ELSEVIER

International Journal of Pharmaceutics 119 (1995) 165–171

international journal of pharmaceutics

Calculation of the blood level of a drug taken orally with a diffusion controlled dosage form

B. Nia, E.M Ouriemchi, J.M. Vergnaud *

Faculty of Sciences, University of St Etienne, 23 Dr. P. Michelon, 42023 St Etienne, France

Received 4 August 1994; revised 24 October 1994; accepted 27 October 1994

Abstract

Oral dosage forms with controlled release are generally investigated either by in vitro or in vivo tests and the problem of correlating these results appears. A numerical model is built, taking into account the characteristics of drug release out of the dosage form along the gastrointestinal tract, the stages of absorption in the blood compartment and of elimination. The dosage form is obtained by dispersing theophylline as a drug in Eudragit RS playing the role of a polymer matrix. The process of drug release is controlled by diffusion, with a constant diffusivity. The following results are obtained: the kinetics of release of the drug out of the dosage form, the kinetics of the drug in the blood compartment, and the kinetics of drug elimination.

Keywords: Drug release; Controlled release; Kinetics

1. Introduction

Various oral dosage forms with controlled release of the drug are prepared by dispersing the drug in a polymer and compressing the dry mixture into tablets or pressing the humid paste into beads and drying them (Vergnaud, 1992). When these monolithic devices are in contact with a liquid, the liquid enters the polymer, dissolves the drug and enables the drug to leave the device. The polymer matrix may be eroded or not, and the two main mechanisms (Feijen, 1984) controlling drug release appear with erosion of the polymer (Heller, 1984; Bidah and Vergnaud, 1990) or diffusion through the polymer (Vergnaud, 1993). As a result, the drug is released from the dosage form over a long period of time. When the process is controlled by diffusion, the rate of drug release decreases exponentially with time. These devices are evaluated using in vitro tests by determining the kinetics of drug release in a synthetic gastric liquid at 37°C at a given rate of stirring, and the parameters of interest are, in the case of a diffusional process, the diffusivity, the partitioning factor and the coefficient of mass transfer on the surface (Bakhouya et al., 1994).

Dosage forms with controlled release are evaluated using in vivo tests with healtly volunters performed under given conditions (Skelly et al., 1990). Of course, in vivo tests necessitate greater investment than in vitro tests, and attempts have

* Corresponding author.

SSDI 0378-5173(94)00385-8

Glossary

Symbol	Meaning
β_{1n}	positive roots of Eq. 4
β_{rn}	positive roots of Eq. 6.
C	concentration of the drug in the dosage form
D	diffusivity (cm^2/s)
h	coefficient of mass transfer on the surface (cm/s)
$2L$	height of the cylinder
M_t, M_∞	amount of drug released out of the dosage form after time t, after infinite time
R	radius of the cylinder
R_1, R_r	dimensionless numbers
X	amount of drug in the gastrointestinal tract
Y	amount of drug in the blood compartment
Z	amount of drug eliminated
r, z	radial, longitudinal coordinates for the cylinder

been made in order to find correlations between in vitro and in vivo tests. The kinetics of drug release obtained with in vitro tests were thus compared to the input function resulting from deconvolution of the drug level-time history in the blood compartment (Aoki et al., 1992; Koch, 1992). In order to obtain an acceptable correlation between these curves, the operational conditions for the in vitro test were sometimes modified (Aly Sas and Megwa, 1989). Some parameters were found to be of interest: the rate of stirring selected for the in vitro test (Nicklasson, 1990); the residence time of the dosage form along the gastrointestinal tract (Sournac et al., 1988). In vitro and in vivo evaluation was performed with oral sustained release floating dosage forms made of various hydrophilic polymers (Hilton and Deasy, 1992). The nature of the food in the stomach was also considered as a parameter for the release with in vivo tests (Verhoeven et al., 1989; Junjinger et al., 1990). Very often, important deviations were shown between in vitro and in vivo curves (Finne and Urtti, 1992). In fact, the process of drug transport is different with in vitro and in vivo tests (Ouriemchi et al., 1995). With the in vitro test, the system is closed, while it is open with the in vivo test, the drug being constantly transferred out of the dosage form into the blood compartment and then eliminated. Moreover, two kinds of dosage forms with a polymer matrix are on the market, that in which the release is controlled by diffusion and the other where the process is controlled by erosion (Vergnaud, 1993; Bakhouya et al., 1994)

The first purpose in this study is to build a numerical model able to describe the process of drug transfer in vivo, by considering a dosage form with drug release controlled by diffusion. The model takes all the known facts into account: the kinetics of drug release obtained with in vitro tests and the two main characteristics with the diffusivity and the coefficient of mass transfer at the surface; the rate constants of absorption in the blood compartment and of elimination, and the volume of the blood compartment. The case of a dosage form cylindrical in shape is selected, as it is widely used. The residence time of the dosage form along the gastrointestinal tract is also considered.

The second objective is to use the model for calculating various kinetics of interest in the case of theophylline: not only the kinetics of release of the drug out of the dosage form obtained with in vitro tests at various pH values, but also the kinetics of the drug in the blood compartment and elimination are evaluated. A mathematical treatment is considered for the diffusion of the drug through the polymer device with a constant diffusivity. As this diffusivity varies slightly with the pH, a mean value for the diffusivity is determined by considering the residence times in the various parts of the gastrointestine (Sournac et al., 1988). By using the data associated with the pharmacokinetics of theophylline, it is thus also possible to determine the drug level in the blood compartment.

2. Theoretical

2.1. Assumptions

The following assumptions are made:

(i) The oral dosage form is cylindrical in shape and the drug concentration is initially uniform.

(ii) The process of release of the drug out of the dosage form is controlled by diffusion, as

shown from in vitro experiments, with a finite coefficient of mass transfer on the surface.

(iii) The diffusivity slightly varies with the pH as shown from in vitro experiments carried out at various pH ranging from 1.2 to 8. By considering the gastrointestinal transit of the dosage form, an average diffusivity is obtained.

(iv) The drug is transferred by following the pattern: release out of the dosage form in the gastrointestine, absorption in the blood compartment and elimination.

(v) The following data: gastrointestinal tract history, rate constants of absorption and elimination, volume of the blood compartment, are taken from the literature (Sournac et al., 1998).

2.2. Calculation

Two stages are considered in succession: the transient diffusion of the drug through the dosage form and the transfer into and out of the blood compartment.

2.2.1. Stage of diffusion through the dosage form

With the assumption of the constant mean diffusivity, an analytical solution exists for the transient diffusion of the drug through the dosage form.

The basic equation with radial and longitudinal diffusion is:

$$\frac{\partial C}{\partial t} = D \cdot \left[\frac{\partial^2 C}{\partial z^2} + \frac{\partial^2 C}{\partial r^2} + \frac{1}{r} \cdot \frac{\partial C}{\partial r} \right] \tag{1}$$

The boundary conditions are:

$$\begin{aligned} t > 0 \quad r = R \quad & -D \cdot \frac{\partial C}{\partial r} = h(C_R - C_{ext}) \\ z = \pm L \quad & -D \cdot \frac{\partial C}{\partial z} = h(C_L - C_{ext}) \end{aligned} \tag{2}$$

expressing that the rate at which the drug is released out of the surface of the dosage form is constantly equal to the rate at which the drug is brought to the surface by internal diffusion.

The solution of the problem is given by the product of the two series expressing the solution for the radial and the longitudinal diffusion (Vergnaud, 1993).

$$\frac{M_\infty - M_t}{M_\infty} = \sum \frac{2R_1^2}{\beta_{ln}^2(\beta_{ln}^2 + R_l^2 + R_1)} \cdot \exp\left(- \frac{\beta_{ln}^2}{L^2} Dt \right) \cdot \sum \frac{4R_r^2}{\beta_{rn}^2(\beta_{rn}^2 + R_r^2)} \cdot \exp\left(- \frac{\beta_{rn}^2}{R^2} Dt \right) \tag{3}$$

where the β_{ln}s are the positive roots of

$$\beta \cdot \tan \beta = R_1 \tag{4}$$

and the dimensionless number R_1

$$R_1 = \frac{L \cdot h}{D} \tag{5}$$

L being half the height of the cylinder and the β_{rn}s are the roots of

$$\beta_r \cdot J_1(\beta_r) = R_r \cdot J_0(\beta_r) \tag{6}$$

and

$$R_r = \frac{R \cdot h}{D} \tag{7}$$

2.2.2. Stage of transfer through the body

The rate of the drug in the blood compartment is:

$$\frac{dY}{dt} = k_a \cdot X - k_e \cdot Y \tag{8}$$

and the rate of elimination of the drug is:

$$\frac{dW}{dt} = k_e \cdot Y \tag{9}$$

2.2.3. Calculation of the amount of drug transferred

The amounts of drug at the following times t_1, $t_2..t_i$, t_n with an increment of time Δt are calculated in the gastrointestinal volume and in the blood.

3. Experimental

3.1. Dosage forms

Theophylline and Eudragit RL in powder form are intimately mixed in the ratio 50:50 by weight.

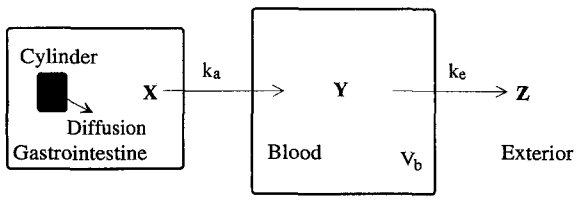

Fig. 1. Scheme of the process.

The mixture is thus pressed into cylinders with the following characteristics: 500 mg; diameter, 1.15 cm; height, 0.44 cm. The hardness is 8.9 (meaning that breaking rupture is attained for 89 N). The apparatus is an excentric tablet machine AM 28.50 (Frogerais).

3.2. In vitro tests

A cylinder is placed in a flask with 200 ml of liquid, maintained at 37°C under a stirring at 250 rpm. The pH values of the liquids are 1.2, 4, 6 and 8, respectively.

At intervals, 0.5 ml of liquid is extracted and analyzed using a UV spectrometer (Hitachi U 1.100) calibrated at 271 nm.

4. Results

Three kinds of results are considered: the first obtained with the in vitro tests leading to the parameters of diffusion of the drug out of the dosage forms, the second with the calculation of the kinetics of the drug transferred through the body, and especially with the drug level in the blood compartment; the last with the effect of the dimensions of the dosage forms.

4.1. In vitro tests.

The kinetics of release of the drug out of the dosage forms obtained with in vitro tests are controlled by transient diffusion, as shown in Fig. 2. The kinetics obtained either by experiments or by calculation using Eq. 1 are well superimposed. Moreover, the diffusivity is constant and the coef-

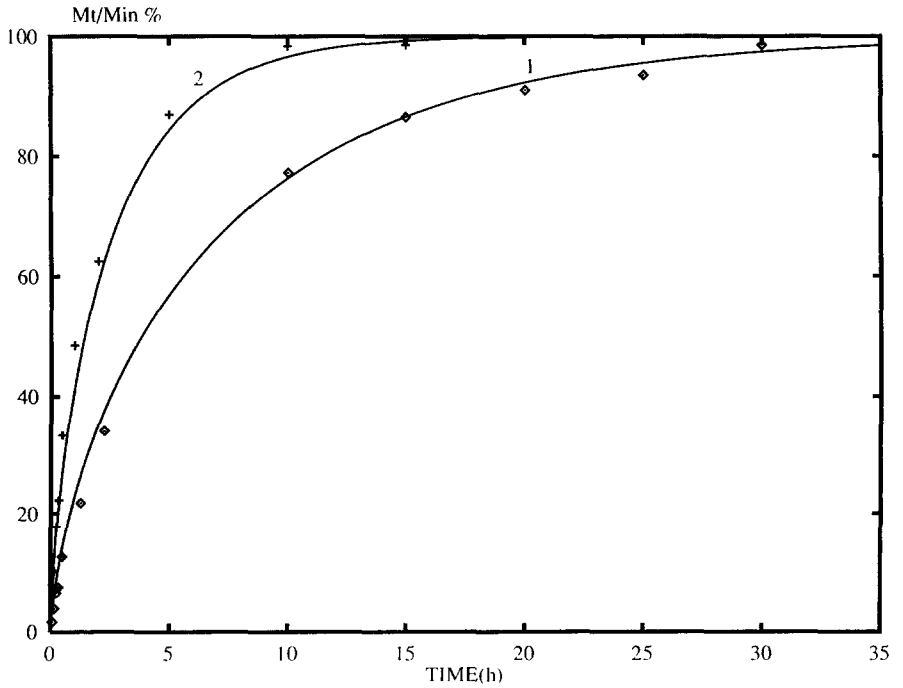

Fig. 2. In vitro tests. Kinetics of release of the drug out of the dosage form. (1) pH 1.2; (2) pH 8.

Table 1
Characteristics of the release of the drug

	pH			
	1.2	4	6	8
D ($\times 10^7$) (cm^2/s)	5.3	7	8	15
h ($\times 10^5$)(cm^2/s)	2	2	2	2

Table 2
Characteristics for theophylline

$k_a = 6.03/h$	$k_e = 0.089/h$
$V_b = 26.41$	

Time, 15 min (stomach); 105 min (duodenal-cecal); 460 min (gastro-cecal).

ficient of mass transfer on the surface is finite, as the tangent at the origin of time is not vertical. The coefficient of mass transfer on the surface h is about the same for the various liquids at different pH and the diffusivity slightly increases with the pH, as shown in Table 1.

4.2. *In vivo calculation*

The characteristics for theophylline are given in the literature (Sournac et al., 1988) as well as the time of the gastrointestinal tractus. (Table 2).

It is necessary to have a constant diffusivity when using Eq. 3.

An average value is determined for the diffusivity of the drug through the dosage form by considering the time of residence in the various parts of the gastrointestine at various pH. The value of 13.4×10^{-7} cm^2/s is thus obtained.

The following kinetics are thus obtained by calculation, expressing the amount of drug-time histories in various parts (Fig. 3): the kinetics in the gastrointestine (1) and in the blood compartment (3); the kinetics of the drug eliminated out of the blood compartment (4) and of the drug released out of the dosage form (4).

Moreover, the drug level in the blood compartment is obtained from the kinetics of the amount of drug in the blood and the volume of liquid in the blood compartment (Fig. 4).

Some conclusions can be drawn from these curves.

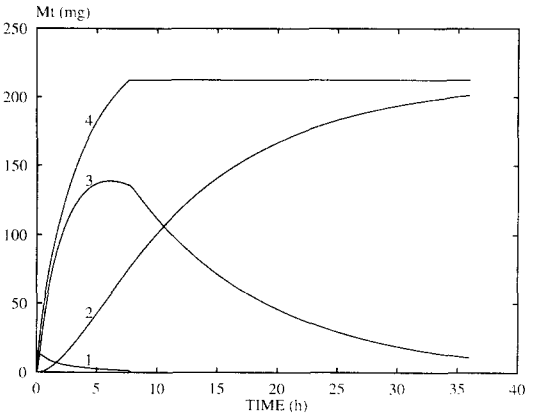

Fig. 3. In vivo calculation. Kinetics of the amount of drug: in the gastrointestinal tract (1); in the blood compartment (3); eliminated (2); released out of the dosage form (4). Dosage form, 500 mg with 50% theophylline; cylinder with radius 0.57 cm and height 0.44 cm.

(i) The amount of drug located in the gastrointestine is rather low at any time.

(ii) The kinetics of the drug in the blood compartment follows a typical pattern with a rather flat maximum. The maximum is attained after around 6 h and the concentration of drug at this time is 5.2 mg/1. The shape of this drug level-time history is similar to that obtained from experiment with Theostat tablets (Sournac et al., 1988) exhibiting a maximum at around 6 h 15 min and a drug level of 6.2 mg/l with a dose of theophylline of 300 mg.

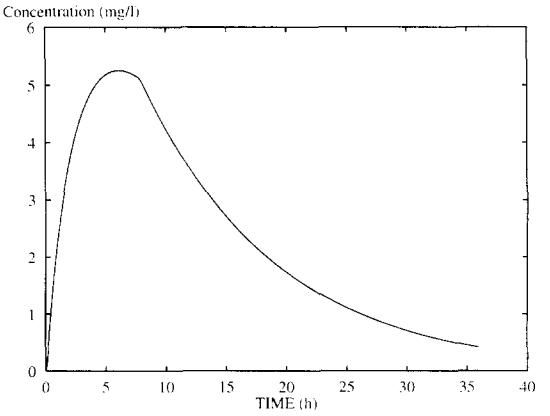

Fig. 4. Drug level time history in the blood compartment with the dosage form: 500 mg with 50% theophylline.

(iii) The ratio of the values of the drug level in the blood compartment obtained with the dosage forms made of cylinders with 250 mg drug and with the Theostat tablets with 300 mg drug is about the same.

(iv) Curve 4 in Fig. 3 is of interest, as it shows clearly the effect of the residence time of the dosage form along the gastrointestine tract. About 6% of the drug remains in the dosage form at the end of the stage in the gastrointestinal tract. In fact, the same drawback was observed for the Theostat tablet (Sournac et al., 1988).

(v) As the process of release of the drug out of the dosage form is controlled by diffusion, it is possible to determine the effect of the dimension of the dosage form on the process of drug transfer, and especially on the kinetics of drug release out of the dosage form.

4.3. *Effect of the dimensions of the dosage forms.*

As the process is controlled by diffusion, it is clear that the time necessary for a given ratio of drug released M_t/M_∞ is proportional to the square of the dimensions of the dosage form, by considering the dimensionless numbers Dt/L^2 or Dt/R^2 in Eq. 3.

The process of drug transfer has thus been studied by considering three types of dosage forms with the same amount of theophylline and the same drug/Eudragit ratio. The three dosage forms have the dimensions shown in Table 3.

The various kinetics of drug transfer are shown in Fig. 5 as obtained by calculations by keeping the same values shown in Tables 1 and 2.

The blood level-time histories are also depicted in Fig. 6.

The following conclusions can be drawn:

Table 3
Dimensions of the dosage forms

Dosage form (i) number	Radius (cm)	Height (cm)	Drug weight (mg)
1 C (1)	0.575	0.44	250
2 C (2)	0.456	0.35	250
3 C (8)	0.287	0.22	250

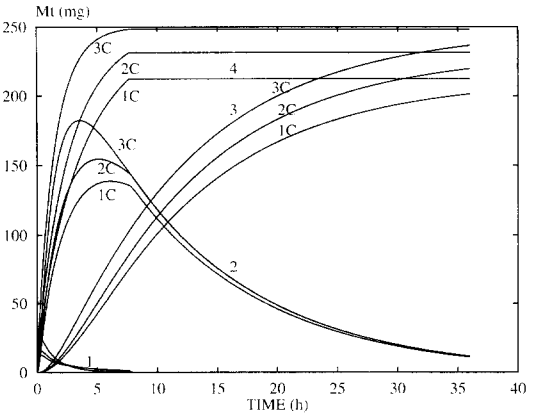

Fig. 5. In vivo calculations for dosage forms of various dimensions with the sane amount of drug: in the gastrointestinal tract (1); in the blood compartment (2); eliminated (3); released out of the dosage form (4). 1C, one dosage form with 250 mg drug; 2C, two dosage forms with 125 mg drug each; 3C, eight dosage forms with 31.25 mg drug each.

(i) Of course, the smaller the dosage form, the faster the kinetics of drug release out of the dosage form.

(ii) This above conclusion is of importance, because the transit time in the gastrointestinal tract becomes so long that the whole drug is extracted from these small dosage forms.

(iii) Of course, as a result of the increase in the rate of drug release, a higher blood level is attained with the smaller dosage forms. Moreover,

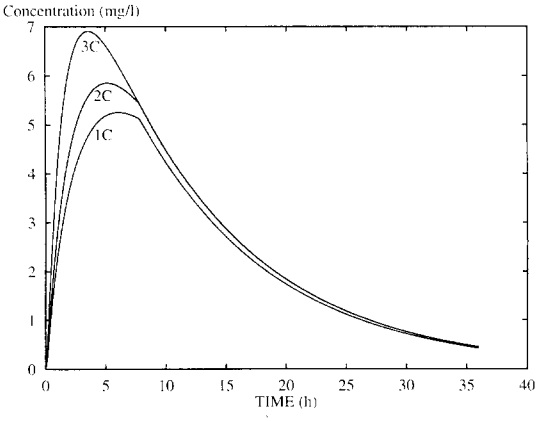

Fig. 6. In vivo calculation, drug level in the blood compartment: one dosage form 250 mg drug (1C); two dosage forms with 125 mg drug each (2C); eight dosage forms with 31.25 mg drug each (3C).

the maximum of the drug concentration in the blood is reached at a shorter time.

(iv) A compromise has to be made for selecting the desired dimensions of the dosage forms. Small dosage forms can lead to the complete release of the drug along the gastrointestinal tract, but they are responsible for a higher drug level in the blood compartment.

5. Conclusions

Prediction of the kinetics curves obtained with in vivo tests is possible by calculation for oral dosage forms with controlled release. The calculation can be rather simple by incrementing time during the process when the diffusivity of the drug through the dosage form is considered as constant, while a numerical model with finite differences is necessary when the diffusivity is not constant.

Calculation has been performed in the case of an oral dosage form, cylindrical in shape, with theopylline and Eudragit, the release of the drug being controlled by diffusion. As the diffusivity varies slightly with the pH, an average value of the diffusivity had to be determined by considering the residence time of the dosage form along the gastrointestinal tract and the various values of the pH.

Some results are obtained either from a theoretical or from a practical point of view. The kinetics of the amount of drug transferred in the blood compartment as well as the drug level in the blood are thus obtained.

Not only the drug level-time history in the blood compartment is obtained, but also the amount of drug remaining in the dosage form. By using the numerical model it is thus possible to determine the effect of the dimensions of the dosage form on the drug level in the blood compartment as well as the amount of drug remaining in the dosage form.

References

Aly Sas and Megwa, S.A., In vitro/in vivo release of thiamine hydrochloride from microcapsules acrylic resin. *Pharm. Ind.*, 51 (1989) 1163–1167.

Aoki, S., Uesugi, K., Tatsuishi, K., Ozawa, H. and Kayano, M., Evaluation of the correlation between in vivo and in vitro release of phenylpropanolamine HCl from controlled-release tablets. *Int. J. Pharm.*, 85 (1992) 65–73.

Bakhouya, Abd., Bidah, D. and Vergnaud, J.M., Process of drug delivery oral dosage forms whith a polymer matrix made of Gelucires. *J. Polym. Eng.*, (1994) 249–260.

Bidah, D. and Vergnaud, J.M., Kinetics of in vitro release of sodium salicylate dispersed in Gelucire. *Int. J. Pharm.*, 58 (1990) 215–220.

Feijen, J., Controlled drug delivery on the use of synthetic polymers, Rouen, *XIVth Meeting of the French Polymer Group*, Nov. 1984.

Finne, U. and Urtti, A., Pharmacokinetic simulation reveals in vivo deviations from in vitro release of timolol from polymer matrices. *Int. J. Pharm.*, 84 (1992) 217–22.

Heller, J., Biodegradable polymers in controlled drug delivery. *CRC Crit. Rev. Ther. Drug Carrier Systems*, 1 (1984) 1–34.

Hilton, A.K. and Deasy, P.B., In vitro and in vivo evaluation of an oral sustained release floating dosage form of amoxycillin trihydrate. *Int. J. Pharm.*, 86 (1992) 79–88.

Junginger, H.E., Verhoeven, J. and Peschier, L.J.C., A new in vitro model to detect interactions between controlled release dosage forms and food. *Acta Pharm. Technol.*, 36 (1990) 155–60.

Koch, H.P., Computer simulation von Blutspiegelprofilen: Wirkstoffliberation aus zwei Retardpraparaten und Computer-simulation der Ein-und Mehrdosen-Pharmakokinetik. *Pharmazie*, 47 (1992) 547–52.

Nicklasson, M., Association between in vitro and in vivo. *Paperback APV*, 22 (1990) 155–173.

Ouriemchi, E.M., Bouzon, J. and Vergnaud, J.M., Modelling the process of controlled release of in in vitro and in vivo tests. *Int. J. Pharm.*, 113 (1995) 231–240.

Skelly, J.P., Amidon, G., L., Barr, W.H., Benet, L.Z., Carter, J.E., Robinson, J.R., Shah, V.P. and Yacoubi, A., In vitro and in vivo testing and correlation for oral controlled/modified release dosage forms. Report of the 2nd Workshop, Dec. 1988, Washington DC, USA. *J. Controlled Release*, 14 (1990) 95–106; *Int. J. Pharm.*, 63 (1990) 83–93.

Sournac, M., Maublant, J.C., Aiache, J.M., Veyre, A. and Bougaret, J., Scintigraphic study of the gastro-intestinal transit and correlations with the drug absorption kinetics of a sustained release theophylline tablet. *J. Controlled Release*, 7 (1988) 139–146.

Vergnaud, J.M. Drug delivery from dosage forms consisting of a drug dispersed in a non-erodible polymer. *Controlled Drug Release of Oral Dosage Forms*, Ellis Florwood, Chichester, 1993, ch. 10, pp. 199–259.

Vergnaud, J.M. Drying of dosage forms for medical applications. Drying of dosage forms for medical applications. *Drying of Polymeric and Solid Materials*, Springer, Berlin, 1992, ch. 15, pp. 291–318.

Verhoeven, J., Schutte, S.C., Peschier, L.J.C., Danhof, M., and Junginger, H.E., The design of a dry-coated controlled-release tablet for oxprenolol with microporous polypropylene powder. *J. Controlled Release*, 10 (1989) 205–17.