Development and characterization of an oral dosage form containing Entacapone, Carbidopa, and L-dopa

Luciana Ferreira Fonseca Rodovalho-Mitani[1], Raphael Caixeta Serpa[2], Erika Crispim Resende[1], Eliana Martins Lima[3], Giulliano Gardenghi[4*]

[1] *Health Sciences Graduate Program, Universidade Federal de Goiás, Goiânia, GO, Brazil*
[2] *Laboratório Teuto Brasileiro S/A, Anápolis, GO, Brazil*
[3] *School of Pharmacy, Universidade Federal de Goiás, Goiânia, GO, Brazil*
[4] *Hospital ENCORE, Aparecida de Goiânia, GO, Brazil; Hospital e Maternidade São Cristóvão, São Paulo, SP, Brazil.*

***Correspondence:** Giulliano Gardenghi. Rua 05, número 432, apartamento 602 Setor Oeste, Goiânia, GO, Brasil. Tel: +55(62) 3212-6047, e-mail: ggardenghi@encore.med.br

Resumo

Entacapone é um inibidor da catecol-o-metiltransferase (COMT) usado em associação com carbidopa e L-dopa para o tratamento da doença de Parkinson. Os comprimidos contendo entacapone associado a carbidopa e L-dopa devem também conter elementos para promover a sua biodisponibilidade, pois o entacapone é fármaco de baixa solubilidade e baixa permeabilidade. Este trabalho teve como objetivos o desenvolvimento e a caracterização físico-química de comprimidos contendo a associação de entacapone, carbidopa e L-dopa utilizando Stalevo® como medicamento referência. Para tanto, diferentes lotes de comprimidos foram produzidos contendo tensoativos como o dodecil sulfato de sódio e os poloxamers 118 e 407 utilizando o método de granulação por via úmida em misturador de alto cisalhamento. Os núcleos dos comprimidos obtidos foram aprovados quanto às seguintes características físico-químicas: friabilidade, dureza, peso médio, desintegração e teor do componente ativo. Os comprimidos revestidos contendo poloxamer 407 apresentaram perfil de dissolução semelhante ao do medicamento referência.

Palavras chave: Levodopa, Carbidopa, Entacapone, Poloxamer, Tecnologia farmacêutica, Doença de Parkinson.

Abstract

Entacapone is a catechol-o-methyltransferase (COMT) inhibitor used in association with carbidopa and L-dopa in the treatment of Parkinson's disease. The tablets containing entacapone associated with carbidopa and L-dopa should also contain elements to promote its bioavailability, since entacapone presents low solubility and low permeability. The objectives of this study were the development and physicochemical characterization of tablets containing an association of entacapone, carbidopa, and L-dopa using Stalevo® as a reference medication. To achieve these goals, different batches of tablets were produced containing surfactants such as sodium dodecyl sulfate and poloxamers 118 and 407 using the wet granulation method in a high shear mixer. The tablet cores obtained were approved regarding the following physicochemical properties: friability, hardness, disintegration, content of active ingredient, and dissolution. The coated tablets containing poloxamer 407 presented dissolution profile similar to the reference medication.

Keywords: Levodopa, Carbidopa, Entacapone, Poloxamer, Pharmaceutical Technology, Parkinson Disease.

INTRODUCTION

Entacapone ((E)-2-cyano-N,N-diethyl-3-(3,4-dihydroxy-5-nitrophenyl) propenamide) (Bäckström *et al.*, 1989) is a selective catechol-o-methyltransferase (COMT) inhibitor (Figure 1) that improves the activity of L-dopa in the treatment of Parkinson's disease (PD) (Bäckström *et al.*, 1989; Katajamäki *et al.*, 1998).

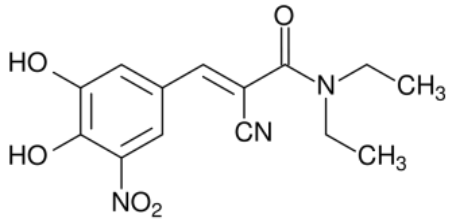


FIGURE 1 – Chemical structure of entacapone ($C_{14}H_{15}N_3O_5$), molecular weight 305.29 (Merck Index XIV Ed). **Source:** The Merck Index (2006).

The administration of entacapone associated with carbidopa and L-dopa in tablets increases the bioavailability of the latter, prolongs its elimination time (Kaakkola, Gordin, Männistö, 1994), and improves the management of this compound end-of-dose motor fluctuations (Stocchi *et al.*, 2004). More continuous movement behavior in PD patients and improved quality of life can be provided by the association of these three substances in one oral dosage form compared to L-dopa/carbidopa treatment (Müller *et al.*, 2007; Fung, Herawati, Wan, 2009). According to the Biopharmaceutics Classification System (BCS), entacapone is considered a drug substance class IV, since it presents low solubility, low permeability, and low bioavailability (Kalantri, 2010).

Granulation is a process used in the pharmaceutical industry to obtain tablets in which particles are agglomerated in the presence of a liquid or solid binder. This procedure improves the flow and compressibility characteristics of particles and increases the homogeneity of the final product (Reynolds *et al.*, 2005). High shear mixer granulation converts fine cohesive powders into granules in a multiphase process in a shorter time (Giry *et al.*, 2009). The concomitant use of the mixer, the chopper, and the heating jacket in the high shear mixer can form dense and agglomerated granules to be consequentially compressed to obtain tablets in the pharmaceutical industry (Chitu, Oulahna, Hemati, 2011).

Several studies have been conducted to improve the solubility of compounds that present low solubility in water aiming to increase the bioavailability of orally administered medications. The low solubility of certain compounds may be improved using nanotechnology (Diniz *et al.*, 2008), production of drug-cyclodextrin inclusion compounds (Freitas *et al.*,

2012), surfactants (Kallakunta *et al.*, 2012), and polymers (Marinich, Ferrero, Jiménez-Castellanos, 2011). Poloxamers are anphiphilic surfactants formed by different amounts of propylene and ethylene oxides added during manufacture, which form nonionic polyoxyethylene-polyoxypropylene copolymers (Rowe, Sheskey, Quinn, 2009). Therefore, poloxamers have been used to improve the dissolution rate of poorly water soluble compounds (Yong *et al.*, 2001; Kolašinac *et al.*, 2012).

The present investigation concerns the development of oral dosage forms containing an association of entacapone, carbidopa, and L-dopa, using a laboratory scale high shear mixer, aiming to obtain a drug similar to Stalevo®. Nowadays in the pharmaceutical market there is only one drug containing the association of this three substances, Stalevo®(Novartis™). This research aims to innovate the pharmaceutical market proposing as association of entacapone, carbidopa and L-dopa in a single tablet, considering the generic pharmacy market in Brazil. The association of the three drugs is still under patent protection. One second patent was published in 2011, describing some modifications in the formula aiming to achieve a better equivalence (Talwar et al, 2011). This fact may explain the poor literature available concerning the development of this pharmacotechnical mixture. The physicochemical evaluations of the oral dosage forms developed (friability, hardness, disintegration, content of active ingredient, and dissolution) establish the quality of the formulated tablets.

MATERIALS AND METHODS

Materials

Entacapone, carbidopa, and L-dopa were purchased from Ra Chem Pharma Ltd, Sochinaz SA, and Guangxi Baise Tianxing Plant Science Co., Ltd., respectively. The following excipients were used: mannitol (Getec Guanabara Química Industrial S/A); sodium dodecyl sulfate and titanium dioxide (JT Baker); poloxamers 407 and 188 (BASF); polivinylpyrrolidone (PVP) K90®, pregelatinized starch, and Opadry® YS1 7006 (Colorcon®); croscarmellose sodium (Blanver); Aerosil® (Evonik Degussa Brasil Ltda.); magnesium stearate (Faci Spa); and red iron oxide (Eskisa S.A.). All substances were of pharmaceutical grade. The reference drug product used was Stalevo® (Novartis) batch 1270413. Given that a confidentiality agreement was signed, the detailed formulation of the tablets is not given here.

Therefore, the ranges of excipients used in the development of the core tablets is described in Table I for all batches.

TABLE I – Formulas of batches developed with a quantitative description expressed as percent by weight (%) used to obtain core tablets of 770 mg

Stage 1 – granulation 1	Batch 1 (%)	Batch 2 (%)	Batch 3 (%)
Entacapone	25.0	25.0	25.0
Mannitol	15–40	15–40	15–40
Poloxamer 407	–	–	0.5 - 10
Poloxamer 188	0.5–10	–	–
Polivinylpyrrolidone (PVP) K90®	–	0.5–10	–
Sodium dodecyl sulfate	–	0.5–10	–
Stage 2 – granulation 2	Batch 1 (%)	Batch 2 (%)	Batch 3 (%)
L-dopa	18.8	18.8	18.8
Carbidopa	5.0	5.0	5.0
Polivinylpyrrolidone (PVP) K90®	0.5–10	0.5–10	0.5–10
Pregelatinized starch	1–20	1–20	1–20
Croscarmellose sodium	1–20	1–20	1–20
Stage 3 – final mixture	Batch 1 (%)	Batch 2 (%)	Batch 3 (%)
Aerosil®	0.1–5	0.1–5	0.1–5
Magnesium stearate	0.1–5	0.1–5	0.1–5

Aiming to obtain 800-mg coated tablets with 3% weight gain, the following excipients were used for coating tablet cores of batches 1 and 3, and their quantities are expressed as percent by weight: 70–90% Opadry® YS 1 7006; 10–30% titanium dioxide; and 1–10% red iron oxide. Alcohol 90% (v/v) was used as solvent.

Methods

Content assay

The samples were analyzed using high-performance liquid chromatography (HPLC) in a Varian® chromatograph containing a vacuum degasser and a quaternary pump (ProStar 240), a thermostated column compartment (MetaTherm®), an autosampler (ProStar 210), and a diode-array detector (DAD) (ProStar-335), with DELL® hardware and Galaxie® software version 1.9. Chromatographic separations were performed in OmniSpher Varian® RP-18A column (250 mm × 4.6 d.i., particle of 5 μm), at 25°C (± 1°C), with a mobile phase consisting

of methanol-sodium phosphate buffer (pH 3.0 adjusted with phosphoric acid 10% v/v), at a flow rate of 1.0 mL/min, detection with DAD at 282 nm, and injection volume of 20 μL. The mobile phase was under linearly programmed gradient mobile-phase conditions and during the initial 6 min, it was gradually modified, from the proportion of 90:10 (0.2 M sodium phosphate pH 5.0: methanol pH 3.0) to the proportion of 30:70, which was maintained until the end of the chromatographic run (12 min). The HPLC method was validated according to the criteria established by ICH (2005).

A sample of 20 tablets collected at random was ground and an amount of the powder equivalent to one tablet was weighed, transferred to a 100-mL volumetric flask, and the volume was completed with a specific solvent for each active ingredient analyzed, namely potassium phosphate buffer pH 5.5 for entacapone and 0.1 N hydrochloric acid (HCl) for carbidopa and L-dopa. The solution was sonicated for 10 min and filtered through 0.45-μm Millex® filter. Further dilutions were carried out to obtain the final concentrations of the solutions of entacapone (200 μg/mL), carbidopa (37.5 μg/mL), and L-dopa (150 μg/mL). Two different solvents were used to complete the volume of the tablets samples due to the differences of solubility and permeability. According to the Biopharmaceutics Classification System (BCS), entacapone is considered a drug substance class IV, since it presents low solubility, low permeability, and low bioavailability (Kalantri, 2010).

Dissolution

Dissolution studies were performed in a Vankel VK 7000 dissolution apparatus using a single tablet per dissolution vessel. The process was carried out in: a) 900 mL of potassium phosphate buffer medium, adjusting to pH 5.5 with phosphoric acid as needed, in apparatus II (paddle), with the basket rotating at 120 rpm for entacapone; b) in 750 mL of 0.1 N hydrochloric acid, in apparatus I (basket), with the basket rotating at 50 rpm for carbidopa and L-dopa. Both experiments were performed at 37°C and the samples were collected at 10, 20, 30, 45, and 60 min without replacing the dissolution media, initially filtered through 1-mm membrane filter and posteriorly through 0.45-μm Millex® filter, and analyzed using HPLC. The final concentrations of the solutions were: entacapone – 222 μg/mL, carbidopa – 50 μg/mL, and L-dopa – 200 μg/mL. The method was validated according to the guidelines established by FDA (2000) and ICH (2005).

Statistical calculations were performed between the curves of the batches and the model drug, as recommended by Brasil (2004), using the difference factor (f_1) and the similarity factor (f_2) to establish a correlation index between the dissolution profiles with the following equations:

$$f_1 = \left[\frac{\sum_{i=1}^{n} | R_t - T_t |}{\sum_{i=1}^{n} R_t} \right] x\ 100$$

$$f_2 = 50\ x\ \log \left\{ \left[1 + \left(\frac{1}{n} \right) x \sum_{i=1}^{n} (R_t - T_t)^2 \right]^{-0,5} x\ 100 \right\}$$

where:

n = number of points of time of collection

R_t = value of dissolution of the batch of the reference medication at a time t

T_t = value of dissolution of the test product at a time t

In general, the optimal result is achieved when f1 is lower than 15 (0–15) and f2 is higher than 50 (50–100), showing the similarity between the dissolution profiles (Costa, 2002).

Granule manufacture

The granules were produced in a horizontal laboratory scale high shear mixer (P/VAC 10-60, Diosna Dierks & Sohne GmbH, Germany) equipped with a heating jacket. The conditions of the experiment are described in Table II. Drying was carried out *in situ* using the heating jacket, the vacuum system, and the gas-stripping nozzles, and the granules were sifted through a 20-mesh sieve after removal from the pan of the high shear mixer.

TABLE II – High shear mixer features

Parameter	Mixture	Granulation	Drying
Impeller speed (rpm)	200	200	20
Chopper speed (rpm)	1.500	1.500	–
Massing time (s)	600	120	3.000
Filter cleaning time (s)	5	5	3
Pump speed (rpm)	–	50	–
Heating jacket temperature (°C)	–	–	60
Product temperature (°C)	–	–	37.5

Density, Hausner index, flow, and moisture

The powder density of active ingredients and granules was determined using an automated compactor (SVM 203, Erweka GmbH, Germany), by placing 40 g of each sample in graduated test tubes which underwent 500 and 750 total strokes, respectively, according to USP 30/NF 25 (2007).

The Hausner index was calculated based on powder density results to elucidate the compressibility index of the tested compounds (USP 30/NF 25, 2007).

The granulate flow time was evaluated using a Granulate and Powder Flow Tester (GTB Flowmeter, Erweka GmbH, Germany). A 40-g aliquot of each granulate batch was placed in a funnel with an orifice of 10 mm, and the product was allowed to flow exclusively under the force of gravity. The instrument automatically evaluated the granulate flow time and the average of three determinations was calculated.

The granule moisture was analyzed in a drying system that combines a semi-analytical scale with a ceramic infrared dryer (IV 2500 Infrared Moisture Analyzer, Gehaka, Brazil). The heat function was set at a drying range of 0.5%/min and maximum temperature of 90°C. Hardware RS-232 serial with an USB output printer provided the final moisture measurement of the sample when the value was stabilized.

Tablet preparation

After the granulate preparation, Aerosil® and magnesium stearate were added consecutively in a final step, using a "V" mixer (Lawes, Brazil), with agitation at 20 rpm for 15 min and 5 min, respectively. The final granulates were fed manually into the die of an instrumented rotary tableting machine (model 2000 – R&D Line, Lawes, Brazil) using oval-faced punches and dies. The choice of punches (type and diameter) was made aiming to obtain tablets similar to the model drug, which measures 14.50 mm × 9.45 mm. Punch height adjustment was made manually, the granulate was placed into the hopper, and the compression started. The core tablets weighed 770 mg (± 1%).

Coating was performed in a GS 600 coating machine (IMA Pharmaceutics, Italy) equipped with four spray guns and a 140-L solution preparation tank. The coating conditions applied were: distance between the core and the guns – 22 cm; atomization pressure – 2 bar; pump flow rate – 200 mL/min; inlet air temperature – 60°C; bowl speed – 6 rpm. The guns were equipped with 1.8-mm nozzles, 0.6-mm needles, and 2-mm cover. The air flow entering the coating machine for heating the cores was 1650 m^3/h. The temperature in the tablet cores was maintained at 38°C (± 3°C) during the process. The coated tablets weighed 800 mg (± 1%).

Determination of physicochemical properties

The friability of 20 tablets from each batch was determined using a friabilator (model Ta-UZ, Erweka, Germany) rotating at 20 rpm for 5 min. The crushing strength was measured with a hardness tester (model TBH 30, Erweka, Germany), analyzing 10 tablets from each batch. The disintegration time was tested in six tablets from each batch using the disintegration test apparatus (model ZT 3, Erweka, Germany), analyzing six tablets from each batch, using water at 37°C as medium and the basket raised and lowered at a constant frequency of 30 cycles/min (USP 30/NF 25, 2007).

RESULTS AND DISCUSSION

The content assay method using HPLC was validated and it accomplished the criteria established by ICH (2005): system suitability, specificity, linearity, precision, reproducibility, accuracy, and robustness. The data from this study show that the reproducibility precision among analysts was of 0.28% relative standard deviations (RSD) to the peak mean areas, and so, fulfills the evaluation criteria. The values from the recuperation tests varied from 95.57% to 104.63%, for all three studied substances. The evaluated recuperation indicated the precision of the chosen method. The quantification limits values to entacapone, carbidopa and L-dopa were 2.8 μg/mL, 0.649 μg/mL e 2.52 μg/mL respectively. The results from detection limits to entacapone, carbidopa and L-dopa were 0.84 μg/mL, 0.19 μg/mL e 0.75 μg/mL respectively. Brief variations in some experimental parameters did not show any effect over the chromatographic behavior of the actives evaluated in this research.

Due to the solubility properties of entacapone, the dissolution studies were performed in two separate phases, according to the method recommended by FDA (2007). The dissolution method was validated according to the guidelines established by FDA (2000) and ICH (2005): specificity, linearity, precision, and accuracy. The method was proved to be linear as the correlation coefficients of the obtained derivates were of 0,995 at minimum (table III). The validated method is selective and specific presenting retention times demonstrating the complete separation among peaks of entacapone (10 min), carbidopa (4.9 min), L-dopa (3.5 min) and placebo. Concerning the precision and accuracy, the reproducibility results of the method obtained relative standard deviations (RSD) below 5% to the concentration ranges

presented. The results for intermediate range of precision of both days of analysis also evidence RSD below 5% for the presented concentration intervals. The method presented itself as robust, once the alterations in some analytic parameters did not impact the calibration curves.

TABLE III – Linearity of the proposed dissolution method

Active ingredient	Linearity range (μg/mL)	Slope	Intercept	Regression coefficient (r^2)
Entacapone	124–212	30.763	564.18	0.995
Carbidopa	28–47	9.4289	6.9446	0.9958
L-dopa	118–198	12.314	92.915	0.999

The thin aspect of entacapone observed experimentally, its low density, and the cohesion force of the particles could affect its flow properties, as mentioned by Staniforth (2005). It is well-known that wet granulation is used to improve the flow properties of pharmaceutical formulations (Cantor, Kothari, Koo, 2009). Therefore, according to the total amount of the active ingredients present in the formulations (48.8%), the amount of entacapone in the formulations (25%), its density (0.459 g/mL), and the low compressibility results obtained by the Hausner index for the three active ingredients (entacapone – 1.92; carbidopa – 1.29; L-dopa – 1.46), the wet granulation method was chosen for obtaining the tablets so that the characteristics of mixing, flow, and compression of the pre-planned formulations could be improved.

The granulation process was performed in two separate steps, as suggested by Talwar *et al.* (2011), because of the very adverse physicochemical characteristics of entacapone, carbidopa, and L-dopa, especially solubility and permeability. First, carbidopa and L-dopa were granulated separately only with water. After that, entacapone was granulated with the binder solution (water-alcohol) containing the binder and/or the surfactant. Therefore, the release of entacapone in the dosage form, its maintenance in the dissolved state throughout the gastrointestinal track, and its permeation could be improved at the same time that carbidopa and L-dopa suffered no influence of the modified formulation.

The high shear mixer allowed the usage of a multiphase process in a single equipment to obtain agglomerated granules posteriorly compressed to produce tablets. This reduced

transferences during the wet granulation process and ensured the uniformity of the mixture due to the use of a closed system to homogenize the ingredients, the continuous passage of the granulation solution, the reduction of agglomerates formed during the wet granulation process, and the drying phase in the heating jacket. The characterization of the granules obtained in the present study (Table IV) confirms the parameters of the high shear mixer for this purpose according to USP 30/NF 25 (2007).

TABLE IV – Technological characterization of the granules after preparation in the high shear mixer

Technological property	Batch 1	Batch 2	Batch 3
Moisture (%)	2.8	2.6	2.6
Tap density (g/mL)	0.645	0.687	0.675
Flow (s)	10.4	11.3	10.7

Additionally, the physical properties of the core tablets obtained (Table V) as well as the results of the content assays performed in all batches certify the method in the high shear mixer proposed and used in the present study. The results of the performed tests aiming to establish the uniformity of the contents were satisfactory to all the studied lots.

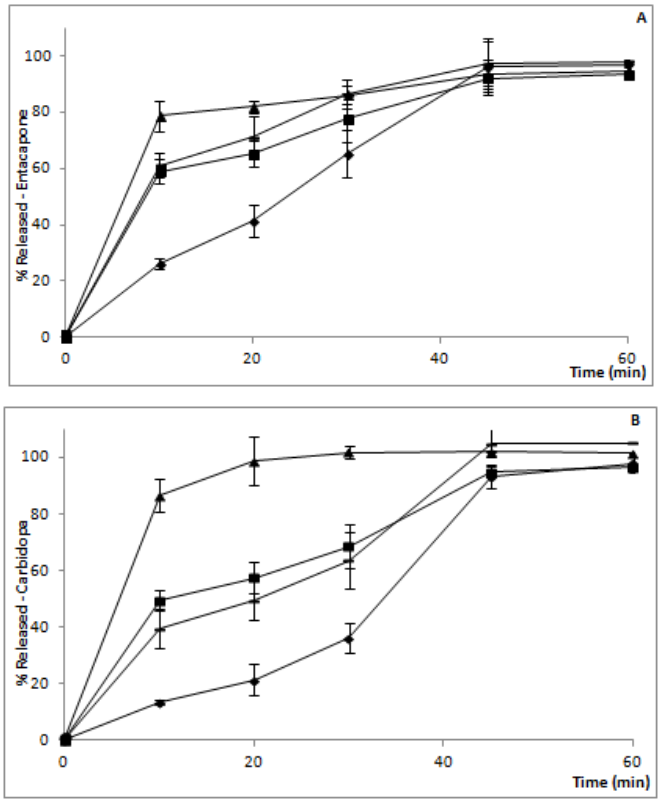
TABLE V – Physical properties of the core tablets obtained by granule compression

Physical property	Batch 1	Batch 2	Batch 3
Friability (%)	<1.0	<1.0	<1.0
Crushing strength (kgf)	17.2	18.8	18.3
Tablet weight (g)	0.772	0.769	0.778
Disintegration time (min)	4:23	3:45	4:17
Entacapone assay (%)	99.20	99.42	99.93
Carbidopa assay (%)	100.53	99.25	100.32
L-dopa assay (%)	99.84	100.14	99.78

Analyzing the dissolution profile of entacapone in each batch of core tablets, it was possible to observe that the presence of PVP K90®, used to promote powder aggregation due to the low density of entacapone, associated with sodium dodecyl sulfate, caused the

dissolution curves of batch 1 to be closer to the dissolution curves of the reference medication (Figure 2). The optimization of the drug release profiles, in order to be similar to the reference medication, was achieved by changing the surfactant used in the formulation. The dissolution profile of core tablets in batch 3, containing poloxamer 407, was closer to that of the reference medication than the dissolution profile of core tablets in batch 2, containing poloxamer 118, for entacapone, carbidopa, and L-dopa. The same was observed for carbidopa and L-dopa.

The improvement on the dissolution profile of core tablets in batch 3 compared to core tablets in batch 2 can probably be attributed to the enhanced solubility of entacapone due to the presence of poloxamer 407 in the former. The long chain of polyoxypropylene, which is hydrophobic, is presumed to interact with entacapone, and simultaneously, the long chain of polyoxyethylene, which is hydrophilic, makes it more soluble than when associated with poloxamer 188. Therefore, due to its surfactant properties already mentioned, poloxamer 407 proved to be the most suitable solubilizer for formulations containing entacapone (BCS class IV).



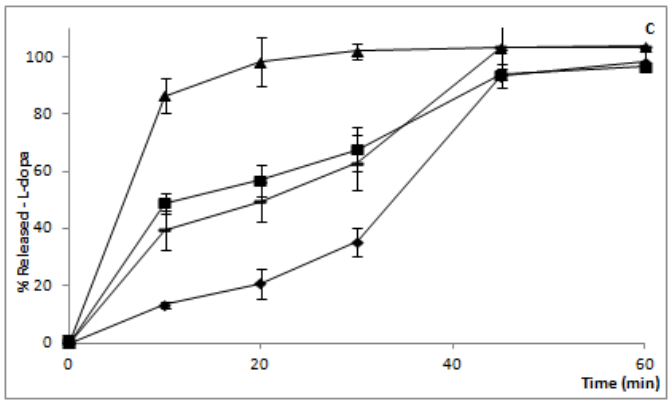


FIGURE 2 – Mean cumulative percent release profiles of entacapone (A), carbidopa (B), and L-dopa (C) in core tablets according to time. Stalevo® (◆); batch 1 (■); batch 2 (▲); batch 3 (–).

Based on the statistical analyses of the difference factor (f_1) and the similarity factor (f_2) (Table VI), it was possible to confirm that the less different (f_1) and more similar (f_2) dissolution profiles of the core tablets in relation to the reference medication were batches 1 and 3, for entacapone, carbidopa, and L-dopa. Consequently, only batches 1 and 3 underwent the coating process. The statistical analyses of f_1 and f_2 of the coated batches, named 1C and 3C, confirmed the observation and the analyses of the dissolution curves (Table VI), since f_1 calculated for batch 3C was lower than that for batch 1C, and f_2 was higher for batch 3C than for batch 1C.

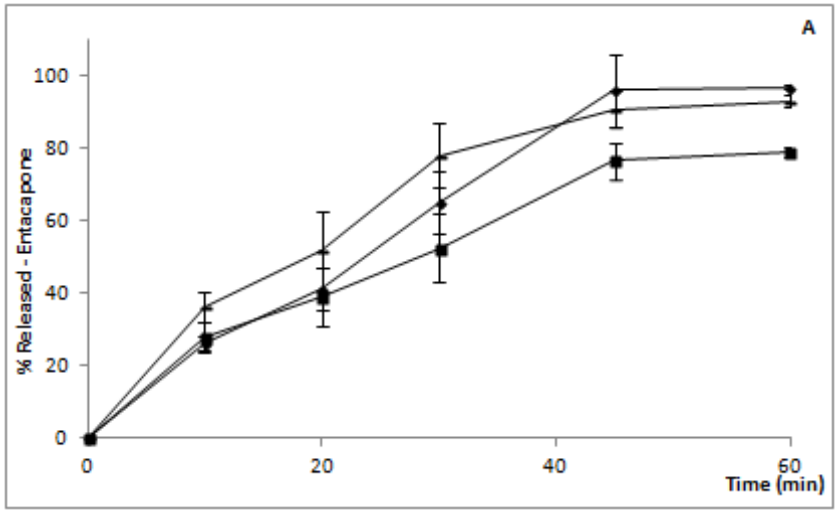
Therefore, batch 3C proved to be more similar to the reference medication than batch 1C and closer to the reference parameters established for f_1 and f_2, consequently presenting a pharmacotechnical behavior similar to the reference medication, even though the difference factor (f1) for L-dopa was out of the specified limit (0-15). All the batches had their dissolution profiles analyzed (Figure 3) and the dissolution curves of both coated batches were closer to the dissolution curves of the reference medication for all active ingredients. Thus, the coating employed (3% weight gain) influenced the dissolution profile of the tablets probably as a result of the formation of a hydroxypropilmethyl cellulose (hypromellose) and macrogol film on their surface due to the use of Opadry® YS 1 7006.

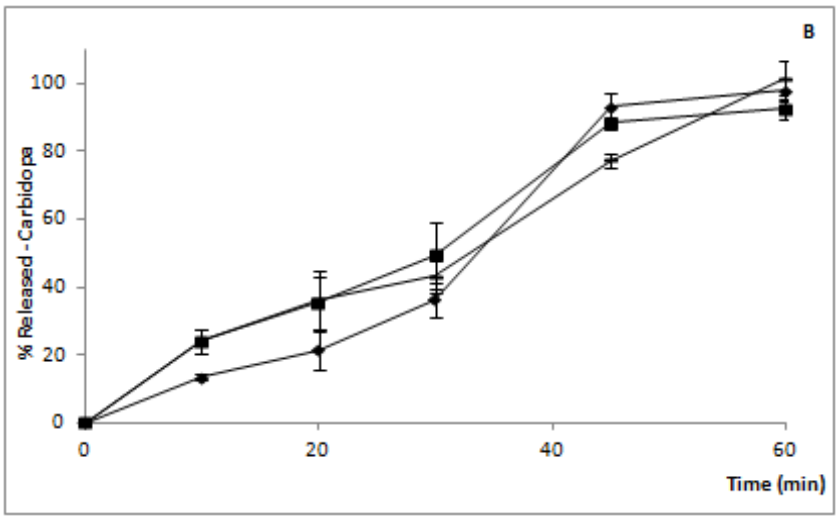
TABLE VI – Calculation of the difference factor (f_1) and similarity factor (f_2) of the dissolution profiles of the core tablets in batches 1, 2, and 3 as well as of the coated tablets in batches 1C and 3C

Batch	Entacapone		Carbidopa		L-dopa	
	f_1	f_2	f_1	f_2	f_1	f_2
1	23.67	35.80	41.02	28.39	40.80	28.52

2	36.40	25.32	87.31	12.52	89.12	12.40
3	27.08	32.21	38.42	32.85	37.70	32.88
1C	16.56	43.89	18.33	49.17	18.42	49.01
3C	12.99	52.16	9.16	59.33	17.50	51.44

Reference values: $0 > f1 < 15$; $50 > f_2 < 100$ (Costa, 2002).





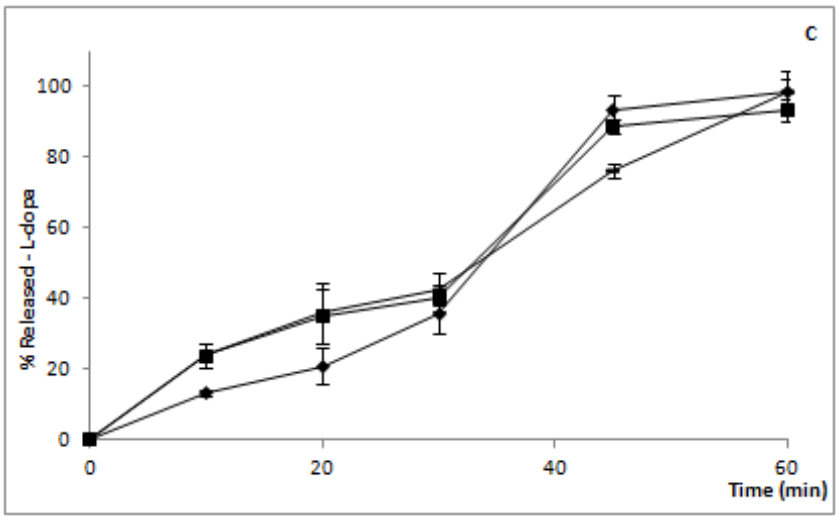


FIGURE 3 – Mean cumulative percent release profiles of entacapone (A), carbidopa (B) and L-dopa (C) in coated tablets according to time. Stalevo® (◆); batch 1C (■); batch 3C (–).

CONCLUSION

The use of poloxamer 407 proved to be a good option for the development of tablets containing the association of entacapone, carbidopa, and L-dopa, as long as the wet granulation method is employed and that entacapone is granulated in an exclusive phase, separated from carbidopa and L-dopa, and associated with a surfactant. The coating showed to have influence on the dissolution profile of tablets with 3% weight gain.

ACKNOWLEDGEMENTS

The authors are thankful to CAPES, CNPq, and FINEP for the financial support, as well as to Laboratório Teuto Brasileiro S/A.

REFERENCES

- Bäckström R, Honkanen E, Pippuri A, Kairisalo P, Pystynen J, Heinola K, Nissinen E, Linden IB, Männistö PT, Kaakkola S, Pohto P. Synthesis of some novel potent and selective catechol-O-methyltransferase inhibitors. *J. Med. Chem*. 32(4): 841-846, 1989.
- Brasil. Ministério da Saúde. Agência Nacional de Vigilância Sanitária. Resolução-RE nº 310, de 1. de setembro de 2004. Diário Oficial da União, Brasília, DF, 3 Sept. 2004. Available at: <http://www.interfarma.org.br/site2/images/Site%20Interfarma/Informacoesdosetor/RE/Registro/2004/RE%20setembro%20310-04%20SIMILAR.pdf>. Access: Jun. 13, 2012.
- Cantor SL, Kothari S, Koo OMY. Evaluation of the physical and mechanical properties of high drug load formulations: wet granulation vs. novel foam granulation. *Powder Technol.* 195: 15-24, 2009.
- Chitu TM, Oulahna D, Hemati M. Wet granulation in laboratory scale high shear mixers: Effect of binder properties. *Powder Technol*. 206(1): 25-33, 2011.

- Costa PJC. Avaliação in vitro da bioequivalência de formulações farmacêuticas. *Braz. J. Pharm. Sci.* 38(2): 141-153, 2002.
- Diniz DGA, Alves CPI, Castro NC, Rodovalho LFF, Benfica PL, Valadares MC, Lima EM. Isotretinoin-containing liposomes: obtention, characterization and in vitro cytotoxicity on leukemia cells. *Appl. Cancer Res.* 28(3): 106-112, 2008.
- FDA. U.S. Food and Drug Administration. Dissolution methods, carbidopa/entacapone/levodopa. Silver Spring, 2007. Available at: <http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm>. Access: Jun. 25, 2012.
- FDA. U.S. Food and Drug Administration. Guidance for industry. Analytical procedures and methods validation: chemistry, manufacturing, and controls documentation. Rockville, 2000.
- Freitas MR, Rolim LA, Soares MFR, Rolim-Neto PJ, Albuquerque MM, Soares-Sobrinho JL. Inclusion complex of methyl-β-cyclodextrin and olanzapine as potential drug delivery system for schizophrenia. *Carbohydr. Polymers.* 89(4): 1095-1100, 2012.
- Fung VSC, Herawati L, Wan Y. Quality of life in early Parkinson's disease treated with L-dopa/carbidopa/entacapone. *Mov. Disord.* 24(1): 25-31, 2009.
- Giry K, Viana M, Genty M, Wüthrich P, Chulia D. Switch from single pot to multiphase high shear wet granulation process, influence of the volume of granulation liquid in a pilot scale study. *Chem. Eng. Process. Process Intens.* 48(8): 1293-1301, 2009.
- ICH. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: validation of analytical procedures: text and methodology Q2(R1). Geneva, 2005. Available at: <http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1__Guideline.pdf>. Access: Jun. 25, 2012.
- Kaakkola S, Gordin A, Männistö PT. General properties and clinical possibilities of new selective inhibitors of catechol-O-methyltransferase. *Gen. Pharmacol.* 25(5): 813-824, 1994.
- Kalantri MR. Pharmaceutical compositions of entacapone. US Patent 20100104634. 29 Apr. 2010.

- Kallakunta VR, Bandari S, Jukanti R, Veerareddy PR. Oral self emulsifying powder of lercanidipine hydrochloride: formulation and evaluation. *Powder Technol.* 221: 375-382, 2012.
- Katajamäki J, Honkanen A, Piepponen TP, Lindén IB, Zharkovsky A, Ahtee L. Conditioned place preference induced by a combination of L-dopa and a COMT inhibitor, entacapone, in rats. *Pharmacol. Biochem. Behav.* 60(1): 23-26, 1998.
- Kolašinac N, Kachrimanis K, Homšek I, Grujić B, Durić Z, Ibrić S. Solubility enhancement of desloratadine by solid dispersion in poloxamers. *Int. J. Pharm.* 436(1): 161-170, 2012.
- Marinich JA, Ferrero C, Jiménez-Castellanos MR. Graft copolymers of ethyl methacrylate on waxy maize starch derivatives as novel excipients for matrix tablets: drug release and fronts movement kinetics. *Eur. J. Pharm. Biopharm.* 80(3): 674-681, 2012.
- Müller T, Erdmann C, Muhlack S, Bremen D, Przuntek H, Woitalla D. Entacapone improves complex movement performance in patients with Parkinson's disease. *J. Clin. Neurosci.* 14(5): 424-428, 2007.
- Reynolds GK, Fu JS, Cheong YS, Hounslow MJ, Salman AD. Breakage in granulation: a review. *Chem. Eng. Sci*. 60(14): 3969-3992, 2005.
- Rowe RC, Sheskey PJ, Quinn ME. Handbook of pharmaceutical excipients. 6. ed. London: Pharmaceutical Press; Washington, DC: American Pharmacists Association, 2009.
- Staniforth J. Fluxo de pós. *In:* Aulton ME. (Ed.). Delineamento de formas farmacêuticas. 2. ed. Porto Alegre: Artmed, 2005. p. 208-221.
- Stocchi F, Barbato L, Nordera G, Bolner A, Caraceni T. Entacapone improves the pharmacokinetic and therapeutic response of controlled release levodopa/carbidopa in Parkinson's patients. *J. Neural Transm.* 111(2): 173-180, 2004.
- Talwar M, Kapoor R, Mashalkar M, Jain GK. Pharmaceutical compositions of entacapone, levodopa and carbidopa with improved bioavailability. US Patent 20110091558. 21 Apr. 2011.
- THE MERCK index: an encyclopedia of chemicals, drugs, and biologicals. 14 ed. Whitehouse Station: Merck Research Laboratories, 2006.
- USP 30/NF 25. United States Pharmacopeia & National Formulary. Rockville: United States Pharmacopeial Convention, 2007.

- Yong CS, Choi JS, Quan QZ, Rhee JD, Kim CK, Lim SJ, Kim KM, Oh PS, Choi HG. Effect of sodium chloride on the gelation temperature, gel strength and bioadhesive force of poloxamer gels containing diclofenac sodium. *Int. J. Pharm.* 226(1): 195-205, 2001.