PREDICTING SHELF LIFE STABILITY OF LYOPHILIZED DRUG PRODUCTS

FIELD OF THE DISCLOSURE

[0001] The present application relates generally to lyophilized drug products, and more specifically to stability over the shelf life of lyophilized drug products.

BACKGROUND

[0002] During manufacture, certain pharmaceutical drug products are lyophilized, or "freeze dried," in order to increase stability and shelf life. In a typical lyophilization process, a vial containing the drug product is placed within a special lyophilization chamber, and the drug product is frozen by reducing the temperature within the chamber. The chamber is then evacuated, after which heat is added to the drug product to cause water (ice) in the drug product to sublimate (i.e., transition directly from the solid state to a gaseous state). By removing moisture from the drug product in this manner, the drug product is generally made more stable. However, the resulting drug product "cake" retains an intrinsic amount of moisture after the lyophilization cycle, and is susceptible over time to additional moisture migrating from the typically rubber closure (stopper) and the external ambient environment. If the moisture content in the cake becomes too high at any point during the shelf life of the drug product, physical instability (collapse) and/or chemical instability of the cake/product can result. Unfortunately, measuring the moisture content of the cake over the shelf life can be expensive in terms of labor, equipment, etc., and is inherently time consuming given the relatively long shelf life expected of most drug products (typically on the order of two to five years). Thus, any attempt to prolong drug product shelf lives by the judicious selection or design of various components/processes/conditions (e.g., vial type, stopper type, starting cake moisture, storage conditions, etc.) typically requires a long and costly process of trial and error. Accordingly, there is a need for methods and systems that can quickly and accurately estimate shelf life stability for new drug products (and/or particular vial/stopper combinations, storage conditions, etc.).

BRIEF SUMMARY

[0002a] In one aspect, described herein is a method of computational modeling to predict stability of a lyophilized drug product, the method comprising: receiving, by processing hardware of a computing system, model parameters describing a virtual cake, a virtual vial, a virtual stopper, and a virtual ambient environment; computing, by the processing hardware implementing a computational model and at each of a plurality of virtual time steps, a change in water amount or concentration in each of (i) the virtual cake, (ii) virtual air within the virtual vial, and (iii) the virtual stopper, wherein computing the changes in water amount or concentration includes applying the model parameters to the computational model; and generating, by the processing hardware, information for display to a user via a user interface, the information being indicative of at least the water amount or concentration of the virtual cake at one or more time steps of the plurality of virtual time steps.

[0003] **[0002b]** In one aspect, described herein is a computing system comprising: processing hardware; and one or more memories storing instructions that, when executed by the processing hardware, cause the computing system to perform the method as described herein. Systems and methods described herein generally provide *in silico* modeling of a vial, stopper, and lyophilized drug product (cake) to predict the water content of the cake over a particular time horizon (e.g., over a desired or expected shelf life for the drug product). The model solves for water concentration (or amount) in three domains of the virtual, modeled environment: cake, air (within the vial), and stopper. The model may be a finite-element analysis (FEA) model, for example, and a solver may solve for water concentrations in the cake, air, and stopper domains by discretizing the time and space domains into a resolved

mesh, and then solving the resulting equations subject to the appropriate boundary and initial conditions. In some implementations, the equations output a water concentration profile and water mass flux as a function of time. The model may assume an axisymmetric configuration of both vial and stopper, in which case the equations can be solved in two dimensions and integrated over 180 degrees of rotation relative to the vial/stopper central axis.

[0004] Inputs to the model may include the geometries (physical configurations) of the vial/stopper combination, as well as various properties of the drug product, the stopper, and the storage conditions under consideration. For example, model inputs provided by a user and/or the model developer may include the starting fill weight and moisture content of the drug product/cake, sorption/desorption moisture isotherms for the stopper-air and cake-air interfaces, the moisture diffusivity coefficient of the stopper, the temperature and relative humidity of the ambient storage environment, and so on.

[0005] The model predictions can provide immediate insight into the shelf life stability of a drug product and can be used in various ways. For example, the model inputs may be varied over successive model runs in order to facilitate the design or

WHAT IS CLAIMED:

1. A method of computational modeling to predict stability of a lyophilized drug product, the method comprising:

receiving, by processing hardware of a computing system, model parameters describing a virtual cake, a virtual vial, a virtual stopper, and a virtual ambient environment;

computing, by the processing hardware implementing a computational model and at each of a plurality of virtual time steps, a change in water amount or concentration in each of (i) the virtual cake, (ii) virtual air within the virtual vial, and (iii) the virtual stopper, wherein computing the changes in water amount or concentration includes applying the model parameters to the computational model; and

generating, by the processing hardware, information for display to a user via a user interface, the information being indicative of at least the water amount or concentration of the virtual cake at one or more time steps of the plurality of virtual time steps.

2. The method of claim 1, wherein computing the changes in water amount or concentration further includes:

applying boundary conditions (i) between an external surface of the virtual stopper and the virtual ambient environment, (ii) between an internal surface of the virtual stopper and the virtual air, and (iii) between the virtual air and the virtual cake

3. The method of claim 2, wherein applying the boundary conditions includes computing partition coefficients using function representations of one or both of:

a stopper-air sorption and/or desorption moisture isotherm; and

a cake-air sorption and/or desorption moisture isotherm.

4. The method of any one of claims 1 through 3, wherein the computational model is a finite-element analysis (FEA) model, such that computing the changes in water amount or concentration includes computing, at each of at least some of the plurality of virtual time steps, a water amount or concentration and a water mass flux for each of a plurality of discrete spatial elements within the virtual cake, the virtual air, and the virtual stopper.

5. The method of claim 4, wherein the FEA model is a two-dimensional axisymmetric model that assumes symmetric vial and stopper configurations.

6. The method of any one of claims 1 through 5, wherein the model parameters include geometries of the virtual vial and the virtual stopper.

7. The method of any one of claims 1 through 6, wherein the model parameters include one or more of:

a moisture diffusivity coefficient of the virtual stopper;

a density of the virtual stopper; or

a starting water amount or concentration of the virtual stopper.

8. The method of any one of claims 1 through 7, wherein the model parameters include one or both of:

a starting weight and/or density of the virtual cake; and

a starting water amount or concentration of the virtual cake.

9. The method of any one of claims 1 through 8, wherein the model parameters include one or both of:

a temperature of the virtual ambient environment; and

a humidity of the virtual ambient environment.

10. The method of any one of claims 1 through 9, wherein the information is indicative of the water amount or concentration of the virtual cake as a function of time.

11. The method of any one of claims 1 through 10, wherein the information is indicative of a change in weight of the virtual cake.

12. The method of any one of claims 1 through 11, wherein the information is indicative of whether the water amount or concentration of the virtual cake at a particular time step, or steps, of the plurality of virtual time steps satisfies one or more stability criteria associated with the lyophilized drug product.

13. The method of any one of claims 1 through 12, further comprising using the displayed information to select one or more of:

a stopper type to use for the lyophilized drug product;

a vial type to use for the lyophilized drug product;

an ambient environment temperature to maintain for the lyophilized drug product;

an ambient environment humidity to maintain for the lyophilized drug product; or

a stopper drying target.

14. A computing system comprising:

processing hardware; and

one or more memories storing instructions that, when executed by the processing hardware, cause the computing system to perform the method of any one of claims 1 to 12.

15. The computing system of claim 14, wherein the instructions, when executed, cause the computing system to use the displayed information to select one or more of:

a stopper type to use for the lyophilized drug product;

a vial type to use for the lyophilized drug product;

an ambient environment temperature to maintain for the lyophilized drug product;

an ambient environment humidity to maintain for the lyophilized drug product; or

a stopper drying target.