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Original Article

Dissolution method for delapril and manidipine combination tablets based on an absorption profile of manidipine ☆

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ABSTRACT

The present study describes the development and validation of a dissolution method for delapril (DEL) and manidipine (MAN) combination tablets, using a simulated absorption profile based on *in vivo* data for MAN. The suitable *in vitro* dissolution profile for this formulation was obtained using 900 mL of citrate buffer pH 3.2 at $37\,°C \pm 0.5\,°C$ as dissolution medium and USP apparatus 2 (paddle) at 75 rpm. All samples were analyzed by a liquid chromatography (LC) method. Under these conditions, a significant linear relationship between the absorbed (calculated by deconvolution approach) and dissolved fractions of MAN was obtained ($R=0.997$) and an *in vivo-in vitro* (IVIV) correlation for this particular formulation containing MAN can be established. Validation parameters for dissolution methodology such as the specificity, linearity, accuracy and precision were also evaluated according to the international guidelines, giving results within the acceptable range. Therefore, the proposed dissolution conditions can be applied for the simultaneous release analysis of DEL and MAN from the solid dosage form, contributing to the improvement of the quality control of pharmaceutics and minimizing the number of bioavailability studies.

1. Introduction

After oral administration, drug absorption is dependent on its release from the pharmaceutical formulation, dissolution in the physiological medium, and permeability across the gastrointestinal tract [1,2]. The dissolution test is an important tool to guide the development of new formulations and manufacturing process evaluation, and to assess lot-to-lot quality. Furthermore, the *in vitro* method may be more attractive if the analytical conditions allow an analogy with *in vivo* data, and consequently, an *in vivo-in vitro* (IVIV) correlation can be established [3,4].

Delapril hydrochloride (DEL) is a lipophilic carboxyl-alkyldipeptide with potent angiotensin-converting enzyme inhibitory activity. It is a prodrug, and after the oral administration, it is converted *in vivo* by esterolysis to an active diacid derivative which is converted in turn to an active 5-hydroxy-indane diacid [5,6]. Manidipine dihydrochloride (MAN) is a third-generation dihydropyridine calcium channel antagonist. It is lipophilic and vasoselective, and has strong membrane binding ability which is responsible for the gradual onset and long duration of pharmacologic action [7,8]. The combination of DEL and MAN is capable of inducing a significant, smooth and persistent blood pressure reduction throughout the dosing interval, and may be regarded as an optimal antihypertensive drug treatment in patients with mild to moderate essential hypertension inadequately controlled by monotherapy with either component [9,10]. The chemical structures of both drugs are shown in Fig. 1.

Analytical methods, i.e., liquid chromatography (LC), capillary electrophoresis, and LC coupled to mass spectrometry, were developed and validated for determination of DEL and MAN in pharmaceutical formulation [11–13]. However, there is no available method for the evaluation of dissolution profile of DEL and MAN in fixed dose combinations.

Then, the aim of the present study was to develop and validate a dissolution method for simultaneous release analysis of DEL and MAN in commercial tablets using an optimized LC method for quantification. The conditions of the dissolution method were optimized considering the MAN *in vivo* pharmacokinetic data obtained from the literature [14].
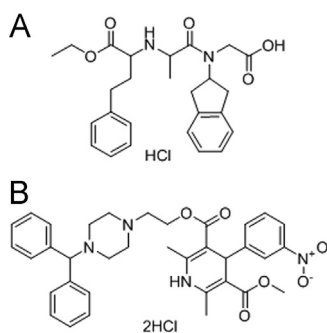
Fig. 1. Chemical structures of DEL (A) and MAN (B).

2. Experimental

2.1. Chemicals and reagents

DEL (purity 99.6%) and MAN reference substances (purity 99.7%) were kindly supplied by Chiesi Farmaceutici (Parma, Italy). Hipertil® tablets (Chiesi Farmacêutica Ltda, SP, Brazil) containing 30 mg of DEL and 10 mg of MAN were purchased from commercial source and used within their shelf life period. The excipients contained in the dosage form (lactose monohydrate, magnesium stearate, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, riboflavin and aluminum lake) were all of pharmaceutical grades and acquired from different suppliers for placebo preparation. All chemicals used were of pharmaceutical or special analytical grade. Purified and ultrapure water was obtained using a Milli-Q Plus® (Milli Q Gradient System, Millipore Corp. Bedford, MA, USA).

2.2. Reference solutions

The stock solutions of the drugs were prepared by accurately weighing 15 mg of DEL and 5 mg of MAN reference substances and diluting to volume with methanol to obtain the concentration of 0.75 mg/mL and 0.25 mg/mL for DEL and MAN, respectively. The stock solutions were stored at 2–8 °C, protected from light and daily diluted to an appropriate concentration, with the respective medium for each case.

2.3. Chromatographic instrumentation and conditions

The LC system consists of a Shimadzu LC model (Shimadzu Corp., Kyoto, Japan) composed of an LC-20AT pump, an SPD-M20A photodiode array (PDA) detector, a CBM 20A system controller, a DGU-20A$_5$ prominence degasser, a column thermostat oven CTO-20AC and an autosampler SIL-20AC. Data were acquired and processed using LC solution software. The determination of DEL and MAN was performed using the published LC method [11]. Briefly, the chromatographic separation was performed on a reversed-phase Shimadzu Shim-pack C$_8$ analytical column (250 mm × 4.6 mm 5 μm) maintained at 35 °C. The LC system was operated isocratically using a mobile phase (pH 3.0) consisting of acetonitrile and 0.3% triethylamine (55:45, v/v) at a flow rate of 1.2 mL/min, with PDA detection at 220 nm. The injection volume was modified to 50 μL to improve the sensitivity.

2.4. Solubility and sink conditions

The solubility and sink conditions of both DEL and MAN reference substances were determined in different dissolution media such as 0.1 M HCl, citrate buffer pH 3.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8. Excess contents of drugs were added

separately into different tubes containing 5 mL of dissolution media ($n = 2$) and maintained in a water bath thermostatized at 37 ± 0.5 °C with gently shaking. The tubes were centrifuged after 6 h, and a volume (2 mL) was removed from each tube, filtered through a 0.45 μm membrane filter and properly diluted with the mobile phase as necessary. The final solutions were analyzed by LC method.

2.5. Dissolution instrumentation and selected conditions

The dissolution analyses were performed with a Vankel® VK 7010 (Agilent Technology Group, USA) multi-bath ($n = 8$) dissolution station, with VK 8000 auto-sampling station, VK bidirectional peristaltic pump and a VK 750D digitally controlled heater/circulator. Amber vessels were used to avoid drug degradation. Tablets containing 30 mg of DEL and 10 mg of MAN were evaluated using 900 mL (37 ± 0.5 °C) of citrate buffer pH 3.2 as dissolution medium and USP apparatus 2 (paddle) at a rotation of 75 rpm. The sampling was performed by withdrawing 5 mL of aliquots with immediate filtration through 10 μm filters connected to the cannulas of the equipment. A correction approach was included in the calculations to account for the drug removed from the sampling. The dissolution samples were analyzed by the LC method at predetermined time intervals (10, 15, 30, 45, 60, 90 and 120 min), without dilution due to the low concentration of the drugs in the pharmaceutical formulation. The cumulative percentage of drug release was plotted against time in order to obtain the release profile and calculate the *in vitro* dissolution data.

2.6. In vivo data evaluation of MAN

The plasma concentration of MAN after oral administration was obtained from the literature [14] and fitted by a non-linear regression software (Micromath Scientist®, v.2.01) using a two-compartment open model. The calculations followed the equation, and its parameters were used to estimate intermediate plasma concentration data points.

$$Cp = A. e^{-\alpha.t} + B. e^{-\beta.t} - C. e^{-k_a.t}$$

where Cp is the plasma concentration at time t; α and β are the distribution and elimination constants, respectively; Ka is the absorption rate constant; t is the time of sampling; A, B and C constants are intercepts on the y axis for each extrapolated segment of the curve, referring to the distribution, elimination and absorption stages, respectively [15].

The model-independent numerical deconvolution was utilized to estimate the percentage of drug absorbed (FA) in relation to time. These FA values were analyzed against the dissolved fraction (FD) data obtained by the proposed dissolution method. The results were evaluated by linear regression analysis in order to obtain an IVIV correlation for MAN.

2.7. Validation of dissolution procedure

The validation process is fundamental for ensuring that an analytical methodology is accurate and reproducible over the specified range [16]. In order to demonstrate that the method was adequate for dissolution test purposes, it was validated by analyzing specificity, linearity, precision and accuracy, following the current international guidelines [17,18]. Moreover, the drug stability, dissolution medium deaeration and filter suitability were assessed.

To prepare the sample solutions for validation procedure, tablets containing 30 mg of DEL and 10 mg of MAN were weighed and crushed to fine powder. An amount of 120 mg (equivalent to

average weight of tablets) was transferred into a 10 mL volumetric flask, diluted to volume with methanol, kept in vortex for 5 min, sonicated for 10 min and filtered through a 0.45 μm membrane filter (Millipore Corp) to obtain sample solutions with theoretical concentrations of 3.0 mg/mL for DEL and 1.0 mg/mL for MAN. The sample solutions were stored at 2–8 °C, protected from light and diluted to an appropriate concentration with the respective medium for each case.

3. Results and discussion

3.1. Solubility and sink conditions evaluation

In this protocol, the solubility test (Table 1) showed that DEL presented sink conditions at all the tested media. On the other hand, some inconsistent results for MAN were observed using acetate buffer pH 4.5 (total dose dissolved, but without sink conditions) and phosphate buffer pH 6.8 (unable to dissolve the drug). According to the international guidelines, the sink conditions are desirable, but not mandatory [1,18]. However, the solubility results were used as the basis for the selection of dissolution medium for DEL and MAN tablets and also for ensuring sink conditions.

3.2. Dissolution method optimization

In order to develop a suitable dissolution method for simultaneous release analysis of DEL and MAN in combination tablets, several conditions were evaluated. Preliminary tests were conducted using the USP apparatus 2 (paddle) at 50 rpm, with 900 mL of medium volume (37 ± 0.5 °C).

The dissolution test must be accomplished in at least three different dissolution media, spanning the physiological pH range [1]. In this context, several dissolution media were initially tested, including 0.1 M and 0.01 M HCl, water, citrate buffer pH 3.0, acetate buffer pH 4.5, and phosphate buffer pH 6.8. All of the dissolution media were prepared according to USP requirements [18].

The results showed that 0.1 M HCl provided fast and complete release for DEL and MAN (> 80% at 15 min) (Fig. 2A) and also ensured sink state. Accordingly, these conditions conform to the recommendations for quality control of immediate release tablets and can be considered promising for its evaluation in different production batches [1].

The fast and high drug dissolution may affect the discriminative ability of the method and the *in vivo* behavior of the pharmaceutical product after oral administration [2]. Therefore, the method screening was desired in order to obtain an adequate differentiation of the drugs release at the initial collection times, which improved the potential discriminative power of the method.

The DEL and MAN release remained limited using acetate buffer pH 4.5, phosphate buffer pH 6.8 and water as dissolution media. In order to improve the drugs dissolution, the rotating of

Table 1
Solubility test of DEL and MAN in different dissolution media at 37 °C.

Medium	Concentration (μg/mL)	
	DEL	MAN
0.1 M HCl	14302.9	144.2
Citrate buffer pH 3.2	6949.4	87.1
Acetate buffer pH 4.5	2350.9	19.4
Phosphate buffer pH 6.8	5022.8	ND

*ND = not detected.

the apparatus (speed of 50 and 75 rpm) and the addition of a sodium dodecyl sulfate (SDS) surfactant (concentration of 0.1% and 0.5%) were also investigated. Some of these results are shown in Fig. 2B and C. The results showed no relevant improvement after these changes in the dissolution conditions, which suggests that the drugs release depends on a sum of different factors such as rotational speed, drugs lipophilicity and ionization.

Changes in the pH of the dissolution medium can cause significant alterations in the drug ionization and modify its solubility [19]. During the method development, the dissolution media tested in the acid pH range showed increased release for DEL and MAN. Thus, the citrate buffer at the pH range of 2.5–3.5 was studied, and better results for gradual release were obtained using citrate buffer at pH 3.2.

Based on these results, the use of citrate buffer (50 mM; pH 3.2) as dissolution medium (900 mL) in combination with paddle at rotation of 75 rpm resulted in an appropriate and reproducible dissolution profile of both drugs, allowing the simultaneous quality control of DEL and MAN in combination tablets, as well as a promising condition for MAN IVIV correlation study. The dissolution results and overlay profile of DEL and MAN are shown in Table 2 and Fig. 2D, respectively.

3.3. In vivo data evaluation

The biopharmaceutical classification system (BCS) is an established approach for drugs classification based on their aqueous solubility and intestinal permeability [20]. Correlation between *in vivo* results and dissolution tests (*in vitro* results) may be expected for class II drugs, because in this case, the dissolution rate is the primary limiting aspect of absorption [3,4].

The BCS of DEL was not found in the research literature. Moreover, the DEL pharmacokinetic data are primarily related to its active metabolites, which adds difficulties to the direct analogy with *in vitro* dissolution data. Thus, the mathematical evaluation of the *in vivo* data was performed only for MAN.

According to the BCS, MAN is a class II drug [21], which presents a low solubility (1.0 μg/mL) and high permeability (*logP* ∼ 5.5) [22,23]. Moreover, the drug exhibits high first-pass metabolism and hence has a low systemic bioavailability [23]. Thus, in the biopharmaceutics drug disposition classification system (BDDCS), a BCS modification, the drug could also be classified as class II (low solubility and extensive metabolism), suggesting a high permeability and, thus, a high absorption [24,25].

As previously mentioned, *in vivo* oral data of MAN were obtained from the literature [14], and analyzed by a non-linear regression software. The two-compartment open model could describe the plasma concentration curve versus time of MAN, and the best fitting was proved through the statistical parameters of model selection criteria (2.44) and coefficient of correlation (0.981). Based on the oral data parameters, it was possible to obtain the distribution rate constants of the drug between the compartments (k_{12} and k_{21}) and simulate the intravenous data for MAN (data not described in the literature). The simulated oral and intravenous curves are shown in Fig. 3. The model ability in describing the data obtained was proved through the bioavailability calculation using the area under the curve (AUC) of oral and intravenous simulations. The result showed a very low systemic bioavailability of MAN, corroborating with other dihydropyridine derivatives (1%–10%) [26,27].

The modeling parameters were used to estimate the intermediate oral and intravenous plasma concentration data points of MAN in the same sampling time of the dissolution method. Using the deconvolution approach (Microsoft Office Excel 2010 as statistical software), the data were transformed into fraction of FA versus time for IVIV correlation evaluation.
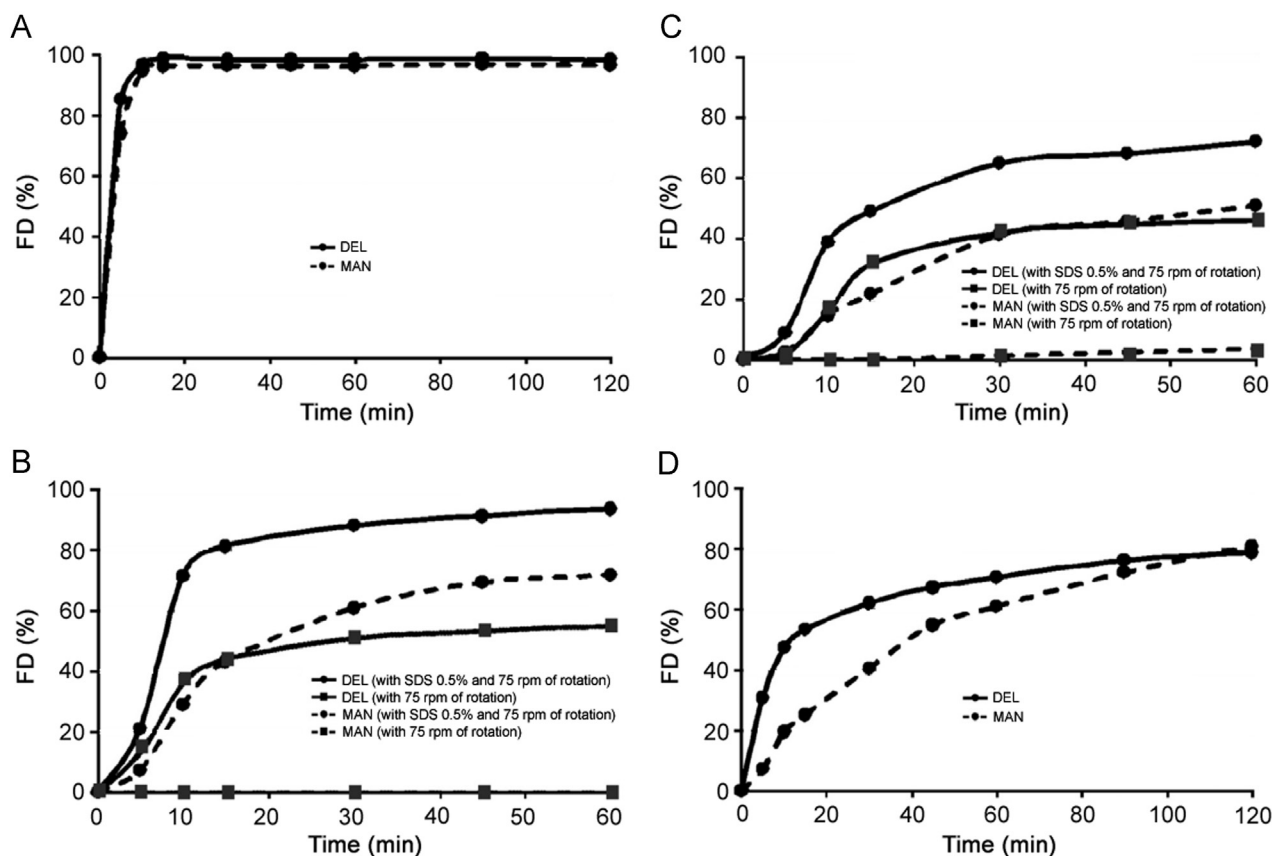
Fig. 2. Dissolution profiles of DEL and MAN combination tablets ($n=6$) using (A) 0.1 M HCl (50 rpm); (B) phosphate buffer pH 6.8 (50 rpm) and phosphate buffer 6.8 added of 0.5% SDS (75 rpm); (C) acetate buffer pH 4.5 (50 rpm) and acetate buffer pH 4.5 added of 0.5% SDS (75 rpm); and (D) citrate buffer pH 3.2 (75 rpm).

Table 2
Dissolution test in pH 3.2 citrate buffer using apparatus 2 at 75 rpm ($n=6$).

Time (min)	DEL		MAN	
	Dissolution (%)	RSD (%)	Dissolution (%)	RSD (%)
10	47.30	2.91	19.42	7.69
15	53.23	1.72	25.06	0.93
30	61.89	2.06	40.59	4.35
45	67.16	1.46	54.69	5.18
60	70.56	1.54	60.89	7.35
90	76.18	1.15	72.15	8.78
120	80.02	2.65	80.72	2.32

The aim of developing IVIV correlation is to establish a rational relationship between a biological property and a percent of FD in order to allow the *in vitro* data to be used as a surrogate for *in vivo* behavior [3]. The correlation for this particular formulation containing MAN was evaluated using the linear regression analysis and the validity of the correlation model. The utilization of citrate buffer pH 3.2 as dissolution medium showed an excellent correlation ($R=0.997$) between the FA and FD, with slope value of 1.00 (Fig. 4A). These results were considered suitable due to the optimum slope value and the linear relationship, which suggests that the dissolution profile can be representative of the drug absorption [18,28].

Additionally, the internal validation was also performed. This approach could be used to verify if the correlation model accurately describes the data used for its development [3,29]. The determination was done by calculating the internal prediction error between the observed and predicted FA using the correlation equation ($y=1.00x - 5.28$). The obtained difference was less than

10% at all verified points (Table 3), showing the validity of the developed correlation, which can be used to simulate an *in vivo* MAN profile. The overlay of FD, FA calculated and FA predicted by the correlation model is shown in Fig. 4B.

3.4. Validation of dissolution method

3.4.1. Specificity
The specificity of the proposed method was established by preparing the placebo samples (mixture of all of the tablet excipients in their usual concentration in pharmaceutical formulations) without the active ingredient. The samples were transferred to separate vessels ($n=3$) with 900 mL of the dissolution medium (37 ± 0.5 °C), and stirred for 120 min at 75 rpm using paddle. Aliquots were withdrawn, filtered and analyzed by LC.

The chromatograms demonstrated no interference of pharmaceutical excipients in the same retention time of both drugs (Fig. 5). Moreover, an excellent peak purity was obtained by PDA detector, showing that the DEL and MAN signals were free from co-eluting peak.

3.4.2. Linearity
Three independent analytical curves with seven concentrations of both drugs were constructed for linearity evaluation. The analyzed ranges were from 0.75 to 45 µg/mL (0.75, 1.5, 3, 9, 15, 30, 45 µg/mL) for DEL and 0.25 to 15 µg/mL (0.25, 0.5, 1, 3, 5, 10, 15 µg/mL) for MAN. All solutions were prepared using the dissolution medium as diluent. The results were subjected to linear regression analysis by the least squares method and analysis of variance (ANOVA) for assuring the linear fit.

The analytical curves were found to be linear with adequate values of coefficient of determination (R^2) for DEL ($R^2=0.9985$)
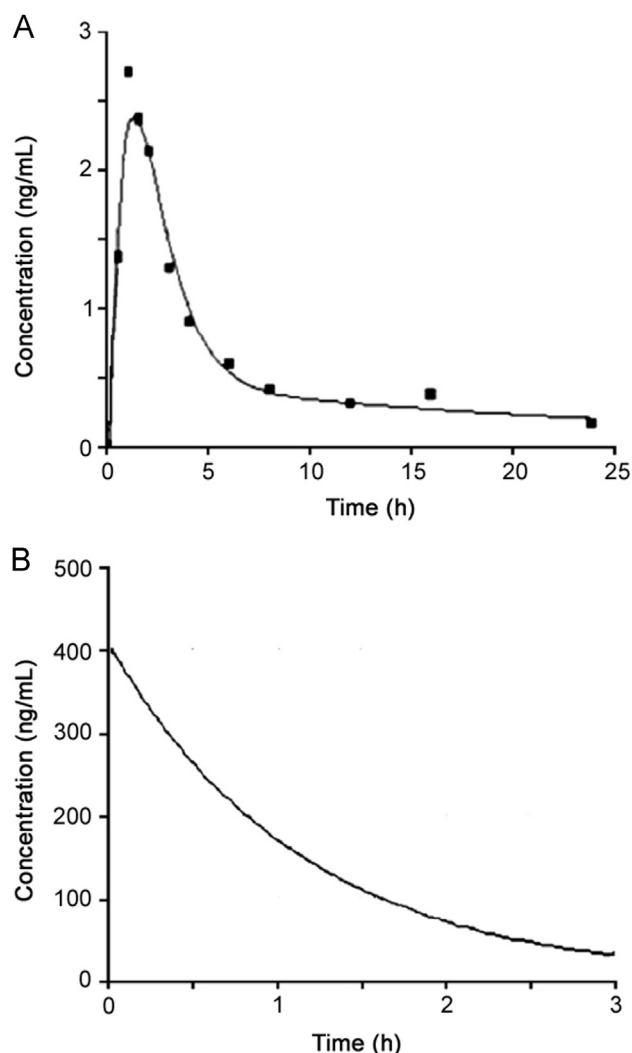
Fig. 3. Plasmatic profiles of MAN. Superposition of experimental values: (A) simulated oral curve (black symbols from [14]) and (B) Simulated intravenous curve.

Fig. 4. (A) Plot for the mean FA versus FD of MAN using citrate buffer pH 3.2 as dissolution media and (B) Plot for MAN FD, MAN FA calculated and MAN FA predicted by the correlation model.

Table 3
Prediction errors calculated between the observed and predicted FA for MAN using the *in vitro-in vivo* correlation equation ($y = 1.00x - 5.28$).

Time (min)	FD (%)	FA observed	FA predicted	Error (%)
10	19.42	15.14	14.23	5.97
15	25.06	21.76	19.90	8.52
30	40.59	33.36	35.51	− 6.44
45	54.69	47.32	49.67	− 4.97
60	60.89	54.77	55.91	− 2.08
90	72.15	68.53	67.22	1.91
120	80.72	77.39	75.83	2.02

and MAN ($R^2 = 0.9956$). Moreover, the ANOVA results showed significant linear regression ($p < 0.05$) and no deviation from linearity ($p > 0.05$) for both compounds, indicating the linearity of the analytical method.

3.4.3. Accuracy and precision

The accuracy of the dissolution method was accomplished by the recovery test of known concentrations of both drugs sample solutions added to dissolution medium. Aliquots of 2.0, 10.0 and 12.0 mL of DEL and MAN sample solutions (previously mentioned) were added to vessels ($n = 2$) containing dissolution medium and placebo to a final volume of 900 mL, pre-heated at 37 ± 0.5 °C and rotated with paddle at 75 rpm. The theoretical concentrations were 6.67, 33.33, and 39.99 µg/mL for DEL and 2.22, 11.11, and 13.34 µg/mL for MAN, respectively corresponding to 20%, 100%, and 120% of the nominal assay concentration. Aliquots of the sample solutions were withdrawn after 120 min and analyzed by LC. The same solutions used in the accuracy test were analyzed in order to assess the precision of the method. Repeatability (intra-day) and intermediate precision (inter-day) were evaluated based on the relative standard deviation (RSD) of the results.

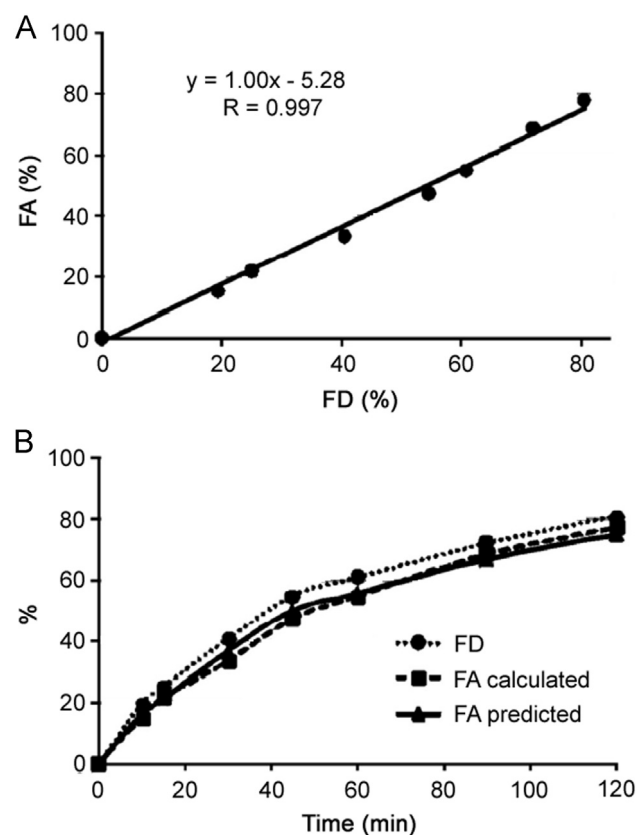Method accuracy/precision was evaluated on two different days, and the mean percentage recovered comprising the three levels added ($n = 2$) was 99.02% for DEL and 101.70% for MAN, indicating that the method is accurate within the desired range. Moreover, the low RSD ($\leq 2.85\%$ for both drugs) demonstrated adequate precision of the method. The results are presented in Table 4.

3.4.4. Drugs stability

The drugs stability in the optimized dissolution medium was studied, which verified the chromatograms obtained by the LC method (peak area decreasing and degradation products formation). The results showed that both DEL and MAN were stable in the test conditions for 120 min at the temperature of 37 ± 0.5 °C (total time of dissolution test) and after 24 h at room temperature (24 ± 2 °C). There was no evidence of degradation for both drugs under these conditions.
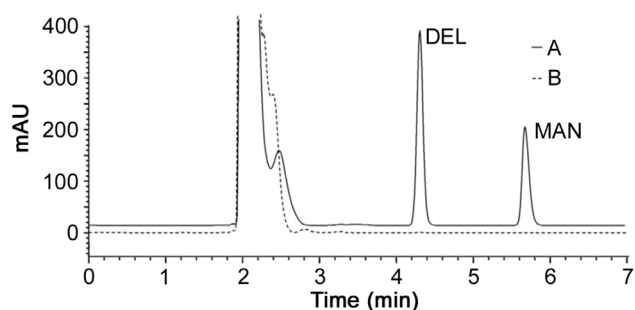
Fig. 5. Overlapping LC chromatograms for (A) DEL and MAN reference solution; (B) placebo sample solution. Chromatographic conditions: Shim-Pack C_8 column (250 mm × 4.6 mm, 5 μm), 35 °C; mobile phase: acetonitrile/0.3% triethylamine (pH 3.0) (55:45, v/v); flow rate: 1.2 mL/min; detection: 220 nm.

Table 4
Accuracy and precision of the proposed dissolution method.

Drug	Concentration (μg/mL)	Day	Accuracy (%)		Precision (RSD, %)	
			Intra-day	Inter-day	Intra-day	Inter-day
DEL	6.67 (20%)	1	99.52	100.26	0.38	1.05
		2	101.01		1.83	
	33.33 (100%)	1	98.15	98.28	1.48	0.18
		2	98.40		1.88	
	39.99 (120%)	1	98.39	99.76	1.50	1.94
		2	101.13		1.52	
MAN	2.22 (20%)	1	101.76	101.25	1.08	0.70
		2	100.75		2.85	
	11.11 (100%)	1	100.73	102.26	2.39	2.11
		2	103.78		0.10	
	13.34 (120%)	1	99.56	101.14	0.92	2.21
		2	102.72		0.64	

3.4.5. Filter suitability and medium deaeration

The filter suitability was evaluated like the accuracy test. The sample solution was added to the vessels at 37 ± 0.5 °C to obtain a theoretical concentration of 33.33 μg/mL for DEL and 11.11 μg/mL for MAN. After 120 min of agitation, aliquots were withdrawn and automatically filtered using 10 μm filters. The same procedure was performed, but the aliquots were centrifuged for 5 min at 3000 rpm instead of being filtered. Then, these solutions were filtered (0.45 μm), analyzed by LC method and compared. The different filters did not interfere in the results of the analysis, giving values within 98%–102% for the filtered samples compared with the centrifuged solutions, as specified [18].

Finally, to complete the dissolution validation, the medium deaeration was checked. The dissolved air can change the pH of an unbuffered solution and interfere with the fluid-flow patterns through bubble formation [30]. Thus, the dissolution profiles were performed with deaerated (by ultrasonic bath at 37 ± 0.5 °C during 10 min) and non-deaerated media. No significant difference on results was observed; therefore, the deaeration was not necessary.

4. Conclusion

The *in vitro* dissolution evaluation is essential for providing process control and quality assurance of pharmaceutical products and can indicate the *in vivo* performance of the formulation [1,3]. The dissolution test for DEL and MAN immediate-release tablets was developed using 900 mL of citrate buffer pH 3.2 as dissolution medium and paddle (USP apparatus 2) at 75 rpm of rotation. The percentage of drugs dissolved was determined by the LC method.

These conditions provided an adequate coefficient of correlation between the FD and FA for MAN, and an IVIV correlation for this particular formulation was possible to be established. The proposed dissolution method was successfully validated according to the international requirements [17,18], proving to be adequate for DEL and MAN analysis, and contributing to the improvement of the quality control of pharmaceutics and minimizing the number of bioavailability studies.

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