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RESEARCH PAPER

Evaluation of Ethylcellulose-Coated Pellets Optimized Using the Approach of Taguchi

G. F. Palmieri[1] and P. Wehrlé[2]

[1]*Dipartimento di Scienze Chimiche, Università di Camerino, via S. Agostino Camerino, Italy*
[2]*Laboratoire de Pharmacotechnie, Faculté de Pharmacie ULP-Strasbourg B.P. 24 - F67401 Illkirch Cedex, France*

ABSTRACT

Spherical granules of theophylline with microcrystalline cellulose and lactose were prepared in a high-speed granulator. An original experimental design based on the philosophy of Taguchi was applied to optimize the yield of the produced granules. Successively, the optimized pellets were coated with an ethylcellulose pseudolatex preparation (Surelease®) in a fluid bed coating machine using a bottom spray nozzle and a Wurster® column. Finally, these granules were c ompressed into tablets of different hardnesses. The chosen statistical approach proved efficient not only to find the optimal operating conditions for granulation but it also appeared to define the characteristics of a process that was robust and nonsensitive to noise factors. Dissolution studies revealed a zero-order release of theophylline from the coated granules, but after the compression step, the ethylcellulose film was damaged and the drug release was immediate.

INTRODUCTION

Fluid bed coating is currently a widely used technique because it allows, among the other applications, crystals or granules to be coated with a variety of available polymers to provide gastro-resistance or controlled-release systems. Surelease® (ethylcellulose pseudolatex) is one of the more effective polymeric preparations for controlled-release systems (1), used alone (2–5) or associated with hydrophilic polymers such as hydroxypropyl methylcellulose (6–9).

In previous studies of the mechanism of film formation and the influence on it of parameters (such as inert powders, quantity and type of plasticizer, different kinds of equipment and experimental parameters, and addition of hydrosoluble polymers or molecules) or realization of a specific pharmaceutical formulation, the authors have presented the coating of activated pellets (9) or loaded

non-pareils (4,7) previously purchased, or granules obtained by the extrusion–spheronization technique (2,3,5, 6,8).

The use of a classical high-speed granulator was proved efficient to produce coarsely spherical granulates (10), which have been coated with success with an aqueous acrylic resin, leading to a sustained release of 8 hr (11). The aim of this work is to optimize the wet granulation process in a high-speed granulator in order to obtain the largest amount of a theophylline coarsely spherical granulate. These pellets are then coated with ethylcellulose (Surelease) in a fluid air bed under different operating conditions, and evaluated.

MATERIALS AND METHODS

Wet Granulation Optimization

An original and simple method for theophylline beads production using a common high-speed granulator dedicated to conventional granulates (Stephan UMC5®, Germany) was developed. To improve the process, an optimization approach was chosen. But rather than trying to bring the process to the target values, an attempt was made to find optimal operating conditions leading also to stable and nonsensitive pellet characteristics. The classic experimental design methodology was completed by using Taguchi's philosophy. Dr. Genichi Taguchi, a Japanese engineer and quality consultant, has developed original ideas and statistical procedures that have been used in Japan for decades, but it was the mid-1980s when the Western world became aware of his views toward process control and quality improvement (12). The purpose of his approach is to reduce system variability while simultaneously decreasing costs and increasing productivity. The general methodology is based on:

- Separation of factors by role,
- Extensive use of experimental design,
- Use of measures of variability as responses,
- Dual objectives of process centering and noise minimization.

The theory of experimental designs and Taguchi's approach have been reported (10). One of the main contributions of Taguchi's methodology in optimization procedures consists of applying performance statistics that give information about both the optimum location and the spread of the studied characteristic. This in only one type of composite response variable.

The studied pellets were built up with theophylline (20.0 %, Boehringer Ingelheim, Germany), lactose EFC (30.0 %, Sucre de lait s.a., France), and microcrystalline cellulose (50% Avicel PH101, FMC, Ireland). The granulating liquid was a 15% hydro-alcoholic solution (ethanol/water, 30/70, v/v) of hydroxypropylmethylcellulose (Pharmacoat 603, Shin Etsu, Japan). After a 5-min dry-blending phase at 300 rpm in the high-speed granulator (Stephan UMC5), the granulating liquid was added with a peristaltic pump at a flow rate of 30 ml/min. During this stage, the impeller rotated at different high-speed levels, precisely set near a target value according to the methodology described below. Different amounts of granulating liquid and kneading times were also tested. The granulates were then dried, under vacuum at 50°C, in the granulator shell, the impeller working at the lower rotation speed (300 rpm). Pellets were obtained with 230 ml of granulating liquid and an impeller rotation speed of 1200 rpm without any additional kneading after the mass was wetted. These coarsely spherical granulates were characterized by the particle size distribution reported in Fig. 1.

An attempt was then made to improve the yield defined as the cumulative percentage of particles refused on the 200, 400, and 630 μm sieves by varying the quantity of granulating liquid (Q) and the kneading time (T). If the impeller rotation speed could theoretically be fixed at precise levels, in actual production it might be subject to small random variations, and therefore affect the pellets' characteristics. To find the operating conditions leading not only to predefined target characteristics (such as highest pellet yield) but also to define a robust process not sensitive to noise factors, the classical experimental design was completed by using the general philosophy of Taguchi.

Taguchi's specific experimental designs do not belong to the optimization methodology, mathematically speaking (13). A more efficient approach was then chosen. The full 3^k-type experimental design, well-known for optimization operation when only a few factors are to be tested simultaneously, was combined with some of the elements specific to Taguchi's approach (10). In this work, where the two main controlled factors were the quantity of granulating liquid (Q) and the kneading time (T), the inner array of the experimental design according to Taguchi's general method therefore corresponded to a 3^2 classical experimental design, while the outer array (allowing the study of noise factors) constituted a 2^1 experimental design performed for each point of the inner array with two levels for impeller rotation speed

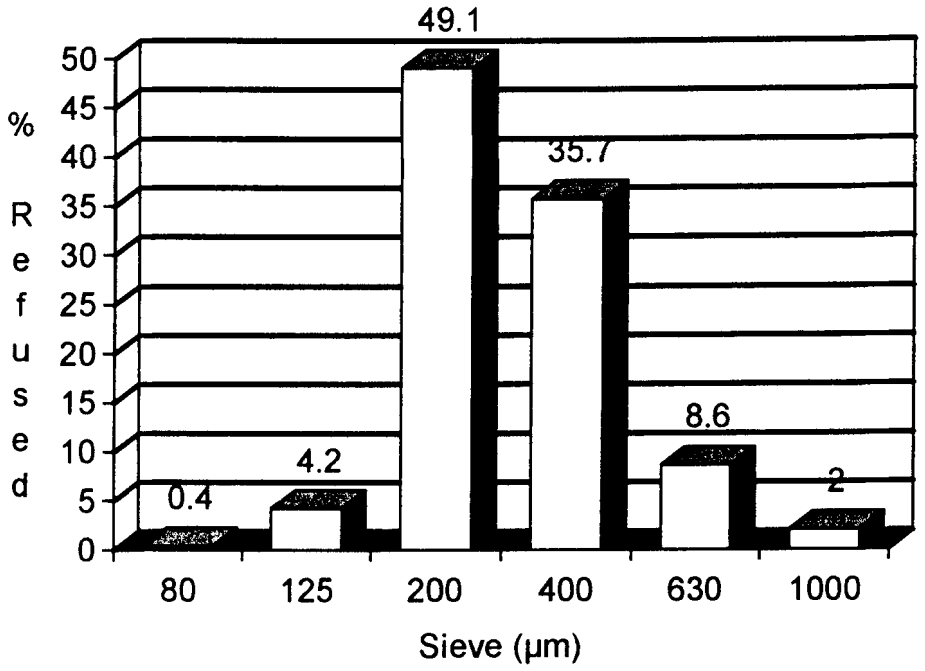

Figure 1. Particle size distribution.

close to the target value of 1100 rpm. The final resulting experimental design is represented on Fig. 2. All of the experimental collected results were used to evaluate, by multiple regression, a second-order model that efficiently describes the response surface curvature for the yield:

$$Y = b_0 + b_1Q + b_2T + b_{12}QT + b_{11}Q^2 + b_{22}T^2$$

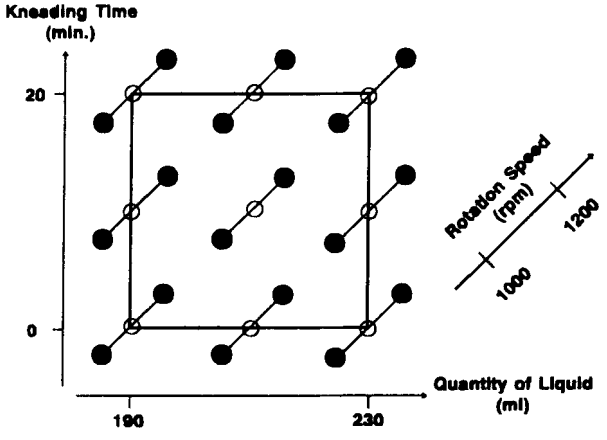

Figure 2. Experimental design including a noise factor (impeller speed).

To define the operating conditions leading not only to the highest yield and but also to a yield not sensitive to small impeller rotation speed variations, Taguchi's "larger-is-better" criterion (14) was adopted:

$$\{SN_L\} = -10 \cdot \log_{10}\left[\frac{1}{n} \cdot \sum_{i=1}^{n} \left(\frac{1}{y_i}\right)^2\right]$$

This performance statistic is used when the objective is to make the response as large as possible. When all of the responses in an outer array are large and positive, this larger-is-better performance statistic is as large as possible.

Coating Procedure

The coating dispersion was first prepared by dispersing in water a quantity of talc corresponding to 50% of the weight of the dry polymer used, and stirring for 10 min. The talc was able to avoid the polymer tackiness without affecting the homogeneity and integrity of the ethylcellulose film. Then, an amount of Surelease (Colorcon, UK) was blended with the dispersion, and the final dispersed system was stirred for other 10 min before spraying. No plasticizer is added because Surelease already contains sufficient concentration of it. The tested

Table 1

Composition of the Coating Dispersions

	5.0% Coat	7.5% Coat	10.0% Coat	12.5% Coat
Surelease	60.00	90.00	120.00	150.00
Talc	7.50	11.25	15.00	18.75
Water	52.50	78.75	105.00	131.25

formulations used are presented in Table 1, in which the percentages refer to the amount of polymer.

The quantity of water was adjusted in order to have always a solid content of 20%; a higher quantity of solid, increasing the viscosity of the system, could modify the spraying or even plug the nozzle. When the coating dispersion was ready, the granulate was fluidized in the air bed (Uniglatt, Germany), and after 10 min of preheating, it was coated with two series of parameter settings, while the coating dispersion was stirred. The operating conditions are summarized in Table 2. The coated granulate was successively dried in the same apparatus during 30 min at 60°C for both settings.

UV Analysis

The uniformity of theophylline content of the coated and uncoated granules was controlled by UV measurements in ethanol at 288 nm, after an appropriate amount of granulate was milled in a mortar.

Hard Gelatin Capsule Preparation

The formulation with 10% polymeric coating was used for the realization of this pharmaceutical dosage form. Hard gelatin capsules (size#1) were filled with 400 mg of coated granules, corresponding to 75 mg of theophylline.

Table 2

Processing Conditions of Coating

Parameters	Setting 1	Setting 2
Granulate load	300 g	300 g
Inlet temperature	40°C	60°C
Outlet temperature	35°C	55°C
Fluidization air volume	40–60 m^3/hr	40–60 m^3/hr
Flow rate	6 ml/min	6 ml/min
Atomization air pressure	1.2 kg/cm^2	1.2 kg/cm^2
Nozzle width	1 mm	1 mm

Compression of Granules

Two formulations were prepared with granules coated at 40°C with 10% of polymer. The first formulation was realized by compressing at different hardnesses (4, 8, and 12 Kp) a mixture of coated granules (66.6%), Avicel PH 101 (32.4%), and magnesium stearate (1%), to obtain tablets of 600 mg (corresponding to 75 mg of theophylline). The second formulation was realized by compressing at the same described hardnesses, a mixture of coated granules (57%), Avicel PH 101 (42%), and magnesium stearate (1%), to obtain tablets of 700 mg (corresponding to 75 mg of theophylline).

In Vitro Dissolution Studies

Dissolution studies were carried out in distilled water at 37°C with a Prolabo Dissolutest (France), assaying the samples spectrophotometrically at 288 nm for 8 hr with a UV-2101 PC scanning spectrophotometer (Shimadzu, Japan) connected to a microcomputer.

RESULTS AND DISCUSSION

Granulation Process Optimization

The results obtained after performing the experimental design are reported in Table 3. The performance statistic level is then calculated for each couple of values (Table 4).

The second-order models were then calculated and evaluated (Table 5). All the models revealed a multiple correlation coefficient greater than 0.85. If a risk $\alpha = 0.15$ is fixed as a limit, the analysis of variance shows that all the models are validated, the performance model displaying the best statistical indices.

Table 3

Experimental Design Points and Corresponding Responses

	Factors			
Exp. #	Liquid (ml)	Time (min)	Speed (rpm)	Yield
1	190	0	1000	48%
5	190	0	1200	66%
13	190	10	1000	84%
17	190	10	1200	76%
2	190	20	1000	84%
6	190	20	1200	79%
11	210	0	1000	74%
15	210	0	1200	83%
9	210	10	1000	86%
10	210	10	1200	88%
12	210	20	1000	50%
16	210	20	1200	75%
3	230	0	1000	82%
7	230	0	1200	85%
14	230	10	1000	56%
18	230	10	1200	36%
4	230	20	1000	21%
8	230	20	1200	53%

Table 4

Performance Statistics

Liquid (ml)	Time (min)	Yield (Mean)	Performance Statistic
190	0	57.4%	34.86
190	10	79.6%	38.17
190	20	81.2%	38.17
210	0	78.5%	37.87
210	10	86.8%	38.76
210	20	62.3%	35.37
230	0	83.4%	38.42
230	10	46.1%	32.63
230	20	36.7%	28.78

The response surface and contour plot are represented for the yield performance statistic (Figs. 3 and 4).

The yield performance statistic displays no single optimum but a typical ridge with a "minimax." This ridge (broken line on Fig. 4) gives the optimal operating conditions that led to a maximum and stable yield level that was not sensitive to small impeller rotation speed variations. The optimal operating conditions could be determined graphically or precisely defined by calculating the derivative function of the model, differentiating the model equation with respect to first Q and the T, and equating the results to zero. The solution of the system of equations was Q = 199 ml and T = 11.7

Table 5

Statistical Analysis of the Second-Order Models

	Student t-Test (p, %)							
Response Variable	1	Q	T	$Q \cdot T$	Q^2	T^2	R^2	ANOVA (p, %)
Yield	21.4	20.6	5.0	4.7	21.8	62	0.867	14.7
Performance	8.6	6.4	1.0	1.0	6.8	34.3	0.958	2.7

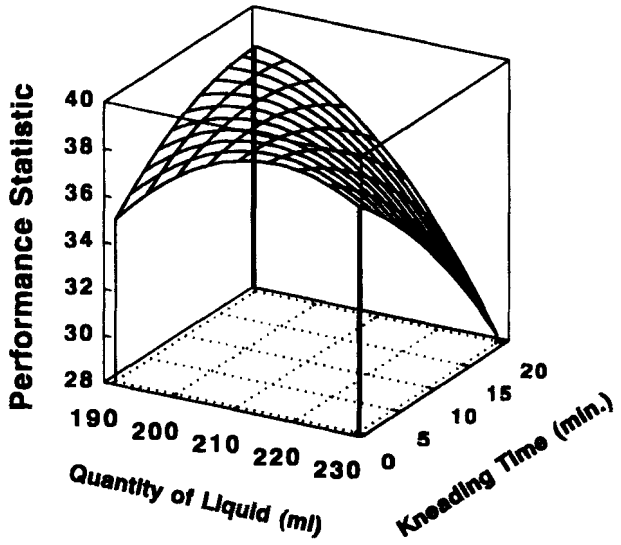

Figure 3. Response surface for the yield performance statistic.

min. For the optimum definition of performance statistic, a very good and stable yield was reached (82 ± 3%). The mean particle size of these pellets was 340 μm.

The operating conditions defined for the optimum (199 ml, 11.7 min) were then selected to produce active pellets of theophylline coated in a fluidized air bed apparatus.

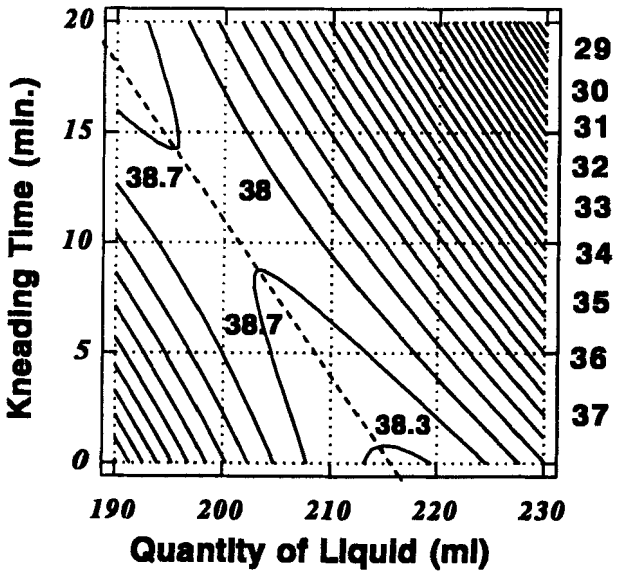

Figure 4. Contour plot for the yield performance statistic.

Coated Pellets Evaluation

All of the experiments were repeated three times without showing significant differences; this confirms the high reproducibility of the results.

Figs. 5 and 6 show the theophylline release from the granules coated at 40° and 60°C, respectively. As expected, the release depended on the thickness of the film applied all around and it gradually decreased with the increasing quantity of polymer. On the contrary, unexpectedly, the coating process carried out at 40°C gave better results than the one performed at 60°C, which is the temperature normally used to coat particles with ethylcellulose. In fact, each coating produced at 40°C, compared with the same process performed at 60°C, had a higher capability of slowing the drug release, and this phenomenon is more remarkable with the increased of coating. This suggests that instead of using the same temperature (60°C) for the whole coating process, the spraying of the coating dispersion could be carried out at 40°C, followed by a drying step at 60°C, for the time necessary to avoid any aging phenomena, which may induce a variation in drug release. Both of the temperature settings, excluding the very first minutes, led to a good linearity (zero-order release) for the higher percentages of coating. On the other hand, the lowest polymer percentage showed a first-order release kinetics. The granules with the 10% of polymeric coating were chosen for the preparation of the capsules and the tablets because they release nearly 90% of theophylline after 10 hr, conserving, at the same time, a good linearity.

Evaluation of Capsules and Compressed Granules

Fig. 7 shows the theophylline release from the 600 mg tablets of 4, 8, and 12 Kp hardness, respectively, compared with the capsules. While the capsules conserved the same drug release characteristics of the free granulates (excepted a few minutes time lag due to the capsules opening), the compression cleaved all of the polymeric films, causing the immediate release of the theophylline, even with a low applied compression force. Increasing the quantity of Avicel up to 700 mg tablets (Fig. 8) produced no substantial change. This means that ethylcellulose-coated beads seem not to keep

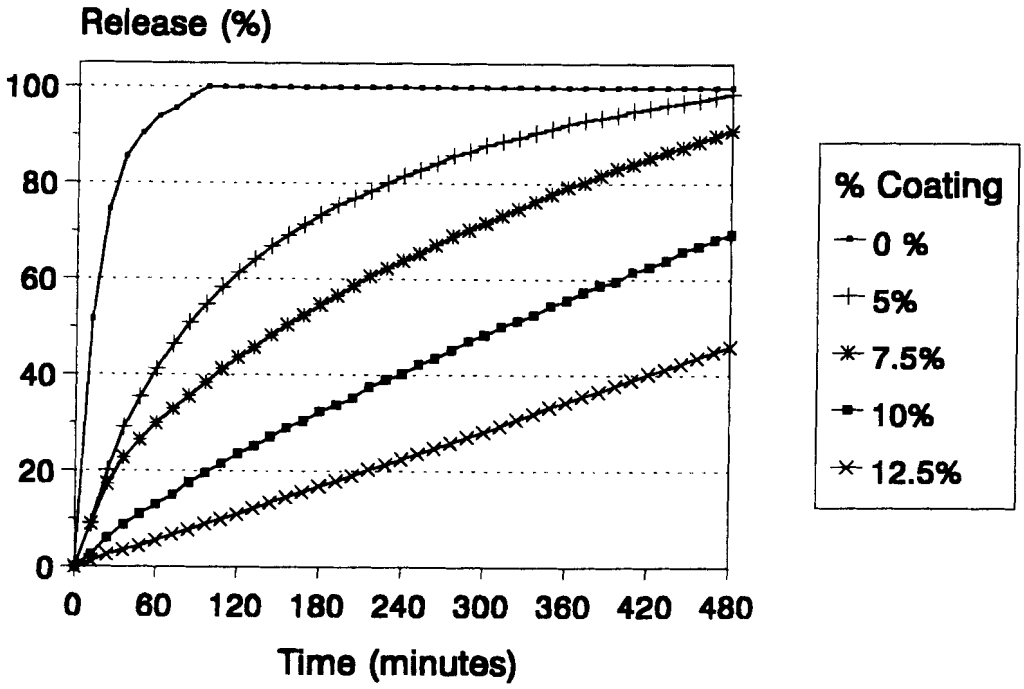

Figure 5. Theophylline release from pellets coated with the 40°C procedure.

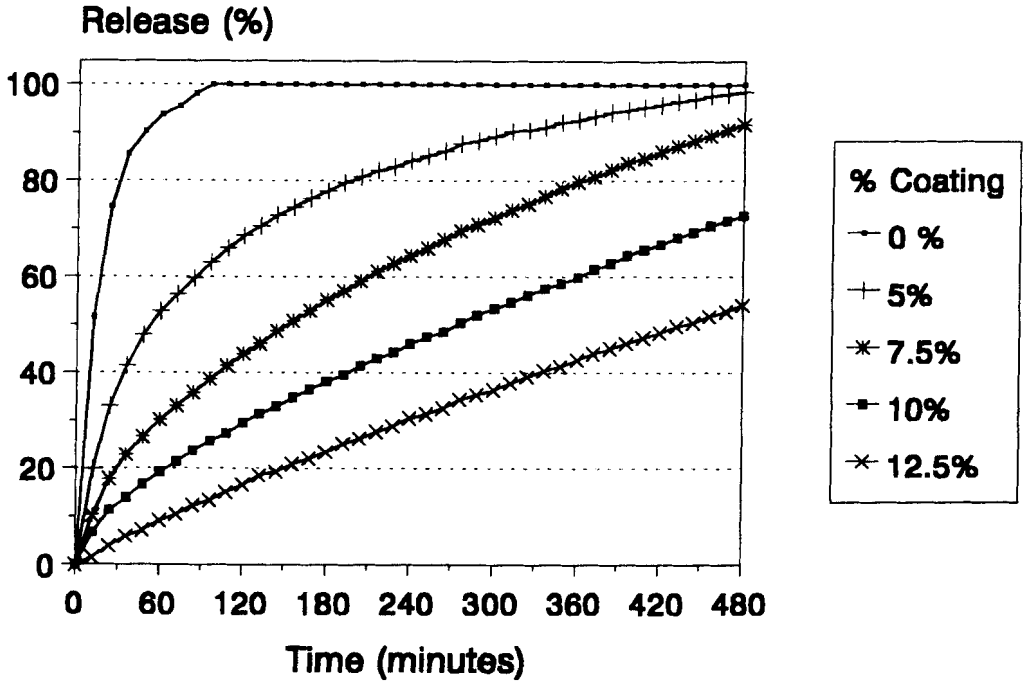

Figure 6. Theophylline release from pellets coated with the 60°C procedure.

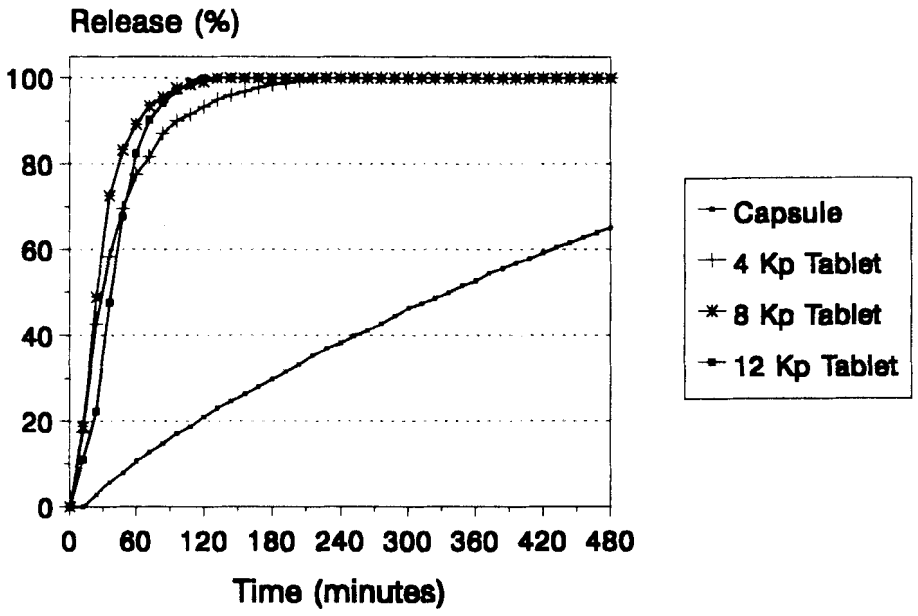

Figure 7. Release from compressed beads with a small amount of Avicel compared with pellets in capsules.

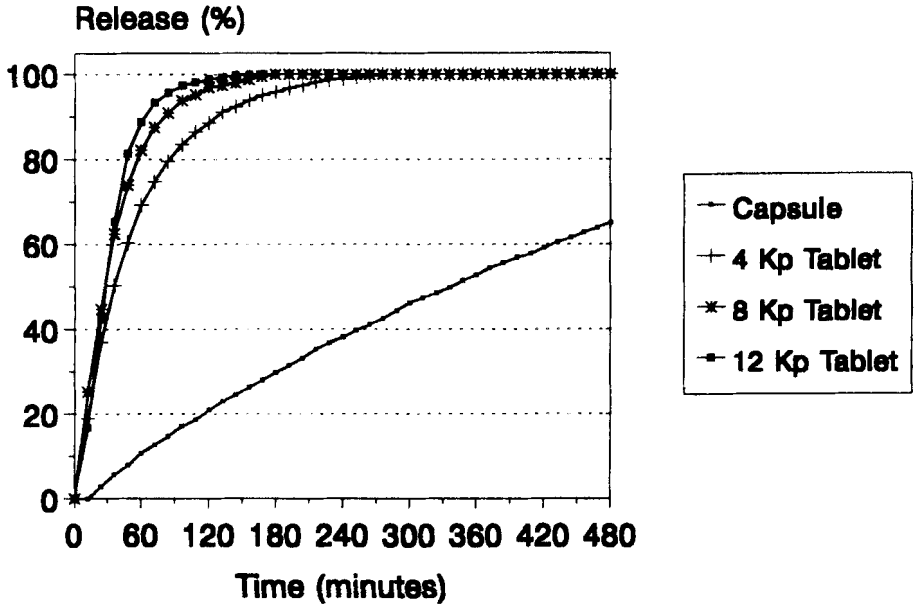

Figure 8. Release from compressed beads with a large amount of Avicel compared with pellets in capsules.

their characteristics even if a high percentage of a good excipient for direct compression is used with a small compression force.

CONCLUSION

By combining an experimental design well known for optimization and Taguchi's philosophy, it was possible to identify the operating conditions leading to an optimal and stable yield for the production of theophylline pellets. The studied process was performed in a simple high-speed granulator generally used to produce conventional granules. The optimized pellets were easily coated to realize a "reservoir" system. Ethylcellulose (Surelease) was confirmed to be a very useful polymer for controlled-release delivery systems. Between the two tested oral solid dosage forms, the capsule revealed the best properties; the dissolution profile was nearly the same as the free-coated granules. Ethylcellulose-coated beads could not be easily compressed without breaking the applied polymeric film, explaining the fast release of theophylline from the tablet.

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