United States Patent Application Publication	20250255831
Kind Code	A1
Publication Date	August 14, 2025
Inventor(s)	Neikirk; Colin C.

VAPOR PHASE COATING TECHNOLOGY FOR PHARMACEUTICAL ABUSE DETERRENT FORMULATIONS

Abstract

A method of preparing an abuse deterrent 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. This produces an abuse deterrent pharmaceutical composition comprising a drug containing core enclosed by one or more metal oxide materials.

Inventors: **Neikirk; Colin C. (Sunnyvale, CA)**

Applicant: **Applied Materials, Inc.** (Santa Clara, CA)

Family ID: **1000008563475**

Appl. No.: **19/032715**

Filed: **January 21, 2025**

Related U.S. Application Data

parent US continuation 17004827 20200827 parent-grant-document US 12233169 child US 19032715
us-provisional-application US 62892465 20190827

Publication Classification

Int. Cl.: **A61K9/51** (20060101); **B82Y5/00** (20110101); **B82Y30/00** (20110101); **B82Y40/00** (20110101); **C23C16/40** (20060101); **C23C16/44** (20060101)

U.S. Cl.:

CPC **A61K9/5192** (20130101); **A61K9/5115** (20130101); B82Y5/00 (20130101); B82Y30/00 (20130101); B82Y40/00 (20130101); C23C16/40 (20130101); C23C16/4408 (20130101)

Background/Summary

CROSS-REFERENCE TO RELATED APPLICATIONS [0001] This application claims priority to U.S. patent application Ser. No. 17/004,827, filed Aug. 27, 2020, which claims priority to U.S. Provisional Patent Application Ser. No. 62/892,465, filed Aug. 27, 2019, the disclosure of which is incorporated by reference.

TECHNICAL FIELD

[0002] This disclosure pertains to pharmaceutical compositions and methods of preparing metal oxide encapsulated pharmaceuticals for abuse deterrence.

BACKGROUND

[0003] Existing abuse deterrent formulations (ADF) require many processing steps and the inclusion of large amounts of excipient materials which may interact negatively with the active pharmaceutical ingredient (API). ADF technologies utilize primarily wet phase coating or dry particle blending. Such process complexity adds significantly to their cost of manufacture, which is undesirable. More importantly, the excipients used to prevent drug abuse must not interfere with the actual pharmacological activity of the drug. This can be a large challenge as the excipients are specifically designed to, for instance, prevent dissolution.

SUMMARY

[0004] The present disclosure describes ADF technology that employs dry (vacuum/vapor phase) coating processes to deposit existing materials for ADFs. The technology may also enable coating of new materials of interest for ADF which are not amenable to coating by existing technologies.

[0005] The methods described herein enable thin, uniform, conformal, and dense coatings, regardless of particle size. These highly precise coatings can minimize the coating overburden required to provide effective abuse deterrent, thereby minimizing the risk of the deterrent formulation impacting pharmacological performance. Additionally, hybrid organic-inorganic coating structures can be prepared which enable new modes of abuse deterrence, combining both physical and chemical barriers in a single process.

[0006] This technology is intended to produce abuse deterrent pharmaceutical formulations through advanced vapor phase coating techniques. These coatings may be organic polymers, inorganic oxides, or some combination thereof. Coatings for ADF function by providing a physical or chemical barrier to drug dissolution or crushing to prevent various forms of dose loading, such as dissolution in alcohol, syringing, crushing, or chewing. Physical barriers may have a pH switching component to prevent dose loading by the consumer, without affecting pharmacokinetics in the body. Chemical barriers may also function as a pH solubility switch which, when used in combination with a pH modifying excipient, can prevent dissolution outside the body without affecting pharmacokinetics in the body. ADFs may also include an aversive component, which changes the texture, taste, or smell of the compound so as to make dose loading undesirable. For example, the aversive component may result in the formation of a highly viscous gel when the drug is dissolved which prevents it from being drawn into a syringe. Other mechanisms of abuse deterrence are also possible (such as agonist/antagonist pairs); however, this disclosure relates specifically to physical and chemical barriers and aversive coatings.

[0007] Metal oxide materials are coated through one or more of an atomic layer deposition (ALD) or chemical vapor deposition (CVD) 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.

[0008] ALD deposition of metal oxides takes place at temperatures from about room temperature to 300 C by alternating doses of precursors such as TMA or TiCl.sub.4 and oxidizers such as water vapor or ozone. The superior chemical inertness and physical strength of metal oxides make them promising new candidates for ADFs. They may 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, reactants are pulsed into a closed reactor and allowed to dwell in the reactor until consumed. 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, which may or may not be heated or ionized to enhance efficiency of the purge. The cycle is then repeated with the second reactant. In flow-through mode, the flow rate of the reactant is set such that it is fully or nearly fully consumed in the reactor without closing the reactor exhaust. Organic polymer layers can be deposited in this reactor via either molecular layer deposition 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. pH responsive polyesters or polyamides are commonly used in pharmaceutical enteric coatings and are also of interest for chemical and physical barrier based ADFs. Depending on their chemical formulation, they may also form gels for aversive formulations. 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.

[0009] 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) in particular are commonly used in ADFs due to their pH dependent swelling behavior. Additionally, hydrogel materials (such as crosslinked acrylamides) can show a high degree of swellability and are therefore prime candidates for aversive coatings. 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 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.

[0010] These processes result in dense, conformal, highly uniform films, which cannot be produced by incumbent pharmaceutical coating processes today. These precision coatings can achieve good abuse deterrence while minimizing the coating's effect on pharmacological behavior. Furthermore, they can minimize excipient loadings by enabling identical performance in thinner coatings, allowing increased drug dosage in a smaller dosage form factor. Additionally, dense, continuous metal oxide coatings enabled by this technique are a new class of physical barriers which has not previously been explored. Finally, these processes can be used in combination to create laminate structures with multiple physical and chemical barriers, resulting in a unique combination of abuse deterrent properties that cannot be achieved using a single material alone.

[0011] In one aspect, a method of preparing a pharmaceutical composition having a drug-containing core enclosed by one or more metal oxide materials and having abuse deterrent properties 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. This produces a pharmaceutical composition comprising a drug containing core enclosed by one or more metal oxide materials.

[0012] Implementations may include one or more of the following features.

[0013] 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.

[0014] The reactor pressure may be allowed to stabilize following step (a), step (b), and/or step (d).

[0015] The reactor contents may be agitated prior to and/or during step (b), step (c), and/or step (e).

[0016] A subset of vapor or gaseous content may be pumped out prior to step (c) and/or step (e).

[0017] The metal oxide layer may have a thickness in range of 0.1 nm to 100 nm.

[0018] The particles may include a drug and one or more pharmaceutically acceptable excipients.

[0019] The particles may have a median particle size, on a volume average basis, between 0.1 μm and 1000 μm.

[0020] The pharmaceutical composition may be removed from the reactor and admixed with a pharmaceutically acceptable diluent or carrier.

[0021] The particles may consist essentially of the active pharmaceutical ingredient (API).

[0022] The API may be any drug subject to abuse, for example an opioid (oxycodone, naloxone, morphine, naltrexone, hydrocodone, sufuntanil, oxymorphone, codeine, fentanyl, hydromorphone, codeine, fentanyl and tapentadol).

[0023] 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.

[0024] The one or more metal oxide materials may consist of aluminum oxide and/or titanium oxide.

[0025] The oxidant may be selected from the group of water, ozone, and organic peroxide.

[0026] 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

[0027] 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 disclosure belongs. Methods and materials are described herein for use in the present disclosure; 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.

[0028] Other features and advantages of the disclosure will be apparent from the following detailed description and figures, and from the claims.

Description

BRIEF DESCRIPTION OF THE DRAWINGS

[0029] FIG. **1** is a schematic illustration of a rotary reactor for ALD and/or CVD coating of particles, e.g., drugs.

[0030] FIG. **2** is a table showing representative process conditions for the method.

[0031] 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

[0032] The present disclosure provides methods of preparing pharmaceutical compositions comprising drugs encapsulated by one or more layers of metal oxide. Such pharmaceutical compositions abuse deterrent properties, for example, reduced crushability and/or reduced solubility. 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.

[0033] 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). Preferably, the entire reaction takes place at 35° C. or below.

[0034] Herein are 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.

Metal Oxide Material

[0035] 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)

[0036] 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)

[0037] 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

[0038] 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.

[0039] 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.

[0040] 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.

[0041] 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.

[0042] 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.

[0043] The chamber **20** is also coupled to a chemical delivery system **30**. The chemical delivery system **20** includes three or more gas sources **32***a*, **32***b*, **32***c* coupled by respective delivery tubes **34***a*, **34***b*, **34***c* and controllable valves **36***a*, **36***b*, **36***c* 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.

[0044] 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 **32***a* can provide gaseous trimethylaluminum (TMA) or titanium tetrachloride (TiCl.sub.4), whereas the second gas source **32***b* can provide water vapor.

[0045] 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.

[0046] 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 1**00** rpm. Alternatively, the drum can be directly connected to a vacuum source through a rotary union.

[0047] 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**.

[0048] 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.

[0049] 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 um), 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.

[0050] 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**.

[0051] 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**.

[0052] 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 **32***a*, **32***b*, **32***c*, the rotation rate of the motor **44**, etc.

[0053] The controller **60** can receive the recipe as computer-readable data (e.g., that is stored on a non-transitory computer readable medium).

[0054] 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

[0055] 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.

[0056] 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.

[0057] In particular, the controller **60** can operate the reactor system **10** as follows.
[0058] In a first reactant half-cycle, while the motor **44** rotates the drum **40** to agitate the particles **50**: [0059] i) The gas distribution system **30** is operated to flow the first reactant gas, e.g., TMA, from the source **32***a* 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. [0060] 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**. [0061] 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.
[0062] 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.
[0063] Next, in a first purge cycle, while the motor **44** rotates the drum to agitate the particles **50**: [0064] iv) The gas distribution system **30** is operated to flow the inert gas, e.g., N2, from the source **32***c* into the chamber **20** until a second specified pressure is achieved. The second specified pressure can be 1 to 100 Torr. [0065] 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. [0066] 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.
[0067] 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.
[0068] In a second reactant half-cycle, while the motor **44** rotates the drum **40** to agitate the particles **50**: [0069] vii) The gas distribution system **30** is operated to flow the second reactant gas, e.g., H2O, from the source **32***a* 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. [0070] 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**. [0071] 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.
[0072] 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.
[0073] 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.
[0074] 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.
[0075] 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
[0076] 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.

[0077] 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).

[0078] 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 insert 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 insert gas.

[0079] 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

[0080] Pharmaceutically acceptable excipients include, but are not limited to: [0081] (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; [0082] (2) binding agents such as cellulose, cross-linked polyvinylpyrrolidone, microcrystalline cellulose; [0083] (3) filling agents such as lactose monohydrate, lactose anhydrous, microcrystalline cellulose and various starches; [0084] (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; [0085] (5) sweeteners such as any natural or artificial sweetener including sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acesulfame K; [0086] (6) flavoring agents; [0087] (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; [0088] (8) buffers; [0089] (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; [0090] (10) wetting agents such as corn starch, potato

starch, maize starch, and modified starches, and mixtures thereof; [0091] (11) disintegrants; such as croscarmellose sodium, crospovidone, sodium starch glycolate; and [0092] (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
[0093] 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
[0094] 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
[0095] In brief, the method comprised the sequential steps of: [0096] (a) loading particles comprising the drug into a reactor; [0097] (b) reducing the reactor pressure to less than 1 Torr; [0098] (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; [0099] (d) pressurizing the reactor to at least 1 Torr by adding a vaporous or gaseous TMA; [0100] (e) allowing the reactor pressure to stabilize; [0101] (f) agitating the reactor contents; [0102] (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. [0103] (h) performing a sequence of pump-purge cycles on the reactor using nitrogen gas; [0104] (i) pressuring the reactor to at least 1 Torr by adding water vapor; [0105] (j) allowing the reactor pressure to stabilize; [0106] (k) agitating the reactor contents; [0107] (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; [0108] (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
[0109] 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.

Claims

1. A method of preparing an abuse deterrent pharmaceutical composition comprising a drug-containing core enclosed by a combination of thin conformal organic polymer and metal oxide coatings, the method comprising the sequential steps of: (a) loading particles comprising a drug into a reactor; (b) applying a vaporous or gaseous metal precursor to the particles in the reactor; (c) performing two or more pump-purge cycles of the reactor using inert gas, wherein each pump-purge cycle comprises flowing an inert gas into the reactor to a pressure of 1-100 torr and after a delay time evacuating the reactor to reduce the pressure of the inert gas to below 1 torr; (d) applying a vaporous or gaseous oxidant to the particles in the reactor, wherein the oxidant is water; (e) performing two or more pump-purge cycles of the reactor using inert gas, wherein each pump-purge cycle comprises flowing an inert gas into the reactor to a pressure of 1-100 torr and after a delay time evacuating the reactor to reduce the pressure of the inert gas to below 1 torr; and (f) applying an organic polymer coating, thereby producing an abuse deterrent pharmaceutical composition comprising a drug containing core enclosed by a combination of thin, conformal organic polymer and metal oxide coatings.

2. The method of claim 1, wherein the sequential steps (b)-(e) are repeated one or more times to increase the total thickness of the metal oxide coating.

3. The method of claim 1, wherein the reactor pressure is allowed to stabilize following step (a), step (b), and/or step (d).

4. The method of claim 1, wherein the reactor contents are agitated prior to and/or during step (b), step (c), and/or step (e).

5. The method of claim 1, wherein a subset of vapor or gaseous content is pumped out prior to step (c) and/or step (e).

6. The method of claim 1, wherein the metal oxide coating layer has a thickness in range of 0.1 nm to 100 nm.

7. The method of claim 1, wherein the particles comprise a drug and one or more pharmaceutically acceptable excipients.

8. The method of claim 1, wherein the particles have a median particle size, on a volume average basis between 0.1 μm and 1000 μm.

9. The method of claim 1, wherein the pharmaceutical composition is removed from the reactor and admixed with a pharmaceutically acceptable diluent or carrier.

10. The method of claim 1, wherein the particles consist essentially of the drug.

11. The method of claim 1, wherein the drug is an opioid.

12. An abuse deterrent pharmaceutical composition comprising a drug-containing core enclosed by a combination of thin conformal organic polymer and metal oxide coatings, wherein the abuse deterrent pharmaceutical composition is prepared by a method comprising the sequential steps of: (a) loading particles comprising a drug into a reactor; (b) applying a vaporous or gaseous metal precursor to the particles in the reactor; (c) performing two or more pump-purge cycles of the reactor using inert gas, wherein each pump-purge cycle comprises flowing an inert gas into the reactor to a pressure of 1-100 torr and after a delay time evacuating the reactor to reduce the pressure of the inert gas to below 1 torr; (d) applying a vaporous or gaseous oxidant to the particles in the reactor, wherein the oxidant is water; and (e) performing two or more pump-purge cycles of the reactor using inert gas, wherein each pump-purge cycle comprises flowing an inert gas into the reactor to a pressure of 1-100 torr and after a delay time evacuating the reactor to reduce the pressure of the inert gas to below 1 torr; and (f) applying an organic polymer coating, thereby producing an abuse deterrent pharmaceutical composition comprising a drug containing core enclosed by a combination of thin conformal organic polymer and metal oxide coatings.

13. The composition of claim 12, wherein the sequential steps (b)-(e) are repeated one or more times to increase the total thickness of the metal oxide coating.

14-22. (canceled)

23. The method of claim 1, wherein the metal oxide coating is less than 2**00** nanometers thick.

24. The method of claim 1, wherein the metal oxide coating is less than 100 nanometers thick.

25. The method of claim 1, wherein the metal oxide coating is less than 50 nanometers thick.

26. The method of claim 1, wherein the metal oxide coating is less than 10 nanometers thick.

27. The method of claim 1, wherein the particles have a median particle size, on a volume average basis, of less than 10 microns.

28. The method of claim 1, wherein the particles have a median particle size, on a volume average basis, of less than 1 micron.

29. The method of claim 1, wherein the particles have a median particle size, on a volume average basis, of less than 100 nanometers.