CURE PHARMACEUTICAL

PATENT PORTFOLIO OVERVIEW

The advantages below are present with multiple CURE products and platform technologies. Some of these advantages are expressly described in CURE's patent documents, as shown below. Other advantages are present in specific products and platform technologies but not outlined in the patent documents. Additionally, the patent documents below are publicly available. As such, additional advantages are described in pending and unpublished patent documents.

<u>Oral thin films (OTFs) compared to other dosage forms (e.g., tablets and capsules)</u>

- Potential for rapid onset of action (especially useful for, e.g., motion sickness, erectile dysfunction, seizures, allergic attack or coughing, bronchitis or asthma) – Can rapidly dissolve and disintegrate in the oral cavity because of surface area which has potential for lowering dosage interval, improvement of onset of action (high capillary area), can also improve safety profile of therapy, e.g., reduce gastric irritation or absorption issues.
- Convenient administration. Difficulty swallowing tablets and capsules can be a problem for many individuals and can lead to a variety of adverse events and patient noncompliance with treatment regimens. It is estimated that over 16 million people in the United States have some difficulty swallowing, also known as dysphagia. Studies in adults evaluating the effect of tablet and capsule size on ease of swallowing suggest that increases in size are associated with increases in patient complaints related to swallowing difficulties at tablet sizes greater than approximately 8 mm in diameter.
- Can readily be taken without the need for water or beverage
- Configured and has the physical dimensions such that it is relatively easy and convenient to store and carry (patient can conveniently carry multiple dissolvable films in his pocket or wallet)
- A single dose of strip can be carried individually without requiring the secondary container. Even though not necessarily sterile, they don't contact other doses as they are packed individually. Tensile strength and plasticity of OTF strips allow for handling single, individual dose units without damage to the dosage form.
- Upon administrating, there will be a relatively low risk of the patient choking (especially good for patients suffering from motion sickness, dysphagia, repeated emesis)
- High patient compliance
- Offers patent extension of active ingredients and methods of use thereof
- Can be administered easily for bedridden and non-cooperative patients (e.g., geriatric, pediatric, and psychiatric). They are hard to spit out.
- Improved carbon footprint
- Improved anti-counterfeit management and dose management
- Adaptable for use with dispensing devices for pharmacy preparation or self-administration
- Oral films are more flexible and are not brittle as ODTS
- Accuracy in the administered dose can be better assured for each strip or film
- Can be easily and conveniently handled, stored, and transported

- Potential to buccally administer active ingredients that degrade in the GI tract

CURE's OTFs compared to other thin films

- Multiple and unique ways to mask the bitter taste of active ingredient – pleasant tasting even with bitter active ingredient
    - Patent #10092611: Pharmaceutical composition and method of manufacturing ("The thin film described herein can include a bitter blocker. "Bitter blocker" refers to a substance capable of blocking or diminishing the bitter taste of another substance.")
    - Patent # US20140335153: THIN FILM WITH HIGH LOAD OF ACTIVE INGREDIENT ("One advantage of the encapsulation of the thin films described herein is the ability to employ bitter substances (e.g., bitter active ingredients), while having the bitter flavor of those substances be at least partially masked…"; "The present invention provides a thin film (e.g., an oral thin film) that includes: (a) solvent, (b) binder, (c) lipid, (d) emulsifier, and (e) active ingredient. The thin film can optionally further include at least one of a flavoring agent, a sweetener, a dye or pigment, a preservative, a powder coating, a bitter blocker, and an absorption enhancer. Additionally, the active ingredient can optionally be at least partially encapsulated by the lipid."; Claim #62: "The thin film of any one of the above embodiments, further including a bitter blocker.")
    - Patent # US20170100327: PHARMACEUTICAL COMPOSITION WITH IONICALLY CROSSLINKED POLYMER ENCAPSULATION OF ACTIVE INGREDIENT ("One advantage of the encapsulation of the thin films described herein is the ability to employ bitter substances (e.g., bitter active ingredients), while having the bitter flavor of those substances be at least partially masked. The encapsulation can be partial or complete."; Claim #20: "The present invention also provides the composition of any one of the above embodiments, wherein the first ionically-functionalized polymer is at least partially ionically crosslinked to at least one of the second ionically-functionalized polymer and polyionic compound, such that the crosslinking provides a matrix that at least partially encapsulates the active ingredient.")
    - Patent # 8999372: Methods for modulating dissolution, bioavailability, bioequivalence and drug delivery profile of thin film drug delivery systems, controlled-release thin film dosage formats, and methods for their manufacture and use ("…the microencapsulation of active ingredients in accordance with the present invention provides other advantages, including decreasing the rate of degradation of active ingredients by moisture and oxidation, evaporation and sublimation. In addition, the active ingredient is protected from reacting with other ingredients, and the unpleasant taste of some active ingredients may be effectively masked."; "The first polymeric material in the coacervation process is generally one that… (3) provides for effective taste masking of the drug, if that is the goal desired…")
- Can load multiple active ingredients on same strip
    - Patent # US20150174068: Apparatus, Composition, and Related Methods for Transdermal Delivery of Active Ingredients (Claim #1: "A composition for applying to skin, the composition comprising: one or more pharmaceutically active ingredients contained in a plurality of hydrophobic carriers dispersed throughout a hydrogel…")

- Patent # 10092611: Pharmaceutical composition and method of manufacturing ("In specific embodiments, the color of the thin film can indicate the contents (e.g., one or more active ingredients) contained therein.")
- Patent # 8840919 Method and apparatus for minimizing heat, moisture, and shear damage to medicants and other compositions during incorporation of same with edible films (Example I: "Benzocaine powder (as a medicant) is combined with carboxymethylcellulose powder (as an adhesive), modified food starch (as a bulking agent), carrageenan (as adhesive), sucralose (intense sweetener), talc (as flow/partitioning agent), and menthol (as a medicant) in a fluidized bed container to form a powder matrix… powder matrix is drawn from the fluidized bed container and is applied to the upper exposed surface of the film layer…" & Example II: "Coral calcium powder (as a medicant) is combined with carboxymethylcellulose powder (as an adhesive), modified food starch (as a bulking agent), carrageenan (as adhesive), sucralose (intense sweetener), talc (as flow/partitioning agent), menthol (as a medicant), and a lipid in a fluidized-bed container to produce a powder matrix.")
- Patent # US20140335153: THIN FILM WITH HIGH LOAD OF ACTIVE INGREDIENT ("This can be advantageous in those embodiments wherein multiple active ingredients are employed, each having different chemical and/or physical properties (e.g., pharmacokinetics, absorption kinetics, stability, solubility, bioavailability, etc.). The thin films described herein therefore possess the potential to allow the development of sensitive drug targets that may otherwise not be feasible in tablet or liquid formulations."; "It is also possible to combine any active ingredient described herein with one or more other active ingredients in a unitary dosage form for simultaneous or sequential administration to a patient.")
- Patent # US20170100327: PHARMACEUTICAL COMPOSITION WITH IONICALLY CROSSLINKED POLYMER ENCAPSULATION OF ACTIVE INGREDIENT ("This can be advantageous in those embodiments wherein multiple active ingredients are employed, each having different chemical and/or physical properties (e.g., pharmacokinetics, absorption kinetics, stability, solubility, bioavailability, etc.). The thin films described herein therefore possess the potential to allow the development of sensitive drug targets that may otherwise not be feasible in tablet or liquid formulations."; "The sweetener can include one or more artificial sweeteners, one or more natural sweeteners, or a combination thereof."; "In specific embodiments, the color of the thin film can indicate the contents (e.g., one or more active ingredients) contained therein.")
- Patent #9561182: Edible films for administration of medicaments to animals, methods for their manufacture and methods for their use for the treatment of animals ("The applied coating is a powder matrix including one or more medicants.")
- Patent # 8999372: Methods for modulating dissolution, bioavailability, bioequivalence and drug delivery profile of thin film drug delivery systems, controlled-release thin film dosage formats, and methods for their manufacture and use ("The applied coating includes a powder matrix having one or more active ingredients… one or more controlled-release active ingredients."; "While in accordance with this embodiment of the invention one or more active ingredients may be contained in either layer, preferably the dry coat layer will contain one or more active ingredients."

    - Patent # 9155698: Method and apparatus for minimizing heat, moisture, and shear damage to medicants and other compositions during incorporation of same with edible films ("The applied coating is a powder matrix including one or more medicants.")
    - Patent # WO/2013/039994A2: APPARATUS, COMPOSITION, AND RELATED METHODS FOR TRANSDERMAL DELIVERY OF ACTIVE INGREDIENTS (Claim #1: "A composition for applying to skin, the composition comprising: one or more pharmaceutically active ingredients contained in a plurality of hydrophobic carriers dispersed throughout a hydrogel")
    - Patent #WO/2013/039994A3: APPARATUS, COMPOSITION, AND RELATED METHODS FOR TRANSDERMAL DELIVERY OF ACTIVE INGREDIENTS ("a composition for applying to skin comprises one or more pharmaceutically active ingredients contained in a plurality of hydrophobic carriers dispersed throughout a hydrogel")
- Can accommodate high drug load (e.g., > 200 mg)
    - Patent # US20140335153: THIN FILM WITH HIGH LOAD OF ACTIVE INGREDIENT ("In various embodiments, the thin film described herein can be manufactured to include a relatively high load of active ingredient. For example, the active ingredient can be present in about 25-40 wt. %.")
    - Patent # US20170100327: PHARMACEUTICAL COMPOSITION WITH IONICALLY CROSSLINKED POLYMER ENCAPSULATION OF ACTIVE INGREDIENT ("The thin films described herein can be useful to deliver a high load of active ingredients to the intended target… thin film can be manufactured to include a relatively high load (e.g., up to about 40 wt. %) of active ingredient.")
    - Patent # 8999372: Methods for modulating dissolution, bioavailability, bioequivalence and drug delivery profile of thin film drug delivery systems, controlled-release thin film dosage formats, and methods for their manufacture and use ("The pharmaceutically active ingredient or agent may be present in any effective amount, including, for example, in an amount ranging from about 0.5 to 40 wt. %, 1 to 30 wt. %, 5 to 15 wt. %, 0.5 to 15 wt. %.")
- Quickly dissolving/disintegrating (e.g., < 2 minutes)
    - Patent # 10092611: Pharmaceutical composition and method of manufacturing ("In specific embodiments, advantages of OTFs include the thin film is typically more stable, durable and quicker dissolving than many other conventional dosage forms.")
    - Patent # 8840919 Method and apparatus for minimizing heat, moisture, and shear damage to medicants and other compositions during incorporation of same with edible films (Claim #1: "A method of manufacturing a rapidly dissolving thin film for delivering a medicant in the oral cavity, comprising the steps of: providing a film layer, wherein the film layer is rapidly dissolving…"; Claim #2: "The method of claim 1 wherein the film layer dissolves within thirty seconds of being placed in an oral cavity."; Claim #3: "The method of claim 1 wherein the film layer dissolves within fifteen seconds of being placed in the oral cavity.")
    - Patent # US20140335153: THIN FILM WITH HIGH LOAD OF ACTIVE INGREDIENT ("In various embodiments, the thin film described herein provides for a stable, durable and quick dissolving dosage form.")
    - Patent # US20170100327: PHARMACEUTICAL COMPOSITION WITH IONICALLY CROSSLINKED POLYMER ENCAPSULATION OF ACTIVE INGREDIENT ("The thin films can be prepared typically using hydrophilic polymers

that rapidly dissolve on the tongue or buccal cavity, delivering the active ingredient to the systemic circulation via dissolution when contact with liquid is made.
    - Patent #9561182: Edible films for administration of medicaments to animals, methods for their manufacture and methods for their use for the treatment of animals ("The film has an acceptable dissolution rate in the oral cavity for a particular thickness of film. For example, if the film has a thickness of 50 microns, it may be desirable for the film to dissolve in the oral cavity within about fifteen seconds.")
    - Patent # 8999372: Methods for modulating dissolution, bioavailability, bioequivalence and drug delivery profile of thin film drug delivery systems, controlled-release thin film dosage formats, and methods for their manufacture and use ("A film in accordance with the present invention is generally of a size adapted such that the film is fast dissolving."; "The film has an acceptable dissolution rate in the oral cavity for a particular thickness of film. For example, if the film has a thickness of 50 microns, it may be desirable for the film to dissolve in the oral cavity within about fifteen seconds.")
    - Patent # 9155698: Method and apparatus for minimizing heat, moisture, and shear damage to medicants and other compositions during incorporation of same with edible films ("The film has an acceptable dissolution rate in the oral cavity for a particular thickness of film. For example, if the film has a thickness of 50 microns, it may be desirable for the film to dissolve in the oral cavity within about fifteen seconds.")
- Potential for low moisture level (e.g., < 10 wt.% water)
    - Patent # 10092611: Pharmaceutical composition and method of manufacturing (Claim # 19. The thin film of claim 1, having a moisture content of less than about 10 wt. % water.")
    - Patent # 8840919 Method and apparatus for minimizing heat, moisture, and shear damage to medicants and other compositions during incorporation of same with edible films ("The dry powder matrix will normally contain a minor amount of retained or bound water or other liquid, typically less than about ten percent by weight.")
    - Patent # US20140335153: THIN FILM WITH HIGH LOAD OF ACTIVE INGREDIENT ("In the above formulations, the finished product may include about 8-10 wt. % moisture.")
    - Patent #9561182: Edible films for administration of medicaments to animals, methods for their manufacture and methods for their use for the treatment of animals ("The dry powder matrix will normally contain a minor amount of retained or bound water or other liquid, typically less than about ten percent by weight.")
    - Patent # 8999372: Methods for modulating dissolution, bioavailability, bioequivalence and drug delivery profile of thin film drug delivery systems, controlled-release thin film dosage formats, and methods for their manufacture and use ("The dry powder matrix will normally contain a minor amount of retained or bound water or other liquid, typically less than about ten percent by weight.")
    - Patent # 9155698: Method and apparatus for minimizing heat, moisture, and shear damage to medicants and other compositions during incorporation of same with edible films ("The dry powder matrix will normally contain a minor amount of retained or bound water or other liquid, typically less than about ten percent by weight.")

- Can achieve desired performance characteristics while maintaining pleasant feeling in the mouth (e.g., soft, plush feeling with bendable & pliable strip)
    - Patent # 10092611: Pharmaceutical composition and method of manufacturing ("In specific embodiments, the thin film described herein can be soft. "Soft" refers to an article being relatively smooth and agreeable to the touch; not rough or coarse. Such an article will be capable of producing agreeable sensations, pleasant or comfortable, upon contact with an animal such as a human.")
    - Patent # 8840919 Method and apparatus for minimizing heat, moisture, and shear damage to medicants and other compositions during incorporation of same with edible films ("… the film layer can be produced using a highly water-soluble polymer comprising a natural or synthetic water-soluble polymer. The polymer preferably has good film moldability, produces a soft flexible film, and is safe for human consumption."; "The smoother powder matrix layer also improves the feel to an individual of the medicant composition in the mouth because the medicant composition is not as dry on the tongue.")
    - Patent # US20140335153: THIN FILM WITH HIGH LOAD OF ACTIVE INGREDIENT (Claim #51: "The thin film of any one of the above embodiments, which is palatable to a human."; Claim #54: "The thin film of any one of the above embodiments, which is pliable."; Claim #57: "The thin film of any one of the above embodiments, which is relatively soft to touch.")
    - Patent # US20170100327: PHARMACEUTICAL COMPOSITION WITH IONICALLY CROSSLINKED POLYMER ENCAPSULATION OF ACTIVE INGREDIENT ("Claim #42: The present invention also provides a thin film manufactured from the composition of any one of the above embodiments, which is palatable to a human."; Claim #45: "The present invention also provides a thin film manufactured from the composition of any one of the above embodiments, which is pliable."; Claim #48: "The present invention also provides a thin film manufactured from the composition of any one of the above embodiments, which is relatively soft to touch.")
    - Patent #9561182: Edible films for administration of medicaments to animals, methods for their manufacture and methods for their use for the treatment of animals ("The film layer is made from any polymer, softener, filler, matrix, or other composition."; "The gel can, if desired, cause the strip to become chewable, similar to a very soft jelly-bean."; "The smoother powder matrix layer also improves the feel to an individual of the medicant composition in the mouth because the medicant composition is not as dry on the tongue.")
    - Patent # 8999372: Methods for modulating dissolution, bioavailability, bioequivalence and drug delivery profile of thin film drug delivery systems, controlled-release thin film dosage formats, and methods for their manufacture and use ("An edible film in accordance with the present invention may be made from any effective polymer, softener, filler, matrix, or other composition."; "The polymer preferably has good film moldability, produces a soft flexible film, and is safe for human consumption."; "The gel can, if desired, cause the strip to become chewable, similar to a very soft jelly-bean.")
    - Patent # 9155698: Method and apparatus for minimizing heat, moisture, and shear damage to medicants and other compositions during incorporation of same with edible films ("The polymer preferably has good film moldability, produces a soft flexible film, and is safe for human consumption."; "The smoother powder matrix

layer also improves the feel to an individual of the medicant composition in the mouth because the medicant composition is not as dry on the tongue.")

- Can achieve desired performance characteristics while formulating active ingredients with stability issues (e.g., pH, light, heat, moisture, and air)
    - Patent # 8840919 Method and apparatus for minimizing heat, moisture, and shear damage to medicants and other compositions during incorporation of same with edible films ("In a further respect, the invention pertains to a method for making a film including a medicant that minimizes the exposure of the medicant in the film to moisture, heat, and shear during the manufacturing process.")
    - Patent # US20140335153: THIN FILM WITH HIGH LOAD OF ACTIVE INGREDIENT ("… the thin film can be manufactured such that the thin film provides for an immediate release (IR), controlled release (CR), modified release (MR), extended release (ER), or combination thereof, of active ingredient. This can be advantageous in those embodiments wherein multiple active ingredients are employed, each having different chemical and/or physical properties (e.g., pharmacokinetics, absorption kinetics, stability, solubility, bioavailability, etc.). The thin films described herein therefore possess the potential to allow the development of sensitive drug targets that may otherwise not be feasible in tablet or liquid formulations.")
    - Patent # US20170100327: PHARMACEUTICAL COMPOSITION WITH IONICALLY CROSSLINKED POLYMER ENCAPSULATION OF ACTIVE INGREDIENT ("… the thin film can be manufactured such that the thin film provides for an immediate release (IR), controlled release (CR), modified release (MR), extended release (ER), or combination thereof, of active ingredient. This can be advantageous in those embodiments wherein multiple active ingredients are employed, each having different chemical and/or physical properties (e.g., pharmacokinetics, absorption kinetics, stability, solubility, bioavailability, etc.). The thin films described herein therefore possess the potential to allow the development of sensitive drug targets that may otherwise not be feasible in tablet or liquid formulations.")
    - Patent #9561182: Edible films for administration of medicaments to animals, methods for their manufacture and methods for their use for the treatment of animals ("In a further respect, the invention pertains to a method for making a film including a medicant that minimizes the exposure of the medicant in the film to moisture, heat, and shear during the manufacturing process.")
    - Patent # 8999372: Methods for modulating dissolution, bioavailability, bioequivalence and drug delivery profile of thin film drug delivery systems, controlled-release thin film dosage formats, and methods for their manufacture and use ("Said dry coat layer and similar layers are especially effective with low dose active ingredients that require a very low moisture environment to remain stable.")
    - Patent # 9155698: Method and apparatus for minimizing heat, moisture, and shear damage to medicants and other compositions during incorporation of same with edible films (Claim #1:"…wherein the powder matrix, prior to application to the film layer, is admixed in a fluidized bed that minimizes the generation of shear and heat…"; "the invention pertains to a method for making a film including a medicant that minimizes the exposure of the medicant in the film to moisture, heat, and shear during the manufacturing process.")