Latin American Journal of Pharmacy
(formerly *Acta Farmacéutica Bonaerense)*
Lat. Am. J. Pharm. **27** (1): 62-7 (2008)

Trabajos originales

Recibido el 30 de noviembre de 2007
Aceptado el 16 de diciembre de 2007

Optimization of a Meprobamate Fast Released Tablet Formulation Using Mixture Design

Mirna FERNÁNDEZ CERVERA [1]*, Yamila Lisandra MARÍN [1],
Eutimio G. FERNÁNDEZ [2], Irela PÉREZ SÁNCHEZ [1] & Bárbara JIMÉNEZ CUELLAR [3]

[1] *Institute of Pharmacy and Food, University of Havana. Street 23 No. 21425 be/ 214 and 222, La Coronela, La Lisa. Havana City, Cuba*

[2] *Inorganic Chemistry Department. Center for Engineering and Chemical Researches. F Street, # 115 be/ Ave 5th and Calzada. Havana 10400. Cuba*

[3] *Novatec Laboratories. Playa. Havana City, Cuba.*

SUMMARY. At present, meprobamate is not a drug with a broad commercial spectrum. In order to get an optimal pharmaceutical formulation for this kind of drug or others more competitive, experimental design methodology is a statistical tool very useful for reach them. The principal aim of this work was to apply D-Optimal mixture design for optimization of meprobamate (400 mg) fast released tablets manufactured by wet granulation. The excipients included in this study were maize starch (filler), Kollidom K25 (binder), sodium lauryl sulfate (surfactant) and Acdisol (disintegrant). Different granulate and tablet properties were modeled as functions of the four ingredient percentages. The optimization criteria for this medicament were a maximum percentage of drug dissolution and a high granulate flowability. The proportions of the optimal mixture were 10.4% maize starch, 6.0% Kollidon K25, 1.02% sodium lauryl sulfate, and 5.0% Acdisol.

RESUMEN. "Optimización de tabletas de liberación rápida de meprobamato usando diseños con mezclas". Actualmente, el meprobamato no es un fármaco de amplio espectro comercial. Con el objetivo de obtener una formulación farmacéutica óptima para este fármaco u otros más competitivos, la metodología de diseños experimentales es una herramienta estadística muy útil para lograrlo. El propósito principal de este trabajo fue aplicar un diseño con mezcla D-Optimal para la optimización de tabletas de liberación rápida de meprobamato (400 mg), elaboradas por granulación húmeda. Los excipientes incluidos en este estudio fueron: almidón de maiz (relleno), Kollidom K25 (aglutinante), lauril sulfato de sodio (surfactante) y Acdisol (desintegrante). Diferentes propiedades de los granulados y las tabletas fueron modeladas en función de los porcentajes de los cuatro ingredientes. Los criterios de optimización para esta formulación farmacéutica fueron una máxima disolución del fármaco y una alta fluidez del granulado. Las proporciones de la mezcla óptima fueron: almidón de maíz, 10,4%; Kollidon K25, 6,0%; lauril sulfato de sodio, 1,02% y Acdisol, 5,0%.

INTRODUCTION

Meprobamate is a propanediol dicarbamate that has been in extensive clinical use in the late 1950s and 1960s as an anxiolytic drug [1]. Though the use of this drug was mostly uncontrolled, it seems that very few serious side effects have occurred [2,3]. Lately, meprobamate has been replaced by the benzodiazepines [1] but it is still very used in some countries like France [4] as anxiolytic agent and in Cuba as muscle relaxant.

Oral suspension and tablets are the principal commercially forms of this drug [5]. Solid oral dosages offer convenience, physical and chemical stability, ease of product handling, high throughput, and low manufacturing costs [6]. These reasons could justify the exclusive presence of meprobamate as tablet in pharmaceutical Cuban market.

A large number of factors, such as the chemical-physical properties of raw materials (both drug and excipients), the composition and component's relative amounts in the formulations, as well as the manufacturing process parameters, can influence on the drug release behavior [7] and

KEY WORDS: *D*-optimal mixture design, Drug dissolution, Fast release tablets, Meprobamate, Optimization of tablet formulation.
PALABRAS CLAVE: Diseño con mezcla *D*-Optimal, Disolución de drogas, Meprobamato, Optimización de la formulación de tabletas.

* Author to whom correspondence should be addressed. *E-mail:* mirnafc@yahoo.com

ISSN 0326-2383

the rest of quality markers from the pharmaceutical products [8].

Statistical experimental design methodologies are powerful, efficient and systematic tools in the design of pharmaceutical dosage forms [9]. Specifically mixture design is a tool that has been used for percentage excipient optimization in extended release [10-12] and fast-release [8,13] tablets. Nowadays the publication numbers where this kind of design has been applied could be considered poor taking into consideration its utility in pharmaceutical technology [8,14].

The purposes of the present paper were to evaluate, by means of D-optimal mixture design, the influence of four excipients on quality control parameters of granulates and meprobamate (400 mg) tablets, and to optimize the product for improving granulate flowability and drug in vitro dissolution using a numerical procedure.

MATERIALS AND METHODS

Materials

The following reagents were used: meprobamate (Xinan, China), maize starch (Roquette, Italia), polyvinylpyrrolidone (Kollidon K25) (Basf, Alemania), sodium lauryl sulfate (Basf, Alemania), sodium croscarmellosa (Acdisol) (Blanver, Brasil). All other chemical and solvents were of analytical reagent grade.

Preparation of meprobamate tablets

The evaluated components and their studied range in meprobamate tablets formulations are listed in Table 1. The mixtures of active ingredient and excipients were prepared according to the 20-run D-optimal mixture design. The drug and additives were mixed in a tubular mixer by 20 min. The total amount of the mixture was kept constant, and the relative amounts of the different excipients varied according to the mixture design. Wet massing and drying of meprobamate granules was performed using a fluidized bed drier Glatt® model GPCG (Germany). The wet masses were dried for 15 min at 55 °C, and then blended with of magnesium stearate (Degussa, Belgium) and colloidal silicon dioxide (Aerosil) (Degussa, Belgium). Each tablet of 600 mg containing 400 mg meprobamate was compressed using a single punch tabletting machine (Kilian, model KS) (Germany) using flat-faced, beveled punches of 12.7 mm diameter. The hardness of the tablets was fixed at 8 kgf/Monsanto.

Components	Proportion restrictions (% w/w)
x_1 maize starch	$9.50 \leq x_1 \leq 14.50$
x_2 Kollidon K25	$3.00 \leq x_2 \leq 6.00$
x_3 sodium lauryl sulphate	$0.00 \leq x_3 \leq 2.00$
x_4 Acdisol	$5.00 \leq x_4 \leq 10.00$

Table 1. Variables in the mixture design and their restrictions.

Determination of the granulate properties

The particle size characterization was performed by applying a shaking sieve with a set of sieves consisting of sieves with 1250, 800, 630, 450, 250, 125 µm apertures.

For the determination of bulk and tap densities, an appropriate amount of the sample was poured in a 100 mL tared graduated cylinder. The volume was then read directly from the cylinder and used to calculate the bulk density according to the mass/volume ratio. For tap density the cylinder was tapped 1000 times using a tap density analyzer (Erweka SVM1, Germany).

The granulate flow rate was measured by a glass funnel with a round orifice of 120 mm, its outlet is separated 100 mm respect to a horizontal surface, and with a wall angle of 45 degrees [15].

Determination of the physical-mechanical properties of meprobamate tablets

The percentages of friability and the resistance to abrasion were examined by using a Pharma Test, model TTSR-A (Germany) friabilator and Pharma Test, model TTSR-A (Germany) abrasion tester. Tablet height was measured with 0-1 inch Ultra-Micrometer Fowler (USA). The disintegration time in seconds was determined by using a SOTAX-typeDT2 (Switzerland) apparatus. Deionized water at 37±1 °C was used as immersion medium. All measurements were made in triplicate.

Determination of in vitro dissolution of meprobamate tablets

The USP basket method was used for all the in vitro dissolution studies by using a Pharma Test, model PTW S3C (Germany) dissolution tester. The deionized water was used as dissolution medium. The rate of stirring was 100rpm. The meprobamate tablets were placed in 900 mL of deionized water for 30 minutes. Six tablets of each formulation were determined. The mean and standard deviation of dissolved drug were calculated. The amounts of model substance released from tablets were analyzed

using a HPLC Knauer (Germany) like is described in USP method [5].

Data analysis

All the responses for granulates and tablets were treated by Design –Expert Version 6.0.1 (Stat-Ease, Inc., Minneapolis, USA) software. The numbers of experimental points in the D-Optimal Design were enough to adjust up special cubic models for the evaluated responses. The best fitting mathematical models related with the evaluated components to each response was selected based on the comparisons of the predicted residual sum of square (PRESS) and the desirability function was used for optimizing meprobamate tablets formulation, proved by Design-Expert software.

RESULTS AND DISCUSSION

Different models for granulates and meprobamate tablet properties were obtained based on the experimental design (Tables 2 and 3).

One of the most important limitations of this drug to elaborate tablet dosage forms is its low flowability (response angle and flow rate could not be quantified because the drug no flowed, Carr Index value was 29.4 %). The high dose and the poor flow properties of this pharmaceutical active substance conduced to use wet granulation as elaboration method for meprobamate tablets.The models to describe tapped and bulk densities for granulates were independent of the excipient proportions included in the experimental plan. The percentage of compressibility, like indirect measure of the flowability, [8] was not necessary to calculate it. The flow rate, a direct parameter to characterize powder and granulate flowabilty, was experimentally determined and showed a linear relation with the studied component proportions. In order to improve the predictive capacity of the mathematical model was required to transform the values for this response. The equation [**1**] as a Scheffé's polynomial model was:

$$Ln(Flow\ velocity + 50) = 0.17133 \cdot x_1 + 0.20964 \cdot x_2 + 0.17778 \cdot x_3 + 0.16656 \cdot x_4 \quad [\mathbf{1}]$$

The authentic influence of the ingredient proportion is better visualized by means of trace graph (Fig. 1), it is the graphical mode of the Cox model for mixture problems. This kind of model is useful when mixture region is irregular [16] like in this case.

The most marked influence corresponds to Kollidon K25 proportion. The results showed that the flowability of granulates increases with increasing percentage of Kollidon K25 in the

Run	Variable factors				Results			
	X1	X2	X3	X4	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Flow rate (g/cm^2s)	Mean size (µm)
1	9.50	6.00	0.00	7.00	0.42	0.61	0.00	282.74
2	9.50	3.00	0.00	10.00	0.42	0.60	0.00	249.16
3	9.50	3.00	2.00	8.00	0.41	0.50	6.12	220.16
4	9.50	3.00	2.00	8.00	0.43	0.61	0.00	229.15
5	14.50	3.00	0.00	5.00	0.43	0.57	0.00	281.40
6	9.50	3.00	0.00	10.00	0.43	0.54	0.00	247.54
7	11.25	4.50	0.00	6.75	0.37	0.56	7.90	310.91
8	9.50	6.00	2.00	5.00	0.41	0.54	6.94	276.53
9	14.50	3.00	0.00	5.00	0.43	0.58	0.00	319.23
10	10.50	4.00	2.00	6.00	0.41	0.61	0.00	282.35
11	12.71	3.64	0.43	5.71	0.41	0.55	5.70	236.25
12	9.50	4.50	0.00	8.50	0.42	0.58	5.30	239.76
13	12.50	3.00	2.00	5.00	0.43	0.58	4.80	256.07
14	9.50	4.50	1.00	7.50	0.42	0.58	5.30	259.92
15	9.50	6.00	2.00	5.00	0.44	0.62	7.37	302.77
16	12.50	3.00	2.00	5.00	0.44	0.62	0.00	286.68
17	12.00	4.50	1.00	5.00	0.43	0.58	7.96	275.13
18	9.50	6.00	1.00	6.00	0.44	0.60	13.70	283.60
19	12.00	3.00	0.00	7.50	0.44	0.60	0.00	234.26
20	11.50	6.00	0.00	5.00	0.48	0.60	10.60	284.28

Table 2. Experimental matrix for the D-Optimal design and granulate properties results.

Run	Results				
	Height (mm)	Abrasivity (%)	Dissolution (%)	Disintegration time (s)	Friability (%)
1	4.3	0.18	98.54	159	0.25
2	4.3	0.33	98.55	240	0.36
3	4.5	0.13	95.80	240	0.36
4	4.4	0.19	98.99	186	0.38
5	4.4	0.20	97.21	121	0.33
6	4.4	0.16	99.70	110	0.31
7	4.3	0.16	93.91	186	0.32
8	4.3	0.09	92.57	460	0.18
9	4.3	0.19	85.91	288	0.25
10	4.5	0.15	71.31	127	0.29
11	4.5	0.10	100.57	103	0.21
12	4.5	0.09	95.87	109	0.45
13	4.5	0.27	97.22	226	0.22
14	4.4	0.16	97.52	250	0.29
15	4.7	0.43	98.23	306	1.24
16	4.5	0.37	97.93	59	1.33
17	4.5	0.11	95.64	213	0.30
18	4.6	0.02	95.65	282	0.45
19	4.5	0.24	97.03	38	3.22
20	4.6	0.13	97.15	262	0.21

Table 3. Experimental runs for the D-Optimal design and tablet properties results.

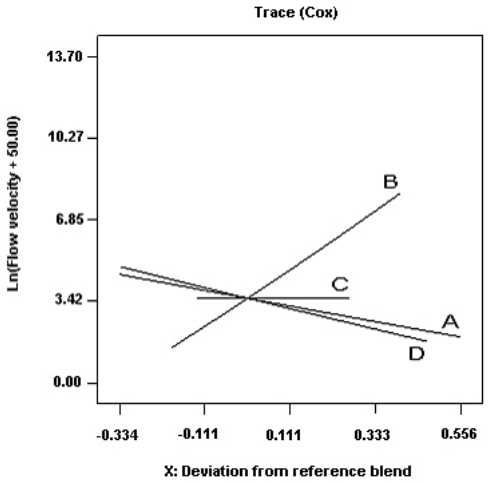

Figure 1. Cox trace graph for visualization of ingredient proportion influence on the granulate flow rate. **A**: Maize starch. **B**: Kolidon K25. **C**: Sodium lauryl sulphate. **D**: Acdisol.

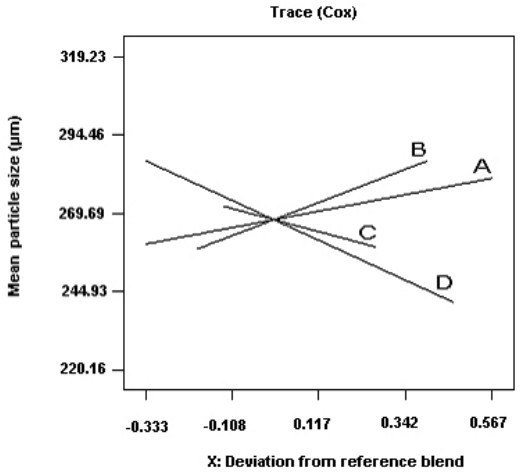

Figure 2. Cox trace graph for visualization of ingredient proportion influence on the mean granulate size. **A**: Maize starch. **B**: Kolidon K25. **C**: Sodium lauryl sulphate. **D**: Acdisol.

mixtures. Contrary effects are showed for Acdisol and maize starch but less marked than the binder agent. On the other hand, sodium lauryl sulfate did not affect the flow rate.

In most cases the expected relation between mean particle size and flow rate is direct. Fine particles usually have a high surface to mass ratio, are most cohesive. However, when particle size increases, then particles are generally relative free flowing [17]. Nevertheless granulates contain multitude of different interacting surface and consequently flow properties take place in the complex manner [18]. As seen in Fig. 2 the augment of percentage of binder and filler increase the mean particle size but disintegrant and surfactant showed opposite effects.

The mathematical equation for average particle size [**2**] was linear too:

$$Average\ particle\ size = 14.22995 \cdot x_1 + 19.56984 \cdot x_2 + 5.58781 \cdot x_3 + 4.02663 \cdot x_4 \quad [2]$$

Maize starch had an undesired effect on the flow rate when its percent increase in the mixtures (Table 2). This behavior explains the non direct relation between flow rate and mean granule size in our case.

Physical and chemical parameters of meprobamate tablets were independent of the four ingredient percentage, except for in vitro dissolution. Table 4 illustrates the values of probability for two important statistical indicators which define the satisfactory adjust of the model to the experimental data. The probabilities values for model signification test and lack of fit test over than 0.05 indicate a behavior around a central value, which is independent of excipient percentages for the height, friability, disintegration time and abrasivity.

Dependent Variable	Signification model test (p value)	Lack of fit (p value)
Height	0.2348	0.8323
Friability	0.9081	0.1161
Abrasivity	0.5377	0.8312
Disintegration time	0.0575	0.7484

Table 4. Probability (p) values for signification model tests and lack of fit tests. Dependent Variables for meprobamate tablets: Height, Friability, Abrasivity and disintegration time. These p values belong to the best adjusted model for each variable (linear).

The best model for drug dissolution *(D)* was special cubic and Equation [**3**] is the mathematical expression without non significant interactions.

$$D = 3.37638 \cdot x_1 + 10.81077 \cdot x_2 - 676.46409 \cdot x_3 + 5.95134 \cdot x_4 - 0.27461 \cdot x_1 \cdot x_2 + 38.45456 \cdot x_1 \cdot x_3 + 0.031106 \cdot x_1 \cdot x_4 + 103.52535 \cdot x_2 \cdot x_3 - 0.66051 \cdot x_2 \cdot x_4 + 38.53288 \cdot x_3 \cdot x_4 - 5.94612 \cdot x_2 \cdot x_3 \cdot x_4 \quad [3]$$

The particular influence of each analyzed component is shown in Figure 3. The disintegrant (Acdisol) and filler (maize starch) showed a direct relation with this property. However, binder and surfactant influences changed through their evaluated ranges. The best dissolution values are achieved with high values of the Acdisol, Maize starch and low values of Kollidon K25. For this formulation the better results for dissolution are obtained in middle of the range for sodium lauryl sulfate (close 1.00 %).

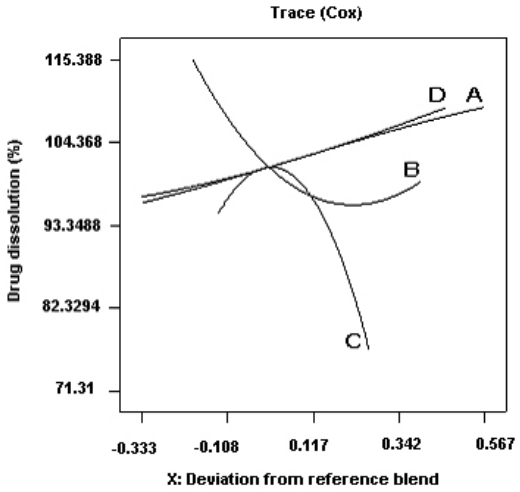

Figure 3. Cox trace graph for visualization of ingredient proportion influence on drug dissolution percent. **A**: Maize starch. **B**: Kolidon K25. **C**: Sodium lauryl sulphate. **D**: Acdisol.

For optimization of this oral dosage form was used a numerical method based on desirability function, this method takes into consideration some criteria for different variables in only one mathematical equation. The relative importance among the interest variables is defined employing an importance scale from 1 to 5. In this case the formulation was optimized as is point up in Table 5. The most important goals were to assurance a higher dissolution and at the same time a satisfactory flowability. The last variable is important in order to guarantee dose uniformity.

Dependent Variable	Optimization criteria	Importance values
Flow rate	Is maximum	4
Drug dissolution percent	Is maximum	5

Table 5. Optimization criteria and importance values for flow rate and drug dissolution percent.

On the basis of the present results, the proportions that satisfied the optimization criteria are: maize starch, 10.4%; Kollidon K25, 6.00%; sodium lauryl sulfate, 1.02% and acdisol, 5.0% (Fig. 4).

In order to verify the critical value of the percent of drug dissolution for the optimal mixture was carried out experimentally six repetitions of the optimal formulation. The predicted (100.099%) and observed (98.46 ± 2.43) results % for the optimized tablet formulation showed no significant difference (t-test, p = 0.159415 >

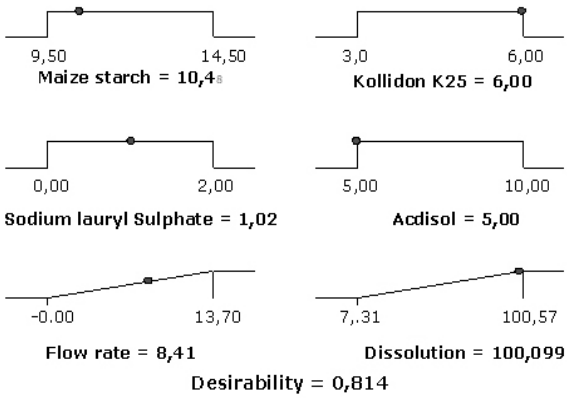

Figure 4. Ramp's graph for optimal tablet formulation.

0.05) and the predicted error was 1.64%, indicating that *D*-Optimal mixture design was quite useful for optimizing meprobamate fast-release tablets. This formulation also met all the rest official pharmaceutical specifications [5].

CONCLUSIONS

An optimized formulation of meprobamate tablet (400 mg) by wet granulation was found. D-Optimal mixture design was employed to get the best combination of excipient percentages in this solid dosage form which showed good flowability and high dissolution of drug.

Acknowledgments. This study was possible thanks to financial support from Novatec Laboratories and Biel Bermúdez's assistance in manuscript elaboration. Relma Tavares de Oliveira is greatly acknowledged for her inspiration.

REFERENCES

1. Frey, H. & I. Bartels (1997) *Epilepsy Res*. **27**: 151-64.
2. Meyler, L. & A. Herxheimer (1968) *Side effects of drugs,* Vol. VI, Exerpta Medica, Amsterdam.
3. Rall, T.W. (1990) *"Hypnotics and sedatives: ethanol"* In "The Pharmacological Basis of Therapeutics" (A. Goodman Gilman, T.W. Rall, A.S. Nies & P. Taylor, eds.), 8th Edn., Pergamon Press, New York, págs. 345-82.
4. Lavit, M., S. Saivin & G. Houin (2000) *Rev. Fr. Laborat*. **322**: 61-3.
5. USP 27 (2004) *Meprobamate Oral Suspension. Meprobamate Tablets.* The United States Pharmacopoeial Convention Inc., pág. 1167.
6. Zhang, G.G.Z., D. Lawa, E.A. Schmittb & Y.Qiu (2004) *Adv. Drug Deliv. Rev.* **56**: 371-90.
7. Furlanetto, S., M. Cirri, F. Maestrelli, G. Corti &P. Mura (2006) *Eur. J. Pharm. Biopharm.* **62**: 77-84.
8. Martinello, T., T.M. Kaneko, M.V. Robles Velasco, M.E. Santos Taqueda & V.O. Consiglieri (2006) *Int. J. Pharm*. **322**: 87-95.
9. Gabrielsson, J., N.O. Lindberg & T. Lundstedt (2002) *J. Chemometr*. **16**: 141-60.
10. Bodea, A. & S.E. Leucuta (1997) *Int. J. Pharm*. **153**: 247-55
11. Huang, Y.-B., Tsai, Y.-H., Lee, S.-H., Chang, J.-S. & Wu, P.-C. (2005) *Int. J. Pharm*. **289**: 87–95
12. Huang, Y.-B., Y.-H.Tsai, S.-H. Lee, J.-S. Chang & P.-C. Wu (2005) *Int. J. Pharm*. **289**: 87-95.
13. Perissutti, B., F. Rubessa, M. Moneghini & D.Voinovich (2003) *Int. J. Pharm*. **256**: 53-63.
14. Cafaggi, S., R. Leardi, B. Parodi, G. Caviglioli &G. Bignardi (2003) *Chemometr. Intell. Lab. Syst*. **65**: 139-47.
15. Iraizoz, A., O. Bilbao & M.A. Barrios (1990) *"Conferencias de Tecnología Farmacéutica II"*. Facultad de Farmacia y Alimentos. Departamento de Tecnología y Control de Medicamentos. Universidad de La Habana, ENPES, Ciudad Habana, págs. 170-181.
16. Eriksson, L., E. Johansson & C. Wikström (1998) *Chemometr. Intell. Lab. Syst*. **43**: 1-24.
17. Antikainen, O. (2003) "New methods to evaluate applicability of powders and granules for tablet compression". Pharmaceutical Technology Division. Department of Pharmacy. Universityof Helsinki. Finland, págs. 3-4
18. York, P. (1980) *Int. J. Pharm* **6**: 89-117