by deposit includes at least one non-cannabinoid bioactive agent and at least one cannabinoid.

TITLE

Method and System for Manufacturing Oral Soluble Films, Compositions of Oral Soluble Films, Oral Soluble Films Made by Thereby, and Methods of Use Thereof

CROSS-REFERENCE TO RELATED APPLICATION:

This application is a continuation-in-part of U.S. Patent Application No. 17/180,419, filed February 19, 2021, which is a continuation-in-part of U.S. Patent Application Serial No. 16/926,093, filed 07/10/2020, the contents of each of which are incorporated herein by reference in their entireties.

This application discloses improvements to the subject matter described in, *inter alia*, U.S. Patent application Serial Nos. 15/486,331, filed April 13, 2017, now U.S. Patent No. 9,901,545; 15/866,729, filed January 10, 2018, now U.S. Patent No. 10,195,142; and 16/703,992, filed December 5, 2019, the contents of each of which are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

Active ingredients, such as but not limited to drugs or pharmaceuticals, may be prepared in a tablet form to allow for accurate and consistent dosing. However, this form of preparing and dispensing medications has many disadvantages perhaps a very significant example is the need for a granulation step in most tablets which can be destructive to certain bioactives such as but not limited to, vaccines , sensitives drugs etc. but also make the use of very low dosage units quite difficult because of the dilutive and mixing steps, also including a large proportion of

adjuvants that must be added to obtain a size able to be handled, that a larger medication form requires additional storage space, and that dispensing includes counting the tablets which has a tendency for inaccuracy. In addition, many persons, estimated to be as much as 28% of the population, have difficulty swallowing tablets and perhaps a higher percentage have a perceived difficulty of same.

While tablets may be broken into smaller pieces or even crushed as a means of overcoming swallowing difficulties, this is not a suitable solution for many tablet or pill forms. For example, crushing or destroying the tablet or pill form to facilitate ingestion, alone or in admixture with food, may also destroy the controlled release properties, taste masking properties, or otherwise effect the pharmacokinetic properties of the drug.

As an alternative to tablets and pills, films may be used to carry active ingredients such as drugs, pharmaceuticals, dermals, cosmeceuticals, botanicals and the like.

However, historically films and the process of making drug delivery systems therefrom have suffered from a number of unfavorable characteristics, and the industry struggled to develop a commercially viable way to manufacture films for consumers.

Films that incorporate a pharmaceutically active ingredient are disclosed in expired U.S. Pat. No. 4,136,145 to Fuchs, et al. ("Fuchs") (hereby incorporated by reference as if fully set forth). These films may be formed into a sheet, dried and then cut into individual doses. The Fuchs disclosure alleges the fabrication of a uniform film, which includes the combination of water-soluble

polymers, surfactants, flavors, sweeteners, plasticizers and drugs. These allegedly flexible films are disclosed as being useful for oral, topical or enteral use. Examples of specific uses disclosed by Fuchs include application of the films to mucosal membrane areas of the body, including the mouth, rectal, vaginal, nasal and otic areas.

Commentators have suggested that examination of films made in accordance with the process disclosed in Fuchs, however, reveals that such films suffer from the aggregation or conglomeration of particles, i.e., self-aggregation, making them inherently non-uniform. See US 8,658,437 (Yang et al., including the instant applicants) (hereby incorporated by reference as if fully set forth) discussing Fuchs.

The formation of agglomerates randomly distributes the film components and any active present as well. When large dosages are involved, a small change in the dimensions of the film would lead to a large difference in the amount of active per film. If such films were to include low dosages of active, it is possible that portions of the film may be substantially devoid of any active.

What constitutes true uniformity in a cast film? It is usually not a true molecular uniformity but rather a dispersion of active in which a given size film falls within generally accepted guidelines. In other instances, it may involve molecular uniformity, either measured for specific geographies, or within the film layer or layers themselves, this is substantially limited to active agents that are totally soluble in the film matrix.

Since sheets of film are usually cut into unit doses, certain doses may therefore be devoid of or contain an insufficient amount of active for the recommended treatment. Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms.

Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage units based on films, this virtually mandates that uniformity of the drug in the film be present. As a practical matter, stricter tolerances may be required by individual manufacturers, e.g. vary not more than 5%. In addition, there is a direct relationship to dosage size and as dosage size decreases this challenge increases.

The problems of self-aggregation leading to non-uniformity of a film were addressed in U.S. Pat. No. 4,849,246 to Schmidt ("Schmidt") (hereby incorporated as if fully set forth). Schmidt specifically pointed out that the methods disclosed by Fuchs did not provide a uniform film and recognized that that the creation of a non-uniform film necessarily prevents accurate dosing, which as discussed above is especially important in the pharmaceutical area.

Schmidt abandoned the idea that a mono-layer film, such as described by Fuchs, may provide an accurate dosage form and instead attempted to solve this problem by forming a multi-layered film. Schmidt forms an initial water-soluble wet cast film. Next, “an aqueous coating material is

prepared from the active ingredient, as well as starches, gelatins, glycerol and/or sorbitol, as well as optionally natural and/or synthetic resins and/or gums, and … the coating material is continuously applied by means of a roll coating process and in a precisely predetermined quantity (i.e. via coating thickness) to at least one side of the support film…. With the aid of modern roll application processes the active ingredient-containing coating can be applied with a constant thickness, so that the necessary tolerances can be respected."

The Schmidt process is a multi-step process that adds expense and complexity and is not practical for commercial use and is in fact no more a guarantee of uniformity than is Fuchs. In fact, the Schmidt patent has expired without, to the personal knowledge of the instant inventors, any commercial use. Yang et al describe a related approach, wherein, in a cast film, "particles or particulates may be added to the film-forming composition or matrix after the composition or matrix is cast into a film. For example, particles may be added to the film 42 prior to the drying of the film 42. Particles may be controllably metered to the film and disposed onto the film through a suitable technique, such as through the use of a doctor blade (not shown) which is a device which marginally or softly touches the surface of the film and controllably disposes the particles onto the film surface" (US 9,108,340) (hereby incorporated by reference as if fully set forth).

Other U.S. patents directly addressed the problems of particle self-aggregation and non-uniformity inherent in conventional film forming techniques.

U.S. Pat. No. 5,629,003 to Horstmann et al. and U.S. Pat. No. 5,948,430 to Zerbe et al. (each,

hereby incorporated by reference as if fully set forth) incorporated additional ingredients, i.e. gel formers and polyhydric alcohols in wet cast films, respectively, to increase the viscosity of the film prior to drying.

In addition to the concerns associated with degradation of an active during extended exposure to moisture, the conventional drying methods themselves may be unable to provide uniform films.

The length of heat exposure during conventional processing, often referred to as the "heat history", and the manner in which such heat is applied, have a direct effect on the formation and morphology of the resultant film product.

Uniformity is particularly difficult to achieve via conventional drying methods where a relatively thicker film, which is well-suited for the incorporation of a drug active, is desired. Thicker uniform films are more difficult to achieve because the surfaces of the film and the inner portions of the film do not experience the same external conditions simultaneously during drying.

Thus, according to commentators (US 7,425,292) (hereby incorporated by reference as if fully set forth), observation of relatively thick films made from such conventional processing shows a non-uniform structure caused by convection and intermolecular forces and may require moisture to remain flexible. The amount of free moisture can often interfere over time with the drug leading to potency issues and therefore inconsistency in the final product.

Put simply, the practitioner may walk a tightrope between moisture needed for desired

mechanical attributes (flexibility of the self-supported film), and potentially deleterious consequences for chemical stability of the active ingredient associated with moisture.

Some discussion of mechanical attributes is important. In a conventional wet cast film at the large manufacturing scale, the film is coated on to an inert flexible substrate, dried, then rolled (wound) onto itself. The film is then transported to the next discrete processing step where it is unrolled (unwound) and then processed to make it suitable for transport and handling. Typically, the edges are removed (trimmed, with loss of active), and the web (width) is cut into narrower-width sections (typically called "slitting") that can be accommodated by the film packaging machine (typically called "conversion" of the film). The film is then re-rolled (re-wound) upon itself after slitting and may or may not have been removed from its coating substrate, but either way requires sufficient mechanical strength to accommodate this processing.

If films lack the requisite pliability and tensile strength, they will tend to break during packaging causing substantial losses in process yield. Such breakage issues presumably led to the filing of a patent on methods of film splicing by Novartis (Slominski et al US 20060207721 A1). Some pliable, strong wet cast films use polyethylene oxide (PEO) based compositions (See Yang et al. US 2005/0037055 A1) (hereby incorporated by reference as if fully set forth). The strength of these films has led to the subsequent use of PEO in formulations commercially sold by Novartis. The reality is that physical strength and resulting breakage and process yield issues caused by breakage have been significant problems for many of the wet cast films.

However, as regards pliability, again the practitioner walks a tightrope. If the film is too pliable

(ductile or rubbery), it may stretch (elongate), particularly in the packaging stage where the film is under tension in the packaging lanes. Typically, in film packaging (conversion), the sub-roll of film is slit into lanes (each lane representing the width of the final dose) and then processed into unit dose foil packages. The final dosage is premised on relatively uniform total distribution of drug in the individual film, and then cutting equally dimensioned pieces of films based on the calculated drug concentration. Hopefully that concentration is known *ex ante* (before coating), but it can also be determined *ex post* (after coating).

However, if the film is too pliable, it may stretch under tension (most commonly in the packaging stage here). The effect of such stretching will decrease the concentration of the drug in the film. For a "stretched" film, the given calculated dimensions (that did not anticipate stretch/elongation) will now yield an under-strength dosage form.

As a result, the formulator must provide a film that, when dried, is sufficiently pliable to accommodate conversion (and not, say, break under tension). At the same time, the film cannot be too pliable or it will stretch

Even if the film's mechanical properties are sufficient for conversion and packaging, physical stability of the final dosage form over time is not necessarily assured.

The issue of physical stability is also an issue for wet cast films--expensive barrier packaging is often used as a matter of necessity. Still, physical stability is not always a given. Boots Chemists launched a Vitamin C strip manufactured by BioProgress in Tampa Fla. that had to be removed

from the shelves because it was crumbling in the package--earning the name "chips not strips."

This story is not unique--many projects have failed to move out from development to commercialization due to physical stability issues.

The formulator must accommodate these needs while still achieving the required performance when used (e.g. desired disintegration time, desired muco-adhesion if a buccal film, desired solid state of the drug etc.).

Conventional drying methods generally include the use of forced hot air using a drying oven, drying tunnel, and the like. The difficulty in achieving a uniform film is directly related to the rheological properties and the process of solvent evaporation in the film-forming composition as well as but not limited to the matters described above.

When the surface of a polymer solution is contacted with a high temperature air current, such as a film-forming composition passing through a hot air oven, the surface solvent is immediately evaporated and theoretically forms a polymer film or skin on the surface. This can seal the remainder of the film-forming composition beneath the surface, forming a barrier through which the remaining solvent must force itself as it is evaporated in order to achieve a dried film. As the temperature outside the film continues to increase, vapor pressure builds up under the surface of the film, stretching the surface of the film, and ultimately ripping the film surface open allowing the solvent to escape. As soon as the solvent has escaped, the polymer film surface reforms, and this process is repeated, until the film is completely dried. The result of the repeated destruction

and reformation of the film surface is observed as a "ripple effect" which produces an uneven, and often non-uniform film. Frequently, depending on the polymer, a surface will seal so tightly that the remaining water is difficult to remove, leading to very long drying times, higher temperatures, and higher energy costs.

Other factors, such as mixing techniques, also play a role in the manufacture of a pharmaceutical film, particularly a wet cast film, suitable for commercialization and regulatory approval. Air can be trapped in the composition during the mixing process or later during the film making process, which can leave voids in the film product as the moisture evaporates during the drying stage. The film may collapse around the voids resulting in an uneven film surface and therefore, non-uniformity of the final film product. Uniformity is still affected even if the voids in the film caused by air bubbles do not collapse. This situation also provides a non-uniform film in that the spaces, which are not uniformly distributed, are occupying area that would otherwise be occupied by the film composition and more importantly because there is a single mix in prior art casting, voids mean “no active present” here.

Some discussion of coating methods is needed, and the present inventors provide a good primer in US 7,824,588 (Yang et al including the present inventors) (hereby incorporated by reference as if fully set forth):

“Coating or casting methods are particularly useful for the purpose of forming the films of the present invention. Specific examples include reverse roll coating, gravure coating, immersion or dip coating, metering rod or meyer bar coating, slot die or extrusion coating, gap or knife over

roll coating, air knife coating; curtain coating, or combinations thereof, especially when a multi-layered film is desired. In this procedure, the coating material is measured onto the applicator roller by the precision setting of the gap between the upper metering roller and the application roller below it. The coating is transferred from the application roller to the substrate as it passes around the support roller adjacent to the application roller. Both three roll and four roll processes are common."

"The gravure coating process relies on an engraved roller running in a coating bath, which fills the engraved dots or lines of the roller with the coating material. The excess coating on the roller is wiped off by a doctor blade and the coating is then deposited onto the substrate as it passes between the engraved roller and a pressure roller."

"Offset Gravure is common, where the coating is deposited on an intermediate roller before transfer to the substrate."

"In the simple process of immersion or dip coating, the substrate is dipped into a bath of the coating, which is normally of a low viscosity to enable the coating to run back into the bath as the substrate emerges."

"In the metering rod coating process, an excess of the coating is deposited onto the substrate as it passes over the bath roller. The wire-wound metering [bar], smetimes known as a Meyer [Rod], allows the desired quantity of the coating to remain on the substrate. The quantity is determined by the diameter of the wire used on the rod."

"In the slot die process, the coating is squeezed out by gravity or under pressure through a slot and onto the substrate. If the coating is [substantially or 100% solid material (i..e very low solvent or no solvent use)], the process is termed 'Extrusion.'"

The '588 continues: "The gap or knife over roll process relies on a coating being applied to the substrate which then passes through a 'gap' between a 'knife' and a support roller. As the coating and substrate pass through, the excess is scraped off. Air knife coating is where the coating is applied to the substrate and the excess is 'blown off' by a powerful jet from the air knife. This procedure is useful for aqueous coatings. In the curtain coating process, a bath with a slot in the base allows a continuous curtain of the coating to fall into the gap between two conveyors. The object to be coated is passed along the conveyor at a controlled speed and so receives the coating on its upper face."

Yang et al, including the present inventors, teach a "selection of a polymer or combination of polymers that will provide a desired viscosity, a film-forming process such as reverse roll coating, and a controlled, and desirably rapid, drying process which serves to maintain the uniform distribution of non-self-aggregated components without the necessary addition of gel formers or polyhydric alcohols." See US 9,108,340 (hereby incorporated by reference as if fully set forth).

Yang et al. strongly rely on viscosity in the pre-cast film solution to maintain drug content uniformity, and on said viscoelastic properties of the film composition to retard and avoid excess migration of drug during both the casting and drying process.

As US 8,603,514 (Yang et al.) (hereby incorporated by reference as if fully set forth) describes: "the viscosity of the liquid phase is critical and is desirably modified by customizing the liquid composition to a viscoelastic non-Newtonian fluid with low yield stress values. This is the equivalent of producing a high viscosity continuous phase at rest. Formation of a viscoelastic or a highly structured fluid phase provides additional resistive forces to particle sedimentation. Further, flocculation or aggregation can be controlled minimizing particle-particle interactions. The net effect would be the preservation of a homogeneous dispersed phase."

Yang et al. invoke Stokes' law to support this high viscosity approach. US 8,603,514 describes: "One approach provided by the present invention is to balance the density of the particulate (ρ_p) and the liquid phase (ρ_l) and increase the viscosity of the liquid phase(μ). For an isolated particle, Stokes law relates the terminal settling velocity (Vo) of a rigid spherical body of radius (r) in a viscous fluid, as follows: $V_o=(2gr^r)(\rho_p-\rho_l)/9\mu$"

Accordingly, claim 1 of US 8,603, 514 requires, *inter alia*, the following element concerning the viscosity of the film forming matrix: "matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix."

The film compositions of Yang et al. (and other film artisans cited above) are so viscous that mechanical means (i.e. a physical means/physical object) in contact with the composition) are required to form a film by spreading the film composition on to the substrate. Put simply, the compositions are too viscous and have surface tension that is too high to pour. This is helpful in the coating process; after all, if the composition were too flowable it would roll/flow off the substrate. US 8,906,277 (Yang et al.) (hereby incorporated by reference as if fully set forth) describes the ability of the mechanical coating apparatus as providing the upper limit on viscosity of the film formulation: "the viscosity must not be too great as to hinder or prevent the chosen method of casting, which desirably includes reverse roll coating due to its ability to provide a film of substantially consistent thickness."

After the Yang et al. film compositions have been coated, Yang et al. describe a controlled drying process to avoid agglomeration of drug and resultant loss of content uniformity.

US 8,603,514 (Yang et al.) describes: "In conventional oven drying methods, as the moisture trapped inside subsequently evaporates, the top surface is altered by being ripped open and then reformed. These complications are avoided by the present invention, and a uniform film is provided by drying the bottom surface of the film first or otherwise preventing the formation of polymer film formation (skin) on the top surface of the film prior to drying the depth of the film. This may be achieved by applying heat to the bottom surface of the film with substantially no top air flow, or alternatively by the introduction of controlled microwaves to evaporate the water or other polar solvent within the film, again with substantially no top air flow. Yet alternatively, drying may be achieved by using balanced fluid flow, such as balanced air flow, where the

bottom and top air flows are controlled to provide a uniform film. In such a case, the air flow directed at the top of the film should not create a condition which would cause movement of particles present in the wet film, due to forces generated by the air currents. Additionally, air currents directed at the bottom of the film should desirably be controlled such that the film does not lift up due to forces from the air. Uncontrolled air currents, either above or below the film, can create non-uniformity in the final film products. The humidity level of the area surrounding the top surface may also be appropriately adjusted to prevent premature closure or skinning of the polymer surface."

"This manner of drying the films provides several advantages. Among these are the faster drying times and a more uniform surface of the film, as well as uniform distribution of components for any given area in the film. In addition, the faster drying time allows viscosity to quickly build within the film, further encouraging a uniform distribution of components and decrease in aggregation of components in the final film product."

High viscosity, high surface tension, and difficult flowability is a given in coating line systems. The picture at this link shows (www.matik.com/olbrich-answers-the-call-from-customers/) a standard Olbrich coating line. Olbrich is a leading manufacturer of coating equipment. The coating apparatus is physically below the drying tunnel, with the freshly coated substrate taking off at a severe (high) angle going up to the drying tunnel. When before any drying, it is necessary that the freshly coated film will not roll or flow off the substrate despite gravitational forces associated with this take off angle. It is important to note that drying methodology here is

essential to uniformity. In the invention to be described here, the dose unit is confined and the drying method has substantially no role in dosage uniformity.

The Yang et al. approach has proved dominant in the marketplace for film. The most successful commercial orally soluble film product (measured by sales) is Suboxone® thin film, which has exceeded one billion in US sales in certain years. The FDA Orange Book references two patents of Yang and the present inventors in connection with Suboxone: US 8,017,150 and US 8,603,514. A third patent listed in the Orange Book for this product– US 8,475,832 which deals with pH issues specific to Suboxone (as distinct from wet cast film manufacture generally) -- has been found invalid by the District Court for Delaware (although this '832 pH patent may be under further judicial appeal).

To date, several sophisticated ANDA filers, including Watson Pharmaceuticals, TEVA Pharmaceuticals (the world's largest generic company with revenues exceeding twenty billion dollars) and PAR Pharmaceuticals, have been unable in judicial proceedings to show invalidity of the Suboxone-Orange Book listed patents, though the certain ANDA filers have succeeded in launching generic products.

The next largest commercial orally soluble film success is the acquisition by Sunovion of Cynapsus for $624 million USD to acquire Cynapsus' apomorphine sublingual film. Cynapsus has a licensing arrangement to the same patent estate as Suboxone according to publicly available information (globenewswire.com/news-release/2016/04/04/825387/0/en/Cynapsus-Therapeutics-and-MonoSol-Rx-Announce-Global-IP-Licensing-Agreement.html). Following

the acquisition of Cynapsus by Sunovion, apomorphine film has been launched under the tradename Kynmobi®.

Moreover, the owner of the same patent estate recently sued BioDelivery Sciences for patent infringement for its Belbuca™ product, claiming infringement of another progeny of the same patent estate, US 8,765,167 (Yang et al).

The subject of loss (yield) and wet casting must be addressed. As we have discussed, wet cast film compositions are very viscous in the initial mixing stage. This viscosity, together with high surface tension, means that the film composition will experience loss with adhered product in the mixing apparatus and tubing from the mixing apparatus to the coater. Some mild loss may occur on the coating apparatus itself. There will be initial loss of product to bring the coater online until the product is running at standard parameters. Similarly, there will be loss at the end of a run bringing the coater offline (i.e. when too little material remains to maintain the coater running at standard parameters). As discussed, supra, product will be lost in the conversion stage by edge trimming, as well as cases where the width of usable web does not evenly divide by the input width required by the packaging line.

The packaging machine must be brought online (and offline at the end of a run), necessitating waste. Any breakage of film during packaging will result in waste in connection with lost

product and restarting of the line. And so on – this is not a non-limitative list, but offers some insight into the innate wastefulness of the process

The fact is that yields of wet cast film products are low, can result in substantial product loss, which is particularly concerning when casting expensive active pharmaceutical ingredients (API) (excipients being relatively inexpensive by comparison to API). Loss can be higher than 25% of API, high as 35% API and even approaching 50% API loss. Such API loss may be acceptable for high value branded targets, but ultimately restricts the success of oral soluble film in competitive Rx, OTC and other consumer fields.

The oral soluble film format is generally preferred by consumers over orally disintegrating tablets, but the latter is currently less expensive to make (as compared with wet cast films). For example, generic ondansetron orally disintegrating tablets sell for $8/dose (www.drugs.com/price-guide/ondansetron#oral-tablet-disintegrating-4-mg); whereas ondansetron orally soluble film has a retail price of $35/dose (www.drugs.com/price-guide/zuplenz). In an era when drug prices are under fire publicly, and third-party payers take a hard pencil to formulary reimbursement rates, this is a hard price differential to support. For orally soluble film to help deliver value to more patients, a more cost-effective method of film manufacture is needed.

One way to avoid some of the product loss associated with wet casting is hot melt extrusion. Insofar as an extruder acts as a mixer and typically starts with substantially dry, non-aqueous compositions, hot melt extrusion avoids mixing loss associated with wet casting.

One of the present applicants has two US patents dealing with hot melt extrusion products and methods: US 9,125,434 (Fuisz) (hereby incorporated by reference as if fully set forth) and US 8,613,285 (Fuisz) (hereby incorporated by reference as if fully set forth). Hot melt extrusion offers other advantages including a much smaller manufacturing footprint than a wet casting line, and the ability to make longer lasting films/sheets than can be made with wet casting. However, hot melt extrusion as a process has its own limitations (vis a vis wet casting). A principal limitation of hot melt extrusion is a smaller menu of film formers that readily extrude, which makes formulation far more challenging (as compared with wet casting). Taste masking and controlled release and incorporation of heat-labile active ingredients may also be harder. Heat stability of the active pharmaceutical ingredient may also be an issue. Despite its strengths, applicants are not aware of any significant commercial film product made using hot melt extrusion, and applicants believe that the smaller menu of available film formers is a reason for this.

Discussion of the Zydis system is appropriate. The Zydis system is an orally disintegrating tablet, and is classified by the FDA as such (as distinct from orally soluble film). The Zydis system is well regarded for its rapid disintegration (relative to other orally disintegrating tablets), though the system has some limitations in terms of drug loading, taste masking and fragility. A primer on the history of orally disintegrating tablets, including reference to one of the present inventors, is available here: en.wikipedia.org/wiki/Orally_disintegrating_tablet.

The Zydis system, which is a freeze-dried tablet, is described in U.S. Pat. Nos. 4,371,516; 4,305,502; 4,758,598; 4,754,597, and 5,631,023, the teachings of all of which are incorporated herein by reference as if fully herein stated. The Zydis manufacturing method uses a pre-prepared liquid composition including a solvent, a granular therapeutic agent, and a gelatin containing carrier material.

The liquid composition (including the drug) is placed into one or more shaped depressions in a tray or mold to define liquid composition filled depressions. The liquid composition in the filled depressions is frozen, then the liquid portion of the liquid composition sublimed to define a solid medicament tablet. Sublimation is accomplished by freeze drying and can take several days. Thus, the tablet manufacturing process is not continuous; Zydis tablets-in-sublimation are stored in racks in a special chamber for sublimation. Only after sublimation can they be packaged.

Some mention of the CIMA orally disintegrating tablet is appropriate. The CIMA tablet uses a base-acid reaction (effervescence) to effect oral tablet disintegration. There is some support for the proposition that effervescence enhances buccal absorption. See US 6,200,604 which is hereby incorporated by reference. Applicants are aware of no commercial oral soluble film product with effervescence, and attribute this to the practical difficulties of including acid and base in a wet cast film composition (without the product prematurely effervescing).

Finally, some mention of three-dimensional printing is warranted. 3D printing has garnered much attention as a possible method for manufacturing pharmaceutical dosage forms. The products are printed layer by layer (using binding materials in between the layers of powder to

adhere powder one layer to the other). The reality has failed to meet the hype, although a single printed dose product approval was obtained by Aprecia Pharmaceuticals for a product using its Zipdose technology licensed from MIT.

Applicants hereby incorporate by reference their oral film prior patents as if fully stated herein – these include: US 7,425,292 (Thin film with non-self-aggregating uniform heterogeneity and drug delivery systems made therefrom); US 7,666,337 (Polyethylene oxide-based films and drug delivery systems made therefrom); US 7,824,588 (Method of making self-supporting therapeutic active-containing film); US 7,897,080 (Polyethylene-oxide based films and drug delivery systems made therefrom); US 7,972,618 (Edible water-soluble film containing a foam reducing flavoring agent); US 8,017,150 (Polyethylene oxide-based films and drug delivery systems made therefrom); US 8,568,777 (Packaged film dosage unit containing a complexate); US 8,603,514 (Uniform films for rapid dissolve dosage form incorporating taste-masking compositions); US 8,613,285 (Extrudable and extruded compositions for delivery of bioactive agents, method of making same and method of using same); US 8,617,589 (Biocompatible film with variable cross-sectional properties); US 8,652,378 (Uniform films for rapid dissolve dosage form incorporating taste-masking compositions); US 8,663,687 (Film compositions for delivery of actives); US 8,685,437 (Thin film with non-self-aggregating uniform heterogeneity and drug delivery systems made therefrom); US 8,900,498 (Process for manufacturing a resulting multi-layer pharmaceutical film); US 8,906,277 (Process for manufacturing a resulting pharmaceutical film); US 9,108,340 (Process for manufacturing a resulting multi-layer pharmaceutical film); US 9,125,434 (Smokeless tobacco product, smokeless tobacco product in the form of a sheet, extrudable tobacco composition); US 9,150,341 (Unit assembly and method of making same);

US 9,901,545 (Method and Composition for making an oral soluble film, containing at least one active agent); US 10,111,810 (Thin film with non-self-aggregating uniform heterogeneity and drug delivery systems made therefrom); US 10,195,142 (Method and composition for making an oral soluble film, containing at least one active agent); US 10,238,600 (Package, system and methods for custody and control of drugs); US 10,285,910 (Sublingual and buccal film compositions); US 10,335,872 (Smokeless tobacco product, smokeless tobacco product in the form of a sheet); and US 10,730,207

SUMMARY OF THE INVENTION

One aspect of the invention relates to an oral soluble film containing at least one active agent, the oral soluble film being made by a method comprising providing a well of a predetermined size; depositing a film forming composition in the well; metering a predetermined amount of an active agent composition in the well separately from the film forming composition, the active agent composition being different than the film forming composition, the film forming composition and the active agent composition forming a single layer in the well; and drying the single layer in the well to form the oral soluble film containing the at least one active agent.

Another aspect of the invention relates to an oral soluble film containing at least one active agent, the oral soluble film being made by a method comprising continuously stirring a suspension of a film forming composition and particulates of at least one active agent in a tank; depositing the suspension of the film forming composition and the particulates of the at least one active agent separately into each of a plurality of wells while continuously stirring the suspension in the tank, the suspension of the film forming composition and the particulates of the at least

one active agent having a yield stress of less than 30 Pa and forming a contact angle with the well of less than 90°, wherein the suspension of the film forming composition and the particulates of the at least one active agent flows into a film in the well within 20 seconds and has a viscosity below 600 centipoise; and drying the film using hot air currents to form the oral soluble film containing the at least one active agent.

One aspect of the invention relates to an oral soluble film containing at least one active agent, the oral soluble film being made by a method comprising providing a well of a predetermined size; depositing a film forming composition which also contains an active agent dissolved within it, in the well; the film forming composition and the active agent composition forming a single layer in the well; and drying the single layer in the well to form the oral soluble film containing the at least one active agent.

One aspect of the invention relates to an oral soluble film containing at least one active agent, the oral soluble film being made by a method comprising providing a well of a predetermined size; depositing a film forming composition which also contains an active agent suspended within it, in the well; the film forming composition and the active agent composition forming a single layer in the well; and drying the single layer in the well to form the oral soluble film containing the at least one active agent.

Another aspect of the invention relates to an oral soluble film containing at least one active agent, the oral soluble film being made by a method comprising a film forming composition and

at least one dissolved active agent within the film forming composition; depositing the solution of the film forming composition and the dissolved active agent together into each of a plurality of wells without stirring, having a yield stress of less than 30 Pa and forming a contact angle with the well of less than 90°, wherein the solution of the film forming composition and the at least one active agent flows into a film in the well within 20 seconds and has a viscosity below 600 centipoise; and drying the film using hot air currents to form the oral soluble film containing the at least one active agent.

In another aspect, the invention relates to a multi-layered film comprising a plurality of layers, at least one of the plurality of layers being an oral soluble film layer containing at least one active agent, the at least one oral soluble film layer being made by a method comprising providing a well of a predetermined size; depositing a film forming composition in the well; metering a predetermined amount of an active agent composition in the well separately from the film forming composition, the active agent composition being different than the film forming composition, the film forming composition and the active agent composition forming a single layer in the well; and drying the single layer in the well to form the at least one oral soluble film layer containing the at least one active agent. The multi-layered may include an insoluble backing layer. The multi-layered film may include a semi-insoluble backing layer. The multi-layered film may have multiple layers each with a different active agent. The multi-layered composition may have a mucoadhesive layer and a barrier or backing layer. The multi-layered composition may have a mucoadhesive gelling layer and a barrier or backing layer. The multi-layered composition may have a thermo-reversible gelling layer and a barrier or backing layer.

In another aspect, the invention relates to a multi-layered film comprising a plurality of layers, at least one at least one of the plurality of layers being an oral soluble film layer containing at least one active agent, the oral soluble film layer being made by a method comprising continuously stirring a suspension of a film forming composition and particulates of at least one active agent in a tank; depositing the suspension of the film forming composition and the particulates of the at least one active agent separately into each of a plurality of wells while continuously stirring the suspension in the tank, the suspension of the film forming composition and the particulates of the at least one active agent having a yield stress of less than 30 Pa and forming a contact angle with the well of less than 90°, wherein the suspension of the film forming composition and the particulates of the at least one active agent flows into a film layer in the well within 20 seconds and has a viscosity below 600 centipoise; and drying the film using hot air currents to form the oral soluble film layer containing the at least one active agent. The multi-layered may include an insoluble backing layer. The multi-layered film may include a semi-insoluble or slow-dissolving backing layer. The multi-layered film may have multiple layers each with a different active agent.

In certain embodiments, the dosage may comprise films from two or more adjacent wells and have different actives which are packaged to be administered in tandem or concert.

A single slow dissolving mucoadhesive layer may be first deposited within a well followed by a droplet or droplets of drug containing solution in the center (or other geographic region) of the mucoadhesive composition. The mucoadhesive composition when placed within the buccal mucosa may now have the opportunity to adhere on both sides of the composition. This is unlike

typical multi-layer mucoadhesive compositions with one side containing a barrier layer and another side containing a mucoadhesive layer with drug. Stated another way, in this embodiment, the drug containing layer 13 or area has smaller outward dimensions (smaller surface area) than the mucoadhesive backing layer. In other embodiments, the drug containing layer has larger outward dimensions than the mucoadhesive layer.

Similarly, other multilayer embodiments have an insoluble or slowing dissolving backing layer that has larger outward dimensions than a drug containing layer, or have an insoluble or slowly dissolving backing layer with smaller outward dimensions than a drug containing layer. Drying may occur after all layers are deposited, or after one or more layers is deposited.

By "slowly dissolving" layer, we mean a layer that dissolves in more than three minutes, preferably more than five minutes, preferably more than ten minutes, and most preferably more than fifteen minutes, in its intended usage site (e.g. buccal, sublingual, interoral, vaginal, anal, wound-care, etc.).

Certain embodiments involve effervescent films. Typically, these are multilayer; at least one layer comprises the base and at least one distinct layer comprises the acid. These layers may be separated by a barrier to deter confluence or mixing of the acid and base during manufacture. The barrier may be achieved using differing layer forming compositions with different rheological properties that retard miscibility. Drying a first layer before depositing the next layer can also deter and substantially eliminated mixing during manufacture.

In still other embodiments, multiple mucoadhesive layer points (i.e. discrete mucoadhesive areas) are deposited onto a drug containing layer.

In certain embodiments, A multilayer oral soluble film made by deposit, comprising at least one drug containing layer, a separate slowly dissolving backing layer not comprising drug, wherein the drug containing mucoadhesive layer has smaller outward dimensions than the backing layer.

For example, as shown in Figs. 10A, 10B, a single slow dissolving mucoadhesive layer 12 may be first deposited within a well followed by a droplet 13 or droplets of drug containing solution in the center of the mucoadhesive composition 12. The mucoadhesive composition 12 when placed within the buccal mucosa may now have the opportunity to adhere on both sides of the composition. This is unlike typical multi-layer mucoadhesive compositions with one side containing a barrier layer and another side containing a mucoadhesive layer with drug. Stated another way, in this embodiment, the drug containing layer 13 or area has smaller outward dimensions (smaller surface area) than the mucoadhesive backing layer 12. In other embodiments, as shown in Figs. 11A and 11B, the drug containing layer 13 has larger outward dimensions than the mucoadhesive layer 12. Similarly, other multilayer embodiments have an insoluble or slowing dissolving backing layer 12 that has larger outward dimensions than a drug containing layer 13, or have an insoluble or slowly dissolving backing layer 12 with smaller outward dimensions than a drug containing layer 13. Drying may occur after all layers are deposited, or after one or more layers is deposited.

Another aspect of the present invention relates to a method of making an oral soluble film, containing at least one active agent. The method includes providing a well of a predetermined size; depositing a film forming composition in the well; depositing an active agent composition in the well, the active agent composition being different than the film forming composition, the film forming composition and the active agent composition forming an admixture in the well; and drying the admixture in the well.

Depositing of the film forming composition in the well and depositing of the active agent composition in the well can be carried out sequentially or simultaneously from two (or more) separate deposition devices. If sequential deposition is used, the active agent composition is preferably but not necessarily deposited in the well first and then the film forming composition is deposited in the well, or vice versa given the characteristics of the materials to be deposited and intended products attributes. Various iterations may be employed of film forming composition and active agent compositions.

In another aspect of the invention, a method of making an oral soluble film, containing at least one active agent, includes providing a well of a predetermined size; depositing a film forming composition including at least one active agent in the well, the film forming composition having a viscosity below 2000 centipoise; and drying the film forming composition in the well.

In another aspect of the invention, a method of making an oral soluble film, containing at least one active agent, includes providing a well of a predetermined size; depositing a film forming

composition including at least one active agent in the well, the film forming composition having a viscosity below 3000 centipoise; and drying the film forming composition in the well.

In another aspect of the invention, a method of making an oral soluble film, containing at least one active agent, includes providing a well of a predetermined size; depositing a film forming composition including at least one active agent in the well, the film forming composition having a viscosity below 4000 centipoise; and drying the film forming composition in the well.

In another aspect of the invention, a method of making an oral soluble film, containing at least one active agent, includes providing a well of a predetermined size; depositing a film forming composition including at least one active agent in the well, the film forming composition having a viscosity below 5000 centipoise; and drying the film forming composition in the well.

In another aspect of the invention, a method of making an oral soluble film, containing at least one active agent, includes providing a well of a predetermined size; depositing a film forming composition including at least one active agent in the well, the film forming composition having a viscosity below 4000 centipoise; and drying the film forming composition in the well.

In another aspect of the invention, a method of making an oral soluble film, containing at least one active agent, includes providing a well of a predetermined size; depositing a film forming composition including at least one active agent in the well, the film forming composition having a viscosity below 6000 centipoise; and drying the film forming composition in the well.

In still another aspect of the invention, a film forming composition, suitable for making an oral soluble film, has sufficiently low viscosity and surface tension to flow into a film without mechanical intervention when deposited in a well.

The present invention has a number of aspects, including the following.

1. A multilayer soluble film made by deposit, comprising:

a first soluble layer not containing a pharmaceutical active agent; and

a second soluble layer provided on the first soluble layer by depositing a solution comprising materials forming the second soluble layer to form the solution into a film on the first soluble layer, the second soluble layer containing at least one pharmaceutical active agent and having a surface area different than a surface area of the first soluble layer,

wherein the first soluble layer is a mucoadhesive layer or a slowly dissolving backing layer.

2. The multilayer soluble film according to 1 above, wherein the first soluble layer is a mucoadhesive layer.

3. The multilayer soluble film according to any of 1 and 2 above, wherein the second soluble layer is provided on the first soluble layer by depositing a solution comprising materials forming the second soluble layer without direct mechanical intervention to form the solution into a film on the first soluble layer.

4. The multilayer soluble film according to any of 1-3 above, wherein the first soluble layer is a slowly dissolving backing layer.

5. The multilayer soluble film according to any of 1-4 above, wherein the second soluble layer has a mucoadhesive property.

6. The multilayer soluble film according to any of 1-5 above, wherein at least one of the first and second has a mesomorphic phase.

7. The multilayer soluble film according to any of 1-6 above, wherein the second soluble layer has a surface area smaller than a surface area of the first soluble layer.

8. The multilayer soluble film according to claim any of 1-7 above, wherein the second soluble layer has a surface area larger than a surface area of the first soluble layer.

9. A system for manufacturing a pharmaceutical active agent-containing soluble film by deposit, comprising:

a gantry moveable horizontally in at least an X and Y direction;

a nozzle supported on the gantry, the nozzle being configured to be connected to a source of a film forming composition containing a pharmaceutical active agent, and

a support configured to support a sheet having a plurality of wells,

wherein the gantry and nozzle are configured to deposit the film forming composition into the well in a pattern by moving the gantry horizontally in the X and/or Y direction.

10. A method for manufacturing a pharmaceutical active agent-containing soluble film by deposit using the system according to 9 above, comprising depositing the film forming composition into the well in a pattern while moving the gantry horizontally in the X and/or Y direction.

11. A system or method according to any of 9 and 10 above wherein the gantry and nozzle are configured to deposit the film forming composition into the well in a pattern by moving the gantry in the X, Y or Z direction(s).

11.5 The system or method according to any of 9-11 above, further comprising a machine vision system for determining the proper relative placement of the nozzle and the wells.

12. A system for manufacturing a pharmaceutical active agent-containing soluble film by deposit, comprising:

a support;

a nozzle moveably supported on the support, the nozzle being configured to be connected to a source of a film forming composition containing a pharmaceutical active agent, and

wherein the nozzle is configured articulate to deposit the film forming composition into the well in a shape selected from the group of: circular, elliptical, polygonal and zig-zag.

13. The system according to any of 9-12 above, wherein the nozzle can pulsate on-off during deposit.

14. The system according to any of 9-13 above, wherein the nozzle is configured to deposit with continuous flow.

15. A method for manufacturing a pharmaceutical active agent-containing soluble film by deposit using the system according to claim 9 and 11-14, comprising deposit the film forming composition into the well in a shape selected from the group of: circular, elliptical, polygonal and zig-zag while articulating the nozzle.

16. A system for forming a pharmaceutical active agent-containing soluble film, comprising a sheet including a well of predetermined size, the sheet being softenable by heat, and a support containing a sub-well of a size large enough to accommodate the well, wherein the well of the sheet is provided in the sub-well.

17. The system according to 16 above, wherein the sub-well is configured to be chilled or heated.

18. A method for forming a pharmaceutical active agent-containing soluble film, comprising:

providing a sheet including a well of predetermined size, the sheet being softenable by heat onto a support containing a sub-well of a size large enough to accommodate the well, wherein the well of the sheet is provided in the sub-well; and

depositing a film forming composition containing a pharmaceutical active agent into the well.

19. The method according to 18 above, further comprising heating or chilling the sub-well.

20. A method for promoting release of a soluble film from a surface of a package, comprising providing a sheet with a plurality of wells, a soluble film provided in the bottom of each well and a top sheet covering the plurality of wells, and passing the sheet partially around at least one roller to bend the bottom surface of the well to promote release of an soluble film from the bottom of the well.

21. The method according to 20 above, wherein the roller has protrusions on its surface.

22. A pharmaceutical active agent-containing soluble film, comprising an soluble film containing at least one pharmaceutical active agent, wherein at least part of an edge portion of the soluble film is thicker than a center portion.

23. The pharmaceutical active agent-containing soluble film according to 22 above, wherein a perimeter of the soluble film is thicker than a center portion.

24. The pharmaceutical active agent-containing soluble film according any of 22 and 23 above, wherein a perimeter of the soluble film is more than 10% thicker than a center portion.

25. The pharmaceutical active agent-containing soluble film according to any of 22-24 above, wherein a perimeter of the soluble film is more than 10% thicker than an average thickness of the soluble film.

26. A pharmaceutical active agent-containing soluble film made by deposit, comprising a soluble film containing at least one pharmaceutical active agent, wherein the soluble film contains one or more holes through the film.

27. The pharmaceutical active agent-containing soluble film according to 26 above, wherein in the soluble film has a circular cross-sectional shape with a single hole in the center.

28. A pharmaceutical active agent-containing soluble film made by deposit, comprising a soluble film containing at least one pharmaceutical active agent, wherein the soluble film has a moisture content of 15% or greater

29. The pharmaceutical active agent-containing soluble film according to 28 above, wherein the soluble film has moisture domains within the film.

30. The pharmaceutical active agent-containing soluble film according to any of 28 and 29 above, wherein the soluble film the dried film has a gel-like center.

31. A packaged pharmaceutical active agent-containing soluble film made by deposit, comprising a soluble film containing at least one pharmaceutical active agent, wherein the soluble film contains a crystallization component configured to cause intentional crystallization to promote release of the soluble film from a surface of the package.

32. The packaged pharmaceutical active agent-containing soluble film according to 31 above wherein the crystallization component is provided in the soluble film in an amount of 3-20%, measured from dry weight of the film and is selected from the group of erythritol, xylitol, mannitol, sucrose and citric acid.

33. A palletized stack of packaged pharmaceutical active agent-containing soluble films made by deposit, each packaged pharmaceutical active agent-containing soluble film comprising a package comprising a bottom sheet including a well, a soluble film containing at least one

pharmaceutical active agent provided in the well, and a top sheet covering the soluble film containing at least one pharmaceutical active agent provided in the well, wherein the packages are provided in the palletized stack upside-down with the top sheet provided on the bottom and the well provided on the top.

34. A sheet containing a well for forming a soluble film therein, wherein the well has side portions configured to collapse when a bottom of the well is pushed upwards to present the soluble film for use.

35. The sheet according to 34 above, wherein the side portions of the well are formed in an accordion shape.

36. The sheet according to any of 34 and 35 above, wherein the side portions of the well include a weak point configured to facilitate collapse upwards of the well and/or turning the well inside out.

37. A combination comprising the sheet according to any of 34-36 above, a soluble film provided in the well and a top sheet covering the soluble film in the well.

38. A film made by deposit, the film comprising at least one non-cannabinoid bioactive agent and at least one cannabinoid.

39. The film according to 38 above, wherein the film comprises at least two layers.

40. The film according to any of 38 and 39 above, wherein the film comprises at least two layers, wherein at least one layer comprises a non-cannabinoid, and least one other layer comprises a non-cannabinoid bioactive agent.

41. The film according to any of 38-40 above, wherein the at least one cannabinoid is deposited separately from the at least one non-cannabinoid bioactive agent

42. The film according to any of 38-41 above, wherein the film comprises an emulsifier.

43. The film according to any of 38-42 above, wherein the at least one non-cannabinoid bioactive agent comprises a drug, and the film further comprises a supplement.

44. The film according to any of 38-43 above, wherein the at least one cannabinoid comprises an phytocannabinoid.

45. The film according to any of 38-44 above, wherein the at least one cannabinoid comprises a synthetic cannabinoid.

46. The film according to any of 38-45 above, wherein the film has a dried moisture level of below 3% to prevent hydrolysis of the cannabinoid.

47. The film according to any of 38-46 above, wherein the at least one cannabinoid comprises a psychoactive cannabinoid and a cannabidiol to modulate or attenuate the psychoactivity of the psychoactive cannabinoid.

48. The film according to any of 38-47 above, wherein the at least one non-cannabinoid bioactive agent includes a Reference Listed Drug and the film comprises the non-cannabinoid bioactive agent in an amount at least 20% less than an amount of the non-cannabinoid bioactive agent in comparable strength of the single active Reference Listed Drug,.

49. The film according to any of 38-48 above, wherein the film comprises at least one non-cannabinoid bioactive agent for the treatment of insomnia, selected from the group of zolpidem, suvorexant, butabarbital, quazepam, estalozam, flurazepam, triazolam, tasmelteon, eszopiclone, temazapem, ramelteon, secobarbital, doxepin, zaleplon, hydroxyzine, meclizine diphenhydramine, and doxylamine, and wherein the film further comprises at least one cannabinoid selected from the group of full spectrum oil distillate, CBD, CBDA, CBG, CBN, and THCA.

50. The film according to any of 38-49 above, wherein the film is configured to have a therapeutic indication of seizure control or anti-convulsant, and the at least one non-cannabinoid bioactive agent comprises at least one of diazepam or midazolam.

51. The film according to any of 38-50 above, wherein the at least one non-cannabinoid bioactive agent comprises a triptan for the treatment of migraine selected from the group of almotriptan, frovatriptan, rizatriptan, zolmitriptan, sumatriptan, naratriptan, and eletriptan, and the at least one cannabinoid comprises at least one of delta 9 thc and dronabinol.

52. The film according to any of 38-51 above, wherein the at least one non-cannabinoid bioactive agent comprises eletriptan, and the at least one cannabinoid comprises dronabinol and cannabidiol.

53. The film according to any of 38-52 above, wherein the at least one non-cannabinoid bioactive agent comprises eletriptan, and the at least one cannabinoid comprises cannabidiolic acid or a cannabidiolic acid ester.

54. The film according to any of 38-53 above, wherein the at least one non-cannabinoid bioactive agent comprises ubrogepant, the at least one cannabinoid comprises delta 9 THC or dronabinol, and the film has an ubrogepant Tmax that is at least 20% faster than an ubrogepant RLD orally disintegrating tablet.

55. The film according to any of 38-54 above, wherein the at least one non-cannabinoid bioactive agent comprises ubrogepant, the at least one cannabinoid comprises CBDA, and the film has an ubrogepant Tmax that is at least 20% faster than an ubrogepant RLD orally disintegrating tablet.

56. The film according to any of 38-55 above, wherein the film is configured to treat an opioid use disorder, and the at least one non-cannabinoid bioactive agent comprises at least one selected from the group of naltrexone, lofexidene, and nalmefene.

57. The film according to any of 38-56 above, wherein the film is configured for anti-depressant use, and the at least one non-cannabinoid bioactive agent comprises paroxetine or escitalopram, and the at least one cannabinoid comprises at least one of delta 9 THC and Dronabinol.

58. The film according to any of 38-57 above, wherein the film is configured for anti-inflammatory disease, and the at least one non-cannabinoid bioactive agent comprises a steroid and the at least one cannabinoid comprises CBD.

59. The film according to any of 38-58 above, wherein the film is configured for the treatment of attention deficit disorder, and the at least one non-cannabinoid bioactive agent comprises at least one selected from the group of amphetamine, methylphenidate, dexmethylphenidate, atomoxetine hydrochloride, lisdexamfetamine, and dimesylate.

60. The film according to any of 38-59 above, wherein the at least one non-cannabinoid bioactive agent comprises at least one selected from the group of sildenafil, tadalafil, vardenafil and avanafil, and the at least one cannabinoid comprises at least one selected from the group of delta 9 THC, delta 8 THC, CBD and CBDA.

61. The film according to any of 38-60 above, wherein the film is is configured to treat erectile dysfunction and/or premature ejaculation, and the at least one non-cannabinoid bioactive agent comprises a PDE-5 inhibitor and the at least one cannabinoid comprises CBDA.

62. The film according to any of 38-61 above, wherein the film is configured to treat erectile dysfunction an/or premature ejaculation, and the at least one non-cannabinoid bioactive agent comprises vardenafil and the at least one cannabinoid comprises CBDA.

63. The film according to any of 38-62 above, wherein the film is configured to treat erectile dysfunction and/or premature ejaculation, and the at least one non-cannabinoid bioactive agent comprises avanafil and the at least one cannabinoid comprises CBDA.

64. The film according to any of 38-63 above, wherein the at least one cannabinoid comprises at least one synthetic cannabinoid f selected from the JWH series, HU series, CP series, AM series, AB series, AKB series, THJ series, UR series, XLR series, STS series, and PB series.

65. A method of using the film according to any of 38-64 above, comprising applying the film to a buccal area of a human or animal.

66. A method of using the film according to any of 38-64 above, comprising applying the film to a sublingual area of a human or animal.

67. A method of using the film according to any of 38-64 above, comprising applying the film inside a vagina of a human or animal.

68. A method of using the film according to any of 38-64 above, comprising administering the film per-orally to a human or animal.

69. A method of making a film composition with a heat sensitive active agent, comprising:

forming an absorbent film by deposit in a well, wherein the absorbent film comprises at least one absorbent agent that is soluble or substantially insoluble excipients that impart a porous structure to the film, the at least one absorbent agent being at least one selected from the group

of: ethyl cellulose, cellulose powder, microcrystalline cellulose, nanocrystalline cellulose, polymethacrylates, and silicon dioxide;

drying or substantially drying the film, wherein the absorbent agent is at least 3% of the dried film mass;

depositing a heat sensitive active agent on the dried film, wherein the heat sensitive agent is dissolved or suspended in a solvent; and

allowing the deposited solvent to percolate within a matrix of the dried or substantially dried absorbent film.

70. The method according to 69 above, wherein the heat sensitive active agent is a cannabinoid.

71. The method according to any of 69 and 70 above, wherein the deposited heat sensitive active percolates within the absorbent film matrix

72. The method according to any of 69-71 above, wherein the film is dried again to remove the deposited solvent

73. The method according to any of 69-72 above, wherein the solvent is reduced to acceptable levels

74. The method according to any of 69-73 above, wherein the solvent drying phase is 25 C to 85 C.

75. The method according to any of 69-74 above, wherein the solvent drying phase uses ambient air temperatures.

76. The method according to any of 69-75 above, wherein the absorbent agent is at least 10% of the dried film mass.

77. The method according to any of 69-76 above, wherein the absorbent agent is 5-75% of the dried film mass.

78. The method according to any of 69-77 above, wherein the solvent comprises the absorbent film comprises a surfactant.

79. The method according to any of 69-78 above, wherein the solvent with the heat sensitive agent comprises a surfactant.80. A film made by deposit in a well, wherein the film comprises an effective amount of at least one release agent selected from the group of: polystyrene powder or breads, polymethacrylates and cholestyramine to facilitate release of the dried film from the well.

81. A film for oromucosal delivery made by deposit in a well, wherein the film comprises a plurality of separate domains, at least one domain comprising a prodrug and at least one other domain comprising at least one catalyst.

82. The film according to 81 above, wherein the separate domains are separate layers.

83. The film according to any of 81 and 82 above, wherein the separate domains are in separate layers deposited on an insoluble and/or mucoadhesive film layer.

84. A method of making a film in a well, comprising:

depositing a film former and at least one active agent in a well by at least one deposit nozzle provided on a moveable x-y gantry, wherein no mechanical intervention is used to form the film; and

drying the film; and

applying a top sheet on the film in the well,

wherein depositing the film, drying the film and applying the top sheet are performed on a single production line.

85. The method according to 84 above, wherein a plurality of deposit nozzles are provided on an x-y gantry;

86. The method according to any of 84 and 85 above, wherein at least one deposit nozzle is on an x-y-z gantry

87. The method according to any of 84-86 above, wherein at least one deposit nozzle has a check valve.

88. The method according to any of 84-87 above, wherein at least one nozzle employs suction to prevent dripping.

89. The method according to any of 84-88 above, wherein the nozzle has a drip collection system.

90. The method according to any of 84-89 above, wherein the nozzle has a drip collection tray.

91. The method according to any of 84-90 above, wherein at least one nozzle is moved out and away from the deposit station between deposition.

92. The method according to any of 84-91 above, wherein a drip collection tray is positioned under the nozzles between depositions.

93. The method according to any of 84-92 above, wherein the wells are filled with nitrogen prior to sealing.

94. The method according to any of 84-93 above, wherein the production line stutters.

95. The method according to any of 84-94 above, further comprising determining the proper relative placement of the nozzle and the well before depositing the film former and the at least one active agent in the well.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a perspective view of a roll of pre-formed molds or wells prior to filling.

Fig. 2 is a perspective view showing a deposit device filling a well of the roll of pre-formed molds or wells.

Fig. 3 is an enlarged view of a portion in Fig. 2 showing a deposit device filling a well with a film former composition.

Fig. 4 is an enlarged view of a portion in Fig. 2 showing a deposit device filling a well with active pharmaceutical ingredient with optional excipients, in particulate form.

Fig. 5 is a perspective view showing a drying device deploying hot air currents from above the roll of film wells (which have been already filled).

Fig. 6 is a perspective view showing adhesive being applied to well edges of bottom sheet.

Fig. 7 is a perspective view showing a roll of wells, with films (and drug) deposited, films formed and dried, and guideposts inserted in the ends of the roll of wells for alignment of the top sheet which is placed over the bottom sheet.

Fig. 8 is a perspective view showing a roll of wells, with films (and drug) deposited, films formed and dried, guideposts, and serration of individual doses within the roll of wells.

Fig. 9 is a perspective view showing a finished dosage form removed from a roll of wells, the breakage lines occurring at the lines of serration.

Fig. 10A is a top plan view of a first embodiment of a multilayer oral soluble film made by deposit.

Fig. 10B is a cross-sectional view of first embodiment of a multilayer oral soluble film made by deposit along lines 10B-10B of Fig. 10A.

Fig. 11A is a top plan view of a second embodiment of a multilayer oral soluble film made by deposit.

Fig. 11B is a cross-sectional view of second embodiment of a multilayer oral soluble film made by deposit along lines 11B-11B of Fig. 11A.

Fig. 12 is a schematic view of a system for manufacturing a pharmaceutical active agent-containing oral soluble film by deposit in a pattern.

Fig. 13 is a cross-sectional view of a well contained in a sub-well.

Fig. 14 is a schematic view showing a system and method for pre-releasing the film from the bottom of the mold or well.

Fig. 15 is a plan view of a rectangular-shaped well.

Fig. 16 is a cross-sectional view of the rectangular well along lines 16-16 of Fig. 15.

Fig 17 is a cross-sectional view of a well according to certain embodiments of the invention;

Fig. 18 is an enlarged portion of Fig. 17.

Fig. 19 is an enlarged portion of Fig. 17.

Figs. 20A and 20B are cross-sectional views of a well that is convex and can be pushed to concave to present the film for easy access by the patient.

DETAILED DESCRIPTION OF THE INVENTION

One aspect of the present invention relates to a system for manufacturing an oral soluble film with an active agent, e.g., a pharmaceutical oral soluble film by the deposition of active and film former composition separately into a mold or well.

One aspect of the present invention relates to a system for manufacturing an oral soluble film with an active agent, e.g., a pharmaceutical oral soluble film by the deposition of active pharmaceutical agent(s) and film former together into a mold or well.

One aspect of the present invention relates to a system of continuous manufacture (formation of oral soluble films) and primary packaging of the oral soluble films.

One aspect of the present invention relates to a system for manufacturing an oral soluble film in which the active agent is deposited into a mold or well separately from the film former, and the drug binds or diffuses adequately mixes into the final, dried film matrix.

One aspect of present invention relates to a method of forming an oral soluble film with an active agent, e.g., a pharmaceutical oral soluble film without direct mechanical intervention to spread and/or coat and/or cast the composition into a film, such as by deposit of a sufficiently flowable film former composition into a well or mold and.

One aspect of the present invention relates to the use of a compressed gas to encourage and/or speed the flow of a film composition into a film shape in a mold or well.

One aspect of the present invention relates to the use of a compressed gas to encourage mixing of an active agent with a film former composition in a mold or well.

One aspect of the present invention relates to the use of brief vibration to encourage and/or speed up mixing of an active agent with a film former composition in a mold or well.

One aspect of the present invention relates to the use of brief vibration to encourage and/or speed up the flow of a film composition into a film well shape.

One aspect of the present invention relates to the manufacture of a film-sheet 1 to 40 mils (measured as dry thickness). This is non-limiting and the methodology here allows for thick films and for dermal products.

One aspect of the present invention relates to a mold or well shape that is optimized for film formation by deposit method.

One aspect of the present invention replaces to mold or well material that is selected to be a suitable surface energy substrate to facilitate wetting and spreading of film former composition, i.e. low contact angle and/or surface tension.

One aspect of the present invention relates to pre-treating a mold or well with a surface active agent, a surfactant, or other agent to either promote flow of the film composition, and/or promote easier release of the dried film.

One aspect of the present invention where the surface of the well may have modified textures, indentations, coatings or heat treatment to vary or affect the flow pattern of the film composition.

One aspect of the present invention relates to a composition suitable for making an oral soluble film where the viscosity and/or surface tension and/or interfacial tension of the composition (with the well/mold material, as applicable) is selected to promote flowability of said composition sufficient to form a film in a mold or well, and in certain embodiments to form such

a film rapidly in such mold or well. This categorically teaches away from cast film art in that high viscosity is antithetical to successful formation of a deposit by precluding adequate flowability of the film former composition into a mold or well.

One aspect of the present invention relates to a film former composition with sufficient wettability to mix adequately in a mold or well with a separately deposited active.

One aspect of the present invention relates an oral soluble film made with one or more low molecular weight polymers as film formers

One aspect of the present invention relates to a composition suitable for making an oral soluble film by the deposit method, where such composition is not capable of being wet cast into a film using traditional wet cast coating technologies (e.g. by three roll coater, or doctor blade).

One aspect of the present invention involves an alignment system to ensure the mold or well sheet is aligned with the top sheet. For example, aligning openings on the well sheet and the top sheet may be used so that through, for example, a pin type alignment each is properly oriented to the other.

One aspect of the present invention relates to a drying process that is suitable for the deposited composition to immediately flow into the shape of the mold or well prior to becoming too viscous to flow as a result of loss of solvent effecting viscosity increase.

One aspect of the present invention relates to the material of the mold or well selected that is suitable for the flow of the composition into a film.

One aspect of the present invention relates to the material of the mold or well selected to simultaneously allow the flow of the readily flowing composition while also allowing the dried material to be readily removed or peeled away from the well.

One aspect of the present invention relates to the design of the mold or well so that a user can readily remove the film.

One aspect of the present invention can allow the dosage unit to be sealed (primary packaging) on the same production line as the film is manufactured if desired. Alternatively, the dosage unit can be sealed on an adjacent packaging line. Standard packaging at a later time is also allowable.

One aspect of the invention deals with the stop-start (or stutter) of the film-by-deposit production line, which may be in connection, inter alia, with deposit of a material, drying of the material or drying of a layer, or application of the topsheet.

One aspect of the invention relates to the substrate/laminate layer with pre-formed wells made at line or before line by blister forming methods.

One aspect of the present invention relates to the blisters being collapsible such that when the substrate layer is rolled up on itself, the film within it is loosened enabling easy subsequent removal by the user.

One aspect of the present invention relates to the manufacture and packaging of an oral soluble film, including a multi-layer film, with minimal composition and API loss (less than 30% preferably less than 20%, more preferably less than 10%, even more preferably less than 5%).

One aspect of the present invention relates to a oral soluble film composition that has little or no yield stress. Such compositions are particularly well suited for the present invention (i.e. formation of an oral soluble film by deposit method).

One aspect of the invention involves a rolled adhesive onto the dried bottom sheet/mold/well edges, but excluding the interior of the sheet/mold/wells, so that top sheet can be adhered.

One aspect of the present invention relates to a topsheet on the film wells that is printed for the blister, i.e. not gangprinted.

One aspect of the present invention relates to indicia or identifiers on the individual film that are not gangprinted.

One aspect of the present invention relates to a film former composition with a viscosity below 4000 centipoise, preferably below 3000, preferably below 2000, more preferably below 900

centipoise, still more preferably below 600 centipoise. Such measurements, in the case of a Non-Newtonian film former composition, are measured at low shear rate, < 10 s^{-1}

One aspect of the present invention relates to the use of viscosity reducing agents in oral soluble film compositions. This teaches against the viscosity needed in traditional, wet cast films.

One aspect of the present invention relates to an oral soluble film with sufficiently uniform thickness and appearance for the user, with optional uniform distribution of components in the film. One embodiment of the present invention relates to an oral soluble film that does not have uniform distribution of active agent within the film.

One aspect of the present invention relates to an oral soluble film, made by deposit method, with <20% variability in height, preferably with <10% variability in height (measured from the thickest portion of the film to the thinnest portion, measured vertically). Other embodiments of the oral soluble film of the present invention will have greater variability, particularly where unique shapes are intended with varied film topography

One aspect of the present invention relates to an oral soluble film, made by deposit method, with one or more active agents, e.g., active pharmaceutical agents, wherein the content of said active pharmaceutical agent(s) varies less than 10% from the label claim, preferably less than 5%, preferably less than 2% from the label claim.

One aspect of the present invention relates to a multi-layer film made by deposit method.

One aspect of the present invention relates to the manufacture of a transdermal film, in whole or in part, by the deposit method.

One aspect of the present invention relates to the manufacture of films by deposit for wound care, internal or external to the body.

One aspect of the present invention relates to the manufacture of films by deposit for use in the nasal cavity.

One aspect of the present invention relates to the manufacture of films by deposit for use in the vagina.

One aspect of the present invention elates to the manufacture of films by deposit for use in the anal cavity.

One aspect of this invention is for film comprising a surface numbing agent for use in the skin and in the mouth and in the anus.

While the primary embodiment involves a soluble film for oral use, non-oral uses are expressly contemplated in connection with films of the present invention made by deposit.

The well may in certain embodiments be a flat surface without a "wall." Rather, the film is deposited on a flat substrate. The outward boundaries of the film are determined by one or more of: (a) surface tension of the deposited composition, (b) a spray coating on the flat substrate to define the outward flow of the film, or (c) the flowability of the film forming composition on a given substrate.

In other embodiments the well may simply be an indentation or scored marking on the substrate that prevents flow beyond the scored boundary. In other embodiments a lipophilic material may be deposited as a boundary line in any desired shape and the deposited composition would be repelled by the lipophilic boundary and stay within it.

The composition may be deposited within the well as a single or multiple droplets or sprays at a single centered or off-centered position within the well. Or as multiple discrete droplets or sprays at multiple lateral locations within the well for differential deposition. This may be accomplished by multiple nozzles or, as shown in Fig. 12 by a single nozzle 3 located on a movable X-Y gantry 14 that can move in a lateral (or other) motion to lay droplets or strands of solution (or powder) into the well 2 in various patterns. One or more nozzles may be on a movable x-y gantry that deposits into the well in depositing pattern, a particular geometric shape, or both. The geometric shape may be polygonal, circular, elliptical, zig zag or any other shape caused when the nozzle is not stationary. The shape may involve articulation of the nozzle, movement of the well during deposit or both. During the depositing pattern, the one or more nozzles may be depositing continuously or through one or more droplets or strands of solution (or powder).

In addition to movement on X-Y coordinates, the height of the nozzle or nozzles may be controlled by the gantry or otherwise, in certain aspects of the invention (X-Y-Z coordinates).

In another aspect of the invention that is particularly (though not exclusively) relevant to the use of a nozzle on a gantry, the support for the nozzle, e.g. the gantry, may employ a machine vision system where the vision system is employed to ensure the ongoing correct calibration between the well location and movement of the gantry. For example, if the well alignment should shift over time, the vision system may provide the necessary feedback for the gantry system to auto-correct, such that the nozzle deposit is properly depositing in the intended fashion (i.e. intended placement) in the well. For example, if it is intended for the nozzle to deposit in the center of the well, the vision system confirms location of the well, and it is ensured that the nozzle will deposit in the center of the well. Similarly, if the deposit nozzle is intended to deposit in a particular pattern in the well, the vision system confirms that the deposit nozzle is properly situated to deposit in the desired particular pattern. The vision system includes a camera or other imager or sensor, a processor and software to determine the relation between the well position and the nozzle output.

Simply put, the vision system assures that the nozzle deposits the material in the intended well location or locations. Other non-vision based systems may be employed to ensure the deposit nozzle on the gantry remains calibrated to the intended well location or locations. A similar vision or non vision system may be used where the top sheet is placed on the well, to ensure a desired coordination between the top sheet and well.

In certain embodiments, the x-y or x-y-z gantry itself is capable of moving position on the production line, i.e. not just the nozzle on the gantry but the gantry assembly.

A pin system may be employed analogous to old camera film, where the well is moved through the production line using gears that mesh (or other methods of propulsion that correspond to the holes) with holes at the edge of the web of wells. Optionally, the edge with holes of the web wells is cut in connection with the completion of primary packaging – preferable after drying and application of the top sheet.

In another aspect of the invention, a method of making an oral soluble film, containing at least one active agent, includes providing a well of a predetermined size and/or shape; depositing a film forming composition including at least one active agent in the well, the film forming composition spread within the well by using mechanical means to move the depositing nozzle around to deposit at different locations within the same well to 'paint' different areas of the well with film forming composition in patterns to obtain film with variable thickness or ridges. For example, as shown in Fig. 12, the nozzle 3 can articulate in a swinging fashion as shown by the arrows 15. In this manner, the film former solution can be deposited in a shape selected from the group of: circular, elliptical, polygonal or zig-zag. The nozzle can pulsate on-off during deposit or may be configured to deposit with continuous flow. These methods can allow for the formation of a film with higher solids contents.

One aspect of the oral soluble film where the edge or rim or circumference or border of the film is thicker than the center of the film to improve tear resistance of the film. This may be

accomplished by differential deposition or by modifying the geometry of the well structure. For example, the well structure may have a deeper perimeter at the edge or rim to effect increased thickness at the edge or rim of the film.

In certain embodiments, the edge (or the edge in a particular geography of the film, i.e. not the entire perimeter, edge, rim, circumference) has a thickness that is more than 10% thicker than the center, preferably more than 20% thicker than the center, even more preferably more than 30% thicker than the center. For example and without limitation, at least part of the edge only may have increased thickness over the center.

In certain embodiments, the edge (or the rim, perimeter, rim or circumference) (or the edge in a particular geography of the film, i.e. not the entire perimeter (or rim, or circumference)) has a thickness that is more than 10% thicker than the center of the film or than the film's average thickness, preferably more than 20% thicker than the film's average thickness, even more preferably more than 30% thicker than the film's average thickness. For example, and without limitation, at least part of the edge may have increased thickness over the center. This can be achieved using a well of the type shown in Figs. 17 and 19, described hereinafter.

One aspect of the invention where the well structures may be modified by using 3-D printed or CNC milled or otherwise-fashioned inserts placed within a larger mold to achieve a variety of quickly changeable mold shapes for different shapes and size of film.

One aspect of the invention is to allow for intermittent movement of the well substrate along the production line as opposed to the continuous movement demanded by the wet casting method.

Preferred embodiments of the present invention is described herein with reference to Figs. 1-9, which schematically show examples of the method and system of the present invention. However, applicants' invention is not limited to the particular embodiments/examples shown in the figures.

Fig. 1 shows a roll 1 of pre-formed molds or wells 2 prior to filling by deposit. In other embodiments, the mold or well 2 may be formed on the production line itself from flat roll stock.

Fig. 2 shows a deposit device 3, described in more detail hereinafter, filling a well. The deposit device 3 may be depositing film former composition, an active agent composition with optional excipients, or a film former composition complete with an active agent within it. In Fig. 2, the film former composition, the active agent composition with optional excipients, or a film former composition complete with an active agent are all designated generally with the reference numeral 4.

Fig. 3 shows a deposit device 3 filling a well 2 with a film former composition 4a.

Fig. 4 shows a deposit device 3 filling a well 2 with a composition 4b including active ingredient(s) with optional excipients, in particulate form.

In one aspect of the present invention, a film forming composition 4a is deposited in each well 2 and an active agent composition 4b is deposited in each well 2, the active agent composition 4b being different than the film forming composition 4a. The film forming composition 4a and the active agent composition 4b form an admixture in the well 2. The film forming composition 4a and the active agent composition 4b may be separately deposited in the well 2 at the same time, e.g., through two separate deposit devices 3. Alternatively, depositing of the film forming composition 4a and the active agent composition 4b in each well 2 are carried out sequentially; in this embodiment, it is preferable but not necessary that the active agent composition 4a is first deposited in the well and then the film forming composition 4b is deposited in the well.

Fig. 5 shows a drying device 5 deploying hot air currents from above the roll of film wells 2 (which have been already filled). In certain embodiments, drying occurs in a drying tunnel (here the tunnel is cut away for better visibility).

Fig. 6 shows adhesive 6 being applied to well edges, i.e., to areas of the bottom sheet 1 outside the wells 2 by an applicator 7.

Fig. 7 shows a roll 1 of wells 2, with films (and drug) 4 deposited, films formed and dried, and guideposts 8 inserted in the ends of the roll 1 of wells 2 for alignment of a top sheet 9 which is placed over the bottom sheet 1.

Fig. 8 shows a roll 1 of wells 2, with films (and drug) 4 deposited, films formed and dried, guideposts 8, and serration 11 of individual doses 10 within the roll of wells. Serration can occur in the roll stock prior to deposit of film composition 4 or after the manufacture of film 4.

Fig. 9 shows a finished dosage form 10 removed from a roll 1 of wells 2, the breakage lines occurring at the lines of serration 11.

A summary comparison of films made by certain embodiments of the deposit method of the present invention and films made by wet casting is provided below.

Parameter/Attribute	Wet Cast Oral Soluble Film	Deposit Oral Soluble Film
Viscosity of film former composition	High	Low or optionally high
Flowability of film former composition	Low/None	Low or optionally high
Where Active Drug is added in process	Mixed with film former prior to coating on substrate	Deposited separately from film former composition (or optionally together)
Substrate in Continuous Motion	Coating must occur on substrate in continuous motion	Deposit in mold/well is not continuous (optionally continuous)

Coating substrate removal	Coating substrate must be removed in conversion prior to packaging	Substrate is typically not removed; deposited in final primary packaging
Angle of Flow of film former composition	High angle of flow of film former composition	Low angle of flow of film former composition
Stoke's Law employed to maintain drug content uniformity in film former composition	Stoke's Law employed to maintain drug content uniformity in film former composition	Stoke's Law has virtually no application where drug is deposited separately.
Controlled drying necessary for drug content uniformity	Controlled drying necessary for drug content uniformity	Controlled drying not necessary for drug content uniformity
Cutting of film specific size required to make final dosage form	Cutting of film specific size required to make final dosage form	Cutting of film not required to make final dosage form
Rapid drying required for drug content uniformity?	Rapid drying required for drug content uniformity	Rapid drying not required for drug content uniformity
Active Drug Waste (loss in process)	High API Waste	Low API Waste
Coating steps for Bi-layer film	Typically two separate steps of coating	Can be made in single deposit step.
Cost for Bi-layer	Typically expensive (two steps)	Marginally longer deposit step. Inexpensive

Low Dose Content Uniformity	Potentially challenging	Not challenging
Air bubbles, voids and surface defects create content uniformity issues	Air bubbles, voids and surface defects create content uniformity issues	Air bubbles, voids and surface defects do not create content uniformity issues
Separation of incompatible drug actives in a combination product	Difficult	Simple using separate deposit steps
Film Thickness	Film thickness must be uniform for drug content uniformity	Film thickness can vary as long as volumetrically accurate droplet is deposited
Liquid suspension, solution, emulsion, gel, jellies, jams, mousse, pudding, gelatin, etc.	Can be deposited efficiently but cannot be cast	Deposition is not difficult.

One aspect of the present invention is to enable film formulations which would have not have adequate mechanical properties for traditional oral soluble film manufacturing, i.e. ability to wind into a roll, ability to be trimmed and covered, ability to be released or peeled away from substrate, and ability to be converted in a conventional film packaging machine (e.g. a Doyen Medipharm machine). For example, a formulation that has insufficient tensile strength for

conventional conversion, or a formulation that has propensity for elongation under stress, would be unable to be converted using conventional means but is able to be manufactured using the deposit method.

The drug that is being deposited may be in the form of a powder or a solution in which case the drug solution in the bulk tank from which it is being deposited into wells in aliquots does not have to be stirred. However, it may also be a suspension of fine drug particles that may be continuously and vigorously stirred while the suspension is being deposited in aliquots into wells. Continuous stirring is generally not possible with viscous drug suspensions such as those used in formulations for continuous coating due to the induction of air into the mix which causes film defects and precludes collection of good and uniform product. In the deposit method, the low viscosity generally does not allow air bubbles to form in the film as they are immediately dissipated as the deposited liquid flows into the well as a thin layer. Embodiments where the active drug suspension is separately deposited into the well or mold, it may need to contain none to very low quantities of binder allowing incessant and high-speed mixing thereby preventing settling and ensuring uniformity.

Applicants teach against the fundamental theme of prior film art (Yang et al, Horstman, etc), namely, the use of high viscosity to (i) prevent migration of the active and preserve uniformity of dose content in the mixing stage, (ii) enable the required coating thickness of the film composition, and (iii) prevent migration of the active and preserve content uniformity in the drying stage. Instead, high viscosity (and surface tension) here work contrary to (i) the ability to deposit the film former composition into the well or mold, and (ii) the ability of the film former

to flow (and reasonably rapidly and without mechanical intervention) into a film within the well or mold.

Deposit of a high viscosity film former composition such as those taught by Yang et al. in a well or mold will not generally result in a film at all, but rather simply a dollop-type shape of film former absent physical, mechanical intervention to spread the film former into a film (like a doctor blade, or other coating apparatus). Viscosity and surface tension simply prevent such compositions from flow, let alone sufficient flow to form a film.

It is important to note that to accurately dose and spread film former in a well, a relatively low viscosity is required (and surface tension), otherwise the material will refuse to spread in the well and simple form a dollop of material in part of the well.

Moreover, the embodiments where the drug active is separately deposited in the well or mold, high viscosity and lack of wetting can actually interfere with mixing of the drug active into the film matrix, thereby preventing adequate mixing of drug and film former composition from occurring.

High viscosity is also not needed to enable coating thickness of the composition; in the deposit method of the present invention the film composition can be readily deposited as high as the sides of the well or mold. In certain embodiments, surface tension allows the composition to be deposited higher than the sides of the well or mold, and then shrink below during drying which may form slightly cup shaped films from a side profile.

Film former and active are metered into the wells either singly or by multiple metering devices.

It is important to note that to accurately dose and spread film former in a well, a relatively low viscosity is required (and surface tension), otherwise the material will refuse to wet and spread in the well and simply form a dollop of material in part of the well. Various methods to promote spread are discussed herein.

Preferably, the after deposit, the film former composition will flow into a film in a well or mold within ninety seconds, preferably within sixty seconds, more preferably within twenty seconds, even more preferably within five seconds, and most preferably within one second. By flow into a film, Applicants mean that the film former composition will either reach the ends of the mold/well, or otherwise cease to flow.

The use of one or more depositing nozzles on an x-y (or x-y-z) gantry that deposit as described above may be useful to speed the time it takes for the film former composition to flow into a film. The improvement in time can be demonstrated with comparison to the time it takes for the identical film former composition to flow into a film when deposited in the center of the mold or well. The gantry movement may be combined with specialized nozzle design, the use of pressure, and other techniques taught herein.

This time is important as it will impact production line speed. Output of course may be improved by using a bank of feeders (filling multiple wells forward and horizontally at one time).

Both viscosity and surface tension are connected theoretically to inter-molecular forces, but they are still very different concepts.

Shear Stress is a force that acts on a fluid to cause flow and the viscosity determines velocity gradient. Viscosity is an intrinsic property of the fluid itself. Viscosity is the ratio of the shear stress tensor to the rate of deformation tensor. Roughly speaking, viscosity determines how momentum is transported through a fluid during flow, as it is a measure of resistance to flow.

Contact angle acts not inside the substance, but only on its interfacial boundary with substance of another phase, even if nothing moves. It is not a property of the substance itself, but of a pair of these phases meeting at the boundary. Often the expression "contact angle of water" is used; but what is meant is contact angle of the pair water-air. Combinations water-glass or water-oil have different value of contact angle. Roughly speaking, contact angle says how much energy of interaction is stored when two chemical species are in mutual contact, even in equilibrium.

One way to think about the effective flowability of a film former composition for a given type of surface, is Young's equation. A drop of liquid when placed on a flat, homogenous solid surface comes to equilibrium, assuming a shape which minimizes the total free energy of the system. The angle between the liquid and the solid is called the contact angle, the angle being measured through the liquid. The contact angle may be calculated if the surface tension and interfacial

tension are known, using Young's equation (see en.wikipedia.org/wiki/Wetting#Ideal_solid_surfaces , which is incorporated by reference as if fully stated herein, as retrieved on 3/26/17). For certain embodiments of the present invention, surface tension and interfacial tension are minimized to reduce the contact angle of the system. To wet the substrate well, the contact angle must be $<90^{o}$.

One way to think about the rate of flow or spreading of the composition, is Tanner's law. Tanner's law teaches that the rate of spreading of a droplet is related inversely to the viscosity of the droplet. See Bonn et al, "Wetting and Spreading" (hereby incorporated by reference as if full set forth herein, and Krishnakumar, "Wetting and Spreading Phenomena, available here: guava.physics.uiuc.edu/~nigel/courses/563/Essays_2010/PDF/Krishnakumar.pdf and similarly hereby incorporated by reference as if fully set forth herein).

The preceding teaches away from Yang et al, wherein the film composition yields a high contact angle on the substrate, which allows for relatively thick non-flowing compositions. In fact, wet cast film coatings are so thick and unflowable, Watson has taken the position in its Suboxone ANDA litigation that its film coating should be understood to be a solid immediately after coating: "The physical evidence demonstrates that Watson's casting dispersion forms a viscolelastic solid when the forces of mixing and pumping cease, which happens before the initiation of drying….. The inspection video demonstrates that: (1) by the time Watson's casting dispersion travels up a steep incline for 30 seconds, and prior to any drying, it has already gained sufficient structure to "lock-in" and prevent migration of the active such that the casting dispersion does not flow backwards down the incline , as it would if it were a viscoelastic liquid;

(2) Watson's films are cast as in discrete lanes at the width of the final film, which would not be possible if the casting dispersion were a viscoelastic liquid…" From Document 186, pp. 10-11, Case 1:14-cv-01574-RGA (District Court for Delaware). Thus Watson is stating to the Court that its film composition is simply not flowable at all, absent the mechanical intervention of the coating apparatus

Film compositions of the present invention may be non-Newtonian or Newtonian. It should be noted that in the preferred embodiment, no mechanical force is applied to the film composition after deposit into the mold or well to encourage spreading/flowing of the film former composition. Accordingly, shear thinning or pseudo plastic attributes do not materially affect flowability in the well or mold since there is generally no mechanical source of shear stress other than gravity to affect a reduction in viscosity (as we would see in a coating apparatus).

It is contemplated in certain embodiments that shear force may be achieved by pressurized delivery of film former composition into the well (such shear being affected by the impact of the film former composition against the well). However, there are practical limitations on how much shear can be achieved in this manner with substantial absence of splatter outside of the well. Nozzle design can be optimized to reduce or mitigate splatter. Nozzles may also have check valves and other features such as mechanical shutoff, suction, drip collection trays (or other drip collection systems) to prevent dripping of solutions from the nozzle or prevent strands of solution from the nozzle to the well. Other possible methods of preventing dribbles might be robotically moving the nozzles out and away from the deposit station or positioning a drip

collection tray under the nozzles between depositions. Such methods may also be employed to prevent unintended deposit of solids.

Pressured air may be useful to assist in spread and may be delivered from one or more air nozzles on a moveable gantry. Such air may constitute ambient air pressurized, filtered air pressurized, non-ambient air pressurized, or other gas composition (other than ambient air).

Film compositions of the present invention may have little or no yield stress. In certain embodiments, film compositions of the present invention will have insufficient yield stress to prevent flow on an incline greater than 45%, greater than 25% or even greater than 10%. In certain embodiments, the film composition of the present invention will have a yield stress < 50 pa, preferably <30 pa, most preferably <15 pa.

The focus of the present invention teaches away from the thinking in the cast film art to use high yield stress to prevent sedimentation of drug particles and other components.

Continuous or Stuttered Manufacture

Embodiments of the present invention may employ continuous manufacture or stuttered (intermittent) manufacture.

In conventional wet casting, the substrate must be coated continuously. There is time (and waste) associated with bringing the coating process online to operating parameters with

appropriate coating thickness. As a practical matter, the process must be continuous. This continuous coating typically implies long drying ovens.

Certain embodiments of the deposit method allow for a stuttered manufacturing process. One or more molds/wells is filled. At this time, the mold/well rollstock is stationary or moving (relative to the filler apparatus). After filling, the mold/well can be moved to a dryer. In certain embodiments, the filler may move with the mold/well so as to have no relative speed as between them during filling. Again, the molds or wells may continuously move through the dryer or it may be stationary in the dryer. The dryer apparatus may also be deployed after filling in a single place (i.e. without the mold/well moving).

In many embodiments, the deposit of film former composition and drug (and ensuing flowing into a wet film in the mold/well) is faster than the drying stage. Because deposit is non-continuous, in some embodiments, the mold/wells may be in stage blocks that can be placed or moved on belt feeds into an oven on multiple levels. This allows for a small dryer footprint to accommodate relatively high production.

In other embodiments, there may be two separate banks of feeders, say for multi-layer films. One bank of feeders is placed before an initial drying section. A film is formed (for example, a backing layer). After initial drying, a second feeder bank deposits the next layer (for example, a drug containing layer). After this second feeder bank, there is another drying stage. The line may stutter, at the same time, or separately stutter.

In other embodiments, additional film layers may be deposited before the film enters a drying section. In another embodiment a drug layer may be sprayed or printed on the initially dried layer or layers without additional drying - in this case, the volume of sprayed or deposited solution may be very low or may be composed of a quick drying solvent.

The stuttered option for deposit allows for a very efficient manufacturing in terms of footprint. Skilled artisans will appreciate the various configurations for deposit, drying, and packaging overlay on the molds/wells. A circular or other return layout between filler and dryer may be employed where a follow deposit is desired to be made to an initial dried film layer.

A key advantage is the manufacture of the film product, from start to finished primary packaging, in a single line.

Methods of Deposit

Generally, the materials will be deposited in the well or mold using a flowmeter enabled feeder (any suitable flowmeter and feeder may be employed). The flowmeter may measure mass and/or volumetric flow rate of a liquid or solid. K-tron is a non-limitative example of a suitable feeder. Any suitable apparatus that can reliably deposit film former composition or drug (be it dry or in solution or suspension) may be employed.

Apart from gravity feed, pumps may be employed to feed the material into the well. Speed of deposit is important for line speed/product output. Moreover, it may be desirable to inject material into the mold or well with some additional force beyond gravitational force.

A bank of feeders may be employed to allow for a number of wells/molds across (and forwards) to be simultaneously. Optionally, the bank of feeders may source from a single mother tank, or from a plurality of tanks (or hoppers).

Where the drug is deposited separately, multiple feeders may be employed: one to supply an active drug (or drug combination) (optionally with one or more suitable excipients), and one to supply the film former composition. The drug may be contained in a single mother tank (or hopper), or a plurality of tanks (or hoppers).

If the active drug is a particle, the active drug may be delivered in dry powder form, or in solution (where soluble), suspension or emulsion. One advantage of dry powder form is to avoid the time during which the drug active is in contact with liquid (which can avoid problems with crystallization, drug stability, and the degradation of taste masking or controlled release systems).

Where the drug is soluble, certain embodiments may use a pH for the drug solution optimized for solubility (where pH buffer of the film former composition uses a different, stronger buffer to control the ultimate pH of the dosage form). The drug may be solubilized in any appropriate polar or non-polar solvent.

One advantage of a solution, suspension or emulsion, is to promote mixing of the pharmaceutically active agent with the film former composition, though it is demonstrated in

examples below that dry particles can be adequately mixed with separately metered film former compositions.

The feeders may employ nozzles that are optimized to promote mixing. For example, the nozzle may be selected to broadly disperse material in the well. The nozzle may be aimed to initiate flow in the well or mold. Where the drug is administered separately, the nozzle depositing the drug and the nozzle depositing the film former composition may be aimed in a complimentary fashion to promote mixing of the two. As a non-limitative example, the nozzles may direct the flow of the film former composition and drug in opposite directions. Nozzles may have a design to encourage mixing. In addition, nozzles may be used that have a spray pattern which is matched or otherwise calibrated to the well dimension.

Nozzles can be articulated to move position relative to the geography of the well or mold during deposit. Such articulation may be useful for a range of purposes, including without limitation: (a) more evenly spreading the polymer and/or drug in the well or mold; (b) permitting faster deposit of the material to shorten the time it takes to spread the material adequately in the mold or well; (c) deposit a film former composition that would not readily self-flow to the ends of the well or mold if it were deposited in a single place in the well or mold (c) with a less flowable composition, to create an intentional (intended) thickness in certain geographies of the film.

Nozzle articulation, when depositing, may be circular, square, trapezoidal, or any shape. It may deposit in parallel lines, or in zig-zag fashion. The nozzle may disperse continuously during

articulation (continuous flow), or may pulsate on-off, in some cases coordinated with the movement-geography of the nozzle articulation.

Pressure from the nozzle may be constant or may pulsate intentionally.

The above-described nozzle articulation is in addition to embodiments where the feeder bank may itself move in a coordinated fashion with the wells or molds to be filled.

Where the drug is administered separately from the film former composition, the two may be deposited in sequence, or contemporaneously (in which case the deposit rates may be calibrated in terms of time), or metered in a rotating sequence (for example and without limitation, film former composition, drug: drug, film former composition). Where multiple drugs, and/or multiple film layers are used, the sequences can become more coupled (for example, and without limitation): Drug, film former composition, drug, film former composition. Film former composition, drug, film former composition, drug, film former composition. Backing layer composition, drug, film former composition. Backing layer composition, film former composition, drug. Drug, film former composition, backing layer composition. Film former composition, drug, backing layer composition. These sequences are non-limitative examples.

Where delivered separately, each of the film former composition and the drug (be it in particulate, solution, suspension, emulsion etc) may optionally be paired with any suitable excipient.

Separate administration of film former composition from drug is the preferred embodiment. First, the viscosities of a film former composition to resist sedimentation of the active would be too high for the film-by-deposit method of the present invention. Second, even soluble drugs may tend to come out of solubility in the film former composition, due to the relative low levels of solvent, interaction with other materials in the film former composition, and other chemical processes. Generally, greater control and reliability of target dose deposit is associated with separate administration of drug.

Drugs may be separately and/or sequentially deposited in the case of incompatible drugs. For example, multiple layers may deposited, each with a different active. In certain embodiments, the second layer is deposited after the preceding lawyer has been dried. In some instances, the active and the film former and the excipients could all be in one mix and dispensed simultaneously through a single deposition from one deposer. In embodiments in which the second layer deposited after the first layer is dried, it could be on top and include, without limitation, active in sustained release form, taste masking, absorption enhancers, pH modifiers and other modifiers such as an acid and base to produce effervescence. When introduced however, with things like coloring the mix, the top layer could become the bottom re the patient directions.

Separate deposit of drugs may be particularly desirable when one active drug takes a different form from that of the other, i.e., one drug is an oil, and the second is a powder. Or, one drug is a resin, and the second is a powder.

It may be desirable to heat the film former composition to promote flowability prior to, or after deposited in the mold or well. Attention must be paid to degradation temperature, and the sustained temperature should not exceed the drug's known degradation temperature. Temperature increase will tend to decrease viscosity and surface tension provided that the solvent is not permitted to escape (or otherwise not replenished).

The Well or Mold

In this application, we use the terms well and mold interchangeably.

The well or mold will generally be of suitable depth to contain the wet height of the desired film composition. As a practical matter, the film tends to reduce in thickness when dried.

The well or mold may be pretreated with silicone, hydrophobic agents, surfactants or and other suitable material that promotes flow of the film composition and/or promotes release of the final dry film from the well or mold. In certain embodiments, the pre-treatment agent to promote release is a powder. Preferably, the powder is not soluble (or substantially insoluble) in water or other solvent deposited with the film forming composition. In certain embodiments, the pretreatment agent is combined with a sweetener and/or flavor so as to avoid imparting unpleasant taste to film dosage unit.

The pretreatment agent may be applied to the forming material before or after the formation of the well or mold. However, in preferred embodiments it is applied after formation of the well or

mold, and preferably via a spray method. Individual spray pump nozzles may be employed, particularly to avoid or substantially avoid application of the pre-treatment agent to the outer portion of the well or mold where the top sheet is sealed.

Round shapes of the well or mold are desirable, but non limiting, to form a round film. Circular shapes may be particularly desirable but square or rectangular forms are also possible, as shown in Figs. 15 and 16. In the case of circular shapes, the film composition can be deposited in the center and flow outward. Any regular or irregular polygonal shape may also be possible. The mold or well may also be shaped for form three dimensional attributes on the bottom of the film.

The sides of the well or mold may be perpendicular or angled (outward from the planar bottom surface) as shown in Figs. 15 and 16. The sides may be curved, and the bottom may be curved.

In certain embodiments, the well or mold is sufficiently flexible to allow a consumer to readily push the bottom of the well or mold up to present the film for easy access by the patient. In one embodiment shown in Figs. 20A and 20B, the well 2 is convex (see Fig. 20A) but can be pushed to concave (see Fig. 20B) to present the film 4 for easy access by the patient. In certain embodiments, when pushed to concave, the well stays concave. In other embodiments, the well snaps back to convex when support is removed.

In other embodiments, the sides of the well are designed to collapse upwards towards the top sheet (typically after the top sheet has been removed prior to use) to present to film for easier access. For example, as shown in Figs. 17 and 18, the sides of the well 2 may be formed like or

in an accordion shape 18 as more clearly shown in Fig. 18. Accordion folds 18 may be angles (i.e. straight line folds, or curves, wavy etc.). The well may collapse upwards will occur when the bottom is pushed up, and the well may be turned "inside out". In other embodiments, the well sides may be formed with an intended weak point or weak points to facilitate the collapse upwards of the well (or again, its turning inside out).

As shown in Figs. 17 and the enlarged view in Fig. 19, the well 2 can have a portion 19 at the edge (or the rim, perimeter, rim or circumference) (or the edge in a particular geography of the well, i.e. not the entire perimeter (or rim, or circumference)) shaped to provide a film formed therein with a thickness that is more than 10% thicker than the center of the film or than the film's average thickness as described earlier.

The well or mold material must be able to withstand drying temperatures of the drying process, without substantially deviating from its intended shape.

In certain embodiments, the mold or well is formed using mechanical tools (including without limitation, dies or stamps) as part of the continuous production process. For example, the process may begin with a suitable, flexible rollstock in which the required wells are formed by a die tooling, such formation occurring prior to the deposit step in production.

The well or mold may be thermoformed, cold-formed, thermo-cold-formed, or formed using any other known process. Where the well or mold is thermoformed or otherwise heated in

connection with in-line formation, it may be desirable to chill or cool the well or mold prior to the film deposit stage.

The well or mold may take various forms and shapes, typically configured to receive a single dose. However, in certain embodiments, the well or mold may accommodate a plurality of doses.

The outer rim of the well or mold may rise at a gentle (acute) angle from the bottom of the well or mold (the "side angle"). The use of a gentle (acute) angle may permit the use of substrate materials for which more severe angles (for example, right angles or tending towards 90 degrees) overly stress the substrate material. For example, as shown in Fig. 19, the side angle α of the well is preferably acute, more preferably less than 60 degrees, still more preferably less than 45 degrees, most preferably less than 30 degrees. Comparable curves may be employed.

The use of gentle side angles may permit more ready use of substrate materials to form the well that are more prone to stress fracture when formed into severe angles. For example, metal or substantially metal foils, such as aluminum may have this issue.

In certain embodiments, the well or mold is sufficiently flexible and shallow enough to allow for the well or mold, after deposit, drying, and application of top sheet, to be rolled onto itself after drying. In other embodiments, the wells or molds or cut in blocks and stacked after application of the top sheet.

In most embodiments, the area of the mold or well defines the dimensions of the film. The mold or well is of fixed size. Generally, the mold or well with have a deposit surface of 2 square inches or less, preferably 1.5 square inches or less. Larger size are possible but smaller sizes are preferred for comfort (in oral use), as well as to speed flow of the film composition to ultimate dimensions (i.e. a shorter distance to travel).

In certain embodiments, the molds or wells are fixed and the dried films are removed from said molds or wells which can then be reused.

In some embodiments, the well may have an annular shape such that the film forming composition is not deposited in the center of the well but around the center to create a dried film shape with a hole or multiple holes. In one embodiment, the film is in the shape of a circle with a hole in the center, akin to a doughnut.

In certain embodiments, the well or mold is made of metal foil, e.g., aluminum foil, or plastics, and combinations. Suitable materials may include, without limitation, polyvinyl chloride (PVC), polyethylene (PE), polypropylene (PP), polyester (PET), polystyrene, MYLAR-**PET**, Copolyesters, Polyvinylidene chloride (PVDC), Polychlorotrifluoro ethylene (PCTFE), cyclic olefin copolymers (COC) or polymers (COP), monomer polyethylene (LDPE or HDPE), Ethylene vinyl alcohol (EVOH), Aclar, paper aluminum combinations, paper/PET/aluminum laminates, and other aluminum based laminates.

It some embodiments, a substrate may be inserted (an insert) into the bottom of the well, after well formation and prior to deposit of the film materials. Generally, the insert is hydrophobic. The insert however may not necessarily be uniform in properties; for example the insert may be hydrophobic in certain geographies, have non-uniform surface and other attributes intended to help shape the film, and otherwise release the film. The insert may be free-floating or adhered to the surface of the well.

Heating the Well in Connection with Drying

The use of the well or mold is applied in this case with novelty insofar as the well is used (in most embodiments) in film formation (when film is deposited on the well as a substrate), film drying and final primary packaging.

As a result, in most embodiments, the well material used must be capable of withstanding heat exposure associated with the drying method selected.

Softening of the well material (or components of the well material in the case of laminate or other multi-layer material) may be experienced where the well material approaches (meets or exceeds) its softening point or melting point.

Softening of the well material may be addressed by having the well 2 contained in a rigid sub-well 16 on the conveyor as shown, e.g., in Fig. 13, in a shape substantially mated or otherwise adapted to the well 2. The sub-well 16 will typically be larger than the well 2, in order to

accommodate the well 2. In certain embodiments, the sub-well shape mirrors the shape of the well so that the well 2 can be supported when and if the well softens due to temperature.

The sub-well provides support for a well or mold that is softening from heat. The sub-well on the conveyor may be chilled or otherwise temperature controlled, either prior to entering the drier or while moving through the dryer. Softening is generally acceptable provided that substantially no (or no) leaching occurs, or no leaching of an unacceptable impurity occurs, and provided the final well shape is as intended.

In certain embodiments, the sub-well is chilled, prior to deposit, to 15 C or below, to 12.5C or below, or to 10C or below. In certain embodiments, the sub-well is chilled to maintain a temperature of at least 10C below the temperature of air currents in the oven, at least 20C below the temperature of air currents in the oven, at least 30C below the temperature of air currents in the oven, or at least 40C below the temperature of air currents in the oven.

The sub-well may also be heated. In some embodiments, the sub-well comprises a heating element. On other embodiments, the sub-well is heated, including without limitation by hot air currents, prior to deposit of the film solution, or after deposit and prior to entering the dryer.

The sub-well may be created by thermoforming of substrates that may be composed of a polymeric monolayer or that may be laminate structures composed of various polymeric compositions. The substrate is composed of materials that can withstand the temperature of drying without substantially deforming and altering the geometry or dimensions of the

thermoformed well or otherwise warping and preventing the structure from remaining flat on the drying surface. If the substrate structure is made of malleable materials, the sub-well may be cold formed by pressure using suitable tooling.

The Drying Process

Typically, the film is dried in the well or mold. Drying can occur with little consideration to migration of drug, unlike traditional film wet casting. One consideration relates to enabling suitable mixing of the drug (in embodiments where the drug is separately administered from the film forming composition) into the film matrix.

Some consideration may be directed to ultimate release properties of the film.

Consideration is given to speed, energy use and efficiency of drying, sufficient evacuation of solvent, and minimizing visible imperfections on the film.

Another important distinction, is drying time. In conventional wet casting, the aim is to rapidly dry the film to prevent migration of the active. For example, US '277 claim 1 describes "rapidly increasing the viscosity of said polymer matrix upon initiation of drying within about the first 4 minutes to maintain said uniform distribution of said pharmaceutical active by locking-in or substantially preventing migration of said pharmaceutical active."

Because the present invention meters the desired drug loading, there is no concern for agglomeration of drug from a content uniformity perspective. This allows for longer drying

times. Such longer drying times can serve a variety of purposes, and can be particularly useful in connection thicker films or for actives that are particularly heat sensitive.

For certain actives, it may be desirable to allow the film to dry at ambient conditions, or even controlled, chilled conditions. This may be particularly desirable for heat-labile materials or other heat-sensitive active materials such as biologics including antibodies, antigens, vaccines, proteins, peptides and enzymes.

The solvent or solvents may be partially, substantially or entirely lyophilized.

At the same time, more rapid drying times can be effected as compared with traditional casting, without concern for disruptions to the top of the film surface.

Since cast film requires viscosity rapidly for uniformity of dosage, specific drying is described, oriented towards early bottom drying to prevent volatile release of solvent and disruption of uniformity. On the other hand, the system herein described does not have that requirement and hence simplified top drying, not limited to air, infrared etc. is very workable.

High levels of convection (i.e. airflow) may be desired to maximize heating while the actual air temperature is below the melting temperature of the well material (or well material components). Temperature ranges may be selected to balance sensitivity of the active component with requirements for rapid throughput. For typical pharmaceutical chemicals a drying range from 50C to 225 C is preferred, with a range from 75-175 C more preferred and a range from 100-

150C most preferred. For biological active ingredients, temperatures from 30-100C are preferred with a temperature range from 40-80 more preferred and a range from 50-70 most preferred

In certain embodiments, the air temperature in the oven is at least 40% below the melting temperature of the well material, preferably at least 25% below the melting temperature of the well material, or more preferably at least 10% below the melting temperature of the well material. In certain embodiments, the air temperature may be 40%-15% below the melting temperature of the well material, preferably 40%-30% below the melting temperature or the well material, most preferably 25% to 15% below the melting temperature of the well material.

In other embodiments, the melting temperature of the well material may be exceeded, principally for short durations. In other embodiments, the air temperature may be between the softening point and melting point of the well material.

Convection speeds, and the direction of air flow must be selected so as not to disrupt the film's positioning in the well (bluntly, the air flow cannot literally blow deposited solution or the film out of the well or wells). In certain embodiments, air flow is 20 m/s or greater, 30 m/s or greater, or 40 m/s or greater. Air flow may be directed down directly onto the film the hold the film in place, or directed to the sides of the oven to create a circulatory or air convection effect. What is critical to understand is that the film is not part of a larger film web, as in casting, and so in theory may be dislodged, depending on the strength of adhesion of the film, and air currents associated with the well. But at the same, time, there is greater flexibility in drying because migration of drug in the web is eliminated as an issue.

Infared, microwave, sonic, ultrasonic, acoustic whistles or other acoustic devices, and other known methods of drying may be employed, either alone or in combination with other methods, including air drying. Acoustic whistles together with hot air drying is a preferred method. Such combination approaches may afford more efficient drying cycles, including reduced temperature, lower heat exposure time, and improved energy efficiency.

While surface disturbances associated with sonic, ultrasonic and acoustic devices can be a cause of surface mottle (as is associated with disfavor for the commercial use of sonic drying), the fact that API migration is not of concern where a film is made by deposit in a mold or well, allows for its use.

The sub-well(s) may be heated and may comprise a heater. The sub-well heater is preferably a resistive heater, and the temperature may cycle up and down at different points of the manufacturing process. Sub-well heat may be used to promote flow during the deposit stage, and to speed drying during the drying phase.

Taste Masking

All currently known (and future) methods of taste masking may be employed, including flavors, sweeteners, bitter masking agents, coated particles, ion exchange resins and other methods. A significant advantage of the present method is that the drug residence time can be minimized.

For example, where the drug is deposited separately from the film former, the drug can be completely without solvent. As a non-limitative example, drug in an ion exchange complex can be metered into the well, or coated drug particles. This means that the only exposure to water (or other solvent) in the film forming process is the brief period when the drug is mixed with the film former composition until the solvent is dried.

Preferably, taste masked particles have a particle size with a diameter no greater than the dried height of the film itself. Consideration may also be given to mouthfeel. Preferably for mouthfeel particle size is below 300 microns, preferably below 200 microns most preferably below 100 microns.

It is noted that the deposit method of making films taught herein offers a particular advantage for taste masking, namely, the ability to minimize the time that controlled release drug particles (or complexes) are subject to a solvent.

In the method where the drug active is deposited separately from the film former composition, the drug particles (or complexes) are exposed to the solvent used to hydrate the film former for the very brief period between deposit of the drug particles (or complexes) and the time it takes to substantially remove the solvent by drying. This can have also advantages even where neat drug is used (e.g. to avoid a drug from partially solubilizing in the solvent and then crystallizing).

Accordingly, total residence time of the drug with liquid solvent may be less than fifteen minutes, preferably less than ten minutes, more preferably less than five minutes, and most

preferably less than two minutes. Such low residence times are also of utility with taste masked or controlled release drug particles or complexes.

Controlled Release

The term "controlled release" is intended to mean the release of active at a pre-selected or desired rate. This rate will vary depending upon the application. Desirable rates include fast or immediate release profiles as well as delayed, sustained or sequential release. Combinations of release patterns, such as initial spiked release followed by lower levels of sustained release of active are contemplated. Pulsed drug releases are also contemplated. A non limiting example would be where immediate acting drug is separately deposited together with or separate from the film former and a second or third deposit of drug with a differing release pattern is added.

In another embodiment, controlled release active is deposited in one part of the film, and immediate release active is deposited in another (or they may be mixed together). Such embodiments may be combined with shapes that have varying degrees of thickness, or two joined sections (like the shapes discussed in connection with film scoring), or any other shapes disclosed herein.

Scoring, or partial scoring (weak tear points, with holes and/or reduced thickness) can be employed to ease dose titration. Holes, or depressions, may also be useful to encourage disintegration of the film or of a particular film layer. Holes or depressions may be made mechanically, using lasers or comparable devices. In the case of a laser or comparable device, a particular well material should be selected that can withstand the beam. Reflective well material

is a preferred embodiment, particularly for use with lasers.

The polymers that are chosen for the films of the present invention may also be chosen to allow for controlled disintegration of the active. This may be achieved by providing a substantially water insoluble film that incorporates an active that will be released from the film over time. This may be accomplished by incorporating a variety of different soluble or insoluble polymers and may also include biodegradable polymers in combination. Alternatively, coated controlled release active particles may be incorporated into a readily soluble film matrix to achieve the controlled release property of the active inside the digestive system upon consumption.

Films that provide a controlled release of the active are particularly useful for buccal, gingival, sublingual and vaginal applications. The films of the present invention are particularly useful where mucosal membranes or mucosal fluid is present due to their ability to readily wet and adhere to these areas. In addition, this invention would allow for a barrier layer to be metered in the well at some time after the initial well contents have solidified, thus making a buccal/barrier product. Such barrier layer (soluble or insoluble) may also be deposited first in certain embodiments.

A method of using the film comprises applying the film to a buccal area of a human or animal, applying the film to a sublingual area of a human or animal, applying the film inside a vagina of a human or animal or administering the film per-orally to a human or animal.

The convenience of administering a single dose of a medication which releases active ingredients

in a controlled fashion over an extended period of time as opposed to the administration of a number of single doses at regular intervals has long been recognized in the pharmaceutical arts. The advantage to the patient and clinician in having consistent and uniform blood levels of medication over an extended period of time are likewise recognized. The advantages of a variety of sustained release dosage forms are well known. However, the preparation of a film that provides the controlled release of an active has advantages in addition to those well-known for controlled release tablets. For example, thin films are difficult to inadvertently aspirate and provide an increased patient compliance because they need not be swallowed like a tablet. Moreover, certain embodiments of the inventive films are designed to adhere to the buccal cavity and tongue, where they controllably dissolve. Furthermore, thin films may not be crushed in the manner of controlled release tablets which is a problem leading to abuse of drugs such as Oxycontin. Furthermore, as mentioned the sequential numbering of the unit dose wells allows for identification of a source of the abusive drugs, providing the pharmacist notes the identification indicia during dispensing.

The actives employed in the present invention may be incorporated into the film compositions of the present invention in a controlled release form. For example, particles of drug may be coated with polymers such as ethyl cellulose or polymethacrylate, commercially available under brand names such as Aquacoat ECD and Eudragit E-100, respectively. Solutions of drug may also be absorbed on such polymer materials and incorporated into the inventive film compositions. Other components such as fats and waxes, as well as sweeteners and/or flavors may also be employed in such controlled release compositions.

Film Thickness

Films are typically understood to be up to 10 mils in thickness (final product as dried), and above ten mils the product is referred to in a sheet. For ease of reference, references herein to film are understood to apply film (sheet) both up to, and beyond 10 mils in thickness. Films of the present invention may be 1-200 mils, preferably 3-20 mils, most preferably 5 to 15 mils. Thickness may be augmented above the foregoing thicknesses, including without limitation, for dermal use of the end product.

Guided Placement

The mold or well becomes the bottom of the final package and only requires the guided placement of a top sheet which completes the package and the dose unit is merely cut or weakened from the dosage next to it. By guided placement is meant that markers, physical or printed align the top sheet so that cutting of the final unit dosage unit aligns readily with the cutter or perforator. In addition, full labeling requirements may be resident on the top sheet and bottom wells. In certain embodiments, the top sheet is not gang printed but rather corresponds to the well or well plurality representing a single carton. Guided placement may be achieved using a vision system.

Drugs affected by Hydrolysis

Certain drugs (and inactive ingredients) can have negative issues – typically stability – associated with hydrolysis. This can make such drugs or other ingredients difficult or even

impossible to manufacture in conventional aqueous film casting. However, non-aqueous film manufacturing alternatives, like hot melt extrusion, present their own limitations.

In certain embodiments of the present invention, drugs (and inactive ingredients) susceptible to hydrolysis are deposited in or with a hydrophobic material. For example, and without limitation, with an oil. An emulsifier is also added; preferably separately from the drug, and preferably after drying is commenced. When the film is in contact with saliva or other bodily fluids, the film forms or tends to form an emulsion. The resulting film composition has the merit if a drug or other active that has been added in a hydrophobic medium, but without the film disintegration and/or mouth feel issues that would be presented by the hydrophobic medium or media. This may be particularly useful with cannabinoids that may have issues with hydrolysis, and the method may be applied to cannabis oils, where an emulsifier is separately deposited.

Content Uniformity

The most substantial problem in cast films is the difficulty to have a uniform dosage in a film which is cast with the active diluted by a large number of film formers and other additives plus a time profile for casting plus the fact that true uniformity is never present in all parts of a cast film. Hence a cast film is dependent on the size of the film to meet FDA guidelines.

Ideally, as we will see the film forming materials and the active should be deposited from a separate source and into a well of a fixed size.

An aspect of the present invention is adequate mixing of the drug and film former composition, not from the perspective of uniform distribution of drug in the film, but rather adequately

containing the dose of the drug within the final dried film matrix. This means that substantially all of the drug is contained within the film matrix in most embodiments, meaning the drug is substantially subsumed within the film. However, in certain embodiments, the drug will be deposited and remain on the top surface of the film, or remain on the bottom surface of the film. A polymeric binder may be used when the drug is deposited to ensure that it remains adhered to the film.

Mechanical intervention (Absence of in Film Formation)

Thematically, the Applicants teach low viscosity of the film former composition to form a film in the mold or well. This system teaches away from the high viscosities relied upon for content uniformity equilibrium in cast film.

This patent teaches against the main fundamental of prior film art, namely, the use of high viscosity to prevent migration of the active and preserve uniformity of dose content. Instead, high viscosity here works contrary to the deposition of the film former's dispersion in the well. Accuracy of the active is instead preserved by the direct deposition into the well contains the film former.

By mechanical intervention, we mean physical contact with the film composition to spread the film composition, e.g. a three roll coating apparatus, a doctor blade, or equivalent coating technique.

The high viscosity (and high surface and interfacial tensions) of the prior art (see Watson reference to non-flowing solid/film), required mechanical intervention (via the coating apparatus) to apply as a film. The film compositions of the prior art simply lack the spreading or flow characteristics to make films deposited in wells.

However, it is contemplated that non mechanical compressed air and/or vibration and/or brief ultrasound may be employed to encourage flow of the film composition into a film in the mold or well or surface active agents to reduce surface tension or substrates to reduce contact angle to promote wetting and spreading of film composition. One or more of these techniques may be used together with a deposit nozzle or nozzles on a moveable gantry.

In the case of compressed air used to encourage flow, it is preferable to use ambient temperature compressed air, or preferably chilled compressed air so as to minimize film drying that can interfere with the intended flow of the composition. Compressed air may come from one or more nozzles, which may be configured to blow air in various directions. One or more air curtains may be employed that traverse multiples wells or molds. The air nozzles may also oscillate to push the liquid toward all corners of the well.

In certain, limited embodiments of the present invention, mechanical intervention may be employed to spread the composition into a film within the well or mold.

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Printing/Embossing

Once the film is dry, it is possible to print or emboss an identifier on the film dosage form. For printing, individual print heads are typically required. One advantage of the current invention is that printing can be targeted and calibrated in a precise location on the film. Also, the well may have a chevron such that it leaves an imprint identity on the dried film.

The print head is small enough to extend into the well in most embodiments; i.e., the print head dimensions are smaller than the well dimensions. Typically, there is a bank of print heads. As with the feeder bank, the line may stutter for the print head bank. Alternatively, the identifier may be embossed, either by embossing the dried film, are embossing a logo into the dried film by a shape at the bottom of the well. Such embossment is uniquely possible with films made by deposit. In a preferred embodiments, an inkjet (or other known method) sprays the identifier onto the film from over the planar surface of the top of the well. The inkjet system may have multiple inkjets and may be placed on movable x-y-z gantry above the molds and wells. The inkjet printing head may be larger than the well when printing from a distance above the well.

Multi-layer Films

Multi layer films are possible with this methodology simply by addition depositions of actives, or additional film compositions in the manufacturing process. For example, a semi insoluble (or insoluble) backing layer may be separately deposited on a deposited film. This may be done after the first layer is dried, or where density and miscibility will permit separate deposit on non-dried layers, on a non-dried layer. Similarly, a special layer of muco-adhesive, permeation enhancers, or other excipients disclosed herein may be deposited separately where desired. A

multi-layer film with the same active in each layer may be formed, where one layer has different properties or a carries a controlled release version of the same active. In other embodiments different layers may contain diffent drug actives.

With films of the present invention, it is possible to make a multilayer film wherein one layer has a different shape from the other layer. For example, semi-soluble layer without drug might be a square and a drug containing film might be deposited on top that drys in a circle. Countless other permutations are possible, in which the shape of one layer is different from the shape of a second layer, in a multi-layer film. Divergence of shape can perform a variety of functions. For example, where there is a backing layer in a buccal film, it may be desired that the backing layer extends past the drug containing layer that is against the buccal mucosa.

Covering the Mold or Well

It is contemplated that the mold or well will be covered and sealed as part of a continuous manufacturing process. It is important then that consideration be given relative to ambient humidity prior to sealing the mold or well to avoid bringing excess moisture into the package. It may be desirable to cool the film containing well or mold, or use other method (compressed air, nitrogen or other gas) to reduce humidity prior to packaging.

Various forms of guided placement may be employed to ensure alignment of the mold or well with the top covering. In other embodiments, guided placement is not needed, particularly where the top covering is gang printed.

The top covering will typically be foil, aclar, or other suitable sheet like material with suitable barrier properties to ensure stability of the product for the intended area of use (see ICH global guidelines).

The wells may be filled with nitrogen or other gas (other than ambient air) prior to sealing.

The final package may be child resistant, meaning the well and topsheet primary package may be child resistant. Alternatively, the primary package may be placed in a child resistant outer container or package. In a crude embodiment, a flexible blister of films may be placed in a child resistant bottle, or placed in child resistant outer where the blister is anchored or attached to the child resistant outer.

The molds or wells may be joined together in a group of packages or may be separated. Such separation may occur at the time of filling/deposit or later, i.e. after drying.

The Dried Film

Thematically, film formation by deposit presents much more flexibility than conventional wet casting. This is because in conventional wet casting, uniform distribution of active within the film is necessary so that when cut into final pieces the individual film doses will meet drug content label claims.

In contrast, here the desired level of drug is accurately metered into the mold or well along with the film former composition. Drug migration or agglomeration is not really an issue.

The dried film must have only minimal mechanical strength to allow it to be released from the mold or well. A given film formulation's propensity to elongation is acceptable. Tensile strength and elasticity may be minimal.

The dried film must simply be strong enough for release and use by the consumer.

Issues like surface mottle, or voids do not represent drug content defects, and so are judged on the basis of consumer acceptability.

The dried film of the present invention preferably has less than 10% variability in height (measured from the thickest portion of the film to the thinnest portion, measured vertically). In certain embodiments, additional variability may be acceptable or preferred for a wedged or tapered shape.

Preferably, substantially all of the drug is contained within the dried film matrix in most embodiments. However, in certain embodiments, the drug will be deposited and remain on the top surface of the film, or remain on the bottom surface of the film.

Films made by deposit may comprise non-homogeneous liquid phases, such as emulsions, or loose gels exhibiting syneresis or liquid crystalline mesomorphic phases may also be made by deposit. Films made with such attributes may yield film with unusual visual appearance and

textures. Such unusual textures may promote rapid disintegration and or rapid absorption of the drug actives contained therein.

Moisture Levels

In the case of wet cast films, there is an spoken adage: "the wetter the better." What this means is that relatively high moisture content is associated with easy-to-process films, bearing in mind the mechanical properties required in wet casting, which includes rolling the dried film onto itself to form a roll after drying. As a practical matter, wet cast films that are commercially manufactured have a moisture level of 7-10%.

By commercially manufactured, we mean a product made in a batch size of at least 100,000 doses. Films may be cast with lower moisture levels, but this is typically performed at bench scale, where the films are not rolled onto themselves but simply dried in an oven after casting (and left essentially flat on the substrate on which they were cast).

Films of the deposit method may be dried to a lower moisture level, i.e. a solvent (typically water) content of less than 10%, preferably less than 5%, and even more preferable below 3%. It is possible to dry films of the deposit level to a moisture level of below 2%.

Films of the deposit method, manufactured at commercial scale, may be dried to a solvent (typically water) content of 2-6%, or a higher range of 3-5%.

These low moisture levels have applicability for improved shelf life duration, as well as for actives that are particularly sensitive to moisture levels, for example and without limitation, certain vaccines, certain proteins, and other active and bioactive substances. Low moisture levels in dry films are particularly desirable for films containing cannabinoids, including in connection with stability of the cannabinoid(s) in the film.

Film by deposit enables the manufacture of films with lower moisture content than commercial wet casting; film by deposit may also be used in rare instances to make films with higher moisture content than commercial wet cast films.

It is not practicable in commercial wet cast films to exceed certain moisture levels because the "wet" dried film will tend to adhere to both surfaces when rolled onto itself. Excessive tack and stickiness make this impracticable.

However, in film by deposit, in special cases where high moisture contents are desired, it is possible to "dry" the commercial manufactured film to 10% solvent (water) or greater, 12.5% or greater, 15% or greater, or even as much as 20% solvent (water), or greater. In film be deposit, moisture content may be 12.5% to 25%, or 15% to 20%. Such high moisture films may have moisture domains within the film. Some films will have a gel-like center. Such high moisture films may be single layer, or multilayer. Such films may have unique application where, for stability or bioavailability reasons, the active is intended to be dissolved in, or in close proximity or contact to moisture.

The level of moisture in the film prior to sealing the blister well may be measured in-line within the well using a non-contact probe such as a near infrared (NIR) probe.

Pre-Releasing the Film

In some embodiments, it may be desirable to take steps to pre-release the film from the bottom of the mold or well (such pre-release may be in whole or in part). For example, a roller may be employed with a surface that promotes release of the film from the bottom of the mold or well. Multiple rollers may be employed to crinkle the well (or a plurality of wells), pushing the well up from its formed shape and thereby helping to release the film. The film package may be bent lengthwise, or sidewise. The wells may be bent and unbent by the rollers. For example, as shown in Fig. 14, a sheet 1 with a plurality of wells 2 containing the film, which may be a single layer film or, as shown in Fig. 14 by way of example only a multilayer film 12, 13, and top sheet or covering 17 is bent and unbent around rollers 18, 19 to promote release of the dried film. In some embodiments, there is a top and bottom roller (or one or more) simultaneously operating on the wells. One or more roller have protrusions, or a rough surface to facilitate release.

Other methods may be employed to physically disturb the well to promote release of the dried film.

This step may occur prior to, or after, the covering 17 is placed in top of the mold or the well. The purpose is to make it easier for the patient to remove the film from the mold or well for use. Vacuum may also be employed for this purpose.

In other embodiments, the consumer pre-releases the film by pushing a convexity in the well into a concavity (where the well is formed with a convexity for this purpose). Other methods are discussed herein. Whereas typical blister wells have sharp angles of almost 90 degrees from the web axis, wells designed for deposition may have much shallower angles. Angles may be from 15-75 degrees or more preferably 30-60 degrees or most preferably 40-50 degrees. The angled wells allow the eversion of the well structure by pushing the well from below to change the well bottom from concave to convex, allowing the film to be easily removed from the convex well bottom. The well walls may also have convex or concave curvature to facilitate eversion.

Mechanical Intervention to Release

Occasionally, it may be desirable to employ a particular formulation that when combined with a certain well or mold material experiences substantial adhesion after drying, thereby creating a release issue.

In such instances, it may be desirable to employ a mechanical intervention to assist in releasing the film, in whole or in part, from the well or mold surface. This can be performed using a blade, a scraper or analogous physical apparatus, suction, compressed air, or other method. Such intervention may be performed in conjunction with, and optionally contemporaneously with, the methdods described above (Pre-Releasing the Film) and below (Release through Intentional Crystallization).

Release through Intentional Crystallization

One method to effect or promote a release, or partial release, or easing of release is through an intentional crystallization of the film that manifests on the outer surfaces of the film. Typically, such crystallization would be avoided. However, where film is made by deposit, and is formed on the well as a substrate, it can be desirable to intentionally include one or more crystallization components that will crystallize (typically after the film is dried), and physically push the film off (or partially off of) the bottom of the well. This can promote release of the film from the bottom of the well.

Suitable crystallization components may include without limitation: erythritol, xylitol, mannitol, sucrose and citric acid.

Suitable crystallization components may be included in effective amounts. Sample ranges (measured from dry weight of the film) include: 1-30% or more preferably 3-20% or most preferably 5-10%, or 5-15%.

Additional Release Agents

Release of dried product from the blister wells may be facilitated by the inclusion within the composition of water-insoluble polymers suspended in the composition such as polystyrene powder or beads, polymethacrylates and cholestyramine, to facilitate release of the dried film from the well. Effective amounts are used. The water-insoluble polymers are not complexed with the drug, though in certain embodiments they may be.

In other embodiments insoluble minerals may also be used to carry out this function. Non limitative examples include talc, silicon dioxide, calcium carbonate, aluminum hydroxide.

In yet other embodiments, insoluble non-starch fibers may be used in a dual role as release agents and to form dry absorptive matrices using materials from a non-limitative list of cellulose, hemicellulose, chitins, beta-glucans, lignin and bran. In some embodiments insoluble proteins such as whey and gluten may be used.

Prodrug and Enzymatic Combinations

In one embodiment of the present invention, the film composition comprises a prodrug and one or more enzymes (or other non-enzymatic catalysts) to accelerate conversion of the prodrug into the desired active metabolite.

In certain embodiments, it is desirable to separate the prodrug from catalyst in the composition. This can be achieved by depositing the catalyst in a separate domain from the prodrug. For example, the catalyst and prodrug may be in separate layers.

In certain preferred embodiments, the prodrug and catalyst combination is for oromucosal delivery.

In certain preferred embodiments, the prodrug and catalyst are deposited in smaller layers (i.e. layers with a smaller geography) on top of a less soluble backing layer, like Figure 11B except

with two distinct smaller dimension top layer deposits that are both smaller (individually, and in the aggregate) than the backing layer.

In other embodiments, the product is in one layer, and the catalyst is in the other. The two layers may have equal (or substantially equal) geographies (dimensions) are different geographies (dimensions).

The separate domains may be in separate layers deposited on an insoluble and/or mucoadhesive film layer.

In preferred embodiments, the catalyst and prodrug are deposited from different nozzles.

Storage to Promote Release

With conventional wet cast film, the film is delaminated from the coating substrate prior to packaging. While it is sometimes possible to determine visually the "top" side of the film (i.e. the top side when it was dried), insofar as the film has been de-laminated from its coating substrate there is not a meaningful film top- and bottom with respect to the foil pouch the film is typically packaged into. In contrast, a film made by deposit in a well or mold clearly has an identifiable "bottom." One method to promote release of the film is to store the film wells upside down in the carton and store cartons (e.g. when palletized) to maintain this same upside-down posture. This method may be particularly employed where the top sheet is not in contact with the dried film when the top sheet is first applied.

The film is held upside for a certain duration prior to release, e.g. at least seven days, at least fourteen days, at least thirty days. In this way, upside storage can be validated for product release specifications. It is also possible to palletize the film with boxes pointed downwards, again to encourage release. Such palletization ensures that the product is facing downwards in distribution.

Other methods may be used to effect release the film from the well substrate such as temperature cycling by subjecting the blisters to one or more alternating cylces of refrigeration or freezing followed by thawing to room temperature.

Film-Forming Polymers

The non limiting polymer may be water soluble, water swellable, water insoluble, or a combination of one or more either water soluble, water swellable or water insoluble polymers. These may include homopolymers or various molecular weights or co-polymers of varying fractions or different polymer units. The polymer may include cellulose or a cellulose derivative. Specific examples of useful water soluble polymers include, but are not limited to, pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium aginate, polyethylene glycol, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, polyvinyl alcohol – polyethylene glycol copolymers, carboxyvinyl copolymers, starch, gelatin, pectin 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.

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 swellable polymers. The materials useful with the present invention may be water soluble or water swellable at room temperature and other temperatures, such as temperatures exceeding room temperature. Moreover, the materials may be water soluble or water swellable at pressures less than atmospheric pressure. Desirably, the water-soluble polymers are water soluble or water swellable having at least 20 percent by weight water uptake. Water swellable polymers having a 25 or greater percent by weight water uptake are also useful. Films or dosage forms of the present invention formed from such water-soluble polymers are desirably sufficiently water soluble to be dissolvable upon contact with bodily fluids.

Other polymers useful for incorporation into the films of the present invention include, but are not limited to, biodegradable polymers, copolymers, block polymers and combinations thereof. Among the known useful polymers or polymer classes which meet the above criteria are: poly(glycolic acid) (PGA), poly(lactic acid) (PLA), polydioxanoes, polyoxalates, poly(.alpha.-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, 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 polyurethane and poly(lactic acid), copolymers of .alpha.-amino 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 and mixtures thereof. Binary and ternary systems are contemplated.

Other specific, but non limiting, polymers useful include those marketed under the Medisorb and Biodel trademarks. The Medisorb materials are marketed by the Dupont Company of Wilmington, Del. and are generically identified as a "lactide/glycolide co-polymer" containing "propanoic acid, 2-hydroxy-polymer with hydroxy-polymer with hydroxyacetic acid." Four such polymers include lactide/glycolide 100 L, believed to be 100% lactide having a melting point within the range of 338°-347° F. (170°-175° C.); lactide/glycolide 100 L, believed to be 100% glycolide having a melting point within the range of 437°-455° F. (225°-235° C.); lactide/glycolide 85/15, believed to be 85% lactide and 15% glycolide with a melting point within the range of 338°-347° F. (170°-175° C.); and lactide/glycolide 50/50, believed to be a copolymer of 50% lactide and 50% glycolide with a melting point within the range of 338°-347° F. (170°-175° C.).

The Biodel materials represent a family of various polyanhydrides which differ chemically.

Generally, lower molecular weight polymer grades will be favored for certain embodiments of the present invention, as they will make lower viscosity film former compositions.

Such lower molecular weight grades will generally disintegrate faster than higher molecular weight grades. Where longer disintegration times are desired, it may be desirable to include non-water-soluble polymers.

Suitable Excipients

Any suitable excipient known in the art may be using in compositions of the present invention. Apart from film formers, a non-limiting list includes, pH buffers, permeation enhancers, surfactants, viscosity reducing agents, wetting agents, de-gassing agents, gassing agents, flavors, bitter masking agents, plasticizers, anti-caking agents, co-solvents, antioxidants and any other known excipient.

Excipients may be included in sufficient or effective amounts.

As discussed above, excipients may be added with the film former composition, or the drug (where the two are deposited separately).

Solvents

The following is a non-limiting list of solvents that may be employed: water, ethanol, acetone, DMSO, isopropanol, glycerol, propylene glycol, polyethylene glycol, propylene carbonate, ethyl acetate, d-limonene.

pH Buffers

Buffering agents may be used to control pH (acidic or base), including without limitation, sodium bicarbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, calcium carbonate, dipotassium phosphate, potassium citrate, sodium phosphate, Formic Acid/Sodium Formate, Hydrogen Chloride/Potassium Chloride, Hydrogen Chloride/Glycine, Hydrogen Chloride/Potassium Hydrogen Phthalate, Citric Acid/Sodium Citrate, Acetic Acid/Sodium Acetate, Citric Acid/Disodium Hydrogen Phosphate, Citric Acid/Trisodium Citrate Dihydrate, etc., and any other such buffer system.

The buffer system may be designed to dynamically control the pH of the product taking into consideration the effect of saliva during use, i.e., a dynamic buffer system. Non limitative, examples of buffer systems to obtain a pH include dibasic sodium phosphate and monobasic sodium phosphate. Both are FDA accepted buffer materials used and listed in the inactive ingredients list.

For example, for a pH of 7, the ratio of monobasic/dibasic can be 4.6/8.6; for a pH of 7.5 the ratio of monobasic/dibasic can be 1.9/11.9; and for a pH of 8.0 the ratio of monobasic/dibasic can be 0.6/13.4. These are mathematically calculated buffer numbers and will need to be adjusted according to the other ingredients added to the formula.

They also need to be adjusted for the length of time designed for the dissolution of the dosage unit on the buccal mucosa since saliva can be of a pH of about 6.8 but as it is made in larger amounts in the mouth the pH of saliva can sometimes become more basic. Thus, this dynamic

buffer range is adjusted in the dosage unit by the amount s of the buffer system since saliva is freshly renewable in the mouth. See Fuisz U.S. Patent Application Publication Nos. 2009/0098192 A1 and US 2011/0318390 A1 discussing dynamic buffering and incorporated herein by reference. The dynamic buffer systems of the present invention may be acidic or basic.

Fillers

Fillers may be useful to increase the percentage of solids in the formulation and reduce solvent requirement allowing for more rapid evaporation and faster throughput. Fillers may be soluble of insoluble. Non-limiting examples are polydextrose, maltodextrin, inulin, microcrystalline cellulose.

Surfactants

Surfactants may be useful in connection with the present invention to reduce surface tension. Reducing surface tension is helpful to promote flowability of the film composition (see Young Equation discussed above), and may also be useful to promote mixing of the film former composition with separately added drug.

Non limiting surfactants may include non-ionic surfactants, like polyol esters (e.g. glycol or glycerol esters, sorbitan derivatives); polyoxyethylene esters (e.g. polyethylene glycol (the "PEGs"; and poloxamers. Common ionic surfactants include ethers of fatty alcohols.

Any suitable surfactant may be employed.

In the approach of Yang et al, too much surfactant will create a product with a contact angle that is too low (Young's Equation) for coating on the substrate. Here, the formulator will want to use more surfactant to decrease the contact angle and promote flowability.

Emulsifiers:

Surfactants may also be useful in film compositions for reduction of interfacial tension that may facilitate the emulsification of an oily drug or drug oleoresin or a drug dissolved in an oily vehicle within the film forming composition.

Non limiting emulsifiers may include mono and diglycerides, fatty acid derivatives, lecithin, polysorbates, polyglycerol esters, propylene glycol esters and also sucrose esters such as sucrose acetate isobutyrate.

Permeation Enhancers

The film made by deposit may comprise one or more penetration agents, i.e., a substance that enhances absorption through the mucosa, mucosal coating and epithelium (otherwise known (see U.S. Patent Application Publication No. 2006/0257463 A1, the content of which is incorporated herein by reference) as a "penetration enhancer" or "permeability enhancer"). The penetration agent may comprise but is not limited to polyethylene glycol (PEG), diethylene glycol monoethyl ether (Transcutol), 23-lauryl ether, aprotinin, azone, benzalkomin chloride, cetylperidium chloride, cetylmethylammonium bromide, dextran sulfate, lauric acid, lauric acid/propylene glycol, lysophosphatilcholine, menthol, methoxysalicylate, oleic acid, phosphaidylcholine, polyoxyethylene, polysorbate 80, sodium EDTA, sodium glycholated, sodium glycodeoxycholate, sodium lauryl sulfate, sodium salicylate, sodium taurocholate,

sodium taurodeoxycholate, sulfoxides, and various alkyl glycosides or, as described in U.S. Patent Application Publication No. 2006/0257463, bile salts, such as sodium deoxycholate, sodium glycodeoxycholate, sodium taurocholate and sodium glycocholate, surfactants such as sodium lauryl sulfate, polysorbate 80, laureth-9, benzalkonium chloride, cetylpyridinium chloride and polyoxyethylene monoalkyl ethers such as the BRIJ.RTM. and MYRJ.RTM. series, benzoic acids, such as sodium salicylate and methoxy salicylate, fatty acids, such as lauric acid, oleic acid, undecanoic acid and methyl oleate, fatty alcohols, such as octanol and nonanol, laurocapram, the polyols, propylene glycol and glycerin, cyclodextrins, the sulfoxides, such as dimethyl sulfoxide and dodecyl methyl sulfoxide, dodecyl maltoside, tetradecyl maltoside, the terpenes, such as menthol, thymol and limonene, urea, chitosan and other natural and synthetic polymers. Preferably, the penetration agent is a polyol, e.g., polyethylene glycol (PEG), glycerin, maltitol, sorbitol etc. or diethylene glycol monoethyl ether (Transcutol)), d-α-Tocopheryl polyethylene glycol 1000 succinate (vitamin E-TPGS), Aprotinin, Ceramides, Decanoyl carnitine, Lauric acid, Lauroyl carnitine, Lysophosphatidylcholine, Poloxamer 407, Poloxamer F68.

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Preferably, the dried film composition may comprise 0.01% to 10% permeation enhancer by mass, more preferably 0.1% to 5%.

Viscosity Reducing Agents

Various agents may be employed to reduced viscosity. In particular and without limitation, hydrophobic salts may serve to reduce viscosity, which is of use in connection with the film

former composition. Without limitation, the following agents have been found useful: arginine hydrochloride, sodium thiocyanate, ammonium thiocyanate, ammonium sulfate, ammonium chloride, calcium chloride, zinc chloride, or sodium acetate. The teaching of US 20150071925, hereby incorporated herein by reference as if fully stated. Organic esters may also be useful. See US 20150071925, hereby incorporated herein by reference as if fully stated.

Effective amounts are used.

Anti-Caking Agents

Anti-Caking Agents are particularly useful where the drug active is added separately from the firm former composition in powder or particulate form.

Moisture, pressure and temperature all adversely affect powdered and granulated products. These conditions can make products cake, lump, bridge, clog equipment and cause flo and performance problems. Anti-caking and Free-flow powder agents can improve the flow behavior and storage stability of a broad variety of food products.

Silica derived materials are preferred.

A non limitative list includes: tricalcium phosphate, powdered cellulose, magnesium stearate, sodium bicarbonate, sodium ferrocyanide, potassium ferrocyanide, calcium ferrocyanide, bone phosphate, sodium silicate, silicon dioxide, calcium silicate, magnesium trisilicate, talcum powder, sodium aluminosilicate, potassium aluminium silicate, calcium aluminosilicate, calcium carbonate, bentonite, aluminium silicate, stearic acid, and polydimethylsiloxane.

Effective amounts are employed for reliable flow of powder/particulate.

Absorbent Agents and Absorbent Film Matrices

For certain actives, the use of an absorbent film matrix may be useful to reduce or even eliminate heating requirements. This approach is particularly well suited to active agents that are heat sensitive and may be degraded by conventional drying techniques.

For this approach, the film formulation includes an effective amount of one or more absorbent agents. Absorbent agents are insoluble or substantially insoluble excipients that impart a porous structure in the film to create a wicking or capillary action to allow fluids deposited on the film to permeate into the film.

Typically, the absorbent film, comprising an absorbent agent is formed (preferably by deposit). The film is dried, substantially dried or partially dried. Next, a suitable solvent or solvents (see below) is deposited on the film. The suitable solvent carries one or more active agents, which may be dissolved, substantially dissolved, or suspended. The deposited solvent quickly percolates or spreads within the matrix instead of remaining of top of the film as would typically occur on a non-absorbent film.

Typically, the deposited solvent percolates or spreads within the absorbent film matrix within fifteen seconds, preferably ten seconds, more preferably five seconds. Optionally, the solvent is deposited in a pattern, optionally employing a moveable gantry.

Next, the film may optionally be dried again to remove or substantially remove the deposited solvent. Typically, the temperature used to remove the solvent is substantially reduced from the

temperature used to dry the film the first time (i.e. after film formation and prior to the deposit of the solvent) (the "solvent drying phase").

It is not necessary to fully remove the solvent but simply to reduce the solvent to acceptable levels (see, e.g. USP standards for class 3 residual solvents).

A preferred drying temperature range for the solvent drying phase is 25 C to 85 C, preferable 25 C to 40 C. However, it is also contemplated that ambient air may be used, or slightly elevated temperatures (over ambient) may be employed.

Preferred ranges for absorbent agents in the dried film (by mass) are at least 3%, preferably at least 5%, more preferably at least 10%, and most preferably at least 15%.

Preferred ranges are these excipients are used in the range of 5-75%, preferably 10-45%, more preferably 15-35%

A non limitative list of absorptive agents includes: ethyl cellulose, cellulose powder, microcrystalline cellulose, nanocrystalline cellulose, polymethacrylates, silicon dioxide.

A non-limitative list of solvents useful for depositing on absorbent films include water, ethanol, isopropanol, acetone and mixtures thereof. Surfactants may also be added to the matrix composition and/or in the deposited solution to facilitate the spreading and rapid uptake of liquids into the matrix.

In certain embodiments, the absorbent film is formed with one more active agents, and one or more additional active agents are added after during using the technique described above. For example, and without limitation, an absorbent film may be formed with one (or more) active agents, with one (or more) additional active agents added using the technique described above.

The absorbent film may comprise a single layer in a multilayer film, as described herein. For example, and without limitation, a relatively insoluble film layer may serve as the backing layer to a second absorbent layer on top (into which an active agent is added). In another non-limitative example, the absorbent layer has a different (typically smaller) geography from the first non-absorbent layer. A non-absorbent layer (i.e. a conventional film) may be added to an absorbent layer.

Pharmaceutical Actives (also referred to herein as active pharmaceutical ingredients or drugs)

By the term pharmaceutical active agent, we mean a drug as described below. By pharmaceutical active agent composition, we mean any composition containing one or more pharmaceutical active agents. However, it is expressly contemplated that the compositions and methods taught herein are not limited to drugs but may include any active agent as more fully described below.

The active agents that may be incorporated into the films of the present invention include, without limitation bioactive agents such as pharmaceutical active agents, vaccines, cosmetic active agents, drugs, medicaments, botanicals, antigens or allergens such as ragweed pollen, spores, microorganisms, plant actives, enzymes and vitamins, as well as other active agents such

as seeds, mouthwash components, flavors, fragrances, preservatives, sweetening agents, colorants, spices, and combinations thereof. An active agent composition is a composition containing one or more of the active agents described herein.

A wide variety of non-limiting medicaments, bioactive active substances and pharmaceutical compositions may be included in the dosage forms of the present invention.

Examples of useful drugs include ace-inhibitors, antianginal 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, 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, biological response modifiers, 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, 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 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 suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

Examples of medicating active ingredients contemplated for use in the present invention include antacids, H_2-antagonists, and analgesics. For example, antacid dosages can be prepared using the ingredients calcium carbonate alone or in combination with magnesium hydroxide, and/or aluminum hydroxide. Moreover, antacids can be used in combination with H_2-antagonists.

Analgesics include opiates and opiate derivatives, such as oxycodone (available as Oxycontin.RTM.), ibuprofen, aspirin, acetaminophen, and combinations thereof that may optionally include caffeine.

Other preferred drugs for other preferred active ingredients for use in the present invention include anti-diarrheals such as immodium AD, anti-histamines, anti-tussives, decongestants, vitamins, and breath fresheners. Common drugs used alone or in combination for colds, pain, fever, cough, congestion, runny nose and allergies, such as acetaminophen, chlorpheniramine

maleate, dextromethorphan, pseudoephedrine HCl and diphenhydramine may be included in the film compositions of the present invention.

Also contemplated for use herein are anxiolytics such as alprazolam (available as Xanax.RTM.); anti-psychotics such as clozopin (available as Clozaril.RTM.) and haloperidol (available as Haldol.RTM.); non-steroidal anti-inflammatories (NSAID's) such as dicyclofenacs (available as Voltaren.RTM.) and etodolac (available as Lodine.RTM.), anti-histamines such as loratadine (available as Claritin.RTM.), astemizole (available as Hismanal.TM.), nabumetone (available as Relafen.RTM.), and Clemastine (available as Tavist.RTM.); anti-emetics such as granisetron hydrochloride (available as Kytril.RTM.) and nabilone (available as Cesamet.TM.); bronchodilators such as Bentolin.RTM., albuterol sulfate (available as Proventil.RTM.); anti-depressants such as fluoxetine hydrochloride (available as Prozac.RTM.), sertraline hydrochloride (available as Zoloft.RTM.), and paroxtine hydrochloride (available as Paxil.RTM.); anti-migraines such as Imigra.RTM., ACE-inhibitors such as enalaprilat (available as Vasotec.RTM.), captopril (available as Capoten.RTM.) and lisinopril (available as Zestril.RTM.); anti-Alzheimer's agents, such as nicergoline; and Ca.sup.H-antagonists such as nifedipine (available as Procardia.RTM. and Adalat.RTM.), and verapamil hydrochloride (available as Calan.RTM.).

Erectile dysfunction therapies include, but are not limited to, drugs for facilitating blood flow to the penis, and for effecting autonomic nervous activities, such as increasing parasympathetic (cholinergic) and decreasing sympathetic (adrenersic) activities. Useful non-limiting drugs include sildenafils, such as Viagra.RTM., tadalafils, such as Cialis.RTM., vardenafils,

apomorphines, such as Uprima.RTM., yohimbine hydrochlorides such as Aphrodyne.RTM., and alprostadils such as Caverject.RTM..

The popular H_2-antagonists which are contemplated for use in the present invention include cimetidine, ranitidine hydrochloride, famotidine, nizatidien, ebrotidine, mifentidine, roxatidine, pisatidine and aceroxatidine.

Active antacid ingredients include, but are not limited to, the following: aluminum hydroxide, dihydroxyaluminum aminoacetate, aminoacetic acid, aluminum phosphate, dihydroxyaluminum sodium carbonate, bicarbonate, bismuth aluminate, bismuth carbonate, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate, bismuth subsilysilate, calcium carbonate, calcium phosphate, citrate ion (acid or salt), amino acetic acid, hydrate magnesium aluminate sulfate, magaldrate, magnesium aluminosilicate, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, milk solids, aluminum mono-or dibasic calcium phosphate, tricalcium phosphate, potassium bicarbonate, sodium tartrate, sodium bicarbonate, magnesium aluminosilicates, tartaric acids and salts.

Cough suppressant ingredients including centrally acting agents including but not limited to clofenadol, codeine, dextromethorphan and cloperastine. Agents also include peripherally or locally acting agents such as levodropropizine, benzocaine, menthol, phenol, dyclonine, eucalyptol, amylmetacresol and dicholorobenzyl alcohol.

Other preferred drugs for other preferred active ingredients for use in the present invention are drugs that enhance mental function as either cognitive enhancers, nootropics or alertness/wakefulness promoting drugs. These include but are not limited to fencamfamine, modafinil, methylphenidate, pitolisant, amphetamine, dextroamphetamine, armodafinil and caffeine.

The pharmaceutically active agents employed in the present invention may include allergens or antigens, such as, but not limited to, plant pollens from grasses, trees, or ragweed; animal danders, which are tiny scales shed from the skin and hair of cats and other furred animals; insects, such as house dust mites, bees, and wasps; and drugs, such as penicillin.

Botanicals may be employed, including marijuana, tobacco, psilocybins, mescaline and any derivative thereof, including tetrahydrocannabinol and cannabidiol and cannabinoids).

Compositions may comprise at least one cannabinoid as a plant isolate or synthetically created in essentially or nearly pure form, or as a component of a plant extract or essential oil, or resin.

Typically, the at least one cannabinoid is present in a therapeutically effective amount.

In some embodiments, the *cannabis* plant material provided to the composition is obtained from a *cannabis* plant selected from the non-limitative group consisting of *Cannabis sativa, Cannabis indica*, and *Cannabis ruderalis.* Hemp may be used as a source.

In some embodiments, the composition provided herein comprises at least one cannabinoid selected from the group consisting of delta 9 tetrahydrocannabinol (Delta 9 THC), iso-

tetrahydrocannabinol (iso-THC), delta 9 tetrahydrocannabinolic acid (Delta (THCA), delta 8 tetrahydrocannabinol (Delta 8 THC), delta 8 tetrahydrocannabinolic acid (Delta 8 THCA), cannabidiol (CBD), cannabidiolic acid (CBDA), cannabinol (CBN), cannabinolic acid (CBNA), cannabinol methyl ether (CBNM), cannabinol-C4 (CBN-C4), cannabinol-CZ (CBN-C2), cannabiorcol (CBN-C1), cannabinodiol (CBND), cannabigerol (CBG), cannabigerolic acid (CBGA), cannabigerolic acid monomethyl ether (CBGAM), cannabigerol monomethyl ether (CBGM), cannabigerovarinic acid (CBGVA), cannabichromene (CBC), cannabichromanon (CBCN), cannabichromenic acid (CBCA), cannabichromevarin (CBCV), cannabichromevarinic acid (CB CVA), tetrahydrocannabivarin (THCV), cannabidivarin (CBDV), cannabielsoin (CBE), cannabielsoic acid A (CBEA-A), cannabielsoic acid B (CBEA-B), cannabigerovarin (CBGV), cannabidiolic acid (CBDA), cannabidiol monomethyl ether (CBDM), cannabidiol-C4 (CBD-C4), cannabidivarinic acid (CBDVA), and cannabidiorcol (CBD-C1), cannabicyclol (CBL), cannabicyclolic acid (CBLA), cannabicyclovarin (CBLV), cannabitriol, cannabitriolvarin (CBTV), ethoxy-cannabitriolvarin (CBTVE), cannabivarin (CBV), cannabidivarin (CBVD), cannabitriol, cannabitriolvarin (CBTV), ethoxy-cannabitiolvarin (CBTVE), cannabifuran (CBF), dehydrocannabifuran (DCBF), and cannabiripsol (CBR), β-caryophyllene epoxide; mentha-1,8(9)-dien-5-ol; pulegone; limonene; limonene oxide; α-terpinene; terpinen-4-ol; carvacrol; carvone; 1,8-cineole; p-cymene; fenchone; pulegone-1,2epoxide; β-myrcene; cannaflavin A; and cannaflavin B, or pharmaceutically acceptable salts thereof, solvates, metabolites, metabolic precursors, isomers or derivatives thereof.

Composites of cannabinoids are also contemplated; unrefined or semi-refined oils or extracts, including without limitation full spectrum oils and partial spectrum oils.

Compositions may comprise purely synthetic cannabinoids or mixtures thereof. Synthetic cannabinoids are drugs that bind to endocannabinoid receptors and/or other receptors to which phytocannabinoids also bind. Typically, the at least one cannabinoid is present in a therapeutically effective amount.

Synthetic cannabinoids may be of from any category such as classical cannabinoids, non-classical cannabinoids, hybrid cannabinoids, aminoalkylindoles, and eicosanoids. From a chemical structure classification viewpoint they may belong to the groups of Naphthoylindoles, Naphthylmethylindoles, Naphthoylpyrroles, Naphthylmethylindenes, phenylacetylindoles, Cyclohexylphenols, Tetramethylcyclopropylindoles, Adamantoylindoles, Indazole carboxamides and Quinolinyl esters. The cannabinoids may include any specific stereoisomer or a combination or racemic mixture.

The composition provided herein comprises at least one cannabinoid selected from the group consisting of various synthetic cannabinoid families such as the JWH series, HU series, CP series, AM series, AB series, AKB series, THJ series, UR series, XLR series, STS series, PB series.

The composition may non-limitatively include eicosanoids or endocannabinoids such as anandamide, methanandamide and 2-arachidonoylglycerol.

The composition may include synthetic compounds that indirectly modulate the effect of phytocannabinoids or endocannabinoids by inhibiting their metabolism via fatty acid amide hydrolase (FAAH), Monoacyl glycerol lipase (MAGL) or other pathways. Non limitative examples include 4-nonylphenyl boronic acid, palmitoylsulfonyl fluoride, Cyclohexyl [1,1'-biphenyl]-3-ylcarbamate.

In some embodiments, the film composition may comprise of synthetic cannabinoids in combination with phytocannabinoids.

In certain embodiments, the film is sold as a dietary supplement, food, medical food, or as a pharmaceutical. In some embodiments, the composition provided herein is formulated in the form a pharmaceutical composition, a nutraceutical, a cosmeceutical, a nutricosmetic, a cosmetic composition, a body care product, a personal hygiene product or a food product.

In preferred embodiments, an isolate is used which may be extracted and purified from plant material (i.e., any cannabis or hemp varietal) or chemically synthesized. Preferred methods of extraction may be solvent or super-critical fluid extraction. Preferred methods of purification including conventional separation methodologies such as post-extraction liquid/liquid chromatography, or HPLC columns. Extraction techniques can also be calibrated to separate cannabinoids though typically post extraction separation is required for greater purity.

The isolate is preferably 97% pure or greater, more preferably 98% pure or greater, and most preferably 99% pure or greater. Due to the expense of synthesized cannabinoid ingredients, film by deposit is a preferred manufacturing method due to its high yields (low waste).

In some embodiments, the at least one cannabinoid is Delta 9 THC and/or CBD.

In some embodiments, the at least one cannabinoid is an anxiolytic cannabinoid from the group of CBD, THCA, CBDA and their esters for the treatment of generalized anxiety disorder, panic attack, PTSD, social anxiety disorder, phobias, separation anxiety disorder and premature ejaculation.

In some embodiments, the film comprises, either in a single layer, or separately in different film layers, at least two cannabinoids. So, a film layer may comprise at least two cannabinoids, optionally with a non-cannabinoid layer. A bi-layer film may comprise a single layer with at least one cannabinoid, and a second layer with at least one cannabinoid.

In some embodiments, certain of which are described below, a film composition may comprise at least one cannabinoid, and at least one non-cannabinoid drug.

In some embodiments, described below, a film composition may comprise at least one cannabinoid, and at least one non-cannabinoid bioactive agent. The at least one non-cannabinoid bioactive agent may comprise any bioactive agent, where said bioactive agent is not a drug.

A preferred embodiment comprises a supplement combined within a single film composition with more than one cannabinoid to use or take advantage of the entourage effect between cannabinoids as well as a synergistic effect with non-cannabinoid supplements.

The entourage effect is a mechanism by which other cannabinoid compounds modulate or attenuate the overall psychoactive effects of delta 9 THC.

A preferred embodiment comprises a drug molecule combined within a film composition with more than one cannabinoid to take advantage of the entourage effect between cannabinoids as well as a synergistic effect with non-cannabinoid drugs via different pharmacological mechanisms of action.

A preferred embodiment comprises combining a drug molecule with delta 9 THC and cannabidiol to modulate or attenuate the psychoactivity of delta 9 THC.

A preferred embodiment comprises combining a drug molecule with delta 9 THC and terpenes like pinene and limonene to modulate or attenuate the psychoactivity of delta 9 THC.

A preferred embodiment comprises combining a drug molecule with delta 9 THC and cannabidiol and terpenes like pinene and limonene to modulate or attenuate the psychoactivity of delta 9 THC.

Insomnia is a therapeutic category that may be addressed with a film dosage form, including a film made by deposit. One embodiment is the combination of at least one non-cannabinoid drug for insomnia, together with at least one cannabinoid drug. The at least one non-cannabinoid

drug may be selected from the non-limitative group of: zolpidem, suvorexant, butabarbital, quazepam, estalozam, flurazepam, triazolam, tasmelteon, eszopiclone, temazapem, ramelteon, secobarbital, doxepin, zaleplon, hydroxyzine, meclizine diphenhydramine, and doxylamine. While the cannabinoid in the combination may be any known cannabinoid, preferred cannabinoids include the one from the non-limitative group of: full spectrum oil distillate, CBD, CBG, CBN, or THCA. The combination of at least drug for insomnia together with at least one cannabinoid may further comprise at least one supplement. Such supplement may include one from the non-limitative group of: melatonin, lavender, gamma-aminobutyric acid, valerian, kava, glycine, chamomile, 5-hydroxytryptophan, passionflower, magnesium, or magnolia bark.

Other preferred embodiments comprise a film further comprising at least one cannabinoid and at least one supplement from the non-limitative group of: melatonin, lavender, gamma-aminobutyric acid, valerian, kava, glycine, chamomile, 5-hydroxytryptophan, passionflower, magnesium, or magnolia bark.

A preferred embodiment is a film comprising 2.5 to 15 mg of zolpidem together with 1 to 10 mg of THCA. A preferred embodiment contains zolpidem to THCA within a ratio range of 5:1 to 1:5. More preferably, the film contains zolpidem to THCA within a ratio range of 3:1 to 1:3. Most preferably, the film contains zolpidem to THCA within a rationrange of 2:1 to 1:2. The preferred embodiment may further comprise 1 to 10 mg of melatonin or another supplement. The film is preferably for sublingual or buccal delivery. Per-oral use is also contemplated.

A preferred embodiment is a film comprising 2.5 to 15 mg of zolpidem together with 1 to 50 mg of CBN. Preferably, the film contains zolpidem to CBN in a ratio range of 1:1 to 1:20. The

preferred embodiment may further comprise 1 to 10 mg of melatonin or another supplement. The film is preferably for sublingual or buccal delivery. Per-oral use is also contemplated.

A preferred embodiment is a film comprising 5 to 15 m of zolpidem together with 5 to 50 mg of CBD. Preferably, the film contains zolpidem to CBD in a ratio range of 1:1 to 1:20. The preferred embodiment may further comprise 1 to 10 mg of melatonin. The film is preferably for sublingual or buccal delivery. Per-oral use is also contemplated.

A preferred embodiment is a film comprising 5 to 15 mg of zaleplon together with 1 to 10 mg of THCA. Preferred embodiment contain zaleplon to THCA within a ratio range of 5:1 to 1:4. More preferably, the embodiment contains zaleplon to THCA within a ratio range of 2:1 to 1:2. The preferred embodiment may further comprise 1 to 10 mg of melatonin. The film is preferably for sublingual or buccal delivery. Per-oral use is also contemplated.

A preferred embodiment is a film comprising 5 to 15 mg of zaleplon together with 1 to 30 mg of CBN. The preferred embodiment may further comprise 1 to 10 mg of melatonin. The film is preferably for sublingual or buccal delivery. Per-oral use is also contemplated.

A preferred embodiment is a film comprising 5 to 15 m of zaleplon together with 10 to 40 mg of CBD. The preferred embodiment may further comprise 1 to 10 mg of melatonin. The film is preferably for sublingual or buccal delivery. Per-oral use is also contemplated.

A preferred embodiment for insomnia comprises a supplement and a cannabinoid.

A preferred embodiment is a film comprising meclizine and CBN, or meclizine and CBD, or meclizine and a combination of CBN and CBD. The film is preferably for sublingual or buccal

delivery. Per-oral use is also contemplated. The preferred indication is for the treatment or prevention of emesis associated with migraine, motion sickness, vertigo or other conditions. Preferably, the film contains 20 to 100 mg of meclizine, more preferably 25 mg to 50 mg. The film may contain 1 to 30 mg of CBN. The film may contain 4 to 40 mg of CBD.

A preferred embodiment is a film comprising buclizine and CBN, or buclizine and CBD, or buclizine and a combination of CBN and CBD. The film is preferably for sublingual or buccal delivery. Per-oral use is also contemplated. The preferred indication is the treatment or prevention of emesis associated with migraine, motion sickness, vertigo or other conditions. Preferably, the film contains 6.25 to 50 mg of buclizine, more preferably 25 mg to 50 mg. The film may contain 1 to 30 mg of CBN. The film may contain 4 to 40 mg of CBD.

A preferred embodiment is a film comprising hydroxyzine and one or both of CBD and CBN. The preferred indication is anxiety or insomnia. The film is preferably for sublingual or buccal delivery. Per-oral use is also contemplated. The film preferably comprises 10 to 60 mg of hydroxyzine. The film may comprise 1 to 30 mg of CBN. The film may comprise 5 to 50 mg of CBD.

A preferred embodiment is a film comprising midazolam and CBD. The preferred indications are anxiety, panic attack, PTSD and seizure control or anti-convulsant. The film is preferably for sublingual or buccal delivery. Per-oral use is also contemplated. The film may contain 0.125 to 0.25 mg of brotizolam. The film may contain 4 to 70 mg of CBD.

Another preferred embodiment is a film containing midazolam and delta 9 Cannabidivarin.

Another preferred embodiment is a film containing midazolam and CBDV

A preferred embodiment is a film comprising brotizolam and CBD. The preferred indications are severe insomnia, anxiety, panic attack, and seizure control or anti-convulsant. The film is preferably for sublingual or buccal delivery. Per-oral use is also contemplated. The film may contain 2.5 to 15 mg of midazolam. The film may contain 4 to 80 mg of CBD.

A preferred embodiment is a film comprising diazepam and CBD. The preferred indications are anxiety, panic attack, and seizure control or anti-convulsant. The film is preferably for sublingual or buccal delivery. Per-oral use is also contemplated. The film may contain 2 to 20 mg of diazepam. The film may contain 4 to 80 mg of CBD.

A preferred embodiment is a film comprising ondansetron and CBD. The preferred indication is an anti-emetic. The film is preferably for peroral use, or for buccal or sublingual delivery. The film may contain 2 to 10 mg of ondansetron, preferably 4 to 8 mg. The film may contain 4 to 70 mg of CBD.

With many of the combinations contemplated herein, one active may be contemplated for buccal or sublingual absorption, whereas another active may be contemplated for absorption in the GI tract.

A preferred embodiment is 4-8 mg of ondansetron with 25-50 mg of CBD.

A preferred embodiment is a film comprising 50 to 150 mg of CBD, for oromucosal, preferably buccal delivery, with a buccal disintegration time of three to fifteen minutes in the buccal cavity.

A preferred set of embodiments combine a triptan drug with one or more cannabinoids. Preferably, the cannabinoid is Delta 9 THC (or Dronabinol). More preferably a cannabinoid

combination of delta 9 THC and Cannabidiol is employed. The triptan may be selected from the group of: A The triptan may be selected from the group of: almotriptan, frovatriptan, rizatriptan, zolmitriptan, sumatriptan, naratriptan, or eletriptan, or any other known triptan. A preferred indication is migraine relief. A preferred route of administration is buccal or sublingual. Per-oral use is also contemplated. The Delta 9 THC may serve as an anti-emetic, and or reduce the required dose of the conventional triptan. THCA may also be used, as a substitute for Delta 9 THC, or in addition. CBD may be used in certain embodiments, including without limitation to attenuate the potential anxiogenic effects of THC. The preferred range of ratios of THC to CBD is 1:1 to 1:20 and more preferably 1:2 to 1:10 and most preferably 1:3 to 1:5. CBD may be used in certain embodiments as the only cannabinoid in the composition along with a triptan. In other embodiments, CBDA or THCA may be used either alone or in combination.

A preferred embodiment is almotriptan 4 - 12.5 mg, plus .5 to 1.5 mg of Delta 9 THC (or Dronabinol). Preferably, the dose of almotriptan is 5.5 mg or less for the lower strength, and preferable the dose of almotriptan is 10.5 mg or less for the higher strength. In preferred embodiments, the film has an almotriptan Tmax that is at least 20% faster than the RLD tablet of comparable strength. The film may further comprise an additional cannabinoid, including inter alia CBD.

A preferred embodiment is frovatriptan 2.5 mg, plus .5 to 1.5 mg of Delta 9 THC (or Dronabinol). Preferably, the dose of frovatriptan is 2 mg or less, plus .5 to 1.5 mg of Delta 9 THC (or Dronabinol). In preferred embodiments, the film has a frovatriptan Tmax that is at least 20% faster than the RLD tablet. The film may further comprise an additional cannabinoid, including inter alia CBD.

A preferred embodiment is rizatriptan 3 - 10 mg, plus .5 to 1.5 mg of Delta 9 THC (or Dronabinol). Preferably, the rizatriptan dose is 4 mg or less for the lower strength, and 8 mg or less for the higher dose plus .5 to 1.5 mg of Delta 9 THC (or Dronabinol). In preferred embodiments, the film has a rizatriptan Tmax that is at least 20% faster than the RLD tablet. The film may further comprise an additional cannabinoid, including inter alia CBD.

A preferred embodiment is zolmitriptan 3-6 mg, plus .5 to 1.5 mg of Delta 9 THC (or Dronabinol). Preferably, the dose contains 4 mg or less of zolmitriptan plus .5 to 1.5 mg of Delta 9 THC (or Dronabinol). In preferred embodiments, the film has a zolmitriptan Tmax that is at least 20% faster than the RLD tablet. The film may further comprise an additional cannabinoid, including inter alia CBD.

A preferred embodiment is sumatriptan 20 to 110 mg plus .5 to 1.5 mg of Delta 9 THC (or Dronabinol). Preferably, the lower strength contains 20 mg or less of sumatriptan, plus .5 to 1.5 mg of Delta 9 THC (or Dronabinol), and the higher strength contains 40 mg or less of a sumatriptan, plus .5 to 1.5 mg of Delta 9 THC (or Dronabinol). In preferred embodiments, the film has a zolmitriptan Tmax that is at least 20% faster than the RLD tablet. The film may further comprise an additional cannabinoid, including inter alia CBD.

A preferred embedment is naratriptan .6 to 2.5 mg plus .5 to 1.5 mg of Delta 9 THC (or Dronabinol). Preferably, the lower strength contains .8 mg mg or less of naratriptan, plus .5 to 1.5 mg of Delta 9 THC (or Dronabinol), and the higher strength contains 2 mg or less of a naratriptan, plus .5 to 1.5 mg of Delta 9 THC (or Dronabinol). In preferred embodiments, the film has a naritriptan Tmax that is at least 20% faster than the RLD tablet. The film may further comprise an additional cannabinoid, including inter alia CBD.

A preferred embodiment is a film comprising 10- 50 mg of eletriptan plus .5 to 1.5 mg of Delta 9 THC (or Dronabinol). Preferably, the lower strength contains 20 mg or less of elitriptan, plus .5 to 1.5 mg of Delta 9 THC (or Dronabinol), and the higher strength contains 40 mg or less of a elitriptan, plus .5 to 1.5 mg of Delta 9 THC (or Dronabinol). In preferred embodiments, the film has an elitriptan Tmax that is at least 20% faster than the RLD tablet. The film may further comprise additional cannabinoid, including inter alia CBD.

Another preferred embodiment is a film comprising eletriptan and THCA. Preferably, the film is for buccal or sublingual delivery.

Another preferred embodiment is a film comprising eletriptan and Cannabidiolic Acid (CBDA). Preferably the film is for buccal or sublingual delivery. Preferred compositions may comprise 20 mg of eletriptan along with 0.1 to 10 mg of CBDA.

Another preferred embodiment is a film comprising eletriptan and a synthetic cannabinoid such as nabilone along with one or more natural or synthetic cannabinoids.

The film compositions leverage three key pharmacological approaches in an altogether novel way – oromucosal absorption; the entourage effect of cannabinoids; and synergistic pharmacological effects. The rapid absorption of cannabinoids via the buccal or sublingual oromucosal routes provides rapid relief while also reducing the overall dose required by avoiding the hepatic first pass effect which metabolizes and inactivates more than 80% of orally absorbed cannabinoids. The reduced hepatic first pass metabolism allows a significantly lower required dose for pharmacological efficacy. The entourage effect is leveraged by including CBD to

modulate the endocannabinoid receptors thereby attenuating the undesirable psychostimulant effects of delta 9 THC in a clinical setting while at the same time enhancing its antiemetic effect and promoting an overall anxiolytic effect. The synergistic pharmacological effect of combining a 5HT1B/1D serotonin receptor agonist drug for treatment of migraine pain with cannabinoids that act as 5HT1A receptor agonists, may address associated symptoms such as a) nausea and vomiting that arises prior to a migraine attack in about 15% of migraine patients and b) nausea caused by the serotonin receptor agonist itself and c) anticipatory nausea and anxiety that may arise from an impending migraine attack. The oromucosal formulation takes advantage of differential absorption of the serotonin receptor agonist and the cannabinoids. Rapid absorption into the systemic circulation of the highly lipophilic cannabinoids by the oromucosal route serves as a premedication that provides immediate relief from nausea symptoms of an impending migraine attack while also preventing the nausea and vomiting caused by the serotonin receptor agonist which is not absorbed as quickly or extensively from the oromucosal cavity but is absorbed later from the gastrointestinal tract when the dosage form has been dissolved and swallowed.

Furthermore, the overall anxiolytic effect promoted by a cannabinoid or cannabinoid combination may further address the anxiety of migraine sufferers.

It is goal of certain embodiments, of the present invention to reduce the amount of the non-cannabinoid drug, as compared with the amount of that same drug in the single active, Reference Listed Drug (RLD) version, achieved through additional or synergistic effect with at least one cannabinoid. Preferably the amount of the non-cannabinoid drug is used in an amount (as

compared with the comparable strength of the single active Reference Listed Drug (the "comparator") that is more than 10% less than the comparator, preferably more than 20% less than the comparator, more preferable more than 30% less than the comparator, and most preferably more than 35% less than the comparator.

Another class of drugs that may be combined with cannabinoids for synergistic effects are the gepants which may be selected from a non-limitative group of ubrogepant or rimegepant combined with one or more anxiolytic or anti-emetic cannabinoids such as CBD, CBDA, THCA and delta 9 THC.

A preferred embodiment is a film comprising ubrogepant and delta 9 THC (or Dronabinol), preferably for migraine use. Preferable, the film comprises 25 to 125 mg of ubgroepant, plus .5 to 1.5 mg of Delta 9 THC (or Dronabinol). Preferably, the film is for buccal or sublingual delivery. Per-oral use is also contemplated. Preferably, the film comprises 40 mg of less of ubrogepant for the lower dose, and 80 mg or less of ubrogepant for the higher dose. In preferred embodiments, the film has an ubrogepant Tmax that is at least 20% faster than the RLD orally disintegrating tablet. The film may further comprise an additional cannabinoid, including inter alia CBD.

Opioid use disorder (OUD) is a preferred indication for film. A preferred embodiment is naltrexone plus one or more from the group of: CBD, CBDA, THCA, nabilone, dronabinol, Delta 9 THC, or any other cannabinoid. Preferably the film is for peroral use, but sublingual and

buccal use are also contemplated. The cannabinoids in these compositions may provide relief from anxiety, panic and craving.

A preferred embodiment is 20 to 60 mg of naltrexone, and 10 to 30 mg of CBD. Optionally the film is for per-oral, optionally for BID, TID or QID use. Another preferred embodiment is naltrexone 20 to 60 mg and nabilone .75 to 3 mg, optionally for BID, TID or QID use. In preferred embodiments, the film has a naltrexone Tmax that is at least 20% faster than the RLD tablet.

A preferred embodiment is naltrexone 20 to 60 mg and .75 to 3 mg of either dronabinol or delta 9 THC, optionally for BID use.

Another preferred embodiment for opioid use disorder is an alpha 2a adrenergic receptor agonist combined with an anxiolytic cannabinoid in film compositions of this invention. Non-limitative examples include clonidine, lofexidine, guanfacine, xylazine and dexmedetomidine.

Another preferred embodiment for opioid use disorder is lofexidine together with a cannabinoid.

A preferred embodiment is a film comprising lofexidene and CBD. Preferably the film is for buccal or sublingual use but peroral use is also contemplated. In a preferred embodiment, the film comprises 0.1 to .25 mg of lofexidene, and 25 to 75 mg of CBD.

A preferred embodiment is a film comprising lofexidene, dronabinol and CBD. Preferably the film is for per-oral use, but buccal and sublingual use are also contemplated. In a preferred embodiment, the film comprises 0.1 to .25 mg of lofexidene, and .5 to 3 mg of dronabinol. A

preferred ratio range is lofexidene to dronabinol of: 1:5 to 1: 10. CBD is optionally present from 10 to 50 mg in the film. Delta 9 THC may be substituted from dronabinol in the same amounts.

In preferred embodiments, films comprising lofexidene achieve a Tmax at least 20% faster than the reference listed lofexidene tablet.

A preferred embodiment for OUD indication is a film comprising nalmefene and Delta 9 THC. A preferred dose is 0.3 to 0.7 mg of nalmefene and .5 to 1.5 mg of Delta 9 THC. A preferred ratio is 1:2 parts nalmefene to Delta 9 THC (or a ration within a 20% band of that rang). The nalmefene dose may range from 0.25 mg to 2.5 mg; the Delta 9 THC dose may range from 0.4 mg to 2.5 mg. Dronabinol may be substituted for Delta 9 THC. The film may further comprise CBD or other cannabinoids. Per-oral delivery is the preferred embodiment, but buccal and sublingual delivery are also contemplated. In preferred embodiments, films comprising lofexidene achieve a Tmax at least 20% faster than the nalmefene tablet sold as Selincro®.

Another preferred embodiment for OUD is a film comprising lofexidene, naltrexone and CBD. Preferably the film is for buccal or sublingual use but peroral use is also contemplated. In a preferred embodiment, the film comprises 0.1 to .25 mg of lofexidene, and 25 to 50 mg of CBD.

A preferred embodiment is a film comprising lofexidene, nalmefene and CBD. Preferably the film is for buccal or sublingual use but peroral use is also contemplated. In a preferred embodiment, the film comprises 0.1 to .25 mg of lofexidene, 2 to 20 mg of nalmefene, and 25 to 50 mg of CBD.

Other preferred embodiments are films comprising clonidine or lofexidine along with CBDA or THCA.

Embodiments of the present invention may be useful as anti-depressants.

A preferred embodiment is a film comprising escitalopram and delta 9 THC. The film is preferably for per-oral use but may also be used buccally or sublingually. A preferred dose is 10-20 mg of escitalopram and 1 to 2 mg of delta 9 THC. Dronabinol may be substituted for delta 9 THC. Preferably, the film is used BID. In preferred embodiments, films comprising escitalopram achieve a Tmax at least 20% faster than the reference listed escitalopram tablet.

An additional preferred embodiment for anti-depressant use is a film comprising paroxetine and CBD. The film is preferably for per-oral use but may also be used buccally or sublingually. A preferred dose is 10 mg of paroxetine and 1 – 50 mg of CBD. Dronabinol may be substituted for delta 9 THC. In preferred embodiments, films comprising paroxetine achieve a Tmax at least 20% faster than the reference listed paroxetine tablet.

Other actives suitable for use as an antidepressant together with a cannabinoid include, without limitation: doxepin, clomipramine, bupropion, amoxapine, nortriptyline, brexipipzole, citalopram, duloxetine, trazodone, venlafaxine, selegiline, eskatamine, perphenazine, amitriptyline, levomilnacipran, desvenlafaxine, lurasidone, lamotrigine, chlordiazepoxide, isocarboxazid, phenelzine, desipramine, trazodone, tranylcypromine, fluoxetine, desvenlafaxine, mirtazapine, quetiapine, nefazodone, doxepin, trimipramine, imipramine, vortioxetine, vilazodone, protriptyline, sertraline, etc.

The combination of a steroid together with CBD or another cannabinoid may be useful for inflammatory disease and other steroid-responsive disorders. Steroids by be selected from the group of: prednisolone, prednisone, methylprednisolone, triamcinolone, cortisone, hydrocortisone, betamethasone, dexamethasone, fludrocortisone, or other known steroids. The anti inflammatory properties of CBD or other cannabinoids may be used to reduce the steroid dose, and thereby reduce the adverse side effect profile or frequency of the sterioid. Per-oral delivery is the preferred embodiment, but buccal and sublingual delivery are also contemplated. In certain embodiments, the anti-inflammatory properties of CBD are used to lower the dose of the steroid, as compared to current therapies.

A cannabinoid may be combined with a non-cannabinoid drug for treatment of attention deficit and hyperactivity disorder. Non cannabinoid drugs suitable for this indication may be selected from the group of: amphetamine, methylphenidate, dexmethylphenidate, atomoxetine hydrochloride, lisdexamfetamine dimesylate, or isomers or pro-drugs thereof. Per-oral delivery is the preferred embodiment, but buccal and sublingual delivery are also contemplated.

A preferred embodiment is methylphenidate and CBD, for buccal, sublingual or per-oral use.

A cannabinoid may be combined with an opioid for the treatment of pain. Delta 9 THC and Delta 8 THC are preferred cannabinoids for pain treatment. The opioid may be selected from the group of: codeine, oxycodone, hydrocodone, tramadol, morphine, hydromorphone, fentanyl, carfentanil, oliceridine, or isomers or pro-drugs thereof. Sublingual or buccal delivery are preferred, but per-oral delivery is also contemplated. In preferred embodiments, the film achieves a opioid Tmax at least 20% faster than the reference listed opioid tablet.

A cannabinoid may be combined with an anti-pruritis agent, such as nalbuphine or nalmefene.

All references to specific drugs herein may include various salts thereof, and prodrugs.

A cannabinoids or combination of cannabinoids may also be used for the treatment of erectile dysfunction or premature ejaculation.

Cannabinoids may be combined with an PDE-5 inhibitor drug for the treatment of erectile dysfunction and premature ejaculation as well as for increasing sexual desire. The PDE-5 inhibitors may be selected from the group of sildenafil, tadalafil, vardenafil and avanafil. Certain embodiments may contain Delta-9-THC and delta 8 THC or other phytocannabinoids or synthetic cannabinoids with or without modulators of CB-1 agonist action such as CBD, CBDA or terpenes in combination with PDE-5 inhibitors.

The combination of an antipsychotic medication along with CBD, CBDA or other cannabinoids in the film compositions of the present invention may be useful for the treatment of schizophrenia and other associated psychotic disorders as well as dementia. Antipsychotics may be selected from a group of aripiprazole, asenapine, cariprazine, clozapine, lurasidone, olanzapine, quetiapine and risperidone but not limited to these compounds.

The combination of an anti-depressant medication along with anxiolytic cannabinoids like CBD, CBDA, THCA or other cannabinoids in the film compositions of the present invention may be useful for the treatment of Major Depressive Disorder, Persistent Depressive Disorder, Bipolar Disorder, Postpartum Depression, Premenstrual Dysphoric Disorder and Seasonal Affective Disorder. Anti-depressant medications used along with cannabinoids may include Selective

serotonin reuptake inhibitors, Serotonin-noradrenaline reuptake inhibitors (SNRIs), Noradrenaline and specific serotonergic antidepressants and Tricyclic antidepressants.

Cannabinoid films, including in combination of with non-cannabinoid drugs, may be useful for vaginal delivery or use. It is expressly contemplated that films for vaginal delivery may be used as one of more individual films, or the films may be attached to an absorbent device such as a tampon or a non-absorbent device. Certain embodiments may utilize the first pass uterine effect. Dysmenorrhea is a preferred therapeutic indication.

When combining a cannabinoid with a non-cannabinoid drug, preferred embodiments of the present invention involve complimentary pharmacokinetic properties. The complimentary nature of pharmacokinetic properties is use dependent. Contrast for example, a rescue medication (e.g. certain anti-convulsants, certain anti-anxiety, etc.), or a non-rescue medication used episodically (e.g. migraine, certain erectile dysfunction drugs), versus a combination for chronic use. Accordingly, the Tmax, AUC and half-life of the drug or cannabinoid must be carefully considered.

In certain embodiments, at least one cannabinoid in film composition with at least one non-cannabinoid drug, will each (both) achieve a Tmax within 60 minutes (one from the other), preferably within 45 minutes (one from the other), most preferably within 30 minutes (one from the other). Formulation techniques are employed to achieve this banding of Tmax. Both may be absorbed buccally or sublingually; or one may be absorbed principally buccally or sublingually (and open may be absorbed in the GI tract). As taught herein, film disintegration,

penetration or permeation enhancers, controlled release mechanisms, backing layers, multi-layers, droplets on film layers and other methods. In some embodiments, the film composition may comprise two layers each containing one or more drug and each layer with different dissolution characteristics that allow drug/s in one layer to be quickly dissolved and swallowed for peroral absorption while the other layer may remain in contact within the sublingual buccal cavity allowing predominantly oromucosal drug absorption.

Depending on the rate of dissolution of the film composition, drug/s may also be partially absorbed from the oromucosal cavity and partially absorbed from the GI.

In some embodiments, it may be advantageous for on drug to be quickly absorbed oromucosally to treat an early onset symptom of a disease condition while the other drug present in the composition may have more delayed action. For example, a composition may contain an anti-emetic drug and/or an anxiolytic drug combined with a drug for treating migraine pain such that the anti-emetic or anxiolytic drug is absorbed rapidly to prevent the premonitory nausea or anxiety that arises from an imminent migraine attack and the migraine drug may have more delayed action to treat the subsequent migraine pain. In this case, the anti-emetic drug may also prevent the nausea that may inherently arise from the migraine drug itself.

In certain embodiments, the at least one cannabinoid composition with at least one non-cannabinoid bioactive agent, will each (both) have a complimentary pharmacokinetic half-life. In certain embodiments, each (both) have a half-life within 180 minutes, preferably within 120

minutes, most preferably within 60 minutes. Other embodiments will fall outside of these bands, particularly in the case where a lipophilic agent is combined with a non-lipophilic agent. In such cases, the half-life difference may be more than 180 minutes, in other embodiments more than 360 minutes.

These complimentary bands may also apply where one or more non-cannabinoid bio-active agents are combined with one or more cannabinoid actives, and may also apply where the non-cannabinoid bio-active is a supplement.

In certain embodiments, the administration of a drug via buccal or sublingual cavity may reduce the overall dose required to treat the condition. This is particularly true for cannabinoids which experience significant hepatic first pass effect when absorbed into the systemic circulation from the gastrointestinal tract where up to 85% of the drug may be immediately metabolized by the liver. The reduced dose may ultimately attenuate toxicities or other undesirable side effects from the administration of the drug.

While film is the preferred delivery vehicle, it is expressly contemplated that non-film dosage forms may be employed, whether made by deposit or other means. Such non-film dosage forms include gummies, lozenges, tablets, orally disintegrating tablets, capsules, pessaries, suspensions, solutions, gels, hydrogrels, creams, lotions, foams, emulsions, gums, injectables (including auto-injectors, wearable injectors, conventional injections), inhalation systems (including inter alia,

dry powder inhalers, inhalers, vaporizers), transdermal systems, drug coated or infused stent, vaginal ring, drug coated or infused implant, and any other known dosage form or system.

The injectable may take the form of a long-acting injectable depot form, akin to a product like once-monthly Sublocade®.

A preferred embodiment is a long-acting depot injectable, comprising naltrexone and CBD for opioid use disorder. Another preferred embodiment is a long acting injectable for opioid use disorder comprising buprenorphine and a cannabinoid, preferably CBD.

A preferred embodiment combines at least one cannabinoid with a non-cannabinoid drug for intramuscular or subcutaneous injection.

A preferred embodiment combines at least one cannabinoid with at least one non-cannabinoid biologic. Preferably, the non-limitative route of administration is intramuscular or subcutaneous injection, infusion or intravenous delivery. The at least one non-cannabinoid biologic may be a biosimilar. The least one non-cannabinoid biologic may be selected from the non-limitative group of: abciximab, alteplase, reteplase, Tenecteplase, abobotulinumtoxinA, onabotulinumtoxinA, incobotulinumtoxinA, anakinra, rimabotulinumtoxinB, follitropin alpha, collagenase, ecallantide, collagenase clostridium histolyticum, aflibercept, ranibizumab, ocriplasmin, bevacizumab, pegaptanib, abatacept, adalimumab, adalimumab-atto, certolizumab pegol, etanercept, etanercept-szzs, golimumab, infliximab, infliximab-dyyb, secukinumab, tocilizumab, ustekinumab, anakinra, canakinumab, golimumab, infliximab, infliximab-dyyb,

rituximab, tocilizumab, ustekinumab, interferon beta-1b, daclizumabdaclizumab, interferon beta-1a, natalizumab, interferon beta-1a, peginterferon beta-1a, adalimumab-atto, certolizumab pegol, etanercept, etanercept-szzs, golimumab, infliximab, infliximab-dyyb, secukinumab, adalimumab, ixekizumab, ustekinumab, brodalumab, Rilonacept, belimumab, interferon gamma-1b, interferon alfa-2b, Obinutuzumab, asparaginase, asparaginase erwinia chrysanthemi, blinatumomab, interferon alfa-2b, Obinutuzumab, ofatumumab, pegaspargase, sargramostim, nivolumab, brentuximab vedotin, nivolumab, ibritumomab tiuxetan, Obinutuzumab, rituximab, ado-trastuzumab emtansine, pertuzumab, trastuzumab, aldesleukin, daratumumab, elotuzumab, nivolumab, pembrolizumab, nivolumab, ipilimumab, aldesleukin, atezolizumab, necitumumab, ramucirumab, cetuximab, bevacizumab, cetuximab, panitumumab, ramucirumab, ziv-aflibercept, capromab pendetide, ramucirumab, trastuzumab, olaratumab, elosulfase alfa, idursulfase, iaronidase, asfotase alfa, pegloticase, hypercholesterolemia, alirocumab, evolocumab, albiglutide, dulaglutide, becaplermin, agalsidase beta, alglucosidase alfa, canakinumab, galsulfase, metreleptin, rasburicase, sebelipase alfa, parathyroid hormone, bezlotoxumab, peginterferon alfa-2a, peginterferon alfa-2b, palivizumab, siltuximab, pegfilgrastim, sargramostim, epoetin alfa, methoxy polyethylene glycol-epoetin beta, basiliximab, belatacept, sargramostim, palifermin, eculizumab, oprelvekin, romiplostim, glucarpidase, idarucizumab, obiltoxaximab, raxibacumab, dornase alfa, mepolizumab, reslizumab, omalizumab, human growth hormone. The preceding list is non-limitative, and a cannabinoid may be combined with any non-cannabinoid biologic.

In certain embodiments, Nicotine salts may be employed. Botanicals may or may not be approved for pharmaceutical use or otherwise understood to be pharmaceutically active.

Mitragyna speciosa, also known as kratom, may be employed, together with its derivatives or synthetic versions thereof.

Active agents may include proteins such as, enyzmes and antibodies or other biologics such as (and without limitation) live atttenuated and inactive viruses or other antigenic material for use as vaccines or drug delivery agents or nucleotide-based vaccines consisting of DNA, RNA or plasmids

An anti-oxidant may also be added to the film to prevent the degradation of an active, especially where the active is photosensitive.

Cosmetic active agents may include breath freshening compounds like menthol, other flavors or fragrances, especially those used for oral hygiene, as well as actives used in dental and oral cleansing such as quaternary ammonium bases. The effect of flavors may be enhanced using flavor enhancers like tartaric acid, citric acid, vanillin, or the like. Anti-tartar agents for dental use may also be employed.

Combination Products

Films of the present invention may involve more than one drug, or more than one bioactive agent.

Two or more bioactive agents may be present in a single film layer. Said two or more bioactive agents may be deposited together with the film former composition, or separate from the film former composition, and optionally separate from one another. Separate from one another may be particularly desirable where the bioactive agents are incompatible, or where they are in different forms (powder versus oil; powder versus resin) or carried in different media (different solvents; one in solution, one in suspension or emulsion, etc).

The two or more bioactive agents may be present in different film layers. Such different film layers may have similar or different disintegration profiles. Using standard dissolution testing, one film layer may have a slower disintegration time of more than 125%, more than 150%, more than 200%, or more than 250% of the disintegration time of a second layer.

One bioactive agent may be present in a film layer, with a second drug deposited on top of the film layer containing the first bioactive agent.

Both drugs in a combination drug film composition may be intended for mucosal absorption. One drug may be suited or intended for mucosal absorption, and a second drug in the film composition suited or intended for absorption in the GI draft.

Multiple layers may be particularly valuable to separate active agents where one active agent may interfere with the chemical stability of a second active agent. This may be particularly applicable to cannabinoids.

The cannabinoid or cannabinoid combination may be present in the film as a solution in an oil like sesame or peanut oil or as a pure oily resin. The oil solution or resin may be emulsified in the coating solution and when the water is removed, the polymeric film matrix would contain an embedded pre-emulsion or pre-microemulsion or pre-nanoemulsion. When the film dissolves in saliva an emulsion or microemulsion or nanoemulsion may be spontaneously created with the judicious use of appropriate surfactants. The emulsion systems may promote rapid absorption from the oral cavity. The second non-cannabinoid drug may be present as a solid in the polymeric film matrix which disperses or dissolves when the film dissolves upon contact with the saliva. The layer containing the emulsion and the layer containing the dissolved or dispersed drug may also be separately deposited in the well.

The oily cannabinoid containing layer may also be formulated to dissolve slowly in the oromucosal cavity while the non-cannabinoid drug layer may be formulated to dissolve quickly in saliva allowing it to be swallowed for absorption within the gastrointestinal cavity while leaving behind a slower dissolving cannabinoid layer for

Coloring Agents

Also, color additives can be used in preparing the films. Such color additives 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 or 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%, based on the weight of all the components.

Flavors

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, grape, lime and grapefruit and fruit essences including apple, pear, peach, grape, strawberry, raspberry, cherry, plum, pineapple, apricot or other fruit flavors.

The films containing flavorings may be added to provide a hot or cold flavored drink or soup. These flavorings include, without limitation, tea and soup flavorings such as beef and chicken.

Other useful flavorings include aldehydes and esters such as benzaldehyde (cherry, almond), citral i.e., alphacitral (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 sweeteners such as aspartame; dihydrochalcone compounds,

glycyrrhizin; Stevia Rebaudiana (Stevioside); chloro derivatives of sucrose such as sucralose; sugar alcohols such as sorbitol, mannitol, xylitol, isomalt and the like. Also contemplated are hydrogenated starch hydrolysates and the synthetic sweetener 3,6-dihydro-6-methyl-1-1-1,2,3-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. Sweeteners may be employed from 1% to 50%, preferably 10-35%, more preferably 20-30% of the composition (by weight or mass)

Isomalt is particularly useful with certain embodiments of the present invention insofar as it resists crystallization when made with compositions suitable for forming films by the deposit methods taught herein. Moreover, isomalt is thermally and chemically stable with low hygroscopicity.

When the active is combined with the polymer in the solvent, the type of matrix that is formed depends on the solubilities of the active and the polymer. If the active and/or polymer are soluble in the selected solvent, this may form a solution. However, if the components are not soluble, the matrix may be classified as an emulsion, a colloid, or a suspension.

Transdermal Films

In certain embodiments, the deposit method of the present invention may be used to make transdermal films. Since transdermal films are typically multilayer, different layers may be deposited in series, if necessary between drying intervals. Backing layers of materials not readily depositable may be inserted into the mold or well (including inter alia microneedles).

The following patents, describing transdermal compositions, are incorporated by reference as if fully stated herein (including incorporations into such patents): US9089527 B2 (assigned to Lohmann); US8696637 (assigned to Lohmann); US 6117448 (assigned to Lohmann); US 5820876 (assigned to Lohmann). Obviously, different compositions, and different excipients are used in transdermal systems from oral soluble films and so the teaching of the incorporated patents is important for such embodiments.

Examples

A number of template molds were made, 10 mil recess thick, and adhered to a Teflon sheet. The compositions are shown in Table 1A, and Table 2A and Table 3. Results after deposit and drying for the compositions of Table 1A and Table 2A, are found in Tables 1B and 2B, respectively.

As the results in Table 1B demonstrate, the compositions described in Table 1A were generally too viscous and exhibited too much surface tension to adequately flow into a mold.

A number of the examples of 2A successfully flowed into films, and certain examples demonstrated good embedding of solids. For example, sample D of Table 2A showed good embedding of calcium carbonate particulate, which was used as a "dummy" drug particulate. The flowability of these examples would preclude their ability to be coated using conventional wet casting techniques. Their very proclivity to flow would lead them to roll off the substrate in a conventional casting process.

The compositions of Table 3 are non-aqueous. Sample NA4, comprising 29.7% PEO (300,000) and 70.3% PEG400 is a promising approach for a slow release film of the present invention. Applicants observed that a range of 20-40% PEO (300,000 mw and above), together with PEG 80 as a solvent may be an attractive formulation option where slow release is desired from a film made by the deposit method.

Table 4 contains surface tension values.

Table 1A: Aqueous Evaluation Samples

Sample ID	Instagel	Corn Starch	HPMC	HPMC	HPC	PVP	PG	PEG2000
			K15M	F50				
1	1.45%	1.99%						
2	9.15%							
3		4.32%		6.81%		4.48%		8.16%
4		3.74%		5.79%		2.23%	6.83%	
5				2.57%			1.05%	
6			5%					
7			1.25%					
8			1.00%					
9				1.86%				
10				0.90%				

Table 1B: Aqueous Evaluation Samples Post Thermal Treatment			
Sample ID	Pass	Fail	Cause
1		x	high contact angle on silicon mold, did not wet or spread, did not embed solids, does not disperse in water
2		x	high contact angle on silicon mold, did not wet or spread, did not embed solids, does not disperse in water
3		x	too viscous
4		x	very viscous, produced thick film that did not disperse readily in water
5		x	film very thin and brittle, poor wetting and spreading on substrate, strong adhesion to teflon substrate when dried
6		x	too viscous
7		x	film too brittle and too thin
8		x	film too brittle and too thin
9		x	too viscous to add to template
10		x	too viscous to add to template

Table 2A: Aqueous PEO Film Former Compositions							
Sample ID	PEO 100K	PEO 300K	PEO 900K	PEG400	PG	PS 20	Viscosity cps
A			9.09%	18.18%			
B	10.58%			6.68%			331*
C	10.59%				7.30%		366*
D	10.69%			5.59%			306*
E	4.76%						
F			6.52%		12.90%	1.65%	
G		5.71%			3.50%		2243-1261**
H		5.79%		4.05%			
I	18.31%				7.44%		1846-1155**
J	18.31%			8.80%			
K	12.38%				4.45%		413*
L	10.53%			5.61%			
M	7.06%	1.77%			5.60%		
N		4.76%					653-468**
O		3.67%					217*
P		6.28%					
* Newtonian fluid viscosity							
**Non-Newtonian fluid viscosity range from 10 to 100 s^{-1}							

Table 2B: Aqueous PEO Film Former Post Thermal Treatment Evaluations			
Sample ID	Pass	Fail	Cause
A	x		films .2mm think easily disperse in water
B	x		good spreading and wetting, low viscosity
C	x		good spreading and wetting, low viscosity
D	x		film former added to calcium carbonate, good embedding of solids
E	x		viscous, but good spreading and wetting, thin film easily disperses in water
F	x		viscous, films .15mm, easily disperse in water
G	x	x	viscous composition, can produce good thin film, readily dispersible in water
H	x	x	viscous composition, can produce good film, easily dispersible in water
I		x	too viscous, thick film, not easily dispersible in water
J		x	too viscous, thick film, not easily dispersible in water
K	x		good spreading and wetting, low viscosity
L	x		good spreading and wetting, low viscosity
M	x		good spreading and wetting, low viscosity
N	x		produced film with good dissolution in water
O	x		produced thin film with good dissolution in water
P	x		produced thin film easily dispersible in water

Table 3: Non-Aqueous PEO Compositions Post Thermal Treatment 90°C						
Sample ID	PEO100K	PEO300K	PEG400	Pass	Fail	Cause
NA1	8.88%		91.12%		x	lacks cohesion, waxy dispersion
NA2	9.51%		90.49%		x	lacks cohesion, waxy dispersion
NA3		10.22%	89.78%		x	weak, wet, thick (1.23mm) and fragile film; poor dissoution in water
NA4		29.70%	70.30%	x	x	viscous dispersion, poor flowability, opaque thick (1.6mm) strong film; slow dissolution in water, tacky vehicle when wet

Table 4: Examples of Surface Tension Values		
	Temp	□
	°C	mN/m
Water	25	71.97
	40	69.56
	80	62.6
PEG200	20	43.5
ISP	25	23

Example AA

The film of Example AA is a relatively slow-dissolving film, i.e. more than 10 minutes in the oral cavity of a user to dissolve.

The table below sets forth the ingredients of the film of Example AA.

Ingredients	%	Amount
Klucel LF	18	4.5
PEO N 10	2.5	0.625
Natrosol 250 L	50.075	12.51875
PVA	2.5	0.625
Carbopol 934P	0.5	0.125
Magnasweet	0.3	0.075
Sucralose	0.75	0.1875

Sodium Benzoate	0.375	0.09375
Total:	100	25

% Solids	20	20
Total weight	500	125
Water Amt	400	100

Klucel LF is hydroxypropylcellulose; PEO N 10 is polyethylene oxide, polyox WSR N 10; Natrosol 250 L is hydroxyethylcellulose, natrosol 250 L; Kollicoat Protect is polyethylene glycol polyvinyl alcohol copolymer; PVA is polyvinyl alcohol; Carbopol 934P is carbomer, Carbopol 934P; Magnasweet is monoammonium glycyrrhizinate, Magnasweet MM 100.

The above composition was mixed and made into several circular-shaped films by deposit. The films were flexible and non-tacky. They were thin, strong (good tensile strength) and appeared to be well suited for their intended application. They were easily removable from the carrier strips without breakage and held up well to handling. The films appeared to be a composite of several liquid phases, solids, and aeration.

The films were examined under both transmitted and dark field surface illumination with cross polarizers. There was evidence of liquid crystalline mesomorphic phases and this phase appeared to be distributed throughout the film. Further, it appeared that interfaces within the film are coated. Under some conditions, these phases could promote rapid oromucosal absorption of drugs incorporated therein.

With transmitted light, again under cross polarization, the dispersed particles appeared to be covered with a thick coating. This also appeared to be true at interfaces in general within the film samples

Examination of the liquid formulation used to make the films, after it was allowed to sit, showed physical separation with at least two phases. One appeared to be an opaque gel-like substance surrounded by a liquid phase which appears to be of lower viscosity. This appears to be due to a syneresis effect.

What is claimed is:

1. A multilayer soluble film made by deposit, comprising:

a first soluble layer not containing a pharmaceutical active agent; and

a second soluble layer provided on the first soluble layer by depositing a solution comprising materials forming the second soluble layer to form the solution into a film on the first soluble layer, the second soluble layer containing at least one pharmaceutical active agent and having a surface area different than a surface area of the first soluble layer,

wherein the first soluble layer is a mucoadhesive layer or a slowly dissolving backing layer.

2. The multilayer soluble film according to claim 1, wherein the second soluble layer is provided on the first soluble layer by depositing a solution comprising materials forming the second soluble layer without direct mechanical intervention to form the solution into a film on the first soluble layer.

3. A system for manufacturing a pharmaceutical active agent-containing soluble film by deposit, comprising:

a gantry moveable horizontally in at least an X and Y direction;

a nozzle supported on the gantry, the nozzle being configured to be connected to a source of a film forming composition containing a pharmaceutical active agent, and

a support configured to support a sheet having a plurality of wells,

wherein the gantry and nozzle are configured to deposit the film forming composition into the well in a pattern by moving the gantry horizontally in the X or Y direction.

4. The system according to claim 3, wherein the gantry and nozzle are configured to deposit the film forming composition into the well in a pattern by moving the gantry horizontally in the X, Y or Z direction(s).

5. The system according to claim 3, further comprising a machine vision system for determining the proper relative placement of the nozzle and the wells.

6. A method for manufacturing a pharmaceutical active agent-containing soluble film by deposit using the system according to claim 3, comprising depositing the film forming composition into the well in a pattern while moving the gantry horizontally in the X or Y direction.

7. The method according to claim 6, comprising depositing the film forming composition into the well in a pattern while moving the gantry in the X, Y and/or Z direction(s).

8. A system for manufacturing a pharmaceutical active agent-containing soluble film by deposit, comprising:

a support;

a nozzle moveably supported on the support, the nozzle being configured to be connected to a source of a film forming composition containing a pharmaceutical active agent, and

wherein the nozzle is configured articulate to deposit the film forming composition into the well in a shape selected from the group of: circular, elliptical, polygonal and zig-zag.

9. A method for manufacturing a pharmaceutical active agent-containing soluble film by deposit using the system according to claim 8, comprising deposit the film forming composition into the well in a shape selected from the group of: circular, elliptical, polygonal and zig-zag while articulating the nozzle.

10. A system for forming a pharmaceutical active agent-containing soluble film, comprising a sheet including a well of predetermined size, the sheet being softenable by heat, and a support containing a sub-well of a size large enough to accommodate the well, wherein the well of the sheet is provided in the sub-well.

11. A method for forming a pharmaceutical active agent-containing soluble film, comprising:

providing a sheet including a well of predetermined size, the sheet being softenable by heat onto a support containing a sub-well of a size large enough to accommodate the well, wherein the well of the sheet is provided in the sub-well; and

depositing a film forming composition containing a pharmaceutical active agent into the well.

12. A method for promoting release of a soluble film from a surface of a package, comprising providing a sheet with a plurality of wells, an soluble film provided in the bottom of each well and a top sheet covering the plurality of wells, and passing the sheet partially around at least one roller to bend the bottom surface of the well to promote release of an soluble film from the bottom of the well.

13. A pharmaceutical active agent-containing soluble film, comprising an soluble film containing at least one pharmaceutical active agent, wherein at least part of an edge portion of the soluble film is thicker than a center portion.

14. A pharmaceutical active agent-containing soluble film made by deposit, comprising a soluble film containing at least one pharmaceutical active agent, wherein the soluble film contains one or more holes through the film.

15. A pharmaceutical active agent-containing soluble film made by deposit, comprising a soluble film containing at least one pharmaceutical active agent, wherein the soluble film has a moisture content of 15% or greater

16. A packaged pharmaceutical active agent-containing soluble film made by deposit, comprising a soluble film containing at least one pharmaceutical active agent, wherein the soluble film contains a crystallization component configured to cause intentional crystallization to promote release of the soluble film from a surface of the package.

17. A palletized stack of packaged pharmaceutical active agent-containing soluble films made by deposit, each packaged pharmaceutical active agent-containing soluble film comprising a package comprising a bottom sheet including a well, a soluble film containing at least one pharmaceutical active agent provided in the well, and a top sheet covering the soluble film containing at least one pharmaceutical active agent provided in the well, wherein the packages

are provided in the palletized stack upside-down with the top sheet provided on the bottom and the well provided on the top.

18. A sheet containing a well for forming a soluble film therein, wherein the well has side portions configured to collapse when a bottom of the well is pushed upwards to present the soluble film for use.

19. A combination comprising the sheet according to claim 18, a soluble film provided in the well and a top sheet covering the soluble film in the well.

20. A film made by deposit, the film comprising at least one non-cannabinoid bioactive agent and at least one cannabinoid.

21. A method of using the film according to claim 20, comprising applying the film to a buccal area of a human or animal.

22. A method of using the film according to claim 20, comprising applying the film to a sublingual area of a human or animal.

23. A method of using the film according to claim 20, comprising applying the film inside a vagina of a human or animal.

24. A method of using the film according to claim 20, comprising administering the film per-orally to a human or animal.

25. A method of making a film composition with a heat sensitive active agent, comprising:

forming an absorbent film by deposit in a well, wherein the absorbent film comprises at least one absorbent agent that is soluble or substantially insoluble excipients that impart a porous structure to the film, the at least one absorbent agent being at least one selected from the group of: ethyl cellulose, cellulose powder, microcrystalline cellulose, nanocrystalline cellulose, polymethacrylates, and silicon dioxide;

drying or substantially drying the film, wherein the absorbent agent is at least 3% of the dried film mass;

depositing a heat sensitive active agent on the dried film, wherein the heat sensitive agent is dissolved or suspended in a solvent; and

allowing the deposited solvent to percolate within a matrix of the dried or substantially dried absorbent film.

26. A film made by deposit in a well, wherein the film comprises an effective amount of at least one release agent selected from the group of: polystyrene powder or breads, polymethacrylates and cholestyramine to facilitate release of the dried film from the well.

27. A film for oromucosal delivery made by deposit in a well, wherein the film comprises a plurality of separate domains, at least one domain comprising a prodrug and at least one other domain comprising at least one catalyst.

28. A method of making a film in a well, comprising:

depositing a film former and at least one active agent in a well by at least one deposit nozzle provided on a moveable x-y gantry, wherein no mechanical intervention is used to form the film; and

drying the film; and

applying a top sheet on the film in the well,

wherein depositing the film, drying the film and applying the top sheet are performed on a single production line.

29. The method according to claim 28, further comprising determining the proper relative placement of the nozzle and the well before depositing the film former and the at least one active agent in the well.

FIG. 1

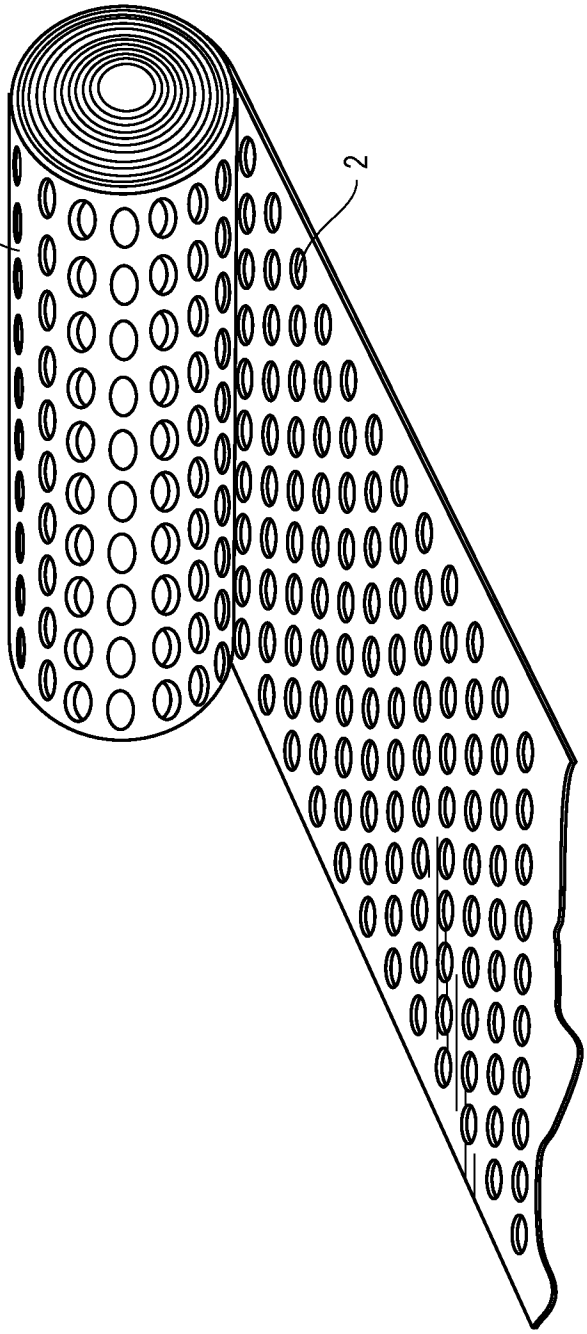


FIG. 2

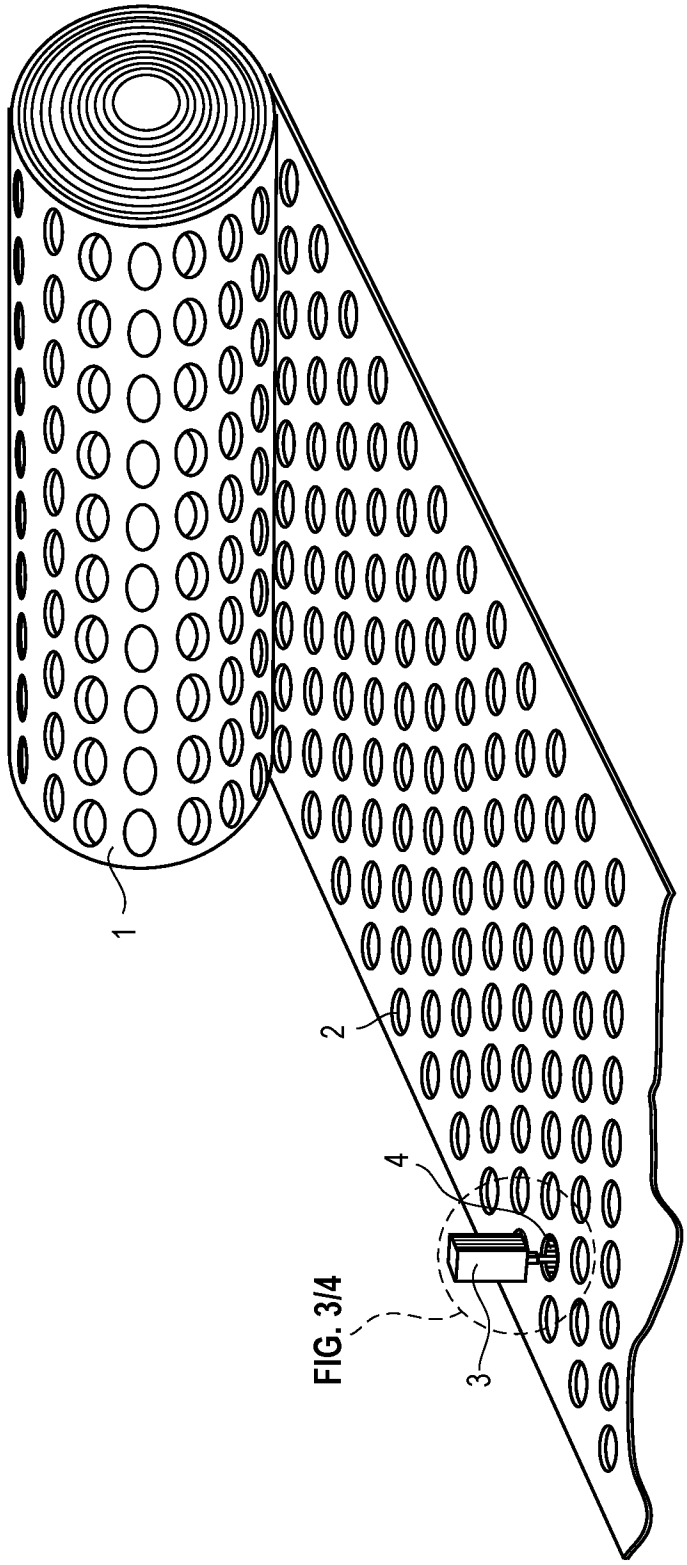


FIG. 3/4

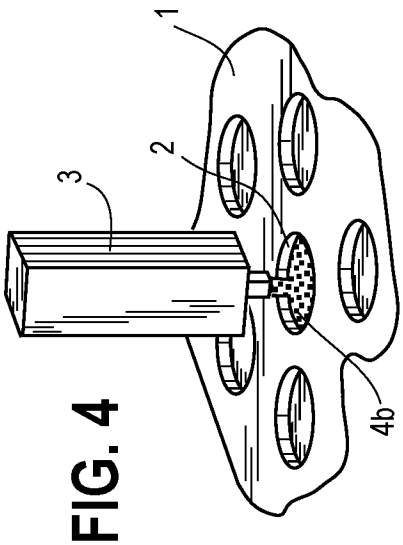


FIG. 4

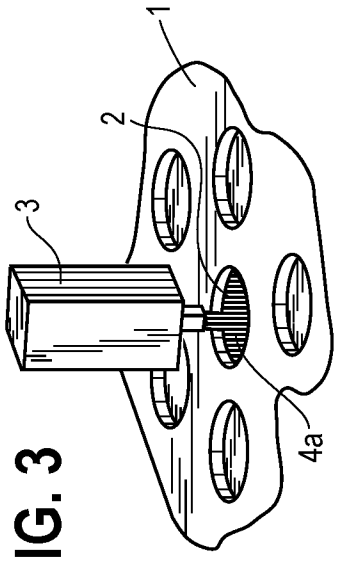


FIG. 3

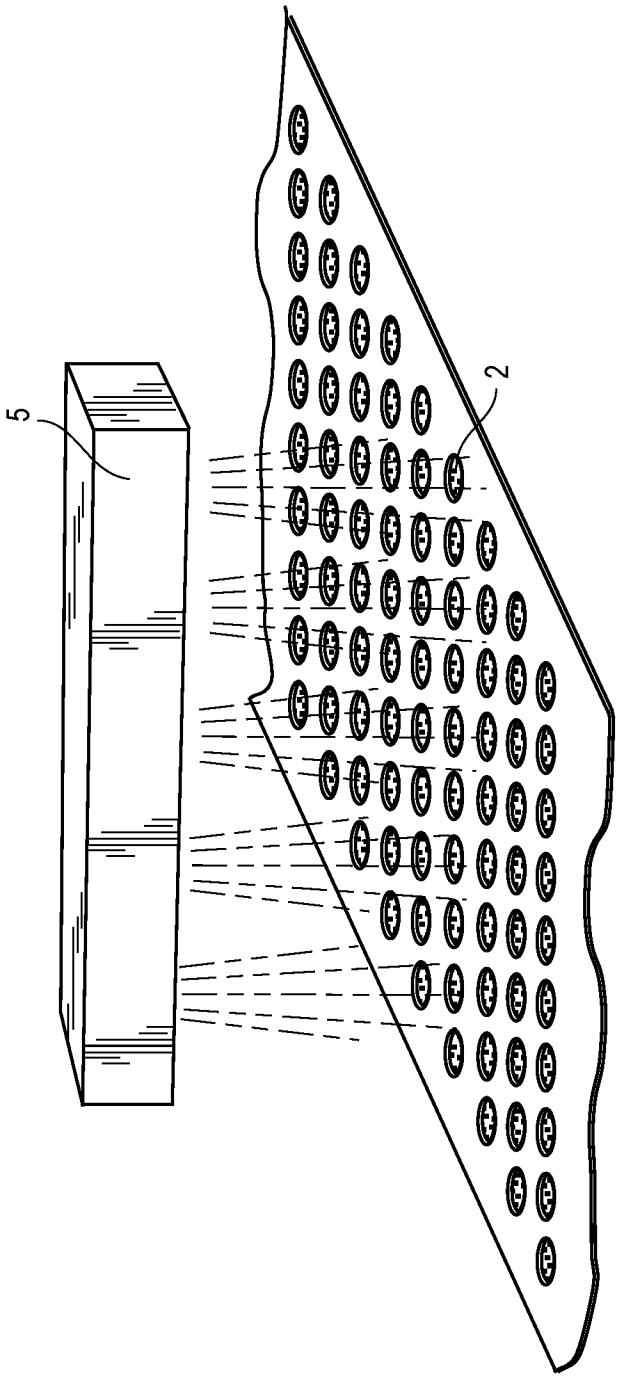


FIG. 5

FIG. 6

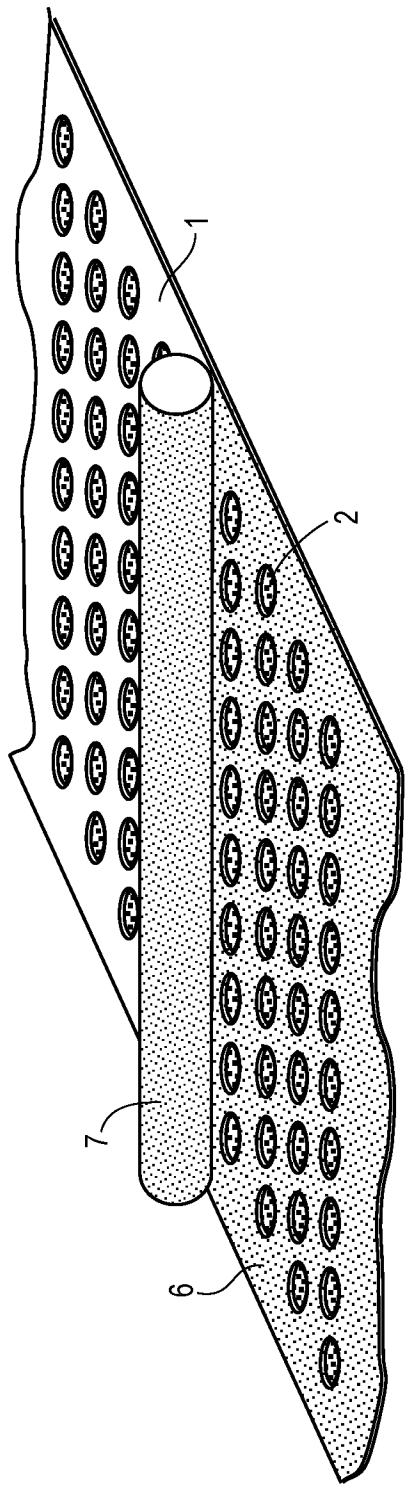


FIG. 7

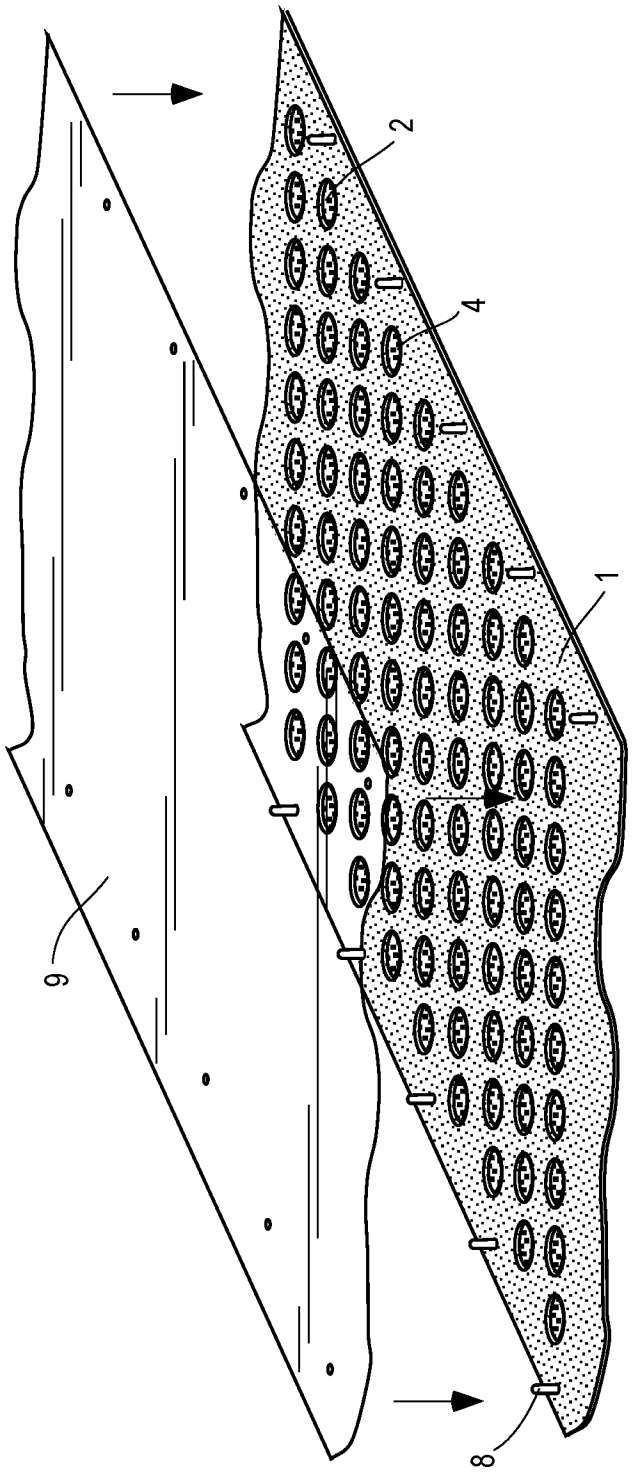


FIG. 8

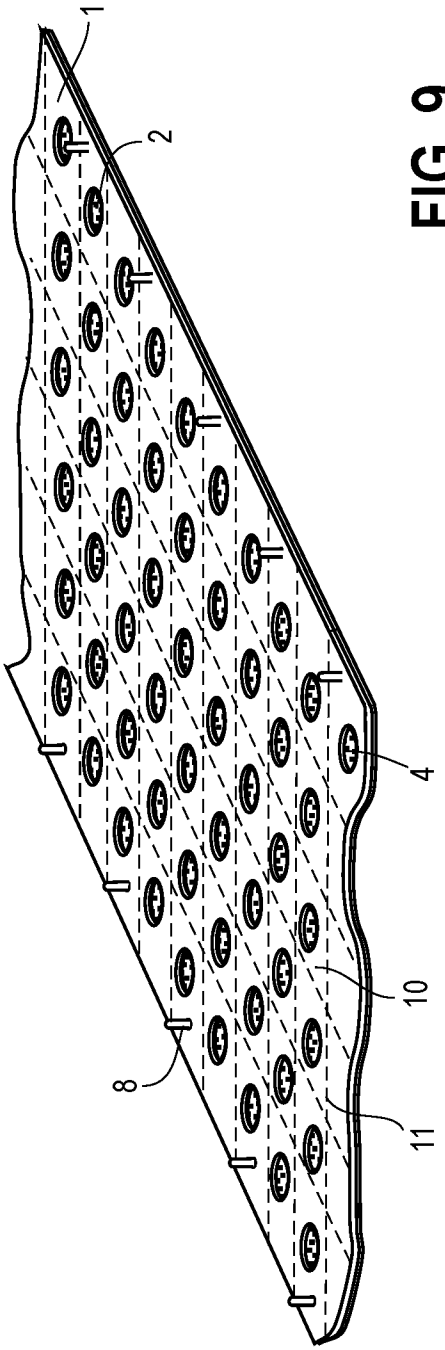


FIG. 9

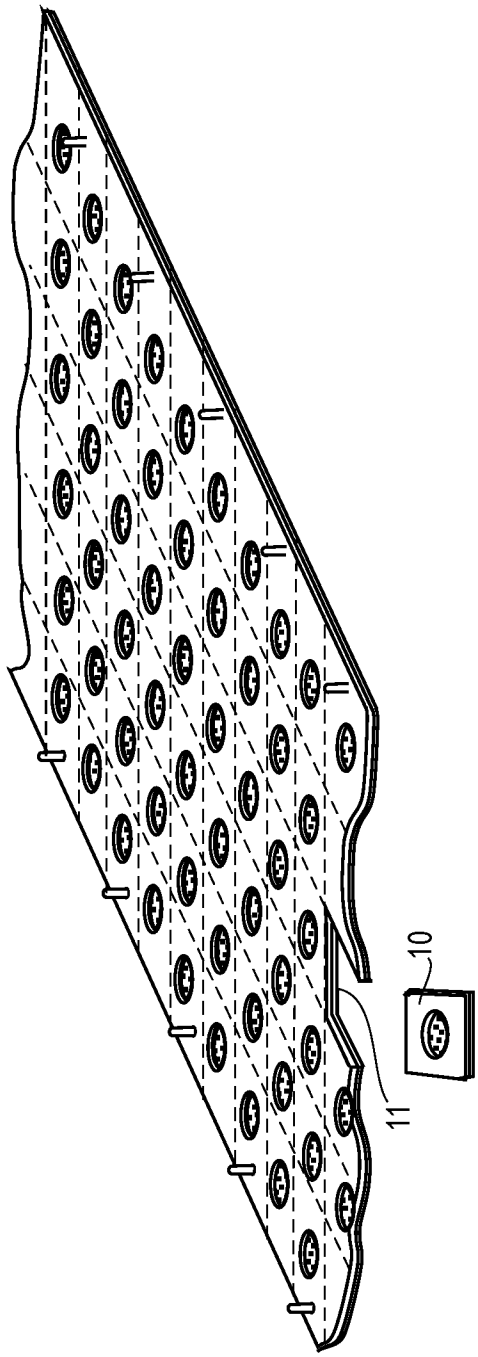


FIG. 10A

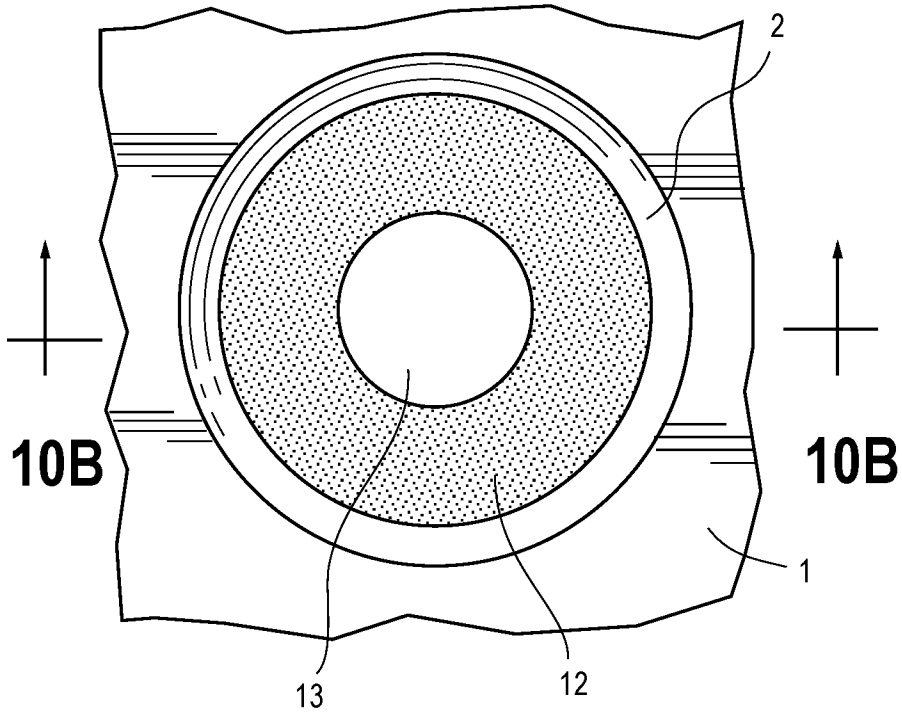


FIG. 10B

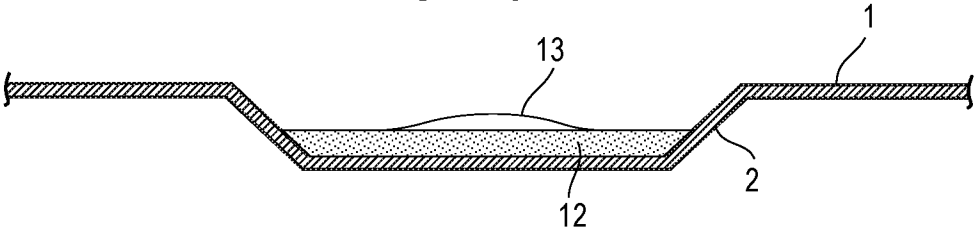


FIG. 11A

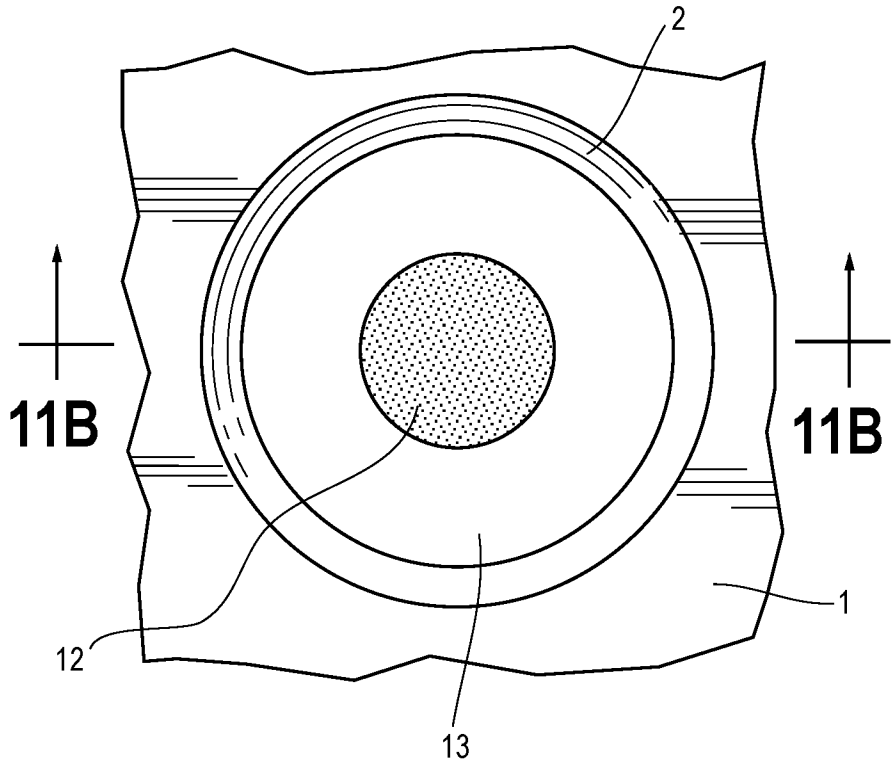


FIG. 11B

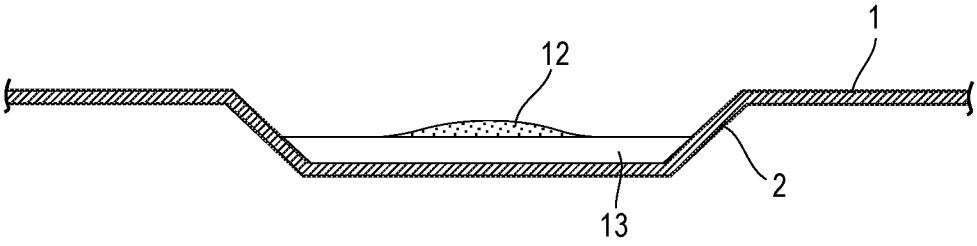


FIG. 12

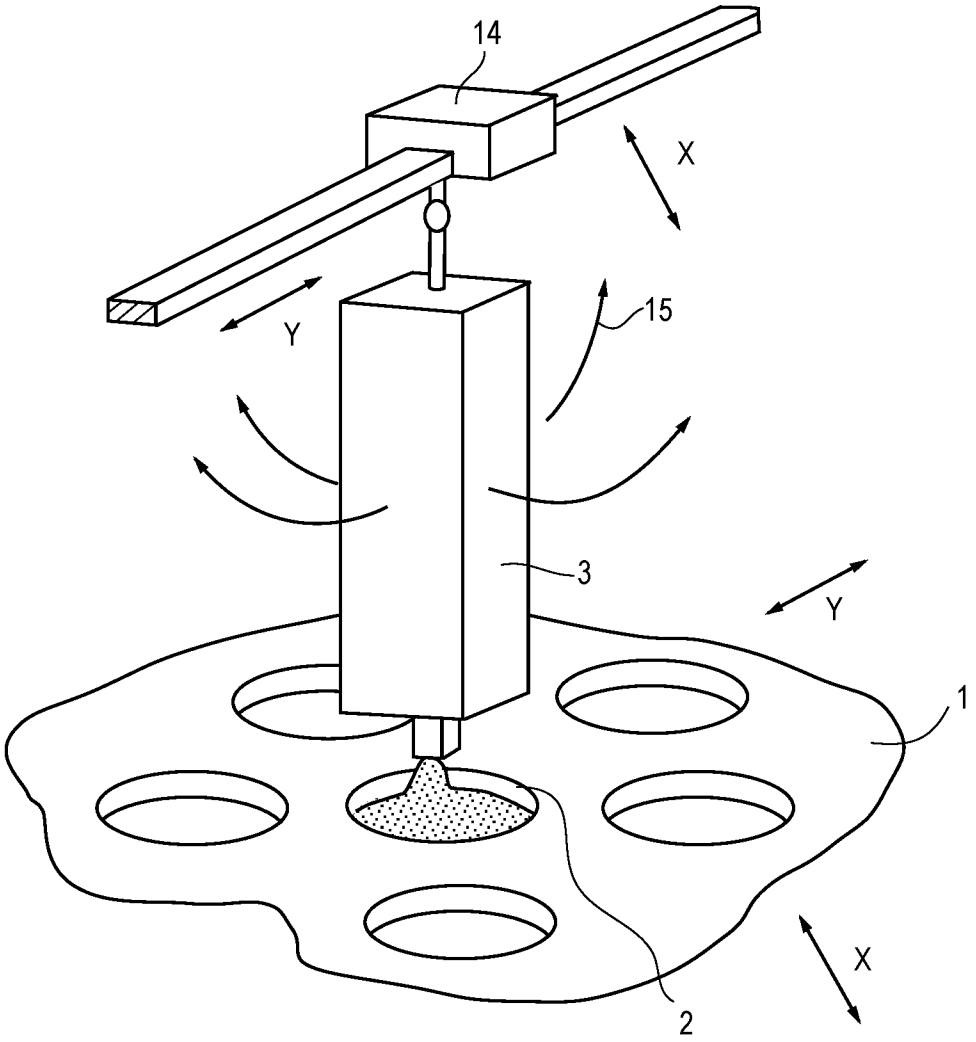


FIG. 13

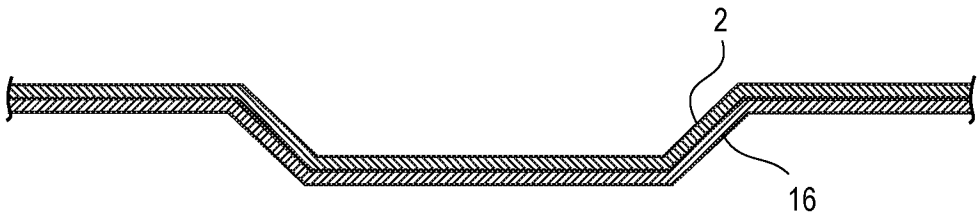
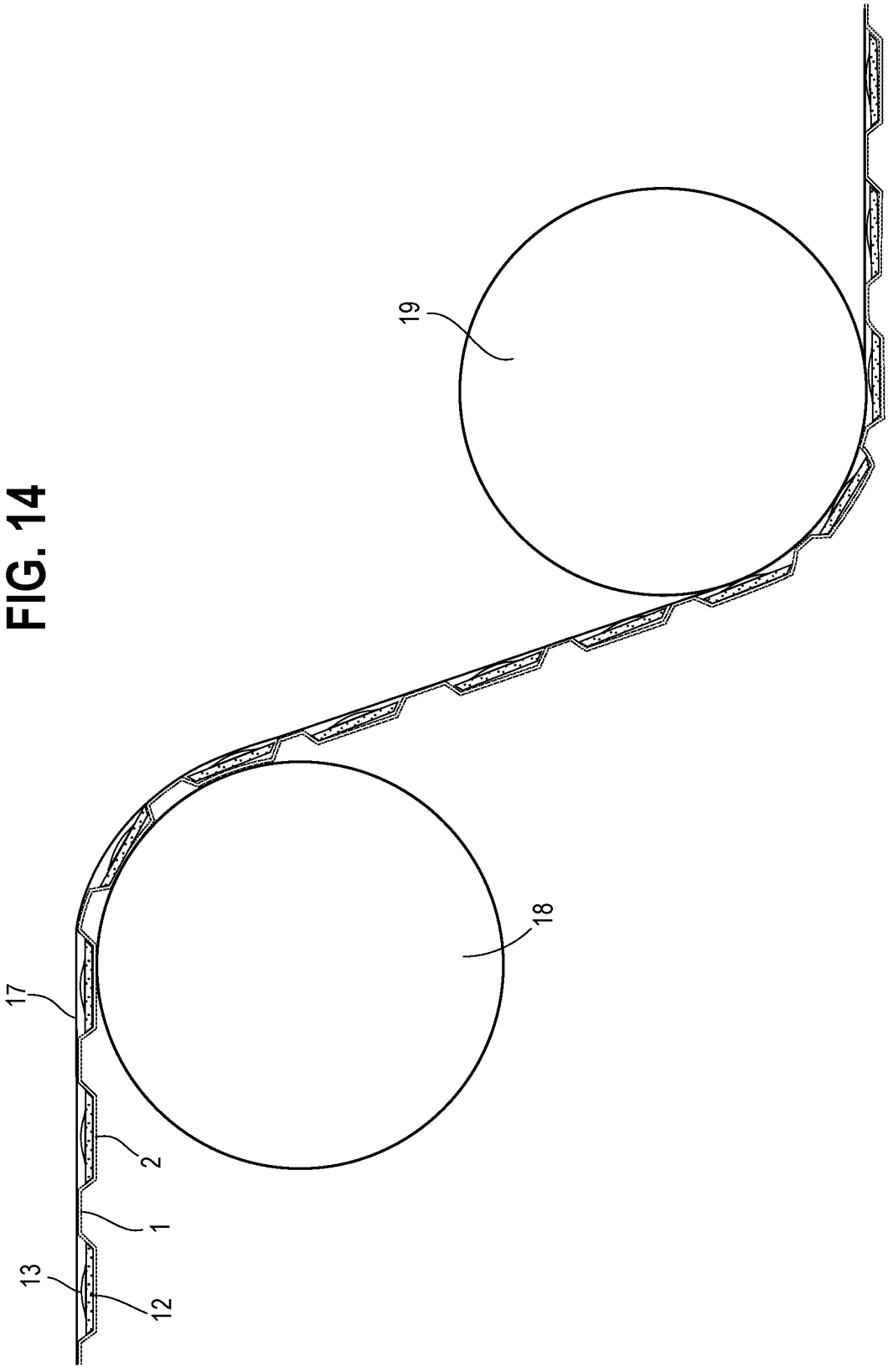


FIG. 14



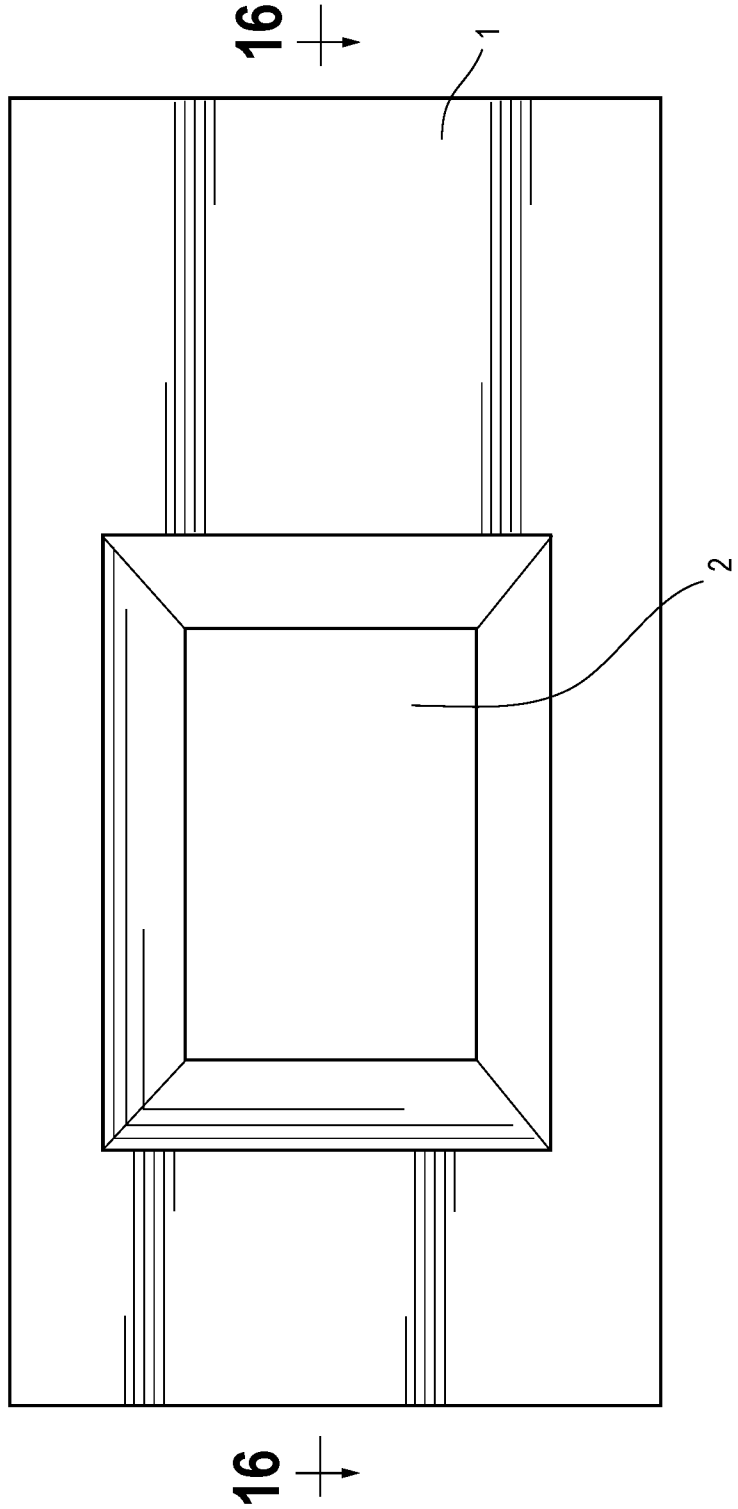


FIG. 15

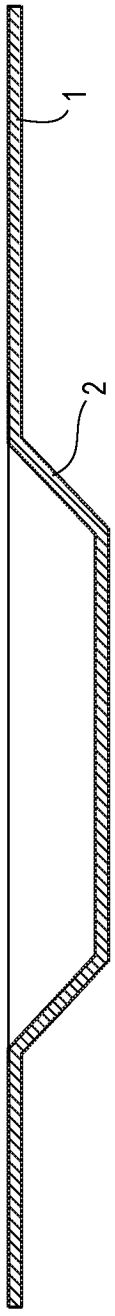


FIG. 16

FIG. 17

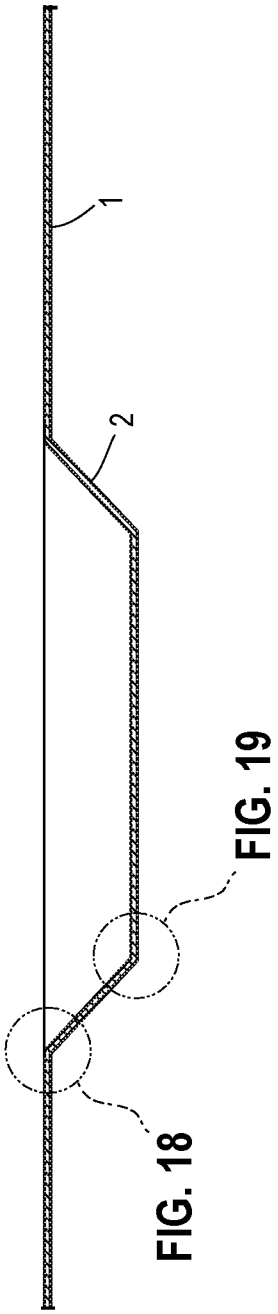


FIG. 19

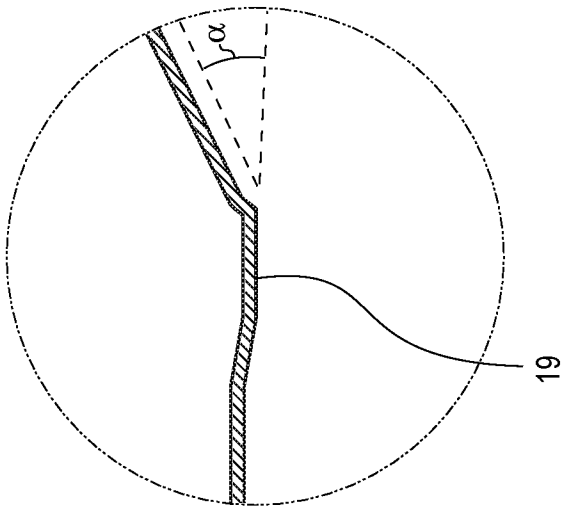


FIG. 18

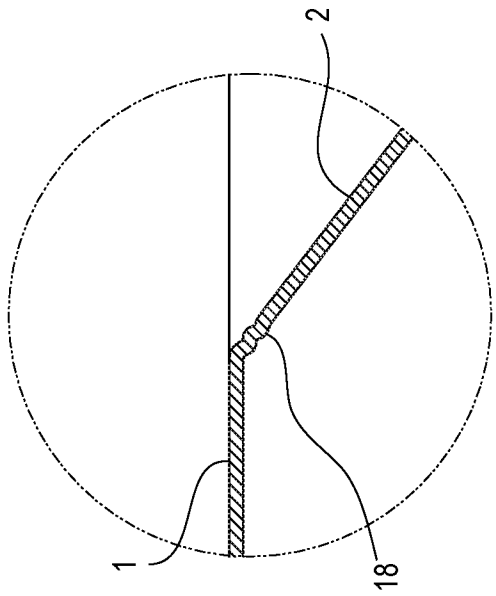


FIG. 20A

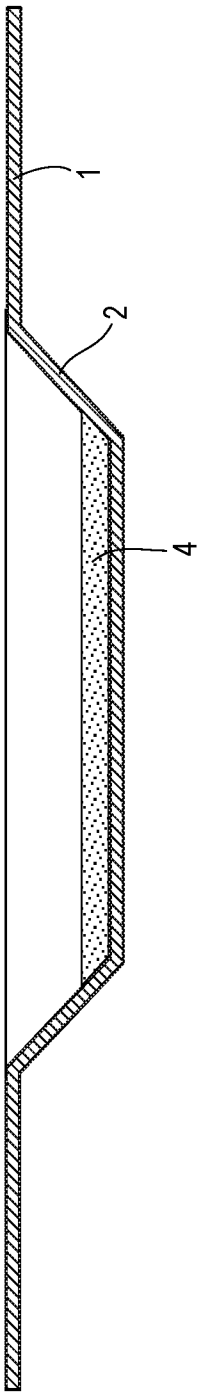
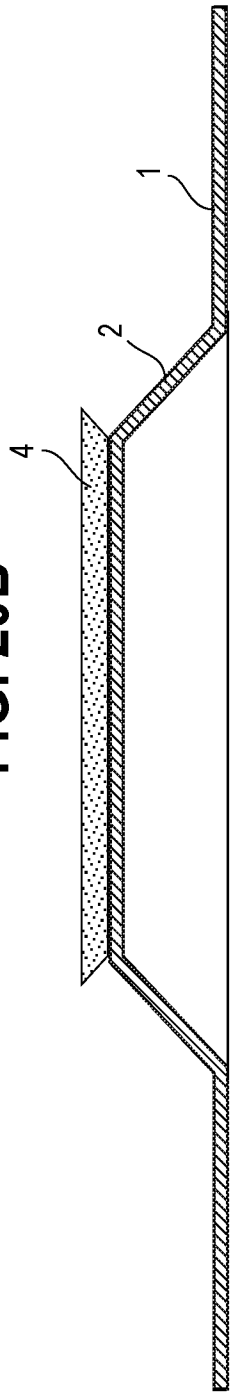


FIG. 20B



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/41065

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 9/00; A61K 9/70 (2021.01)
CPC - A61K 9/0056; A61K 9/006; A61K 9/7007

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2020/0108012 A1 (NOVA Thin Film Pharmaceuticals LLC) 9 April 2020 (09.04.2020) Entire document, especially Abstract, para [0068]; [0070]-[0071]; [0091]; [0095]; [0103]; [0108]-[0109]; [0115]; [0118]; [0141]; [0196]; [0202]; [0245]-[0246]; [0250]; [0252]; [0255]; [0275]-[0276]; [0278]; [0282]; [0296]; [0308]-[0309]; [0311]; [0313]; [0330]; [0361]; [0375]; Fig. 8-9	1-2, 10-13, 18-25 --- 3-7, 27-29
X --- Y	US 8,252,234 B2 (Clarke et al.) 28 August 2012 (28.08.2012) Entire document, especially Abstract, col 4 ln 55-60; col 11 ln 6-22, 37-41; col 14 ln 43-45; col 15 ln 38-51; col 24 ln 32-36; col 28 ln 38-41; col 29 ln 2-5	8-9 --- 3-7, 28-29
X	US 2014/0170204 A1 (Desai et al.) 19 June 2014 (19.06.2014) Entire document, especially Abstract, para [0021]; [0051]; [0090]; [0094]-[0095]	14
X	US 9,205,089 B2 (Trout et al.) 8 December 2015 (08.12.2015) Entire document, especially Abstract, col 10 ln 40-43; col 13 ln 56-60; col 15 ln 48-54; col 22 ln 16-32; col 24 ln 34-37	15
X	US 2014/0037734 A1 (Monosol Rx, LLC) 6 February 2014 (06.02.2014) Entire document, especially Abstract, [0091]; [0117]; [0298]	26

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
8 November 2021 (08.11.2021)	DEC 17 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/41065

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 9,433,638 B1 (University of Kentucky Research Foundation) 6 September 2016 (06.09.2016) Entire document, especially Abstract, col 3 ln 26-47; col 4 ln 62-63; col 5 ln 4-24; col 9 ln 35-39	27
A	US 2009/0010998 A1 (Marchitto et al.) 8 January 2009 (08.01.2009) Entire document	1-15, 18-29
A	US 7,557,167 B2 (Swetlin et al.) 7 July 2009 (07.07.2009) Entire document	1-15, 18-29
A	US 7,425,292 B2 (Yang et al.) 16 September 2008 (16.09.2008) Entire document	1-15, 18-29
A	US 2006/0257463 A1 (Elsohly et al.) 16 November 2006 (16.11.2006) Entire document	1-15, 18-29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/41065

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

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

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

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

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

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

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

-- See Extra Sheet --

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.:
1-15, 18-29

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

International application No.

PCT/US 21/41065

Continuation of:
Box III: Observations where unity of invention is lacking

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

Group I: Claims 1-2, 13-15, 20-24, and 26-27 directed to films made by deposit, comprising: a first soluble layer not containing a pharmaceutical active agent; and a second soluble layer provided on the first soluble layer by depositing a solution comprising materials forming the second soluble layer to form the solution into a film on the first soluble layer, the second soluble layer containing at least one pharmaceutical active agent and having a surface area different than a surface area of the first soluble layer, wherein the first soluble layer is a mucoadhesive layer or a slowly dissolving backing layer; films wherein at least part of an edge portion of the soluble film is thicker than a center portion; wherein the soluble film contains one or more holes through the film; wherein the soluble film has a moisture content of 15% or greater; films comprising at least one non-cannabinoid bioactive agent and at least one cannabinoid; films made by deposit in a well, wherein the film comprises an effective amount of at least one release agent selected from the group of: polystyrene powder or breads, polymethacrylates and cholestyramine to facilitate release of the dried film from the well; and films for oromucosal delivery made by deposit in a well, wherein the film comprises a plurality of separate domains, at least one domain comprising a prodrug and at least one other domain comprising at least one catalyst.

Group II: Claims 3-12, 18-19, 25, and 28-29 directed to a system for manufacturing a pharmaceutical active agent-containing soluble film by deposit, comprising: a gantry moveable horizontally in at least an X and Y direction; a nozzle supported on the gantry, the nozzle being configured to be connected to a source of a film forming composition containing a pharmaceutical active agent, and a support configured to support a sheet having a plurality of wells, wherein the gantry and nozzle are configured to deposit the film forming composition into the well in a pattern by moving the gantry horizontally in the X or Y direction; a system for manufacturing a pharmaceutical active agent-containing soluble film by deposit, comprising: a support; a nozzle moveably supported on the support, the nozzle being configured to be connected to a source of a film forming composition containing a pharmaceutical active agent, and wherein the nozzle is configured articulate to deposit the film forming composition into the well in a shape selected from the group of: circular, elliptical, polygonal and zig-zag; a system for forming a pharmaceutical active agent-containing soluble film, comprising a sheet including a well of predetermined size, the sheet being softenable by heat, and a support containing a sub-well of a size large enough to accommodate the well, wherein the well of the sheet is provided in the sub-well; a method for forming a pharmaceutical active agent-containing soluble film, comprising: providing a sheet including a well of predetermined size, the sheet being softenable by heat onto a support containing a sub-well of a size large enough to accommodate the well, wherein the well of the sheet is provided in the sub-well; and depositing a film forming composition containing a pharmaceutical active agent into the well; a method for promoting release of a soluble film from a surface of a package, comprising providing a sheet with a plurality of wells, an soluble film provided in the bottom of each well and a top sheet covering the plurality of wells, and passing the sheet partially around at least one roller to bend the bottom surface of the well to promote release of an soluble film from the bottom of the well; a sheet containing a well for forming a soluble film therein, wherein the well has side portions configured to collapse when a bottom of the well is pushed upwards to present the soluble film for use; a method of making a film composition with a heat sensitive active agent, comprising: forming an absorbent film by deposit in a well, wherein the absorbent film comprises at least one absorbent agent that is soluble or substantially insoluble excipients that impart a porous structure to the film, the at least one absorbent agent being at least one selected from the group of: ethyl cellulose, cellulose powder, microcrystalline cellulose, nanocrystalline cellulose, polymethacrylates, and silicon dioxide; drying or substantially drying the film, wherein the absorbent agent is at least 3% of the dried film mass; depositing a heat sensitive active agent on the dried film, wherein the heat sensitive agent is dissolved or suspended in a solvent; and allowing the deposited solvent to percolate within a matrix of the dried or substantially dried absorbent film; and a method of making a film in a well, comprising: depositing a film former and at least one active agent in a well by at least one deposit nozzle provided on a moveable x-y gantry, wherein no mechanical intervention is used to form the film; and drying the film; and applying a top sheet on the film in the well, wherein depositing the film, drying the film and applying the top sheet are performed on a single production line.

Group III: Claims 16 and 17 directed to a packaged pharmaceutical active agent-containing soluble film made by deposit, comprising a soluble film containing at least one pharmaceutical active agent, wherein the soluble film contains a crystallization component configured to cause intentional crystallization to promote release of the soluble film from a surface of the package; and a palletized stack of packaged pharmaceutical active agent-containing soluble films made by deposit, each packaged pharmaceutical active agent-containing soluble film comprising a package comprising a bottom sheet including a well, a soluble film containing at least one pharmaceutical active agent provided in the well, and a top sheet covering the soluble film containing at least one pharmaceutical active agent provided in the well, wherein the packages are provided in the palletized stack upside-down with the top sheet provided on the bottom and the well provided on the top.

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

Special Technical Features:

Group I requires a film made by deposit, the film comprising at least one non-cannabinoid bioactive agent and at least one cannabinoid, not specifically required by Groups II-III.

Group II requires a system for manufacturing a pharmaceutical active agent-containing soluble film by deposit, comprising: a gantry moveable horizontally in at least an X and Y direction; a nozzle supported on the gantry, not specifically required by Groups I or III.

Group III requires a palletized stack of packaged pharmaceutical active agent-containing soluble films made by deposit, wherein the packages are provided in the palletized stack upside-down with the top sheet provided on the bottom and the well provided on the top, not specifically required by Groups I-II.

-- See Extra Sheet --

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/41065

Continuation of:
Box III: Observations where unity of invention is lacking

Common Technical Features:

Groups I-III share the technical feature of a film made by deposit in a well, comprising: a pharmaceutical active agent in a well.

Groups II and III share the technical feature of a film made by deposit in a well, comprising: a soluble sheet with a plurality of wells, and a top sheet covering the soluble film with the wells.

However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated by US 2020/0108012 A1 to NOVA Thin Film Pharmaceuticals LLC (hereinafter 'NOVA'). NOVA discloses a film made by deposit in a well (Abstract - '...The oral soluble film may be made, e.g., by a method comprising providing a well of a predetermined size; depositing a film forming composition in the well...'), comprising: a pharmaceutical active agent in a well (para [0073] - '...If sequential deposition is used, the active agent composition is preferably but not necessarily deposited in the well first and then the film forming composition is deposited in the well...').

Groups II and III share the technical feature of a film made by deposit in a well, comprising: a soluble sheet with a plurality of wells, and a top sheet covering the soluble film with the wells.

NOVA discloses a film made by deposit in a well (Abstract - '...The oral soluble film may be made, e.g., by a method comprising providing a well of a predetermined size; depositing a film forming composition in the well...'), comprising: a soluble sheet with a plurality of wells, and a top sheet covering the soluble film with the wells (para [0108] - '...One aspect of the present invention involves an alignment system to ensure the mold or well sheet is aligned with the top sheet...'; para [0118] - '...One aspect of the invention involves a rolled adhesive onto the dried bottom sheet/mold/well edges, but excluding the interior of the sheet/mold/wells, so that top sheet can be adhered...'; para [0275] - '...This may be accomplished by incorporating a variety of different soluble or insoluble polymers and may also include biodegradable polymers in combination...').

As the shared technical features were known in the art at the time of the invention, they cannot be considered common technical features that would otherwise unify the groups. Therefore, Groups I-III lack unity under PCT Rule 13.