Tropical Journal of Pharmaceutical Research November 2015; 14 (11): 2061-2069
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v14i11.16

Original Research Article

In vitro Evaluation of Trimethoprim and Sulfamethoxazole from Fixed-Dose Combination Generic Drugs using Spectrophotometry: Comparison of Flow-Through Cell and USP Paddle Methods

Raúl Medina[1]*, Maximiliano Miranda[1], Marcela Hurtado[1], Adriana M Domínguez-Ramírez[1], Octavio Reyes[1] and Juan C Ruiz-Segura[1,2]
[1]Departamento de Sistemas Biológicos, UAM-Xochimilco Mexico, [2]Departamento de Química Analítica, Fac. de Química UNAM Mexico

For correspondence: **Email: rmlopez@correo.xoc.uam.mx*

Received: 6 August 2014 *Revised accepted: 3 September 2015*

Abstract

Purpose: *To develop a first-order derivative spectrophotometric method for the determination of trimethoprim* (TMP) *and sulfamethoxazole* (SMX) *from fixed-dose combination generic products using a flow-through cell technique.*
Methods: *Absorbance measurement was achieved at 247.8 and 257.9 nm for trimethoprim and sulfamethoxazole, respectively. USP Apparatus 4 with 22.6 mm cells, laminar flow at 16 ml/min, and 0.1 N HCl at 37 °C as dissolution medium, were used. Dissolution profiles were compared with model-dependent and independent methods.*
Results: *All the products met the pharmacopeial dissolution criterion (Q ≥ 70 %, at 60 min), except SMX in two products (SC 400 mg and SB1 800 mg) using the flow-through cell (53.62 and 49.74 % dissolved, respectively). Using both USP apparatuses, significant differences in mean dissolution time and dissolution efficiency values were found ($p < 0.05$). All products were in line with Weibull's kinetics and significant differences in derived parameters (Td) values were found ($p < 0.05$).*
Conclusion: *Determination of TMP and SMX by derivative spectrophotometry can easily be employed for dissolution studies using the flow-through cell technique. However, it would be necessary to determine correlation with in-vivo test results in order to assure safe interchangeability.*

Keywords: *Trimethoprim, Sulfamethoxazole, Flow-through cell method, First-order derivative spectrophotometry, Fixed-dose combination generic drugs*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Recently, several authors have been worried about safe interchangeability between branded products and its generic counterpart or even among different generic products. For several drugs, interesting and different results have been reported [1,2]. Importance of *in-vitro* dissolution test to guarantee a best quality in generic medications is widely discussed by regulatory organisms [3]. According to FDA and WHO guidelines, some generic drugs can be registered on the basis of only *in-vitro* data (dissolution test) without testing their *in-vivo* performance [4]. In Mexico, as in other parts of the world, trimethoprim-sulfamethoxazol (TMP-SMX) immediate-release oral fixed-dosage forms are marketed as generic drugs. The combination is

prepared in different formulations but tablets are the most commonly used, mainly for the advantages of patient management and intake of a solid dosage form.

TMP-SMX inhibits 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. The fixed 1:5 formulation of TMP-SMX is indicated primarily for treating genitourinary, gastrointestinal, and respiratory tract infections as well as skin-associated infections and HIV-infected patients [5]. Development of bacterial resistance and adverse reactions are well documented [6].

According to Biopharmaceutical Classification System, TMP and SMX are classified as Class II drugs [7]. Due to their low aqueous solubility, dissolution rate is the rate-limiting step for absorption. TMP and SMX are well absorbed after oral administration however; TMP is absorbed more rapidly than SMX and is more widely distributed throughout the body. Because of this unequal distribution, a widely range of concentrations is achieved in different tissues and body fluids [6]. Furthermore, *in-vitro* dissolution data offer the best method to predict *in-vivo* performance formulation. In this regard, some authors have been documented differences in *in-vitro* release characteristics of TMP-SMX commercial products [8].

Spectrophotometric approaches for simultaneous analysis of binary and ternary mixtures in commercial tablets were previously reported [9,10]. Studies are often focused on *in-vitro* dissolution profiles of TMP-SMX without previous extraction steps and interference of matrix effect; however, alkaline or a combination of alkaline/methanolic solutions are usually used in those studies but pharmacopeial dissolution method is carried out in acidic medium (0.1 N HCl). Other kinds of solutions are not the natural environment where drugs will be dissolved within the first minutes after tablets intake. Dissolution profiles of TMP-SMX commercial products with derivative spectrophotometry were also reported. The aid of some devices and continuous-flow methodology knowing as multi-commutation is included [11]. For pharmaceutical analysis of TMP-SMX brand products, automated dissolution systems fitted with an integrated multicomponent detector was reported [8]. Determination of multicomponent dissolution profiles of TMP-SMX pharmaceutical products by *in-situ* fiber-optic UV measurements was also described [12]. For current pharmaceutical laboratories these equipments are not easily available and routine dissolution profiles comparisons with binary mixtures is difficult to carry out.

For the evaluation of dissolution profiles of TMP-SMX tablets, the United States Pharmacopeia (USP) [13] specifies the use of USP paddle method at 75 rpm with 900 ml of 0.1 N HCl as dissolution medium and not less than 70 % (Q) of TMP-SMX is dissolved in 60 min. HPLC analysis for drugs quantification is recommended. An alternative to evaluate *in-vitro* drug release is the flow-through cell system (USP Apparatus 4). Its advantages over the conventional basket and paddle methods (USP Apparatus 1 and 2, respectively) are widely demonstrated, especially for the dissolution of poorly soluble drugs [14,15]. The USP Apparatus 4 best simulates the hydrodynamic conditions that are found in the gastrointestinal tract. Therefore, it is important to investigate the applicability of the flow-through cell system on the assessment of TMP-SMX dissolution profiles in order to ensure the adequate biopharmaceutical evaluation of fixed-dose combination generic drugs.

The aim of this study was to apply a first-order derivative spectrophotometric method, especially developed for dissolution studies (USP paddle method), in the determination of dissolution profiles of TMP and SMX from fixed-dose combination generic drugs obtained with the flow-through cell system. Results were compared with data obtained with the pharmacopeial method, USP Apparatus 2.

EXPERIMENTAL

Products and standard solutions

Seven TMP-SMX immediate-release commercial products were used. Different letter was assigned to each one (A, B and C for 80 mg of TMP and 400 mg of SMX tablets) and (A1 and B1 for 160 mg of TMP and 800 mg of SMX tablets). Dissolution profiles of generic drugs were compared to dissolution profiles of the Mexican reference products (R and R1) Bactrim® and Bactrim® F (Productos Roche, SA de CV, Mexico). Hydrochloric acid and methanol analytical grade were purchased from JT Baker-Mexico. TMP and SMX 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 TMP (0.2 mg/ml) and SMX (1 mg/ml) in 0.1 N HCl to achieve the concentrations of 10–50 µg/ml of TMP and 250–350 µg/ml of SMX in the same medium.

Content uniformity and assay

Content uniformity and assay tests were performed with all products, according the procedures described in the USP [13].

Analytical method validation

The proposed analytical method was validated according to the International Conference on Harmonization (ICH) guidelines [16]. The system linearity, accuracy and precision were analyzed.

Pharmacopeial dissolution method (USP Apparatus 2)

TMP-SMX dissolution profiles were carried out according the procedures described in the USP [13]. An USP paddle apparatus (Sotax AT-7 Smart, Switzerland) with a piston pump (Sotax CY7-50, Switzerland) was used. Tablets were added on 900 ml of 0.1 N HCl at 37.0 ± 0.5 ºC (n = 6). Rotational speed of 75 rpm was tested. 10 ml of filtered samples were withdrawn at 15, 20, 30, 45, and 60 min and replaced with an equal volume of fresh dissolution medium to maintain a constant total volume.

Flow-through cell method (USP Apparatus 4)

TMP-SMX dissolution profiles were obtained with an automated flow-through cell system, USP Apparatus 4 (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 degassed 0.1 N HCl was used as the dissolution medium, at a flow rate of 16 ml/min and an open system was used. Dissolution samples were taken at 15, 20, 30, 45 and 60 min (n = 6).

First-order derivative spectrophotometric analysis

Simultaneous determination of TMP-SMX was carried out with a first-order derivative spectroscopic method previously developed in our laboratory [17]. 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 first-derivative mode with scan speed 240 nm/min, slit width 2.0 nm, and sampling interval 1.0 nm. The amounts of TMP-SMX dissolved in both dissolution apparatuses were determined at 247.8 and 257.9 nm respectively, with reference to standard calibration curves.

Data analysis

TMP-SMX dissolution data of each product were used to calculate model-independent parameters: % dissolved at 60 min (Q), mean dissolution time (MDT) [18] and dissolution efficiency (DE) [19]. The values of these parameters from generic drugs were compared with the reference products 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 TMP and SMX from the used products, dissolution data were fitted to different kinetic models: First order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell, Weibull and Logistic. The model with highest determination coefficient ($R^2_{adjusted}$) and minimum Akaike Information Criterion (AIC) was chosen as the best fit [20]. Data analysis was carried out using Excel add-in DDSolver program [21]. To compare dissolution profiles with model-dependent methods a parameter derived from the best fit model was compared with an univariate one-way ANOVA followed by Dunnett's or Dunnett's T3 multiple comparisons test. Differences were considered significant if $p < 0.05$.

RESULTS

Pharmacopeial tests

All products met the content uniformity and assay tests specified in the USP. The percentages of TMP-SMX on the content uniformity test ranged from 85–115 % and the assay test was between 90 and 110 %, Table 1.

Analytical method validation

The mean regression equation from three standard calibration curves was y = 0.0349x + 0.0124 for TMP and y = –0.0100x + 0.2756 for SMX. The relative standard deviation (RSD) values of response factor were 2.08 and 1.79 % for TMP and SMX ranges, respectively. Considering dissolution of 80, 100 and 120 % of dose, the regression equation to assess the method linearity was y = 1.0005x – 0.0227 for TMP and y = 1.0013x + 0.4559 for SMX (R^2 = 0.998; $p < 0.05$). The method accuracy was

Table 1: Mean content uniformity and assay results of trimethoprim (TMP) and sulfamethoxazole (SMX); *n* = 10

Drug	Code	Dose (mg)	Content uniformity (min-max)	Assay (%)
TMP	TR	80	99.17-101.03	100.09
	TA	80	102.59-104.89	103.77
	TB	80	103.50-106.24	104.68
	TC	80	100.72-103.22	102.21
SMX	SR	400	103.68-105.62	104.65
	SA	400	98.38-100.58	99.51
	SB	400	99.01-101.63	100.13
	SC	400	101.97-104.50	103.48
TMP	TR1	160	100.84-103.00	101.88
	TA1	160	99.06-100.44	99.95
	TB1	160	101.48-103.83	102.61
SMX	SR1	800	97.48-99.56	98.48
	SA1	800	99.70-101.09	100.59
	SB1	800	101.84-104.20	102.98

99.94 % for TMP and 100.27 % for SMX. The higher RSD value calculated to assess the method precision was 1.59 %. All commercial products met standard validation criteria too.

Dissolution profiles

TMP-SMX dissolution profiles obtained with the flow-through cell system and the USP paddle method are shown in Figure 1. Considering a single point specification (Q ≥ 70 % in 60 min) all products met the pharmacopeial dissolution criterion in both USP apparatuses, excepting SMX in products SB (400 mg) and SB1 (800 mg) using USP Apparatus 4 (53.62 and 49.74 % dissolved, respectively). TMP-SMX dissolution test using the USP paddle method did not differentiate between the dissolution profiles; based on the pharmacopeial specifications all products tested reached the Q value.

Model-independent comparisons

MDT and DE mean values ± standard error for products under study in both USP apparatuses are shown in Table 2. Considering model-independent comparisons significant differences in dissolution profiles of all generic drugs were found.

Model-dependent comparisons

In order to describe the TMP-SMX release kinetics from generic drugs, data were fitted to several kinetics models. Low values of $R^2_{adjusted}$ and high values of AIC were found with almost all models. The dissolution data of all products in the flow-through cell system and the USP paddle method were best fitted by Weibull's function and the comparison of dissolution profiles was made analyzing the derived parameter (Td) from this function. Significant differences in Td values between generic drugs and the reference products were found ($p < 0.05$) in both USP apparatuses, Table 3.

DISCUSSION

First-derivative spectroscopic method was successfully applied for TMP-SMX determination together with the flow-through cell apparatus. In USP Apparatus 2 the UV analysis is also adequate because in both apparatuses, TMP and SMX achieved an extent of dissolution of 100 ± 3 % at 60 min from the reference products. In all sampling times the RSD was lower than 3 %. Results in USP Apparatus 4 showed a slower dissolution rate than the one found with the USP paddle method. This behavior can be explained by the hydrodynamic conditions that characterize the flow-through cell, where no agitation mechanisms exists and the dosage form and the drug particles are continuously exposed to a uniform laminar flow, similar to the natural environment of the gastrointestinal tract, causing different *in-vitro* dissolution pattern [22]. *In-vitro/in-vivo* correlation (IVIVC) using the flow-through cell at flow rates of 8, 16 and 32 ml/min has been previously discussed [23] as well as flow rates of 4, 8 and 16 ml/min are also in the European Pharmacopeia and the USP.

The analytical method validation was done with all products used in the present study however, as an example and in order that method validation is not the main objective of this work, only the reference product R (80/400 mg-dose) data are shown.

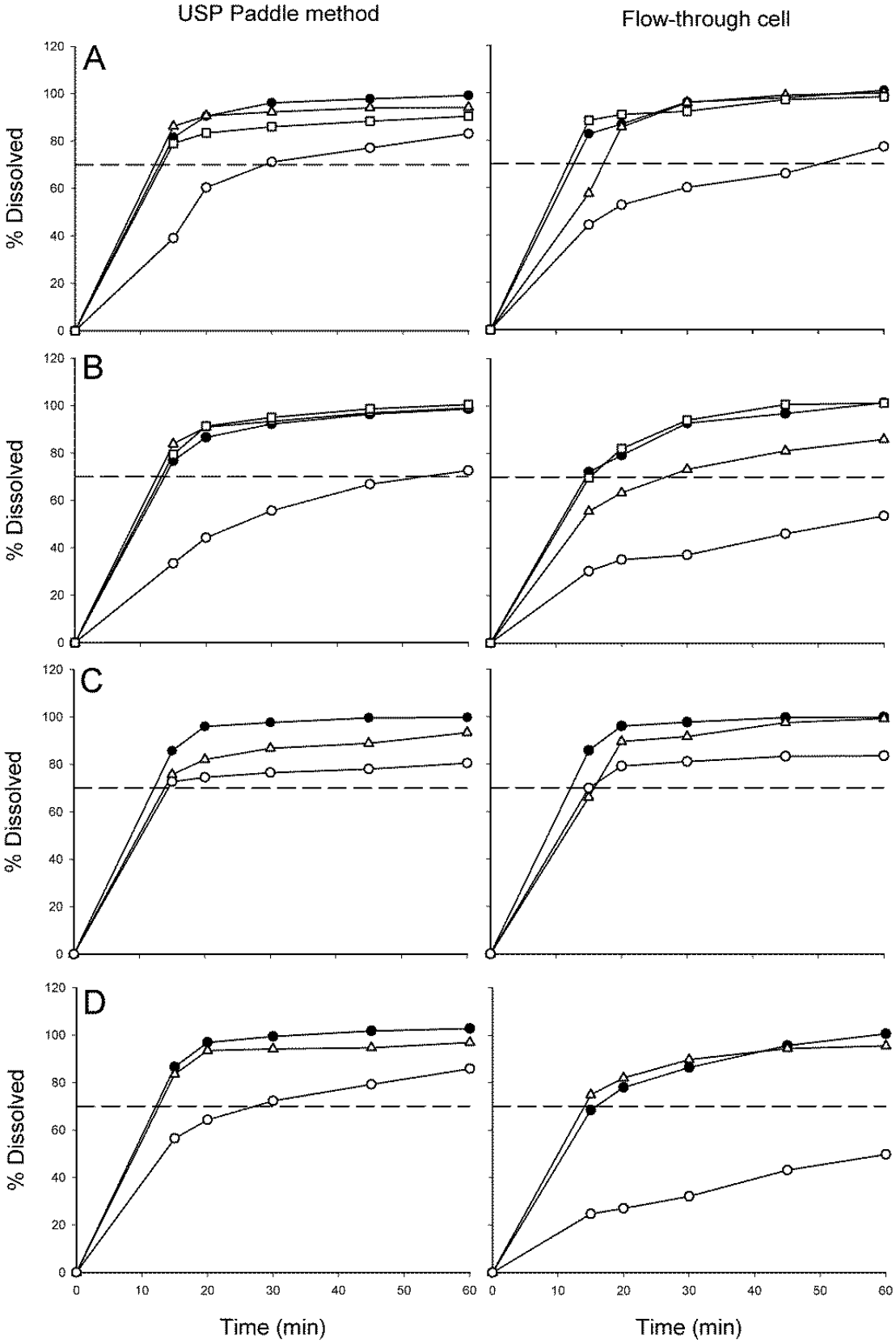

Figure 1: Dissolution profiles of trimethoprim-sulfamethoxazole from fixed-dose combination reference and generic products (Key: A) ● TR, Δ TA, ○ TB and □ TC. B) ● SR, Δ SA, ○ SB and □ SC. C) ● TR1, Δ TA1 and ○ TB1. D) ● SR1, Δ SA1 and ○ SB1) evaluated with the USP paddle method and the flow-through cell system. Mean, *n* = 6. Error bars were omitted for clarity

Table 2: Model-independent parameters: percentage dissolved at 60 min, mean dissolution time (MDT), and dissolution efficiency (DE) of trimethoprim (TMP) and sulfamethoxazole (SMX) from fixed-dose combination generic drugs. Data are mean ± SEM, $n = 6$: *$p < 0.05$

Drug	Code	Dose (mg)	% Diss. at 60 min	MDT (min)	DE (%)
		USP Paddle method			
TMP	TR	80	99.28±0.45	10.55±0.14	81.81±0.21
	TA	80	94.24±0.58*	8.92±0.23*	80.22±0.44
	TB	80	83.13±0.96*	17.78±0.78*	58.53±1.56*
	TC	80	90.53±0.73*	10.33±0.33	74.94±0.77*
SMX	SR	400	98.63±0.26	11.79±0.18	79.25±0.18
	SA	400	98.95±0.15	10.65±0.13*	81.39±0.21*
	SB	400	72.59±2.38*	19.93±0.41*	48.46±1.54*
	SC	400	100.44±0.46*	11.22±0.18	81.65±0.27*
TMP	TR1	160	99.74±0.23	9.47±0.10	83.99±0.12
	TA1	160	93.39±1.73*	11.92±0.71*	74.84±1.80*
	TB1	160	80.50±0.33*	10.10±0.17	66.94±0.14*
SMX	SR1	800	102.77±0.39	10.07±0.17	85.52±0.14
	SA1	800	96.87±0.46*	9.83±0.22	81.00±0.23*
	SB1	800	85.81±0.20*	15.92±0.12*	63.04±0.12*
		Flow-through cell method			
TMP	TR	80	100.96±0.48	11.43±0.24	81.72±0.40
	TA	80	99.95±1.01	13.50±0.17*	77.46±0.58*
	TB	80	77.23±1.29*	19.12±0.58*	52.59±0.72*
	TC	80	98.31±0.64	10.06±0.10*	81.82±0.42
SMX	SR	400	101.36±0.39	13.76±0.19	78.12±0.59
	SA	400	85.90±0.90*	15.67±0.37*	63.44±0.22*
	SB	400	53.62±0.22*	20.40±0.10*	35.39±0.10*
	SC	400	101.22±0.42	13.03±0.08*	79.24±0.37
TMP	TR1	160	100.88±0.52	9.71±0.19	84.54±0.20
	TA1	160	99.13±0.39	12.77±0.17*	78.02±0.17*
	TB1	160	83.47±0.74 *	9.93±0.16	69.65±0.59*
SMX	SR1	800	100.59±0.41	14.89±0.09	75.64±0.38
	SA1	800	95.51±0.28*	11.65±0.23*	76.96±0.46
	SB1	800	49.74±0.20*	22.38±0.02*	31.19±0.12*

Results of the present study agree with those found by other authors where TMP from commercial tablets dissolved rapidly while SMX dissolved slowly [12,24]. For the study, USP Apparatus 2 at 75 rpm was used. In another work, considering TMP-SMX generic drugs comparisons, dissolution profile of SMX from a commercially available product was slower than SMX profiles of other two evaluated products [8]. Authors used USP paddle method and 50 rpm as agitation rate.

In order to compare the *in-vitro* dissolution data of TMP and SMX from fixed-dose combination generic drugs, model-independent parameters MDT and DE were calculated. These parameters have been proposed as adequate parameters for some IVIVC levels [25]. IVIVC Level B represents a relationship between MDT and the mean residence time, both calculated by statistical moments theory. IVIVC of oral TMP-SMX formulations using data derived from statistical moments analysis was previously reported [26]. Three formulations gave R^2 of 0.99885 including both drugs in the same analysis. One of them was a commercially available product. 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 AUC, 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 [19].

Comparison of dissolution profiles using model-dependent methods is a common methodology. Several authors reported adjustments of TMP-SMX dissolution profiles of commercially available formulations (tablets) to Higuchi's kinetic model. They suggested that Higuchi's equation allows an easy comparison of the parameters and curves and it fits better than polynomial equations [11]. However, results obtained in the present work 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 [14,15].

Table 3: Model-dependent parameters: *α, β* and *Td* values derived from the trimethoprim (TMP) and sulfamethoxazole (SMX) data adjusted to Weibull's kinetic model. Data are mean ± SEM, $n = 6$: *$p < 0.05$

Drug	Code	Dose (mg)	*α*	*β*	*Td* (± SEM)
			USP Paddle method		
TMP	TR	80	21.16	1.19	9.14±0.48
	TA	80	79.07	82.77	5.57±1.19*
	TB	80	1987.27	1.90	17.92±0.64*
	TC	80	84.95	84.83	5.66±0.60*
SMX	SR	400	8.76	0.92	9.24±0.59
	SA	400	4.13	0.67	5.66±0.90*
	SB	400	44.48	1.15	24.83±1.86*
	SC	400	55.31	1.28	9.81±0.70
TMP	TR1	160	132.06	1.87	10.15±0.47
	TA1	160	423.84	34.22	8.02±0.85
	TB1	160	1036.11	43.36	2.95±0.83*
SMX	SR1	800	66.86	1.51	9.38±0.79
	SA1	800	4979.41	2.17	10.04±0.92
	SB1	800	126.62	7.79	19.73±2.03*
			Flow-through cell method		
TMP	TR	80	4.35	0.68	7.51±0.36
	TA	80	3319.53	2.88	15.67±0.11*
	TB	80	9.59	0.71	24.20±1.84*
	TC	80	1.17	0.25	1.91±0.18*
SMX	SR	400	9.25	0.87	12.43±0.25
	SA	400	1661.94	1.78	17.33±1.67
	SB	400	5870.83	1.71	82.50±0.62*
	SC	400	22.75	1.19	13.28±0.13
TMP	TR1	160	3.73	0.57	3.66±1.16
	TA1	160	3058.52	2.89	14.22±0.07*
	TB1	160	146.75	1.73	9.70±1.57*
SMX	SR1	800	1514.87	1.26	14.49±0.16
	SA1	800	1512.08	1.10	9.86±0.73*
	SB1	800	1967.28	1.55	86.22±0.54*

The interchangeability of generic drugs is understood to mean the possibility for their mutual replacement in clinical practice while maintaining pharmacological response unaltered. The assessment of generics drugs interchangeability by *in-vitro* studies is one of the important task of the International Pharmaceutical Federation represented by the publication of "biowaiver monographs" [27]. Moreover, and with reference in the experience of a few countries, the role of generic medicines in healthcare systems and the need to establish and implement generic medicines policies is widely discussed by some authors [28]. Suitable *in-vitro* dissolution studies help to maintain an adequate quality control in formulations that may present potential bioequivalence problems.

CONCLUSION

First-order derivative spectroscopy is a useful technique for the simultaneous determination of TMP and SMX dissolution profiles from fixed-dose combination generic drugs using the flow-through cell method. The USP Apparatus 4 is effective in discriminating *in-vitro* dissolution characteristics of the different generic products.

REFERENCES

1. *Ruiz ME, Gregorini A, Talevi A, Volonté MG. Dissolution studies of generic medications: new evidence of deviations from the transitivity principle. Dissol Technol 2012; 19(1): 13−24.*
2. *Al Ameri MN, Nayuni N, Anil Kumar KG, Perrett D. The differences between the branded and generic*

medicines using solid dosage forms: In-vitro dissolution testing. Results Pharma Sci 2012; 2: 1−8.

3. *Anand O, Yu LX, Conner DP, Davit BM. Dissolution testing for generic drugs: an FDA perspective. AAPS J 2011; 13(3): 328−335.*
4. *Ramenskaya GV, Shokin IE. Modern approaches to quality evaluation of generic drugs for their registration (a review). Pharm Chem J 2009; 43(9): 512−515.*
5. *Masters PA, O'Bryan TA, Zurlo J, Miller DQ, Joshi N, Trimethoprim-sulfamethoxazole revisited. Arch Int Med 2003; 163: 402−410.*
6. *Kielhofner MA. Trimethoprim-sulfamethoxazole: pharmacokinetics, clinical uses, and adverse reactions. Tex Heart Inst J 1990; 17(2): 86−93.*
7. *Lindengerb M, Kopp S, Dressman JB. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. Eur J Pharm Biopharm 2004; 58: 265−278.*
8. *Fuerte V, Maldonado M, Rees GD. The multicomponent automated dissolution system: an alternative in the development and pharmaceutical analysis of generic polydrugs. J Pharm Biomed Anal 1999; 21: 267−272.*
9. *Ribone MÉ, Pagani AP, Olivieri AC. Simultaneous multivariate spectrophotometric analysis of binary and ternary mixtures of sulfamethoxazole, trimethoprim and phenazopyridine in tablets. Anal Lett 1999; 32(7): 1389−1401.*
10. *Markopoulou CK, Malliou ET, Koundourellis JE. Chemometric and derivative methods as fexible spectrophotometric approaches for dissolution and assaying tests in multicomponent tablets. Il Farmaco 2004; 59: 627−636.*
11. *Tomšů D, Catalá Icardo M, Martínez Calatayud J. Automated simultaneous triple dissolution profiles of two drugs, sulphamethoxazole-trimethoprim and hydrochlorothiazide-captopril in solid dosage forms by a multicommutation flow-assembly and derivative spectrophotometry. J Pharm Biomed Anal 2004; 36: 549−557.*
12. *Gemperline PJ, Cho J, Baker B, Batchelor B, Walker DS. Determination of multicomponent dissolution profiles of pharmaceutical products by in situ fiber-optic UV measurements. Anal Chim Acta 1997; 345: 155−159.*
13. *United States Pharmacopeia 30 National Formulary 24, United States Pharmacopeial Convention, Inc. Rockville, MD: 2007.*
14. *Hurtado M, Vargas Y, Domínguez-Ramírez AM, Cortés AR. Comparison of dissolution profiles for albendazole tablets using USP Apparatus 2 and 4. Drug Dev Ind Pharm 2003; 29: 777−784.*
15. *Medina JR, Salazar DK, Hurtado M, Cortés AR, Domínguez-Ramírez AM. Comparative in vitro dissolution study of carbamazepine immediate-release products using the USP paddles method and the flow-through cell system. Saudi Pharm J 2014; 22: 141−147.*
16. *International Conference on Harmonization, ICH Q2(R1). 2005. Validation of Analytical Procedures: Text and Methodology.*
17. *Medina JR, Miranda M, Hurtado M, Domínguez-Ramírez AM, Ruiz-Segura JC. Simultaneous determination of trimethoprim and sulfamethoxazole in immediate-release oral dosage forms by first-order derivative spectroscopy: application to dissolution studies. Int J Pharm Pharm Sci 2013; 5, (Suppl 4): 505−510.*
18. *Podczeck F. Comparison of in vitro dissolution profiles by calculating mean dissolution time (MDT) or mean residence time (MRT). Int J Pharm 1993; 97: 93−100.*
19. *Anderson NH, Bauer M, Boussac N, Khan-Malek R, Munden P, Sardaro M. An evaluation of fit factors and dissolution efficiency for the comparison of in vitro dissolution profiles. J Pharm Biomed Anal 1998; 17: 811−822.*
20. *Yuksel N, Kanik AE, Baykara T. Comparison of dissolution profiles by ANOVA-based, model-dependent and -independent methods. Int J Pharm 2000; 209: 57−67.*
21. *Zhang Y, Huo M, Zhou J, Zou A, Li W, Yao C, Xie S. DDSolver: an add-in program for modeling and comparison of drug dissolution profiles. AAPS J 2010; 12: 263−271.*
22. *Langenbucher F, Benz D, Kurth W, Moller H, Otz M. Standardized flow-cell method as an alternative to existing pharmacopoeial dissolution testing. Pharm Ind 1989; 51: 1276−1281.*
23. *Sunesen VH, Pedersen BL, Kristensen HG, Müller A. In vitro in vivo correlations for a poorly soluble drug, danazol, using the flow-through dissolution method with biorelevant dissolution media. Eur J Pharm Sci 2005; 24: 305−313.*
24. *Athanassiou GC, Rekkas DM, Choulis NH. Development of sulphamethoxazole-trimethoprim spheroidal granules: factors affecting drug release in vitro. Int J Pharm 1991; 72: 141−147.*
25. *Demirtürk E, Öner L. In vitro-In vivo correlations. FABAD J Pharm Sci 2003; 28: 215−224.*
26. *Athanassiou GC, Rekkas DM, Choulis NH. Correlation of in vitro dissolution data with in vivo plasma concentrations, for three, orally administered, formulations of sulphamethoxazole-trimethoprim, by statistical moment analysis. Int J Pharm 1993; 90: 51−58.*
27. *Shokin IE, Ramenskaya GV, Vasulenko GF, Malalshenko EA. Assessment of the possibility of using comparative in vitro dissolution kinetics (biowaiver) instead of in vitro bioequivalence evaluation for establishing the interchangeability of generic drugs. Pharm Chem J 2011; 45(2): 107−109.*
28. *Hassali MA, Alrasheedy AA, McLachlan A, Nguyen TA, AL-Tamimi SK, Mohamed Ibrahim MI, Aljadhey H. The experiences of implementing generic medicine policy in eight countries: A review and recommendations for a successful promotion of*

generic medicine use. Saudi Pharm J 2014. On line *http://dx.doi.org/10.1016/j.jsps.2013.12.017*