

VAPOR PHASE COATINGS FOR PHARMACEUTICAL SOLUBILITY CONTROL

BACKGROUND

Thick pharmaceutical coatings can impart desired functional behavior, such as solubility control under a specified temperature or pH range. However, their thickness introduces significant new problems, such as changes in pharmacokinetics, or reduction of API content in the final formulation.

Existing methods of applying coatings for solubility modification require the inclusion of large amounts of coating materials to ensure complete coverage of all particles regardless of their size or shape. As a result of this coating overburden the coatings may negatively impact pharmacological activity of the drug. Our coatings provide dense, conformal, defect free films at low thicknesses (< 100 nm) to mitigate these concerns.

SUMMARY

Described herein is a method enables thin, uniform, conformal, and dense coatings on particles of an active pharmaceutical ingredient, regardless of particle size. These highly precise coatings can minimize the coating overburden required to provide effective solubility control, thereby minimizing the risk of the solubility control formulation impacting pharmacological performance. Additionally, hybrid organic-inorganic coating structures can be prepared which enable new modes of solubility control and stimuli response.

This technology is intended to produce pharmaceutical coatings for formulations which have modified solubility outside the body while minimizing the impact on pharmacological performance in vivo. This can be achieved using a combination of thin (< 100nm), conformal organic and inorganic coatings which show unique stimuli responsive solubility behavior. The inorganic coatings may consist of metal oxides such as Al₂O₃ or TiO₂. Organic coatings may consist of condensation polymers, such as polyesters or polyamides, or chain growth polymers, synthesized from esters or aminoesters of acrylic acid and methacrylic acid, acrylamides, styrenes, and their copolymers. The coatings are unique for their

ultrathin (< 100nm), uniform, and conformal structures, even on particles with high size polydispersity, surface roughness, or aspect ratios.

Metal oxide materials are coated through one or more of an atomic layer deposition (ALD) or chemical vapor deposition (CVD) on process. Polymers are coated through one or more of a molecular layer deposition (MLD), initiated (hot filament) chemical vapor deposition (iCVD), or aerosol-assisted spray deposition process (AA-CVD). These technologies share the unique benefits of high coating uniformity, independent of particle size, with good conformal coverage and a relative lack of pinhole defects, and are amenable to a common reactor architecture, described elsewhere. The particles being coated are agitated (by rotation, gas flow, or vibration) during deposition to ensure high throughput and good uniformity

ALD deposition of metal oxides takes place at temperatures from about room temperature to 300 C by alternating doses of precursors such as trimethylaluminum (TMA) or TiCl_4 and oxidant such as water vapor or ozone. The superior chemical inertness and physical strength of metal oxides made by this process make them promising new candidates for solubility control. They also show pH dependent solubility properties. In the coating process, precursors are dosed into a reactor in either static mode or flow-through mode. In static mode, the metal precursor is pulsed into a closed reactor and allowed to dwell in the reactor until it is consumed by reaction with the surface. Reaction byproducts are then pumped out and the reactant is pulsed again until all reaction sites on the powder have been occupied. The reactor is then purged of residual reactant by a flow of an inert gas. The cycle is then repeated with the oxidant. In flow-through mode, the flow rate of the metal precursor is set such that it is fully or nearly fully consumed in the reactor without closing the reactor exhaust. The exhaust is monitored to identify the reaction end point, at which time the reactor is purged with an inert gas and the process is repeated with the oxidant. In either flow through or static mode, this cycle is repeated until the desired film thickness is achieved.

Organic polymer layers can be deposited in a similar manner via either molecular layer deposition (MLD) or initiated (hot filament) chemical vapor deposition (iCVD). MLD is an alternating process analogous to the process described for ALD above and can be used for the deposition of condensation polymers such as polyamides and polyesters, which may be branched or crosslinked. Certain pH responsive polyesters or polyamides are particularly useful for their ability to

differentially control solubility in varying environments. In the MLD process, particles are coated by dosing alternating physisorbed or chemisorbed monolayers consisting of one or more complimentary pairs of multifunctional Lewis acids and bases. The Lewis bases may consist of multifunctional alcohols such as diethylene glycol or amines such as ethylene diamine. The Lewis acids may consist of multifunctional acid chlorides such as succinyl chloride, glutaryl chloride, or adipoyl chloride. Trifunctional Lewis acids or bases such as trimesoyl chloride can be used to introduce branching or crosslinking. Hybrid organic-inorganic materials can also be prepared using a metal-organic precursor (such as TMA) as the Lewis acid. These alternating layers can be dosed in either static or flow through mode, as specified for ALD above.

An iCVD process can be used for the deposition of chain-growth polymers, such as poly(acrylates), poly(methacrylates), and poly(styrenes) and their copolymers. Among these materials, amino-esters of acrylic and methacrylic acid (such as pDMAEMA and pEMAEMA) are of particular interest due to their sharp pH dependent transition in solubility. Additionally, hydrogel materials (such as crosslinked polyacrylamides) can also show significant effects on solubility due to their swellability. In the iCVD process, one or more monomer precursors chosen from the subset of vinyl, acrylate, methacrylate, acrylamide, methacrylamide, or styrene chemistries flow into the reactor through a vapor delivery system (i.e. bubbler or direct liquid injection) capable of delivering 1-100 g/min of monomer vapor. Copolymers can also be prepared by coinjection of multiple different monomers. Relative saturation ratios and rates of reaction will determine the composition of the deposited film. A second injector provides delivery of a thermal initiator, such as an organic peroxide. The initiator flows over a heated element before entering the reactor. This heated element cracks the initiator to form two peroxy radicals without interacting with the monomer vapor. These radicals then induce chain growth polymerization of monomer species physically adsorbed on the surface of the particles to be coated.

These processes all result in dense, conformal, highly uniform films, which cannot be produced by incumbent pharmaceutical coating processes today. These precision coatings can achieve good solubility control due to stimuli or thermal response, while minimizing the coating's effect on pharmacological behavior due to their extreme thinness. Furthermore, they can minimize excipient loadings by

enabling identical performance in thinner coatings, allowing increased drug dosage in a smaller dosage form factor. Finally, these processes can be used in combination to create laminate structures with unique environmentally dependent solubility controls, allowing the drug solubility to be tailored while minimizing the effect of coatings on in vivo performance.

In one aspect, a method of preparing a pharmaceutical composition having a drug-containing core enclosed by one or more metal oxide materials is provided. The method includes the sequential steps of (a) loading the particles comprising the drug into a reactor, (b) applying a vaporous or gaseous metal precursor to the particles in the reactor, (c) performing one or more pump-purge cycles of the reactor using inert gas, (d) applying a vaporous or gaseous oxidant to the particles in the reactor, and (e) performing one or more pump-purge cycles of the reactor using inert gas. The temperature of the particles does not exceed 35 °C. This produces a pharmaceutical composition comprising a drug containing core enclosed by one or more metal oxide materials.

Implementations may include one or more of the following features.

The temperature of the interior of the reactor need not exceed 35°C.

The sequential steps (b)-(e) may be repeated one or more times to increase the total thickness of the one or more metal oxide materials that enclose the core.

The reactor pressure may be allowed to stabilize following step(a), step (b), and/or step (d).

The reactor contents may be agitated prior to and/or during step (b), step (c), and/or step (e).

A subset of vapor or gaseous content may be pumped out prior to step (c) and/or step (e).

The metal oxide layer may have a thickness in range of 0.1 nm to 100 nm.

The particles may include a drug and one or more pharmaceutically acceptable excipients.

The particles may have a median particle size, on a volume average basis, between 0.1 µm and 1000 µm.

The pharmaceutical composition may be removed from the reactor and admixed with a pharmaceutically acceptable diluent or carrier.

The particles may consist essentially of the drug.

The drug may be a small molecule, virus particle, polypeptide, polynucleotide, a composition comprising polypeptide and lipid, or a composition comprising polynucleotide and lipid.

The one or more metal oxide materials may include aluminum oxide, titanium oxide, iron oxide, gallium oxide, magnesium oxide, zinc oxide, niobium oxide, hafnium oxide, tantalum oxide, lanthanum oxide, and/or zirconium dioxide.

The one or more metal oxide materials may consist of aluminum oxide and/or titanium oxide.

The oxidant may be selected from the group of water, ozone, and organic peroxide.

The polypeptide may be an antibody or antibody fragment.

The antibody or antibody fragment may be selected from the group of: alemtuzumab, bevacizumab, cetuximab, gemtuzumab ozogamicin, ipilimumab, ofatumumab, panitumumab, pembrolizumab, ranibizumab, rituximab, or trastuzumab.

The small molecule drug may be selected from the group of: acetaminophen, clarithromycin, azithromycin, ibuprofen, fluticasone propionate, salmeterol, pazopanib HCl, palbociclib, or amoxicillin potassium clavulanate.

In another aspect, a pharmaceutical composition having a drug-containing core enclosed by one or more metal oxide materials may be prepared by any of the above methods

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present invention; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the invention will be apparent from the following detailed description and figures, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic illustration of a rotary reactor for ALD and/or CVD coating of particles, e.g., drugs.

FIG. 2 is a table showing representative process conditions for the method.

FIG. 3 is a graph depicting representative residual gas analysis traces measuring during steps (d), (h), (i), and (m) for one cycle of the method.

DETAILED DESCRIPTION

The present disclosure provides methods of preparing pharmaceutical compositions comprising drugs encapsulated by one or more layers of metal oxide. Such pharmaceutical compositions have enhanced flowability, solubility, stability over time and contain a high fraction of drug that is functional before or following administration of the pharmaceutical composition to a subject in need. Overall, the provided methods of preparing the pharmaceutical compositions are able to safely, reliably, and predictably generate pharmaceutical compositions with the aforementioned properties. As result, the provided pharmaceutical compositions and methods of preparing metal oxide encapsulated drugs have increased therapeutic value, increased commercial value, and lower production cost per therapeutic dose.

The manufacture of the advantageous pharmaceutical compositions was enabled by the discovery that sequentially applying vaporous or gaseous metal precursor and vaporous or gaseous oxidant (and performing one or more pump-purge cycles using an inert gas after each application of said metal or oxidant) allowed the entire method to be preformed at lower temperatures – e.g., not exceeding 35 °C. Known methods of coating drug with metal oxide using vaporous or gaseous precursors when performed at temperatures lower than 50 °C do not yield pharmaceutical compositions with improved properties due to elevated levels of oxidant (e.g., water) in the reactor as the temperature is decreased below 50 °C. The elevated and persistent levels of oxidant in the reactor can negatively affect the reaction (and adsorption) of the metal precursors and oxidant with the particle surface and with each other. Additionally, the elevated levels of oxidant in the reactor can interfere with the ability to remove unreacted metal precursor, gaseous byproduct from the reaction of metal precursor with exposed hydroxyl groups on the substrate or on surface of particle, and/or unreacted oxidant that are not incorporated into metal oxide layers around the drug, which can lead to formation of contaminating metal

oxide particles and/or to reduced predictability concerning the number and uniformity of metal oxide layers formed around the drug. Without wishing to be bound to a particular theory, the step of pump-purge cycles may mediate a kinetic effect to knockoff oxidant molecules on the particle surface and on the internal surface of the reactor that are kinetically, not thermodynamically, trapped there. As a result, problematic moisture content in the reactor is reduced below the amount expected based on thermodynamic principles, well known in the art, that are dictated by the pressure, temperature, and number of molecules in the reactor.

Herein a method is provided that utilizes a mechanical system and a chemical engineering process. The present disclosure also provides exemplary components and operating conditions of said system and process and exemplary drug substrates, vaporous and gaseous metal precursors, and vaporous and gaseous oxidants.

Drug

The term “drug,” in its broadest sense includes small molecule, virus particle, polypeptide, polynucleotide, polypeptide, a composition comprising polypeptide and lipid, and a composition comprising polynucleotide and lipid. The drug could be selected from the group consisting of an analgesic, an anesthetic, an anti-inflammatory agent, an anthelmintic, an anti-arrhythmic agent, an antiasthma agent, an antibiotic, an anticancer agent, an anticoagulant, an antidepressant, an antidiabetic agent, an antiepileptic, an antihistamine, an antitussive, an antihypertensive agent, an antimuscarinic agent, an antimycobacterial agent, an antineoplastic agent, an antioxidant agent, an antipyretic, an immunosuppressant, an immunostimulant, an antithyroid agent, an antiviral agent, an anxiolytic sedative, a hypnotic, a neuroleptic, an astringent, a bacteriostatic agent, a beta-adrenoceptor blocking agent, a blood product, a blood substitute, a bronchodilator, a buffering agent, a cardiac inotropic agent, a chemotherapeutic, a contrast media, a corticosteroid, a cough suppressant, an expectorant, a mucolytic, a diuretic, a dopaminergic, an antiparkinsonian agent, a free radical scavenging agent, a growth factor, a haemostatic, an immunological agent, a lipid regulating agent, a muscle relaxant, a protein, a peptide, a polypeptide, a parasympathomimetic, a parathyroid calcitonin, a bisphosphonate, a prostaglandin, a radio-pharmaceutical, a hormone, a sex hormone, an anti-allergic agent, an appetite

stimulant, an anorectic, a steroid, a sympathomimetic, a thyroid agent, a vaccine, a vasodilator and a xanthine.

Exemplary types of small molecule drugs include, but are not limited to, acetaminophen, clarithromycin, azithromycin, ibuprofen, fluticasone propionate, salmeterol, pazopanib HCl, palbociclib, and amoxicillin potassium clavulanate. Exemplary types of polypeptide drugs include, but are not limited to, proteins (e.g., antibodies), peptide fragments (e.g., antibody fragments), alemtuzumab, bevacizumab, cetuximab, gemtuzumab ozogamicin, ipilimumab, ofatumumab, panitumumab, pembrolizumab, ranibizumab, rituximab, or trastuzumab. Exemplary types of polynucleotide drugs include, but are not limited to, one or more of DNA, RNA including messenger mRNA (mRNA), hybrids thereof, RNAi-inducing agents, RNAi agents, siRNAs, shRNAs, miRNAs, antisense RNAs, ribozymes, catalytic DNA, triple helix formation inducing RNAs, aptamers, and vectors. Exemplary types of lipids include, but are not limited to fats, waxes, sterol-containing metabolites, vitamins, fatty acids, glycerolipids, glycerophospholipids, sphingolipids, saccharolipids, and polyketides, and prenol lipids.

In the present disclosure, the drug loaded into the reactor may be in powdered form. Exemplary methods of preparing drugs in powdered form include, but are not limited to processes utilizing lyophilization, freeze-drying, precipitation, and dry compacting.

Metal Oxide Material

The term “metal oxide material,” in its broadest sense includes all materials formed from the reaction of elements considered metals with oxygen-based oxidants. Exemplary metal oxide materials include, but are not limited to, aluminum oxide, titanium dioxide, iron oxide, gallium oxide, magnesium oxide, zinc oxide, niobium oxide, hafnium oxide, tantalum oxide, lanthanum oxide, and zirconium dioxide. Exemplary oxidants include, but are not limited to, water, ozone, and inorganic peroxide.

Atomic Layer Deposition (ALD)

Atomic layer deposition is a thin film deposition technique in which the sequential addition of self-limiting monolayers of an element or compound allows deposition of a film with thickness and uniformity controlled to the level of an atomic

or molecular monolayer. Self-limited means that only a single atomic layer is formed at a time, and a subsequent process step is required to regenerate the surface and allow further deposition.

Chemical Vapor Deposition (CVD)

Chemical vapor deposition is a thin-film deposition technique by which an element or chemical compound is deposited on a surface by chemical reaction in the gas phase or on a surface. It is distinct from atomic layer deposition in that the deposition is not self-limited, i.e., the film will continue to grow as long as chemistry is supplied. It is distinct from physical vapor deposition in that a chemical reaction results in a deposited film that is chemically different from the precursor species.

Reactor System

The term “reactor system” in its broadest sense includes all systems that could be used to perform ALD or mixed ALD/CVD or CVD. An exemplary reactor system is illustrated in FIG. 1 and further described below.

FIG. 1 illustrates a reactor system 10 for performing coating of particles, e.g., thermally sensitive particles, with thin-film coatings. The reactor system 10 can perform the coating using ALD and/or CVD coating conditions. The relative contribution of ALD and CVD processes to the thin-film coating can be controlled by appropriate selection of process conditions. In particular, the reactor system 10 permits a primarily ALD process, e.g., an almost entirely ALD process, to be performed at low processing temperature, e.g., below 50 °C, e.g., at or below 35 °C. For example, the reactor system 10 can form thin-film metal oxides on the particles primarily by ALD at temperatures of 22-35 °C, e.g., 25-35 °C, 25-30 °C, or 30-35 °C. In general, the particles can remain or be maintained at such temperatures. This can be achieved by having the reactant gases and/or the interior surfaces of the reactor chamber (e.g., the chamber 20 and drum 40 discussed below) remain or be maintained at such temperatures.

Performing ALD reaction at low temperature conditions permits coatings to be formed on the particles without degradation of the biological components, e.g., the vaccine or bio-pharma ingredients. For example, a biological component in amorphous form can be coated without breaking down the biological component or converting the biological component to a crystalline form.

The reactor system 10 includes a stationary vacuum chamber 20 which is coupled to a vacuum pump 24 by vacuum tubing 22. The vacuum pump 24 can be an industrial vacuum pump sufficient to establish pressures less than 1 Torr, e.g., 1 to 100 mTorr, e.g., 50 mTorr. The vacuum pump 24 permits the chamber 20 to be maintained at a desired pressure, and permits removal of reaction byproducts and unreacted process gases.

In operation, the reactor 10 performs the ALD thin-film coating process by introducing gaseous precursors of the coating into the chamber 20. The gaseous precursors are spiked alternatively into the reactor. This permits the ALD process to be a solvent-free process. The half-reactions of the ALD process are self-limiting, which can provide Angstrom level control of deposition. In addition, the ALD reaction can be performed at low temperature conditions, such as below 50 °C, e.g., below 35 °C.

The chamber 20 is also coupled to a chemical delivery system 30. The chemical delivery system 20 includes three or more gas sources 32a, 32b, 32c coupled by respective delivery tubes 34a, 34b, 34c and controllable valves 36a, 36b, 36c to the vacuum chamber 20. The chemical delivery system 30 can include a combination of restrictors, gas flow controllers, pressure transducers, and ultrasonic flow meters to provide controllable flow rate of the various gasses into the chamber 20. The chemical delivery system 30 can also include one or more temperature control components, e.g., a heat exchanger, resistive heater, heat lamp, etc., to heat or cool the various gasses before they flow into the chamber 20. Although FIG. 1 illustrates separate gas lines extending in parallel to the chamber for each gas source, two or more of the gas lines could be joined, e.g., by one or more three-way valves, before the combined line reaches the chamber 20. In addition, although FIG. 1 illustrates three gas sources, the use of four gas sources could enable the in-situ formation of laminate structures having alternating layers of two different metal oxides.

Two of the gas sources provide two chemically different gaseous reactants for the coating process to the chamber 20. Suitable reactants include any of or a combination of the following: monomer vapor, metal-organics, metal halides, oxidants, such as ozone or water vapor, and polymer or nanoparticle aerosol (dry or wet). For example, the first gas source 32a can provide gaseous trimethylaluminum (TMA) or titanium tetrachloride (TiCl_4), whereas the second gas source 32b can provide water vapor.

One of the gas sources can provide a purge gas. In particular, the third gas source can provide a gas that is chemically inert to the reactants, the coating, and the particles being processed. For example, the purge gas can be N₂, or a noble gas, such as argon.

A rotatable coating drum 40 is held inside the chamber 20. The drum 40 can be connected by a drive shaft 42 that extends through a sealed port in a side wall of the chamber 20 to a motor 44. The motor 44 can rotate the drum at speeds of 1 to 100 rpm. Alternatively, the drum can be directly connected to a vacuum source through a rotary union.

The particles to be coated, shown as a particle bed 50, are placed in an interior volume 46 of the drum 40. The drum 40 and chamber 20 can include sealable ports (not illustrated) to permit the particles to be placed into and removed from the drum 40.

The body of the drum 40 is provided by one or more of a porous material, a solid metal, and a perforated metal. The pores through the cylindrical side walls of the drum 40 can have a dimension of 10 μm .

In operation, one of the gasses flows into chamber 20 from the chemical delivery system 30 as the drum 40 rotates. A combination of pores (1-100 μm), holes (0.1-10 mm), or large openings in the coating drum serve to confine the particles in the coating drum while allowing rapid delivery of precursor chemistry and pumping of byproducts or unreacted species. Due to the pores in the drum 40, the gas can flow between the exterior of the drum 40, i.e., the reactor chamber 20, and the interior of the drum 40. In addition, rotation of the drum 40 agitates the particles to keep them separate, ensuring a large surface area of the particles remains exposed. This permits fast, uniform interaction of the particle surface with the process gas.

In some implementations, one or more temperature control components are integrated into the drum 40 to permit control of the temperature of the drum 40. For example, resistive heater, a thermoelectric cooler, or other component can in or on the side walls of the drum 40.

The reactor system 10 also includes a controller 60 coupled to the various controllable components, e.g., vacuum pump 24, gas distribution system 30, motor 44, a temperature control system, etc., to control operation of the reactor system 10. The controller 60 can also be coupled to various sensors, e.g., pressure sensors, flow

meters, etc., to provide closed loop control of the pressure of the gasses in the chamber 20.

In general, the controller 60 can operate the reactor system 10 in accord with a “recipe.” The recipe specifies an operating value for each controllable element as a function of time. For example, the recipe can specify the times during which the vacuum pump 24 is to operate, the times of and flow rate for each gas source 32a, 32b, 32c, the rotation rate of the motor 44, etc. The controller 60 can receive the recipe as computer-readable data (e.g., that is stored on a non-transitory computer readable medium).

The controller 60 and other computing devices part of systems described herein can be implemented in digital electronic circuitry, or in computer software, firmware, or hardware. For example, the controller can include a processor to execute a computer program as stored in a computer program product, e.g., in a non-transitory machine readable storage medium. Such a computer program (also known as a program, software, software application, or code) can be written in any form of programming language, including compiled or interpreted languages, and it can be deployed in any form, including as a standalone program or as a module, component, subroutine, or other unit suitable for use in a computing environment. In some implementations, the controller 60 is a general purpose programmable computer. In some implementations, the controller can be implemented using special purpose logic circuitry, e.g., an FPGA (field programmable gate array) or an ASIC (application specific integrated circuit).

Operation

Initially, particles are loaded into the drum 40 in the reactor system 10. The particles can have a solid core comprising a drug, e.g., one of the drugs discussed above. Once any access ports are sealed, the controller 60 operates the reactor system 10 according to the recipe in order to form the thin-film metal oxide layers on the particles.

In particular, the two reactant gases are alternately supplied to the chamber 20, with each step of supplying a reactant gas followed by a purge cycle in which the inert gas is supplied to the chamber 20 to force out the reactant gas and by-products used in the prior step. Moreover, one or more of the gases (e.g., the reactant gases and/or the inert gas) can be supplied in pulses in which the chamber 20 is filled with the gas to a

specified pressure, a delay time is permitted to pass, and the chamber is evacuated by the vacuum pump 24 before the next pulse commences.

In particular, the controller 60 can operate the reactor system 10 as follows.

In a first reactant half-cycle, while the motor 44 rotates the drum 40 to agitate the particles 50:

i) The gas distribution system 30 is operated to flow the first reactant gas, e.g., TMA, from the source 32a into the chamber 20 until a first specified pressure is achieved. The specified pressure can be 0.1 Torr to half of the saturation pressure of the reactant gas.

ii) Flow of the first reactant is halted, and a specified delay time is permitted to pass, e.g., as measured by a timer in the controller. This permits the first reactant to flow through the particle bed in the drum 40 and react with the surface of the particles 50 inside the drum 40.

iii) The vacuum pump 50 evacuates the chamber 20, e.g., down to pressures below 1 Torr, e.g., to 1 to 100 mTorr, e.g., 50 mTorr.

These steps (i)-(iii) can be repeated a number of times set by the recipe, e.g., two to ten times, e.g., six times.

Next, in a first purge cycle, while the motor 44 rotates the drum to agitate the particles 50:

iv) The gas distribution system 30 is operated to flow the inert gas, e.g., N₂, from the source 32c into the chamber 20 until a second specified pressure is achieved. The second specified pressure can be 1 to 100 Torr.

v) Flow of the inert gas is halted, and a specified delay time is permitted to pass, e.g., as measured by the timer in the controller. This permits the inert gas to flow through the pores in the drum 40 and diffuse through the particles 50 to displace the reactant gas and any vaporous by-products.

vi) The vacuum pump 50 evacuates the chamber 20, e.g., down to pressures below 1 Torr, e.g., to 1 to 500 mTorr, e.g., 50 mTorr.

These steps (iv)-(vi) can be repeated a number of times set by the recipe, e.g., six to twenty times, e.g., sixteen times.

In a second reactant half-cycle, while the motor 44 rotates the drum 40 to agitate the particles 50:

vii) The gas distribution system 30 is operated to flow the second reactant gas, e.g., H₂O, from the source 32a into the chamber 20 until a third specified pressure is

achieved. The third pressure can be 0.1 Torr to half of the saturation pressure of the reactant gas.

viii) Flow of the second reactant is halted, and a specified delay time is permitted to pass, e.g., as measured by the timer in the controller. This permits the second reactant to flow through the pores in the drum 40 and react with the surface of the particles 50 inside the drum 40.

ix) The vacuum pump 50 evacuates the chamber 20, e.g., down to pressures below 1 Torr, e.g., to 1 to 500 mTorr, e.g., 50 mTorr.

These steps (vii)-(ix) can be repeated a number of times set by the recipe, e.g., two to ten times, e.g., six times.

Next, a second purge cycle is performed. This second purge cycle can be identical to the first purge cycle, or can have a different number of repetitions of the steps (iv)-(vi) and/or different delay time and/or different pressure.

The cycle of the first reactant half-cycle, first purge cycle, second reactant half cycle and second purge cycle can be repeated a number of times set by the recipe, e.g., one to ten times.

As noted above, the coating process can be performed at low processing temperature, e.g., below 50 °C, e.g., at or below 35 °C. In particular, the particles can remain or be maintained at such temperatures during all of steps (i)-(ix) noted above. In general, the temperature of the interior of the reactor chamber does not exceed 35°C during of steps (i)-(ix). This can be achieved by having the first reactant gas, second reactant gas and inert gas be injected into the chamber at such temperatures during the respective cycles. In addition, physical components of the chamber of the chamber can remain or be maintained at such temperatures, e.g., using a cooling system, e.g., a thermoelectric cooler, if necessary.

Process for Preparing Pharmaceutical Compositions Comprising Drugs Encapsulated By One or More Layers of Metal Oxide

Provided are two exemplary methods for a pharmaceutical composition comprising a drug-containing core enclosed by one or more metal oxide materials. The first exemplary method includes the sequential steps of: (a) loading the particles comprising the drug into a reactor, (b) applying a vaporous or gaseous metal precursor to the substrate in the reactor, (c) performing one or more pump-purge cycles of the reactor using inert gas, (d) applying a vaporous or gaseous oxidant to the substrate in

the reactor, and (e) performing one or more pump-purge cycles of the reactor using inert gas. While performing the method the temperature of the particles does not exceed 35 °C.

In some embodiments of the first exemplary method, the sequential steps (b)-(e) are optionally repeated one or more times to increase the total thickness of the one or more metal oxide materials that enclose the solid core of the coated particles. In some embodiments, the reactor pressure is allowed to stabilize following step (a), step (b), and/or step (d). In some embodiments, the reactor contents are agitated prior to and/or during step (b), step (c), and/or step (e). In some embodiments, a subset of vapor or gaseous content is pumped out prior to step (c) and/or step (e).

The second exemplary method includes (e.g., consists of) the sequential steps of (a) loading the particles comprising the drug into a reactor, (b) reducing the reactor pressure to less than 1 Torr, (c) agitating the reactor contents until the reactor contents have a desired moisture content, (d) pressurizing the reactor to at least 10 Torr by adding a vaporous or gaseous metal precursor, (e) allowing the reactor pressure to stabilize, (f) agitating the reactor contents, (g) pumping out a subset of vapor or gaseous content and determining when to stop pumping based on analysis of content in reactor including metal precursor and byproduct of metal precursor reacting with exposed hydroxyl residues on substrate or on particle surface, (h) performing a sequence of pump-purge cycles of the reactor using inert gas, (i) pressuring the reactor to at least 10 Torr by adding a vaporous or gaseous oxidant, (j) allowing the reactor pressure to stabilize, (k) agitating the reactor contents, (l) pumping out a subset of vapor or gaseous content and determining when to stop pumping based on analysis of content in reactor including metal precursor, byproduct of metal precursor reacting with exposed hydroxyl residues on substrate or on particle surface, and unreacted oxidant, and (m) performing a sequence of pump-purge cycles of the reactor using inert gas. While performing the method the temperature of the particles does not exceed 35 °C.

In some embodiments of the second exemplary method, the sequential steps (b)-(m) are optionally repeated one or more times to increase the total thickness of the one or more metal oxide materials that enclose the solid core of the coated particles.

Pharmaceutically acceptable excipients, diluents, and carriers

Pharmaceutically acceptable excipients include, but are not limited to:

- (1) surfactants and polymers including: polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), sodium lauryl sulfate, polyvinylalcohol, crospovidone, polyvinylpyrrolidone- polyvinylacrylate copolymer, cellulose derivatives, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, carboxymethylethyl cellulose, hydroxypropylmethyl cellulose phthalate, polyacrylates and polymethacrylates, urea, sugars, polyols, carbomer and their polymers, emulsifiers, sugar gum, starch, organic acids and their salts, vinyl pyrrolidone and vinyl acetate;
- (2) binding agents such as cellulose, cross-linked polyvinylpyrrolidone, microcrystalline cellulose;
- (3) filling agents such as lactose monohydrate, lactose anhydrous, microcrystalline cellulose and various starches;
- (4) lubricating agents such as agents that act on the flowability of a powder to be compressed, including colloidal silicon dioxide, talc, stearic acid, magnesium stearate, calcium stearate, silica gel;
- (5) sweeteners such as any natural or artificial sweetener including sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acesulfame K;
- (6) flavoring agents;
- (7) preservatives such as potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic chemicals such as phenol, or quarternary compounds such as benzalkonium chloride;
- (8) buffers;
- (9) Diluents such as pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing;
- (10) wetting agents such as corn starch, potato starch, maize starch, and modified starches, and mixtures thereof;
- (11) disintegrants; such as croscarmellose sodium, crospovidone, sodium starch glycolate; and
- (12) effervescent agents such as effervescent couples such as an organic acid (e.g., citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts), or a carbonate (e.g., sodium carbonate, potassium carbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate) or bicarbonate (e.g. sodium bicarbonate or potassium bicarbonate).

EXAMPLES

The following materials and methods were used in the Examples set forth herein.

Example 1: Prepare particles comprising drug encapsulated by uniform, thin layers of aluminum oxide coating with nanometer level precision

In this Example, one of the methods disclosed for preparing metal oxide encapsulated drugs is performed and the data is presented. In this Example, the vaporous or gaseous metal precursor is tri-methyl aluminum (TMA), the byproduct gaseous methane is formed after TMA reacts with exposed hydroxyl groups on the particles or on surface of the coated particles, and the oxidant is water vapor.

Method

In brief, the method comprised the sequential steps of:

- (a) loading particles comprising the drug into a reactor;
- (b) reducing the reactor pressure to less than 1 Torr;
- (c) agitating the reactor contents until the reactor contents has a desired water content by performing residual gas analysis (RGA) to monitor levels of water vapor in the reactor;
- (d) pressurizing the reactor to at least 1 Torr by adding a vaporous or gaseous TMA;
- (e) allowing the reactor pressure to stabilize;
- (f) agitating the reactor contents;
- (g) pumping out a subset of vapor or gaseous content, including gaseous methane and unreacted TMA, and determining when to stop pumping by performing RGA to monitor levels of gaseous methane and unreacted TMA in the reactor.
- (h) performing a sequence of pump-purge cycles on the reactor using nitrogen gas;
- (i) pressuring the reactor to at least 1 Torr by adding water vapor;
- (j) allowing the reactor pressure to stabilize;
- (k) agitating the reactor contents;
- (l) pumping out a subset of vapor or gaseous content, including water vapor, and determining when to stop pumping by performing RGA to monitor levels of water vapor in the reactor;

(m) performing a sequence of pump-purge cycles on the reactor using nitrogen gas.

While performing the method the internal reactor temperature did not exceed 35°C. Additionally, the steps of (b)-(m) were repeated more than once to increase the total thickness of the aluminum oxide that enclose said solid core. FIG. 2 includes representative process conditions for performing this method.

Results

FIG. 3 shows representative residual gas analysis traces measuring during steps (d), (h), (i), and (m) for one cycle of the method. This method reproducibly shows growth rates between 2 and 4 angstroms of metal oxide coating per cycle. In contrast, a different method that limits growth to ALD only exhibited average growth per cycle of 1 angstroms per cycle. Without wishing to be bound to a particular theory, given the observed growth rate for this method the growth may be mediated by a combination of ALD and CVD.