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Original Article

IN VITRO EVALUATION OF NAPROXEN SODIUM AND ACETAMINOPHEN FROM FIXED-DOSE COMBINATION GENERIC DRUGS USING THE FLOW-THROUGH CELL METHOD

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ABSTRACT

Objective: The aim of this study was the *in vitro* evaluation of naproxen sodium and acetaminophen from fixed-dose combination generic drugs based on the hydrodynamic environment generated by the flow-through cell method (USP Apparatus 4).

Methods: Dissolution studies were carried out using a USP Apparatus 4 Sotax CE6 with 22.6 mm cells, laminar flow at 16 ml/min, and 0.1 M phosphate buffer pH 7.4 at 37.0±0.5 °C as dissolution medium. Both drugs were identified and quantified by a validated first-order derivative spectrophotometric method. Measurements were achieved at 243.26 and 297.0 nm for naproxen sodium and acetaminophen, respectively. Dissolution profiles of generic drugs were compared with similarity factor f_2, $t_{50\%}$, $t_{85\%}$, $t_{90\%}$ values as well as model-dependent and independent methods.

Results: According to f_2 values, dissolution profiles of all generic drugs were considered dissimilar to the dissolution profiles of the reference product (f_2<50). Significant differences in $t_{50\%}$, $t_{85\%}$, $t_{90\%}$, mean dissolution time and dissolution efficiency values were found (*P<0.05). Dissolution data better adjusted to Makoid-Banakar and Weibull's kinetic models.

Conclusion: The flow-through cell method was adequate for the *in vitro* evaluation of fixed-dose combination generic drugs containing naproxen sodium and acetaminophen. It should be necessary to evaluate the *in vivo* performance of fixed-dose generic formulations that contain naproxen sodium and acetaminophen in order to assure bioequivalence.

Keywords: Naproxen sodium, Acetaminophen, Flow-through cell method, Fixed-dose combination generic drugs, First-order derivative spectrophotometry.

INTRODUCTION

Generic drug products are off-patent formulations that contain the same active ingredient in the same dose as the reference product, and are administered by the same route [1]. At the clinic, is desirable to achieve the same therapeutic effect when the reference product is replaced by a generic formulation. The best way to assure an adequate *in vivo* performance of a generic drug is to conduct a bioequivalence study in humans. However, sometimes *in vitro* dissolution studies might contribute to establishing the inter-changeability of generic drugs [2].

From a public health point of view, the development of fixed-dose combination formulations has recently gained importance. These formulations are cheaper than the separate products [3]. During the development of fixed-dose formulations *in vitro* dissolution studies can be helpful in understanding the critical parameters that affect the *in vivo* performance of drugs [4].

In Mexico, the fixed 1:09 formulation of naproxen sodium and acetaminophen is marketed as an over-the-counter (OTC) product. Naproxen is a poorly soluble non-steroidal anti-inflammatory drug that is used for the treatment of rheumatoid disorders (arthritis and osteoarthritis), dysmenorrhea, and pain [5]. Acetaminophen shows adequate analgesic and antipyretic properties but weak anti-inflammatory activity and it is used in the symptomatic management of moderate pain and fever [6]. Co-administration of naproxen sodium and acetaminophen is indicated for the treatment of symptomatic pain and fever [7]. Chemical structures of both drugs are presented in fig. 1.

According to Biopharmaceutical Classification System, drugs are classified on the basis of their solubility and gastrointestinal permeability: Naproxen has been classified as a Class II drug [8] (low solubility/high permeability), and acetaminophen as a Class III drug [6] (high solubility/low permeability). *In vitro* dissolution studies might be used to predict *in vivo* performance for Class II drugs and an *in vitro/in vivo* correlation (IVIVC) can be expected. For certain drugs, international guidelines suggest the waiver of bioequivalence studies by *in vitro* dissolution studies; a bio-waiver monograph for acetaminophen tablets has been previously reported [6]. The pharmacopeial dissolution test for naproxen and acetaminophen tablets are separately described [9] but to date, no official dissolution test is indicated for the fixed-dose combination formulation [10].

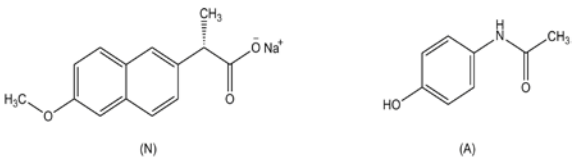

Fig. 1: Chemical structure of naproxen sodium (N) and acetaminophen (A)

A bioequivalence study for a fixed-dose combination formulation containing naproxen sodium and acetaminophen was previously published [7]. The study was carried out with healthy volunteers and 275/300 mg tablets. The test formulation was found to be bioequivalent to the corresponding reference product. On the other hand, an *in vitro* dissolution study of naproxen sodium and acetaminophen from different fixed-dose combination formulations was previously reported [11]. Dissolution profiles were carried out with the USP paddle apparatus at 75 rpm and 900 ml of 0.1 M phosphate buffer pH 7.4 as dissolution medium. Both drugs were quantified by a first-order derivative spectrophotometric method.

Using similarity factor f_2 only two of five commercial formulations were considered similar to the reference product (f_2 >50). With model-independent comparisons significant differences in all generic formulations were found (*P <0.05).

An alternative to evaluate the *in vitro* drug release from oral dosage forms is the open flow-through cell method (USP Apparatus 4) [12-14]. Its advantages over traditional closed rotating basket apparatus (USP Apparatus 1) and rotating paddle type (USP Apparatus 2) are widely demonstrated, especially in the dissolution of poorly soluble drugs [15-16]. IVIVC for these drugs has been established using the USP Apparatus 4 [17-18]. The method is more reliable, reproducible, and discriminative than others [19-20]. Therefore, it is important to investigate its utility on the assessment of naproxen sodium and acetaminophen dissolution profiles in fixed-dose combination formulations.

The objective of this study was to evaluate the *in vitro* release of naproxen sodium and acetaminophen from fixed-dose combination generic drugs based on the hydrodynamic environment generated by the flow-through cell method, USP Apparatus 4.

MATERIALS AND METHODS

Products and standard solutions

Five Mexican naproxen sodium and acetaminophen tablets (coded as A, B, C, D and E) from fixed-dose combination generic drugs (275 mg of naproxen sodium/300 mg of acetaminophen) were used. Dissolution profiles of these products were compared to the dissolution profiles of Febrax® product (Siegfried Rhein, S. A. de C. V., Mexico). Mexican health regulatory agency (COFEPRIS) has established this product as the reference to be used in bioequivalence studies [21]. 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 samples were filtered through 0.45 µm nitrocellulose filters (Millipore®, Ireland).

Standard solutions of both drugs were separately prepared by serial dilutions of the stock solutions of naproxen sodium (0.1 mg/ml) and acetaminophen (1 mg/ml) in 0.1 M phosphate buffer pH 7.4 to achieve concentrations of 10–50 and 100–300 µg/ml, respectively.

Content uniformity and assay

Content uniformity and assay tests were performed with all fixed-dose combination drugs, according to the procedures described in the USP [9].

Analytical method validation

The analytical method was previously validated according to ICH guidelines [22]. The system linearity, accuracy, and precision were analyzed.

Flow-through cell system

Dissolution profiles of naproxen sodium and acetaminophen tablets were obtained with an automated flow-through cell method [23-25] (Sotax CE6, Sotax AG, Switzerland) with 22.6 mm cells (i.d.) and a piston pump (Sotax CY7–50, Sotax AG, Switzerland). In all experiments, laminar flow (with a bed of 6 g of glass beads) at 37.0±0.5 °C was used. The deaerated 0.1 M phosphate buffer pH 7.4 at a flow rate of 16 ml/min was used as dissolution medium. Dissolution samples were withdrawn at 10, 20, 30, 45, and 60 min. In all cases, twelve tablets were used.

First-order derivative spectrophotometric analysis

Simultaneous determination of naproxen sodium and acetaminophen was carried out with a first-order derivative spectroscopic method [11]. A double beam UV/Vis spectro-photometer (Perkin Elmer Lambda 35, Waltham MA, USA) with 0.1 cm quartz cells was utilized. The operating conditions were the first-derivative mode with scan speed 240 nm/min, slit width 2.0 nm, and sampling interval 1.0 nm. The amounts of naproxen sodium and acetaminophen in each sample were determined at 243.26 and 297.0 nm respectively, with reference to standard calibration curves.

Data analysis

Dissolution profiles of naproxen sodium and acetaminophen of fixed-dose combination generic drugs were compared with dissolution profiles of the reference product using the similarity factor f_2. An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar. Furthermore, dissolution data of each formulation were used to calculate model-independent parameters: time to dissolved 50, 85, and 90% of the dose ($t_{50\%}$, $t_{85\%}$, $t_{90\%}$), mean dissolution time (MDT) and dissolution efficiency (DE). The values of these parameters 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. Additionally, in order to evaluate the release kinetics of naproxen sodium and acetaminophen from the generic drugs, dissolution data were fitted to different kinetic models: First-order, Higuchi, Hixson-Crowell, Makoid-Banakar, and Weibull. The model with a highest determination coefficient ($R^2_{adjusted}$) and minimum Akaike Information Criterion (AIC) was chosen as the best fit [26]. Data analysis was carried out using Excel add-in DD Solver program [27].

RESULTS AND DISCUSSION

Pharmacopeial tests

All fixed-dose combination generic drugs met the content uniformity and assay tests specified in the USP. The percentages of naproxen sodium and acetaminophen on the content uniformity test ranged from 85 to 115%, and the assay test was between 90 and 110% [11].

Analytical method validation

The analytical method validation was previously reported [11]. All fixed-dose combination generic drugs met standard validation criteria.

Dissolution profiles

Naproxen sodium and acetaminophen dissolution profiles obtained with the flow-through cell method, USP Apparatus 4, are shown in fig. 2.

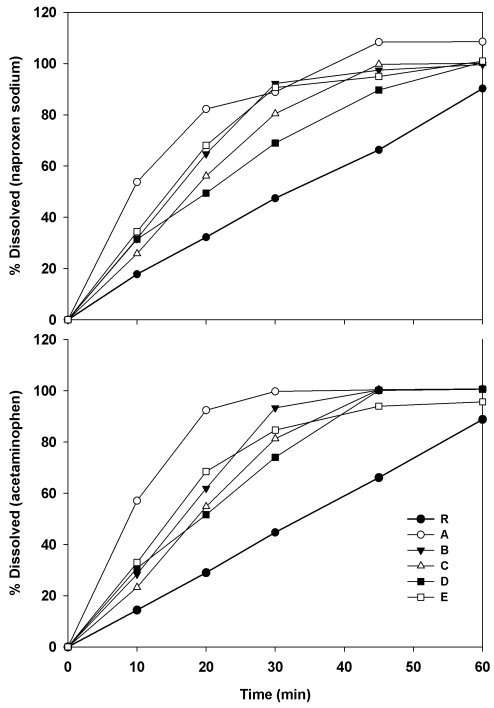

Fig. 2: Dissolution profiles of naproxen sodium and acetaminophen from reference (R) and fixed-dose combination formulations (A-E) using the flow-through cell method. Mean, *n*=12. Error bars were omitted for clarity

Results showed slower dissolution rates than those reported with the use of USP paddle method [11]. This behavior can be explained by the hydrodynamic conditions that characterize this dissolution

equipment that better reflects the natural environment of the gastrointestinal tract, causing different *in vitro* dissolution pattern [28]. In this study, flow rate of 16 ml/min was used because is one of the three flow rates (4, 8, and 16 ml/min) suggested by the American and European Pharmacopoeias [29]. Additionally, IVIVC using flow-through cell data at flow rates of 8, 16, and 32 ml/min has been previously discussed [30]. Similarity factor f_2 for each fixed-dose combination generic drugs are shown in fig. 3. By the results obtained (f_2<50) none of the dissolution profiles, of naproxen sodium or acetaminophen, of the generic formulations were considered similar to the dissolution profiles of the reference product.

Model-independent comparisons

$t_{50\%}$, $t_{85\%}$, $t_{90\%}$ values and model-independent parameters MDT and DE mean values±standard error medium (SEM) for the studied products are shown in table 1. Considering $t_{50\%}$, $t_{85\%}$, $t_{90\%}$ values and model-independent parameters, significant differences in dissolution profiles of naproxen sodium and acetaminophen from all fixed-dose combination generic drugs were found (*P <0.05).

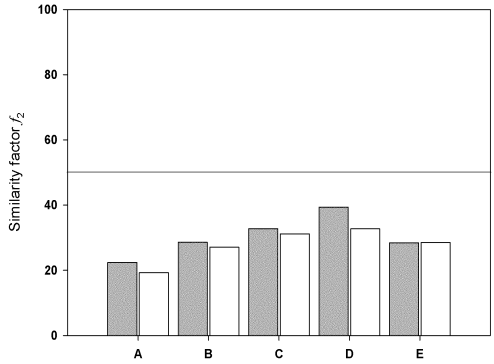

Fig. 3: Similarity factor f_2 of naproxen sodium (grey bars) and acetaminophen (white bars) from fixed-dose combination formulations (A-E). None dissolution profile was considered similar to the dissolution profile of the reference product (f_2<50).

Table 1: $t_{50\%}$, $t_{85\%}$, $t_{90\%}$ values and model-independent parameters: mean dissolution time (MDT) and dissolution efficiency (DE) from fixed-dose combination generic formulations (A-E). mean±SEM, *n*=12. *P<0.05

Code	$t_{50\%}$ (min)	$t_{85\%}$ (min)	$t_{90\%}$ (min)	MDT (min)	DE (%)
Naproxen sodium					
R	32.03±0.22	56.94±0.10	60.69±0.13	29.37±0.14	46.08±0.20
A	8.50±0.23*	23.76±0.43*	27.73±0.44*	14.75±0.17*	81.85±0.39*
B	13.23±0.20*	33.66±0.32*	38.36±0.32*	16.56±0.20*	72.09±0.32*
C	16.60±0.17*	37.72±0.21*	41.96±0.21*	19.34±0.13*	67.83±0.23*
D	19.04±0.27*	42.59±0.27*	47.24±0.24*	22.51±0.19*	83.77±1.05*
E	12.64±0.37*	33.20±0.60*	38.14±0.63*	17.01±0.37*	85.45±1.95*
Acetaminophen					
R	33.86±0.18	57.65±0.20	61.06±0.22	30.17±0.11	44.15±0.23
A	6.14±0.07*	20.43±0.18*	25.06±0.21*	10.29±0.13*	83.35±0.17*
B	13.97±0.14*	33.72±0.19*	37.98±0.18*	17.03±0.11*	72.12±0.20*
C	17.05±0.24*	37.78±0.29*	41.82±0.27*	19.71±0.16*	67.62±0.34*
D	17.45±0.26*	38.94±0.29*	43.16±0.26*	20.18±0.19*	84.35±0.98*
E	13.17±0.55*	36.14±0.92*	42.02±0.97*	16.11±0.44*	77.98±2.62*

Table 2: Criteria used for the selection of the best kinetic model

Code	First-order	Higuchi	Hixson-Crowell	Makoid-Banakar	Weibull
$R^2_{adjusted}$					
Naproxen sodium					
R	0.9210	0.8291	0.9598	0.9976	0.9853
A	0.8853	0.8118	0.9207	0.9514	0.8170
B	0.9128	0.8504	0.9617	0.9780	0.9945
C	0.9092	0.8866	0.9636	0.9974	0.9967
D	0.9482	0.9506	0.9864	0.9927	0.9955
E	0.9330	0.8615	0.9703	0.9639	0.9837
Acetaminophen					
R	0.9065	0.7941	0.9481	0.9987	0.9924
A	0.9279	0.1390	0.9238	0.9204	0.9966
B	0.8812	0.8405	0.9408	0.9801	0.9960
C	0.8913	0.8681	0.9499	0.9988	0.9972
D	0.9132	0.9137	0.9664	0.9704	0.9862
E	0.9463	0.8400	0.9640	0.9693	0.9915
AIC					
Naproxen sodium					
R	29.71	33.58	26.29	11.80	21.61
A	29.22	31.54	27.20	25.08	31.96
B	30.38	33.08	26.25	23.98	16.77
C	31.46	32.56	26.74	10.61	12.96
D	27.53	27.19	20.70	17.83	15.52
E	28.28	31.96	24.02	25.11	20.0
Acetaminophen					
R	30.93	34.89	27.92	4.67	18.69
A	25.0	37.46	25.11	25.88	6.27
B	32.75	34.24	29.24	24.10	15.10
C	32.81	33.77	28.86	8.92	13.85
D	30.87	30.82	26.06	25.99	22.11
E	26.51	32.06	24.42	22.72	16.15

Mean, *n*=12

Model-independent parameters MDT and DE have been proposed as adequate parameters for some IVIVC levels [31]. Level B represents a relationship between MDT and the mean residence time, both calculated by statistical moment's theory, and Level C is established by the association of a dissolution time point ($t_{50\%}$, $t_{90\%}$, etc.) to one pharmacokinetic parameter such as area under the curve, C_{max}, or T_{max}. Some authors have taken the DE as a suitable parameter that expresses a global drug dissolution performance useful for comparison of dissolution profiles [32].

From the obtained results with fixed-dose combination generic drugs of naproxen sodium and acetaminophen, the flow-through cell method was more discriminative than the USP paddle apparatus [11].

Model-dependent comparisons

In order to describe the naproxen sodium and acetaminophen release kinetics from fixed-dose combination generic drugs, data were fitted to several kinetic models. The dissolution data of naproxen sodium obtained from R, A, and C formulations were best fitted to Makoid-Banakar's function and for B, D, and E generic drugs by Weibull's equation. Dissolution data of acetaminophen from R and C formulations better adjusted to Makoid-Banakar's model while A, B, D, and E generic drugs adjusted to Weibull's equation. Results are shown in table 2.

Because some fixed-dose combination generic drugs adjusted to different kinetic model to the one presented by the reference product, comparison of dissolution profiles by model-dependent methods was not possible. To compare dissolution profiles by this approach, all formulations should be adjusted at the same kinetic model [26].

Results of the present study agree with those previously reported for naproxen sodium and acetaminophen in fixed-dose combination formulations using the USP paddle apparatus [11]. Naproxen sodium data from A and E products as well as acetaminophen from A, B, D, and E generic formulations better adjusted to Weibull's model while acetaminophen from the reference product better adjusted to Makoid-Banakar's kinetics.

In vitro evaluation of fixed-dose combination generic drugs must be a continuous control in order to verify the biopharmaceutical quality of all marketed drug products. In addition, *in vitro* dissolution profiles evaluation of generic formulations represents a regulatory specification for bio-waivers. Efforts should be made to ensure that, as much as possible, the *in vitro* dissolution methods employed reflect the *in vivo* performance of the studied generic drugs [33].

CONCLUSION

The flow-through cell method, USP Apparatus 4, was proved to be a more discriminative *in vitro* dissolution method for the evaluation of the release performance of naproxen sodium and acetaminophen from different fixed-dose combination generic drugs.

CONFLICT OF INTERESTS

All authors have none to declare.

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