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Original Article

SIMULTANEOUS DETERMINATION OF NAPROXEN SODIUM AND ACETAMINOPHEN IN FIXED-DOSE COMBINATIONS FORMULATIONS BY FIRST-ORDER DERIVATIVE SPECTROSCOPY: APPLICATION TO DISSOLUTION STUDIES

JOSE RAUL MEDINA*, CARLOS ALFONSO LOPEZ-TABLEROS, GERARDO HERNANDEZ-ALTAMIRANO, GEORGINA ALARCON-ANGELES, MARCELA HURTADO, ADRIANA MIRIAM DOMINGUEZ-RAMIREZ

Departamento de Sistemas Biológicos, Universidad Autónoma Metropolitana-Xochimilco, Mexico DF, Mexico.
Email: rmlopez@correo.xoc.uam.mx

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ABSTRACT

Objective: To validate and apply a new and easy zero-crossing derivative method for the simultaneous determination of naproxen sodium and acetaminophen in fixed-dose combinations formulations.

Methods: Measurement was achieved using the first-derivative (^{1}D) signals at 243.42 nm for naproxen sodium and at 297.10 nm for acetaminophen. The method was validated according to International Conference on Harmonization (ICH) guidelines and was used to obtain the dissolution profiles (USP Apparatus 2, 75 rpm and 900 ml of 0.1 M phosphate buffer pH 7.4) of five generic products and the reference product Febrax® (275/300 mg of naproxen sodium and acetaminophen, respectively). Dissolution data: percent of drug dissolved at 60 min, mean dissolution time (MDT) and dissolution efficiency (DE) were compared by a univariate one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparisons test. Differences were considered significant if *P<0.05. Additionally, data were adjusted to different kinetic models.

Results: The method was linear (R^2>0.99, *P<0.05) in the range of 10–50 µg/ml and 100–300 µg/ml for naproxen sodium and acetaminophen, respectively. The within-day and between-day precision and accuracy were within the acceptable criteria (relative standard deviation (RSD)<3% and 100±3%). Significant differences in MDT and DE values from all studies products were found (*P<0.05). All dissolution profiles were adjusted to Weibull's kinetics and significant differences in *Td* values were found (*P<0.05).

Conclusion: The proposed derivative spectrophotometry method can be used for the simultaneous determination of naproxen sodium and acetaminophen in dissolution studies. The method is rapid, simple, accurate, and precise without the need of high cost investment.

Keywords: Naproxen sodium, Acetaminophen, First-order derivative spectroscopy, Zero-crossing method, Fixed-dose combinations formulations.

INTRODUCTION

Naproxen sodium [(*S*)-6-Methoxy-α-methyl-2-naphthaleneacetic acid sodium salt] is a non-steroidal anti-inflammatory drug (NSAID) used in pain treatment, fever and inflammation caused by migraine, rheumatoid arthritis and degenerative joint diseases. It is also used for the primary dysmenorrheal, fig. 1. Due to poor solubility of naproxen (weak acid with pka = 4.15) naproxen sodium is prepared to enhance the dissolution properties of naproxen. According to Biopharmaceutical Classification System (BCS) drugs with low solubility/high permeability belong to Class II drugs [1]. For this kind of drugs, dissolution is the rate-limiting step for absorption and a significant *in vitro*/*in vivo* correlation (IVIVC) is expected. Acetaminophen, also named as paracetamol [*N*-Acetyl-p-aminophenol], is an effective and safe analgesic-antipyretic drug widely used for the relief of mild to moderate pain, fig. 1. Acetaminophen is a Class III drug [2] with high solubility/low permeability and by the previously reported information there is a monograph that suggests the waiver of bioequivalence studies by *in vitro* dissolution studies [3]. The combination of naproxen sodium and acetaminophen (as fixed-dose combinations formulations) is widely used as over-the-counter products and it is used for the treatment of symptomatic pain and fever.

In vitro dissolution studies are useful to assess the lot-to-lot quality of pharmaceutical formulations, changes in their manufacturing process and prediction of *in vivo* performance of some drugs. United States (US) Pharmacopeia describes by separate the *in vitro* dissolution test for naproxen sodium and acetaminophen tablets [4] but to date, no official dissolution method is described for naproxen sodium and acetaminophen in fixed-dose combinations formulations [5]. The development of fixed-dose combinations products is becoming increasingly from a public health perspective and has advantages when all the actives contribute to the overall therapeutic effect. Dissolution studies for this kind of formulations are data required for approval of fixed-dose combinations [6].

There is enough information for the individual quantification of naproxen sodium and acetaminophen by different analytical methods [7, 8]. However, information about simultaneous determination of these drugs in the same formulation is scarce. A high-performance liquid chromatography (HPLC) method was previously reported [9]. Electrochemical determination was used for simultaneous determination of both drugs in pharmaceutical formulations [10] and biological fluid [11] however, for all these techniques special equipment is required. On the other hand, spectroscopic methods are widely used for identification of metal ions, pharmaceutical compounds and food ingredients [12–14]. Derivative spectrophotometry is an economic and useful technique for the suppression of additive interferences due to compounds mixture with overlapping spectra. Despite these advantages, none derivative spectrophotometry methodology for simultaneous quantification of naproxen sodium and acetaminophen in fixed-dose combinations formulations has been previously reported.

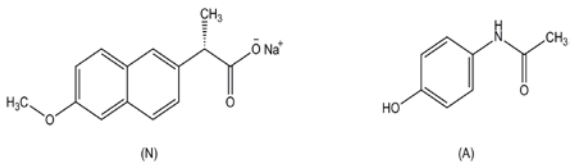

Fig. 1: Chemical structures of naproxen sodium (N) and acetaminophen (A)

The purpose of this study was to validate and apply a simple, economic and rapid zero-crossing ^{1}D spectrophotometric method for the simultaneous determination of *in vitro* dissolution profiles of naproxen sodium and acetaminophen in fixed-dose combinations

generic formulations and to compare their dissolution profiles with the dissolution profiles of naproxen sodium and acetaminophen from the reference product Febrax® (Mexico). The method was validated according to ICH guidelines and dissolution profiles were compared by model-dependent and-independent approaches.

MATERIALS AND METHODS

Materials

Five fixed-dose generic formulations were used in this study. Naproxen sodium and acetaminophen doses were 275/300 mg, respectively. Different letters were assigned to each drug product (A, B, C, D, and E). Dissolution profiles of generic drugs were compared to dissolution profile of the Mexican reference (R) product Febrax® (Siegfried Rhein, S. A. de C. V., Mexico). Phosphate salts were purchased from J. T. Baker-Mexico. Naproxen sodium and acetaminophen standards were purchased from Sigma-Aldrich Co. (St. Louis MO, USA). All dissolution medium were filtered through glass microfiber filters (Whatman®, UK).

Content uniformity and assay

Content uniformity and assay tests were performed by HPLC with all fixed-dose combinations formulations, according the procedures described by Singh *et al.* [9].

Standard solutions

Stock solutions of naproxen sodium and acetaminophen in 0.1 M phosphate buffer pH 7.4 were separately prepared by dissolving 10 mg of naproxen sodium in 100 ml of 0.1 M phosphate buffer pH 7.4 and 25 mg of acetaminophen in 25 ml of 0.1 M phosphate buffer pH 7.4. Standard solutions were prepared by serial dilutions of the stock solutions to contain the required concentrations for the calibration curves. Naproxen sodium and acetaminophen calibration curves in 0.1 M phosphate buffer pH 7.4 were prepared in the concentrations range of 10–50 µg/ml and 100–300 µg/ml, respectively.

Instruments

For dissolution studies, USP Apparatus 2 (Sotax AT-7 Smart, Switzerland) rotating paddle was used. For spectrophotometric measurement, a double beam UV/VIS spectrophotometer (Perkin Elmer Lambda 35, Waltham MA, USA) with 0.1 cm quartz cells was utilized. The operating conditions for UV analysis were ^{1}D mode with scan speed 240 nm/min, slit width 2 nm and sampling interval 1 nm. The amounts of naproxen sodium and acetaminophen dissolved were determined at 243.42 and 297.10 nm respectively, with reference to standard calibration curves.

Analytical method validation

The proposed ^{1}D spectrophotometric method was validated according to ICH guidelines [15]. Method linearity, accuracy, precision were determined and drugs stability in dissolution medium was evaluated.

Linearity

To verify the validation of Beer's law, three series of calibration curves in 0.1 M phosphate buffer pH 7.4 were plotted using the ^{1}D spectra in the range of the calibration curve of each drug. Data obtained were fitted by linear regression analysis and the coefficients of regression and regression ANOVA were calculated. The response *versus* naproxen sodium or acetaminophen concentration proportionality was demonstrated for each drug by calculating the percentage RSD: [((standard deviation)/mean) × 100] of the response factor across the entire range of the calibration curve.

Accuracy and precision

In order to verify the accuracy and precision of the proposed derivative analysis, the added standard method was used, thus matrix effects can easily be removed. This method can be used for resolving binary mixtures in complex samples with unknown matrices as commercial oral dosage forms have. Twenty tablets were accurately weighed and milled in a mortar; then, quantities of powder of naproxen sodium/acetaminophen tablets plus a quantity of naproxen sodium or acetaminophen standard (10 mg) to finally give the equivalent of 80, 100 and 120% of the dose of each drug, were separately dissolving in 900 ml of 0.1 M phosphate buffer pH 7.4 at 37.0±0.5 ºC. The USP Apparatus 2 at 75 rpm was used. At 60 min, the amounts of naproxen sodium and acetaminophen dissolved in each sample were calculated with reference to a calibration curve prepared on the day of the experiment. Each determination was performed in triplicate. The percentage relative error (RE): [((found–added)/added) × 100] was taken as a measure of the accuracy and the RSD as a measure of precision. Experiments were done in three consecutive days.

Stability

Stability of analytical solutions was evaluated analyzing two solutions of naproxen sodium (15 and 45 µg/ml) and two solutions of acetaminophen (140 and 260 µg/ml) prepared in 0.1 M phosphate buffer pH 7.4. These solutions are a low and a high concentration of the calibration ranges and were analyzed by the proposed ^{1}D spectrophotometric method at 0, 24 and 48 h after stored at 4 ºC. At 24 and 48 h, the percentage absolute difference (AD): [((initial–final)/initial) × 100] recovered of each drug was determined.

Dissolution studies

Naproxen sodium and acetaminophen dissolution profiles were performed using USP Apparatus 2. Tablets were added on 900 ml of 0.1 M phosphate buffer pH 7.4 at 37.0±0.5 ºC as dissolution medium (n = 12). Prior to use, the dissolution medium was deareated by vacuum. Rotational speed of 75 rpm was tested. 10 ml of filtered samples were withdrawn at 10, 20, 30, 45, and 60 min without replacement of dissolution medium. The samples were then analyzed by the ^{1}D proposed methods to know the rate and extent of dissolution of naproxen sodium and acetaminophen from all fixed-dose combinations formulations used.

Data analysis

Naproxen sodium and acetaminophen dissolution profiles were compared with similarity factor f_2 [16]. Additionally, dissolution data of each product were used to calculate model-independent parameters: % dissolved at 60 min, MDT [17] and DE [18]. The values of these parameters from generic drugs were compared with the reference product values by ANOVA followed by Dunnett's or Dunnett's T3 multiple comparisons test as appropriate. Data analysis was carried out using SPSS software (Version 17.0). Differences were considered significant if *P<0.05.

Table 1: Content uniformity and assay results. Mean, n = 10

Product	Drug	Content uniformity (min–max)	Assay (%)
R	N	(98.65–102.45)	100.44
	A	(99.25–103.07)	101.05
A	N	(99.35–104.14)	102.15
	A	(96.48–101.13)	100.34
B	N	(101.80–104.50)	102.96
	A	(98.49–101.10)	99.61
C	N	(100.53–102.24)	101.47
	A	(98.90–100.59)	99.83
D	N	(100.97–104.56)	102.64
	A	(100.21–103.77)	101.87
E	N	(101.19–102.27)	101.65
	A	(97.67–98.72)	98.12

Moreover, in order to evaluate the release kinetics of naproxen sodium and acetaminophen from the studied products, dissolution data were fitted to different kinetic models: First order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell and Weibull. The model with highest determination coefficient ($R^2_{adjusted}$) and minimum Akaike Information Criterion (AIC) was chosen as the best fit [19]. Data analysis was carried out using Excel add-in DDSolver program [20]. To compare dissolution profiles with model-dependent methods a parameter derived from the best fit model was compared with a univariate one-way ANOVA followed by Dunnett's or Dunnett's T3 multiple comparisons test. Differences were considered significant if *P<0.05.

RESULTS AND DISCUSSION

Content uniformity and assay

The percentages of naproxen sodium and acetaminophen on the assay and content uniformity tests are shown in table 1.

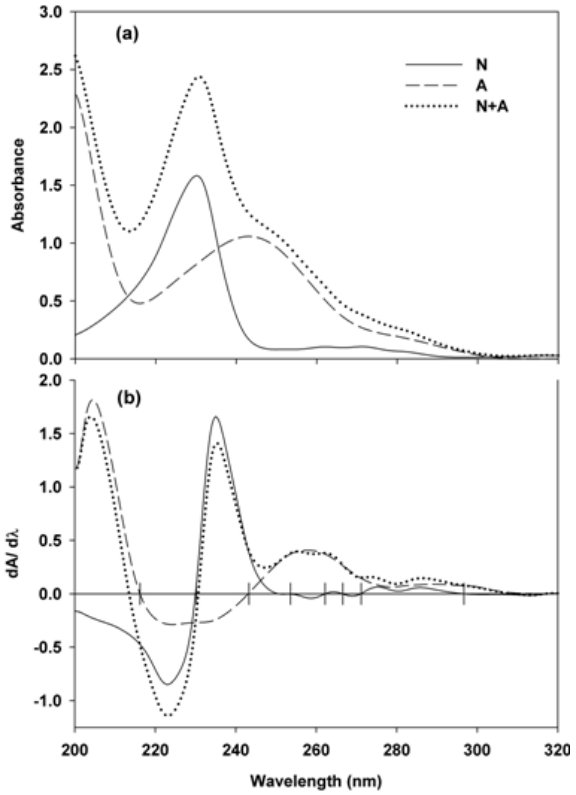

Fig. 2: Zero-order spectra of 30 µg/ml of N, 150 µg/ml of A and their mixture (N+A) at the same concentrations in 0.1 M phosphate buffer pH 7.4 (a) and first-derivative spectra of the same solutions (b). Small vertical lines indicate zero-crossing points

^{1}D spectrophotometric method

The zero-order spectra of naproxen sodium (30 µg/ml) and acetaminophen (150 µg/ml) standard solutions in 0.1 M phosphate buffer pH 7.4 were separately and combined measured at 200–320 nm using 0.1 M phosphate buffer pH 7.4 as blank, fig. 2a. The zero-order spectra demonstrated a marked overlapping. As a result, simultaneous direct spectroscopy determination of naproxen sodium and acetaminophen in fixed-dose combination products was not possible. Then, the ^{1}D spectra of these solutions was obtained, fig. 2b. As seen in fig. 2b, the ^{1}D spectra of naproxen sodium revealed six zero-crossing points for acetaminophen determination (230.51, 253.29, 262.41, 266.96, 271.27 and 297.10 nm) and the ^{1}D spectra of acetaminophen revealed two zero-crossing points for naproxen determination (216.46 and 243.42 nm).

The ^{1}D spectra of naproxen sodium (10–50 µg/ml) and acetaminophen (100–300 µg/ml) standard solutions were determined, fig. 3. The suitable zero-crossing points were selected based on the best linear response to the naproxen sodium concentration in the presence of acetaminophen or the acetaminophen concentration in the presence of naproxen sodium. Only the ^{1}D response at 243.42 and 297.10 nm were proportional to the naproxen sodium and acetaminophen concentrations, respectively.

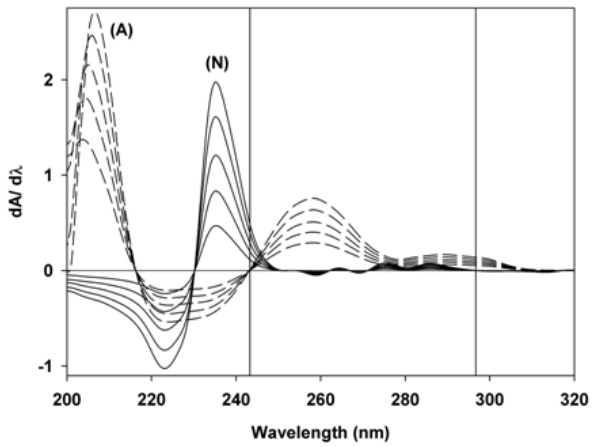

Fig. 3: First-derivative spectra of 10–50 µg/ml of N and 100–300 µg/ml of A in 0.1 M phosphate buffer pH 7.4. Vertical lines indicate 243.42 and 297.10 nm, respectively

Method validation

Linearity

The mean regression equation from three standard calibration curves was: y = 0.0065x+0.0131 for naproxen sodium and y = 0.0003x+0.0063 for acetaminophen. Both linear regressions were significant (R^2 = 0.99; *P<0.05). The RSD values of response factor were 2.3 and 2.0% for naproxen sodium and acetaminophen ranges, respectively.

Accuracy and precision

In order to prove the accuracy and precision of the proposed ^{1}D spectrophotometric method, analysis of varying percentage of dose of each drug was carried out for three days (n = 3/d). The within-day and between-day precision and accuracy were calculated, table 2. The RSD obtained was in the range of 0.81–2.84% and the RE was lower than 1.20% for both drugs which indicate good accuracy and precision of the method.

Table 2: Accuracy and precision data for simultaneous determination of N and A by first-order derivative spectroscopy. Mean±SD

		Within-day (n = 3)			Between-day (n = 9)		
Drug/dose (mg)	**Added (mg)**	**Found (mg)**	**RSD (%)**	**RE (%)**	**Found (mg)**	**RSD (%)**	**RE (%)**
N/275	221.29	221.79±1.98	0.89	0.23	221.09±2.57	1.16	−0.09
	277.27	279.02±2.25	0.81	0.63	278.13±3.22	1.84	0.49
	330.86	333.18±4.01	1.20	0.70	335.17±4.14	1.23	1.20
A/300	241.20	240.10±1.98	0.82	−0.46	237.30±4.63	1.95	−1.50
	299.81	301.03±8.56	2.84	0.41	303.25±5.80	1.91	1.03
	360.23	360.53±3.73	1.04	0.08	359.12±7.08	1.97	−0.52

Table 3: Absolute difference (%) respect zero time to evaluate stability at 4ºC of N and A in 0.1 M phosphate buffer pH 7.4. Mean, *n* = 6

Drug	Conc. (µg/ml)	24 h	48 h
N	15	3.73	7.54
	45	2.84	8.08
A	140	0.96	4.16
	260	0.29	4.46

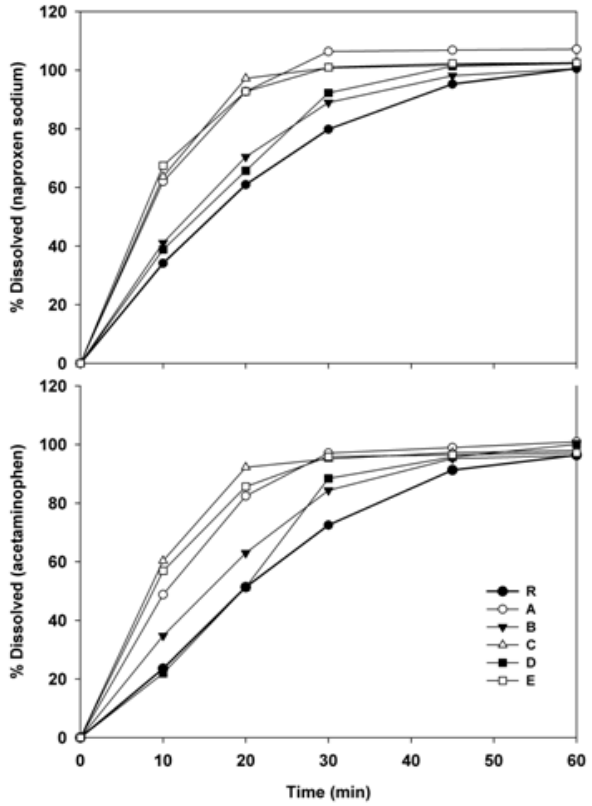

Fig. 4: Dissolution profiles from fixed-dose combinations formulations obtained with the proposed [1]D spectrophotometric method. Error bars were omitted for clarity. Mean, *n* = 12

Stability

The stability of the [1]D spectrophotometric method was assessed analyzing two solutions of naproxen sodium and two solutions of acetaminophen (low and high concentrations for each one). AD values at 24 and 48 h are shown in table 3. As seen in table 3, both drugs solutions were less stable at the second day of have been prepared.

Data obtained indicate good linearity, accuracy and precision of the proposed zero-crossing derivative method for simultaneous determination of naproxen sodium and acetaminophen in fixed-dose combinations formulations. According to complementary ICH guideline [21], limit of detection and limit of quantitation are characteristics not normally evaluated in dissolution assays. For both drugs, lack of linearity, accuracy, and precision was determined working out of the proposed range for the calibration curves.

Dissolution studies

Dissolution profiles of naproxen sodium and acetaminophen obtained with USP Apparatus 2 are shown in fig. 4. Dissolution rate of both drugs, from product R, was slower than the studied generic products. Both drugs were completely dissolved until 60 min. Naproxen sodium and acetaminophen dissolution profiles were compared with similarity factor f_2, fig. 5. Only dissolution profiles of naproxen sodium and acetaminophen from generic products B and D showed similar dissolution profiles to the reference product's profiles (f_2>50).

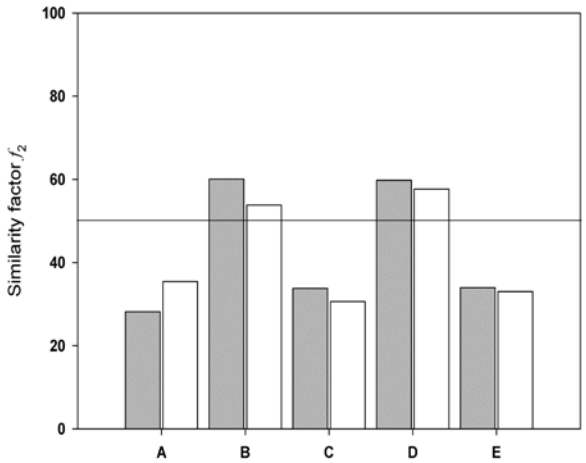

Fig. 5: Similarity factor f_2 calculated with dissolution data of naproxen sodium (grey bars) and acetaminophen (white bars) reference and fixed-dose combinations generic products

[1]D spectroscopic method was successfully applied for simultaneous determination of naproxen sodium and acetaminophen without interference of each other. The method was applied to routine *in vitro* dissolution studies. Almost all fixed-dose combinations formulations achieved 100% dissolved at 60 min and in all sampling times the RSD was lower than 10%.

Table 4: Percentage dissolved at 60 min and dissolution parameters MDT and DE. Mean±SEM, *n* = 12. *P<0.05

Drug	Product	% Diss. at 60 min	MDT (min)	DE (%)
N	R	100.56±0.82	18.92±0.26	68.86±0.74
	A	107.14±1.09*	10.67±0.33*	88.04±0.63*
	B	100.52±0.90	15.69±0.34*	74.22±0.74*
	C	102.61±1.59	9.64±0.39*	86.05±0.93*
	D	102.26±1.44	16.13±0.24*	84.08±4.13*
	E	102.51±0.57	9.59±0.23*	90.00±2.78*
A	R	96.35±0.69	21.12±0.45	62.44±0.90
	A	100.90±1.45	12.77±0.27*	79.44±1.30*
	B	96.20±1.43	16.57±0.29*	69.68±1.37
	C	97.98±0.40	9.91±0.36*	81.79±0.63*
	D	100.05±0.76*	19.79±0.27*	79.51±4.29*
	E	97.14±0.82	10.61±0.27*	82.50±3.52*

Model-independent comparisons

% dissolved at 60 min, MDT and DE mean values±standard error medium (SEM) for products under study are shown in table 4. Considering model-independent comparisons significant differences in dissolution profiles of all fixed-dose combination generic drugs were found (*P<0.05) except for DE value of acetaminophen from generic product B.

In order to compare the *in vitro* dissolution data of naproxen sodium and acetaminophen from fixed-dose combinations formulations, model-independent parameters MDT and DE were calculated. These parameters have been proposed as adequate parameters for some IVIVC levels [22]. IVIVC Level B represents a relationship between MDT and the mean residence time, both calculated by statistical moments theory. On the other hand, Level C represents a single point correlation between one dissolution time point ($t_{50\%}$, $t_{90\%}$, etc.) to one pharmacokinetic parameter such as area under the curve, C_{max} or T_{max}. DE was taken by some authors as a suitable parameter that expresses global drug dissolution performance useful for comparison of *in vitro* dissolution profiles [18].

Model-dependent comparisons

In order to describe the naproxen sodium and acetaminophen release kinetics from fixed-dose combinations formulations, data were fitted to several equations and results are shown in table 5. Considering established criteria to choose the best kinetic model (highest $R^2_{adjusted}$ and lowest AIC values) only naproxen sodium in products A, B and E as well as acetaminophen in products A, B, D, and E better fitted to Weibulls model. Acetaminophen in product R better adjusted to Makoid-Banakar's equation. According to Costa *et al.*, [23] Weibull's equation can be successfully applied to almost all kind of dissolution curves and is commonly used in these studies. Due to several formulations adjusted to Weibull's model and $R^2_{adjusted}$ values of both drugs in product R were>0.99 in this work comparison of dissolution profiles by a model-dependent approach was made analyzing the derived parameter (*Td*) from Weibull's function. *Td* value can be calculated with α and β values and is equivalent to the MDT value calculated with statistical moments. Significant differences in *Td* values for both drugs and between all fixed-dose combinations generic drugs and product R were found (*P<0.05), table 6.

Table 5: Criteria used for the selection of the best kinetic model. Mean, *n* = 12

Product	First-order	Higuchi	Korsmeyer-Peppas	Hixson-Crowell	Makoid-Banakar	Weibull
$R^2_{adjusted}$						
naproxen sodium						
R	0.9950	0.9474	0.9786	0.9933	0.9975	0.9969
A	0.9796	0.5752	0.9419	0.9695	0.9695	0.9825
B	0.9902	0.8707	0.9621	0.9913	0.9913	0.9933
C	0.9890	0.4246	0.9857	0.9889	0.9889	0.9891
D	0.9578	0.8819	0.9092	0.9756	0.9756	0.9692
E	0.9900	0.5439	0.9657	0.9855	0.9855	0.9904
acetaminophen						
R	0.9920	0.9636	0.9711	0.9953	0.9979	0.9971
A	0.9890	0.6596	0.9604	0.9557	0.9777	0.9914
B	0.9819	0.8909	0.9433	0.9801	0.9926	0.9985
C	0.9771	0.4551	0.9774	0.8724	0.9703	0.9830
D	0.9335	0.8816	0.8779	0.9630	0.9558	0.9786
E	0.9921	0.5592	0.9644	0.9403	0.9823	0.9942
AIC						
naproxen sodium						
R	14.82	27.45	22.68	14.70	16.85	12.20
A	18.22	34.74	24.34	28.08	16.17	17.05
B	16.11	30.53	24.48	17.14	15.01	14.41
C	11.88	34.51	9.68	30.22	3.15	3.34
D	24.53	31.28	29.87	23.92	22.06	20.43
E	9.60	32.54	17.56	29.13	9.80	6.17
acetaminophen						
R	18.35	26.15	25.30	15.50	10.58	13.28
A	16.06	34.83	23.16	22.99	18.39	14.94
B	21.33	30.34	27.46	21.49	14.26	–6.16
C	13.23	33.96	14.77	25.44	9.91	22.15
D	29.45	33.63	33.42	25.99	27.29	23.22
E	12.80	33.77	20.76	22.80	13.97	11.24

Table 6: Weibull's parameters and *Td* values derived from the data adjusted to this kinetic model. Mean, *n* = 12. *P<0.05

Drug	Product	α	β	F_{max}	*Td* (±SEM)
N	R	43.33	1.19	105.73	22.55±0.55
	A	27.16	1.29	107.93	11.36±0.28*
	B	36.83	1.26	101.86	17.22±0.46*
	C	98.24	1.74	101.93	10.04±0.36*
	D	52.95	1.35	104.58	18.06±0.28*
	E	15.22	1.17	102.75	9.46±0.27*
A	R	116.75	1.47	99.96	25.05±0.70
	A	49.69	1.43	100.58	13.43±0.31*
	B	59.48	1.37	98.07	18.92±0.44*
	C	432.23	1.91	97.29	10.16±0.29*
	D	638.64	2.02	99.77	22.13±0.18*
	E	24.36	1.32	97.23	11.10±0.23*

Previously, dissolution profiles (USP Apparatus 2, 50 rpm) of naproxen alone have been adjusted to Korsmeyer-Peppas kinetic model [24]. Drug was loaded in mesoporous silica materials (ideal materials for encapsulation of pharmaceutical drugs) and simulated intestinal fluid pH = 6.8 was used as dissolution medium. Other authors adjusted *in vitro* release of naproxen to Higuchi's equation [25]. In this case, naproxen was loaded in poly-ε-caprolactone, nanoparticles used for extending the pharmacological action and reducing the frequency of administration. On the other hand, dissolution profiles (USP Apparatus 1, 100 rpm) of acetaminophen alone were adjusted to both Korsmeyer-Peppas and Higuchi'smodel [26]. Drug release was evaluated in silicone adhesive matrix tablets. Assays were carried out with simulated intestinal fluid pH = 6.8 too. Almost all dissolution profiles obtained in the present work, with commercial products, adjusted to Weibull's kinetic model. This model has proven to be useful to describe *in vitro* release kinetics of poorly soluble drugs in immediate-release oral dosage forms [27–29].

CONCLUSION

^{1}D derivative spectroscopy is a useful technique for the simultaneous determination of naproxen sodium and acetaminophen dissolution profiles from fixed-dose combinations formulations without interference of each other and the matrix effect. This method could be used for the analysis of active pharmaceutical ingredients in dissolution studies and for quality control purposes. The method is rapid, simple, and economic without the need of high cost investment. Considering the observed differences between generic drugs, it is possible to state that naproxen sodium and acetaminophen in fixed-dose combinations products are candidates to demonstrate bioavailability differences and therefore, it will be necessary to evaluate their *in vivo* performance before considering that they are safely interchangeable.

CONFLICT OF INTERESTS

Declared None

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