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A NON-LINEAR ISOTHERMAL MODEL FOR MIGRATION OF DRUGS IN WET GRANULATIONS

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ABSTRACT

A non-linear isothermal model for migration of drugs during drying period in wet granulations is proposed and some of its important properties are introduced. The mathematical expression is derived from physical fundamentals in such a way that computer implementation is feasible. The model includes the well-known Rumpf and Washburn equations, and it can be used as a suitable starting point for numerical simulation experiments.

INTRODUCTION

Assessment of migration of drugs in wet granulations can be very valuable in development of a new

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dosage form, particularly in studies of the influence of all additives present in the granulations. With the increasing use of computers, simulation of this problem can be carried out to avoid rather tedious preliminary laboratory investigations. In this paper a model is developed to describe the mass transport in a hypothetical granulations bed, with a non-linear distribution isotherm. The model is derived from physical principles in such a way that computer implementation is possible.

ASSUMPTIONS

A theoretical homogeneous granulations bed with an infinite area is considered; the thickness of the bed is assumed to be independent of the area. Furthermore a migrating phase and a granulations bed can be distinguished. The temperature is assumed to be invariant in time and place. The equilibrium between the two phases is thermodynamically reversible. The equilibrium concentrations between granulations and migrating phase may be described by an expression $X_G = F(X_m)$, distribution isotherm, where X_G and X_m are the active ingredient concentrations in the granulations and the migrating phase respectively. The functional dependence is assumed to be invariant with time, place, and with a given formulation.

THE MODEL

The model is formulated according to a mass conservation law of a granulations bed in a fixed domain with the distinction of a migrating phase (i.e., the granulating fluid containing active ingredient(s) and a granulations bed, and a partition of active ingredient(s) between the migrating phase and granulations. In a fixed domain K with volume of A (h_2-h_1), the rate of change of total amount of active ingredient is equal to the following so-called differential conservation law(1).

$$\partial X(t,h)/\partial t = -\partial R(t,h)/\partial h \qquad (1)$$

Where X denotes the total active ingredient concentration in the migrating phase and the granulations, A the surface of the granulations bed, $h_2-h_1 = h$ thickness of the bed, t the time, and R(t,h) the rate of the migration. The thickness, h, is assumed to be independent of A. It is further assumed that the migration occurs only in the wet layer of the granulation bed with fraction of f_h, which means that the rate will be

$$R(t,h) = [X_m(t,h)](\upsilon)f_h - TD_{f_h}[\partial X_m(t,h)]/\partial h \qquad (2)$$

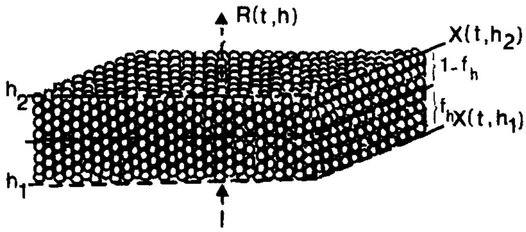

Fig 1. A hypothetical granulations bed.

where $X_m(t,h)$ denotes the concentration of active ingredient(s) in migrating phase, f_h the wet fraction of the cross-sectional area of the granulations bed (Fig. 1), D the diffusion coefficient, and υ the average velocity of the migrating phase and can be assumed to be equal to the rate of penetration with the following well known Washburn equation (2):

$$\upsilon^2 = (r.\cos\,\theta)\,.\,\frac{\gamma}{2\eta}\,.\,t \qquad (3)$$

where r.cos θ denotes the wetting constant, γ surface tension and η viscosity. T in equation 2 denotes the tensile strength with the following basic equation, proposed by Rumpf (3), for calculating the tensile strength of a bed of ideal monosize spheres:

$$T = \frac{9}{8}\left(\frac{1-\varepsilon}{\pi d^2}\right) KH \qquad (4)$$

where ε = porosity (i.e., $\varepsilon = [1 - \frac{\text{Apparent Density}}{\text{True Density}}]$), d = sphere diameter, K = coordination number, and H = mean bonding force at point of contact. The value of H is dependent on the nature of interparticle effect and its value can be presented as

$$H = Ad/24g^2 \qquad (5)$$

where A is a constant about 10^{-12} dyne cm., and g is the distance between the sphere surfaces and is less than 1000A° (4).

With the equation

$$X = f_h X_m + (1-f_h)X_G \qquad (6)$$

where X_G is the concentration of active ingredient in the granulations, and $(1-f_h)$ is the dry fraction of the cross-sectional area of granulation bed, we find

$$f_h X_m = X/[1 + [(1-f_h)X_G/f_h X_m]]. \qquad (7)$$

Substituting equation 7 into equation 2 gives the rate of migration in terms of X, i.e.,

$$R(t,h) = V_E[X(t,h)] - \frac{\partial}{\partial h}[D_E[X(t,h)]] \quad (8)$$

where

$$V_E = (\upsilon)/[1 + ((1-f_h)/f_h)(X_G/X_m)] \text{ and} \quad (9)$$

$$D_E = TD_{f_h}/[1 + ((1-f_h)/f_h)(X_G/X_m)]$$

The mass transport equation can be derived by substituting equation 8 into equation 1

$$\frac{\partial X(t,h)}{\partial t} = -\frac{\partial V_E[X(t,h)]}{\partial h} + \frac{\partial^2 D_E[X(t,h)]}{\partial h^2} \quad (10)$$

Equation 10 is an appropriate mathematical model describing mass transport during drying period in wet granulations with non-linear distribution isotherm. One of the advantages of this model is that it retains the divergence form, which is extremely useful for numerical simulation.

Using

$$\partial V_E X(t,h)/\partial h = f_h(\upsilon)\partial X_m/\partial h = [f_h(\upsilon)dX_m/dX(t,h)][\partial X/\partial h] \quad (11)$$

and the equations 6 and 10 we obtain

$$\frac{\partial[X(t,h)]}{\partial h} = -\bar{V}_E \frac{\partial[X(t,h)]}{\partial h} + (\frac{\partial}{\partial h})[\bar{D}_E \frac{\partial[X(t,h)]}{\partial h}] \quad (12)$$

where $\bar{V}_E = (\upsilon)/1 + [(1-f_h/f_h)dX_G/dX_m]$ (13)

and $\bar{D}_E = TD_{f_h}/1 + [(1-f_h/f_h)dX_G/dX_m]$ (14)

A similar mathematical expression can be derived in terms of migrating phase concentrations.

$$\frac{\partial[X_m(t,h)]}{\partial t} = -\bar{V}_E[\partial X_m(t,h)]/\partial h + \bar{D}_E\partial^2[X_m(t,h)]/\partial h^2 \quad (15)$$

DISCUSSION

With the assumed simplifications, the methematical model for non-linear mass transport in granulations bed can be described in the most simple way by equation 10. This equation is also the most suitable form, as starting point, for numerical simulation experiments. For the solution of the mathematical model in differential or difference equation form, a choice can be made between several solution techniques. Of course, in general the evaluation of a complete solution of the mathematical problem makes simulation superfluous. Nevertheless, complete solutions of parts of the mathematical problem can be used to check the simulation results. The simulation can be utilized to evaluate the ability of tablet additives to inhibit the migration of active ingredient(s).

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