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Original Article

PREDICTION OF SULFAMETHOXAZOLE AND TRIMETHOPRIM PLASMA LEVELS FROM TABLETS AND DISSOLUTION MEDIA OF PHYSIOLOGICAL RELEVANCE

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ABSTRACT

Objective: To estimate plasma concentrations-time profiles of Sulfamethoxazole (SMZ) and Trimethoprim (TMP) from fixed-dose combination formulations through *in vitro* data of dissolution media of physiological relevance and a convolution model.

Methods: Dissolution profiles of SMZ/TMP tablets (400/80 mg) were obtained with USP paddle apparatus at 100 rpm and 900 ml of 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer. The reference drug product and two generic formulations were tested. Drugs were quantified by a derivative method. Dissolution profiles were compared with model-dependent and independent methods. SMZ/TMP plasma levels were simulated with dissolution data and published *in vivo* information. Percent of prediction error (PE) for peak plasma concentration (C_{max}) and area under the curve from zero time to infinity ($AUC_{0\text{-}inf}$) at each condition were calculated.

Results: In all used conditions, similar dissolution profiles were found excepting for TMP at pH 1.2 (f_2<50). The *in vitro* release performance for reference and generic formulations was explained by the Weibull function only for SMZ at pH 6.8 and TMP at pH 4.5. Values of PE>19% for both generic formulations were found with TMP at pH 1.2.

Conclusion: Significant differences in TMP dissolution profiles of generic formulations at pH 1.2 reflect the subsequent differences found in predicted C_{max} and $AUC_{0\text{-}inf}$.

Keywords: Convolution, Fixed-dose formulations, Sulfamethoxazole, Trimethoprim, Prediction error

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INTRODUCTION

Sulfamethoxazole (SMZ) and Trimethoprim (TMP) inhibit bacterial synthesis of tetrahydrofolic acid, the physiologically active form of folic acid and a necessary cofactor in the synthesis of thymidine, purines, and bacterial DNA [1]. SMZ and TMP have low solubility/high permeability and according to Biopharmaceutical Classification System (BCS) both drugs are classified as Class II drugs [2]. Pharmacopeial dissolution test for SMZ/TMP tablets suggests USP Apparatus 2 (paddle) at 75 rpm with 900 ml of 0.1 N HCl at 37.0±0.5 °C. Considering these conditions, not less than 70% of the labeled amount of SMZ and TMP is dissolved in 60 min [3].

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 (IVIVC) and/or use of the BCS approach; and 4. To ensure batch-to-batch consistency for product performance [4].

Some authors have studied fixed-dose combination formulations of SMZ/TMP (tablets) in 0.1 M HCl as dissolution medium and differences in release characteristics have been found [5]. The influence of dose and USP apparatus in the release performance of SMZ and TMP from commercial tablets has been reported and significant differences between reference and generic formulations have also been found. [6]. Given the *in vitro* release conditions in which all formulations were tested these differences could be of clinical implication.

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 [7]. 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 [8].

The aim of this work was to predict the SMZ and TMP plasma concentrations-time profiles through *in vitro* data obtained with dissolution media of physiological relevance and pharmacokinetic published information. An adjustment in time scale of dissolution profiles and a convolution approach were used to estimate the *in vivo* behavior. The results may be important for the evaluation of fixed-dose combination formulations manufactured with SMZ and TMP.

MATERIALS AND METHODS

Reagents and chemicals

SMZ/TMP fixed-dose reference tablets (coded as R formulation) (Bactrim® 400/80 mg respectively, Produtos Roche Químicos e Farmaceuticos S. A., Brasil) and two generic formulations (coded as A and B drug products) with same doses were tested. Mexican health authorities have established the fixed-dose combination formulation Bactrim® as the reference drug product [9]. HCl, sodium acetate, and phosphate monobasic and dibasic salts were acquired from J. T. Baker-Mexico (Xalostoc, Mexico). SMZ and TMP standard were acquired from Sigma-Aldrich Co. (St. Louis MO, USA).

In vitro release studies

Dissolution profiles of SMZ and TMP were obtained using an USP paddle apparatus at 100 rpm (Sotax AT7-Smart, Sotax AG, Switzerland). Vessels were filled with 900 ml of 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer at 37.0±0.5 °C as dissolution media. To document the *in vitro* release performance of

each drug, dissolution samples were taken at 15-, 20-, 30-, 45-, and 60-min using fiberglass filters (n=12). Several analytical methods have been published to quantify SMZ and TMP [10-12] however, the amount of each dissolved drug was determined by a spectrophotometric derivative method previously developed by our research group [13]. Standard calibration curves in each dissolution medium were prepared (SMZ: 250-350 µg/ml and TMP: 10-50 µg/ml).

Dissolution data analysis

To compare dissolution profiles (generic drug product *vs*. reference formulation) by a model-independent approach the f_2 similarity factor was calculated (f_2 50-100 = similar dissolution profiles). Additionally, the percent of dissolved drug at 60 min (Q_{60}), dissolution efficiency (DE), and mean dissolution time (MDT) were calculated and statistically compared (univariate one-way ANOVA followed by a Dunnett's multiple comparison test). The values of DE and MDT were determined with the Excel add-in DDSolver program [14]. To compare dissolution profiles by a model-dependent approach dissolution data were adjusted with Higuchi, Korsmeyer-Peppas, Hixson-Crowell, and Weibull model. The model with the highest adjusted determination coefficient ($R^2_{adjusted}$) and lower Akaike Information Criterion (AIC) was chosen as the best-fit model [15].

Prediction of SMZ and TMP plasma levels

SMZ and TMP plasma concentrations were predicted using *in vitro* dissolution data, a simple numerical convolution method previously described [8, 16] and *in vivo* information of both drugs [17, 18]. SMZ and TMP plasma levels were simulated with the Inverse Release Function approach [19]. This methodology allows and adjustment in the time scale of the dissolution profile. Once the new time scale was calculated, predicted plasma concentrations were obtained, and data were adjusted with a non-compartment model using the Excel add-in PKSolver program [20]. Values of predicted C_{max} and $AUC_{0\text{-}inf}$ were compared with *in vivo* data by the calculation of %PE ([observed parameter - predicted parameter/observed parameter] × 100). The PE should not exceed 15% [21-23].

RESULTS AND DISCUSSION

***In vitro* release studies**

Dissolution profiles of SMZ and TMP of all used fixed-dose combination formulations are shown in fig. 1. A decrease in drug release proportional to decreasing acidity of the dissolution medium was observed. Considering the physicochemical characteristics of both drugs it was expected; however, *in vitro* release studies in dissolution media of physiological relevance are requested by international regulations, especially in media of pH 1.2, 4.5, and 6.8 [24]. Values of f_2 similarity factors are shown in table 1. Dissolution profiles of both generic formulations and reference drug product were similar (f_2 50-100) excepting for TMP at pH 1.2 (f_2<50).

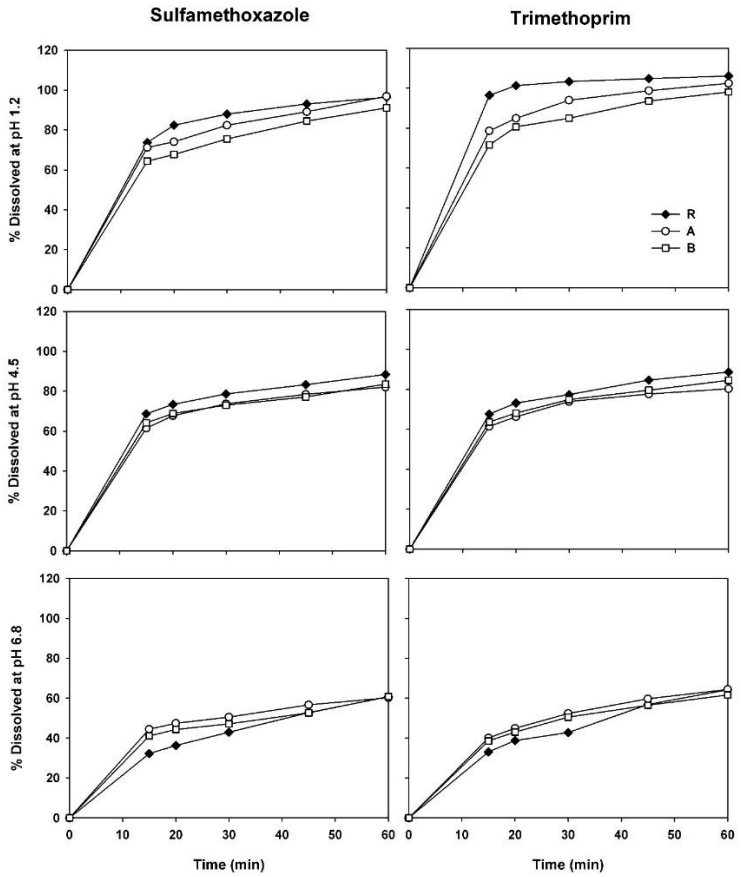

Fig. 1: Dissolution profiles of sulfamethoxazole/trimethoprim reference tablets (R) and generic formulations (A and B), results are given as mean, n=12

Table 1: Values of f_2 similarity factor calculated to compare dissolution profiles

pH	Sulfamethoxazole		Trimethoprim	
	A	B	A	B
1.2	66	50	47	39
4.5	63	65	60	69
6.8	55	63	62	67

Values of model-independent parameters Q_{60}, DE, and MDT calculated to compare dissolution profiles (generic drug products *vs*. reference formulation) are shown in table 2. In almost all comparisons significant differences were found (*P<0.05).

Values of $R^2_{adjusted}$ and AIC calculated to fit *in vitro* data to mathematical equations are shown in table 3. Considering results diversity, *in vitro* release of SMZ and TMP of all formulations, in all dissolution media can be mathematically explained by different equations. Only SMZ at pH 6.8 and TMP at pH 4.5 of reference and both generic formulations were explained by Weibull function.

Table 2: Model-independent parameters calculated to compare dissolution profiles

Code	Sulfamethoxazole			Trimethoprim		
	R	A	B	R	A	B
pH 1.2						
Q_{60} (min)	96.37±0.43	96.90±0.97	91.05±0.42*	106.16±0.38	102.50±0.41*	98.12±0.24*
DE (%)	76.23±0.50	72.70±0.39*	67.41±0.27*	89.76±0.37	80.83±0.33*	75.39±0.22*
MDT (min)	12.54±0.30	14.96±0.29*	15.57±0.12*	9.27±0.08	12.68±0.19*	13.90±0.14*
pH 4.5						
Q_{60} (min)	88.43±0.31	82.09±0.58*	83.59±0.37*	88.72±0.47	80.37±0.87*	84.55±0.46*
DE (%)	68.88±0.40	63.94±0.41*	64.25±0.24*	68.82±0.29	63.40±0.55*	65.22±0.25*
MDT (min)	13.26±0.24	13.26±0.19	13.88±0.11	13.45±0.16	12.65±0.17*	13.71±0.09*
pH 6.8						
Q_{60} (min)	60.72±0.42	60.17±0.22	60.81±0.15	64.18±0.47	64.32±0.44	61.61±0.21*
DE (%)	39.62±0.14	45.53±0.13*	42.95±0.08*	41.49±0.36	46.15±0.23*	44.12±0.14*
MDT (min)	20.83±0.35	14.60±0.12*	17.62±0.12*	21.19±0.44	16.94±0.25*	17.03±0.12*

Results are given as mean±SEM; n=12, *P<0.05; Q_{60}: dissolved drug at 60 min; DE: dissolution efficiency; MDT: mean dissolution time. Reference tablets (R) and generic formulations (A and B).

Table 3: Adjusted determination coefficient and akaike information criterion ($R^2_{adjusted}$/AIC) calculated to choose the best-fit model

Code	Sulfamethoxazole			Trimethoprim		
	R	A	B	R	A	B
pH 1.2						
Higuchi	-2.33/36.32	-0.54/34.00	0.17/32.04	-42.07/40.95	-1.76/36.59	-0.69/34.96
Korsmeyer-Peppas	0.87/19.57	0.97/12.94	0.98/11.22	-	0.92/18.14	0.95/15.69
Hixson-Crowell	0.36/27.95	0.24/30.18	0.15/32.07	-11.29/34.70	0.76/23.02	0.62/27.41
Weibull	0.96/11.43	0.95/16.70	0.98/10.73	-	0.93/18.06	0.94/16.94
pH 4.5						
Higuchi	-2.30/35.21	-1.22/33.83	-1.94/34.43	-1.47/34.72	1.49/34.06	-1.09/33.90
Korsmeyer-Peppas	0.97/10.65	0.96/13.79	0.97/11.41	0.97/11.71	0.93/15.81	0.98/8.44
Hixson-Crowell	-1.36/33.67	-1.90/35.09	-2.79/35.68	-0.87/33.28	-2.37/35.47	-1.46/34.67
Weibull	0.97/10.33	0.98/4.17	0.96/12.96	0.97/11.32	0.96/9.53	0.98/7.40
pH 6.8						
Higuchi	0.98/13.01	-0.48/29.51	0.36/27.05	0.95/16.91	0.75/24.54	0.75/24.32
Korsmeyer-Peppas	0.98/12.42	0.98/6.49	0.93/15.92	0.94/18.23	0.97/13.75	0.98/10.32
Hixson-Crowell	0.55/29.41	-4.11/35.75	-1.78/34.50	0.65/29.11	-0.32/33.22	-0.45/33.25
Weibull	0.99/9.87	0.98/5.48	0.95/13.22	0.93/18.11	0.97/12.75	0.98/7.37

Results are given as mean, n=12. Reference tablets (R) and generic formulations (A and B).

Prediction of SMZ and TMP plasma levels

Considering *in vitro* release data of SMZ and TMP obtained with the USP paddle apparatus and dissolution media of physiological relevance (pH 1.2–6.8) as well as pharmacokinetic information, previously published simulated plasma profiles were calculated and pharmacokinetic parameters C_{max} and $AUC_{0\text{-}inf}$ were predicted. Results were compared with real pharmacokinetic data and PE values were calculated. Values are shown in table 4.

Table 4: Prediction error for C_{max} and $AUC_{0\text{-}inf}$ calculated with simulated SMZ and TMP plasma concentrations and published *in vivo* data

	Sulfamethoxazole			Trimethoprim		
	R	A	B	R	A	B
pH 1.2						
C_{max} (µg/ml)	-1.62	-0.55	1.63	1.56	19.75	22.61
$AUC_{0\text{-}inf}$ (µgh/ml)	-8.42	-8.11	-0.90	13.42	29.56	32.11
pH 4.5						
C_{max} (µg/ml)	0.19	3.33	2.12	23.73	26.10	24.59
$AUC_{0\text{-}inf}$ (µgh/ml)	1.51	9.52	7.50	38.86	45.13	42.48
pH 6.8						
C_{max} (µg/ml)	24.85	24.88	24.38	38.67	38.38	40.66
$AUC_{0\text{-}inf}$ (µgh/ml)	34.59	34.74	34.19	57.28	57.08	58.90

Reference tablets (R) and generic formulations (A and B).

PE<15% for C_{max} and $AUC_{0\text{-}inf}$ were achieved with SMZ of all used drug products at pH 1.2 and 4.5 as well as with TMP only from reference formulation at pH 1.2. In the remaining conditions, PE>15% were found. Apparently, of the used conditions in the present work, the USP paddle apparatus and dissolution media of pH 1.2 was the best option to predict the *in vivo* performance of SMZ and TMP given that PE values for C_{max} and $AUC_{0\text{-}inf}$ of reference formulation showed PE values<15%. It is important to note that differences in TMP dissolution profiles of generic formulations at pH 1.2 (f_2<50) reflect the subsequent differences found in the prediction of both pharmacokinetic parameters (PE>15%).

The IVIVC is the establishment of a relationship between a biological property, or a parameter derived from a biological property produced by a dosage form, and physicochemical characteristics of same dosage form. Typically, the parameter derived from the biological property is $AUC_{0\text{-}inf}$ or C_{max}, while the physicochemical property is the *in vitro* dissolution profile [25]. For class II drugs an IVIVC is expected if *in vitro* dissolution rate is like *in vivo* dissolution rate, unless dose is very high [26]. Some authors have been discussed the use of IVIVC to optimize the development of generic drug formulations [27, 28]. Others have established that to guide fixed-dose combination formulations designs, biorelevant *in vitro* dissolution testing coupled with pharmacokinetic modeling and simulations can provide a quantitative assessment on probability of success for bioequivalence [29].

About, virtual bioequivalence is a pharmaceutical concept that uses computational modelling and simulation techniques to assess the equivalence of generic drugs to their reference or innovator counterparts [30]. 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 dissolutions testing [31].

This is the first work that simulate SMZ and TMP plasma concentrations from fixed-dose combination formulations using the USP paddle apparatus, media of physiological relevance, published pharmacokinetic information, and a convolution approach. PE values of SMZ for all drug products were found within international criteria (<15%) only at pH 1.2 and 4.5, while for TMP these results were found only for reference formulation at pH 1.2. It is important to carry out more research in this regard since fixed-dose generic formulations should estimate pharmacokinetic parameters within the established limits for the two drugs involved and not only for one of them. These kind of drug products must adequately release both drugs to achieve this goal.

CONCLUSION

Results suggest that dissolution conditions to test the *in vitro* release performance of SMZ/TMP tablets (USP paddle apparatus and 0.1 N HCl as dissolution medium) may be a suitable option to predict C_{max} and $AUC_{0\text{-}inf}$ of generic formulations since differences in dissolution profiles found for TMP match with differences in simulated pharmacokinetic parameters. It is important to carry out bioavailability studies with the used fixed-dose combination formulations to corroborate the obtained results.

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Nil

AUTHORS CONTRIBUTIONS

JM Ríos-Rodríguez and JR Medina-López conceived and planned the experiments. JM Ríos-Rodríguez and FD Reyes-Ramírez carried out the experiments. JC Ruiz-Segura and JR Medina-López planned and carried out the simulations. FD Reyes-Ramírez contributed to the sample preparation. JC Ruiz-Segura and JR Medina-López contributed to the interpretation of the results. JM Ríos-Rodríguez took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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