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Mathematical Modeling of Magnesium Oxide Release from Granules Produced by Laboratory Fluidization

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ABSTRACT

The particle size usually has an important effect on the rate of drug liberation from sustained release systems. The nature of that effect depends on the geometry of the system and the mechanism of the drug release (1). The aim of the present study was to characterize the relationship between the drug release profile of granules produced by laboratory fluidization and their particle size. The magnesium oxide release from granules—which are of two different particle sizes and contain Eudragit polymer—was investigated both experimentally and with mathematical models. First-order, cube root, square root, and two-thirds root models were applied for the evaluation of the drug release data. Changes in the particle size of the investigated granules altered the drug release profile.

INTRODUCTION

The design of controlled drug release particles has a great importance as regards therapy. The understanding of the mechanism of drug release may provide a useful means for designing mixtures with predetermined release profiles.

Except for the simple osmotic pump, the mechanism of drug release usually cannot be defined unequivocally. Numerical fits and microscopical examinations of the particles are often used to assign mechanisms of drug release (1-3).

The purpose of our work was to find an appropriate model that describes the drug release profile of granules of two sizes, and thus to predict precisely the drug release of mixtures of particles drawn from two different populations.

MATERIALS AND METHODS

Magnesium Oxide

The basic substance of the granulation is of USP 23 grade, white, loose powder with high volume. Since the

substance adheres onto the wall of the plastic fluidization column, it could not be fluidized without pretreatment.

Hydrophobized Basic Substance

A total of 2.5 g of silicone oil (FERAX Lab. GmbH, Berlin) was blended in 300 g isopropyl alcohol (Reanal, Budapest). In the obtained homogeneous composite 100 g of magnesium oxide was suspended for 30 min using a paddle stirrer (VEB MR25). As soon as the solvent had been evaporated the substance was fractionated. Only fractions of 100–250 μm were used for the granulation.

Laboratory Fluidized Bed Granulation

Base Materials

Hydrophobized magnesium oxide
Copolymers of methacrylic acid ester (Eudragit L100-55, Eudragit S100 from Rohm Pharma, Germany)

Granulation Method

The granules were prepared in AEROMATIC STREA-1 (Aeromatic AG, Switzerland, CH-4416 Bubendorf) laboratory-scale fluidization equipment.

The process parameters were the following:

Quantity of the base material: 400 g
Granulating liquid: 5% (w/w) of Eudragit polymer solved in isopropyl alcohol
Amount of Eudragit in the granules: 20% (w/w)
Inlet air temperature: 40°C
Outlet air temperature: 25°C
Feeding rate of the granulating liquid: 15 rpm
Atomizing pressure: 2 bar
Drying temperature: 40°C

Morphological Characterization of the Granules with Scanning Electron Microscope

In order to characterize the morphology of the granules of two size ranges the samples were studied with scanning electron microscope (Opton DSM 940, Carl Zeiss GmbH, Germany, D-7082 Oberkochen).

The specimens were mounted to aluminum stubs with double adhesive tape. To reduce the charging, the specimens were vacuum coated with gold by Jeol JEE 4B vacuum evaporator. Examination was carried out at 3 kV, 5 kV, or 30 kV accelerating voltage and 50–10,000 times magnifications were used.

In Vitro Dissolution Study: Constant pH Method

The release of the antacid from the granules causes pH increase. When pH increase was observed, 1N hydrochoric acid was added to the system from a burette to keep the pH at a constant (pH = 3) value (4). The difference between the pH value of the digital pH meter and the selected value (pH = 3) was not more than 0.3 pH. Hydrochloric acid consumption was recorded as a function of time.

RESULTS AND DISCUSSION

Mathematical models were chosen (1) to describe the release patterns on the basis of the known physical geometry of the particles—supposing that the granules form a Eudragit matrix that contains the pretreated magnesium oxide in embedded form (5).

1. *First-Order Model*

$$M_t/M_\infty = 1 - \exp(-kt) \quad (1)$$

2. *Higuchi Square Root of Time Model*

$$M_t/M_\infty = kt^{1/2} \quad (2)$$

3. *Baker and Lonsdale Model*

$$3/2[1 - (1 - M_t/M_\infty)^{2/3}] - M_t/M_\infty = kt \quad (3)$$

4. *Hixon and Crowell Cube-Root Equation*

$$(1 - M_t/M_\infty)^{1/2} = 1 - kt \quad (4)$$

5. *Equation*

$$M_t/M_\infty = 1 - \exp[-a(kt)^\alpha] \quad (5)$$

where M_t is the amount of drug released at time t, M_∞ is the amount of drug released at infinity, k is the release constant, a and α are constants that describe stuctural and geometric characteristics of the system.

Since the measured acid consumption values correspond to M_t and the acid consumption values measured for a sufficiently long time (theoretically at infinity) correspond to M_∞, t and V can be substituted (6).

Figures 1 and 2 show the differences in the surface morphology of magnesium oxide granules. The distribution of the Eudragit polymer in the granules changed according to the particle size. It affected the characteristics of the drug release. The initial weight of the particles was the same for both particle sizes examined. As the particle size decreased, the number of particles and the available surface area, and consequently the release constants of each model, increased.

The calculated model parameters are shown in Tables 1 and 2. All the neutralization rate constants were dependent on the sampling time (7), except the ones calculated by Eq. (5).

Figure 1. Scanning electron micrograph of the magnesium oxide granules. Particle size: 0.1–0.16 mm. Magnification: 2000×.

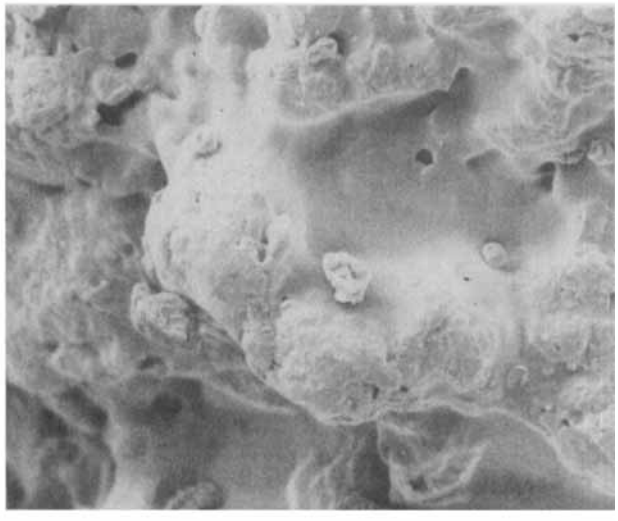

Figure 2. Scanning electron micrograph of the magnesium oxide granules. Particle size: 0.4–0.63 mm. Magnification: 2000×.

Table 1

Neutralization Rate Constants of Magnesium Oxide Granules Calculated According to Various Models

Particle Size	Model	Mean Release Constant k Eudragit L100-55	Mean Release Constant k Eudragit S100
0.1–0.16 mm	First order	0.098	0.116
	Square root of time	0.031	0.033
	Hixon & Crowell	0.021	0.024
	Baker & Lonsdale	0.011	0.013
	Equation (5)	0.017	0.020
0.4–0.63 mm	First order	0.093	0.090
	Square root of time	0.030	0.031
	Hixon & Crowell	0.020	0.021
	Baker & Lonsdale	0.010	0.011
	Equation (5)	0.011	0.013

Table 2

Correlation Coefficients of the Observed Release Data and the Simulated Profiles in Case of Magnesium Oxide Granules

Particle Size	Model	Correlation Coefficient Eudragit L100-55	Correlation Coefficient Eudragit S100
0.4–0.63 mm	First order	0.9824	0.9571
	Square root of time	0.9500	0.9625
	Hixon & Crowell	0.9931	0.9850
	Baker & Lonsdale	0.9357	0.9211
	Equation (5)	0.9997	0.9972
0.1–0.16 mm	First order	0.9981	0.9963
	Square root of time	0.9651	0.9873
	Hixon & Crowell	0.9931	0.9834
	Baker & Lonsdale	0.9839	0.9835
	Equation (5)	0.9982	0.9987

Correlation coefficients for both particle sizes were excellent in the case of model 5. It can be concluded from the results that the drug release of magnesium oxide granules with two different particle sizes cannot be described using models 1–4. Only Eq. (5) can be used for both particle sizes.

Figures 3–6 compare the simulated values with experimental magnesium oxide release data taken from a

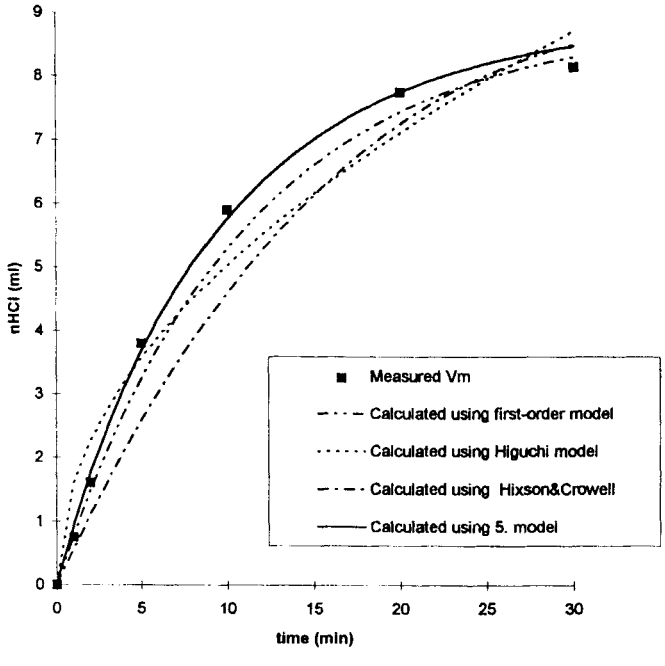

Figure 3. Comparison of simulated acid consumption values with experimental magnesium oxide release data from granules containing Eudragit L100-55. Diameter of the particles: 0.10–0.16 mm.

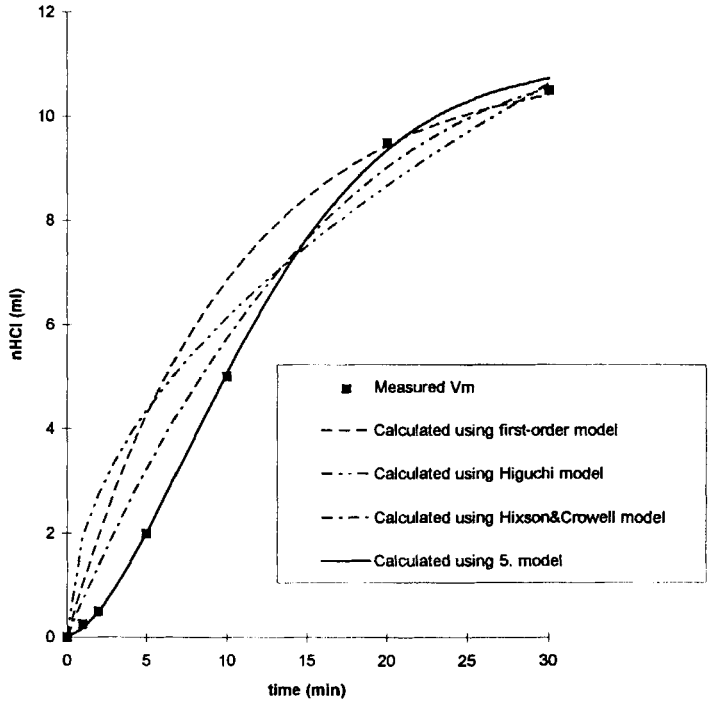

Figure 4. Comparison of simulated acid consumption values with experimental magnesium oxide release data from granules containing Eudragit L100-55. Diameter of the particles: 0.4–0.63 mm.

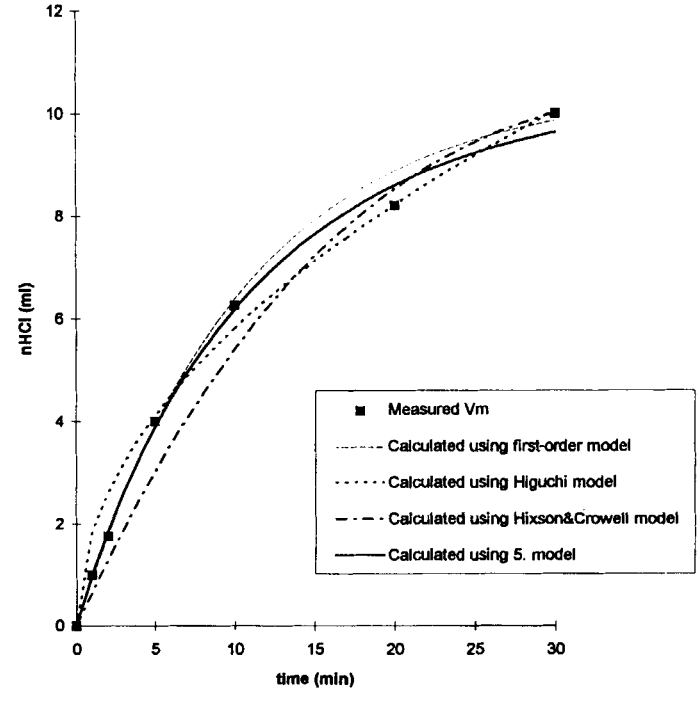

Figure 5. Comparison of simulated acid consumption values with experimental magnesium oxide release data from granules containing Eudragit S100-55. Diameter of the particles: 0.10–0.16 mm.

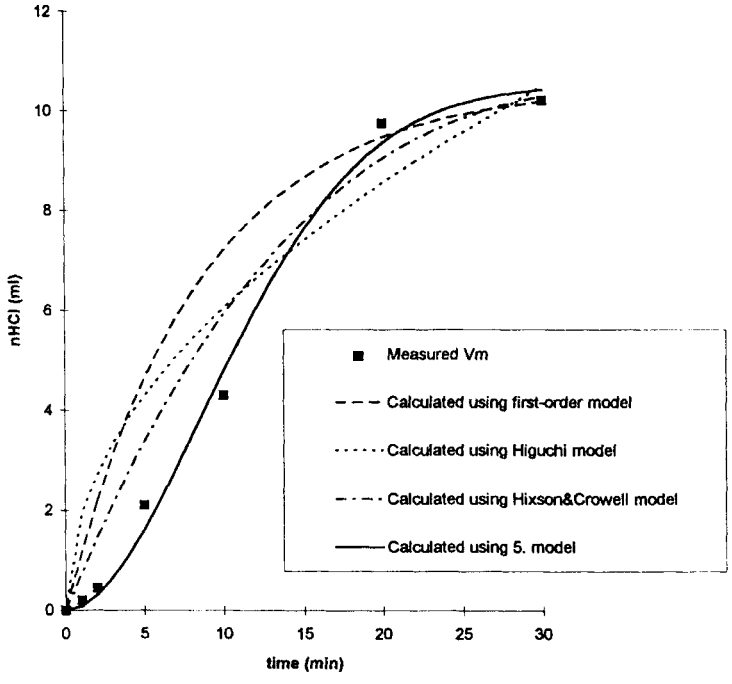

Figure 6. Comparison of simulated acid consumption values with experimental magnesium oxide release from granules containing Eudragit S100-55. Diameter of the particles: 0.4–0.63 mm.

mixture consisting of small (0.1–0.16 mm) and large (0.4–0.63 mm) particles of equal weight.

CONCLUSION

Changes in the particle size of the investigated granules altered the drug release profile. If the drug release profile of granules of two different sizes is given, it is possible to predict precisely the drug release of mixtures of particles drawn from these populations. The time dependence of the drug release can be planned in advance even from inhomogeneous granule fractions.

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