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Mathematical modelling and optimization of a rotary fluidized-bed coating process

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Summary

A three-factor, three-level Box-Behnken design was used to study the rotary fluidized-bed aqueous coating process. 10% theophylline-containing granules were made, dried and subsequently coated in a rotary fluidized-bed. Based on the experimental design, the factor combinations resulted in different theophylline release rates and profiles. An optimization attempt was made to achieve a maximum amount of drug release after 11 h. The percent dissolution-time profiles were found to be significantly affected by the coating temperature and spray nozzle pressure. Theophylline release rates were found to be linearly affected by the polymer amount. Overall, the rotary fluidized-bed was found to be an efficient piece of equipment for granulating and coating processes.

Introduction

Fluidized-bed technology offers many advantages; during the fluidization solids can be added to the bed or can be removed without stopping the process. A fluidized-bed quickly reaches isothermal conditions and the bed temperature can be controlled during an operation. Some of the most commonly used types of fluidized-beds in the pharmaceutical industry are: fluidized-bed dryer, top spray granulator/coater, bottom spray coater and rotary fluidized-bed.

Coating processes with aqueous polymer dispersions in different types of fluidized-beds such as bottom spray or top spray have been reported in the literature (Harris et al., 1986; Lippold et al., 1989; Iyer et al., 1990). However, there are only a few reports about rotary fluidized-bed processing. Jager and Bauer (1982) reported that the rotary fluidized-bed (RFB) was an effective mixer. The content uniformity requirement for 1% butalbital was fulfilled by mixing the components in the rotary fluidized-bed. In addition, they demonstrated that RFB granulation produced spherical and dense particles with a reproducible size distribution. The application of a rotary processor to the production of immediate release acetaminophen pellets was recently reported by Robinson and Hollenbeck (1991).

Its unique air flow patterns combined with centrifugal forces make the rotary fluidized-bed a versatile piece of equipment for pharmaceutical

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processing and there is a need to determine and quantify the factors governing granulation and coating processes.

Therefore, the objective of this study was to investigate the effects of selected factors on theophylline release rate and profiles of fluidized-bed coated granules and to optimize a final product based on the mathematical model.

Experimental Design

A three-factor, three-level Box-Behnken design was used (Box and Behnken, 1960). This design permits the construction of a second-order polynomial model to characterize or optimize a process with a small number of experiments. In addition, the Box-Behnken design will include at least one mid-level (0) setting for every combination of factors. The model has the following form:

$$Y = a_0 + a_1X_1 + a_2X_2 + a_3X_3 + a_4X_1X_2 + a_5X_2X_3 + a_6X_1X_3 + a_7X_{12} + a_8X_{22} + a_9X_{32} + E$$

where a_0–a_9 are the regression coefficients, X_1–X_3 denote the factors, Y is the measured response associated with the factor combinations, and E represents the experimental error term.

Studied factors include polymer amount (mg/cm^2), coating temperature (°C), and spray nozzle pressure (bar). In the study, the factor levels were evenly spaced and coded for low, medium, and high settings as −1.0, 0.0, +1.0, respectively. Table 1 summarizes the factors and their levels; Table 2 shows the experimental design in a randomized form.

TABLE 1

Factors and their levels for Box-Behnken design

Factor	Level		
Polymer amount (mg/cm^2)	4.0	6.5	9.0
Coating temperature (°C)	30	40	50
Spray nozzle pressure (bar)	1.0	2.0	3.0

TABLE 2

Box-Behnken design (randomized)

Run no	Factors		
	Polymer amount	Coating temperature	Nozzle pressure
1	1	0	−1
2	1	0	1
3	0	0	0
4	0	−1	1
5	0	1	−1
6	1	−1	0
7	1	1	0
8	−1	−1	0
9	0	1	1
10	0	−1	−1
11	−1	1	0
12	0	0	0
13	0	0	0
14	−1	0	−1
15	−1	0	1

For the statistical analysis, an experimental design and non-linear optimization software X-STAT (Wiley, New York, 1985) was used along with SAS statistics software (SAS Institute, Cary, NC).

Materials and Methods

The study consisted of the following discrete steps: Granulation and drying of theophylline granules in the RFB, sizing and calculation of surface area, granule coating with an aqueous polymer dispersion in RFB, and finally testing coated granules for their theophylline release in vitro and the statistical evaluation of the data. A total of 15 batches were prepared and evaluated based on the experimental design.

Formula

The basic formula used for granulation was 60 g theophylline anhydrous USP (Boehringer-Ingelheim, Germany), 525 g microcrystalline cellulose (Avicel PH 101, FMC Corp., Newark, DE), 15 g PVP K 26-28 (GAF Corp., Wayne, NJ) for a 600 g batch size. The aqueous film coating was aquacoat (FMC Corp., Newark, DE).

TABLE 3

Conditions for granulation in RFB

Inlet air temperature (°C):	25
Product bed temperature (°C)	16 ± 1
Bottom plate type and rpm	waffle plate, 720
Spray nozzle diameter (mm)	1.20
Spray nozzle air pressure (bar):	1 50
Batch size (g)·	600
Binder spray rate (ml/min)	44
Filter shaking interval and duration.	every 5 s for 3 s
Binder solution	2 5% w/v PVP in water
Pressure drop in product chamber (kPa)·	1 7–1 9
Fluidization air flow rate (m^3/h)	65

Granulation

A laboratory size fluidized-bed (Versa-Glatt, GPCG-1, Glatt Air Techniques, Inc., Ramsey, NJ) with the rotary insert was used. The conditions of granulation were determined upon preliminary experiments in order to achieve a fast and reproducible granulating process with spherical and dense particles. Table 3 summarizes the conditions. After spraying 500 ml of binder solution, samples were withdrawn from the bed every 10 s to monitor the granule growth. When granules reached 0.85–1.00 mm size, the inlet air temperature was set to 50°C and the pressure drop in the chamber was reduced to 1.0 kPa by elevating the bottom plate and increasing the fluidization air flow from 25 to 70% of full fan capacity. Hence, granule growth was inhibited.

Theophylline and moisture contents

The moisture content was determined using an automated gravimetric moisture content analyzer (Computrac, Max-50, Arizona Instruments, Tempe, AZ). From each batch three samples, 8 g each, were tested at 105°C before and after drying.

Theophylline content of each batch was determined by UV spectrophotometry (Beckman DU-70 UV/VIS Spectrophotometer, Beckman, Inc., Fullerton, CA). A sample of finely ground granules between 0.3 and 0.4 g was weighed accurately into a 100 ml volumetric flask. After appropriate dilutions with distilled water, the flask was shaken for 10 min, then the contents were filtered. A blank was prepared under identical conditions with no drug. The absorbances of the final solutions were determined at 271 nm. A series of theophylline standards were run along with the samples.

Drying, sieving and coating

Spherical and dense RFB granules were dried in the rotary fluidized-bed. The granules were

TABLE 4

Conditions of coating in RFB

Product bed temperature (°C)	30, 40, and 50
Bottom plate type and rpm	smooth plate, 280
Spray nozzle diameter (mm)	1.2
Spray nozzle pressure (bar)	1, 2 and 3
Batch size (g)·	300
Coating solution spray rate (ml/min)	8 5
Coating solution	Aquacoat and dibutyl sebacate
Pressure drop in product chamber (kPa)·	1 5
Fluidization air flow rate (m^3/h):	65

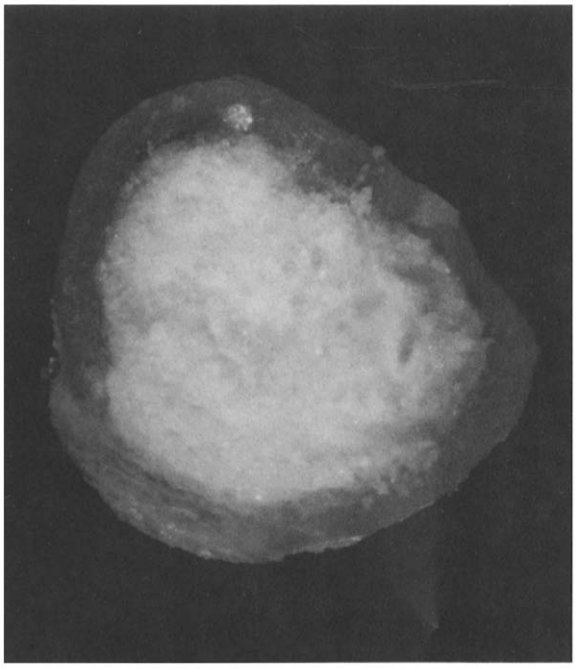

Fig. 1. Cross-section of rotary fluidized-bed coated granule (64 × magnification).

subjected to a sieve analysis using a nest of U.S. Standard sieves (1.70, 1.40, 1.18, 1.00, 0.850 mm opening sizes) to determine the mean statistical particle size ($d_{63.5\%}$) and the idealized specific surface area (A_{Sp}) for each batch using a particle size distribution nomogram (Rosin, Rammler, Sperling, and Bennet function, DIN 4190). After excluding the sieve fractions above 1.70 mm and below 0.850 mm, the remaining granules were transferred to the same RFB unit for coating. The reason for excluding the over and under sizes was as follows: For each batch a surface area calculation was performed, these calculations being based on the range between 1.70 and 0.85 mm, so that before and after coating the surface areas could be compared within as well as among the batches.

An aqueous dispersion of ethyl cellulose (Aquacoat, FMC Corp., Newark, DE) was mixed with 30% dibutyl sebacate (Sigma Chemical Co., St Louis, MO) for 45 min with a propellor-type laboratory mixer. The product chamber of the RFB was warmed up to the coating temperature based on the experimental design. The plasticizer-polymer mixture then was sprayed using the nozzle pressures according to the experimental design. Table 4 summarizes the conditions for coating.

Dissolution test

After the coating, a sieve fraction corresponding to the sizes between 1.40 and 1.18 mm was tested for in vitro theophylline release using the USP basket apparatus with 900 ml of distilled water as the dissolution medium at 37°C and 50 rpm. Samples were withdrawn after 10, 20, 30 min, 1, 2, 3, 5, 8, 11, and 22 h and assayed by UV spectroscopy at 271 nm.

Coating evaluation

Coating thickness measurements were taken by a stereo microscope (Zeiss-DRC, Oberkochen, Germany) equipped with a stage micrometer and camera attachment. Scanning electron microscopy (SEM) pictures were taken to assess the surface characteristics of the granules for uncoated, low-level coated, and high-level coated granules at 700 × magnification.

TABLE 5

Moisture and theophylline contents of batches

Run no.	Moisture (%) (mean ± SD, $n = 3$)	Theophylline (%) (mean ± SD, $n = 6$)
1	5.27 (0 23)	10 62 (0.71)
2	4 03 (0.16)	10.79 (1.02)
3	4 44 (0 08)	9.50 (0.98)
4	6 55 (0.22)	10 07 (0.45)
5	3 40 (0.30)	9.67 (0.34)
6	5.24 (0.83)	10.00 (0.18)
7	3.49 (0.12)	9.82 (0.96)
8	3.27 (0.16)	9 60 (1.17)
9	3.35 (0.05)	9.20 (1.03)
10	4.69 (0 21)	9.90 (1.01)
11	3.65 (0.08)	10.40 (0.67)
12	5 68 (0.10)	10.65 (0.54)
13	5.37 (0.31)	10 13 (0.20)
14	3.95 (0.17)	10 74 (0.23)
15	7 00 (0.05)	10.01 (0 14)

TABLE 6

Statistical mean diameters and specific surface areas for batches

Run no.	$d_{63.2\%}$ (mm)	A_{Sp} (m^2/kg)
1	1.40	4 92
2	1.40	4.89
3	1.30	5.76
4	1.40	5 18
5	1.25	5.65
6	1.20	5.84
7	1.30	5.51
8	1 35	5.60
9	1.25	5.20
10	1.35	5.19
11	1 25	5 60
12	1.30	5.68
13	1.35	5.37
14	1.20	5.00
15	1 10	5 09

Measured Responses

To be able to construct a statistical model for optimization of the coating process, certain measured responses which characterize the product were determined. Percent theophylline release vs time data were fitted to a non-linear equation to obtain the dissolution curve shape factor n, dissolution curve slope factor k and time to release 50% theophylline t_{50} (Sinclair and Peppas, 1984; Baker, 1987). The equation is as follows:

$$P_R = k \cdot tn \text{ and } 50 = k \cdot t_{50}n$$

where P_R represents percent theophylline release, k and n are constants and t denotes time (h).

For each percent dissolution vs time data the dissolution efficiency (DE) (Khan, 1975) values were also calculated and used as the measured responses in the study. The DE was calculated as the area under the percent dissolution-time curve expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. In addition, the values of percent theophylline release after 5, 8, and 11 h were entered into the model as measured responses.

Results and Discussion

Results of granule testing

The results of granule testing including theophylline content, moisture content, statistical mean particle size, and idealized specific surface area values for uncoated granules are presented in Tables 5 and 6.

TABLE 7

Parameters of n and k for 1.18–1.40 mm granule size interval, mean (95% confidence intervals)

Run no.	n	k
1	0.8985 (0.8581–0.9389)	3.9901 (3.6534–4.3268)
2	0.6344 (0.6007–0.6682)	8.5594 (7.9760–9.1428)
3	0.6290 (0.5862–0.6717)	18 5911 (16.990–20.191)
4	0.7995 (0.7323–0.8665)	5.9702 (5.1151– 6.8253)
5	0.8629 (0.8153–0.9106)	7.5841 (6.8181– 8.3500)
6	0.5614 (0.5256–0.5972)	19 1743 (17.814–20.532)
7	1.1557 (1.0971–1.2142)	2.1188 (1.8439– 2.3938)
8	0.8333 (0.7746–0.8921)	8.3090 (7.2786– 9.3394)
9	1.1579 (1.1096–1.2061)	2.2051 (1.9706– 2.4396)
10	0.9904 (0.9376–1.0432)	2.2457 (1.9887– 2 5026)
11	0.9458 (0.9206–0.9711)	7.2147 (6.8228– 7.6065)
12	0.7764 (0.7394–0.8135)	10.5595 (9.7402–11.378)
13	0.6112 (0.5691–0.6534)	19.9744 (18.283–21.666)
14	0.6959 (0.6390–0.7528)	12.7968 (11.303–14.290)
15	0.8420 (0.7957–0.8884)	7.0703 (6.3782– 7.7625)

The granules were dried in RFB from 50% moisture content to a 3–7% moisture level in 13–17 min, therefore, confirming that RFB is a very efficient dryer when compared to tray oven dryers.

Fig. 2 shows a coated granule under the light microscope at 64 × magnification. The coat thickness in Fig. 2 is 109 μm which corresponds to a high polymer level coating. The low polymer level resulted in a mean coating thickness of 46 μm (SD = 4.43) with a relative standard deviation (RSD) of 9.58% (n = 20). The medium polymer level coating gave a mean coating thickness of 67 μm (SD = 13.72, RSD = 20.65%, n = 20). The high polymer level coating reflected itself as a mean coating thickness of 103 μm (SD = 12.23, RSD = 11.85%, n = 20). The three coating levels were significantly different at the 0.05 level ($p <$ 0.0001).

The SEM pictures (at × 700) presented in Figs 2–4 depict the surface textures of an uncoated granule, a granule coated at lower polymer level, and a granule coated at high polymer level, respectively. The uncoated granule surface (Fig. 2) is rough and highly irregular. The low level polymer coat covers the whole surface uniformly; however, many holes approx. 1.25 μm in diameter (Fig. 3) can be observed on the surface. The

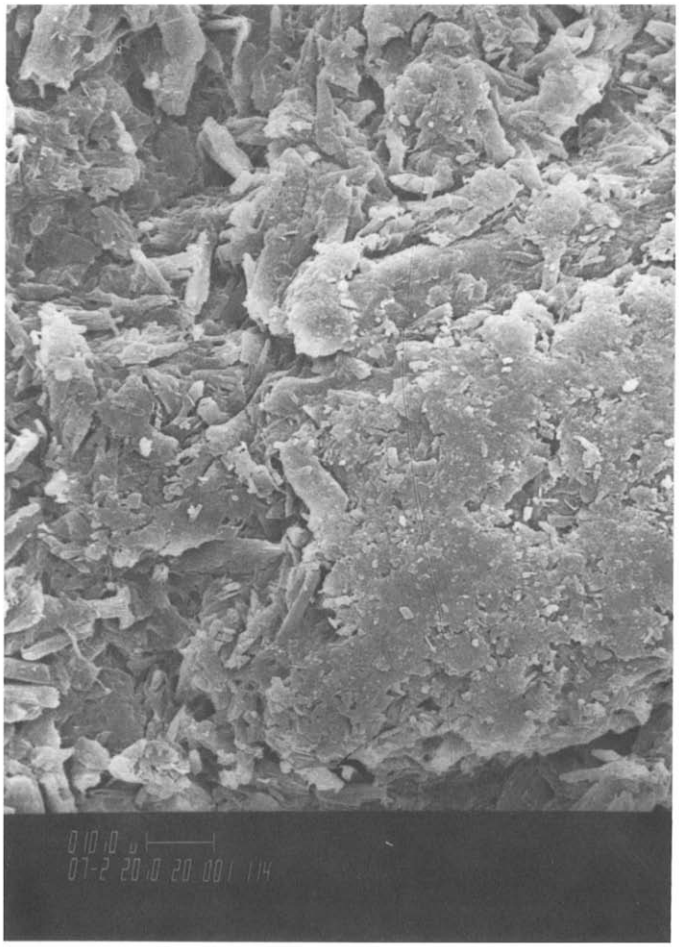

Fig. 2. SEM picture of an uncoated granule (700 × magnification).

Fig. 3 SEM picture of low polymer level coated granule (700 × magnification).

high level polymer coat covers the surface without any holes; in addition, excess polymer aggregates can be observed on the surface (Fig. 4).

Percent theophylline release-time profiles, based on the experimental design (Table 2), showed a broad range of releases from 55 to 100% over a 24 h period with different dissolution curve shapes (Table 7). The time to release 50% theophylline ranged from 4.5 to 23 h depending on the factor combinations (Table 8).

Results of regression analysis

Regression analysis results are summarized in Tables 9 and 10 for the measured responses with their coefficient of determination (R^2), and correlation coefficients (r) for experimentally observed and predicted responses.

Two- and three-dimensional plots for the measured responses were formed based on the model to assess the change of the response surfaces. The generated plots along with the simplex optimization procedure incorporated in X-Stat software were used to optimize for a theophylline release of more than 80% after 11 h from RFB coated granules which would correspond to an average GI transit time in humans (Coupe et al., 1991). Since theophylline is absorbed throughout the GI tract the desired release characteristics could possibly maintain an effective therapeutic level.

The shape factor of the dissolution curve (n) ranged between 0.56 and 1.15. It could be characterized by the effects of coating temperature and spray nozzle pressure terms at least over the range of the factors studied (Fig. 7). High temperature and nozzle pressure combinations, at all levels of the polymer, resulted in large n values ($n > 0.95$). At the lowest polymer level, a temperature region of 1–0.5 to +0.8 with nozzle pressure range of 0.0 to −1.0 can result in a minimum n value which can be associated with maximum release rate. At medium or high polymer levels, temperature was found to have the most significant effect on determining n. Values of percent theophylline release after 5, 8, and 11 h (P_5, P_8, P_{11}) showed a common behavior upon regression analysis of the data. The first-order terms of coating temperature, and spray nozzle pressure were not significant. However, the polymer amount was significant for the first-order term. On the other hand, among the second-order terms, polymer amount turned out to be the least significant for percent therapeutic release, therefore, indicating the effect of polymer amount on theophylline release was more likely a linear one.

Dissolution efficiency (DE) is a parameter that characterizes the overall dissolution process. However, the significant terms of regression analysis results of DE were in agreement with P_5, P_8, and P_{11} data which represent point estimates for

Fig. 4 SEM picture of high polymer level coated granule (700 × magnification).

TABLE 8

Dissolution efficiency (DE) and t_{50} values (granule size = 1 18–1 40 mm)

Run no.	Dissolution efficiency (%)	t_{50} (h)
1	17.28	16 67
2	21 84	16.14
3	48.78	4.79
4	20 97	14.26
5	28.78	8.89
6	44.28	5 48
7	14.90	15.41
8	31.49	8 60
9	15.99	14 81
10	11.32	22.89
11	32.46	7 74
12	36 58	7.39
13	50 51	4 47
14	39 29	7.07
15	27 20	10 20

the dissolution process. This agreement between DE and percent theophylline release results confirmed that the influences of temperature and spray nozzle pressure on theophylline release were not linear.

TABLE 9

Regression analysis results for measured responses fitted to a second order polynomial model

Parameter	Estimates for measured responses		
	n	t_{50}	DE
R^2	0 8845	0.7600	0.8227
r	0.9404	0.8717	0.9070
I	0.6707 [a]	5.6755 [a]	45.2900 [a]
P	−0.0090	2.5137 [a]	−4 0175 [a]
T	0.1178 [a]	−0.5462	−1.9912
N	−0.0006	−0.1033	−1 3337
$P \cdot T$	0.1210 [a]	2.7308 [a]	−7.5875 [a]
$P \cdot N$	−0.1025 [a]	−0.9450	4 1625 [a]
$T \cdot N$	0.1205 [a]	3 7483 [a]	−5.6100 [a]
P^2	0.0074	0.5376	−3.6850 [a]
T^2	0 1940 [a]	3 1759 [a]	−10.822 [a]
N^2	0.0861 [a]	6.5918 [a]	−15.202 [a]

[a] Term is significant at $\alpha = 0\ 05$ level

I, intercept; P, polymer amount; T, coating temperature; N, spray nozzle pressure; R^2, coefficient of determination, r, correlation coefficient.

TABLE 10

Regression analysis results for measured responses fitted to a second order polynomial model

Parameter	Estimates for measured responses		
	P_5	P_8	P_{11}
R^2	0 8071	0 8287	0.8638
r	0.8983	0.9103	0 9294
I	49.7722 [a]	65 3166 [a]	77 1255 [a]
P	−4.6991 [a]	−6.4116 [a]	−8 4721 [a]
T	−2.7983	−1.8250	0 2441
N	−1.4533	−2.2250	−1 8612
$P\ T$	−8.9225 [a]	−9 9641 [a]	−12.2708 [a]
$P \cdot N$	5.0041 [a]	6 1325 [a]	3 8983 [a]
$T\ N$	−7.0691 [a]	−9.2025 [a]	−9.8008 [a]
P^2	−4.7507 [a]	−5.4221 [a]	−4 8377 [a]
T^2	−12.5673 [a]	−13.4721 [a]	−13 5103 [a]
N^2	−17 2357 [a]	−21.7421 [a]	−24 0044 [a]

[a] Term is significant at $\alpha = 0\ 05$ level

I, intercept; P, polymer amount; T, coating temperature; N, spray nozzle pressure; R^2, coefficient of determination, r, correlation coefficient.

The time required to release 50% theophylline (t_{50}) was best characterized by the polymer amount as a first-order term, whereas for the constituents of t_{50}, n and k, coating temperature was the significant first-order term. For t_{50} the second-order terms of temperature and nozzle pressure were significant.

Optimization

Optimization involves maximizing or minimizing a certain response. In this study optimization was performed with certain constraints. Two- and three-dimensional plots for P_{11} and t_{50} are presented in Figs 5 and 6. As previously mentioned, these plots were used along with the simplex optimization procedure to optimize for 80% or more theophylline release after 11 h.

An evaluation of P_5, P_8, and P_{11} together for the highest theophylline release provided the following results: polymer amount, −1.0 to −0.5; coating temperature, 0.0; and spray nozzle pressure, 0.0. According to the model this combination would give more than 80% theophylline release after 11 h.

According to the simplex optimization procedure, the same would be realized with the pro-

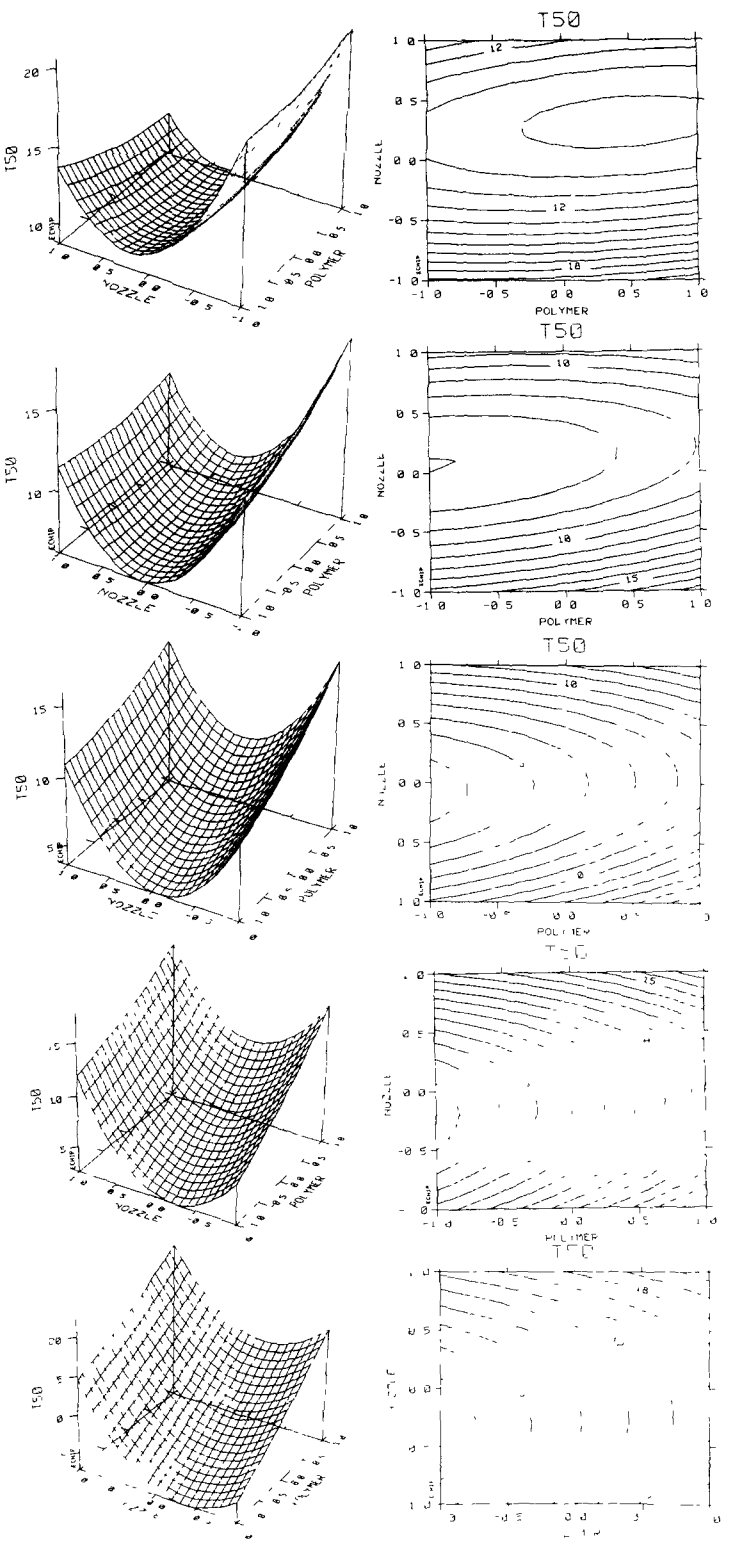

Fig. 5 Two- and three-dimensional plots for time to release 50% theophylline (t_{50}) (effect of coating temperature on t_{50}, temperature increases from top to bottom)

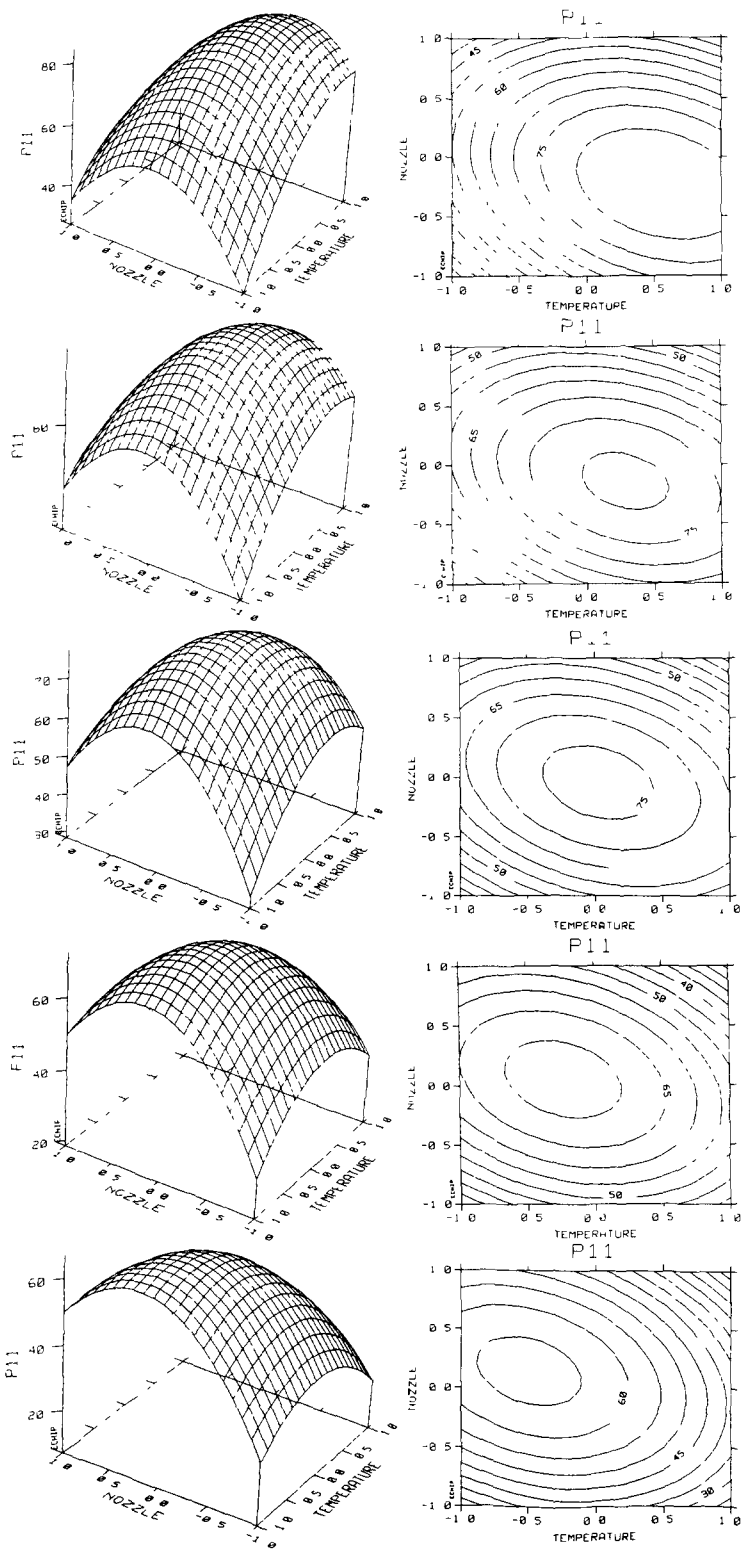

Fig. 6. Two- and three-dimensional plots for percent theophylline release after 11 h (P_{11}) (effect of polymer amount on P_{11}; polymer amount increases from top to bottom).

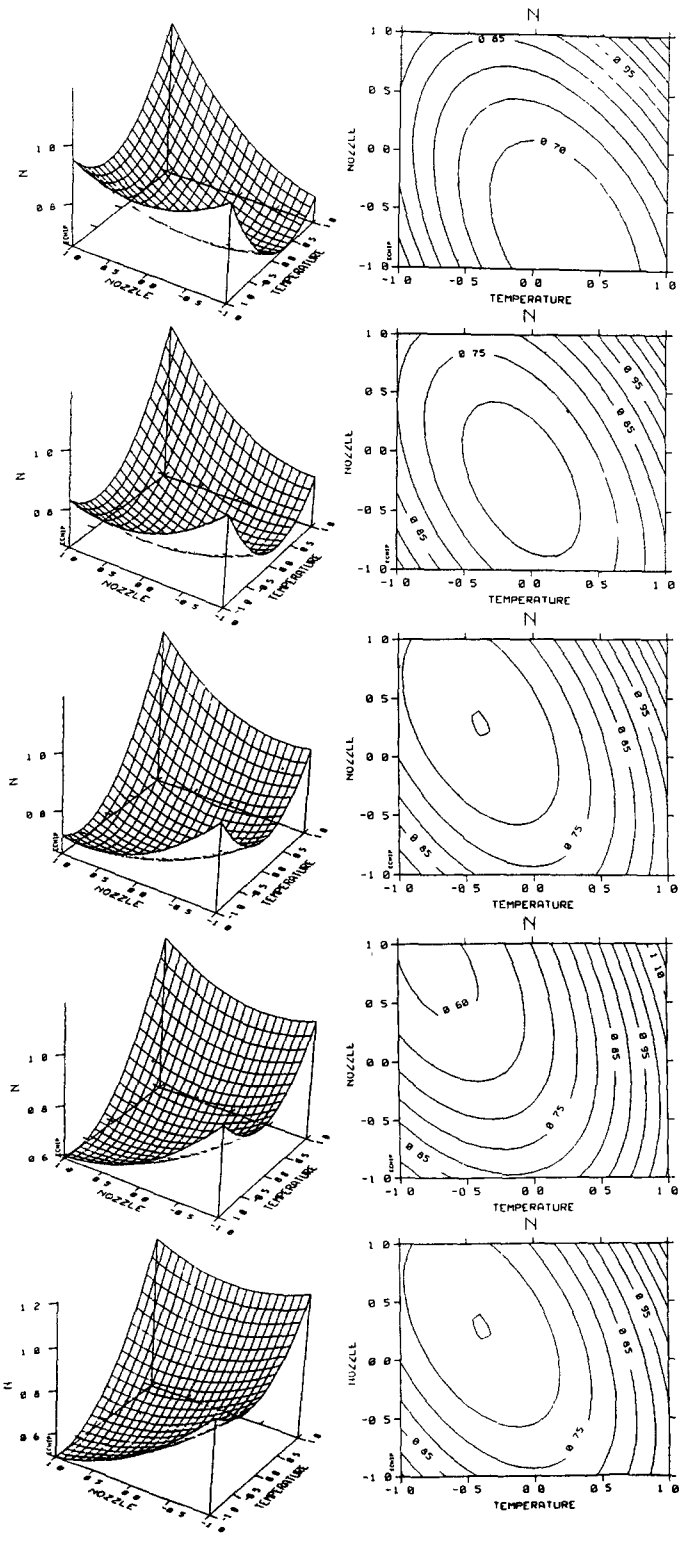

Fig 7. Two- and three-dimensional plots for the percent dissolution-time curve shape factor n (effect of polymer amount on n; polymer amount increases from top to bottom)

jected factor settings of: polymer amount −1.0 (4 mg/cm^2), coating temperature of 0.534 (45°C), and a spray nozzle pressure of −0.233 (1.75 bar). A sieve fraction corresponding to a size between 1.4 and 1.2 mm would have to be used.

The optimized batch was made under the conditions described above and resulted in 91% theophylline release in vitro after 12 h.

Conclusions

The applied experimental plan (Box-Behnken design) has the advantage of performing a small number of experiments, but also the disadvantage of creating an empirical model which is valid only over a certain range of factors.

In this study, the effect of polymer amount on percent theophylline release was found to be linear. It was observed that in the case of the plasticized aqueous polymer dispersion used in the present study, the coating temperature and spray nozzle pressure will have significant effects on percent drug release and the release profile of coated granules. The influences of temperature or nozzle pressure on drug release were not linear.

The design and evaluation of the process in this study resulted in successful product development. The study lends itself to further investigation concerning the application of the proposed empirical model to process transfer.

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