

## ARTÍCULOS ORIGINALES

**Technological development and stability study of meprobamate immediate released tablets****Desarrollo tecnológico y estudio de estabilidad de tabletas de liberación inmediata de meprobamato**

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**ABSTRACT**

The behavior of different technological variants of fast release tablets of Meprobamato (400 mg) obtained by wet granulation. The desintegration time and the percentage of the dissolved drug showed a significant dependence of the sodium lauryl sulfate /sodium croscarmellose ratios present in formulae. The physical and chemical properties of tablets were assessed during 6 months (accelerated stability and dring 24 months (useful life), respectively. From the formulae selected it was possible to obtain granulates and tablets with organoleptic, physicommechanical and technological properties, demonstrating the feasibility of the process of fabrication of this product. Results showed the good stability in the immediate release of Meprobamato tablets selected. The in vitro dissolution hasn't significant differences, thus, neither the time elapsed nor the composition of formula influenced on the percentages of dissolved drug. The assessment demonstrated significant differences, however, assessed formulae fulfilled with official pharmaceutical specifications during 24 months.

**Key words:** Meprobamate, stability study, fast release tablets, drug dissolution.

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## RESUMEN

Se estudió el comportamiento de diferentes variantes tecnológicas de tabletas de liberación inmediata de meprobamato (400 mg), obtenidas por granulación húmeda. El tiempo de desintegración y el porcentaje de fármaco disuelto mostraron dependencia significativa con las proporciones del lauril sulfato de sodio/croscarmelosa sódica en las formulaciones. Se evaluaron las propiedades físicas y químicas de las tabletas durante 6 meses (estabilidad acelerada) y 24 meses (de vida útil), respectivamente. Se obtuvieron a partir de las formulaciones seleccionadas granulados y tabletas con propiedades organolépticas, físico-mecánicas y tecnológicas satisfactorias, lo que indicó la factibilidad del proceso de fabricación de este producto. Los resultados demostraron la buena estabilidad de las formulaciones de tabletas de liberación inmediata de meprobamato seleccionadas. La disolución *in vitro* no mostró diferencias significativas, por lo que ni el tiempo transcurrido ni la composición de la formulación influyeron sobre los porcentajes del fármaco disuelto. La valoración mostró diferencias significativas, sin embargo, las formulaciones evaluadas cumplieron con las especificaciones farmacéuticas oficiales durante 24 meses.

**Palabras clave:** Meprobamato, estudio de estabilidad, tabletas de liberación rápida, disolución de fármaco.

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## INTRODUCTION

Careful selection of the excipients, components of all pharmaceutical products, is essential for the development of stable and effective dosage forms.<sup>1,2</sup> For an efficient development of stable formulations a two-step procedure should be recommended. First, design and optimization of pharmaceutical formulation with appropriate technological properties and minimum trials. For that purpose statistical methods have been widely used.<sup>3</sup> Then, further studies on complete model formulation with selected excipients should be conducted to verify the actual stability of the drug in the final dosage form and identify the most suitable composition in order to maximize drug stability.<sup>4,5</sup>

Stability parameters are useful for drug formulation and storage conditions, good practical decisions have to be made on the basis of the most important parameters like drug dissolution to solid dosage forms.

Nowadays, meprobamate is not a drug with a broad commercial spectrum. Lately, meprobamate has been replaced by the benzodiazepines<sup>6</sup> but it is still very used in some countries like Cuba as muscle relaxant.

In our first work<sup>7</sup> was applied a D-Optimal mixture design for optimization of meprobamate immediate released tablet formulations, elaborated by wet granulation. The excipients included in that study were maize starch (filler), Kollidom K25<sup>®</sup>; (binder), sodium lauryl sulfate (surfactant) and Accisol<sup>®</sup>; (disintegrant). Different granulate and tablet properties were modeled as functions

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of those four ingredient percentages. The optimization criteria for this medicament were a maximum percentage of drug dissolution and a high granulate flowability. On the basis of those results, an optimized formulation of meprobamate tablet (400 mg) was found.

The purpose of the present paper was to verify the behavior of different technological assays of meprobamate (400 mg) immediate released tablets and stability study, during 24 months, of the selected formulations.

## METHODS

### Materials

For the purposes of this study, commonly used excipients were chosen: maize starch (Roquette, Italia), polyvinylpyrrolidone (Kollidon K25<sup>®</sup>; ) (BASF, Alemania), sodium lauryl sulphate (BASF, Alemania) and sodium croscarmellose (Acdisol<sup>®</sup>) (Blanver, Brasil). The active pharmaceutical ingredient was Meprobamate (Xinan, China). All other chemical and solvents were of analytical reagent grade. Distilled water was used in the preparations.

### Preparation of meprobamate tablets

On the basis of previous results, three batches (B1, B2 and B3) of the optimized tablet formulation were elaborated. Besides, of other two formulations, F18 and F20 (one batch), were included in the present study. The composition of the meprobamate tablets formulations is listed in Table 1. The tablets were prepared as described previously.<sup>7</sup> Wet massing and drying of meprobamate granules was performed using a fluidized bed drier Glatt<sup>®</sup>; model GPCG (Germany). Each tablet of 600 mg containing 400 mg meprobamate was compressed on a rotary tablet machine (Killian, model TX 40 AM, Germany) using flat-faced, beveled punches of 12,7 mm diameter at a speed of 110 tablet/min. The hardness of the tablets was fixed at  $8 \pm 1$  Kgf/Monsanto and the height at  $4.5 \text{ mm} \pm 5 \%$ .

**Table 1.** Composition of the selected meprobamate tablets formulations

Components (% w/w)	Optimized formulation (B1, B2, B3)*	F18	F20
Maize starch	10.48	9.50	11.50
Kollidon K25	6.00	6.00	6.00
Sodium lauryl sulphate	1.02	1.00	0.00
Acdisol	5.00	6.00	5.00

\*B: batch.

### **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  $\mu\text{m}$  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 1 000 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.<sup>8</sup>

### **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  $37 \pm 1$  °C was used as immersion medium. All measurements were made in triplicate.

### **Determination of in vitro dissolution of meprobamate tablets**

The U.S.P basket method was used for all the in vitro dissolution studies by using a PHARMA TEST, model PTW S3C (Germany) dissolutor. The deionized water was used as dissolution medium. The rate of stirring was 100 rpm. The meprobamate tablets were placed in 900 mL of deionized water for 30 minutes. Six tablets of each formulation were determined. The mean and S.D of dissolved meprobamate were calculated. The amounts of model substance released from tablets were analyzed and identified using a HPLC KNAUER (Germany) like is described in U.S.P method.<sup>9</sup>

### **Assay**

The amount of model substance in tablets was analyzed employing chromatographic technique using a HPLC KNAUER (Germany) like is described in U.S.P method<sup>9</sup>. The samples were chromatographed on reverse phase L1 (C18) (25 x 4.6 mm, 5  $\mu\text{m}$  particle size) column (Phenomenex, USA). All chromatographic runs were performed using water and acetonitrile (70/30) as the mobile phase. The parameters employed were: flow rate was 1.0 mL/min, UV detection at 200 nm, column temperature 25 °C and at injection volume 20  $\mu\text{L}$ . The technique was previously validated.<sup>10</sup>

### **Stability study**

Selected tablets batches were packaged in PVC and aluminium blisters and kept at  $40 \pm 2$  °C /  $75 \pm 5$  % RH for 6 months (accelerated study) and  $30 \pm 2$  °C/ $70 \pm 5$  % RH for 24 months (long-term study). Samples were withdrawn at initial time, 6, 12 and 24 months for evaluation of drug content and in vitro drug release.

### Data analysis

The technological and analytical properties of all formulations were treated by STATGRAPHICS PLUS version 5.1 (Statistical Graphics Corp., EUA) software.

## RESULTS

Granulates and meprobamate tablet properties of the selected formulations are summarized in Table 2.

**Table 2.** Granulate and tablet properties results

Sample	Granulate Results			
	Bulk density (g/cm <sup>3</sup> )	Tapped density (g/cm <sup>3</sup> )	Flow rate (g/cm <sup>2</sup> s)	Mean size (µm)
B1	0.48 ± 0.01	0.60 ± 0.04	5.30 ± 0.76	248.82 ± 3.27
B2	0.47 ± 0.02	0.60 ± 0.02	6.01 ± 0.61	298.60 ± 4.68
B3	0.48 ± 0.02	0.62 ± 0.00	6.01 ± 0.27	261.87 ± 4.20
F18	0.49 ± 0.01	0.60 ± 0.07	6.01 ± 0.55	257.47 ± 3.81
F20	0.49 ± 0.07	0.62 ± 0.00	6.01 ± 0.69	264.05 ± 4.24
Sample	Tablet Results			
	Abrasivity (%)	Friability (%)	Disintegration time (s)	Height (mm)
B1	0.24 ± 0.04	0.16 ± 0.07	213 ± 0.21	4.53 ± 0.03
B2	0.26 ± 0.01	0.16 ± 0.06	240 ± 0.34	4.56 ± 0.05
B3	0.25 ± 0.03	0.34 ± 0.25	206 ± 0.24	4.55 ± 0.03
F18	0.60 ± 0.21	0.16 ± 0.05	184 ± 0.28	4.57 ± 0.03
F20	0.20 ± .03	0.31 ± 0.23	170 ± 1.10	4.51 ± 0.06

The dissolved drug percentage and the results of the drug content and in vitro drug release corresponding to the accelerated study are showed in Table 3.

**Table 3.** Tablets properties up to 6 months under accelerated stability conditions

Sample	Results					
	Dissolution (%)			Drug content (%)		
	Initial	3 months	6 months	Initial	3 months	6 months
B1	85.78 ± 0.27	89.45 ± 0.10	89.76 ± 0.92	98.48 ± 0.29	98.40 ± 0.27	97.10 ± 0.93
B2	93.81 ± 0.90	84.89 ± 1.77	90.14 ± 0.27	100.02±0.02	98.62 ± 1.07	96.72 ± 0.61
B3	90.37 ± 0.73	84.89 ± 1.56	97.28 ± 1.60	100.04 ± 0.04	97.28 ± 0.58	97.28 ± 1.60
F18	91.89 ± 0.30	88.66 ± 0.19	90.14 ± 0.65	97.67 ± 0.26	97.91 ± 0.64	96.46 ± 0.65
F20	98.46 ± 0.41	89.06 ± 1.61	90.46 ± 1.59	98.00 ± 1.07	98.34 ± 1.11	95.20 ± 1.58

With regard to the long-term stability of the selected formulations, the values obtained are found in Table 4.

**Table 4.** Tablet properties up to 24 months under long-term stability conditions

Sample	Results					
	Dissolution (%)			Drug content (%)		
	6 months	12 months	24 months	6 months	12 months	24 months
B1	95.45 ± 0.17	90.47 ± 0.25	88.14 ± 0.87	97.54 ± 0.15	99.25 ± 0.82	97.02 ± 0.62
B2	94.54 ± 1.27	85.02 ± 1.32	86.06 ± 0.54	96.81 ± 0.27	97.78 ± 0.65	96.22 ± 0.47
B3	97.01 ± 1.43	87.51 ± 0.57	83.07 ± 0.93	97.47 ± 0.94	100.22 ± 0.88	93.29 ± 0.83
F18	95.99 ± 1.73	86.83 ± 0.78	83.07 ± 0.94	95.86 ± 0.15	98.22 ± 0.64	95.92 ± 0.85
F20	91.15 ± 0.45	88.30 ± 1.56	85.17 ± 1.27	96.27 ± 0.23	98.38 ± 0.19	95.10 ± 0.31

From the selected formulations were obtained granulates and tablets with satisfactory organoleptic, physical-mechanical and technological properties, demonstrating the feasibility from the process of production of this product.

The comparative analysis (least significant difference at  $p= 0.05$ ) was done for drug content and in vitro drug release results from the accelerated and long-term stability studies (Tabla 5).

**Table 5.** Probability (p) values for signification to the stability study

Factor	Probability (p) values			
	Accelerated stability		Long-term stability	
	Dissolution	Drug content	Dissolution	Drug content
Time	0.1564	0.0002	0.2278	0.0008
Sample	0.1795	0.0970	0.3763	0.0011

## DISCUSSION

The high dose and the poor flow properties of this pharmaceutical active substance conduced to use wet granulation as elaboration method for meprobamate tablets.<sup>7</sup> Independent of composition of formulations, distribution of particle size showed a normal behaviour ( $D_{max} < D_{critic} = 0.457$ ,  $p > 0.20$ ;  $n = 8$ ;  $\alpha = 0.05$ ). No significant difference ( $p > 0.05$ ) was found between all granules: mean particle size ( $p = 0.5059$ ); tap density ( $p = 0.1619$ ) and bulk density ( $p = 0.2617$ ). The granule properties were independent of the excipient proportions evaluated.

In order to determine if tablet properties are affected by composition of the formulations analysis of simple variance was applied. No significant difference was found between these tablets properties: height ( $p = 0.6974$ ); hardness ( $p = 0.4057$ ) and mean weight ( $p = 0.9767$ ). Three formulations showed good tensile strength with an acceptable disintegration time. Disintegration time less than 900 second was selected as the expected disintegration time. The disintegration time showed a significant dependence ( $p = 0.0494$ ) with maize starch, sodium lauryl sulphate/sodium croscarmellosa proportions. The equation [1], which describes the behavior of disintegration time, was:

$$\text{Disintegration} = 20.791 \text{ maize starch} + 347.386 \text{ sodium lauryl sulphate/sodium croscarmellosa} - 69.095 \text{ [1]}$$

From the equation [1], it can be seen that the minimum disintegration time corresponded with the minimum values of sodium lauryl sulphate and acdisol proportions studied. The coefficient of sodium lauryl sulphate / sodium croscarmellosa was largest, showed that the effect of combination of them was the main influence factor on disintegration of the tablets.

The dissolved drug percentage (Table 3) showed the following behavior [2]:

$$\text{Dissolved drug} = 0.017 \text{ maize starch} - 40.844 \text{ sodium lauryl sulphate/sodium croscarmellosa} + 98.2589 \text{ [2]}$$

From the equation [2] it can be concluded that relation of sodium lauryl sulphate and acdisol has more influence on the dissolved drug percentage of the tablets. Equation [2] indicates that the percentages of dissolved drug decreases with increasing sodium lauryl sulphate/sodium croscarmellosa ratio. The better results for dissolution are obtained in middle of the range for sodium lauryl sulfate.<sup>7</sup>

Physical and chemical parameters of Meprobamate tablets were independent of the composition of the selected formulations, even for in vitro dissolution. According to the described composition of formulations all tablets showed a favourable disintegrating time ( $t < 900$  s), the percentages of dissolved drug higher than 80 % ( $Q \geq 75$  % in 30 min) and values of assay from between 90 and 110 % are within an acceptable limits. It could be stated that after 6 months aging the selected formulations satisfied the official pharmaceutical specifications.<sup>9</sup>

The percentages of dissolved drug higher than 80 % during two years and the values of assay higher of 95 % are considered as being acceptable. Three formulations also kept all the rest official pharmaceutical specifications.<sup>9</sup> According to the stability study was verified that the formulations showed high chemical stability during 24 months.

Accelerated stability testing (high temperature, humidity) can be helpful in judging the long-term stability of a tablet package system. In addition to the stability data generated on the optimal formula, stability data generated on similar formulations can be sometimes be used as supportive stability data.<sup>11</sup>

The in vitro drug release did not reveal any significant difference, indicating no effect of time and the composition of formulations on percentages of dissolved drug. After 6 months, drug content showed significant differences. However, three formulations kept it between 9 and 110 %, which are within acceptable limits.<sup>9</sup>

## CONCLUSIONS

The disintegration time and dissolved drug percentage showed a significant dependence with sodium lauryl sulphate/sodium croscarmellosa proportions. In vitro drug release did not reveal any significant difference, indicating no effect of time and the composition of formulations on percentages of dissolved drug. On the basis of the present results, the selected meprobamate immediate released tablets formulations showed good stability, with optimum disintegration times and in vitro drug release during 24 months, and all the rest official pharmaceutical specifications.

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