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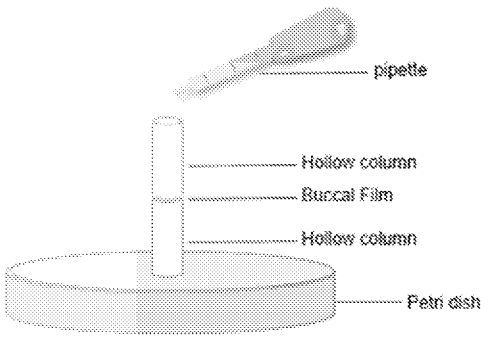

Figure 1

(57) Abstract: The present disclosure concerns methods of compounding an injectable drug into a film or wafer. The method of compounding a drug into a film or wafer comprises solubilising the drug in a pre-mix and optionally in an aqueous medium in order to form a solution; and casting the solution into a mold in order to form the film or wafer. The drug is compounded in its dosage form and is characterised by at least one of the following: unit dose of less than about 200 mg; a volume of less than about 2 mL; a chemical and/or physical stability at less than about 60 °C; and a solubility of more than about 10 mg/mL in a solvent medium.

Methods of Compounding an Injectable Drug into a Film or Wafer and Systems Thereof

Technical Field

The present invention relates, in general terms, to methods of compounding an injectable drug into a film or wafer. The present invention also relates to a system for compounding an injectable drug into a film or wafer.

Background

The parenteral route is the fastest and the second most common way to administer a drug. In this method of administration, drugs are introduced into the body by routes other than the gastrointestinal tract, usually by injection of drugs in form of solution or suspension into the body at various sites and to varying depths using a needle and a syringe. Parenteral administration of drugs can be performed by injection (small volumes), infusion (large volumes), or implant, and while its typical goal is to achieve rapid systemic effects, it can also be used locally on a given region, tissue or organ by injecting the drug substance directly on the site of action, in order to achieve high drug concentrations in the site of action and/or minimize systemic adverse effects. Examples of parenteral administrations are intravenous, intramuscular, and subcutaneous routes.

Patients with clinical dysphagia or medication dysphagia to solid dosage forms (such as tablets and capsules), blocked or excised gastrointestinal tract, chronic neurological, psychiatric and other conditions, injection phobia and/or lack of venous access or requiring emergency or rescue medications, may not be optimally and conveniently treated with drugs via the parenteral route of administration. Other patients in which the parenteral route is not suitable includes paediatric patients and neonates, overweight and obese patients, old and chronically ill patients, and emergency and acute care patients who have, for example, skin burns, hematomas, or dehydration.

Additionally, patients with difficult intravenous access (DIVA) present a challenge for healthcare personnel on a regular basis. Difficult peripheral intravenous (PIVC) access is generally understood as arising when two or more punctures are performed without success, or when puncture support methods are required, or when the impossibility of

obtaining peripheral access means that a central venous catheter (CVC) must be inserted. It is estimated that more than 30% of adults and up to 50% of children requiring a PIVC are found to have a challenging venous access.

Currently, in order to treat patients with difficult intravenous access, the use of longer peripheral intravenous catheters and ultrasound-assisted catheter insertion is recommended. However, this is still painful and burdensome to the patients, in that they have to be careful around the IV site.

Other disadvantages of administration of drugs via the parenteral route (encompasses intravenous, subcutaneous, intramuscular, implant and others), include the following:

- It is irreversible and poses more risks than oral, buccal and other routes;
- It is invasive and can cause fear, pain, infections, and/or tissue damage such as phlebitis (inflammation of veins, seen in 31% of patients), vein collapse, air embolism or blood clots;
- The preparation to be injected has to be sterile and particle-free. Manufacturing and quality systems of parenteral dosage forms require stringent environment and microbial monitoring, installation of pharmaceutical water systems, check for particulate matter;
- Assistance by health or other personnel who is trained in aseptic technique of preparation and administration of injection, is usually required;
- Healthcare personnel who use or may be exposed to needles are at increased risk of needlestick injury. Needlestick injuries can lead to serious or fatal infections with bloodborne pathogens such as hepatitis B virus, hepatitis C virus, or HIV. They suffer more than 2 million occupational needle-stick injuries (NSIs) annually;
- It often requires the one-time (aka single) use of injection disposables and devices, ranging from the basic (such as sterile wipes, syringes, needles, cannula, infusion bags/bottles, tubings etc.) to the advanced gadgets, namely autoinjectors, patch injectors, continuous pumps, cassettes. These generate a lot of waste that is biohazardous and some are sharps, requiring tedious safe handling and costly disposal procedures.
- It can pose risk or hazard for patients who may resist the injection or oral administration, and/or are physically unfit for receiving the injection such as the patient is undergoing an episode of seizure or agitation.

It would be desirable to overcome or ameliorate at least one of the above-described problems.

Summary

The present invention is predicated on the understanding that injections and drugs which may be administered orally and/or parenterally may be replaced with other non-sterile oral dosage forms containing the same drugs.

The present invention provides a method of compounding a drug into a film or wafer, comprising:

a) solubilising the drug in a pre-mix and optionally in an aqueous medium in order to form a solution; and

b) casting the solution into a mold in order to form the film or wafer;

wherein the drug is compounded in its dosage form;

wherein the drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;

ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability at less than about 60 °C; and

iv) a solubility of more than about 10 mg/mL in a solvent medium.

In some embodiments, the drug is selected from Biopharmaceutical Classification System (BCS) classes I, II and III.

In some embodiments, the drug is characterised by at least two of the above criteria.

In some embodiments, the drug is further characterised by a molecular weight of less than about 6000 Da.

In some embodiments, the dosage form of the drug is selected from injection liquid, powder, tablet, capsule, swallowable liquid, inhalation liquid, nasal liquid, eye drop, or eardrop.

In some embodiments, the drug is selected from midazolam, ondansetron,

dimenhydrinate, haloperidol, lidocaine, salbutamol, levalbuterol, dexamethasone, prednisolone, prednisone, methylprednisolone, diazepam, lorazepam, clonazepam, diclofenac, ketoprofen or other non-steroidal anti-inflammatory drugs (NSAIDs), epinephrine, diphenhydramine, dopamine, adenosine, caffeine, naloxone, flumazenil, codeine, fentanyl, ketamine, others, or a combination thereof.

In some embodiments, the drug is provided as a single unit dosage.

In some embodiments, the drug in the solution is about 1 mg/mL to about 200 mg/mL.

In some embodiments, the pre-mix comprises an excipient selected from film forming polymer, binder, bioadhesive material, coating agent, controlled-release agent, dispersing agent, dissolution enhancer, emulsifying agent, emulsion stabilizer, humectant, modified-release agent, film-forming agent, mucoadhesive, plasticiser, solubilizing agent, stabilizing agent, suspending agent, thickening agent, taste-masking agent, colouring agent or a combination thereof.

In some embodiments, the pre-mix comprises a film forming polymer selected from polyethylene oxide, hydroxypropyl methylcellulose, methylcellulose, carboxymethyl-cellulose, polyvinyl pyrrolidone, gelatin, pectin, xanthan gum, polyvinyl alcohol, trehalose, hydroxypropyl Pea Starch (Lycoat RS720), chitosan, pullulan, or a combination thereof.

In some embodiments, the pre-mix comprises at least two film forming polymers.

In some embodiments, the pre-mix comprises one of the following:

a) xanthan gum and polyvinyl alcohol;
b) xanthan gum and pullulan;
c) xanthan gum and polyvinyl pyrrolidone;
d) xanthan gum and trehalose;
e) xanthan gum and Lycoat RS720;
f) xanthan gum and methylcellulose;
g) polyvinyl alcohol and hydroxypropyl methylcellulose;
h) hydroxypropyl methylcellulose and pullulan;
i) hydroxypropyl methylcellulose and polyvinyl pyrrolidone;

j) hydroxypropyl methylcellulose and chitosan;
k) hydroxypropyl methylcellulose and methylcellulose;
l) pullulan and polyvinyl pyrrolidone;
m) pullulan and trehalose;
n) pullulan and Lycoat RS720;
o) pullulan and methylcellulose;
p) polyvinyl pyrrolidone and chitosan;
q) polyvinyl pyrrolidone and methylcellulose;
r) trehalose and methylcellulose; and
s) chitosan and methylcellulose.

In some embodiments, the pre-mix comprises at least three film forming polymers.

In some embodiments, the film forming polymer is about 0.1 % w/v to about 20 % w/v relative to the solution.

In some embodiments, the pre-mix comprises a binder. The binder may be polyvinyl pyrrolidone.

In some embodiments, the binder is about 0.1 % w/v to about 20 % w/v relative to the solution.

In some embodiments, the pre-mix comprises a humectant. The humectant may be glycerol or propylene glycol.

In some embodiments, the humectant is about 0.1 % w/v to about 20 % w/v relative to the solution.

In some embodiments, the pre-mix comprises a solubilising agent. The solubilising agent may be a cosolvent (such as propylene glycol), a complexing agent or a surfactant.

In some embodiments, the pre-mix comprises a taste-masking agent. The taste-masking agent may be maltitol, sorbitol, xylitol, citric acid or sodium chloride.

In some embodiments, the pre-mix further comprises a pH regulator.

In some embodiments, the pH regulator is about 0.1 % w/v to about 20 % w/v relative to the solution.

In some embodiments, the pre-mix further comprises a dental adhesive.

In some embodiments, the dental adhesive powder or gel is about 0.1 % w/v to about 10 % w/v relative to the solution.

In some embodiments, the step of casting the solution further comprises drying the solution.

In some embodiments, the method further comprises a step of UV sterilising the film or wafer.

In some embodiments, the method further comprises a step of further dehydrating the film or wafer.

In some embodiments, the film or wafer is characterised by a thickness of about 0.05 mm to about 1.0 mm.

In some embodiments, the film or wafer is characterised by a disintegration time of about 10 s to about 60 min.

In some embodiments, the film or wafer is characterised by a pH of about 2 to about 8.

In some embodiments, the film or wafer is characterised by a folding endurance of more than about 100 times.

In some embodiments, the film or wafer is characterised by a Young's modulus of at least 50 N/cm^2.

In some embodiments, the film or wafer is for sublingual, buccal and/or sub labial administration.

In some embodiments, the drug is an injectable drug.

The present invention also provides a film or wafer for oral administration of a drug, comprising:

a) the drug of about 1 mg/mL to about 200 mg/mL relative to the film and/or wafer;

b) a film forming polymer of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

c) a humectant of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

wherein the drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;

ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability of less than about 60 °C; and

iv) a solubility of more than about 10 mg/mL in a solvent medium.

The present invention also provides a pre-mix for forming a film or wafer for oral administration of a drug, the pre-mix comprising:

a) a film forming polymer of about 0.1 % w/v to about 20 % w/v relative to the pre-mix; and

b) a humectant of about 0.1 % w/v to about 20 % w/v relative to the pre-mix.

In some embodiments, the pre-mix comprises at least three film forming polymers, each of the three film forming polymers is independently about 0.1 % w/v to about 20 % w/v relative to the pre-mix.

The present invention also provides a method of treating a disease or disorder treatable by a drug, comprising compounding the drug into a film or wafer as disclosed herein, and administering to a subject in need thereof a therapeutically effective amount of the film and/or wafer via sublingual, buccal and/or sublabial administration.

The present invention also provides a film or wafer for use in treating a disease or disorder treatable by a drug, wherein the film and/or wafer comprises the drug and is administrable sublingually, buccally and/or sub labially.

The present invention also provides a use of a film or wafer in the manufacture of a medicament for treating a disease or disorder treatable by a drug, wherein the film and/or wafer comprises the drug and is administrable sublingually, buccally and/or sublabially.

The present invention also provides a system for compounding a drug into a film or wafer, comprising:

a) a drug receiving module for receiving the drug;
b) a pre-mix module for containing and introducing a pre-mix to the drug;
c) a mixing module for mixing the drug with the pre-mix to form a solution;
d) a dosing and dispensing module for dispensing the solution;
e) a mold for containing the dispensed solution; and
f) a curing module for curing the solution in the mold into the film or wafer.

Brief description of the drawings

Embodiments of the present invention will now be described, by way of non-limiting example, with reference to the drawings in which:

Figure 1 shows a set-up to investigate time to initial disintegration of films. Each film is placed between 2 hollow columns. Thereafter, 1 ml of phosphate buffer saline (pH 7.2) is gently added to the top column. The time taken for the phosphate buffer saline to penetrate through the films to collect in the petri dish is recorded as the time to initial disintegration.

Detailed description

Typically, when a drug is compounded, it may not have the same safety, quality, and effectiveness assurances as its corresponding commercially available product.

Without wanting to be bound by theory, the inventors believe that injectable drug solutions, drug powders, tablets, capsules, swallowable/drinkable liquids, inhalation liquids, nasal liquids, eye drops, and/or eardrops may be selected and repurposed by extemporaneously compounding them into films and/or wafers. The films and/or wafer may deliver quality, safe and efficacious doses of medications via oral, sublingual and/or

buccal routes. The films and/or wafer may further be reconstituted for nasogastric tube-feeding routes by dissolving the films in a liquid medium (such as water, enteral feeds), while maintaining acceptable pharmacokinetic properties of the drug.

Drug compounding is the process of combining, mixing, or altering ingredients to create a medication tailored to the needs of an individual patient. In particular, compounding of existing oral and parenteral drugs and other dosage forms into film and/or wafer may meet the pharmaceutical needs of patients with clinical dysphagia, medication dysphagia and obstructed or excised gastrointestinal tract to solid dosage forms (such as tablets and capsules), chronic neurological, psychiatric and other conditions, injection phobia and/or lack of venous access. The film and/or wafer is classified as an "US FDA 505(b)(2)" drug product, which refers to using the same drug ingredient in a product to make the drug in a different physical form.

The present invention allows a drug to be compounded at healthcare facilities, nursing homes and home. This replaces the tedious practice of modifying solid dosage forms (such as tablets and capsules) into a powder and then adding the powder to syrup, beverage or soft foods before measuring the required dose volume for administration. In this regard, it provides greater convenience to the healthcare staff and patients.

The drug may also be compounded at compounding pharmacies, clinics or an outsourced facility. Films/wafers may be produced with low water activity and may reduce the likelihood of microbial contamination, resulting in longer shelf-life compared to liquid extemporaneous formulations which typically have a shelf-life of 2 weeks and for a few of up to 6 weeks. This means that the need for frequent replenishment of the compounded liquid medicines is eliminated, thereby improving medication adherence and convenience with less transport/delivery cost.

The drug may also be compounded for clinical trial and drug research. This offers alternative dosage formulations to tablets, capsules, injections, syrups and others as the preparation process allows for making small batches of varying doses of actives and placebos efficiently.

The drug may also be compounded for travel, military and logistics purposes. It reduces luggage/baggage load as films/wafers are lighter and more compact compared to

tablets, capsules and liquids. This also circumvents restrictions of carry-on baggage of liquids (although medications are exempted) on board an aircraft, aerial or space vehicle. Moreover films/wafer can be self-administered whereas injections are usually administered by trained personnel, requiring syringes, needles and/or IV infusion sets.

Accordingly, the present invention provides a method of compounding a drug into a film or wafer, comprising:

a) solubilising the drug in a pre-mix and optionally with an aqueous medium in order to form a solution; and

b) casting the solution into a mold in order to form the film or wafer;

wherein the drug is compounded in its dosage form;

wherein the drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;

ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability at less than about 60 °C; and

iv) a solubility of more than about 10 mg/mL in a solvent medium.

Advantageously, the pharmaceutical composition of the injection liquid (the API and excipients within the injection liquid) or other dosage forms may be directly compounded; i.e. without any component being first removed. Compounding into films/wafers using commercial pharmaceutical preparations which have been approved by regulatory authorities and met manufacturing quality checks allows for faster manufacturing and accessibility to patients. The sterility and accurate content of APIs in the parenteral products is also assured. The need to procure, stock, test and store large quantities of pure APIs is also eliminated.

The film and/or wafer may be prepared using unit dose method. In this way, accurate dosing is assured. For example, the film and/or wafer may be cut into an appropriate size containing the required dose for administration.

As used herein, "drug" refers to a drug product, which comprises the active ingredient and other excipients. The drug may be a commercially available drug product. In this regard, the drug product may be in its final dosage form which is made available to a patient for consumption. The drug product may be for administration via any route, for example intravenous, intramuscular, subcutaneous, rectal, vaginal, inhaled, oral or

buccal. In this sense, the drug product may be in a form such as a liquid formulation, gel, paste, tablet, capsule, or insert.

As used herein, "compounding" refers to the preparation of a custom formulation of a medication to fit a unique need of a patient that cannot be met with commercially available products. This may be done for medical reasons, such as administration in a different format (ex: tablet to liquid), to avoid a non-active ingredient the patient is allergic to, or to provide an exact dose that is not commercially available. It may also be done for medically optional reasons, such as preference of flavour or texture, or dietary restrictions.

As used herein, an "injectable drug" refers to a drug which is introduced into a bloodstream of a subject via a hollow hypodermic needle or cannula. The needle/cannula is pierced through the skin into the body (usually intravenously, but also at an intramuscular or subcutaneous location). Accordingly, intravenous, intramuscular and subcutaneous modes of administrating a drug are included within the scope of injectable drug.

As used herein, "dosage forms" are pharmaceutical drug products in the form in which they are marketed for use, with a specific mixture of active ingredients and inactive components (excipients), in a particular configuration (such as a capsule shell, for example), and apportioned into a particular dose. For example, two products may both be loperamide 2mg, but one is in capsule and another is in tablet. These represents two dosage forms. Depending on the method/route of administration, dosage forms come in several types. These include many kinds of liquid, solid, and semisolid dosage forms. Common dosage forms include tablet, or capsule, suspension or syrup, among many others. Parenteral dosage forms can include emulsion, liposomal, lipid complex, powder, solution, and suspension.

In some embodiments, the method is a method of compounding a pharmaceutical drug product into a film or wafer, comprising:

a) solubilising the pharmaceutical drug product in a pre-mix and optionally with an aqueous medium in order to form a solution; and

b) casting the solution into a mold in order to form the film or wafer;

wherein the pharmaceutical drug product is characterised by at least one of the

following:

i) a drug unit dose of less than about 200 mg;

ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability at less than about 60 °C; and

iv) a solubility of more than about 10 mg/mL in a solvent medium.

Oral administration of a drug is a route of administration where a substance is taken through the mouth. Oral administration also includes sublingual, buccal and sublabial administration. Sublingual administration occurs when the drug is placed under the tongue where it dissolves and is absorbed into the blood through the tissues. Buccal administration involves placing a drug between the gums and the cheek. Just as with sublingual administration, the drug dissolves and is absorbed into the blood through the tissues. Sub labial administration involves placing the drug under the lip. Such modes of administration minimizing the amount of active drug ingredient being lost to digestion. They also do not require the products to be sterile in contrast to injections.

In some embodiments, the film and/or wafer is for oral administration. In some embodiments, the film and/or wafer is for sublingual, buccal and/or sublabial administration. In some embodiments, the film and/or wafer is for buccal administration.

As used herein, a "film" refers to thin continuous sheet material. The film may be air dried or oven dried. The film may comprise a polymer such as a water-soluble polymer. Examples of water-soluble polymers are, but not limited to, polyethylene oxide, hydroxypropyl methylcellulose, methylcellulose, carboxymethyl-cellulose, polyvinyl pyrrolidone, gelatin, pectin, and pullulan.

As used herein, a "wafer" refers to a film made via a quick drying method such as freeze drying. It is a low temperature dehydration process that involves freezing the product, lowering pressure, then removing the ice by sublimation. This is in contrast to dehydration by most conventional methods that evaporate water using heat. Because of the low temperature used in processing, the original shape of the product is maintained. If the product to be dried is a liquid, the properties of the final product may be optimized by the combination of excipients (i.e., inactive ingredients). As the aqueous or solvent medium is rapidly pulled out from the solution, a porous internal

structure may result, allowing for modulation of the rate of disintegration of the wafer and thus can lead to faster absorption.

In some embodiments, the drug is selected from Biopharmaceutical Classification System (BCS) classes I, II and III. BCS is a system to differentiate the drugs on the basis of their solubility and permeability. This system restricts the prediction using the parameters of solubility and intestinal permeability of the drug. The solubility classification is based on a United States Pharmacopoeia (USP) aperture. The intestinal permeability classification is based on a comparison to the intravenous injection. All those factors are highly important because 85% of the most sold drugs in the United States and Europe are orally administered.

Solubility is the ability of a substance, the solute, to form a solution with another substance, the solvent. Solubility class boundaries are based on the highest dose strength of an immediate release product. A drug is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1 to 9.5. The volume estimate of 250 ml is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass of water.

Permeability class boundaries are based indirectly on the extent of absorption of a drug substance in humans and directly on the measurement of rates of mass transfer across human intestinal membrane. Alternatively non-human systems capable of predicting drug absorption in humans can be used (such as in-vitro culture methods). A drug substance is considered highly permeable when the extent of absorption in humans is determined to be 90% or more of the administered dose based on a mass-balance determination or in comparison to an intravenous dose.

For dissolution class boundaries, an immediate release product is considered rapidly dissolving when no less than 85% of the labelled amount of the drug substance dissolves within 15 minutes using USP Dissolution Apparatus 1 at 100 RPM or Apparatus 2 at 50 RPM in a volume of 900 ml or less in the following media: 0.1 M HCl or simulated gastric fluid or pH 4.5 buffer and pH 6.8 buffer or simulated intestinal fluid.

According to the BCS, drug substances are classified to four classes upon their solubility

and permeability:

Class I - high permeability, high solubility

These compounds (such as metoprolol, paracetamol, ondansetron, diazepam, midazolam, salbutamol) are well absorbed and their absorption rate is usually higher than excretion.

Class II - high permeability, low solubility

The bioavailability of those products (such as glibenclamide, ezetimibe, carbamazepine, cisapride) is limited by their solvation rates. A correlation between the in vivo bioavailability and the in vitro solvation can be found.

Class III - low permeability, high solubility

The absorption of drugs (such as atenolol, famotidine, enalapril) is limited by the permeation rate but the drug is solvated very fast. If the formulation does not change the permeability or gastro-intestinal duration time, then class I criteria can be applied.

Class IV - low permeability, low solubility

These compounds (such as chlorothiazide, furosemide) have a poor bioavailability. They are usually not well absorbed over the intestinal mucosa and a high variability is expected.

The drug is selected based on at least one criterion.

1. Unit dose of 200 mg or less;
2. Contained in a volume of 2 ml or less upon reconstitution;
3. Chemical and/or physical stability at temperature range not exceeding 60°C;
4. Solution compatibility with solvent medium. The solvent medium may contain alcohols, polymers and/or other excipients for taste-masking, adjusting viscosity and pH of the casting solution.

In some embodiments, the unit dose is less than about 180 mg, less than about 160 mg, less than about 140 mg, less than about 120 mg, less than about 100 mg, less than about 80 mg, less than about 60 mg, or less than about 50 mg.

Drugs in aqueous volumes of more than about 2 mL per dose are excluded. In some embodiments, the volume is less than about 1.8 mL, less than about 1.6 mL, less than about 1.4 mL, less than about 1.2 mL, less than about 1.0 mL, less than about 0.8 mL, or less than about 0.5 mL.

A drug is considered "chemically stable" if it is not particularly reactive in the environment or during normal use, and retains its useful properties on the timescale of its expected usefulness. In particular, the usefulness is retained in the presence of air, moisture or heat, and under the expected conditions of application. In other words, the drug is not chemically reactive under the specific conditions and thus degraded. This may be assessed by taking a sample of the drug and determining the amount of degradation and/or activity. Corollary, the drug is "physically stable" if it does not change its physical state under the specific conditions.

For example, the drug may be resistant to degradation such as hydrolysis and/or oxidation at less than about 60 °C. In some embodiments, the drug is characterised by an absence of ester and/or amide moiety. In some embodiments, the drug is characterised by a sterically hindered ester and/or amide moiety such that it is resistant to degradation at less than about 60 °C.

The drug's physical stability may be influenced by temperature, ionic strength, acid-base catalysis, solvent, light and radiations, oxygen, particle size distribution, and moisture, among others. Physical instability includes precipitation, crystallization, agglomeration, phase transformation, polymorphism, and solubility changes. When a drug is physically deteriorated, its physical appearance may change, and optionally its efficacy. In general, the physical stability of a drug may be controlled, to a certain extent, by the excipients. The physical stability of the drug may be further enhanced by excipients in the pre-mix.

The drug may retain its activity or efficacy substantially after being compounded. In some embodiments, the compounded drug retains at least about 90% of its activity, at least about 91% of its activity, at least about 92% of its activity, at least about 93% of its activity, at least about 94% of its activity, at least about 95% of its activity, at least about 96% of its activity, at least about 97% of its activity, at least about 98% of its activity, or at least about 99% of its activity.

The solution compatibility of the drug product with the solvent medium and/or aqueous medium may be assessed first via the list of excipients or ingredients in the drug. Drugs with ingredients compatible with the solvent medium may then be mixed with the solvent medium to confirm the solution compatibility. The two steps are taken to confirm

solution compatibility as the composition or concentration of the ingredients in the list may not be stated and some excipients or ingredients, after exceeding a certain concentration, may not be compatible with the solvent medium.

In some embodiments, the drug is characterised by at least two of the above criteria. In some embodiments, the drug is characterised by three of the above criteria. In some embodiments, the drug is characterised by four of the above criteria.

In some embodiments, the drug is further characterised by a molecular weight of less than about 6000 Da. In some embodiments, the drug is characterised by five of the above criteria.

The term "solvent medium" used herein refers to a solvent system which may be aqueous based or organic based. Such solvents can be either polar or non-polar, and/or either protic or aprotic. Solvent systems refer to combinations of solvents which resulting in a final single phase. Both 'solvents' and 'solvent systems' can include, and is not limited to, pentane, cyclopentane, hexane, cyclohexane, benzene, toluene, dioxane, chloroform, diethylether, dichloromethane, tetrahydrofuran, ethyl acetate, acetone, dimethylformamide, acetonitrile, dimethyl sulfoxide, nitromethane, propylene carbonate, formic acid, alcohols, butanol, isopropanol, propanol, ethanol, methanol, acetic acid, ethylene glycol, diethylene glycol or water.

The term 'aqueous medium' used herein refers to a water based solvent or solvent system, and which comprises of mainly water. Such solvents can be either polar or non-polar, and/or either protic or aprotic. Solvent systems refer to combinations of solvents which resulting in a final single phase. Both 'solvents' and 'solvent systems' can include, and is not limited to, pentane, cyclopentane, hexane, cyclohexane, benzene, toluene, dioxane, chloroform, diethylether, dichloromethane, tetrahydrofuran, ethyl acetate, acetone, dimethylformamide, acetonitrile, dimethyl sulfoxide, nitromethane, propylene carbonate, formic acid, butanol, isopropanol, propanol, ethanol, methanol, acetic acid, ethylene glycol, diethylene glycol or water. Water based solvent or solvent systems can also include dissolved ions, salts and molecules such as amino acids, proteins, sugars and phospholipids. Such salts may be, but not limited to, sodium chloride, potassium chloride, ammonium acetate, magnesium acetate, magnesium chloride, magnesium sulfate, potassium acetate, potassium chloride, sodium acetate, sodium citrate, zinc

chloride, HEPES sodium, calcium chloride, ferric nitrate, sodium bicarbonate, potassium phosphate and sodium phosphate. As such, biological fluids, physiological solutions and culture medium also falls within this definition.

In some embodiments, the solubility in a solvent medium is a solubility in an aqueous medium.

In some embodiments, the drug is characterised by a solubility of about 1 mg/mL to about 1000 mg/mL in the aqueous or solvent medium. In other embodiments, the solubility is about 10 mg/mL to about 1000 mg/mL, about 20 mg/mL to about 1000 mg/mL, about 30 mg/mL to about 1000 mg/mL, about 40 mg/mL to about 1000 mg/mL, about 50 mg/mL to about 1000 mg/mL, about 100 mg/mL to about 1000 mg/mL, about 200 mg/mL to about 1000 mg/mL, about 300 mg/mL to about 1000 mg/mL, about 400 mg/mL to about 1000 mg/mL, about 500 mg/mL to about 1000 mg/mL, about 600 mg/mL to about 1000 mg/mL, about 700 mg/mL to about 1000 mg/mL, or about 800 mg/mL to about 1000 mg/mL. In other embodiments, the solubility is more than about 1 mg/mL, about 5 mg/mL, about 10 mg/mL, about 15 mg/mL, about 20 mg/mL, about 30 mg/mL, about 40 mg/mL, about 50 mg/mL, about 60 mg/mL, about 70 mg/mL, about 80 mg/mL, about 90 mg/mL, about 100 mg/mL, about 150 mg/mL, about 200 mg/mL, or about 250 mg/mL.

The drug is provided in its original dosage form and is compounded as is. In other words, the pharmaceutical drug product is used as is. In some embodiments, the drug is provided in an aqueous or solvent medium or as a powder. The powder is soluble in an aqueous or solvent medium. In other embodiments, the drug is provided in an aqueous or solvent medium. In some embodiments, the dosage form of the drug is selected from injection liquid, powder, tablet, capsule, swallowable liquid, inhalation liquid, nasal liquid, eye drop, or eardrop. When the drug is in a tablet form, it may be crushed to facilitate the compounding. When the drug is a capsule, the particulates within the capsule may be further processed into a powder. In some embodiments, the drug is an injectable drug.

Accordingly, in some embodiments, the method is a method of compounding an injectable drug into a film or wafer, comprising:

a) solubilising the injectable drug in a pre-mix and optionally with an aqueous

medium in order to form a solution; and

b) casting the solution into a mold in order to form the film or wafer;

wherein the injectable drug is compounded in its dosage form;

wherein the injectable drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;

ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability at less than about 60 °C; and

iv) a solubility in a solvent medium.

In some embodiments, the solubility is more than about 10 mg/mL in the solvent medium.

In some embodiments, the method is a method of compounding an injectable drug into a film or wafer, comprising:

a) solubilising the injectable drug in a pre-mix and optionally with an aqueous medium in order to form a solution; and

b) casting the solution into a mold in order to form the film or wafer;

wherein the injectable drug is compounded in its dosage form;

wherein the injectable drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;

ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability at less than about 60 °C;

iv) a solubility of more than about 10 mg/mL in a solvent medium; and

v) a molecular weight of less than about 6000 Da.

In some embodiments, the drug is a BCS class I drug. For example, the BCS class I drug may be acetylsalicylic acid, allopurinol, amantadine hydrochloride, amitriptyline hydrochloride, amlodipine, amoxicillin, ascorbic acid, aspirin, berotralstat, caffeine, clindamycin, diazepam, diltiazem, doxycycline hydrochloride, ertugliflozin, escitalopram oxalate, fluconazole, fluoxetine, gliclazide, imatinib, itopride hydrochloride, ketorolac tromethamine, levetiracetam, levofloxacin, levodopa, levonorgestrel, methimazole, metoprolol, metronidazole, mebocertinib, norethisterone, ofloxacin, osilodrostat, phenobarbital, prednisolone, pregabalin, promethazine hydrochloride, propranolol hydrochloride, pyridoxine hydrochloride, quetiapine fumarate, riboflavin, ruxolitinib, salbutamol sulfate, theophylline, timolol, tramadol, vildagliptin, voriconazole,

zidovudine, ketamine, or dexmedetomidine hydrochloride. In some embodiments, the drug is amitriptyline hydrochloride, amlodipine, berotralstat, caffeine, diazepam, doxycycline hydrochloride, ertugliflozin, escitalopram oxalate, fluoxetine, itopride hydrochloride, ketorolac tromethamine, levodopa, levonorgestrel, methimazole, metoprolol, norethisterone, osilodrostat, phenobarbital, prednisolone, pregabalin, promethazine hydrochloride, propranolol hydrochloride, pyridoxine hydrochloride, quetiapine fumarate, riboflavin, ruxolitinib, salbutamol sulfate, theophylline, timolol, tramadol, vildagliptin, ketamine, or dexmedetomidine hydrochloride. In some embodiments, the drug is ketamine, or dexmedetomidine hydrochloride.

In some embodiments, the drug is a BCS class II drug. For example, the BCS class II drug may be aceclofenac, asciminib, atorvastatin calcium, budesonide, cefuroxime, chlorzoxazone, clonazepam, clopidogrel, clozapine, daclatasvir, danazol, dexlansoprazole, dextromethorphan hydrobromide, diacerien, diclofenac sodium, enzalutamide, eplerenone, etoricoxib, felodipine, fenofibrate, Gefitinib, ibrutinib, ibuprofen, indinavir sulfate, ketoprofen, ivermectin, lansoprazole, mebendazole, montelukast sodium, naproxen, nicardipine, nifedipine, nitrofurantoin, obeticholic acid, olanzapine, omeprazole, oxcarbazepine, ozanimod, palbociclib isethionat, paliperidone palmitate, pemigatinib, phenytoin sodium, posaconazole, pralsetinib, racecadotril, rifampicin, risperidone, rosuvastatin, sertraline hydrochloride, sulfamethoxazole, tamoxifen citrate, telmisartan, terbinafine hydrochloride, trimethoprim, valsartan, venetoclax, vericiguat or dexamethasone. In some embodiments, the drug is aceclofenac, asciminib, atorvastatin calcium, budesonide, cefuroxime, chlorzoxazone, clonazepam, clopidogrel, clozapine, daclatasvir, danazol, dexlansoprazole, dextromethorphan hydrobromide, diacerien, diclofenac sodium, enzalutamide, eplerenone, etoricoxib, felodipine, fenofibrate, gefitinib, ibrutinib, ibuprofen, indinavir sulfate, ketoprofen, ivermectin, lansoprazole, mebendazole, montelukast sodium, naproxen, nicardipine, nifedipine, nitrofurantoin, obeticholic acid, olanzapine, omeprazole, oxcarbazepine, ozanimod, palbociclib isethionat, paliperidone palmitate, pemigatinib, phenytoin sodium, posaconazole, pralsetinib, racecadotril, rifampicin, risperidone, rosuvastatin, sertraline hydrochloride, sulfamethoxazole, tamoxifen citrate, telmisartan, terbinafine hydrochloride, trimethoprim, valsartan, venetoclax, vericiguat or dexamethasone. In some embodiments, the drug is dexamethasone.

In some embodiments, the drug is a BCS class III drug. For example, the BCS class III

drug may be abacavir, acyclovir, atenolol, baclofen, benznidazole, chloramphenicol, cimetidine, dapagliflozin, empagliflozin, glucosamine potassium sulphate, lamivudine, levothyroxine sodium, linagliptin, lisinopril, metformin hydrochloride, methotrexate sodium, methyldopa, mirabegron, neostigmine bromide, olopatadine hydrochloride, pantoprazole sodium, pentosan polysulfate sodium, proguanil hydrochloride, rabeprazole sodium, ranitidine hydrochloride, ribavarin, rizatriptan benzoate, saxagliptin, sitagliptin, sofosbuvir, tenofovir disoproxil, thiamine hydrochloride, valacyclovir, vibegron, vortioxetin hydrobromide, or zinc sulfate.

In some embodiments, the drug is selected from midazolam, ondansetron, dimenhydrinate, haloperidol, lidocaine, salbutamol, levabuterol, prednisolone, prednisone, methylprednisolone, diazepam, lorazepam, clonazepam, diclofenac, ketoprofen or other non-steroidal anti-inflammatory drugs (NSAIDs), epinephrine, diphenhydramine, dopamine, amiodarone, adenosine, magnesium sulfate, furosemide, sodium bicarbonate, naloxone or flumazenil. In some embodiments, the drug is selected from midazolam, ondansetron, dimenhydrinate, haloperidol, or lidocaine. In some embodiments, the drug is selected from midazolam, ondansetron, dimenhydrinate, haloperidol, lidocaine, salbutamol, levalbuterol, dexamethasone, prednisolone, prednisone, methylprednisolone, diazepam, lorazepam, clonazepam, diclofenac, ketoprofen or other non-steroidal anti-inflammatory drugs (NSAIDs), epinephrine, diphenhydramine, dopamine, adenosine, caffeine, naloxone, flumazenil, codeine, fentanyl, ketamine, others, or a combination thereof. In other embodiments, the drug is midazolam.

In some embodiments, the drug is provided as a single unit dosage. A single unit dosage is an amount or unit of a compound, mixture, or preparation containing a controlled substance that is separately identifiable and in a form that indicates that it is the amount or unit by which the controlled substance is separately administered to or taken by an individual.

In some embodiments, the drug in the solution is about 1 mg/mL to about 200 mg/mL. In some embodiments, the drug in the solution is at a concentration of about 1 mg/mL to about 180 mg/mL, about 1 mg/mL to about 160 mg/mL, about 1 mg/mL to about 150 mg/mL, about 1 mg/mL to about 140 mg/mL, about 1 mg/mL to about 120 mg/mL, about 1 mg/mL to about 100 mg/mL, about 1 mg/mL to about 80 mg/mL, about 1

mg/mL to about 60 mg/mL, about 1 mg/mL to about 50 mg/mL, about 1 mg/mL to about 40 mg/mL, about 1 mg/mL to about 20 mg/mL, about 1 mg/mL to about 10 mg/mL, or about 1 mg/mL to about 5 mg/mL. In some embodiments, the drug in the solution is about 2.5 mg/mL.

The pre-mix may be provided as a powder, a solution or a suspension. When the pre-mix is provided as a powder or a suspension, an aqueous medium may be added so that a solution may form with the drug. When the pre-mix is provided as a solution, additionally aqueous or solvent medium may be added to bring the drug and excipients to an appropriate concentration for forming the film and/or wafer.

In some embodiments, the pre-mix comprises an excipient selected from film forming polymer, binder, bioadhesive material, coating agent, controlled-release agent, dispersing agent, dissolution enhancer, emulsifying agent, emulsion stabilizer, humectant, modified-release agent, film-forming agent, mucoadhesive, plasticiser, solubilizing agent, stabilizing agent, suspending agent, thickening agent, sweetening agent, taste-masking agent, colouring agent or a combination thereof. In some embodiments, the pre-mix comprises at least one excipient.

"Excipients" are pharmaceutically inactive substances that serve as the vehicle or medium for a drug or other active substances.

In some embodiments, the pre-mix comprises a film forming polymer. The film forming polymer may be a water-soluble polymer. Water soluble polymers are, but not limited to, polyethylene oxide, hydroxypropyl methylcellulose, methylcellulose, carboxymethyl-cellulose, polyvinyl pyrrolidone, gelatin, pectin, xanthan gum, polyvinyl alcohol, trehalose, hydroxypropyl Pea Starch (Lycoat RS720), chitosan and pullulan. In other embodiments, the film forming polymer is selected from xanthan gum, polyvinyl alcohol, hydroxypropyl methylcellulose, pullulan, trehalose, methylcellulose, hydroxypropyl Pea Starch (Lycoat RS720), or a combination thereof. In some embodiments, the film forming polymer is selected from polyethylene oxide, hydroxypropyl methylcellulose, methylcellulose, carboxymethyl-cellulose, polyvinyl pyrrolidone, gelatin, pectin, xanthan gum, polyvinyl alcohol, trehalose, hydroxypropyl Pea Starch (Lycoat RS720), chitosan, pullulan, or a combination thereof.

It was found that by using a water-soluble polymer as stated above, a clear and smooth film with acceptable mechanical properties may be produced. This indicates that the active pharmaceutical ingredient is at least solubilised within the film and/or wafer. This also ensures that the pharmacokinetic properties of the drug may be reliably reproduced such that it is similar or at least acceptable compared to that of the dosage form.

In some embodiments, the pre-mix comprises the following combinations of film forming polymer (where X indicates that the film forming polymer is present):

Xanthan gum	Polyvinyl alcohol	Hydroxypropyl methylcellulose	Pullulan	Polyvinyl pyrrolidone	Trehalose	Lycoat RS720	Chitosan	Methylcellulose
X	X							
X		X						
X			X					
X				X				
X					X			
X						X		
X							X	
X								X
	X	X						
	X		X					
	X			X				
	X				X			
	X					X		
	X						X	
	X							X
		X	X					
		X		X				
		X			X			
		X				X		
		X					X	
		X						X
			X	X				
			X		X			
			X			X		
			X				X	
			X					X
				X	X			
				X		X		

				X			X	
				X				X
					X	X		
					X		X	
					X			X
						X	X	
						X		X
							X	X

In some embodiments, the pre-mix comprises at least two film forming polymers. In some embodiments, the pre-mix comprises one of the following:

a) xanthan gum and polyvinyl alcohol;
b) xanthan gum and pullulan;
c) xanthan gum and polyvinyl pyrrolidone;
d) xanthan gum and trehalose;
e) xanthan gum and Lycoat RS720;
f) xanthan gum and methylcellulose;
g) polyvinyl alcohol and hydroxypropyl methylcellulose;
h) hydroxypropyl methylcellulose and pullulan;
i) hydroxypropyl methylcellulose and polyvinyl pyrrolidone;
j) hydroxypropyl methylcellulose and chitosan;
k) hydroxypropyl methylcellulose and methylcellulose;
l) pullulan and polyvinyl pyrrolidone;
m) pullulan and trehalose;
n) pullulan and Lycoat RS720;
o) pullulan and methylcellulose;
p) polyvinyl pyrrolidone and chitosan;
q) polyvinyl pyrrolidone and methylcellulose;
r) trehalose and methylcellulose; and
s) chitosan and methylcellulose.

In some embodiments, the pre-mix comprises at least three film forming polymers. In some embodiments, the pre-mix comprises the following combinations of film forming polymer (where X indicates that the film forming polymer is present):

Xanthan gum	Polyvinyl alcohol	Hydroxypropyl methylcellulose	Pullulan	Polyvinyl pyrrolidone	Trehalose	Lycoat RS720	Chitosan	Methylcellulose
X	X	X						
X	X		X					
X	X			X				
X	X				X			
X	X					X		
X	X						X	
X	X							X
X		X	X					
X		X		X				
X		X			X			
X		X				X		
X		X					X	
X		X						X
X			X	X				
X			X		X			
X			X			X		
X			X				X	
X			X					X
X				X	X			
X				X		X		
X				X			X	
X				X				X
X					X	X		
X					X		X	
X					X			X
X						X	X	
X						X		X
X							X	X
	X	X	X					
	X	X		X				
	X	X			X			
	X	X				X		
	X	X					X	
	X	X						X
	X		X	X				
	X		X		X			
	X		X			X		
	X		X				X	
	X		X					X

	X			X	X			
	X			X		X		
	X			X			X	
	X			X				X
	X				X	X		
	X				X		X	
	X				X			X
	X					X	X	
	X					X		X
	X						X	X
		X	X	X				
		X	X		X			
		X	X			X		
		X	X				X	
		X	X					X
		X		X	X			
		X		X		X		
		X		X			X	
		X		X				X
		X			X	X		
		X			X		X	
		X			X			X
		X				X	X	
		X				X		X
		X					X	X
			X	X	X			
			X	X		X		
			X	X			X	
			X	X				X
			X		X	X		
			X		X		X	
			X		X			X
			X			X	X	
			X			X		X
			X				X	X
				X	X	X		
				X	X		X	
				X	X			X
				X		X	X	
				X		X		X
				X			X	X
					X	X	X	
					X	X		X
					X		X	X
						X	X	X

In some embodiments, the pre-mix comprises at least four film forming polymers. In some embodiments, the pre-mix comprises the following combinations of film forming polymer (where X indicates that the film forming polymer is present):

Xanthan gum	Polyvinyl alcohol	Hydroxypropyl methylcellulose	Pullulan	Polyvinyl pyrrolidone	Trehalose	Lycoat RS720	Chitosan	Methylcellulose
X	X	X	X					
X	X	X		X				
X	X	X			X			
X	X	X				X		
X	X	X					X	
X	X	X						X
X	X		X	X				
X	X		X		X			
X	X		X			X		
X	X		X				X	
X	X		X					X
X	X			X	X			
X	X			X		X		
X	X			X			X	
X	X			X				X
X	X				X	X		
X	X				X		X	
X	X				X			X
X	X					X	X	
X	X					X		X
X	X						X	X
X		X	X	X				
X		X	X		X			
X		X	X			X		
X		X	X				X	
X		X	X					X
X		X		X	X			
X		X		X		X		
X		X		X			X	
X		X		X				X
X		X			X	X		
X		X			X		X	
X		X			X			X
X		X				X	X	
X		X				X		X
X		X					X	X
X			X	X	X			
X			X	X		X		
X			X	X			X	

X			X	X				X
X			X		X	X		
X			X		X		X	
X			X		X			X
X			X			X	X	
X			X			X		X
X			X				X	X
X				X	X	X		
X				X	X		X	
X				X	X			X
X				X		X	X	
X				X		X		X
X				X			X	X
X					X	X	X	
X					X	X		X
X					X		X	X
X						X	X	X
	X	X	X	X				
	X	X	X		X			
	X	X	X			X		
	X	X	X				X	
	X	X	X					X
	X	X		X	X			
	X	X		X		X		
	X	X		X			X	
	X	X		X				X
	X	X			X	X		
	X	X			X		X	
	X	X			X			X
	X	X				X	X	
	X	X				X		X
	X	X				X		X
	X		X	X	X			
	X		X	X		X		
	X		X	X			X	
	X		X	X				X
	X		X		X	X		
	X		X		X		X	
	X		X		X			X
	X		X			X	X	
	X		X			X		X
	X		X				X	X
	X			X	X	X		
	X			X	X		X	
	X			X	X			X
	X			X		X	X	
	X			X		X		X
	X			X			X	X
	X				X	X	X	
	X				X	X		X

	X				X		X	X
	X					X	X	X
		X	X	X	X			
		X	X	X		X		
		X	X	X			X	
		X	X	X				X
		X	X		X	X		
		X	X		X		X	
		X	X		X			X
		X	X			X	X	X
		X		X	X	X		
		X		X	X		X	
		X		X	X			X
		X		X		X	X	
		X		X			X	X
		X			X	X	X	
		X			X	X		X
		X			X		X	X
		X				X	X	X
			X	X	X	X		
			X	X	X		X	
			X	X	X			X
			X	X		X	X	
			X	X		X		X
			X	X			X	X
			X		X	X	X	
			X		X	X		X
			X		X		X	X
			X			X	X	X
				X	X	X	X	
				X	X	X		X
				X	X		X	X
				X		X	X	X
					X	X	X	X

In some embodiments, the film forming polymer is about 0.1 % w/v to about 20 % w/v relative to the solution. When more than 1 film forming polymer is present, the total amount of film forming polymer is about 0.1 % w/v to about 20 % w/v relative to the solution.

The various film forming polymers may impart different properties to the film, such as thickness, elasticity, or rate of disintegration. The composition of the film forming polymer in the solution may be adjusted to obtain the desired release profile of the drug. It was found that through a combination of at least 2 film forming polymers, or preferably at least 3 film forming polymers, a synergistic (or at least additive) effect may be obtained for forming a homogeneous film or wafer. This improves (or at least

maintains) the drug's delivery to the patient.

In some embodiments, the pre-mix comprises a binder. The binder may be polyvinyl pyrrolidone.

In some embodiments, the binder is about 0.1 % w/v to about 20 % w/v relative to the solution.

In some embodiments, the pre-mix comprises a humectant. The humectant may be glycerol or propylene glycol.

In some embodiments, the humectant is about 0.1 % w/v to about 20 % w/v relative to the solution.

In some embodiments, the pre-mix comprises a solubilising agent. The solubilising agent may be cyclodextrin. In some embodiments, the solubilising agent is a cosolvent (such as propylene glycol), a complexing agent or a surfactant.

In some embodiments, the solubilising agent is about 0.1 % w/v to about 20 % w/v relative to the solution.

In some embodiments, the pre-mix comprises a sweetening agent. In some embodiments, the pre-mix comprises a taste-masking agent. The sweetening agent or taste-masking agent may be maltitol, sorbitol, xylitol, citric acid or sodium chloride.

In some embodiments, the sweetening agent or taste-masking agent is about 0.1 % w/v to about 20 % w/v relative to the solution.

In some embodiments, the pre-mix comprises a plasticizer. The plasticizer makes the film and/or wafer pliable and soft, and may enhance the flexibility and plasticity of a film. The plasticizer may be glycol, citric acid (tributylcitrate, triethylcitrate) or glycerol (triacetin, tributyrin).

In some embodiments, the plasticizer is about 0.1 % w/v to about 20 % w/v relative to the solution.

In some embodiments, the pre-mix further comprises a pH regulator. The pH regulators are pH control agents and are used to change or maintain pH (acidity or basicity). They may be organic or mineral acids, bases, neutralizing agents, or buffering agents. Typical agents include the following acids and their sodium salts: sorbic acid, acetic acid, benzoic acid, and propionic acid. Acidity regulators may be indicated by their E number, such as E260 (acetic acid).

In some embodiments, the pH regulator is about 0.1 % w/v to about 20 % w/v relative to the solution.

In some embodiments, the pre-mix further comprises a dental adhesive. The dental adhesive may be provided as a powder or gel. Dental adhesives are bonding agents used to bond the film and/or wafer to the teeth. Dental adhesives may be self-cure, light-cure or dual cure, curing times vary between products but are usually under 30 seconds. The addition of dental adhesive renders addition mucoadhesion to the film and/or wafer.

In some embodiments, the dental adhesive powder or gel is about 0.1 % w/v to about 10 % w/v relative to the solution.

After the film forming polymer and other excipients are selected and mixed to form a pre-mix, the drug is solubilised in the pre-mix to form a solution. The solution is then casted into a mold in order to form the film and/or wafer. The mold is thus appropriately sized in order to form a film and/or wafer. For example, the mold may have a depth (or height) of about 10 µm to about 1 cm. Alternatively, a tray may be used as a mold. If a tray is used, the formed film and/or wafer may be subjected to a subsequent cutting step such that an appropriate dosage may be administered to a patient.

In some embodiments, the solution is characterised by a viscosity of less than about 800 cP. In other embodiments, the viscosity is less than about 700 cP, about 600 cP, about 500 cP, about 400 cP or about 300 cP.

In some embodiments, the step of casting the solution further comprises drying the solution.

To form a film, the solution may for example be dried using evaporation means. For example, the solution maybe dried at room or ambient temperature or oven dried. For example, the solution may be dried using a microwave, an incubator, a fan, and/or a desiccator chamber. Depending on the drying duration, residual aqueous medium may still reside within the film.

In some embodiments, the solution is dried at a temperature of about 10 °C to about 80 °C. In other embodiments, the temperature is about 10 °C to about 70 °C, about 10 °C to about 60 °C, or about 20 °C to about 60 °C.

To form a wafer, the solution may for example be dried using freeze drying techniques. The solution may be subjected to several rounds of heating and cooling cycles in order to form the wafer. This may be advantageous for expanding the internal structure of the wafer in order to alter the dissolution rate.

In some embodiments, the method further comprises a step of UV sterilising the film and/or wafer. The microbial stability of the film and/or wafer may be achieved by UV-C radiation of the surfaces of the film and/or wafer. This further step assures the sterility of final product.

In some embodiments, the method further comprises a step of further dehydrating the film and/or wafer. The film and/or wafer may for example be subjected to a further cycle of heating. The elimination of water may result in a low water activity of less than about 0.8. Water activity (a_w) is the partial vapour pressure of water in the film and/or wafer divided by the standard state partial vapour pressure of water. The standard state is most often defined as pure water at the same temperature. Using this particular definition, pure distilled water has a water activity of exactly one. Water activity is the thermodynamic activity of water as solvent and the relative humidity of the surrounding air after equilibration. As temperature increases, a_w typically increases. Lower a_w substances tend to support fewer microorganisms since these get desiccated by the water migration.

In some embodiments, the method further comprises a step after step b) of removing the film from the mold.

In some embodiments, the film and/or wafer is single layered. In other embodiments, the film and/or wafer is multilayered. The drug in the film and/or wafter may be homogeneously dissolved.

The film and/or wafer may be characterised by an immediate release profile, or by a modified release profile. Modified-release dosage is a mechanism that delivers a drug with a delay after its administration (delayed-release dosage) or for a prolonged period of time (extended-release [ER, XR, XL] dosage). For example, sustained-release dosage forms are dosage forms designed to release (liberate) a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects. This can be achieved through a variety of formulations, including liposomes and drug-polymer conjugates (an example being hydrogels). Extended-release dosage aims to release the drug over a prolonged period of time and can consists of either sustained-release (SR) and/or controlled-release (CR) dosage. SR maintains drug release over a sustained period but not at a constant rate. CR maintains drug release over a sustained period at a nearly constant rate. Other forms of modified release include time-dependent release such as pulse release and delayed release.

In some embodiments, the film and/or wafer is characterised by a thickness of about 0.05 mm to about 1.0 mm.

In some embodiments, the film and/or wafer is characterised by a disintegration time of about 10 s to about 60 min.

In some embodiments, the film and/or wafer is characterised by a pH of about 3 to about 7. In some embodiments, the film and/or wafer is characterised by a pH of about 2 to about 8. It was found that some formulations require the addition of acid to promote solubility of the drug into pre-mix.

In some embodiments, the film and/or wafer is characterised by a folding endurance of more than about 100 times. Folding endurance is defined as the logarithm (to the base of ten) of the number of double folds that are required to make a test piece break under standardized conditions.

In some embodiments, the film and/or wafer is characterised by a Young's modulus of at least 50 N/cm^2.

The film and/or wafer is intended to be administrable to a subject in need thereof via oral administration. In other embodiments, the film and/or wafer is for sublingual, buccal and/or sub labial administration. While onset of effect may be slightly delayed and bioavailability may be slightly lower compared to intravenous mode, other pharmacokinetic properties of the film and/or wafer are expected to be similar.

In some embodiments, the drug is an injectable drug.

The present invention also provides a film or wafer for oral administration of a drug, comprising:

a) the drug of about 1 mg/mL to about 200 mg/mL relative to the film and/or wafer;
b) a film forming polymer of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;
c) a humectant of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

wherein the drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;
ii) a volume of less than about 2 mL;
iii) a chemical and/or physical stability of less than about 60 °C; and
iv) a solubility of more than about 10 mg/mL in a solvent medium.

In some embodiments, the solubility is more than about 10 mg/mL in the solvent medium.

In some embodiments, the film or wafer for oral administration of a drug comprises:

a) the drug of about 1 mg/mL to about 200 mg/mL relative to the film and/or wafer;
b) a film forming polymer of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;
c) a humectant of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;
d) a dental adhesive of about 0.1 % w/v to about 10 % w/v relative the film and/or wafer;

wherein the drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;

ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability of less than about 60 °C; and

iv) a solubility of more than about 10 mg/mL in a solvent medium.

In some embodiments, the film or wafer for oral administration of an injectable drug comprises:

a) the injectable drug of about 1 mg/mL to about 200 mg/mL relative to the film and/or wafer;

b) a film forming polymer of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

c) a humectant of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

wherein the injectable drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;

ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability of less than about 60 °C;

iv) a solubility of more than about 10 mg/mL in an aqueous or solvent medium; and

i) a molecular weight of less than about 6000 Da.

In some embodiments, the film or wafer for oral administration of an injectable drug comprises:

a) the injectable drug of about 1 mg/mL to about 200 mg/mL relative to the film and/or wafer;

b) a film forming polymer of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

c) a humectant of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

d) a dental adhesive of about 0.1 % w/v to about 10 % w/v relative the film and/or wafer;

wherein the injectable drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;

ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability of less than about 60 °C;

iv) a solubility of more than about 10 mg/mL in an aqueous or solvent medium; and

v) a molecular weight of less than about 6000 Da.

The present invention also provides a film or wafer for oral administration of a drug, comprising:

a) the drug of about 1 mg/mL to about 200 mg/mL relative to the film and/or wafer;

b) at least two film forming polymers, each of the two film forming polymers is independently about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

c) a humectant of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

wherein the drug is characterised by at least one of the following:

ii) a unit dose of less than about 200 mg;

iii) a volume of less than about 2 mL;

iv) a chemical and/or physical stability of less than about 60 °C; and

v) a solubility of more than about 10 mg/mL in a solvent medium.

In some embodiments, the film or wafer for oral administration of a drug comprises:

a) the drug of about 1 mg/mL to about 200 mg/mL relative to the film and/or wafer;

b) at least two film forming polymers, each of the two film forming polymers is independently about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

c) a humectant of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

d) a dental adhesive of about 0.1 % w/v to about 10 % w/v relative the film and/or wafer;

wherein the drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;

ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability of less than about 60 °C; and

iv) a solubility of more than about 10 mg/mL in a solvent medium.

In some embodiments, the film or wafer for oral administration of an injectable drug comprises:

a) the injectable drug of about 1 mg/mL to about 200 mg/mL relative to the film

and/or wafer;

b) at least two film forming polymers, each of the two film forming polymers is independently about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

c) a humectant of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

wherein the injectable drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;

ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability of less than about 60 °C;

iv) a solubility of more than about 10 mg/mL in an aqueous or solvent medium; and

v) a molecular weight of less than about 6000 Da.

In some embodiments, the film or wafer for oral administration of an injectable drug comprises:

a) the injectable drug of about 1 mg/mL to about 200 mg/mL relative to the film and/or wafer;

b) at least two film forming polymers, each of the two film forming polymers is independently about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

c) a humectant of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

d) a dental adhesive of about 0.1 % w/v to about 10 % w/v relative the film and/or wafer;

wherein the injectable drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;

ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability of less than about 60 °C;

iv) a solubility of more than about 10 mg/mL in an aqueous or solvent medium; and

v) a molecular weight of less than about 6000 Da.

The present invention also provides a film or wafer for oral administration of a drug, comprising:

a) the drug of about 1 mg/mL to about 200 mg/mL relative to the film and/or wafer;

b) at least three film forming polymers, each of the three film forming polymers is

independently about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

c) a humectant of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

wherein the drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;

ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability of less than about 60 °C; and

iv) a solubility of more than about 10 mg/mL in a solvent medium.

In some embodiments, the film or wafer for oral administration of a drug comprises:

a) the drug of about 1 mg/mL to about 200 mg/mL relative to the film and/or wafer;

b) at least three film forming polymers, each of the three film forming polymers is independently about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

c) a humectant of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

d) a dental adhesive of about 0.1 % w/v to about 10 % w/v relative the film and/or wafer;

wherein the drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;

ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability of less than about 60 °C; and

iv) a solubility of more than about 10 mg/mL in a solvent medium.

In some embodiments, the film or wafer for oral administration of an injectable drug comprises:

a) the injectable drug of about 1 mg/mL to about 200 mg/mL relative to the film and/or wafer;

b) at least three film forming polymers, each of the three film forming polymers is independently about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

c) a humectant of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

wherein the injectable drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;
ii) a volume of less than about 2 mL;
iii) a chemical and/or physical stability of less than about 60 °C;
iv) a solubility of more than about 10 mg/mL in an aqueous or solvent medium; and
v) a molecular weight of less than about 6000 Da.

In some embodiments, the film or wafer for oral administration of an injectable drug comprises:

a) the injectable drug of about 1 mg/mL to about 200 mg/mL relative to the film and/or wafer;
b) at least three film forming polymers, each of the three film forming polymers is independently about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;
c) a humectant of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;
d) a dental adhesive of about 0.1 % w/v to about 10 % w/v relative the film and/or wafer;

wherein the injectable drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;
ii) a volume of less than about 2 mL;
iii) a chemical and/or physical stability of less than about 60 °C;
iv) a solubility of more than about 10 mg/mL in an aqueous or solvent medium; and
v) a molecular weight of less than about 6000 Da.

The present invention also provides a film or wafer for oral administration of a drug, comprising:

a) the drug of about 1 mg/mL to about 200 mg/mL relative to the film and/or wafer;
b) at least four film forming polymers, each of the four film forming polymers is independently about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;
c) a humectant of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

wherein the drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;
ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability of less than about 60 °C; and

iv) a solubility of more than about 10 mg/mL in a solvent medium.

In some embodiments, the film or wafer for oral administration of a drug comprises:

a) the drug of about 1 mg/mL to about 200 mg/mL relative to the film and/or wafer;

b) at least four film forming polymers, each of the four film forming polymers is independently about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

c) a humectant of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

d) a dental adhesive of about 0.1 % w/v to about 10 % w/v relative the film and/or wafer;

wherein the drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;

ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability of less than about 60 °C; and

iv) a solubility of more than about 10 mg/mL in a solvent medium.

In some embodiments, the film or wafer for oral administration of an injectable drug comprises:

a) the injectable drug of about 1 mg/mL to about 200 mg/mL relative to the film and/or wafer;

b) at least four film forming polymers, each of the four film forming polymers is independently about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

c) a humectant of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

wherein the injectable drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;

ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability of less than about 60 °C;

iv) a solubility of more than about 10 mg/mL in an aqueous or solvent medium; and

v) a molecular weight of less than about 6000 Da.

In some embodiments, the film or wafer for oral administration of an injectable drug comprises:

a) the injectable drug of about 1 mg/mL to about 200 mg/mL relative to the film and/or wafer;

b) at least four film forming polymers, each of the four film forming polymers is independently about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

c) a humectant of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

d) a dental adhesive of about 0.1 % w/v to about 10 % w/v relative the film and/or wafer;

wherein the injectable drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;

ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability of less than about 60 °C;

iv) a solubility of more than about 10 mg/mL in an aqueous or solvent medium; and

v) a molecular weight of less than about 6000 Da.

In some embodiments, the oral administration is via sublingual, buccal and/or sublabial administration.

The present invention also provides a pre-mix for forming a film or wafer for oral administration of a drug, the pre-mix comprising:

a) a film forming polymer of about 0.1 % w/v to about 20 % w/v relative to the pre-mix; and

b) a humectant of about 0.1 % w/v to about 20 % w/v relative to the pre-mix.

The present invention also provides a pre-mix for forming a film or wafer for oral administration of a drug, the pre-mix comprising:

a) at least two film forming polymers, each of the two film forming polymers is independently about 0.1 % w/v to about 20 % w/v relative to the pre-mix; and

b) a humectant of about 0.1 % w/v to about 20 % w/v relative to the pre-mix.

The present invention also provides a pre-mix for forming a film or wafer for oral administration of a drug, the pre-mix comprising:

a) at least three film forming polymers, each of the three film forming polymers is independently about 0.1 % w/v to about 20 % w/v relative to the pre-mix; and
b) a humectant of about 0.1 % w/v to about 20 % w/v relative to the pre-mix.

The present invention also provides a pre-mix for forming a film or wafer for oral administration of a drug, the pre-mix comprising:

a) at least four film forming polymers, each of the four film forming polymers is independently about 0.1 % w/v to about 20 % w/v relative to the pre-mix; and
b) a humectant of about 0.1 % w/v to about 20 % w/v relative to the pre-mix.

The polymers may be selected from the table as disclosed herein.

In this way, films or wafers can be reconstituted on on-demand basis within healthcare institutions. Further, as the pre-mix is compatible with several APIs, the same formulation platform may be used to incorporate and deliver different APIs separately or in combination to benefit patients with various conditions.

In some embodiments, the pre-mix comprises:

a) a film forming polymer of about 0.1 % w/v to about 20 % w/v relative to the pre-mix; and
b) a glycerol of about 0.1 % w/v to about 20 % w/v relative to the pre-mix.

In some embodiments, the pre-mix comprises:

a) at least two film forming polymers, each of the two film forming polymers is independently about 0.1 % w/v to about 20 % w/v relative to the pre-mix; and
b) a glycerol of about 0.1 % w/v to about 20 % w/v relative to the pre-mix.

In some embodiments, the pre-mix comprises:

a) at least three film forming polymers, each of the three film forming polymers is independently about 0.1 % w/v to about 20 % w/v relative to the pre-mix; and
b) a glycerol of about 0.1 % w/v to about 20 % w/v relative to the pre-mix.

In some embodiments, the pre-mix comprises:

a) at least four film forming polymers, each of the four film forming polymers is independently about 0.1 % w/v to about 20 % w/v relative to the pre-mix; and

b) a glycerol of about 0.1 % w/v to about 20 % w/v relative to the pre-mix.

In some embodiments, the pre-mix further comprises a dental adhesive of about 0.1 % w/v to about 10 % w/v relative the pre-mix.

The present invention also provides a method of treating a disease or disorder treatable by a drug, comprising compounding the drug into a film and/or wafer as disclosed herein, and administering to a subject in need thereof a therapeutically effective amount of the film and/or wafer via sublingual, buccal and/or sublabial administration.

The present invention also provides a film and/or wafer for use in treating a disease or disorder treatable by a drug, wherein the film and/or wafer comprises the drug and is administrable sublingually, buccally and/or sublabially.

The present invention also provides a use of a film and/or wafer in the manufacture of a medicament for treating a disease or disorder treatable by a drug, wherein the film and/or wafer comprises the drug and is administrable sublingually, buccally and/or sublabially.

The medicament may be used to treat diseases or disorders such as migraines, epilepsy and asthma attacks. The ability to administer the medicament sublingually, buccally and/or sublabially may be less hazardous as compared to an injection. The preparation to be injected has to be sterile and particulate-free and there may be a risk of infection at the injection site. Administering the medicament as a film and/or wafer may eliminate the need for an injection, thus reducing the risk of infection.

The present invention also provides a system for compounding a drug into a film or wafer, comprising:

a) a drug receiving module for receiving the drug;
b) a pre-mix module for containing and introducing a pre-mix to the drug;
c) a mixing module for mixing the drug with the pre-mix to form a solution;
d) a dosing and dispensing module for dispensing the solution;
e) a mold for containing the dispensed solution; and
f) a curing module for curing the solution in the mold into the film or wafer.

In some embodiments, the system for compounding an injectable drug into a film or wafer comprises:

a) a drug receiving module for receiving the injectable drug;

b) a pre-mix module for containing and introducing a pre-mix to the injectable drug;

c) a mixing module for mixing the injectable drug with the pre-mix to form a solution;

d) a dosing and dispensing module for dispensing the solution;

e) a mold for containing the dispensed solution; and

f) a curing module for curing the solution in the mold into the film or wafer.

As used herein, "system" refers to one or more devices configured with or interacting with each other based on a set of rules. The set of rules can be provided by a software and/or process protocol. In this sense, a system is a group of interacting or interrelated elements or components that act according to a set of rules to form a unified whole. A system, surrounded and influenced by its environment, is described by its boundaries, structure and purpose and expressed in its functioning.

The system may be modular in that the components of the system may be separated and recombined as required. This offers the benefit of flexibility and variety in use. Various components of the modular system are described below. These components may be used individually, or in any combinations.

The module for premix contains and introduces the pre-mix for making the film or wafer. Various amounts of pre-mix may be added, depending on the desired product. For example, an amount of pre-mix sufficient for a single dosage form or multiple dosage form may be added.

The module for receiving drug is for receiving the drug. The drug may be received as originally formulated. In this regard, the drug is received as a pharmaceutical composition. For example, the drug may be in liquid form aliquoted from an ampule or combined from several ampules. Alternatively, the drug may be a powder or a solution.

The module for mixing allows the combination of the drug with a pre-mix. An aqueous medium may be added as required.

The module for dosing and dispensing allows all or a fraction of the solution to be dispensed. The dispensing may be into a mold. The dispensing may be quantified by weight and/or volume. Other methods may also be used, such as by electrical conductivity.

The mold contains the solution in appropriate molds to form the film or wafer. The module may be configured to produce one or more films and wafers. For example the module may be a tray with 10-50 molds such that each mold will receive the set volume/weight equivalent to one film/wafer from the module for dosing and dispensing.

The module for curing the film or wafer converts the liquid or gel like solution in the mold into a solid. If the viscosity of the solution is high, a press may additionally be included to press and control the thickness of the film/wafer. The curing may involve a light-activated process, such as cross-linking by light of specific wavelength or by mixing with an activator for cross-linking, liquid content removal by evaporation, such as thermal heating, freeze-drying, or diffusion via controlled pore membrane.

The system may optionally comprise a module for surface sterilizing the film or wafer. For example, the module may be a UV light source.

The system may optionally comprise a module for packaging the film or wafer. This allows for safe transportation between the compounded drug and application to patient.

The system may optionally comprise a module for cleaning the system. The module may clean and rinse out all residues from the components of the system.

The system may optionally comprise a sensing and data collection module. The module may record each step of the process for logging and analysis. Such information can be used for trouble shooting.

The system may optionally comprise a control system. The control system can be a computer implemented system. This can involve a computer programme which regulates control of the pre-mix, drug, mixing, sterilising, packaging and/or cleaning. The programme can additionally be configured to enable (such as switch on or off) the detecting means and/or quantifying means in order to detect and/or quantify the

amount of drug in each film or wafer. The control system may also be configured with data relating to the control (calibration plot). The control system may be configured to be connectable to a network for managing the system remotely and/or automatically.

The design of this light-duty, energy-saving, bench-top portable equipment will compound and deliver desired quality and quantity in film/wafer dosage forms containing precise and accurate doses using the aseptic (no-touch) technique.

It provides the possibility of compounding films/wafers of drugs (and injectable drugs) at the point of dispensing/use and address the critical capability gap that hinders the efficient compounding of safe, quality, personalised and environment-friendly medicines for patients and for other applications such as clinical development, military etc.

Examples

General methodology

The method has the following steps:

1. Screening formularies of injectable drugs (eg. ASHP Injectable Drug Information) and selecting those injectable drugs with the following characteristics for formulation development into films/wafers:

(a) Unit dose of 200 mg or less,

(b) Dose contained in a volume of 2 ml or less upon reconstitution,

(c) Chemical and physical stability at temperature range not exceeding 60°C, and

(d) Solution compatibility with aqueous solutions containing alcohols, polymers and/or other excipients for taste-masking, adjusting viscosity and pH of the casting solution.

2. Compounding of film/wafer from an injectable drug or from other dosage forms by:

(a) Preparing a solution containing the drug with the required dose strength using stipulated amounts of specified excipients

(b) Casting an accurate volume of the solution into a mold

(c) Drying the solution to obtain the film/wafer and sterilization under UV light

(d) Removing the film/wafer from the mold and packing the film or wafer

Pre-mix formulations, films and wafers

Pre-mixed packets of polymers and solid excipients for film formulation for injectables of drugs from BCS classes I, II and III may be provided as follows. Polymer pre-mix may be presented in powder, suspension and/or solution forms with detailed step-wise guidance on how to add, mix, dispense, process to obtain the final films/wafers. Injectable requisites are not provided. Alternatively, single and multi-layered films/wafers of fast and slow released formulations of same or combination APIs manufactured using repurposed injectable drug solutions or powders from BCS classes I, II and III may be used.

Premixed powders of polymers and solid excipients or their respective suspension and/or solution forms encompass the formulations listed in the table below. It was found that using a combination of polymers also allows complement of different polymer characteristics. This improves the resultant film's rubbery texture and also allows the film to disintegrate faster. For the manufacture of the films or wafers, first, aqueous polymer solutions with the following compositions are prepared:

Formulation	Xanthan gum (% w/v)	Polyvinyl alcohol (% w/v)	Hydroxypropyl methylcellulose (% w/v)	Pullulan (% w/v)	Polyvinyl pyrrolidone (% w/v)	Trehalose (% w/v)	Lycoat RS720 (% w/v)	Chitosan	Methylcellulose (% w/v)	Glycerol (% w/v)
F1	0.01 - 5	0.01 - 4								0.01 - 10
F2			0.01 – 10	0.01 - 10						0.01-10
F3			0.01 - 10		0.01 - 5			0.01 - 10	0.01 - 5	0.01 - 10
F4	0.01 - 5			0.01 -10		0.01 - 10			0.01 - 5	0.01 - 10
F5	0.01 - 10						0.01 - 8			0.01 - 10
F6				0.01 - 20		0.01 - 20			0.01 - 5	0.01 - 10
F7							0.01 - 15			0.01 - 20
F8	0.01 - 5				0.01 – 5					0.01 - 10

F9			0.01 - 10	0.01 - 10	0.01 - 5			0.01 - 10		0.01 - 10
F10		0.01 - 4	0.01 - 10							0.01 - 10

Next, equal volumes of injectable drug solutions are added to the pre-mix. The mixture is mixed well by acoustic/ultrasonic, dielectrophoretic, electrokinetic time-pulsed, electrohydrodynamic force, thermal actuation, magneto-hydrodynamic flow, electrokinetic instability, or passive microfluidic mixers, such as 2-D serpentine structure, twisted channels, zigzag channels, or embedded barriers, or stirred using a glass rod, magnetic stirrer or mixed using a vortex mixer until uniform.

The mixture may need a pre-treatment to remove air bubbles trapped during mixing. If so, it is then left in an ultrasonic bath at 25°C and 50% to 150% power until bubbles are no longer present in the mixture (now known as the casting solution). Removing bubbles can also be achieved by providing a lower pressure environment for the mixture.

The mixture can be dosed by weight, volume, or be deployed as a whole and the dose of mixture is transferred to a mold or tray. In one embodiment, if by volume, using an volumetric pipette, 0.5 to 2 ml of the casting solution is drawn and deposited onto a mold. Dental adhesive powder/gel may be added to improve the stickiness of film/wafer to mucosal tissues. The water content of the mixture on the mold or tray is then reduced. The reduction of water content can be air-dried in ambient temperature or dried in a convection oven below 60°C. Dried film can be collected from the mold or tray by vacuum, robotic arm, or simple peeling by hand or any hand tool and subjected to sterilisation, of which one of them is UVC sterilization, before being individually packed in a light-protected, waterproof, resealable pouch.

The films formed were evaluated for central thickness using a thickness gauge, optical method, acoustic method, micrometre, or other methods, time to initial disintegration using the set-up in Figure 1, folding endurance using repeated manual folding along the same plane on the film, and surface pH using a pH meter.

Results (range) of single-layered films obtained from using midazolam 5 mg/ml injectable drug solution:

Formulation	Central thickness (mm)	Time to initial disintegration (seconds)	Folding endurance (folds)	Surface pH	Puncture resistance (g)	Moisture content (%)	Drug content (mg)
F1	0.065 - 0.18	18 - 78	42 - >100	3.31 - 3.36	145 – 150	15.3 – 18.2	4.25 – 5.75
F2	0.105 - 0.2	88 - 109	68 - >100	3.31 - 3.36	136 – 146	14.7 – 19	4.25 – 5.75
F3	0.065 - 0.18	18 - 79	71 - >100	3.31 - 3.36	117 – 121	13.9 – 19.7	4.25 – 5.75
F4	0.07 - 0.12	17 - 93	29 - 73	3.31 - 3.36	119 – 132	16.1 – 19.3	4.25 – 5.75
F5	0.085 - 0.195	30 - 111	32 - 87	3.31 - 3.36	118 – 120	12.9 – 18.4	4.25 – 5.75
F6	0.07 - 0.155	19 - 89	83 - >100	3.31 - 3.36	143 – 156	15.3 – 17.6	4.25 – 5.75
F7	0.065 - 0.175	12 - 81	25 - >100	3.31 - 3.36	176—180	14.5 – 18.4	4.25 – 5.75
F8	0.1 - 0.195	61 - 125	58 - >100	3.31 - 3.36	122 – 130	13.7—15.6	4.25 – 5.75
F9	0.105 - 0.215	26 - 269	>100	3.31 - 3.36	143 – 151	14.2 – 18.8	4.25 – 5.75
F10	0.105 - 0.215	31 - 256	>100	3.31 - 3.36	155 – 159	13.8 – 18.7	4.25 – 5.75

Midazolam is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;

ii) a unit dose volume of less than about 2 mL;

iii) a chemical and/or physical stability at less than about 60 °C; and

iv) a solubility of more than about 10 mg/mL in a solvent medium.

Conclusions

The formulations F1 to F10 are suitable for incorporation of injectable drug solutions for the manufacture of medicated films or wafers. The film or wafer may be used for oral administration. For example, and in addition to midazolam, other drugs have been tested such as ondansetron hydrochloride, hyoscine bromide, chlorpheniramine maleate, caffeine hydrochloride, and a combination thereof.

The effectiveness is in relation to the drug content detected in the films was also tested. Based on pharmaceutical standards, the preparation complies with the test if each individual drug content is between 85% and 115% of the average content (European Pharmacopoeia). All formulations have drug content within this range.

By repurposing an injectable drug and administrating it buccally, drugs may be delivered to a patient within/through the buccal mucosa and achieve a local or systemic effect. Via this route, the drug bypasses gastrointestinal enzymatic degradation and the hepatic first-pass effect, and thus may achieve the same effect as via an injection.

It will be appreciated that many further modifications and permutations of various aspects of the described embodiments are possible. Accordingly, the described aspects are intended to embrace all such alterations, modifications, and variations that fall within the spirit and scope of the appended claims.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Throughout this specification and the claims which follow, unless the context requires otherwise, the phrase "consisting essentially of", and variations such as "consists

essentially of" will be understood to indicate that the recited element(s) is/are essential i.e. necessary elements of the invention. The phrase allows for the presence of other non-recited elements which do not materially affect the characteristics of the invention but excludes additional unspecified elements which would affect the basic and novel characteristics of the method defined.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavor to which this specification relates.

Claims

1. A method of compounding a drug into a film or wafer, comprising:

a) solubilising the drug in a pre-mix and optionally in an aqueous medium in order to form a solution; and

b) casting the solution into a mold in order to form the film or wafer;

wherein the drug is compounded in its dosage form;

wherein the drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;

ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability at less than about 60 °C; and

iv) a solubility of more than about 10 mg/mL in a solvent medium.

2. The method according to claim 1, wherein the drug is selected from Biopharmaceutical Classification System (BCS) classes I, II and III.

3. The method according to claim 1 or 2, wherein the drug is characterised by at least two of the above criteria.

4. The method according to any one of claims 1 to 3, wherein the drug is further characterised by a molecular weight of less than about 6000 Da.

5. The method according to any one of claims 1 to 4, wherein the dosage form of the drug is selected from injection liquid, powder, tablet, capsule, swallowable liquid, inhalation liquid, nasal liquid, eye drop, or eardrop.

6. The method according to any one of claims 1 to 5, wherein the drug is selected from midazolam, ondansetron, dimenhydrinate, haloperidol, lidocaine, salbutamol, levalbuterol, dexamethasone, prednisolone, prednisone, methylprednisolone, diazepam, lorazepam, clonazepam, diclofenac, ketoprofen or other non-steroidal anti-inflammatory drugs (NSAIDs), epinephrine, diphenhydramine, dopamine, adenosine, caffeine, naloxone, flumazenil, codeine, fentanyl, ketamine, or a combination thereof.

7. The method according to any one of claims 1 to 6, wherein the drug is provided as a single unit dosage.

8. The method according to any one of claims 1 to 7, wherein the drug in the solution is about 1 mg/mL to about 200 mg/mL.

9. The method according to any one of claims 1 to 8, wherein the pre-mix comprises an excipient selected from film forming polymer, binder, bioadhesive material, coating agent, controlled-release agent, dispersing agent, dissolution enhancer, emulsifying agent, emulsion stabilizer, humectant, modified-release agent, film-forming agent, mucoadhesive, plasticiser, solubilizing agent, stabilizing agent, suspending agent, thickening agent, taste-masking agent, colouring agent or a combination thereof.

10. The method according to any one of claims 1 to 9, wherein the pre-mix comprises a film forming polymer selected from polyethylene oxide, hydroxypropyl methylcellulose, methylcellulose, carboxymethyl-cellulose, polyvinyl pyrrolidone, gelatin, pectin, xanthan gum, polyvinyl alcohol, trehalose, hydroxypropyl Pea Starch (Lycoat RS720), chitosan, pullulan, or a combination thereof.

11. The method according to any one of claims 1 to 10, wherein the pre-mix comprises at least two film forming polymers.

12. The method according to any one of claims 1 to 11, wherein the pre-mix comprises one of the following:

a) xanthan gum and polyvinyl alcohol;
b) xanthan gum and pullulan;
c) xanthan gum and polyvinyl pyrrolidone;
d) xanthan gum and trehalose;
e) xanthan gum and Lycoat RS720;
f) xanthan gum and methylcellulose;
g) polyvinyl alcohol and hydroxypropyl methylcellulose;
h) hydroxypropyl methylcellulose and pullulan;
i) hydroxypropyl methylcellulose and polyvinyl pyrrolidone;
j) hydroxypropyl methylcellulose and chitosan;
k) hydroxypropyl methylcellulose and methylcellulose;
l) pullulan and polyvinyl pyrrolidone;
m) pullulan and trehalose;

n) pullulan and Lycoat RS720;
o) pullulan and methylcellulose;
p) polyvinyl pyrrolidone and chitosan;
q) polyvinyl pyrrolidone and methylcellulose;
r) trehalose and methylcellulose; and
s) chitosan and methylcellulose.

13. The method according to any one of claims 1 to 12, wherein the pre-mix comprises at least three film forming polymers.

14. The method according to any one of claims 10 to 13, wherein the film forming polymer is about 0.1 % w/v to about 20 % w/v relative to the solution.

15. The method according to any one of claims 1 to 14, wherein the pre-mix comprises a binder.

16. The method according to claim 15, wherein the binder is about 0.1 % w/v to about 20 % w/v relative to the solution.

17. The method according to any one of claims 1 to 16, wherein the pre-mix comprises a humectant.

18. The method according to claim 17, wherein the humectant is about 0.1 % w/v to about 20 % w/v relative to the solution.

19. The method according to any one of claims 1 to 18, wherein the pre-mix comprises a solubilising agent.

20. The method according to any one of claims 1 to 19, wherein the pre-mix comprises a taste-masking agent.

21. The method according to any one of claims 1 to 20 wherein the pre-mix further comprises a pH regulator.

22. The method according to claim 21, wherein the pH regulator is about 0.1 % w/v

to about 20 % w/v relative to the solution.

23. The method according to any one of claims 1 to 22, wherein the pre-mix further comprises a dental adhesive.

24. The method according to claim 23, wherein the dental adhesive powder or gel is about 0.1 % w/v to about 10 % w/v relative to the solution.

25. The method according to any one of claims 1 to 24, wherein the step of casting the solution further comprises drying the solution.

26. The method according to any one of claims 1 to 25, wherein the method further comprises a step of UV sterilising the film or wafer.

27. The method according to any one of claims 1 to 26, wherein the method further comprises a step of further dehydrating the film or wafer.

28. The method according to any one of claims 1 to 27, wherein the film or wafer is characterised by a thickness of about 0.05 mm to about 1.0 mm.

29. The method according to any one of claims 1 to 28, wherein the film or wafer is characterised by a disintegration time of about 10 s to about 15 min.

30. The method according to any one of claims 1 to 29, wherein the film or wafer is characterised by a pH of about 2 to about 8.

31. The method according to any one of claims 1 to 30, wherein the film or wafer is characterised by a folding endurance of more than about 100 times.

32. The method according to any one of claims 1 to 31, wherein the film or wafer is characterised by a Young's modulus of at least 50 N/cm^2.

33. The method according to any one of claims 1 to 32, wherein the film or wafer is for sublingual, buccal and/or sublabial administration.

34. The method according to any one of claims 1 to 33, wherein the drug is an injectable drug.

35. A film or wafer for oral administration of a drug, comprising:

a) the drug of about 1 mg/mL to about 200 mg/mL relative to the film and/or wafer;

b) a film forming polymer of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

c) a humectant of about 0.1 % w/v to about 20 % w/v relative to the film and/or wafer;

wherein the drug is characterised by at least one of the following:

i) a unit dose of less than about 200 mg;

ii) a volume of less than about 2 mL;

iii) a chemical and/or physical stability of less than about 60 °C; and

iv) a solubility of more than about 10 mg/mL in a solvent medium.

36. A pre-mix for forming a film or wafer for oral administration of a drug, the pre-mix comprising:

a) a film forming polymer of about 0.1 % w/v to about 20 % w/v relative to the pre-mix; and

b) a humectant of about 0.1 % w/v to about 20 % w/v relative to the pre-mix.

37. The pre-mix according to claim 36, comprising at least three film forming polymers, each of the three film forming polymers is independently about 0.1 % w/v to about 20 % w/v relative to the pre-mix.

38. A method of treating a disease or disorder treatable by a drug, comprising compounding the drug into a film or wafer as disclosed herein, and administering to a subject in need thereof a therapeutically effective amount of the film and/or wafer via sublingual, buccal and/or sublabial administration.

39. A film or wafer for use in treating a disease or disorder treatable by a drug, wherein the film and/or wafer comprises the drug and is administrable sublingually, buccally and/or sublabially.

40. Use of a film or wafer in the manufacture of a medicament for treating a disease or disorder treatable by a drug, wherein the film and/or wafer comprises the drug and is administrable sublingually, buccally and/or sublabially.

41. A system for compounding a drug into a film or wafer, comprising:

a) a drug receiving module for receiving the drug;

b) a pre-mix module for containing and introducing a pre-mix to the drug;

c) a mixing module for mixing the drug with the pre-mix to form a solution;

d) a dosing and dispensing module for dispensing the solution;

e) a mold for containing the dispensed solution; and

f) a curing module for curing the solution in the mold into the film or wafer.

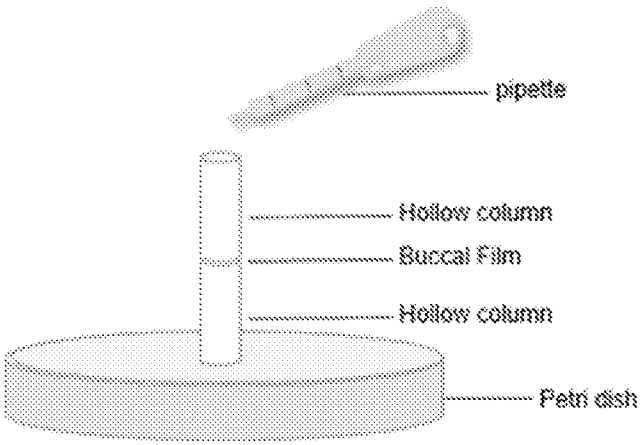
pipette
Hollow column
Buccal Film
Hollow column
Petri dish

Figure 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2023/050762

A. CLASSIFICATION OF SUBJECT MATTER

A61K 9/70 (2006.01) ***A61K 47/36 (2006.01)***

According to International Patent Classification (IPC)

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

EMBASE, MEDLINE, BIOSIS, FAMPAT: orodispersible film, drug wafer, unit dose, casting, and similar terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHAN S. Y. ET AL., Midazolam Buccal Films: Development and Characterization for Palliative Care. *Poster presentation at 2022 PharmSci 360*, 18 October 2022 [Retrieved on 2024-02-27] <DOI: NONE> Whole document; Tables 1A, 1B, 2	1-31, 33-35
X	FOO W. C. ET AL., A novel unit-dose approach for the pharmaceutical compounding of an orodispersible film. *Int J Pharm*, 27 February 2018, Vol. 539, No. 1-2, pages 165-174 [Retrieved on 2024-02-27] <DOI: 10.1016/J.IJPHARM.2018.01.047> Abstract; Pg. 166 left col. third para. - right col. third para.; Tables 1-3	1-10, 14, 17-18, 23-29, 32-35
A	WO 2016/015798 A1 (PHARMATHEN S.A.) 4 February 2016 Example 6	-

☒ 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
27/02/2024 *(day/month/year)*	27/02/2024 *(day/month/year)*

Name and mailing address of the ISA/SG	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2023/050762

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:

Please refer to Supplemental Box (Continuation of Box No. III).

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

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

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

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

   1-35

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/SG2023/050762

Supplemental Box
(Continuation of Box No. III)

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

Invention group 1: Claims 1-35 relate to a method of compounding a drug into a film or wafer, as well as the film or wafer thereof, wherein the drug is characterized by at least one of the following: (i) a unit dose of less than about 200 mg, (ii) a volume of less than about 2 ml, (iii) a chemical and/or physical stability at less than about 60°C, and (iv) a solubility of more than about 10 mg/ml in a solvent medium.

Invention group 2: Claims 36-37 relate to a pre-mix for forming a film or wafer for administration of a drug, wherein the pre-mix comprising a film forming polymer and a humectant.

Invention group 3: Claims 38-40 relate to a medical use of a film or wafer comprising a drug, wherein the film or wafer is administered sublingually, buccally and/or sublabially.

Invention group 4: Claim 41 relates to a system for compounding a drug into a film or wafer, wherein the system comprising a drug receiving module, a pre-mix module, a mixing module, a dosing and dispensing module, a mold, and a curing module.

Please refer to **Box No. IV** of Written Opinion of The International Searching Authority (Form PCT/ISA/237) for detailed explanation.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2023/050762

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TURKOVIĆ E. ET AL., Orodispersible films - Pharmaceutical development for improved performance: A review. *J Drug Deliv Sci Technol*, 18 August 2022, Vol. 75, Article 103708, pages 1-16 [Retrieved on 2024-02-27] <DOI: 10.1016/J.JDDST.2022.103708> Whole document	-

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SG2023/050762

Note: This Annex lists known patent family members relating to the patent documents cited in this International Search Report. This Authority is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016/015798 A1	04/02/2016	CY 1121141 T1	29/05/2020
		LT 3193826 T	25/01/2019
		RS 58120 B1	28/02/2019
		US 2017/0165315 A1	15/06/2017
		PL 3193826 T3	31/07/2019
		HR P20190083 T1	08/03/2019
		EP 3193826 A1	26/07/2017
		SI 3193826 T1	28/02/2019
		HU E041705 T2	28/05/2019
		PT 3193826 T	23/01/2019
		DK 3193826 T3	11/02/2019
		ES 2705610 T3	26/03/2019
		TR 201819662 T4	21/01/2019