In vitro release of ketoprofen suppositories using the USP basket and the flow-through cell dissolution methods

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Abstract: In order to study the release characteristics of ketoprofen suppositories under the hydrodynamic environment generated by USP Apparatus 1 and 4, the dissolution profiles of the Mexican reference product (100 mg) were determined. Phosphate buffer pH 8 and 1% sodium lauryl sulfate (SLS) aqueous solutions were proved as dissolution mediums. Baskets were rotated at 100 rpm with USP Apparatus 1 and different flow rates from 16−32 mL/min with USP Apparatus 4 were used. Drug samples were taken and quantified during 60 min by UV analysis at 260 nm. Mean dissolution time (MDT) and dissolution efficiency (DE) were calculated by model-independent methods. Data were also fitted to several kinetic models. Poor dissolution was found in both dissolution mediums when USP basket method was used (< 10% dissolved) while better results were obtained with USP Apparatus 4 when 1% SLS at 24 mL/min was used (43.6% dissolved, MDT of 25.5 min and DE of 25.0%). Kinetics showed a great variability when the USP Apparatus 1 was used, and Gompertz fitted well for data of 1% SLS at 24 mL/min ($R^2_{adjusted} > 0.99$). The results suggest the need to establish an adequate dissolution method to evaluate the release kinetics of ketoprofen from suppositories.

Keywords: Ketoprofen, suppositories, flow-through cell method, USP basket method, USP Apparatus 4.

INTRODUCTION

Ketoprofen is a non-steroidal anti-inflammatory drug with low solubility and high permeability commonly administered orally; however, ketoprofen suppositories are still widely used for pain management. Rectal dosage forms frequently show low bioavailability due to poor, irregular, and unpredictable rectal absorption. It is well known that the base used in the manufacture of suppositories is a critical factor for drug release and absorption. Since 1977 Roller recommended the use of polyethylene glycol (PEG) for the elaboration of paracetamol pediatric suppositories, and in 1982 Palmieri suggested that specifications for the suppository base used in acetaminophen preparations should be included in official compendiums. In 1980, Ishizaki *et al*. reported a relative bioavailability of 73–93% after the rectal administration of ketoprofen (100 mg) compared to an oral administration (capsules). The study was carried out in a group of male volunteers and no information about the nature of the base used for these suppositories was reported.

Dissolution studies for suppositories are commonly performed with the USP basket method (USP Apparatus 1) and in a less extent with the USP paddle method (USP Apparatus 2). On the other hand, the flow-through cell method (USP Apparatus 4) has also been considered as an alternative to USP vessels systems for evaluating drug release from semi-solid dosage forms. The USP Apparatus 4 involves a continuous drug extraction, simulating the absorption process from the dissolution site into the systemic circulation, generating an intermittent flow of dissolution medium into the cell where the dosage form is placed (Qureshi *et al*., 1994). Previous studies with poorly soluble drugs manufactured in suppositories have shown that *in vitro* data obtained with the flow-through cell method can be related to their *in vivo* performance (Aiache *et al*., 1987; Gjellan and Graffner, 1994a; Lootvoet *et al*., 1992).

Under the USP Apparatus 4, dissolution studies with other drugs have been reported. Paracetamol and codeine suppositories (both drugs in the same formulation) were evaluated with 8 and 16 mL/min and dissolution profiles determined with 8 mL/min were in agreement with the plasma concentration profiles obtained indicating that the lower flow rate reflected the *in vivo* situation more correctly (Gjellan *et al*., 1994). Indomethacin suppositories were tested with 15 and 20 mL/min and *in vitro* dissolutions profiles obtained with the flow of 20 mL/min were useful to predict *in vivo* concentration curves (Lootvoet *et al*., 1992). Paracetamol suppositories were evaluated at 14, 28, and 50 mL/min and the flow rate of 28 mL/min was the flow that better reflected the *in vivo* situation than the others flow rates (Gjellan and Graffner, 1994a). Diversity of results could be associated with the use of different dissolution medium evaluated by the authors: deaereated water with paracetamol formulations and phosphate buffer pH 7.2 with indomethacin suppositories as well as the nature of the base used in the manufacture of each product. Meanwhile, Hurtado *et al*. (2002) proposed the flow rate of 16 mL/min with distilled water or phosphate buffer pH 8 for

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the *in vitro* evaluation of acetaminophen suppositories. In the study, reference product achieved 100% of drug dissolved since the first 20 min in both dissolution mediums and Medina *et al*. (2009) reported flow of 16 mL/min and phosphate buffer pH 8 for an *in vitro-in vivo* study of paracetamol conventional suppositories using rabbits as animal model. Despite the advantages of the flow-through cell method, information about dissolution performance of ketoprofen suppositories under the hydrodynamic environment generated by USP Apparatus 4 is scarce.

To date, there is no a pharmacopeial dissolution method to evaluate ketoprofen release from suppositories. The aim of this study was to evaluate the dissolution performance of ketoprofen commercial reference product, under the hydrodynamic environment generated by the flow-through cell method, and to compare it with the results obtained with the USP basket method.

MATERIALS AND METHODS

Commercial product

Ketoprofen suppositories of the Mexican reference product, sold in the local market were used. Phosphate salts (analytical grade) were purchased from Merck-Mexico. Ketoprofen (99.9% purity) from Sigma-Aldrich Co. (St. Louis MO, USA) was used as standard.

Weight variation and content uniformity

Suppositories were evaluated for weight variation and content uniformity according to USP XXIII specifications.

USP Apparatus 1 (basket method)

Dissolution profiles of ketoprofen suppositories were determined in an automated USP Apparatus 1 (Vankel VK 7000; VanKel Industries Inc., Cary NC, USA) with controlled multi-channel peristaltic pump (Vankel VK 810) and UV/Vis spectrophotometer (Varian Cary 50 tablet; Varian Inc., Palo Alto CA, USA). Ketoprofen suppositories were sprinkled on 900 mL of two different dissolution medium: phosphate buffer pH 8 and 1% sodium lauryl sulfate aqueous solution maintained at 37.0 ±0.5ºC (n=6). Rotational speed of 100 rpm was tested. Sequential sampling using filter probes was automatically taken every two min during 60 min. The amount of ketoprofen dissolved was determined by comparing with a ketoprofen standard solution at a concentration of 0.111 mg/mL, at 260 nm.

USP Apparatus 4 (flow-through cell method)

Dissolution data of ketoprofen suppositories were obtained in an automated USP Apparatus 4 (Dissotest CE-6; Sotax AG, Basel, Switzerland) coupled to an UV/Vis spectrophotometer (Perkin Elmer Lambda 10; Norwalk CT, USA) and a piston pump (Sotax CY7-50; Sotax AG, Basel, Switzerland). Suppositories were placed in the cells designed for this dosage form (n=6). To evaluate ketoprofen release from suppositories a two-factor nested design was used. Three flow rates (16, 24 and 32 mL/min) and two dissolution mediums (phosphate buffer pH 8 and 1% sodium lauryl sulfate aqueous solution) were tested and the percentage dissolved at 60 min was used as response. Filtered samples through 0.45 µm nitrocellulose membranes (Millipore Corporation, Bedford MS, USA) were automatically taken every two min during 60 min. In each experiment, the amount of ketoprofen dissolved was determined with an UV/Vis spectrophotometer (Perkin Elmer Lambda 2S; Norwalk CT, USA) at 260 nm using a calibration curve prepared with ketoprofen standard, dissolved in each dissolution medium.

Data analysis and statistic

Ketoprofen dissolution data were used to calculate model-independent parameters: mean dissolution time (MDT) and dissolution efficiency (DE). The results obtained using the USP basket method were compared by unpaired Student´s t test, while data from the flow-through cell method were compared by ANOVA for nested design followed by pair-wise comparisons corrected according to Bonferroni.

In order to identify the release kinetics, under the conditions where ketoprofen achieved better dissolution extent, data were fitted to different dissolution kinetic models such as zero-order, first-order, Higuchi, Korsmeyer- Peppas, Hixson-Crowell, Makoid-Banakar, Peppas-Sahlin, Weibull, Logistic, and Gompertz. Nonlinear regression to fit the data was used; standard criteria, i.e., higher adjusted coefficient of determination ($R^2_{adjusted}$) and smaller Akaike information criterion were used to select the best model. Data analysis was carried out using the Excel add-in DDSolver program (Zhang *et al*., 2010) and SPSS software (Version 17.0). Differences were considered significant if p<0.05.

RESULTS

Ketoprofen commercial product met the requirements of weight variation and content uniformity test specified by USP XXIII.

Ketoprofen dissolution profiles obtained with the USP basket method, using phosphate buffer pH 8 and 1% sodium lauryl sulfate aqueous solution as dissolution mediums are shown in fig. 1. Under this system, low dissolution extent was found with both dissolution mediums (<10%) and the suppositories only lost their shape.

Even though ketoprofen release from suppositories in 60 min was slightly higher with 1% sodium lauryl sulfate aqueous solution than with phosphate buffer pH 8, the

dissolution medium has not significant effect (p>0.05) when the flow-through cell method was used (fig. 2). The flow rate had a significant effect on the ketoprofen release (p<0.01) increasing the flow rate from 16 to 24 mL/min significant improved the drug percentage dissolved (p< 0.05); however, at 32 mL/min the ketoprofen release kept constant in both dissolution mediums (p>0.05).

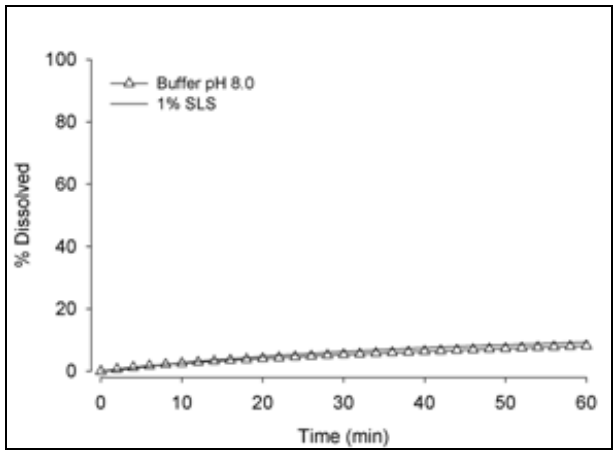

Fig. 1: Dissolution profiles of ketoprofen suppositories using the USP basket method with phosphate buffer pH 8 and 1% sodium lauryl sulfate (1% SLS) aqueous solution as dissolution mediums. Rotational speed of the baskets was 100 rpm. Mean (n=6). Error bars were omitted for clarity.

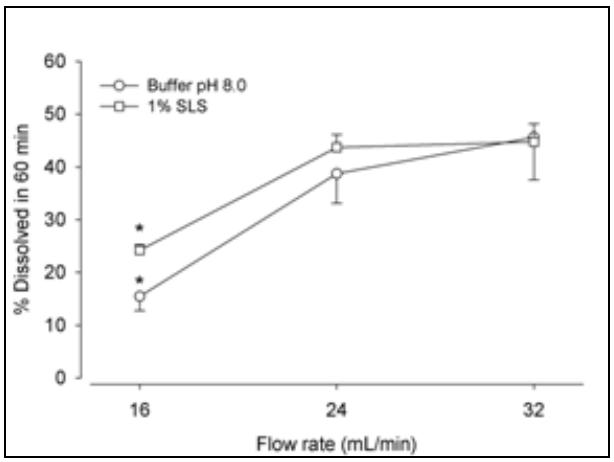

Fig. 2: Percentage dissolved of ketoprofen suppositories as a function of flow rate using the flow-through cell method. Dissolution mediums tested: phosphate buffer pH 8 and 1% sodium lauryl sulfate (1% SLS) aqueous solution. Mean ± SEM (n=6). *p<0.05 compared against higher flow rates.

Comparing with the USP basket method, best extent of ketoprofen release was observed when the USP Apparatus 4 was used, fig. 3. Percentages dissolved with phosphate buffer pH 8 and 1% sodium lauryl sulfate aqueous solution at 24 mL/min were 38.7 and 43.6%, respectively. Therefore, on the basis of the maximum percentage of drug dissolved, these last conditions could be considered as appropriate to evaluate ketoprofen release from suppositories. Furthermore, taking into consideration the variability obtained over all the sampling times, the dissolution with 1% sodium lauryl sulfate aqueous solution at 24 mL/min was the only one that showed coefficients of variation <15%, behind the best condition to evaluate dissolution performance of ketoprofen from suppositories.

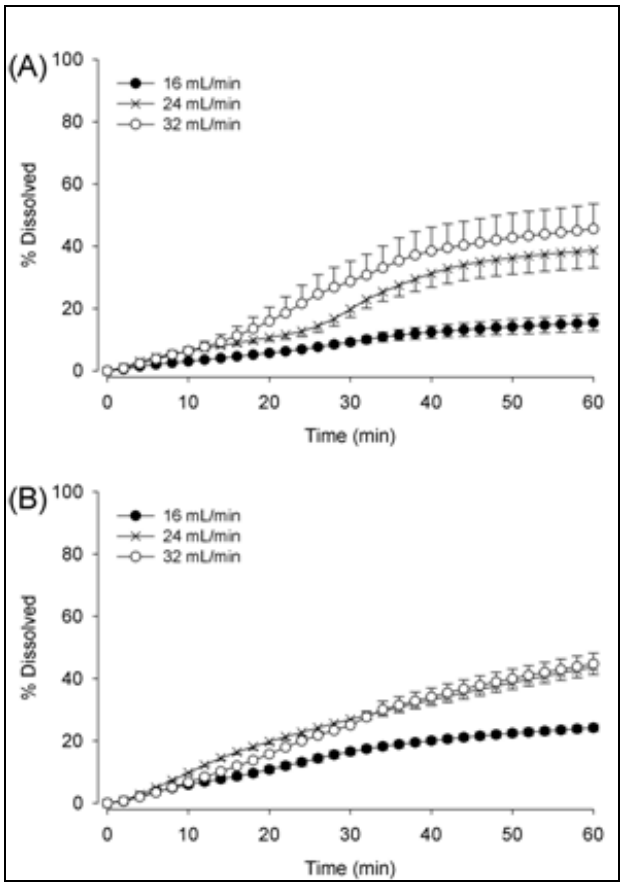

Fig. 3: Dissolution profiles of ketoprofen suppositories using the flow-through cell method with (A) phosphate buffer pH 8 and (B) 1% sodium lauryl sulfate (1% SLS) aqueous solution as dissolution mediums. Different flow rates were tested. Mean ± SEM (n=6).

Model-independent parameters MDT and DE mean values ± standard error of the mean calculated from data obtained in both USP apparatuses are shown in table 1. Ketoprofen MDT was 23.1−23.3 min when USP basket method was used and 25.0-27.4 min when USP Apparatus 4 was used. Ketoprofen showed limited DE with the use of USP Apparatus 1 (4.9−5.7%) while a DE of 25% was reached with the flow-through cell method with 1% sodium lauryl sulfate aqueous solution at 24 mL/min.

Table 1: Model-independent ketoprofen dissolution parameters from suppositories calculated with dissolution data generated with the USP Apparatus 1 and 4. Mean ± SEM (n=6).

USP Apparatus	Dissolution medium	rpm or mL/min	% Dissolved in 60 min	MDT (min)	DE (%)
1	Buffer pH 8	100	8.1±0.1	23.3±0.2	4.9±0.1
	1% SLS	100	9.2±0.2*	23.1±0.5	5.7±0.2*
4	Buffer pH 8	16	15.4±2.7†	25.0±1.2	8.7±1.1†
		24	38.7±5.6	27.2±1.1	20.6±2.5
		32	45.6±8.0	26.5±1.1	25.9±5.2
	1% SLS	16	24.2±1.1†	23.7±1.0	14.7±0.9†
		24	43.6±2.4	25.5±0.3	25.0±1.2
		32	44.7±3.4	27.4±0.8	24.1±1.5

Mean dissolution time (MDT); dissolution efficiency (DE); sodium lauryl sulfate (SLS); standard error of the mean (SEM)
* p<0.05 compared 1% SLS *vs* buffer pH 8
† p<0.05 compared flow rate within dissolution medium

Nonlinear regression analysis to fit the data where ketoprofen achieved better dissolution results was assessed. Dissolution kinetics with phosphate buffer pH 8 at 24 mL/min was inconsistent Makoid-Banakar's model fitted only to three of the six dissolution profiles. On the other hand, Gompertz's model (Eq. 1) was the most appropriate for fitting data obtained with 1% sodium lauryl sulfate aqueous solution as dissolution medium at 24 mL/min ($R^2_{adjusted} > 0.99$).

$$F = F_{max}\, e^{-\alpha e^{-\beta \log(t)}} \quad \text{Eq. 1}$$

Where F is the percentage of drug dissolved at t time, F_{max} is the maximal percentage of drug dissolved at infinite time, α is the scale parameter and β is the shape parameter. After fitting, α and β values were 7.27 and 0.77, respectively.

DISCUSSION

In order to know the release characteristics of ketoprofen suppositories model-independent parameters MDT and DE were calculated from dissolution data. These parameters have been proposed as adequate parameters for some *in vitro-in vivo* correlation levels. *In vitro-in vivo* correlation level B is based on the comparison of MDT parameter calculated by statistical moments and level C requires the calculation of an *in vitro* parameter that expresses global drug dissolution performance, as is the case of DE. Gjellan and Graffner reported MDT data for paracetamol (1994a) and ibuprofen (1994b) suppositories; meanwhile Hanaee *et al*. (2004) reported data called mean dissolution rates to determine which surfactant was more efficient in increasing the dissolution rate of salbutamol suppositories.

Different ketoprofen release kinetics from sustained-release suppositories was previously reported: zero-order by Ermiş and Tarimci (1995) for products containing hydroxypropylmethylcellulose phthalate in PEG bases and first-order and square-root of time for suppositories using chitosan (Tarimci and Ermiş, 1997). Kinetics described by Hixson-Crowell equation was reported by Özgüney *et al*. (2007) for ketoprofen suppositories prepared with different ketoprofen:Eudragit RL 100 ratios but if the ratio is increased in the particles of prepared granules the Fickian diffusion dominates and Higuchi equation better describes the release kinetics.

Ketoprofen dissolution data with 1% sodium lauryl sulfate aqueous solution at 24 mL/min were well fitted to Gompertz's model. This model is more useful for comparing the release profiles of drugs having good solubility and intermediate release rate (Dash *et al*., 2010). Comparisons of dissolution data using the Gompertz's function has been reported by Pabón *et al*. (1994) for the evaluation of controlled drug release from mixed matrices containing hydrophilic and hydrophobic polymeric materials. The purpose of using mathematical models to adjust dissolution data is that they facilitate the analysis and interpretation of the observed data because they describe the dissolution profiles as a function of only a few model parameters that can be statistically compared (Adams *et al*., 2002).

Previous dissolution studies with ketoprofen preformulations have been reported by some authors. Conventional suppositories with Witepsol H15, Massa Estarinum B and PEGs as well as sustained release suppositories with HP55 were prepared by Ermiş and Tarimci (1995). The results showed that ketoprofen release rate was very slow from Witepsol H15 and Massa Estarinum B while drug was released rapidly from the PEG bases. Conventional suppositories with different proportions of PEG were prepared by Tarimci and Ermiş (1997). Formulations released > 80% of drug in 4 h. Both studies were carried out with the USP Apparatus 1 at 50 rpm and phosphate buffer solution pH 7.2 as dissolution medium. In a third study, ketoprofen suppositories using theobroma oil, esterified (c_{10}–c_{18}) fatty acids, and PEG 1000 bases were prepared by Babar *et al*., (1999). Results

showed that suppositories prepared with hydrophilic bases achieved 100% of dose dissolved. In this study, the use of USP basket method, 100 rpm and 900 mL of phosphate buffer pH 8 was reported. In another study, conventional suppositories with Witepsol H15, Massa Estarinum B, Cremao and the mixture of PEG 400:PEG 6000 as well as sustained release formulations with different ketoprofen: Eudragit RL 100 ratios and mixtures of PEG 400:PEG 6000 were prepared by Özgüney *et al*., (2007). Complete drug release from suppositories prepared with PEG mixtures took place in 1 h. Drug release of 63.2 and 25.9% was observed from Massa Estarinum B and Cremao (respectively) in 2 h, and 99% of drug dissolved from products prepared with Witepsol H15 was reported in 4 h. In the study, ketoprofen commercial suppositories (100 mg) were also assayed and 99% of drug dissolved was achieved in 4 h. All experiments were done with the USP Apparatus 1, 50 rpm and phosphate buffer pH 7.2. For the manufacture of commercial products, no information about the nature of the base used was indicated.

Many authors have been proving the use of surfactants to improve the drug release from pharmaceutical dosage forms. Mechanisms proposed by which drug release could be increased following the use of surfactants are improving wetting, solubilisation and the dissolution of the soluble surfactants to form pores in the matrix of the dosage units (Efentakis *et al*., 1991). Other mechanisms described are an increase in the exposed surface area of the suppository mass in the rectal ampulla and a decrease in the interfacial tension between the excipient and the rectal fluid (Hanaee *et al*., 2004). The surfactants can be added as part of the dosage forms (Miyake *et al*., 2004) or within the dissolution medium (Park and Choi, 2006). Sheng *et al*. (2006) evaluated the effect of pH and the use of sodium lauryl sulfate on ketoprofen release from tablets. Results showed that the enhancement of *in vitro* solubility/dissolution attributable to an increase of pH and the presence of sodium lauryl sulfate mimics the *in vivo* solubilization/dissolution behavior of ketoprofen along the gastrointestinal tract. Sodium lauryl sulfate has an hydrophilic-lipophilic-balance (HLB) = 40 so it enhances the moisturizing of lipid excipients (Hanaee *et al*., 2004). The use of sodium lauryl sulfate aqueous solution as dissolution medium for studying ketoprofen release from suppositories is not a common action, but in the present study it was included as an alternative dissolution medium by the results obtained by Sheng *et al*. (2006) as well as to help drug release from the oil nature base. The role of surfactants, as part of rectal formulations, to facilitate the drug dissolution has been successfully investigated by Fontan *et al*. (1991) for carbamazepine; Margarit *et al*. (1992) for sodium valproate, and different concentrations of sodium lauryl sulfate (0.25, 0.75, and 1%) by Hanaee *et al*. (2004) for salbutamol suppositories.

Dissolution results of the present work agree with those encountered by Janicki *et al*. (2001) that worked with four paracetamol commercial suppositories (two of them manufactured by worldwide recognized companies) and found that suppositories of one of these products did not melt at 37.0ºC and drug dissolution was lower than 5% of the dose. The studies were performed in the USP Apparatus 4 with 0.2 M phosphate buffer pH 7.4, 100 mL/h as flow rate, and 6 h of time test. By modifying the original proposed conditions (dissolution medium temperature higher than 39.5ºC) they observed the melting of the suppository inside the dissolution chamber with an adequate drug release, nevertheless, the same authors considered that a dissolution method with a medium temperature of 39.5ºC has no real meaning to establish an *in vitro-in vivo* correlation.

Considering ketoprofen as a Class II drug (low solubility/high permeability) and the technical problems for the manufacture of rectal formulations that express adequate bioavailability as well as a lack of dissolution methods with proved discriminative capacity, it is important to establish official dissolution methods for suppositories evaluation. From the results obtained in this study it might be expected that ketoprofen dissolution process will affect the bioavailability of the drug, so it would be desirable to evaluate the *in vivo* performance of ketoprofen suppositories.

CONCLUSION

Even though the poor dissolution extent of ketoprofen from Mexican brand suppositories found in this study, the flow-through cell method showed to be a suitable option to evaluate their dissolution performance. This study reveals the need to implement a dissolution method for ketoprofen suppositories that can predict the bioavailability of the drug, in order to assure the effectiveness of the product.

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