

THE INFLUENCE OF SOME TECHNOLOGICAL PARAMETERS ON TABLET COATING THICKNESS UNIFORMITY

GABRIEL SARAME^T*, DUMITRU LUPULIASA

*University of Medicine and Pharmacy "Carol Davila" Bucharest,
Faculty of Pharmacy, Department of Pharmaceutical Technology and
Biopharmacy*

**corresponding author: gsaramet@gmail.com*

Abstract

This paper describes the study of the influence of some formulation factors on tablet coating thickness uniformity. The coating polymer used was Acryl-EZE[®] from Colorcon. For this purpose, a reduced experimental design, with four variables and three levels was used. The studied variables were: coating dispersion flow rate, coating dispersion concentration, fluid bed temperature and fluid bed airspeed. It was concluded from the results that the most influential factor is the dispersion flow rate, followed by the fluid bed temperature. The experimental data also lead to an optimized formulation, which was tested experimentally and proven to yield a much better coating thickness uniformity.

Rezumat

În această lucrare s-a studiat influența unor factori de formulare asupra uniformității grosimii învelișului unor comprimate filmate. Polimerul de acoperire utilizat a fost Acryl-EZE[®] de la Colorcon. În acest scop, s-a utilizat un plan experimental fracționat, cu patru variabile și trei nivele. Variabilele studiate au fost: debitul de pompare al dispersiei formatoare de film, concentrația dispersiei formatoare de film, temperatura aerului din patul fluidizat și debitul de aer din patul fluidizat. În urma rezultatelor experimentale, s-a ajuns la concluzia că factorul cel mai important este debitul dispersiei formatoare de film, urmat de temperatura aerului din patul fluidizat. De asemenea, s-a obținut o formulare optimizată, care a fost testată experimental și care a condus la o uniformitate superioară a acoperirii.

Keywords: coating uniformity, coating thickness optimization

Introduction

Coating is a common process that is applied to tablets, and it can be performed for a number of reasons, ranging from aesthetics to very utilitarian purposes, such as gastric protection. Especially for those utilitarian purposes, the film uniformity is very important, since the minimum film thickness will determinate the efficiency of the coating.

Since tablets are not spheres, there will be differences in the coating thickness. These differences can be traced to two causes: firstly, because of irregular shape, a jet of coating dispersion will have different chances to reach different parts of the tablet, and secondly, the wet coating has different chances to be removed/modified due to contacts to other

tablets or equipment, according to its position on the tablet. For those reasons, the film thickness tends to be smaller at tablet edges.

Literature references describe some methods of determining the coating thickness: interferometry, spectroscopic methods (NIR - Near-Infrared spectroscopy, FTIR - Fourier transform infrared spectroscopy, Terahertz, X-Ray, fluorescence), Raman and even tomographic methods [1,2]. However, in order to describe local coating thickness, imaging methods appear to be more appropriate [3,4]. The imaging method described in this paper is based on commercially available macro photography equipment.

Like all industrial processes, tablet coating can be optimized. This paper presents the influence of four technological variables on the coating uniformity.

Materials and methods

Materials

Blank tablets (obtained in-house), Colorcon Opadry[®] and Acryl-EZE[®] (courtesy of Biofarm) as coating materials, Caleva Mini Coater/Drier 2 for coating, Mettler precision scales, Canon EOS 500D digital camera with 105mm Sigma Macro lens for imaging (shot at f8), the GIMP graphic package for image analysis, OpenOffice for calculations.

Experimental design

The tablets used were in-house made, with no active ingredient. The dimensions were chosen to be as far from spherical as possible – namely 12mm diameter, 0.4 g tablets, with an average thickness of 2.79 mm. The punches were beveled, causing the tablet faces to be beveled near the edges. For each experimental batch, 10 such tablets were used.

The coating material, Acryl-Eze[®] [5], is a product based on Eudragit L100-55 acrylic polymer, one of the most used coating materials [6,7]. Since both the tablets and the coating material were white, before the coating, an intermediate, colored film of Opadry[®] was applied, in order to facilitate the evaluation of the enteric coating. A fractionate experimental design was elaborated, optimizing the influence of four independent parameters (shown in Table I) on one dependent parameter.

The independent parameters were: coating dispersion flow rate, fluid bed air speed, fluid bed temperature, coating dispersion concentration. The dependent parameter was the coating uniformity, measured as the ratio between edge thickness and face center thickness. The experimental design was based on a four factor/three level Taguchi plan matrix [8]. The

independent factor levels were chosen so they mostly cover the usable range and are shown in Table I. The experimental design plan is shown in Table II. It will be noted that for X1 and X4, instead of using actual flow rates and airspeed, the displayed percentage on the Mini Coater/ Drier was used. This simplifies the decimal point estimations.

Table I
Independent variables

Independent factors	Symbol	Level 1	Level 2	Level 3
Pump flow rate (%) (Acryl-EZE [®] dispersion flow rate)	X1	40	70	100
Acryl-EZE [®] dispersion concentration (%)	X2	8	15	20
Fluid bed temperature (°C)	X3	40	48	55
Fluid bed air fan flow rate (%) (Fluid bed airspeed)	X4	50	70	90

Table II
The matrix of experimental design

Exp No	Symbol	X1	X2	X3	X4
1	N1	40	8	40	50
2	N2	40	15	48	70
3	N3	40	20	55	90
4	N4	70	8	48	90
5	N5	70	15	55	50
6	N6	70	20	40	70
7	N7	100	8	55	70
8	N8	100	15	40	90
9	N9	100	20	48	50

Imaging

After coating, tablets were fractured and the fracture was photographed. On the digital images, the thickness (pixels) of the coating was measured, and homogeneity was calculated. For each tablet, at least four images were captured, each keeping in focus one “corner” of the fractured tablet. For each image, at least two measurements were attempted: on tablet edge and as close to the tablet center the depth of field allowed. In practice, during the fracture, the “corner” where the fracture ended was not in level with the rest of the fracture plane, and the coating usually peeled. Homogeneity (or uniformity) was calculated as the ratio minimum/maximum thickness for each image.

Results and discussion

The average of the approximately 30 measurements for each of the 9 experiments are shown in Table III. Shown numbers are rounded to the fourth decimal, up to where detector sensibility was estimated to be significant.

Table III

Response (coating uniformity, rounded to 4 decimals)

Exp Name	Y
N1	0.7279
N2	0.9248
N3	0.8762
N4	0.9111
N5	0.9327
N6	0.8146
N7	0.8887
N8	0.8577
N9	0.9164
Average	0.8722

Data analysis

Each experiment generated a response. By using the Taguchi technique, the influence of each independent parameter was determined at each of the three levels. The results are shown in Table IV and graphically displayed in Figure 1. Since this technique offered three points of data for each parameter, quadratic functions that pass through these points could be determined and their maximums were calculated. Second-order Response Surface Methodology (RSM) is one of the frequently used techniques in experimental design [9,10], however a central composite design would have generated a much too large number of experiments. Therefore, the second-order RSM was simplified to its core, the quadratic function.

Table IV

Factor influence matrix (rounded to 4 decimals)

Factor	Level	Y
X1	1	0.8430
X1	2	0.8862
X1	3	0.8876
X2	1	0.8426
X2	2	0.9051
X2	3	0.8691
X3	1	0.8000
X3	2	0.9175
X3	3	0.8992
X4	1	0.8590
X4	2	0.8760
X4	3	0.8817

On average, the initial experiments from the experimental plan yielded an uniformity of 0.872 with a maximum of 0.917 and a minimum of 0.728. Based on independent factors' influence on the response, the optimum values were calculated for each independent factor, using the quadratic function. Those values are shown in Table V. The values are also shown rounded to closest integer, since the settings on the coating machine allows only integer numbers. In order to verify this prediction, a final experiment was conducted, using these theoretical optimal values. The result is shown in Table VI.

Table V
Optimum calculated levels

Factor	X value needed to optimize Y	X value needed to optimize Y (rounded to integer)
X1	86.0549	86
X2	14.8208	15
X3	50.3702	50
X4	89.9354	90

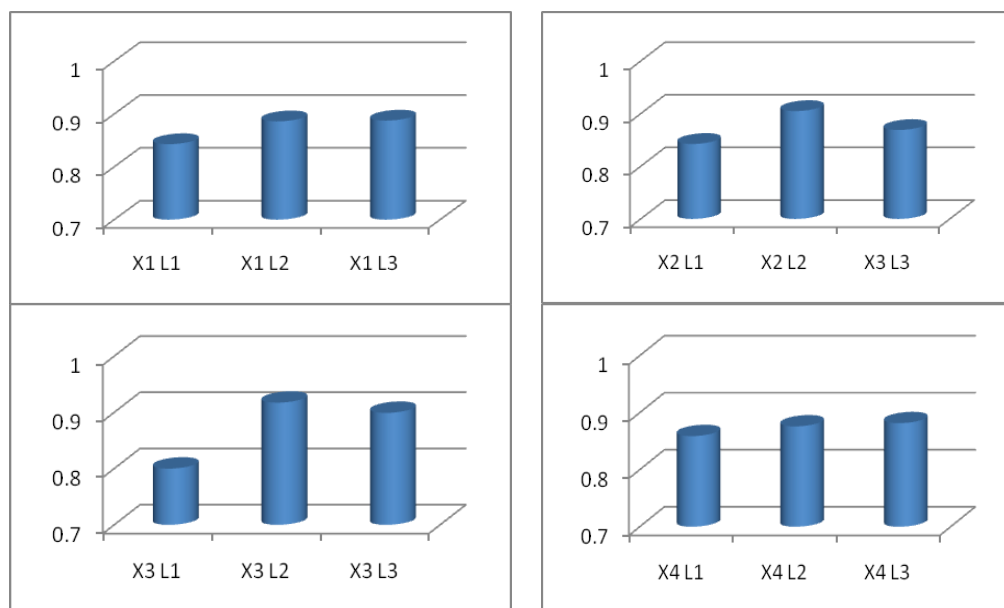


Figure 1

The calculated influences of each factor at each level on the coating uniformity. X (1-4) are factors and L (1-3) are levels, as listed in Table I. Higher uniformity (closer to 1) is better.

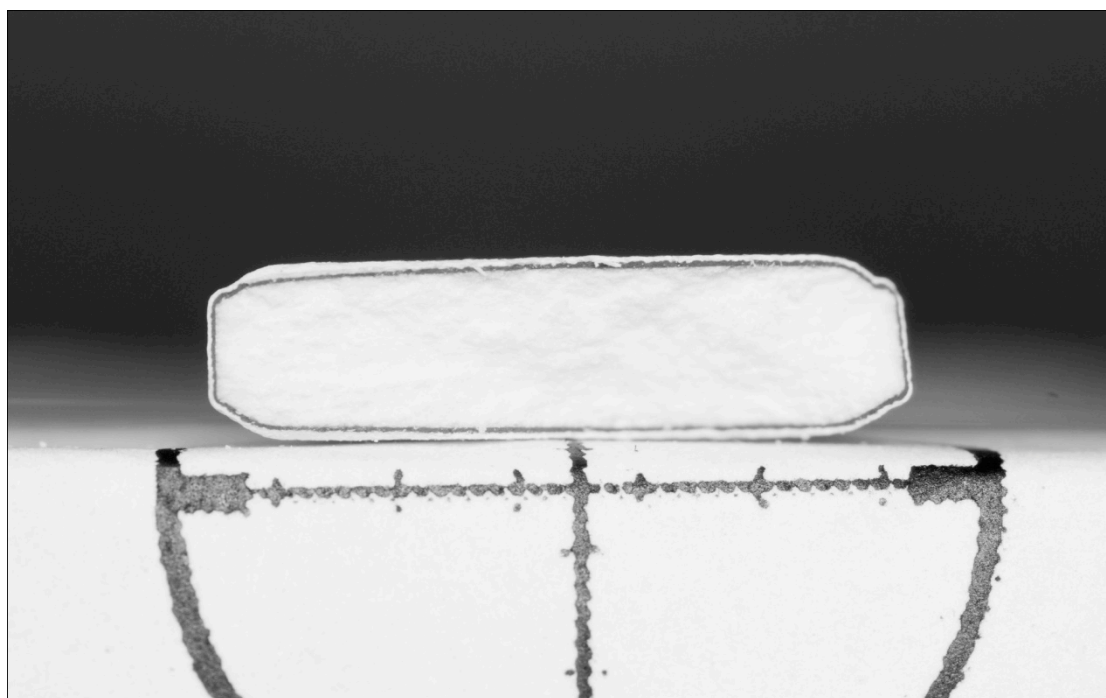


Figure 2

Imaging procedure. Fractured tablets were photographed as close to minimum focusing distance as possible, in order to increase test's sensitivity. Crosshair marker is used to approximately center the tablet and to insure the focusing plane is as parallel as possible to the fracture plane.

Table VI

Final experiment – response (rounded to four decimals)

Exp Name	Y
N10	0.9655

The final experiment yielded an uniformity of 0.965. In order to improve the perception, it is useful to calculate how much the disuniformity was decreased. Starting with an average of 12% it was pushed to about 3%, a four times rate of success. Compared with the best experiment, it decreased from about 8% to 3%, again, almost 3 times.

Imaging resolution. The camera's sensor has a pixel size of 0.0047mm according to the manufacturer data[11]. In other words, the image of a square of 1x1 millimeters is a square of 213/213 pixels. Diagonal measurements could be theoretically more complicated, due to Nyquist limit, but aliasing was not a problem in the measured images. However, this

optical measurement technique allows to measure (and compare) only those parts of the images that are within the depth of field. Since in macro photography depth of field is necessarily very thin, thickness uniformity was considered a much more measurable response parameter than coating thickness itself. Also, due to this very thin depth of field, more sophisticated image analysis techniques [3] are difficult to conduct.

The used combination of RSM and Taguchi design does offer significant advantages, for this particular case, the number of experiments was decreased from 81 (if we consider a full factorial design) or 27 (principal component analysis design – centered faces) to 9 experiments. On the other hand, this simpler combination does not easily allow one to make predictions concerning the response of the optimization process, but only on the independent factors values.

However, since by this technique, the heterogeneity of the coating was reduced in average four times, down to about 3% and a certain heterogeneity is inherent to the coating process, the experimental procedure can be considered successful.

Conclusions

Based on the combination of RSM and Taguchi, an experimental plan was drafted in order to optimize the coating thickness on pharmaceutical tablets. Four independent factors at three levels were considered. All four factors influence the coating uniformity, the most influential being the pump flow rate and the drying temperature. The quality of the coating was improved about four times, on average, compared to starting conditions.

Acknowledgments

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References

1. Sovany T., Nikowitz K., Regdon G. Jr., Kasa P., Pintye-Hodi K., Raman spectroscopic investigation of film thickness, *Polym. Test.* 2009, 28, 770-772
2. Sasic S., Determining the coating thickness of tablets by chiseling and image analysis, *Int. J. Pharm.* 2010, 397, 109-115
3. Garcia-Munoz S., Gierer D. S., Coating uniformity assessment for colored immediate release tablets using multivariate image analysis, *Int. J. Pharm.* 2010, 395, 104-113
4. Mozina M., Tomazevic D., Leben S., Pernus F., Likar B., Digital imaging as a process analytical technology tool for fluid-bed pellet coating process, *Eur. J. Pharm. Sci.* 2010, 41, 156-162
5. https://www.colorcon.com/literature/marketing/mr/Delayed%20Release/Acryl-EZE/English/pi_acryleze_prod_inf_v3_06_2009.pdf

6. Leucuta S. Tehnologie farmaceutica industriala, Editura Dacia, Cluj-Napoca, 2001, 312-322
7. Popovici I., Lupuleasa D. *et al*, Tehnologie Farmaceutică vol 3, Editura Polirom, Iași, 2009, 563-567
8. Alexis J., Metoda Taguchi În Practica Industrială – Planuri de experiențe,, Editura Tehnică București, 2009, 11-30, 143
9. Bradley N, The Response Surface Methodology, master of science thesis, Indiana University of South Bend, 2007
10. Gabrielsson J., Lindberg N-O., Lundstedt T., Multivariate methods in pharmaceutical applications, *J. Chemometr.* 2002, 16, 141-160
11. http://www.canon.co.uk/for_home/product_finder/cameras/digital_slr/EOS_500D/index.aspx?specs=1
12. Stanescu A., Ochiuz L., Cojocaru I., Popovici I., Lupuleasa D., The influence of different polymers on the pharmaco-technological characteristics of propiconazole nitrate bioadhesive oromucosal tablets, *Farmacia*, 2010, 58(3), 279-289
13. Tomuta I., Vlase L., Popa A., Leucuta S.E., *In vitro – in vivo* evaluation of a novel drug delivery system for colonic targeting, *Farmacia*, 2010, 58(3), 368-377
14. Popescu M.L., Dinu M., Toth O., Contributions to the pharmacognostical and phytobiological study on *Leonorus cardiaca* L. (*Lamiaceae*), *Farmacia*, 2009, 57(4), 424-431.

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