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## Simulated acetaminophen plasma profiles from fixed-dose combination formulations: studies using the flow-through cell dissolution method

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### Abstract

The aim of this work was to simulate acetaminophen plasma profiles from two fixed-dose combination formulations (acetylsalicylic acid, acetaminophen, and caffeine of generic vs. reference formulation) and *in vitro* dissolution data generated by the flow-through cell apparatus (laminar flow of 16 ml/min, 22.6 mm cells and 0.1 M phosphate buffer pH 7.4). Results were compared with *in vitro* release information of USP apparatus type II (paddle at 100 rpm and 900 ml of same dissolution medium). Dissolved drugs until 60 min were determined with a ratio-derivative spectrophotometric method. To compare dissolution profiles of each drug, dissolution efficiency and mean dissolution time were calculated. To predict *in vivo* behavior a convolution approach as well as acetaminophen published information were used. Peak plasma concentrations and area under the curve (zero time to infinity) were considered and values of predicted error for these pharmacokinetic parameters were established. When comparing dissolution profiles with Student's *t*-tests significant differences were found ( $p < 0.05$ ). All values of predicted error showed satisfactory results since only data generated by the flow-through cell dissolution method achieved  $< 10\%$  for each pharmacokinetic parameter. It is important to carry out *in vivo* studies with used formulations to corroborate the obtained results.

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### INTRODUCTION

Fixed-dose combination formulations are becoming a popular treatment option because of increased patient compliance and convenience, improved clinical effectiveness, and reduced cost

to the patient, among several other reasons. A commonly applied approach for approval of a fixed-dose combination product is demonstrating bioequivalence between the fixed dose combination and co-administration of individual mono-products if there is adequate safety and efficacy data for co-administration of the individual agents [1]. The development of this kind of drug products is becoming increasingly important from a public health perspective. Fixed-dose combination formulations have advantages when there is an identifiable patient population for whom treatment with a particular combination of actives in a fixed ratio is safe and effective and when all the actives contribute to the overall therapeutic effect. Such combinations of drugs are

particularly useful in the management of chronic diseases [2].

Migraine is the most common multifactorial and multidisciplinary neurologic disorder that is characterized by recurrent attacks of headache. It is also defined as severe throbbing plus unilateral headache related to nausea, photophobia, phonophobia, and vomiting [3]. Non-steroidal anti-inflammatory drugs can be effective for milder migraine headaches. Several are approved as over-the-counter products, including ibuprofen and acetaminophen, acetylsalicylic acid, and caffeine combination (acute treatment of migraine). The use of over-the-counter medications is highly prevalent among the general population and particularly so among patients with primary headaches disorders. Such patients tend to self-medicate with nonprescription products. Hazards associated with analgesic self-medication may include inappropriate use, overuse, overdose, rebound phenomena, toxicity syndromes, and dangerous drug interactions [4].

Acetylsalicylic acid has analgesic, antirheumatic, and antipyretic properties [5]. Due to its high solubility and high permeability acetylsalicylic acid is a class I drug of the Biopharmaceutical Classification System (BCS) [6]. Acetaminophen (paracetamol) has antipyretic, analgesic, and weak anti-inflammatory actions, and is sparingly soluble in water and prone to dissolution and bioavailability problems [7]. Paracetamol shows high solubility and low permeability, and it is classified as class III drug [8]. Caffeine is a stimulant of the central nervous system [9] and it has been added to non-opioid drugs to improve their analgesic effects [10]. The freely available combination of acetylsalicylic acid, acetaminophen, and caffeine has an excellent safety profile and is well tolerated [11]. However, acetaminophen should be respected as a drug with severe toxicities. Liver failure from acetaminophen overdose is the most serious side effect and can vary from mild to severe. The severity of the overdose problem stems from the fact that acetaminophen is an extremely common medication often used casually [12].

On the other hand, and based on the superposition principle, convolution is a model-independent method for computing *in vivo* absorption and modeling *in vitro-in vivo* data. The *in vivo*

pharmacokinetic parameters are predicted by using drug release profiles as input functions and pharmacokinetic parameters of reference formulation as a weighted function [13]. Significant advantages of this technique have been observed 1. The procedure does not require an *in vivo* study as common pharmacokinetic parameters are available in the authentic literature and that can be used. 2. The procedure is independent of the product type. 3. It is not necessary to purchase sophisticated computer software since simple spreadsheet software (MS Excel) may be used and 4. The technique is quite easy to automate so that when dissolution results are entered, one can see the outcome immediately [14].

*In vitro* dissolution tests are carried out for several reasons 1. To guide drug development and select formulations for further *in vivo* studies; 2. To evaluate comparability between products before and after changes in formulation and/or manufacturing; 3. To serve as surrogate for *in vivo* bioequivalence studies, with suitable *in vitro/in vivo* correlations and/or use of the BCS approach; and 4. To ensure batch-to-batch consistency for product performance [15]. Dissolution studies are carried out mainly by two types of equipment, USP apparatus type I (basket) and USP apparatus type II (paddle). Additionally, the advantages of the flow-through dissolution method (USP apparatus type IV) have been described by several authors [16][17]. The USP apparatus type IV can be operated under different conditions such as open and closed system mode as well as different flow rates. The diversity of available cell types allows the application of this apparatus for testing of a wide range of dosage forms including tablets, powders, suppositories, or hard and soft gelatin capsules [15]. One significant advantage is that *sink* conditions are maintained which are independent of drug solubility, and therefore the apparatus is particularly suited as a test for drugs with solubility problems [18].

Several authors have published a biowaiver monograph for acetaminophen oral dosage forms (tablets) where bioequivalence studies can be replaced by *in vitro* dissolution studies [8] however, for fixed-dose combination formulations where class I or III drugs are combined with any other class of drug a biowaiver approach is not applicable [19]. The aim of this study was to simulate acetaminophen plasma profiles through

*in vitro* data of fixed-dose combination formulations. The reference and a generic formulation were tested with the USP apparatus type IV and *in vivo* predictions were carried out with a convolution approach. Results were compared with *in vitro* data generated with a common dissolution device as USP apparatus type II.

## MATERIAL AND METHODS

### Chemicals and fixed-dose combination formulations

The acetylsalicylic acid, acetaminophen, and caffeine standards were acquired from Sigma-Aldrich Co. (St. Louis MO, USA). The sodium phosphate monobasic, and dibasic salts, methanol HPLC grade, and acetic acid were acquired from J.T. Baker-Mexico (Xalostoc-Mexico). The formulations manufactured with acetylsalicylic acid, acetaminophen, and caffeine (250/250/65 mg, respectively) were Excedrin® tablets (GSK Consumer Health, Inc.) and Bioelectro® tablets (Química y Farmacia, S.A. de C.V.). Local health authorities have determined Excedrin® brand as reference formulation [20]. For comparative purposes, analgesic tablets of reference formulation Tylenol® (acetaminophen 500 mg, Janssen-Cilag, S.A. de C.V.) were also used. Content uniformity pharmacopoeial test and assay tests were carried out with all commercial drug products according to pharmacopoeial specifications [21].

### *In vitro* dissolution studies

Dissolution performance of acetylsalicylic acid, acetaminophen, and caffeine from fixed-dose reference formulation was determined with pharmacopoeial settings and alternative conditions. Pharmacopoeial settings were USP apparatus type II (Sotax AT-7 Smart model, Switzerland) at 100 rpm and 900 ml of distilled water at  $37.0 \pm 0.5^\circ\text{C}$  ( $Q_{75}$  at 60 min for each drug) [21]. Alternative conditions were USP apparatus type II at 100 rpm using 900 ml of 0.1 M phosphate buffer pH 7.4. The generic fixed-dose combination formulation (same doses) and Tylenol® tablets were studied with alternative *in vitro* conditions. In all experiments, after addition of tablets to dissolution vessels, 5 ml of filtered samples were withdrawn at 10-, 20-, 30-, 45-, and 60-min. All drug products were tested with the flow-through cell apparatus (Sotax CE6 model, Switzerland).

Conditions were laminar flow at 16 ml/min, 22.6 mm cells, and 0.1 M phosphate buffer pH 7.4 at  $37.0 \pm 0.5^\circ\text{C}$ . Same sampling times were used.

The analytical method (UV-derivative analysis) used to quantify acetylsalicylic acid, acetaminophen, and caffeine from tablets was previously reported [22]. A double beam UV spectrophotometer with 1.0 cm quartz cells was used (Perkin Elmer Lambda 35, Waltham MA, USA). The operating conditions were first derivative (<sup>1</sup>D) or second derivative (<sup>2</sup>D) mode with scan speed of 240 nm/min, slit width of 2.0 nm, and sampling interval of 1.0 nm. Quantification of acetaminophen from Tylenol® tablets was carried out with direct spectrophotometric determination at 243 nm. Dissolved drugs were quantified with standard calibration curves (acetylsalicylic acid, 5 – 25 µg/ml; acetaminophen, 2.5 – 20 µg/ml, and caffeine, 1 – 8 µg/ml).

To compare *in vitro* release curves (generic vs. reference formulation) the model-independent parameters dissolution efficiency (DE) and mean dissolution time (MDT) were calculated using Excel add-in DDSolver program [23]. The *in vitro* release of each drug at 60 min ( $Q_{60}$ ) was also used to compare dissolution profiles. Student's *t*-tests were calculated with Sigmaplot program (Version 11.0) and *p* values less than 0.05 were considered as significant differences.

### Simulation of acetaminophen plasma concentrations

Acetaminophen plasma concentrations were simulated using *in vitro* dissolution data of USP apparatus type II and IV, a convolution model previously published [13], information of an *in vivo* study [24], and data of the acetaminophen biowaiver monograph [8]. Drug levels were predicted considering the Inverse Release Function approach [25]. This procedure allows a new time scale of the *in vitro* release behavior. With the new time scale, simulated plasma concentrations were calculated, and they were adjusted with a compartment model considering the Excel add-in PKSolver program [26]. Values of predicted peak plasma level ( $C_{\text{max}}$ ) as well as area under the curve from zero time to infinity ( $\text{AUC}_{0-\text{inf}}$ ) were *in vivo* compared with the calculation of Prediction Error (%Prediction Error = [observed parameter - predicted parameter / observed parameter] × 100). A value of 10% or less confirms

predictability of the model. A value between 10% and 20% suggests inconclusive predictability and requires additional data. A percentage prediction error of greater than 20% is indicative of inadequate or lack of predictability [14].

## RESULTS AND DISCUSSION

Results of content uniformity test and assay test are depicted in **Table 1**. All studied drug products met the pharmacopoeial criterion.

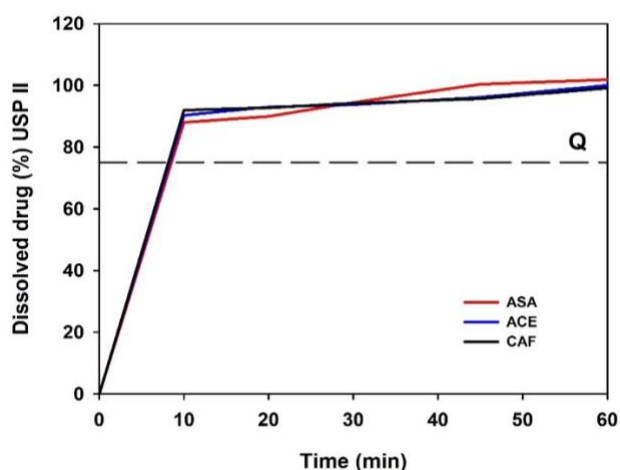
*In vitro* release curves of acetylsalicylic acid, acetaminophen, and caffeine from reference formulation obtained with pharmacopoeial settings are shown in **Figure 1**. All drugs met the pharmacopoeial Q criterion of not less than 75% of dissolved drug should be achieved at 60 min. The values of DE and MDT calculated to describe the release performance of acetylsalicylic acid, acetaminophen, and caffeine are depicted in **Table 2**.

*In vitro* release curves of acetylsalicylic acid, acetaminophen, and caffeine from all used formulations tested with 0.1 M phosphate buffer pH 7.4, flow-through cell method, and USP apparatus type II are shown in **Figure 2**. Reference formulation showed a very rapid dissolution as > 85% of each compound was released at 15 min when USP apparatus type II was used, and acetylsalicylic acid and acetaminophen showed same behavior when USP apparatus type IV was used. Each of the three drugs contained in generic drug product achieved more than 85% dissolved at 30 min hence a rapid dissolution performance can be considered. On the other hand, as reference formulation showed more than 85% of dissolved drugs at 15 min no similarity factors  $f_2$  were calculated, so dissolution profiles were compared with DE and MDT values. After applying Student's *t*-tests significant differences in generic formulations were found in almost all comparisons ( $p < 0.05$ ). Values of  $Q_{60}$ , DE, and MDT of

**Table 1 Results of content uniformity and assay tests. Mean (%) ± standard deviation**

|     | Alone               |             | Reference drug product |             | Generic formulation |            |
|-----|---------------------|-------------|------------------------|-------------|---------------------|------------|
|     | Content uniformity† | Assay‡      | Content uniformity†    | Assay‡      | Content uniformity† | Assay‡     |
| ASA | -                   | -           | 91.70±1.66             | 94.16±1.25  | 95.23±2.06          | 94.81±0.31 |
| ACE | 99.93±1.29          | 101.93±1.34 | 97.38±2.76             | 103.22±2.66 | 99.42±2.56          | 99.22±2.38 |
| CAF | -                   | -           | 102.99±2.66            | 92.61±0.22  | 103.37±3.06         | 93.85±1.60 |

ASA: Acetylsalicylic acid; ACE: acetaminophen; CAF: caffeine; †n = 10; ‡n = 3



**Figure 1 *In vitro* release curves of acetylsalicylic acid (ASA), acetaminophen (ACE), and caffeine (CAF) of reference drug product obtained with pharmacopoeial settings. Dashed straight line represents pharmacopoeial Q criterion. Mean values, n = 12**

acetaminophen from Tylenol® tablets are shown in **Table 3**.

Considering acetaminophen *in vitro* release data from fixed-dose combination formulations obtained with the USP apparatus type II and IV as well as pharmacokinetic information previously published simulated plasma profiles were calculated and pharmacokinetic parameters  $C_{max}$  and  $AUC_{0-inf}$  were predicted. Results were compared with real pharmacokinetic data and prediction error were calculated. Values are shown in **Table 4**.

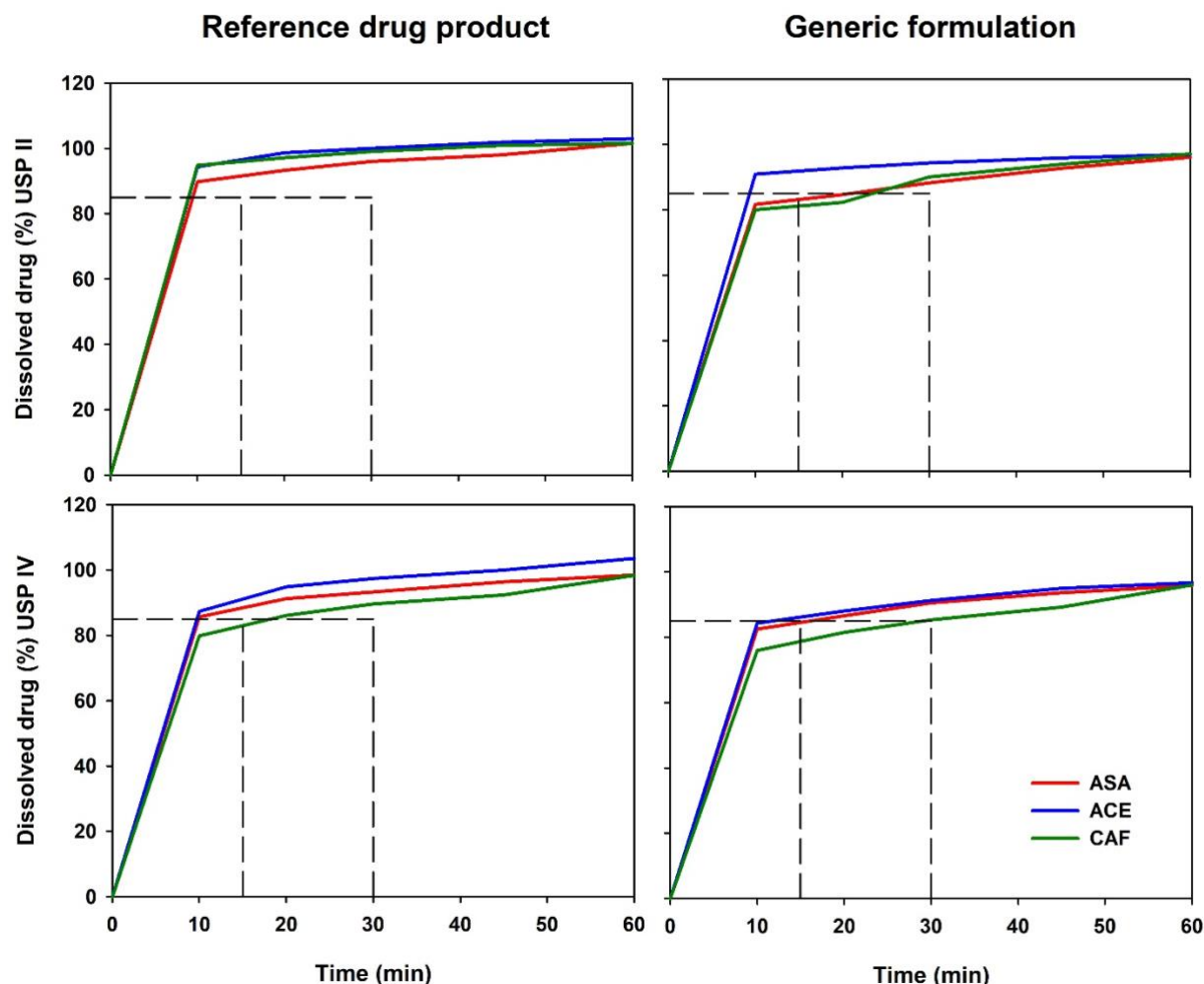
All prediction errors were < 10% only with *in vitro* data of USP apparatus type IV so the flow-through cell can be considered a suitable option to document the acetaminophen release performance and to predict its *in vivo* behavior from fixed-dose combination formulations.

Migraine is a prevalent chronic neurologic disease characterized by painful, debilitating attacks.

**Table 2 Model-independent parameters of acetylsalicylic acid (ASA), acetaminophen (ACE), and caffeine (CAF) obtained with pharmacopoeial settings. Mean  $\pm$  SEM, n = 12**

| Drug                | Reference drug product |                  |                  |
|---------------------|------------------------|------------------|------------------|
|                     | ASA                    | ACE              | CAF              |
| Dose (mg)           | 250                    | 250              | 65               |
| Q <sub>60</sub> (%) | 101.84 $\pm$ 0.32      | 99.96 $\pm$ 0.36 | 99.07 $\pm$ 0.33 |
| DE (%)              | 87.14 $\pm$ 0.16       | 86.57 $\pm$ 0.21 | 86.72 $\pm$ 0.05 |
| MDT (min)           | 8.66 $\pm$ 0.11        | 8.03 $\pm$ 0.27  | 7.48 $\pm$ 0.17  |

Q<sub>60</sub>: released drug at 60 min; DE: dissolution efficiency; MDT: mean dissolution time; SME: standard error medium



**Figure 2** *In vitro* release curves of acetylsalicylic acid (ASA), acetaminophen (ACE), and caffeine (CAF) obtained with the USP apparatus type II (USP II) and flow-through cell dissolution method (USP IV). Dashed straight line represents very rapid and rapid dissolution (> 85% dissolved at 15 and 30 min respectively). Mean values, n = 12

Current acute treatments are often inadequately effective, contributing to the need for more frequent dosing and overuse [27]. Therapy for migraine attacks includes non-steroidal anti-inflammatory drugs, combination analgesics, ergotamine preparations and migraine-specific medications [28]. The risks related to the use of

acetaminophen have prompted increased concern by physicians and regulatory agencies. Acetaminophen will now carry labeling that warns consumers about potential safety risks, including internal bleeding and liver damage, when products containing it are taken to excess or taken along with certain other drugs, such as anticoagulants or

**Table 3 Model-independent parameters of acetylsalicylic acid (ASA), acetaminophen (ACE), and caffeine (CAF). Mean  $\pm$  SEM, n = 12. \* $p < 0.05$  (generic vs. reference formulation).**

|                     | Alone                    | Reference drug product |                   |                   | Generic formulation |                   |                   |
|---------------------|--------------------------|------------------------|-------------------|-------------------|---------------------|-------------------|-------------------|
| Drug                | ACE                      | ASA                    | ACE               | CAF               | ASA                 | ACE               | CAF               |
| Dose (mg)           | 500                      | 250                    | 250               | 65                | 250                 | 250               | 65                |
|                     | USP apparatus type II    |                        |                   |                   |                     |                   |                   |
| Q <sub>60</sub> (%) | 109.15 $\pm$ 0.27        | 101.52 $\pm$ 0.65      | 102.92 $\pm$ 0.49 | 101.54 $\pm$ 0.21 | 96.11 $\pm$ 0.98*   | 96.92 $\pm$ 0.66* | 97.10 $\pm$ 0.52* |
| DE (%)              | 90.52 $\pm$ 0.23         | 87.69 $\pm$ 1.02       | 91.32 $\pm$ 0.65  | 90.52 $\pm$ 0.15  | 81.27 $\pm$ 1.18*   | 86.35 $\pm$ 0.63* | 81.42 $\pm$ 1.00* |
| MDT (min)           | 10.24 $\pm$ 0.15         | 8.19 $\pm$ 0.38        | 6.77 $\pm$ 0.22   | 6.51 $\pm$ 0.11   | 9.28 $\pm$ 0.35*    | 6.54 $\pm$ 0.25   | 9.66 $\pm$ 0.74*  |
|                     | Flow-through cell method |                        |                   |                   |                     |                   |                   |
| Q <sub>60</sub> (%) | 106.95 $\pm$ 0.51        | 98.45 $\pm$ 0.80       | 103.57 $\pm$ 0.63 | 98.35 $\pm$ 1.37  | 95.80 $\pm$ 0.71*   | 96.68 $\pm$ 0.75* | 96.00 $\pm$ 0.75  |
| DE (%)              | 90.29 $\pm$ 1.21         | 85.31 $\pm$ 0.70       | 88.59 $\pm$ 0.63  | 81.72 $\pm$ 1.23  | 82.41 $\pm$ 0.62*   | 83.56 $\pm$ 0.68* | 78.30 $\pm$ 0.73* |
| MDT (min)           | 9.36 $\pm$ 0.48          | 8.00 $\pm$ 0.22        | 8.68 $\pm$ 0.28   | 10.14 $\pm$ 0.30  | 8.39 $\pm$ 0.10     | 8.14 $\pm$ 0.11   | 11.06 $\pm$ 0.24* |

Q<sub>60</sub>: released drug at 60 min; DE: dissolution efficiency; MDT: mean dissolution time; SME: standard error medium

**Table 4 Prediction errors for peak plasma level (C<sub>max</sub>) and area under the curve from zero time to infinity (AUC<sub>0-inf</sub>).**

|                               | Alone                    | Reference drug product | Generic formulation |
|-------------------------------|--------------------------|------------------------|---------------------|
| Dose (mg)                     | 500                      | 250                    | 250                 |
|                               | USP apparatus type II    |                        |                     |
| C <sub>max</sub> (μg/ml)      | 2.15                     | -7.01                  | -2.84               |
| AUC <sub>0-inf</sub> (μgh/ml) | -8.22                    | -21.50                 | -7.15               |
|                               | Flow-through cell method |                        |                     |
| C <sub>max</sub> (μg/ml)      | 2.81                     | 0.83                   | 3.42                |
| AUC <sub>0-inf</sub> (μgh/ml) | -8.21                    | -5.67                  | 0.52                |

steroids [29]. Acetylsalicylic acid is a potent agent that prolongs bleeding time and inhibits platelet aggregation [30]. Because pain involves multiple mechanisms, the use of combinations is especially rational. Also, the use of two drugs almost always means a combination with lower doses of each, thereby minimizing the adverse events that might be associated with higher doses of a single drug [29].

Virtual bioequivalence is a pharmaceutical concept that considers computational (*in silico*) modelling and simulation techniques to evaluate the equivalence of generic formulations to their reference counterpart [31]. On the other hand, the so-called *in vitro-in silico-in vivo* approach has been widely adopted by generic and brand companies to evaluate the impact of formulation, manufacturing

process and manufacturing site changes on bioavailability and bioequivalence. Some authors have demonstrated that this strategy has the potential to be the third common approach to assess the likelihood of bioequivalence between test and reference products *via* a combination of *in silico* tools with appropriate dissolution testing [32]. In clinical practice, it is becoming more common to use analgesic combinations, both in fixed-dose ratios and *ad hoc* dose ratios, to treat chronic moderate to severe pain and this is especially relevant when managing “mixed” pain disorders. Fixed-ratio dose combinations produce a more standardized reproducible clinical effect [29]. Some authors have established that to guide fixed-dose combination formulations designs, biorelevant *in vitro* dissolution testing coupled with pharmacokinetic modeling and simulations

can provide quantitative assessment on probability of success for bioequivalence [1].

When *in vitro* release curves are not bio-predictive it is necessary to identify the underlying causes to improve the predictive capability, a potential reason to address them is the inability to replicate *in vivo* release performance, it means, *in vitro* dissolution actions may not accurately replicate the complex settings of *in vivo* release behavior. Issues such as dissolving medium composition, rotational speed, and flow rate can significantly affect the *in vitro* release [31]. The advantages of the flow-through cell dissolution method over the USP apparatus type I and II have been widely demonstrated. The USP apparatus type IV better simulates the hydrodynamic environment showed in the gastrointestinal tract [33][34] and it is possible to use it as an open system that can operate under *sink* conditions which facilitate the dissolution of drugs with solubility problems [35].

Some authors have found that USP apparatus type IV better predicts pharmacokinetic parameters than other dissolution methods for immediate-release formulations [36] and extended-release [37] formulations. The convolution method uses *in vitro* dissolution data to derive plasma drug levels considering reported pharmacokinetic parameters of a test product [38]. This is the first work that simulate acetaminophen plasma concentrations from fixed-dose formulations using the USP apparatus type IV. Results of PE for simulated  $C_{max}$  and  $AUC_{0-inf}$  were within international criteria.

## CONCLUSION

Results suggest that the flow-through cell dissolution method can be a suitable option to simulate the acetaminophen *in vivo* performance from fixed-dose combination formulations. In this way, there is better quality control of this kind of oral drug products. It is important to carry out bioavailability studies with the studied formulations to corroborate the obtained results.

## Ethical Approval

This research was conducted in accordance with guidelines established by the Institutional Animal Ethic Committee (IAEC). Approval number: was obtained from the IAEC prior to the commencement of the study. All procedures involving animals were carried out with care and

consideration for their welfare, in compliance with ethical standards and regulations.

No ethical approval was necessary for this study.

## Author Contribution

All authors made substantial contributions to the conception, design, acquisition, analysis, or interpretation of data for the work. They were involved in drafting the manuscript or revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring its accuracy and integrity.

## Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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