UNIVERSIDADE DE SÃO PAULO
FACULDADE DE CIÊNCIAS FARMACÊUTICAS
Programa de Pós-Graduação em Fármaco e Medicamentos
Área de Produção e Controle Farmacêuticos

Determination of absorption curves, dissolution profiles and establishment of *in vitro-in vivo* correlation by *in silico* methods using GastroPlus™ and DDDPlus™

Marcelo Dutra Duque

Tese para obtenção do grau de
DOUTOR

Orientador:
Prof. Dr. Humberto Gomes Ferraz
Coorientador:
Prof. Dr. Raimar Löbenberg

São Paulo
2016

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Comissão Julgadora
da
Tese para obtenção do grau de Doutor

Prof. Dr. Humberto Gomes Ferraz
Orientador/presidente

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São Paulo, _____de 2016

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RESUMO

DUQUE, M.D. **Determinação das curvas de absorção, perfis de dissolução e estabelecimento da correlação *in vitro-in vivo* por métodos *in silico* utilizando o GastroPlus™ e o DDDPlus™**. 2016. 86 p. Tese (Doutorado) – Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, 2016.

O uso de programas de computador para prever a absorção de fármacos em humanos e simular perfis de dissolução tem se tornado uma ferramenta bastante valiosa na área farmacêutica. O objetivo deste trabalho foi utilizar métodos *in silico* por meio dos programas de computador GastroPlus™ e DDDPlus™ para simular curvas de absorção de fármacos, perfis de dissolução e estabelecer correlações *in vitro-in vivo* (CIVIVs). O material aqui apresentado é constituído por cinco capítulos incluindo os fármacos cetoprofeno, pirimetamina, metronidazol, fluconazol, carvedilol e doxazosina. No capítulo 1 são apresentadas curvas plasmáticas simuladas para comprimidos matriciais de cetoprofeno, sendo estabelecida a CIVIV. A utilização de simulações de ensaios de dissolução intrínseca para os fármacos pirimetamina e metronidazol como uma ferramenta para classificação biofarmacêutica é detalhada no capítulo 2. No capítulo 3, a simulação de curvas plasmáticas a partir de cápsulas de fluconazol contendo diferentes perfis de dissolução é demonstrada como uma ferramenta para bioisenção. Estudos de CIVIV foram também realizados para comprimidos de liberação imediata de carvedilol a partir dos perfis de dissolução no capítulo 4. Já o capítulo 5 trata da aplicação de simulações de ensaios de dissolução para o desenvolvimento de formulações de liberação prolongada de doxazosina. As simulações das curvas plasmáticas, assim como a CIVIV, obtidas com o auxílio do programa GastroPlus™, além dos ensaios de dissolução intrínsica e os perfis de dissolução obtidos por meio do uso do programa DDDPlus™ apresentaram-se como ferramentas de grande aplicação na previsão de características biofarmacêuticas sobre os fármacos e formulações, permitindo redução de tempo e custo com trabalho experimental em laboratório.

Palavras-chave: GastroPlus™. DDDPlus™. Correlação *in vitro-in vivo*. Perfis de dissolução. Curvas plasmáticas.

ABSTRACT

DUQUE, M.D. **Determination of absorption curves, dissolution profiles and establishment of *in vitro-in vivo* correlation by *in silico* methods using GastroPlus™ and DDDPlus™**. 2016. 86 p. Tese (Doutorado) – Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, 2016.

The use of computer programs to predict drug absorption in humans and to simulate dissolution profiles has become a valuable tool in the pharmaceutical area. The objective of this study was to use *in silico* methods through software GastroPlus™ and DDDPlus™ to simulate drug absorption curves and dissolution profiles, and to establish *in vitro-in vivo* correlations (IVIVCs). The work presented herein is divided into five chapters and includes the drugs ketoprofen, pyrimethamine, metronidazole, fluconazole, carvedilol and doxazosin. In Chapter 1, simulated plasma curves for ketoprofen matrix tablets are presented and IVIVC was established. The use of simulated intrinsic dissolution tests for pyrimethamine and metronidazole as a tool for biopharmaceutics classification is detailed in Chapter 2. In Chapter 3, simulation of plasma curves for fluconazole capsules with different dissolution profiles is demonstrated as a tool for biowaiver. IVIVC studies were also conducted for carvedilol immediate-release tablets from dissolution profiles in Chapter 4. Chapter 5 covers the application of simulated dissolution tests for development of doxazosin extended-release formulations. Simulation of plasma curves and IVIVC using the software GastroPlus™ as well as intrinsic dissolution tests and dissolution profiles using the software DDDPlus™ proved to be a tool of wide application in predicting biopharmaceutical characteristics of drugs and formulations, allowing the reduction of time and costs of experimental laboratory work.

Keywords: GastroPlus™. DDDPlus™. *In vitro-in vivo* correlation. Dissolution profiles. Plasma curves.

CONTENTS

CHAPTER 1

In vitro-in vivo correlation of ketoprofen matrix tablets using GastroPlus™

ABSTRACT

Dissolution profiles of four ketoprofen matrix tablet formulations (FM1, FM2, FM3 and FM4) obtained with USP Apparatus 2 and 3 under different pH conditions, and that of the reference product (Profenid® Retard 200 mg tablets), were used to establish *in vitro-in vivo* correlation (IVIVC) by deconvolution and convolution methods using computer simulations. Zero-order, Higuchi and Korsmeyer-Peppas kinetic models were applied to dissolution profiles. Ketoprofen pKa was estimated from its molecular structure using ADMET Predictor™ and solubility was measured by potentiometry; results were used as input data in GastroPlus™. Dissolution profiles and plasma concentrations of the reference product were obtained from the literature. Korsmeyer-Peppas model showed the best fit for most dissolution profiles. All formulations had high R^2 values for deconvolution. FM1 and FM3 evaluated using Apparatus 2 at pH 6.0 and FM2 and FM4 using Apparatus 2 at pH 6.8 showed better IVIVC under fed conditions, indicating that computer simulations in GastroPlus™ can be successfully used to establish IVIVC for ketoprofen matrix tablets.

Keywords: Ketoprofen. *In silico*. *In vitro-in vivo* correlation (IVIVC). Dissolution.

1 INTRODUCTION

In vitro-in vivo correlation (IVIVC) is defined as a predictive mathematical model describing the relationship between an *in vitro* property, such as drug dissolution of an extended-release (ER) dosage form, and the *in vivo* response, such as drug plasma concentration after administration, that can be established in three categories (Levels A, B and C). Level A is obtained by correlating the amount of drug absorbed *in vivo* mathematically obtained by a deconvolution method and *in vitro* release during dissolution test as a point-to-point comparison. Level B correlation involves the comparison between mean *in vitro* and *in vivo* dissolution time, mean *in vivo* residence time or *in vitro* dissolution rate constant versus absorption constant. Level C is a mathematical model involving the relationship between *in vitro* drug dissolution at a particular time and the corresponding *in vivo* parameter (FDA, 1997; UPPOOR, 2001).

For ER dosage forms, the amount of drug available for absorption is highly dependent on release control by excipients used in formulation, making this drug delivery system a potential candidate for establishing Level A IVIVC (SANKALIA; SANKALIA; MASHRU, 2008). Obtaining IVIVC for ER products is considered an important step to reduce the number of bioequivalence studies (FDA, 1997), allowing formulators to develop products with relevant *in vivo* release (LIU et al., 2012) and appropriate dissolution tests that can better indicate *in vivo* formulation performance (FOTAKI et al., 2009).

Dissolution tests in ER dosage forms can be used to predict plasma concentrations by convolution method, avoiding *in vivo* bioequivalence studies in humans (EMAMI, 2006; O'HARA et al., 2001). The adequate choice of dissolution test conditions, such as apparatus, rotation speed and dissolution media can improve the estimation of *in vivo* formulation performance (FOTAKI et al., 2009). Particularly for drugs with low solubility and high permeability (class II) according to the Biopharmaceutics Classification System (BCS), dissolution is the rate-limiting step for absorption and IVIVC is expected, as it is possible to correlate *in vitro* and *in vivo* dissolution of dosage forms (AMIDON et al., 1995).

Ketoprofen is a poorly soluble and highly permeable (BCS class II) non-steroidal anti-inflammatory drug (NSAID). After oral administration, it is promptly absorbed in the gastrointestinal tract, with peak plasma concentrations at about 0.5 to 2 hours. It is a weak acid compound, with pKa about 4.5; it is reported as a BCS class IIa drug

because even though it is poorly soluble at acid pH, it is soluble at intestinal pH. Therefore, ketoprofen is a candidate to biowaiver according to BCS (SWEETMAN, 2011; TSUME et al., 2014).

Using *in silico* methods to predict plasma concentrations of drugs in solid oral dosage forms and thus estimate IVIVC is a reality today (OKUMO; DIMASO; LÖBENBERG, 2008; OKUMO, DIMASO, LÖBENBERG, 2009; WEI et al., 2008; HONÓRIO et al., 2013; KOSTEWICZ et al., 2014; ALMUKAINZI et al., 2016; KESISOGLOU et al., 2016). These predictions can be obtained using software such as GastroPlus™, which involves Physiologically-Based Pharmacokinetic (PBPK) models describing drug concentration in tissues (KOSTEWICZ et al., 2014) and Advanced Compartmental Absorption and Transit (ACAT) models, both allowing the estimation of plasma concentration of a given dosage form using physicochemical characteristics of the drug as well as other data, such as permeability and metabolism (PARROTT; LAVÉ, 2002).

The aim of this work was to use different dissolution profiles of ketoprofen matrix tablet formulations to establish IVIVC by deconvolution and convolution methods using the software GastroPlus™.

2 MATERIAL AND METHODS

2.1 Material

Ketoprofen (SP Farma, São Paulo, Brazil) was used in solubility experiments. Methanol HPLC grade (J.T. Baker, Hexis, Jundiaí, São Paulo, Brazil), potassium chloride (Synth, Diadema, São Paulo, Brazil), hydrochloric acid P.A. 37% (Synth, Diadema, São Paulo, Brazil), 1 mol/L potassium hydroxide standard solution (Sigma-Aldrich, Steinheim, Germany) and dimethyl sulfoxide P.A. (Synth, Diadema, São Paulo, Brazil) were of analytical grade.

2.2 Determination of pKa and solubility

Ketoprofen pKa was determined from its molecular structure using ADMET Predictor™ (Absorption, Distribution, Metabolism, Elimination and Toxicity Predictor)

(Simulations Plus, Lancaster, CA, USA). Solubility was obtained using a Sirius T3 titration equipment (Sirius Analytical Instruments Ltda., East Sussex, UK).

For solubility determination, 10 mg of ketoprofen was dissolved in 1.5 mL of 0.15 M KCl aqueous solution for ionic strength adjustment. Considering pKa obtained by ADMET Predictor™, acid titration in pH range 2-12 by Cheqsol method (STUART; BOX, 2005) was performed using 0.5 M HCl and 0.5 M KOH solutions under N_2 atmosphere at 37 ± 0.5 °C. Apparent absorption was fixed at 500 nm for detection of precipitation during titration.

2.3 Dissolution kinetics

Dissolution kinetics were carried out with four ketoprofen matrix tablet formulations (FM1, FM2, FM3 and FM4) containing 200 mg of the drug and hypromellose (Methocel® K4M or Methocel® K100M) at the following ratios: FM1 (10% Methocel® K4M), FM2 (10% Methocel® K100M), FM3 (20% Methocel® K4M) and FM4 (20% Methocel® K100M), as previously reported by Pezzini; Ferraz (2009). The authors submitted formulations to dissolution tests using USP Apparatus 3 (Bio-Dis) with 250 mL of dissolution media (pH 1.2-1 h, pH 4.5-0.5 h, pH 6.0-2.5 h; pH 6.8-6 h and pH 7.2-2 h) at 8 dips per minute and 37 °C and USP Apparatus 2 (paddle) with 900 mL of dissolution media (pH 4.5, pH 6.0, pH 6.8 and pH 7.2, 12 h each) at 50 rpm and 37 °C.

Dissolution kinetic models (Zero-order, Higuchi and Korsmeyer-Peppas) were applied to dissolution profiles using the add-in program DDSolver for Microsoft Excel (ZHANG et al., 2010; ZUO et al., 2014). For comparative purposes, the same dissolution kinetic models were applied to the dissolution profile of the reference product Profenid® Retard 200 mg tablets (Ref) obtained from previous work (ÇOMOĞLU et al., 2007), considering dissolution using USP Apparatus 2 with 900 mL of phosphate buffer pH 7.4, at 50 rpm and 37 ± 0.5 °C.

2.4 Computer simulations

The software GastroPlus™ version 9.0 (Simulations Plus Inc., Lancaster, CA, USA), IVIVCPlus™ module, was used to establish IVIVC between plasma concentration profile of the reference product Profenid® Retard 200 mg tablets reported

by Çomoğlu et al. (2007) and *in vitro* drug release of four formulations (FM1, FM2, FM3 and FM4) from Pezzini; Ferraz (2009).

For such, a ketoprofen database was created in GastroPlus™. Solubility and pKa results, molecular weight, dose and human jejunum effective permeability (KASIM et al., 2004) were used as input data in the software. Controlled-release dispersed (CR: dispersed) function was selected in Compound Tab; human physiological fasted and fed states were selected in Physiology Tab to evaluate the influence of food on drug absorption. In PKPlus™ module, plasma concentration profile for intravenous (IV) drug administration reported by Kokki; Karvinen; Suhonen (2003) was used to calculate and fit the compartmental model and resulting pharmacokinetic parameters.

Drug records were generated in ketoprofen database for formulations FM1, FM2, FM3 and FM4, each one containing five dissolution profiles (USP Apparatus 3 (ap3), USP Apparatus 2 (ap2) pH 4.5, pH 6.0, pH 6.8 and pH 7.2) according to Pezzini; Ferraz (2009). A drug record was also created using the dissolution profile of the reference product Profenid® Retard 200 mg tablets previously reported by Çomoğlu et al. (2007).

2.4.1 Deconvolution

Mechanistic absorption model was selected as deconvolution method in IVIVCPlus™ module in software GastroPlus™ to simulate *in vivo* fraction of ketoprofen absorbed considering plasma concentration data of reference product Profenid® Retard 200 mg tablets (ÇOMOĞLU et al., 2007) and then to establish correlation between dissolution profiles for each formulation (PEZZINI; FERRAZ, 2009) and reference product (ÇOMOĞLU et al., 2007). Fasted and fed states were considered for simulations.

2.4.2. Convolution

Mathematical functions obtained from deconvolution methods were used to predict *in vivo* ketoprofen plasma concentrations from each *in vitro* dissolution profile in order to estimate which formulation and dissolution test better reflect *in vivo* performance.

3 RESULTS AND DISCUSSION

Ketoprofen pKa obtained using ADMET Predictor™ was 4.19. Similar values (~ 4.6) were previously reported (KASIM et al., 2004; SHENG et al., 2006). Solubility results (Table 1) were higher for pH > 4.0 due to the weak acid characteristic of ketoprofen.

Table 1 – Ketoprofen solubility at different pH obtained by potentiometry and dose/solubility ratio

pH	Solubility (mg/mL)	Dose/solubility ratio (mL)
1.0	0.6498	307.79
1.2	0.6501	307.64
2.0	0.6536	305.99
3.0	0.6914	289.27
4.0	1.069	187.09
5.0	4.842	41.31
6.0	42.58	4.70
6.8	252.8	0.79

A drug is considered soluble when its highest dose dissolves in 250 mL of aqueous solutions in the pH range 1.2-6.8 (FDA, 2015). Ketoprofen dose (200 mg) was used to calculate dose/solubility ratio (Table 1); it is soluble in 250 mL of aqueous solutions at pH ≥ 4.0 and insoluble at pH < 4.0, showing its low solubility at physiological pH and thus, ketoprofen is reported as a BCS class II drug (TSUME et al., 2012).

The pH dependency of ketoprofen solubility is important to its absorption process in upper small intestine (pH 5.8-6.5) due to its higher solubility as ionized form (SHENG et al., 2006; SHOHIN et al., 2012). It was also reported that ketoprofen solubility characteristics lead to its major absorption in distal small intestine (TSUME et al., 2014).

For BCS class II drugs, dissolution is the rate-limiting step for absorption (AMIDON et al., 1995). However, drug release is a complex process involving physicochemical characteristics of the drug and dosage form, such as solubility, leading to different dissolution kinetics, including one or more phenomena such as diffusion, erosion and swelling, that can be mathematically modeled (SIEPMANN; SIEPMANN, 2008).

Dissolution profiles fit into a specific dissolution kinetic model can lead to a better understanding of processes involved in drug release, aiding in the development of formulations and dissolution tests, mainly for poorly soluble compounds such as BCS class II drugs, for which drug dissolution is expected to reflect *in vivo* performance.

Coefficient of determination (R^2) values for dissolution kinetic models applied to each formulation/dissolution test using the add-in program DDSolver are shown in Table 2.

Table 2 – Dissolution kinetic fitting for ketoprofen matrix tablet formulations (adapted from Pezzini; Ferraz (2009)) *

Formulation/ Dissolution Test	Zero Order	Higuchi	Korsmeyer-Peppas	
	R^2	R^2	R^2	*n*
FM1 ap3	0.8088	0.9882	**0.9981**	0.60
FM1 ap2 pH 4.5	0.9470	0.6354	**0.9692**	0.26
FM1 ap2 pH 6.0	0.1663	0.9371	**0.9914**	0.40
FM1 ap2 pH 6.8	0.3534	0.9668	**0.9932**	0.41
FM1 ap2 pH 7.2	0.2310	0.8555	**0.9977**	0.32
FM2 ap3	0.9393	0.9420	**0.9962**	0.71
FM2 ap2 pH 4.5	0.5224	0.9904	**0.9982**	0.44
FM2 ap2 pH 6.0	0.6914	**0.9884**	0.9877	0.48
FM2 ap2 pH 6.8	0.3704	0.9741	**0.9983**	0.42
FM2 ap2 pH 7.2	0.5804	0.9927	**0.9961**	0.46
FM3 ap3	0.9944	0.8805	**0.9990**	0.89
FM3 ap2 pH 4.5	0.7943	0.9687	**0.9741**	0.54
FM3 ap2 pH 6.0	0.8029	0.9789	**0.9866**	0.59
FM3 ap2 pH 6.8	0.8120	0.9897	**0.9981**	0.57
FM3 ap2 pH 7.2	0.7176	0.9990	**0.9995**	0.51
FM4 ap3	**0.9898**	0.8124	0.9721	1.24
FM4 ap2 pH 4.5	0.9562	0.9295	**0.9744**	0.63
FM4 ap2 pH 6.0	0.9145	0.9616	**0.9968**	0.67
FM4 ap2 pH 6.8	0.9109	0.9648	**0.9979**	0.66
FM4 ap2 pH 7.2	0.9162	0.9608	**0.9952**	0.70
Ref	0.9553	0.9371	**0.9875**	0.78

R^2, coefficient of determination; *n*, Korsmeyer-Peppas release exponent
* For each formulation, the highest R^2 value is highlighted in bold.

For the majority of dissolution profiles of ketoprofen matrix tablet formulations and reference product, Korsmeyer-Peppas was the best fitting kinetic model (Table 2). According to this model, for cylinder dosage forms, drug release occurs as Fickian diffusion for release exponent $n = 0.45$, as anomalous transport for $0.45 < n < 0.89$ and

as case-II transport for n = 0.89 (KORSMEYER et al., 1983; PEPPAS; SAHLIN, 1989). Release exponent $n \leq 0.5$ and $n > 1.0$ indicate Fickian diffusion and super case-II transport, respectively (TATINI et al., 2015).

Korsmeyer-Peppas n value increased according to the percent of polymer used in each formulation: FM1 (10% Methocel® K4M), FM2 (10% Methocel® K100M), FM3 (20% Methocel® K4M) and FM4 (20% Methocel® K100M). For FM1, dissolution profiles obtained with Apparatus 2 had $n < 0.45$, indicating drug release by diffusion process. However, Apparatus 3 showed n value that indicates anomalous transport (diffusion and erosion process) which can be attributed to its superior hydrodynamic with respect to Apparatus 2, which in turn can lead to erosion of hydroxypropyl methylcellulose (HPMC) matrix (PEZZINI et al., 2015).

Anomalous transport was also found for FM2 dissolution profile in Apparatus 3 and in Apparatus 2 at pH 7.2. Drug release occurred only by diffusion process for formulation FM2 evaluated at pH 4.5, 6.0 and 6.8; at pH 6.0, Higuchi equation was the model that best fitted.

Formulations FM3 and FM4 showed the highest n values, indicating zero-order drug release for dissolution profiles with Apparatus 3. Anomalous transport was the dominant drug release mechanism for tests conducted using Apparatus 2 for both formulations.

Dissolution profile for the reference product (ÇOMOĞLU et al., 2007) was best fitted into Korsmeyer-Peppas model, presenting anomalous transport as drug release mechanism.

Differences can be found between *in vitro* dissolution kinetics and *in vivo* absorption, considering dissolution and absorption rates (CARDOT; GARRALT; BEYSSAC, 2015). However, deconvolution and convolution methods can be used to better understand *in vivo* drug release, helping to correlate it with drug dissolution kinetics (EMAMI, 2006).

Deconvolution methods use plasma concentration curves to obtain *in vivo* drug release, which is compared to *in vitro* dissolution profiles in order to establish IVIVC (DUNNE; GAYNOR, 2005). In this work, IVIVC was established using IVIVCPlus™ module in GastroPlus™, which enables deconvoluting drug plasma concentrations and correlating them with dissolution profiles (SIMULATIONS PLUS, 2015).

R^2 values resulting from the deconvolution of plasma concentrations of the reference product for fitting dissolution profiles of each formulation are shown in Table 3 (fasted state) and Table 4 (fed state).

Table 3 – *In vitro-in vivo* correlation fitting (R^2, coefficient of determination) obtained by deconvolution (fasted state) of formulations at different dissolution test conditions

Formulation/ Dissolution Test	**R^2**	**Formulation/ Dissolution Test**	**R^2**
FM1 ap3	0.980	FM2 ap3	0.966
FM1 ap2 pH 4.5	0.979	FM2 ap2 pH 4.5	0.971
FM1 ap2 pH 6.0	0.978	FM2 ap2 pH 6.0	0.965
FM1 ap2 pH 6.8	0.968	FM2 ap2 pH 6.8	0.980
FM1 ap2 pH 7.2	0.989	FM2 ap2 pH 7.2	0.980
FM3 ap3	0.964	FM4 ap3	0.988
FM3 ap2 pH 4.5	0.955	FM4 ap2 pH 4.5	0.940
FM3 ap2 pH 6.0	0.978	FM4 ap2 pH 6.0	0.967
FM3 ap2 pH 6.8	0.963	FM4 ap2 pH 6.8	0.968
FM3 ap2 pH 7.2	0.966	FM4 ap2 pH 7.2	0.961
Ref	0.979		

Table 4 – *In vitro-in vivo* correlation fitting (R^2, coefficient of determination) obtained by deconvolution (fed state) of formulations at different dissolution test conditions

Formulation/ Dissolution Test	**R^2**	**Formulation/ Dissolution Test**	**R^2**
FM1 ap3	0.989	FM2 ap3	0.984
FM1 ap2 pH 4.5	0.984	FM2 ap2 pH 4.5	0.974
FM1 ap2 pH 6.0	0.989	FM2 ap2 pH 6.0	0.972
FM1 ap2 pH 6.8	0.973	FM2 ap2 pH 6.8	0.984
FM1 ap2 pH 7.2	0.973	FM2 ap2 pH 7.2	0.983
FM3 ap3	0.995	FM4 ap3	0.946
FM3 ap2 pH 4.5	0.966	FM4 ap2 pH 4.5	0.954
FM3 ap2 pH 6.0	0.983	FM4 ap2 pH 6.0	0.980
FM3 ap2 pH 6.8	0.968	FM4 ap2 pH 6.8	0.979
FM3 ap2 pH 7.2	0.972	FM4 ap2 pH 7.2	0.976
Ref	0.981		

All formulations evaluated under different dissolution conditions showed high R^2 values for deconvolution considering both fasted (Table 3) and fed (Table 4) states, values that are close to the one obtained for the reference product. This means that high correlation was found for *in vitro* and *in vivo* drug release regardless of the presence of food.

Next, convolution was evaluated to show which formulation/dissolution test condition would lead to the most adequate *in vivo* performance, according to Food and Drug Administration (FDA) guidance for ER products (FDA, 1997). The ability of a mathematical model to predict plasma concentrations from *in vitro* dissolution profiles is evaluated by its percent of prediction error (%PE) between observed and predicted plasma concentration in Level A IVIVC (FDA, 1997). For this purpose, internal predictability of IVIVC was evaluated by convolution method considering fasted (Table 5) and fed (Table 6) states.

Table 5 – Convolution results (fasted state) for formulations at different dissolution test conditions *

Formulation/ Dissolution Test	R^2	Cmax (µg/mL)			AUC (µg/mL h)		
		Obs	Pred	%PE	Obs	Pred	%PE
FM1 ap3	0.697	5.170	3.976	23.100	22.370	24.660	**-10.250**
FM1 ap2 pH 4.5	0.770	5.170	4.973	**3.813**	22.370	24.830	**-10.990**
FM1 ap2 pH 6.0	0.763	5.170	4.595	**11.130**	22.370	24.250	**-8.386**
FM1 ap2 pH 6.8	0.691	5.170	4.097	20.750	22.370	24.660	**-10.240**
FM1 ap2 pH 7.2	**0.809**	5.170	4.426	**14.390**	22.370	24.910	**-11.360**
FM2 ap3	0.647	5.170	4.123	20.260	22.370	24.290	**-8.594**
FM2 ap2 pH 4.5	0.715	5.170	3.979	23.030	22.370	24.820	**-10.940**
FM2 ap2 pH 6.0	0.677	5.170	4.050	21.660	22.370	24.920	**-11.400**
FM2 ap2 pH 6.8	**0.764**	5.170	4.347	15.920	22.370	24.590	**-9.935**
FM2 ap2 pH 7.2	0.745	5.170	4.330	16.250	22.370	25.140	**-12.370**
FM3 ap3	0.570	5.170	3.403	34.170	22.370	24.940	**-11.500**
FM3 ap2 pH 4.5	0.622	5.170	4.412	**14.670**	22.370	24.790	**-10.790**
FM3 ap2 pH 6.0	**0.760**	5.170	4.156	19.610	22.370	24.960	**-11.570**
FM3 ap2 pH 6.8	0.674	5.170	3.889	24.780	22.370	24.770	**-10.740**
FM3 ap2 pH 7.2	0.688	5.170	3.969	23.230	22.370	24.900	**-11.300**
FM4 ap3	**0.794**	5.170	4.190	18.950	22.370	24.800	**-10.860**
FM4 ap2 pH 4.5	0.585	5.170	3.933	23.930	22.370	24.700	**-10.420**
FM4 ap2 pH 6.0	0.698	5.170	4.549	**12.010**	22.370	24.270	**-8.478**
FM4 ap2 pH 6.8	0.726	5.170	4.279	17.230	22.370	24.320	**-8.711**
FM4 ap2 pH 7.2	0.694	5.170	4.365	15.570	22.370	24.280	**-8.540**
Ref	**0.889**	5.170	5.023	**2.843**	22.370	24.210	**-8.200**

R^2, coefficient of determination; Cmax, maximum plasma concentration; AUC, area under the plasma concentration-time curve; Obs, observed value; Pred, predicted value; %PE, percent of prediction error.

* For each formulation, the highest R^2 value and all %PE results < 15 are highlighted in bold.

Table 6 – Convolution results (fed state) for formulations at different dissolution test conditions*

Formulation/ Dissolution Test	R^2	Cmax (µg/mL)			AUC (µg/mL h)		
		Obs	Pred	%PE	Obs	Pred	%PE
FM1 ap3	0.831	5.170	4.332	16.21	22.37	24.09	**-7.69**
FM1 ap2 pH 4.5	0.829	5.170	4.867	**5.86**	22.37	24.90	**-11.28**
FM1 ap2 pH 6.0	**0.858**	5.170	4.671	**9.66**	22.37	24.52	**-9.63**
FM1 ap2 pH 6.8	0.799	5.170	4.256	17.67	22.37	24.91	**-11.34**
FM1 ap2 pH 7.2	0.847	5.170	4.473	**13.48**	22.37	24.20	**-8.15**
FM2 ap3	0.779	5.170	4.073	21.22	22.37	24.68	**-10.32**
FM2 ap2 pH 4.5	0.815	5.170	4.225	18.27	22.37	24.84	**-11.03**
FM2 ap2 pH 6.0	0.805	5.170	4.304	16.75	22.37	24.79	**-10.83**
FM2 ap2 pH 6.8	**0.844**	5.170	4.446	**13.99**	22.37	24.79	**-10.81**
FM2 ap2 pH 7.2	0.827	5.170	4.460	**13.74**	22.37	25.07	**-12.04**
FM3 ap3	0.850	5.170	4.179	19.17	22.37	24.22	**-8.26**
FM3 ap2 pH 4.5	0.792	5.170	4.725	**8.60**	22.37	24.21	**-8.23**
FM3 ap2 pH 6.0	**0.856**	5.170	4.453	**13.87**	22.37	24.68	**-10.32**
FM3 ap2 pH 6.8	0.829	5.170	4.315	16.54	22.37	24.23	**-8.30**
FM3 ap2 pH 7.2	0.814	5.170	4.262	17.57	22.37	24.74	**-10.61**
FM4 ap3	0.693	5.170	4.016	22.32	22.37	23.90	**-6.84**
FM4 ap2 pH 4.5	0.748	5.170	4.095	20.79	22.37	25.13	**-12.31**
FM4 ap2 pH 6.0	0.808	5.170	4.595	**11.13**	22.37	24.68	**-10.33**
FM4 ap2 pH 6.8	**0.841**	5.170	4.396	**14.97**	22.37	24.70	**-10.41**
FM4 ap2 pH 7.2	0.824	5.170	4.452	**13.88**	22.37	24.67	**-10.29**
Ref	**0.928**	5.170	5.078	**1.784**	22.37	23.92	**-6.937**

R^2, coefficient of determination; Cmax, maximum plasma concentration; AUC, area under the plasma concentration-time curve; Obs, observed value; Pred, predicted value; %PE, percent of prediction error.
* For each formulation, the highest R^2 value and all %PE results < 15 are highlighted in bold.

According to FDA guidance on IVIVC for ER oral dosage forms, IVIVC studies are usually conducted under fasting conditions. Fed conditions are employed when a drug is not tolerated otherwise (FDA, 1997). However, depending on formulation excipients and physicochemical properties of the drug, the presence of food may influence drug release and bioavailability (APPARAJU; NALLANI, 2007). Food has been reported to reduce ketoprofen absorption rate without affecting its bioavailability (SWEETMAN, 2011). Such delayed absorption of ketoprofen caused by food interaction may be useful to avoid gastric side effects of this NSAID (APPARAJU; NALLANI, 2007).

Area under the plasma concentration-time curve (AUC) is an important pharmacokinetic indicator related to bioavailability because it represents the fraction of drug absorbed (KANO et al., 2015). Acceptable internal predictability values for %PE

in convolution must be less than 15% for each formulation (FDA, 1997). %PE AUC values for all formulations were in accordance to such criterion for both fasted (Table 5) and fed (Table 6) states, showing that all ketoprofen matrix tablet formulations (FM1, FM2, FM3 and FM4) evaluated under different dissolution conditions showed appropriate *in vivo* performance for AUC. Such findings also confirm that food does not affect ketoprofen bioavailability.

For maximum plasma concentration (Cmax) predicted values considering fasted state (Table 5), only formulations FM1 (pH 4.5, 6.0 and 7.2), FM3 (pH 4.5) and FM4 (pH 6.0), evaluated using Apparatus 2, had %PE < 15. High R^2 values were obtained for convolution results considering fed state, showing that although the presence of food did not affect AUC, it influenced Cmax as lower correlation in fasted state.

Physiology Tab in GastroPlus™ displays nine compartments of the gastrointestinal tract as shown in Table 7 (SIMULATIONS PLUS, 2015). During simulations, passage of dosage forms through each compartment is considered for calculation. Under fed conditions, stomach pH is higher when compared to fasted state, contributing to high *in vivo* dissolution given that ketoprofen solubility is pH-dependent and its pKa is 4.19.

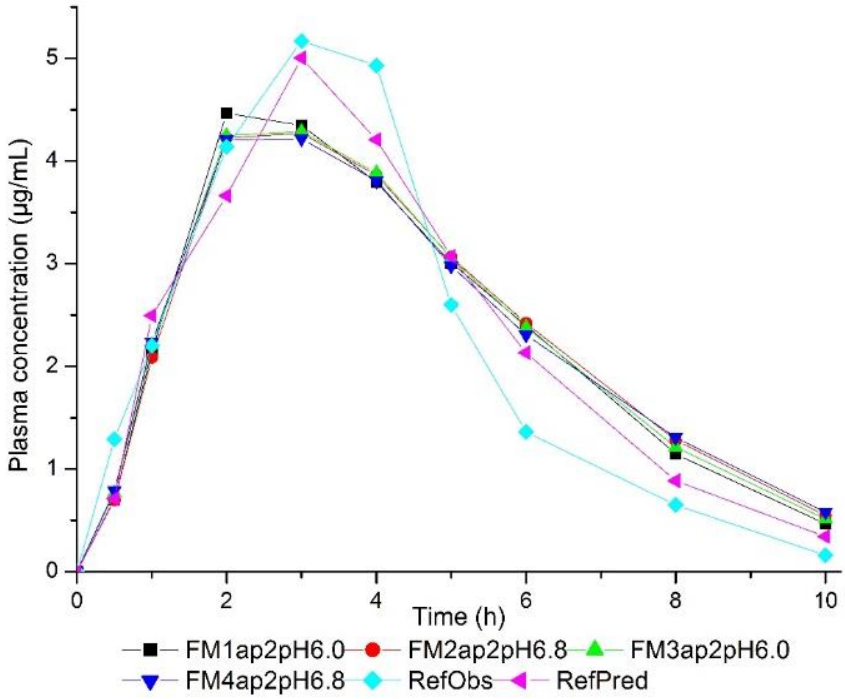
Table 7 – GastroPlus™ human physiological models for fasted and fed states (SIMULATIONS PLUS, 2015)

	Fasted State		Fed State	
Gastrointestinal Compartment	**pH**	**Transit Time (h)**	**pH**	**Transit Time (h)**
Stomach	1.3	0.25	4.9	1.00
Duodenum	6.0	0.26	5.4	0.26
Jejunum 1	6.2	0.93	5.4	0.93
Jejunum 2	6.4	0.74	6.0	0.74
Ileum 1	6.6	0.58	6.6	0.58
Ileum 2	6.9	0.42	6.9	0.42
Ileum 3	7.4	0.29	7.4	0.29
Caecum	6.4	4.19	6.4	4.19
Ascendant Colon	6.8	12.57	6.8	12.57

According to Table 6, Cmax values predicted in fed state showed %PE < 15 for formulations FM1 (pH 4.5, 6.0 and 7.2), FM2 (pH 6.8 and 7.2), FM3 (pH 4.5 and 6.0) and FM4 (pH 6.0, 6.8 and 7.2), evaluated using Apparatus 2. Reference product showed the highest R^2 (0.928), lowest %PE Cmax (1.784) and a very low %PE AUC (-6.937).

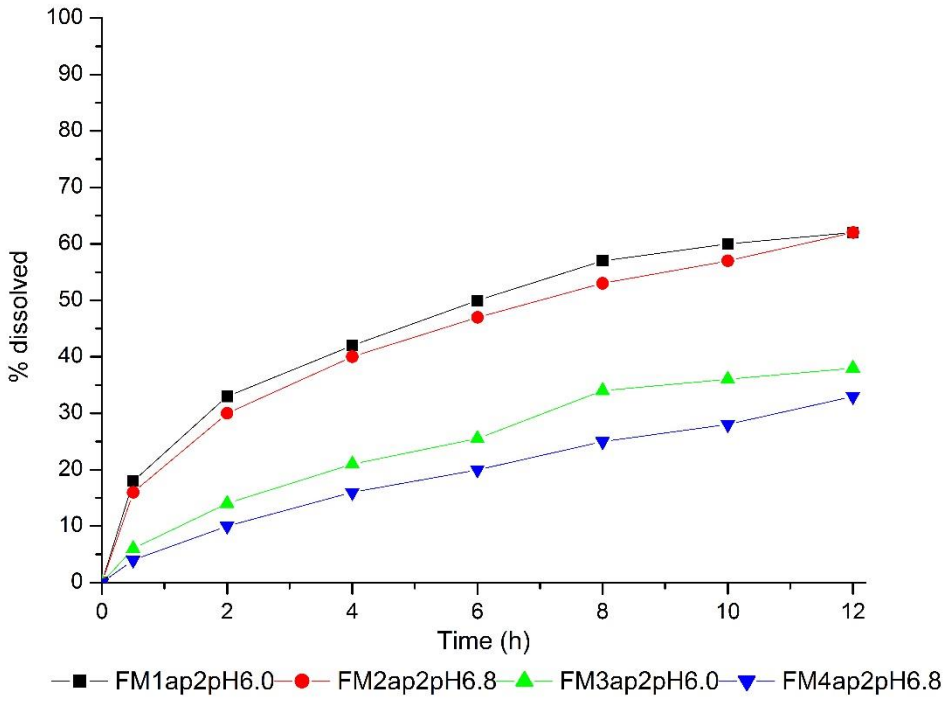
Considering %PE Cmax, %PE AUC and R^2 for convolution results in fed state for each formulation/dissolution test condition and reference product, formulations FM1 (pH 6.0), FM2 (pH 6.8), FM3 (pH 6.0) and FM4 (pH 6.8), evaluated using Apparatus 2, showed adequate IVIVC with respect to plasma concentrations of the reference product Profenid® Retard 200 mg tablets (Table 6 and Figure 1).

Figure 1 – Observed and predicted plasma concentration-time curves for reference product (RefObs, from Çomoğlu et al. (2007), and RefPred, respectively) and convoluted plasma concentration-time curves for ketoprofen matrix tablet formulations obtained using IVIVCPlus™ of GastroPlus™ under fed conditions



In vitro dissolution profiles of these formulations are shown in Figure 2.

Figure 2 – Dissolution profiles of ketoprofen matrix tablet formulations with adequate *in vitro-in vivo* correlation (adapted from Pezzini; Ferraz (2009))



IVICPlus™ module in GastroPlus™ was able to accurately predict plasma concentrations from convolution of dissolution profiles using mathematical functions obtained after performing deconvolution. Reference product predicted plasma curve (RefPred) in fed state (Figure 1) showed the best approximation to *in vivo* plasma curve (RefObs) in terms of Cmax. Convoluted curves for ketoprofen matrix tablet formulations (Figure 1) were very similar to each other, even though dissolution profiles were different (Figure 2).

Formulations FM1 (pH 6.0) and FM2 (pH 6.8) showed similar dissolution profiles, though different from FM3 (pH 6.0) and FM4 (pH 6.8), evaluated using Apparatus 2 (Figure 2). Drug dissolution kinetics for formulations FM1 (pH 6.0) and FM2 (pH 6.8) indicated a diffusion process. Drug release in FM3 (pH 6.0) and FM4 (pH 6.8) occurred by both diffusion and erosion processes. The amount of HPMC used and its viscosity grade can lead to different drug release mechanisms (DUQUE et al., 2013).

Although dissolution profiles and drug release mechanisms were different, these formulations showed *in vivo* performance similar to that of the reference product.

Regarding apparatuses used in dissolution tests, dissolution profiles obtained using Apparatus 3 are expected to better predict *in vivo* dissolution than those obtained using Apparatus 2 (KLEIN et al., 2008; KLANČAR et al., 2013). However, dissolution profiles with Apparatus 2 showed better IVIVC. Dissolution tests performed in Apparatus 3 were conducted at pH 1.2 (1 h), pH 4.5 (0.5 h), pH 6.0 (2.5 h), pH 6.8 (6 h) and pH 7.2 (2 h) (PEZZINI; FERRAZ, 2009). These tests started at the lowest solubility pH for ketoprofen, whereas in Apparatus 2, tablets were in contact with dissolution media in which the drug is more soluble (pH > 4.0) for longer, contributing to the best performance of Apparatus 2 given that ketoprofen solubility is pH-dependent (TSUME et al., 2014).

Although only %PE AUC results showed the viability of using Apparatus 3 for dissolution when establishing IVIVC, all findings must be considered since pH conditions used in *in vitro* dissolution tests using this apparatus were performed representing a fasted state. In fed state, initial pH of dissolution tests should be higher, probably leading to Cmax values closest to that of the reference product given the pH dependency of drug solubility.

4 CONCLUSION

Ketoprofen matrix formulations with high HPMC amounts, although with different viscosity grades, showed drug release by diffusion (FM1 pH 6.0 and FM2 pH 6.8, both Apparatus 2), and diffusion and erosion (FM3 pH 6.0 and FM4 pH 6.8, both Apparatus 2). Even though these formulations showed different *in vitro* dissolution profiles, the same *in vivo* performance was determined according to simulations, with adequate IVIVC to plasma concentration curve of reference product under fed conditions. Simulations using IVIVCPlus™ module from GastroPlus™ were successfully used to establish IVIVC for ketoprofen matrix tablets.

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CHAPTER 2

Intrinsic dissolution simulation using DDDPlus™ as a tool for early BCS classification

ABSTRACT

Intrinsic dissolution test allows characterizing drug substances through its dissolution rate when exposed to a specified surface area in a specific dissolution media. This can be used to determine if a drug substance is highly or poorly soluble. In this work DDDPlus™ version 4.0 (Simulations Plus, Inc.) was used to simulate intrinsic dissolution experiments for pyrimethamine and metronidazole. These drugs have low and high solubility properties. Predicted intrinsic dissolution rates (IDR) were compared to observed *in vitro* IDR. Physicochemical parameters from literature and the experimental conditions of the intrinsic dissolution tests for each drug were used as input data into the software. The program was able to predict the intrinsic dissolution of pyrimethamine and metronidazole within a pH range of 1.0 to 7.2. Observed and predicted IDR intrinsic dissolution tests results for both drugs, showed high correlations ($R^2 > 0.9424$). The IDR values from simulations showed the pH-dependency solubility of pyrimethamine and metronidazole, allowing to classify the solubility according to Biopharmaceutics Drug Classification System (BCS). Intrinsic dissolution tests simulations using DDDPlus™ can be used to obtain an early BCS solubility classification of a drug substance and helping to reduce the number of laboratory experiments.

Keywords: Pyrimethamine. Metronidazole. Intrinsic dissolution. Biopharmaceutics Classification System (BCS). DDDPlus™.

1 INTRODUCTION

Intrinsic dissolution is a characterization test for active pharmaceutical ingredients (API) where the dissolution rate of a drug is determined from a specific surface area exposed to a dissolution medium at certain rotation speed (USP, 2015; WANG; FLANAGAN, 2009). Intrinsic dissolution rate (IDR), can be used to estimate the solubility class of a substance according to Biopharmaceutics Classification System (BCS) (ISSA; FERRAZ, 2011). It can be also valuable to evaluate differences between polymorphs and solvates (WANG; FLANAGAN, 2009).

According to BCS, drugs are classified as high or low soluble (AMIDON et al., 1995). Equilibrium solubility test (shake flask method) is recommended by the Food and Drug Administration (FDA, 2000; FDA, 2015) being used to determine the solubility of drugs, allowing to obtain their BCS class (BREDA et al., 2009; ZHANG et al., 2012; ONO; SUGANO, 2014). However, this method requires the saturation of aqueous solutions, which can be a challenge depending on the drug characteristics, mainly in the early stages of development. For this purpose, intrinsic dissolution is an important characterization test that can be used to obtain the solubility of drugs according to BCS (ISSA; FERRAZ, 2011).

The dissolution of an API in a formulation is affected by different factors such as the test conditions: temperature, rotation speed, pH, nature of dissolution medium; formulation factors: such as compaction pressure and excipient interactions (USP, 2015). Using design of experiments (DOE), is one way to assess the most appropriate test conditions to evaluate such factors (ISSA et al., 2013; GIORGETTI; ISSA; FERRAZ, 2014).

Although an only few milligrams of API is used in intrinsic dissolution testing, developing a method requires a reasonable number of experiments to evaluate the impact of the test conditions in IDR. One of the strategies to reduce the number of experiments is using fractional factorial design to develop appropriate intrinsic dissolution methods (ISSA et al., 2013; GIORGETTI; ISSA; FERRAZ, 2014). However, depending on the quantity of the available sample, this step can be unfeasible, in early stages of the development process, where only limited material is available. Approaches, which can further reduce experimental testing, are highly desirable.

DDDPlus™ (Dose Disintegration and Dissolution) designed by Simulations Plus Inc., is a computer program used to simulate *in vitro* dissolution tests employing USP

apparatuses 1 (basket), 2 (paddle), 4 (flow-through cell) and intrinsic dissolution using the rotating disk method (SIMULATIONS PLUS, 2011). The use of DDDPlus™ to simulate *in vitro* dissolution from tablets containing low soluble drugs montelukast sodium and glyburide was previously demonstrated (ALMUKAINZI et al., 2015). This software can simulate intrinsic dissolution tests, saving time, reducing the number of experiments to investigate suitable IDR conditions.

The objective of this work was to demonstrate the use of the computer program DDDPlus™ as a tool for BCS classification in the early stages of drug development, by simulating intrinsic dissolution tests for the poorly soluble drug pyrimethamine and the highly soluble metronidazole.

2 MATERIAL AND METHODS

2.1 Material

Pyrimethamine and metronidazole were kindly donated by Laboratório Farmanguinhos/Fiocruz (Rio de Janeiro, Brazil) and Micro Service Química Ind. Ltda (São Paulo, Brazil), respectively. Hydrochloric acid P.A. 37%, glacial acetic acid, sodium acetate, potassium phosphate monobasic monohydrate, potassium chloride, potassium biphthalate and sodium hydroxide were purchased from Synth (Diadema, São Paulo, Brazil) and used to prepare the buffer solutions.

2.2 Intrinsic dissolution

For pyrimethamine, intrinsic dissolution test was performed according to a fractional factorial design 3^{3-1} using Statistica® 12.0 (StatSoft, Inc., Tulsa, OK, USA) including factors such as compaction pressure (1.75, 3.5 and 7.0 kN), nature of the dissolution medium (hydrochloric acid pH 1.2; acetate buffer pH 4.5 and phosphate buffer pH 7.2) and rotation speed (50, 100 and 200 rpm), generating the experiments described in Table 1.

Table 1 - Pyrimethamine intrinsic dissolution tests conditions

Standard order	Run order	Compaction pressure (kN)	Dissolution media	Rotation speed (rpm)
1	P1	1.75	Hydrochloric acid pH 1.2	50
2	P4	1.75	Acetate buffer pH 4.5	200
3	P7	1.75	Phosphate buffer pH 7.2	100
4	P2	3.5	Hydrochloric acid pH 1.2	200
5	P5	3.5	Acetate buffer pH 4.5	100
6	P8	3.5	Phosphate buffer pH 7.2	50
7	P3	7.0	Hydrochloric acid pH 1.2	100
8	P6	7.0	Acetate buffer pH 4.5	50
9	P9	7.0	Phosphate buffer pH 7.2	200

Rotating disk apparatuses Varian® (Varian Inc. Palo Alto, CA, USA) coupled to a D-800 Logan Dissolution Tester (Logan Instruments Corp., New Jersey, USA) dissolution equipment was used to perform the intrinsic dissolution tests. About 150 mg of the drug was weighted in triplicate and compacted using a hydraulic press (American Lab., São Paulo, Brazil). The volume of dissolution medium was 900 mL and aliquots of 5 mL were collected in intervals until a sufficient number of points were obtained. The amount of drug dissolved was analyzed by a spectrophotometric method in a UV-VIS Cary 50 (Varian Inc. Palo Alto, CA, USA) equipment using quartz cuvettes of 10.0 mm at 273 nm using each dissolution medium as blank.

Intrinsic dissolution rate (IDR) was calculated according to United States Pharmacopeia (USP, 2015). The amount of drug dissolved (mg) was plotted versus time (seconds) and through linear regression, coefficient of determination (R^2) and the corresponding equation were obtained. The slope of this equation is the dissolution rate and this value was divided by the exposed surface are (0.5 cm^2) to obtain the IDR ($mg/s/cm^2$).

For metronidazole the results from an earlier study (ISSA et al., 2013) were used for the simulations. The authors conducted the experiments according to a 3^{4-1} fractional factorial design, resulting in 27 experiments, including factors such as compaction pressure, rotation speed, dissolution media and metronidazole micronization degree. The study confirmed that API micronization did not influence IDR results (ISSA et al., 2013).

Therefore, in this work, we considered only compaction pressure, rotation speed and dissolution media as parameters, since there is no influence by particle size on IDR. Furthermore, DDDPlus™ disables the use of particle size distribution of the drug

when intrinsic dissolution is selected. It resulted in a 3^{3-1} fractional factorial design (Table 2) which corresponding *in vitro* IDR values were used for comparison.

Table 2 - Metronidazole intrinsic dissolution tests conditions

Standard order	Run order	Compaction pressure (kN)	Dissolution media	Rotation speed (rpm)
1	M1	3.5	Hydrochloric acid 0.1 M	50
2	M8	3.5	Purified water	100
3	M6	3.5	Phosphate buffer pH 7.2	75
4	M16	7.0	Hydrochloric acid 0.1 M	100
5	M14	7.0	Purified water	75
6	M12	7.0	Phosphate buffer pH 7.2	50
7	M22	10.5	Hydrochloric acid 0.1 M	75
8	M20	10.5	Purified water	50
9	M27	10.5	Phosphate buffer pH 7.2	100

2.3 Computer simulations using DDDPlus™

DDDPlus™ version 4.0 software (Simulations Plus Inc., Lancaster, CA, USA) was used to simulate the intrinsic dissolution tests. A database for pyrimethamine and one for metronidazole were created in the software. Physicochemical parameters of the drugs were used as input data for the simulations (Table 3).

Table 3 - Input data used in the program for simulation

Parameter	Pyrimethamine	Metronidazole
Amount (mg)	150	200
Solubility (mg/mL)	0.03 at pH 8.37[a]	13.42 at pH 7.66[a]
pKa	7.4[b]	2.55[c]
Particle density (g/mL)	1.2[d]	1.2[d]
Precipitation time (s)	900[d]	900[d]
Diffusion coefficient ($cm^2/s \times 10^{-5}$)	0.5[d]	0.5[d]

[a]ADMET Predictor™; [b]AMIN et al., 2012; [c]Shemer; Kunukcu; Linden, 2006; [d]Default values from GastroPlus™.

Intrinsic dissolution tests conditions for both pyrimethamine (Table 1) and metronidazole (Table 2) were used as input data into Experimental tab in the software. Single simulations were performed for each experiment. As described in item 2.2, IDR was calculated for the simulated data for both drugs. The values from simulated intrinsic dissolution tests were compared to the *in vitro* results.

2.4 Statistical analysis

Observed IDR values for pyrimethamine and metronidazole were analyzed using Statistica® 12.0 software (StatSoft, Inc., Tulsa, OK, USA). Analysis of Variance (ANOVA) was used with $p < 0.05$ to establish statistical significant differences; Pareto charts where generated for each API.

3 RESULTS AND DISCUSSION

Solubility is one of the most relevant API physicochemical characteristics evaluated in preformulation studies because it is related to drug dissolution and presumably to *in vivo* performance of the drug product (BORHADE et al., 2012). In early stages of drug discovery, solubility can be evaluated using small amounts of API via intrinsic dissolution testing (ISSA; FERRAZ, 2011).

For pyrimethamine, drug dissolved was plotted against time to obtain a slope to calculate IDR. Simulated amount of pyrimethamine dissolved versus time from DDDPlus™ was used to estimate IDR.

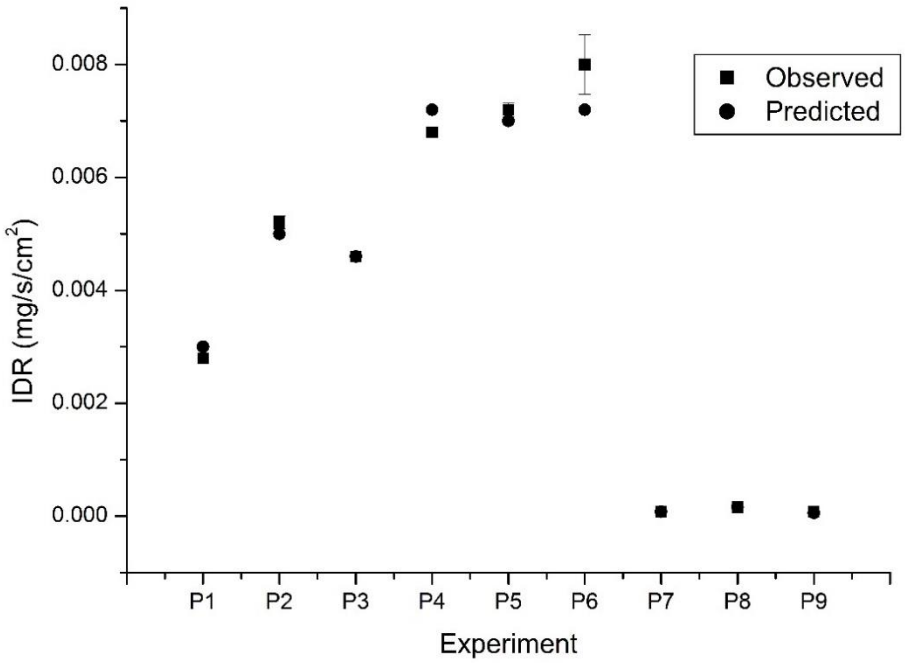
Observed and predicted IDR values for pyrimethamine and the coefficients of determination are shown in Table 4.

Table 4 - *In vitro* (Observed) and *in silico* (Predicted) IDR and coefficients of determination (R^2) values for pyrimethamine

Experiment	IDR (mg/s/cm²)		Observed vs Predicted IDR
	Observed	Predicted	R^2
P1	0.0028	0.0030	0.9956
P2	0.0052	0.0050	0.9987
P3	0.0046	0.0046	0.9919
P4	0.0068	0.0072	0.9976
P5	0.0072	0.0070	0.9865
P6	0.0080	0.0072	0.9860
P7	0.00008	0.00008	0.9762
P8	0.00016	0.00016	0.9881
P9	0.00008	0.00012	0.9424

Figure 1 shows observed and predicted IDR values for each pyrimethamine intrinsic dissolution experiment.

Figure 1 - Observed (experimental data) and predicted IDR values for pyrimethamine, observed data; error bars represent standard deviation (n=3 ± SD)



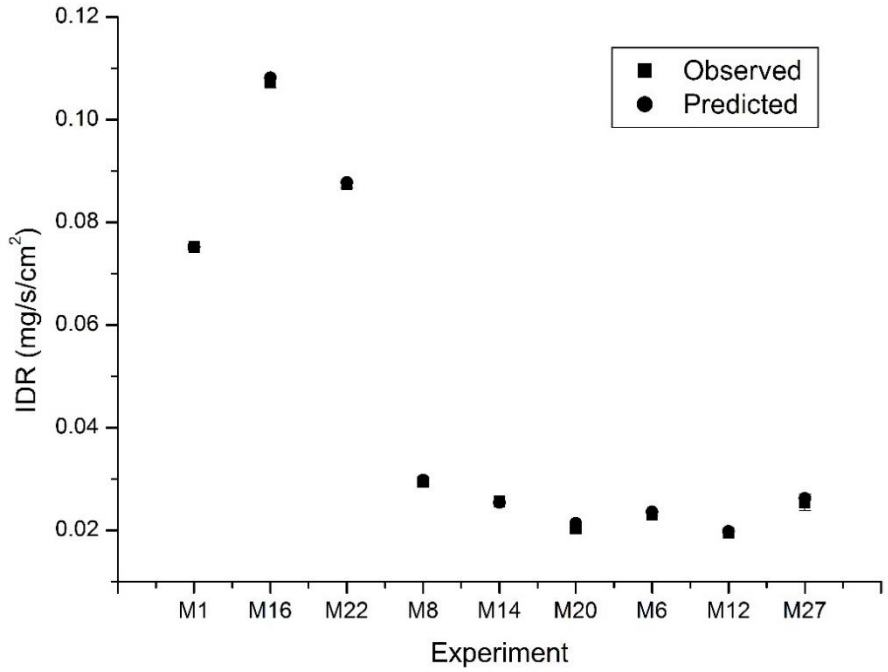
Similarly, for metronidazole the simulated amounts of drug dissolved versus time were used to estimate IDR and *in vitro* IDR data were used to compare to the predicted IDR data with the estimated ones (Table 5).

Table 5 - *In vitro* (Observed) and *in silico* (Predicted) IDR and coefficients of determination (R^2) values for metronidazole

Experiment	IDR (mg/s/cm²)		Observed vs Predicted IDR
	Observed	Predicted	R^2
M1	0.0752	0.0752	0.9994
M8	0.0294	0.0298	0.9997
M6	0.0231	0.0236	0.9996
M16	0.1072	0.1082	0.9996
M14	0.0256	0.0254	0.9992
M12	0.0195	0.0198	0.9974
M22	0.0874	0.0878	0.9993
M20	0.0204	0.0214	0.9970
M27	0.0254	0.0262	0.9998

Observed and predict metronidazole IDR values are presented in Figure 2.

Figure 2 - Observed (experimental data) and predicted IDR values for metronidazole, observed data; error bars represent standard deviation (n=3 ± SD)



Pyrimethamine is a weak base with pKa 7.4 (AMIN et al., 2012), being expected to be ionized at acid pH. This drug had higher observed IDR values for the experiments conducted at pH 4.5 (P4, P5 and P6), followed by pH 1.2 (P1, P2 and P3) and lower values for the experiments P7, P8 and P9, conducted at pH 7.2 (Table 4 and Figure 1). Metronidazole is also a weak basic compound, which is more soluble at pH values below 2 (WU; FASSIHI, 2005), which was confirmed by the higher observed IDR values when intrinsic dissolution was performed using 0.1 M HCl as dissolution medium (M1, M16 and M22). Lower observed IDR values for this drug were observed for the experiments at higher pH test conditions (Table 5 and Figure 2).

The determination of IDR from APIs can be used to evaluate/classify the API's solubility according to BCS when the dose is not too high or very low (YU et al., 2004). Intrinsic dissolution results show that IDR represents the pH-dependent solubility of pyrimethamine and metronidazole, confirming IDR's suitability to determine the solubility classification of both low and highly soluble drugs.

For both drugs, Pareto charts showed that only dissolution media present a significant influence on IDR (Figures 3 and 4), also confirmed by ANOVA of IDR observed results with significant influence for the variable dissolution medium ($p = 0.021$ for pyrimethamine and $p = 0.011$ for metronidazole).

Figure 3 - Pareto chart for the effects of variables: dissolution media, compaction pressure and rotation speed on IDR for pyrimethamine

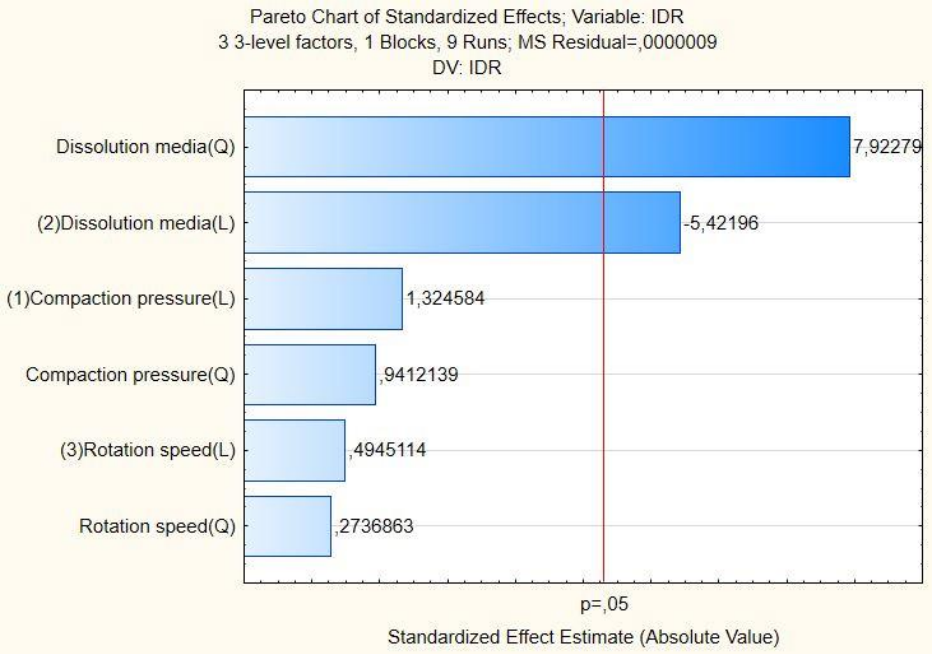
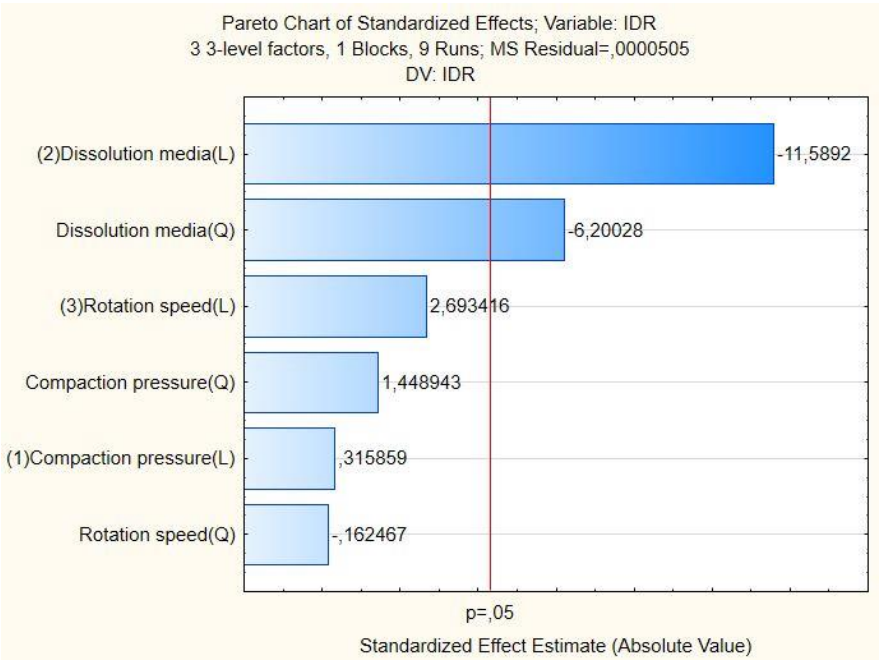


Figure 4 - Pareto chart for the effects of variables: dissolution media, compaction pressure and rotation speed on IDR for metronidazole



Due to its higher solubility at pH 4.5, acetate buffer could be chosen as a suitable dissolution medium for intrinsic dissolution tests for pyrimethamine. For metronidazole, although the dissolution medium impacted IDR, all studied media are suitable, due to

high solubility. Any of the tested compaction pressure or rotation speeds for both drugs can be used for the intrinsic dissolution tests, because they did not have a significant effect on IDR.

The simulations obtained in this work showed a high correlation between observed and predicted IDR values for pyrimethamine (Table 4 and Figure 1) and metronidazole (Table 5 and Figure 2), showing that DDDPlus™ can be used to estimate the intrinsic dissolution of both, low and highly soluble drugs. The IDR values found for both drugs showed a pH-dependency on their solubility.

DDDPlus™ was able to predict the intrinsic dissolution values that were used to calculate IDR for each test condition, showing its accuracy in estimating differences in solubility as the pH changed. IDR values above 0.0017 mg/s/cm^2 indicate a highly soluble drug (ISSA; FERRAZ, 2011). Pyrimethamine did not show IDR results higher than this value, therefore, it can be considered a low soluble drug; while metronidazole presented IDR values above 0.0017 mg/s/cm^2, confirming its high solubility. These findings correlate with the BCS classification of the drugs pyrimethamine – class II or IV and metronidazole – class I (LINDENBERG; KOPP; DRESSMAN, 2004).

Metronidazole's degree of micronization was used as additional factor by a previous study (ISSA et al., 2013) and it was confirmed that particle size does not impact IDR. DDDPlus™ does not use particle size distribution when intrinsic dissolution is selected for simulation, thus micronization differences between metronidazole samples were not considered in simulations. The software was able to simulate IDR values for metronidazole with a high correlation $R^2 \geq 0.9970$ (Table 5) with the *in vitro* data for different intrinsic dissolution test conditions.

DDDPlus™ can accurately predict IDR for the studied drugs, showing that this software can be used to estimate the best conditions for intrinsic dissolution tests, reducing the number of laboratory experiments and helping pharmaceutical companies to save time and costs.

4 CONCLUSION

Computer simulations using DDDPlus™ can help to gain biopharmaceutical understanding of APIs at early stages in the drug development process. Software simulations can be used to predict the intrinsic dissolution of API's in the physiological relevant pH range of 1 to 7.2. This can help to stream line and minimize experimental

lab work. Key experiments can be identified by the simulations and be confirmed by lab results to characterize important biopharmaceutical API properties.

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CHAPTER 3

Prediction of plasma concentrations of fluconazole capsules with different dissolution profiles using GastroPlus™ as a tool for biowaiver

ABSTRACT

Waiver of bioequivalence studies is accepted by the Food and Drug Administration for immediate-release solid oral products containing Biopharmaceutics Classification System (BCS) class I drugs showing rapid or very rapid drug dissolution. However, discussion on biowaiver for BCS class I drugs that do not meet this criterion is lacking. This study aimed to simulate intestinal absorption of fluconazole capsules with different dissolution profiles using the software GastroPlus™ as a tool for biowaiver. Dissolution profiles of two batches of the reference product Zoltec® 150 mg capsules, A1 and A2, and two other products, B1, B2, C1 and C2, as well as plasma concentration-time data of the reference product from the literature were used for simulations. Although products C1 and C2 had drug dissolution < 85% in 30 minutes at 0.1 M HCl, simulation results demonstrated that these products would show the same *in vivo* performance as products A1, A2, B1 and B2. Thus, even though *in vitro* dissolution behavior of products C1 and C2 was not equivalent to a rapid dissolution profile, computer simulations proved to be an important tool for biowaiver of BCS class I drugs in IR solid oral products that do not meet such dissolution criterion.

Keywords: Fluconazole. Biowaiver. Biopharmaceutics Classification System (BCS). GastroPlus™

1 INTRODUCTION

Bioavailability (BA) is the absorption rate and extent of an active pharmaceutical ingredient from a dosage form when it becomes available at the site of action. Drug products that are pharmaceutical equivalents are considered bioequivalent and, therefore, interchangeable, when BA is not statistically different between two products after administration at the same dose and under similar experimental conditions in a bioequivalence (BE) study. For purposes of establishing BE, a test product must be compared to a reference product (SILVA et al., 2010; KANO et al., 2015; FDA, 2014).

For highly soluble and highly permeable drugs, categorized as class I according to the Biopharmaceutics Classification System (BCS), waiver of BE studies can be considered in immediate-release (IR) products (FDA, 2015). In this case, absorption rate and extent are not dependent on drug dissolution but rather solely on gastric emptying (MODI, 2007). In IR products containing BCS class I drugs with rapid (≥ 85% in 30 minutes) or very rapid (≥ 85% in 15 minutes) *in vivo* dissolution in relation to gastric emptying, BA is independent of drug dissolution or gastrointestinal transit time (FDA, 2015).

Fluconazole is a triazole antifungal agent indicated for superficial and systemic infections, available for oral administration in capsules containing 50 - 150 mg of the drug; it is generally well absorbed, showing a BA of about 90% (SWEETMAN, 2011). Due to its clinical and biopharmaceutical characteristics, fluconazole is a candidate for BCS class I biowaiver (CHAROO et al., 2014; CHAROO; CRISTOFOLETTI; DRESSMAN, 2015).

Currently, the prediction of intestinal absorption of drugs based on computer simulations using Advanced Compartmental Absorption and Transit (ACAT) and Physiologically-Based Pharmacokinetic (PBPK) models is a reality (OKUMO; DIMASO; LÖBENBERG, 2008; OKUMO; DIMASO; LÖBENBERG, 2009; WEI et al., 2008; HONÓRIO et al., 2013; KOSTEWICZ et al., 2014; ALMUKAINZI et al., 2016; KESISOGLOU et al., 2016). Computer software can be used to predict oral absorption of drugs from IR products containing different dissolution profiles, helping formulation scientists to decide on the best dissolution test condition or formulation, gaining time and reducing costs in drug development (KOSTEWICZ et al., 2014).

The use of computer simulations for biowaiver extension for BCS class II (TUBIC-GROZDANIS; BOLGER; LANGGUTH, 2008; OKUMO; DIMASO; LÖBENBERG, 2009;

KOVAČEVIĆ et al., 2009) and class III (TSUME; AMIDON, 2010) drugs has been proposed and discussed. However, considering the importance of appropriate dissolution tests and the possibility of requesting waiver of BE studies when *in vitro* dissolution data are available for BCS class I drugs (FDA, 2015), published literature lacks discussion on *in vivo* performance of IR products containing BCS class I drugs that do not show rapid or very rapid dissolution and thus do not meet the criterion for biowaiver.

In this context, the objective of this study was to simulate intestinal absorption of fluconazole capsules with different dissolution profiles using the software GastroPlus™ as a tool for biowaiver, comparing products with rapid or very rapid drug dissolution to products that do not meet this criterion.

2 METHODS

2.1 Computer simulations

The software GastroPlus™ version 9.0 (Simulations Plus Inc., Lancaster, CA, USA) was used to predict oral absorption of fluconazole 150 mg capsules from different manufacturers compared to the reference product, Zoltec® 150 mg capsules.

For such, a fluconazole database was created in GastroPlus™. Input data consisted of values taken from the literature, including, but not limited to drug solubility, pKa and logarithm of partition coefficient (Log P), as well as other parameters obtained using the ADMET Predictor™ (Absorption, Distribution, Metabolism, Elimination and Toxicity Predictor) (Simulations Plus, Lancaster, CA, USA) module in GastroPlus™ (Table 1).

Table 1 – Input data used in GastroPlus™ to simulate plasma concentrations

Parameter	Value	Reference/Data Source
Solubility (mg/mL)	8.03 at pH 0.8 6.91 at pH 4.5 7.82 at pH 6.8 6.90 at pH 7.4	CHAROO et al., 2014; CHAROO; CRISTOFOLETTI; DRESSMAN, 2015
pKa	2.56 2.94 11.01	CHEN et al., 2014; CORRÊA; VIANNA-SOARES; SALGADO, 2012
Log P	0.5	CORRÊA; REICHMAN; SALGADO, 2012
Dose (mg)	150	PORTA; CHANG; STORPIRTIS, 2005; PORTA; YAMAMICHI; STORPIRTIS, 2002
Effective permeability, Peff (cm/s x 10^{-4})	4.06	ADMET Predictor™
Blood/plasma ratio	1.1	ADMET Predictor™
Unbound plasma fraction (%)	27.41	ADMET Predictor™
Physiology	Human, fasting conditions	PORTA; CHANG; STORPIRTIS, 2005
Body weight (kg)	61	PORTA; CHANG; STORPIRTIS, 2005

Plasma concentrations of the reference product (Zoltec® 150 mg capsules) previously reported by Porta; Chang; Storpirtis (2005) were used in the PKPlus™ module in GastroPlus™ to build a compartmental pharmacokinetic (PK) model. PKPlus™ is an optional module in GastroPlus™ that uses intravenous or oral plasma concentration-time data to calculate the most appropriate modeling (one, two or three-compartmental models) and generate PK parameters for simulations (SIMULATIONS PLUS, 2015).

In GastroPlus™ fluconazole database, records were created for two batches of three different products, namely A1, A2, B1, B2, C1 and C2, as previously described by Porta; Yamamichi; Storpirtis (2002); A1 and A2 are batches #1 and #2, respectively, of the reference product, Zoltec® 150 mg capsules, whereas B1, B2, C1 and C2 are batches #1 and #2 of two different products found in the Brazilian market. Dissolution tests performed using the United States Pharmacopeia (USP) Apparatus 1 (basket)

with 900 mL of 0.1 M HCl at 37 ± 0.5 °C and 100 rpm for 30 minutes yielded results were used in the software to simulate the plasma concentration for each product (A1, A2, B1, B2, C1 and C2).

Simulations were run in GastroPlus™ up to 96 hours in order to obtain predicted values of plasma concentration. Concentration curves were compared to that of the reference product (Ref) with respect to regression parameters generated by the software: coefficient of determination (R^2), sum of square error (SSE), root mean square error (RMSE) and mean absolute error (MAE).

The percent of prediction error (%PE) regarding maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) for each convoluted plasma curve was estimated by Equation 1 (FDA, 1997).

$$\%PE = \frac{Obs - \mathrm{Pr}ed}{Obs} \times 100 \qquad \text{(Equation 1)}$$

where *Obs* and *Pred* are the observed and predicted value of a given parameter.

3 RESULTS AND DISCUSSION

After adding plasma concentrations of the reference product, Zoltec® 150 mg capsules, in the software GastroPlus™ and selecting compartmental PK modeling, PKPlus™ module calculated the most appropriate compartmental model (one, two or three compartments) considering the administration of fluconazole 150 mg as IR capsules to subjects with average weight 61 kg under fasting conditions. Compartmental models were compared by evaluating R^2 and Akaike Information Criterion (AIC). As shown in Table 2, the two-compartmental model presented the best fit due to the highest R^2 and lowest AIC value.

Table 2 – Elimination half-life (T1/2), coefficient of determination (R^2) and Akaike Information Criterion (AIC) for compartmental models calculated by PKPlus™ module

Compartmental Models	T1/2 (h)	R^2	AIC
One-compartmental	29.55	0.9936	-80.27
Two-compartmental	30.25	0.9977	-87.53
Three-compartmental	1523.50	0.9976	-83.84

Table 3 presents PK parameters predicted using the selected model.

Table 3 – Pharmacokinetic (PK) parameters from two-compartmental model calculated by PKPlus™ module

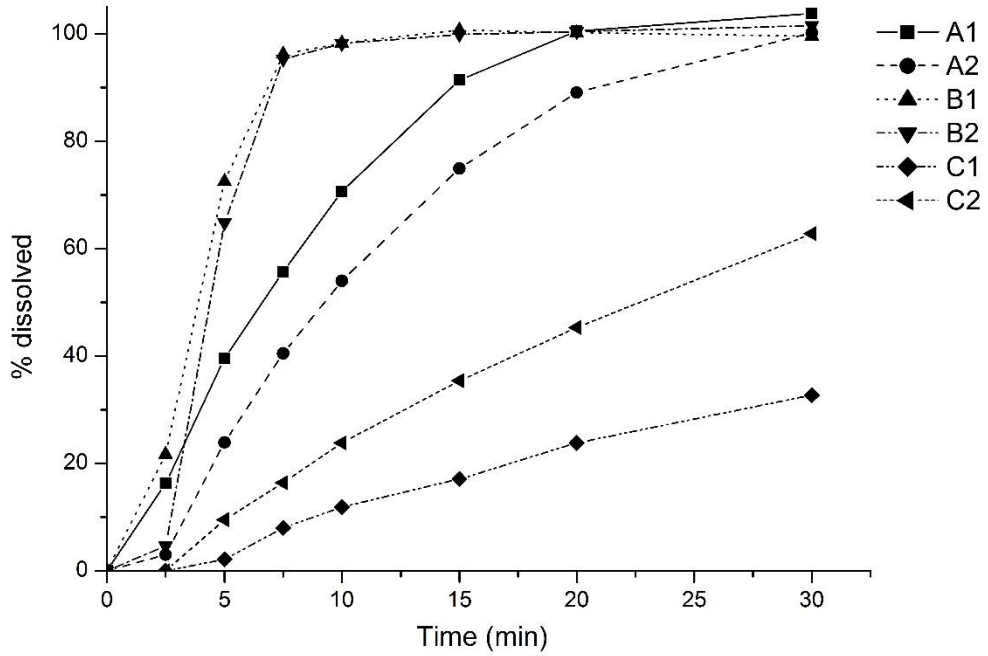
Parameter	Value
Clearance, CL (L/h)	0.99565
Central compartment volume, Vc (L)	30.66
Elimination half-life, T1/2 (h)	30.25
Distribution rate constant from C1 to C2, K12 (h^{-1})	0.16515
Distribution rate constant from C2 to C1, K21 (h^{-1})	0.41884
Distribution volume of second compartment, V2 (L/kg)	0.19817

C1, compartment 1; C2, compartment 2.

Mean (± standard deviation, SD) CL and Vc values for fluconazole in healthy subjects are reported in the literature as 1.272 ± 0.219 L/h and 46.3 ± 7.9 L, respectively (DEBRUYNE, 1997), whereas T1/2 of fluconazole is about 30 hours (SWEETMAN, 2011). Thus, values calculated using PKPlus™ are in accordance to those found in the literature.

Figure 1 shows the percent of fluconazole dissolved over time during dissolution tests of products A1, A2, B1, B2, C1 and C2 (PORTA; YAMAMICHI; STORPIRTIS, 2002).

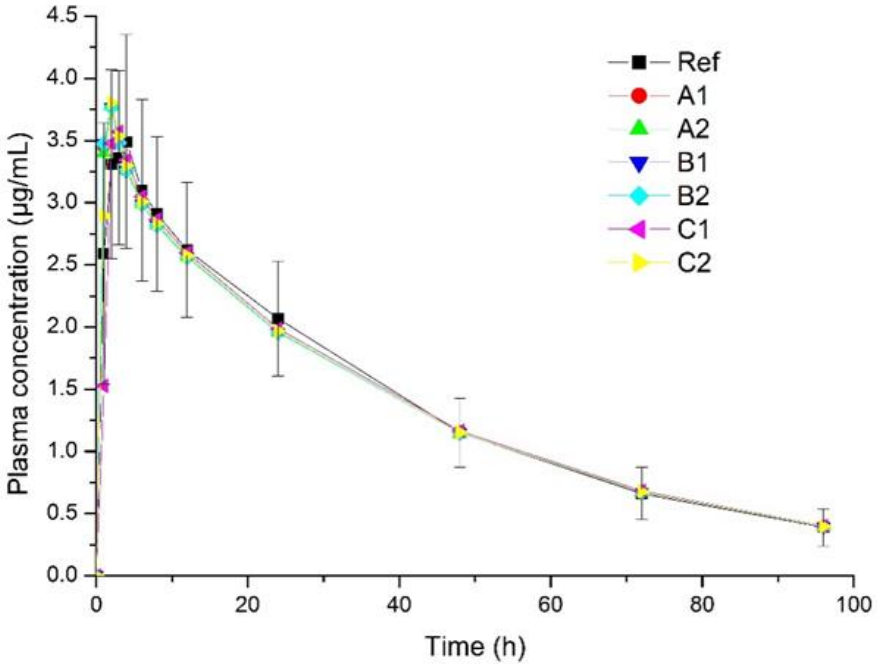
Figure 1 – Dissolution profiles of products A1, A2, B1, B2, C1 and C2, obtained in USP Apparatus 1 (basket) with 900 mL of 0.1 M HCl at 37 ± 0.5 °C and 100 rpm for 30 minutes (adapted from Porta; Yamamichi; Storpirtis, 2002)



Products A1, A2, B1, B2, C1 and C2 had 91.4%, 74.9%, 100.7%, 99.9%, 17.1% and 35.4% of drug dissolved in 15 minutes, respectively. Although product A2 had percent of drug dissolved less than 85% in 15 minutes, only products C1 and C2 had values that did not reach 85% of drug dissolved at the end of each test (Figure 1). Considering these findings, products C1 and C2 are not expected to be bioequivalent to the reference product.

GastroPlus™ was then used to simulate plasma concentration-time curves for all the products, including C1 and C2, and the resulting profiles were then compared to the reference product (Ref) curve plotted with experimental values (Figure 2), in order to evaluate *in vivo* performance.

Figure 2 – Plasma concentration-time curve of reference product (Ref) based on experimental values and of products A1, A2, B1, B2, C1 and C2 created using simulated values given by GastroPlus™; error bars represent standard deviation for reference plot



According to predicted plasma concentration-time curves (Figure 2), all products would show *in vivo* performance compatible to that of the reference product.

Statistical parameters (R^2, SSE, RMSE e MAE) generated by the software for each predicted profile are shown in Table 4.

Table 4 – Statistical parameters generated by GastroPlus™ for each predicted plasma concentration-time curve

Product	R^2	SSE	RMSE	MAE
A1	0.931	1.054E0	3.096E-1	1.875E-1
A2	0.936	9.806E-1	2.986E-1	1.833E-1
B1	0.929	1.097E0	3.158E-1	1.898E-1
B2	0.929	1.094E0	3.154E-1	1.897E-1
C1	0.915	1.234E0	3.349E-1	1.668E-1
C2	0.969	4.301E-1	1.977E-1	1.366E-1

R^2, coefficient of determination; SSE, sum of square error; RMSE, root mean square error; MAE, mean absolute error.

For all predicted profiles, low values were found for prediction error parameters SSE, RMSE and MAE (Table 4), indicating the viability of using GastroPlus™ to predict plasma concentrations of fluconazole from input data. High correlation was

demonstrated between predicted plasma concentration-time curves of all products and experimentally-determined reference curve.

The percent of drug dissolved less than 85% at 30 minutes for products C1 and C2 did not affect *in vivo* performance, as observed in predicted plasma concentration-time curves (Figure 2) and statistical parameters (Table 4).

Cmax and AUC predicted values for products A1, A2, B1, B2, C1 and C2 and experimental ones for the reference product (Ref) are shown in Table 5.

Table 5 – Pharmacokinetic parameters of reference product (Ref) based on experimental curve and of products A1, A2, B1, B2, C1 and C2 obtained using simulated curves given by GastroPlus™

Products			Cmax (µg/mL)			AUC (µg h/mL)		
	F%	Tmax (h)	Obs	Pred	%PE	Obs	Pred	%PE
Ref	90.0	2.96	3.49	--	--	135.77	--	--
A1	99.6	1.60	3.49	3.82	- 9.46	135.77	132.50	2.41
A2	99.6	1.60	3.49	3.83	- 9.74	135.77	132.48	2.42
B1	99.6	1.60	3.49	3.82	- 9.46	135.77	132.51	2.40
B2	99.6	1.60	3.49	3.82	- 9.46	135.77	132.51	2.40
C1	99.4	2.44	3.49	3.65	- 4.58	135.77	131.92	2.84
C2	99.6	1.80	3.49	3.82	- 9.46	135.77	132.37	2.50

%F, oral bioavailability; Tmax, time of Cmax; Cmax, maximum plasma concentration; AUC, area under the plasma concentration-time curve; Obs, observed value; Pred, predicted value; %PE, percent of prediction error.

All %PE values for Cmax and AUC were less than 10%, showing adequate internal predictability for these PK parameters.

Food and Drug Administration (FDA) recommendations for waiver of BE studies considering BCS class I drugs state that IR solid oral products must have rapid or very rapid dissolution in 0.1 M HCl, pH 4.5 and pH 6.8 (FDA, 2015). In this study, even though dissolution tests were carried out only in hydrochloric acid as dissolution medium, products C1 and C2 that did not meet requirements of dissolution rate still showed *in vivo* performance compatible to the reference product. Computer simulations performed in this study can be used to justify biowaiver for BCS class I drugs that exhibit drug dissolution < 85% in 30 minutes.

4 CONCLUSION

For fluconazole, a BCS class I drug, *in vivo* dissolution is unlike to be linked to *in vitro* dissolution, since differences were not observed in simulated absorption curves.

Products C1 and C2 did not meet FDA recommendation of rapid or very rapid drug dissolution for waiver of BE studies, but showed predicted *in vivo* performance compatible to that of the reference product. Thus, when rapid or very rapid drug dissolution was not experimentally achieved, computer simulations were successfully used as a tool for biowaiver of drug products containing BCS class I drugs.

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CHAPTER 4

Comparison of biopharmaceutical performance of carvedilol immediate-release tablets using computer simulations

ABSTRACT

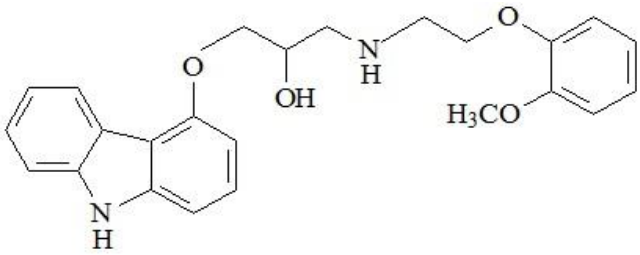
This study aimed at establishing *in vitro-in vivo* correlation (IVIVC) using dissolution profile data of carvedilol 6.25 mg immediate-release (IR) tablets from different manufacturers for computer simulations in GastroPlus™, and comparing biopharmaceutical performance between marketed and reference products. Dissolution tests (USP Apparatus 2 - paddle, 500 mL of citrate buffer pH 4.5 at 37 ± 0.5 °C and 50 rpm for 60 minutes) were carried out for the reference product A (Coreg® 6.25 mg IR tablets) and marketed products B, C, D, E, F, G, H and I. Physicochemical and pharmacokinetic data from the literature and data predicted using ADMET Predictor™ were also used to run simulations. Products A, E, F and H had rapid dissolution (> 85% in 30 minutes), adequate IVIVC, and low percent of prediction error (%PE) for maximum plasma concentration (Cmax) and area under the plasma concentration-time curve. Drug dissolution from products C and D was higher than 80% in 60 minutes, showing that even though the criterion for rapid dissolution was not achieved, IVIVC was established. Low drug dissolution was found for products B, G and I, corroborating low R^2 obtained in the comparison to plasma concentration of the reference product and mainly high %PE Cmax. Computer simulations of plasma concentrations of carvedilol 6.25 mg IR tablets can be used to establish IVIVC and to evaluate biopharmaceutical performance of marketed and reference drug products

Keywords: Carvedilol. GastroPlus™. *In vitro-in vivo* correlation (IVIVC). Immediate-release.

1 INTRODUCTION

Carvedilol, 1-Carbazol-4-yloxy-3-[2-(2-methoxyphenoxy) ethylamino] propan-2-ol (Figure 1) is a non-cardioselective beta-blocker with vasodilating properties due to its blocking activity of α_1-receptors (SWEETMAN, 2011). It is indicated as antihypertensive drug, mainly in the management of congestive heart failure. Carvedilol also exerts protective effect on myocardial cells in relation to oxidative stress (TENERO et al., 2000; XU et al., 2014).

Figure 1 – Carvedilol chemical structure (obtained using ChemWindow® software)



It is a weak base drug that belongs in the Biopharmaceutics Classification System (BCS) class II (low solubility and high permeability) and has a pH-dependent solubility, being more soluble at acid environments (TSUME et al., 2014; HAMED et al., 2015). Carvedilol is commercially available as immediate-release (IR) tablets at doses of 3.125, 6.25, 12.5, 25 mg and as controlled-release dosage forms (SWEETMAN, 2011).

In vitro-in vivo correlation (IVIVC) is defined in the context of extended-release (ER) products as a mathematical model that describes the relationship between *in vitro* characteristics of a drug product, such as dissolution profile, and the corresponding *in vivo* response, such as drug plasma concentration (FDA, 1997). In this context, *in vitro* dissolution test is an important tool in obtaining dissolution profiles that can be correlated to the *in vivo* dissolution profile of a drug product (GONZÁLEZ-GARCÍA et al., 2015). Mainly for BCS class II compounds, where dissolution is the rate-limiting step of drug absorption (EMAMI, 2006), studies have shown that dissolution test can be used to establish a relationship with *in vivo* drug release, helping to establish IVIVC and extending biowaiver to this drug class (YANG, 2010).

The use of computer programs to simulate oral drug absorption from dissolution profiles of IR dosage forms can help to establish IVIVC for BCS drugs of low solubility and high permeability as a surrogate to waiver of bioavailability studies (OKUMO;

DIMASO; LÖBENBERG, 2009). These software use information about physicochemical characteristics, formulation properties, permeability and metabolism of the drug as input data in order to predict drug behavior in the gastrointestinal tract via Physiologically-Based Pharmacokinetic (PBPK) and Advanced Compartmental Absorption and Transit (ACAT) models (KOSTEWICZ et al., 2014; KESISOGLOU et al., 2016).

Considering the same study design, drug products that are pharmaceutical equivalents or pharmaceutical alternatives are considered bioequivalent when the rate and extent of absorption of the active pharmaceutical ingredient is not significantly statistically different (FDA, 2014). Since plasma concentrations of solid oral drug products can be predicted using appropriate software, simulations can be used to evaluate the performance of marketed products from different manufacturers compared to a reference product.

The objective of this study was to use dissolution profiles of carvedilol 6.25 mg IR tablets from different manufacturers to predict plasma concentrations, establishing IVIVC, using the software GastroPlus™ and comparing biopharmaceutical performance between marketed and reference products.

2 METHODS

2.1 Dissolution test

Carvedilol 6.25 mg IR tablets from different manufacturers were purchased from the Brazilian market: A (reference product, Coreg® 6.25 mg tablets), B, C, D, E, F, G, H and I. Samples (n = 6) of each product were submitted to dissolution test using a VK 7010 (Varian Inc., Palo Alto, CA, USA) dissolution equipment at the following conditions: USP Apparatus 2 (paddle), 500 mL of citrate buffer pH 4.5 at 37 ± 0.5 °C and 50 rpm for 60 minutes. Aliquots were withdrawn at 5, 10, 15, 20, 30, 45 and 60 minutes. Amounts of drug dissolved were obtained by analyzing aliquots in a UV-VIS Cary 50 (Varian Inc., Palo Alto, CA, USA) spectrophotometer at 285 nm using 10.0-mm quartz cuvettes.

2.2 Computer simulations

The software GastroPlus™ version 9.0 (Simulations Plus Inc., Lancaster, CA, USA) was used to simulate plasma concentrations of carvedilol 6.25 mg IR tablets from different manufacturers. A database for the drug was created in the software using predicted parameters obtained applying ADMET Predictor™ (Absorption, Distribution, Metabolism, Elimination and Toxicity Predictor) module and data from the literature, as shown in Table 1.

Table 1 – Parameters used as input data in GastroPlus™ to run simulations of carvedilol plasma concentrations

Parameter	Value	Reference/Data Source
Molecular weight (g/mol)	406.47	RASOOL; KHALIL; LÄER, 2015
Logarithm of partition coefficient, Log P	4.19	RASOOL; KHALIL; LÄER, 2015
pKa	8 and 12.94	ADMET Predictor™
Reference solubility (mg/mL)	1.42 at pH 3.0	ADMET Predictor™
Effective permeability, Peff (x 10^{-4} cm/s)	1.94	RASOOL; KHALIL; LÄER, 2015
Blood/plasma ratio	0.71	ADMET Predictor™
Logarithm of distribution coefficient, Log D	3.1 in pH 9.0	ADMET Predictor™
Diffusion coefficient (cm^2/s x 10^{-5})	0.63	ADMET Predictor™
Renal clearance (L/h/kg)	0.25	RASOOL; KHALIL; LÄER, 2015
Total clearance (L/h)	35.34	RASOOL; KHALIL; LÄER, 2015

Up to now, there are no published studies showing human plasma profile for the reference product Coreg® 6.25 mg IR tablets. Therefore, plasma concentration curve of Coreg® 12.5 mg IR tablets previously reported by Patel et al. (2013) was used in PKPlus™ module in GastroPlus™ to build a pharmacokinetic compartmental model and simulate plasma concentration curve for the dose 6.25 mg (Ref). The use of such curve as observed plasma concentration profile for carvedilol 6.25 mg IR tablets was

validated by convolution of the dissolution profile of the reference product (product A) obtained as described in item 2.1.

Carvedilol database records were created and dissolution profiles corresponding to each formulation obtained under the same test conditions were added to the software.

Plasma concentrations of drug products A, B, C, D, E, F, G, H and I were simulated using input data described in Table 1 and dissolution profiles for each product. Single simulations equivalent to 48 hours were performed in GastroPlus™.

Plasma concentrations obtained for each product were compared to the validated plasma concentration curve of the reference product Coreg® 6.25 mg IR tablets (Ref) with respect to regression parameters generated by the software: coefficient of determination (R^2), sum of square error (SSE), root mean square error (RMSE) and mean absolute error (MAE). Additionally, the percent of prediction error (%PE) regarding maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) for each convoluted plasma curve was estimated by Equation 1 (FDA, 1997).

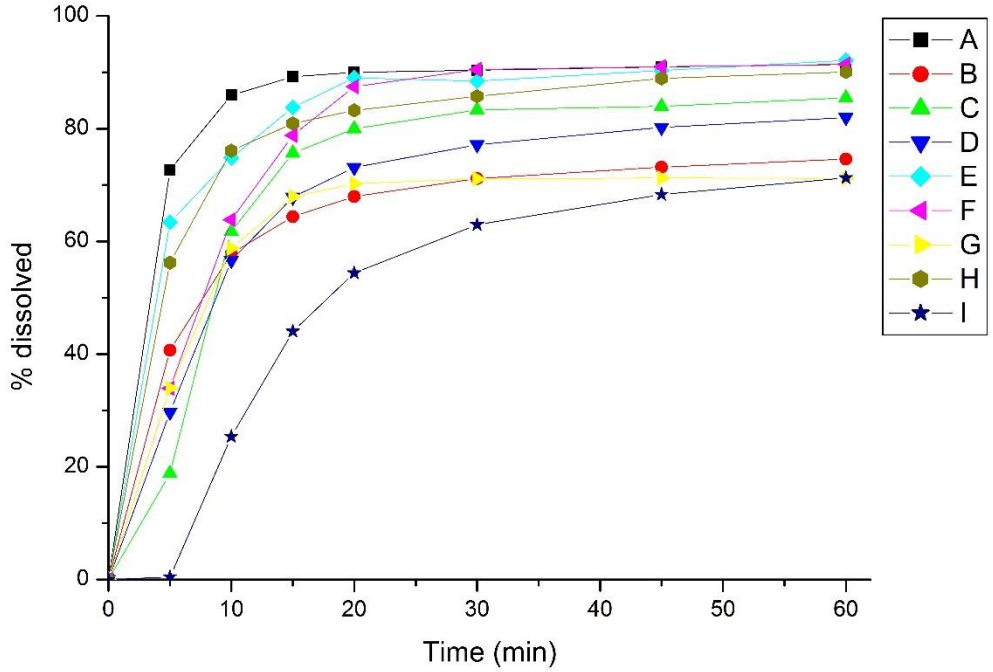
$$\%PE = \frac{Obs - \mathrm{Pr}ed}{Obs} \times 100 \qquad \text{(Equation 1)}$$

where *Obs* and *Pred* are the observed and predicted value of a given parameter.

3 RESULTS AND DISCUSSION

Dissolution profiles of carvedilol 6.25 mg IR tablets A, B, C, D, E, F, G, H and I are shown in Figure 2.

Figure 2 – Dissolution profiles of carvedilol 6.25 mg immediate-release tablets A, B, C, D, E, F, G, H and I obtained with USP Apparatus 2 (paddle), 500 mL of citrate buffer pH 4.5 at 37 ± 0.5 °C and 50 rpm for 60 minutes



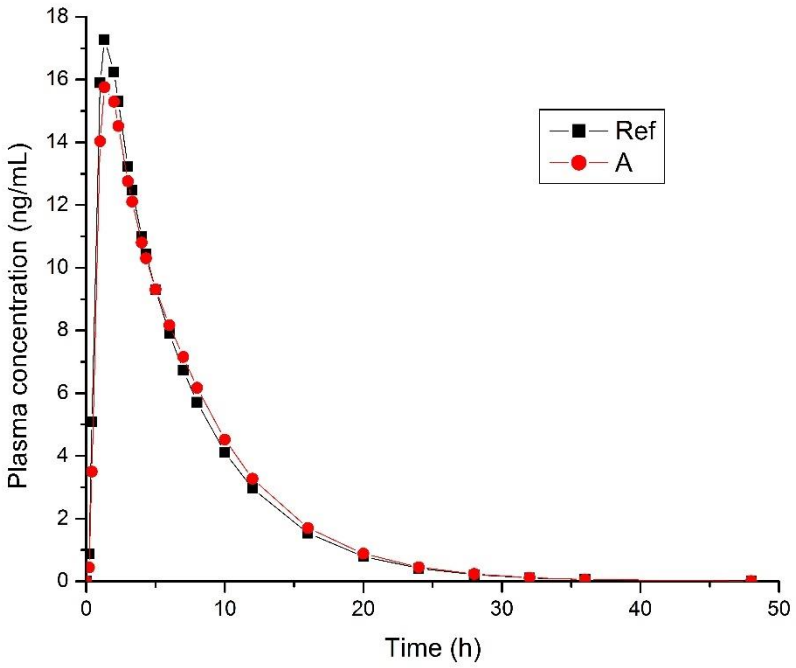
Rapidly dissolving IR products are characterized by drug dissolution ≥ 85% in 30 minutes. This concept includes the use of USP Apparatus 1 (basket) or 2 (paddle), respectively at 100 or 50 rpm, in a dissolution media volume of 900 mL or less at pH 1.2, 4.5 and 6.8 (YU et al., 2002). Products A, B, C, D, E, F, G, H and I had 90.38%, 71.16%, 83.33%, 77.16%, 88.44%, 90.50%, 71.09%, 85.74% and 62.95%, respectively, of carvedilol dissolved in 30 minutes at pH 4.5. Rapid dissolution at pH 4.5 was observed for products A, E, F and H; however, the same drug release profile is not expected at basic pH due to the pH-dependent solubility of carvedilol, since it has shown high solubility at acid pH (1.2-5.0) and low solubility at intestinal pH (6.5-7.8), as reported by Hamed et al. (2015).

Products B, C, D and G did not reach 85% of drug dissolved in 30 minutes; products C and D reached 85.45% and 81.99%, respectively, in 60 minutes. Since *in vitro* dissolution can be the rate-limiting step for absorption in the case of BCS class II drugs such as carvedilol (COOK; ADDICKS; WU, 2008), lower plasma concentrations are expected for these products.

Plasma concentrations of Coreg® 12.5 mg IR tablets reported by Patel et al. (2013) were used to build a pharmacokinetic model and to obtain plasma concentration

curve for the reference product at the dose 6.25 mg (Ref), since carvedilol pharmacokinetics is proportional to the administered dose (TENERO et al., 2000). The use of such plasma concentration curve was validated with the predicted plasma concentration curve obtained by convolution of the dissolution profile of Coreg® 6.25 mg IR tablets (product A) as show in Figure 3.

Figure 3 – Plasma concentration-time curves of reference product, Coreg® 6.25 mg immediate-release tablets, built with observed (Ref) and predicted (A) values



Plasma concentrations of the reference product Coreg® 6.25 mg IR tablets (product A) showed high correlation (R^2 = 0.985) and low predictive errors (Table 2), confirming the viability of using the plasma concentration curve based on Ref.

Statistical data from convolution of dissolution profiles of products A, B, C, D, E, F, G, H and I are shown in Table 2. R^2 is calculated considering predicted plasma concentration for each product tested in this study and plasma concentration curve based on Ref, and statistical prediction errors are SSE, RMSE and MAE.

Table 2 – Statistical parameters generated by GastroPlus™ for each simulated plasma concentration curve (products A, B, C, D, E, F, G, H and I)

Product	R^2	SSE	RMSE	MAE
A	0.985	11.210	0.698	0.458
B	0.873	0.808	1.874	1.226
C	0.953	34.840	1.231	0.738
D	0.938	44.770	1.395	0.847
E	0.986	11.290	0.701	0.392
F	0.976	17.750	0.879	0.526
G	0.758	163.500	2.667	2.034
H	0.977	17.030	0.861	0.516
I	0.861	102.600	2.112	1.288

R^2, coefficient of determination; SSE, sum of square error; RMSE, root mean square error; MAE, mean absolute error.

Statistical results indicate the highest IVIVC (R^2 > 0.97 and low SSE, RMSE, MAE) for products A, E, F and H. Tablets from these formulations had rapid drug dissolution (Figure 2), showing that drug release for carvedilol IR tablets ≥ 85% in 30 minutes can be used as a criterion for *in vivo* performance.

A correlation between plasma concentrations and *in vitro* dissolution was observed for products B, G and I. Drug dissolution from these products was less than 80% in 60 minutes, corroborating low R^2 values found for predicted plasma concentrations. Plasma concentration curves built with predicted values are shown in Figure 4.

Figure 4 – Plasma concentration-time curves of reference product (Ref) built with observed values and of products A, B, C, D, E, F, G, H and I built with simulated values given by GastroPlus™

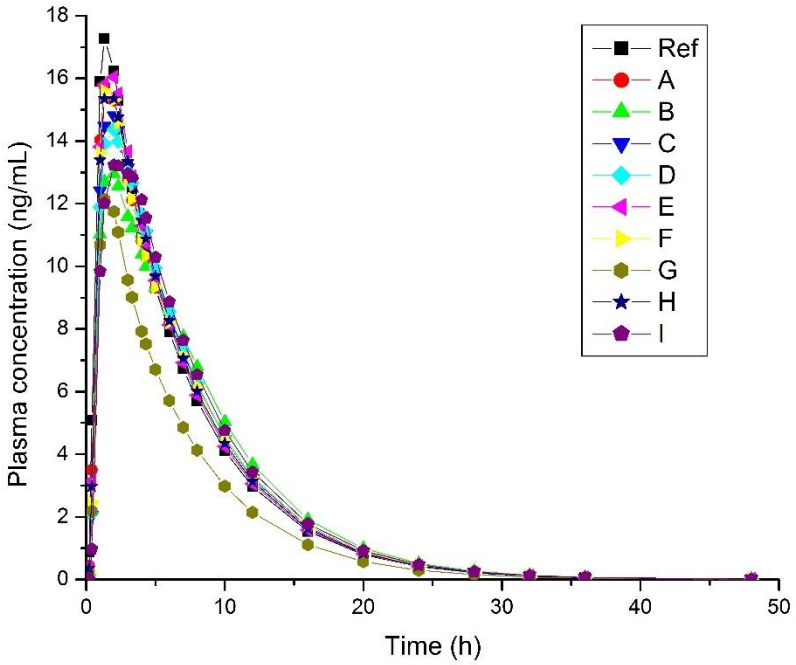


Figure 4 shows that differences between predicted and observed plasma concentrations occurred mainly for Cmax, except in the case of product G, for which low values are clearly evident for both Cmax and AUC. These differences are also evidenced by %PE Cmax values (Table 3).

Table 3 – Pharmacokinetic parameters of reference product (Ref) based on experimental curve and of products A, B, C, D, E, F, G, H and I calculated using simulated curves given by GastroPlus™

Product	Cmax (ng/mL)	%PE Cmax	Tmax (h)	AUC (ng h/mL)	%PE AUC
Ref	17.28	--	1.30	118.26	--
A	16.02	7.29	1.54	118.68	-0.36
B	13.18	23.72	1.64	117.49	0.65
C	15.09	12.67	1.64	117.85	0.34
D	14.56	15.74	1.70	117.82	0.37
E	16.34	5.44	1.64	117.95	0.26
F	15.97	7.58	1.54	117.80	0.38
G	12.37	28.41	1.54	84.05	28.93
H	15.79	8.62	1.60	117.91	0.30
I	13.24	23.38	2.08	117.75	0.43

Cmax, maximum plasma concentration; Tmax, time of Cmax; AUC, area under the plasma concentration-time curve; %PE, percent of prediction error

Since drug dissolution is the rate-limiting step for absorption of BCS class II compounds, IVIVC can be established for IR tablets containing these drugs (EMAMI, 2006). For poorly soluble drugs, dissolution from IR dosage forms is dependent on tablet disintegration, which in turn is influenced by formulation factors such as the type and amount of disintegrant used or manufacturing process (TAKAHASHI et al., 2012).

Given the variety of manufacturers in this study, products evaluated may present differences in formulation composition that could impact tablets disintegration and drug dissolution. Considering %PE AUC (Table 3), a good IVIVC could be established for all products, except for product G due to its high percent of prediction error. The highest %PE Cmax associated with high %PE AUC and low drug dissolution (Figure 2) is an indicator of formulation problems that could be predicted by computer simulations. Such finding demonstrates that computer simulations are an important tool for pharmaceutical companies, helping with the choice of formulations with appropriate *in vivo* performance.

Products B and I also had high %PE Cmax, which corroborates low R^2 for predicted plasma concentrations compared to those of the reference product, expected in cases of low drug dissolution (Figure 2).

Products C and D did not show rapid dissolution at pH 4.5, but reached more than 80% of drug dissolved in 60 minutes. In this case, IVIVC was established although the requirement for rapid dissolution was not met, showing that for carvedilol IR tablets, evaluation of dissolution up to 60 minutes was important to establish correlation.

Products A, E, F and H had the lowest values of %PE Cmax and the best IVIVC, confirming what was indicated by R^2 values for predicted plasma concentrations and those of the reference product (Table 2).

Considering that marketed drug products should be bioequivalent to a reference product, showing the same *in vivo* performance, R^2 was used in our study as a statistical parameter to measure the closeness between predicted plasma concentrations of products evaluated and those of the reference product, as shown in Table 2. Products B, G and I had $R^2 < 0.90$ and high %PE Cmax (Table 3), which can be an indicative of biopharmaceutical problems.

4 CONCLUSION

Food and Drug Administration (FDA) dissolution criterion (> 85% in 30 minutes) for biowaiver of BCS class I and III drugs was applied to carvedilol IR tablets evaluated at pH 4.5. Additionally, IVIVC was established for products that did not meet this criterion but reached more than 80% of drug dissolved at the end of testing (60 minutes). Computer simulations from dissolution profiles of carvedilol 6.25 mg IR tablets were shown to be an important tool to evaluate biopharmaceutical performance of marketed products compared to a reference.

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CHAPTER 5

Computer simulations applied to the development of extended-release tablet formulations

ABSTRACT

Developing extended-release (ER) formulations with appropriate release characteristics is a real challenge for formulation scientists and pharmaceutical companies. The aim of this study was to demonstrate the use of computer simulations of dissolution tests associated to statistical experimental design in the development of ER tablet formulations using doxazosin as model drug. Experimental doxazosin ER tablets (doxazosin mesylate, lactose, hydroxypropyl methylcellulose Methocel® K100M (HPMC K100M) and magnesium stearate) were prepared and submitted to dissolution test using Apparatus 2 (paddle) with 900 mL of simulated gastric fluid without enzyme at 37 ± 0.5 °C and 75 rpm for 960 minutes. Results were used to optimize calibration constants of formulation ingredients and release exponent in the simulation software DDDPlus™. The statistical software Design Expert® was used to obtain different mixtures between lactose and HPMC K100M, creating seven formulations with dissolution profiles simulated in DDDPlus™. After statistical analysis, an optimized doxazosin ER formulation was produced and submitted to *in vitro* dissolution test for comparison with predicted profile. A correlation of 0.99 was obtained for observed and predicted dissolution profiles of the optimized doxazosin ER formulation. The use of test simulations led to a 66.67% reduction in analyst working hours and 77.78% reduction in both equipment usage time and dissolution medium volume. Computer simulations associated to design of experiments can help research laboratories and pharmaceutical companies to save time and reduce costs in the development of ER formulations.

Keywords: Doxazosin. DDDPlus™. Dissolution. Extended-release. Mixture experimental design.

1 INTRODUCTION

Extended-release (ER) tablets are solid oral dosage forms formulated with excipients to make drugs available over a prolonged period of time after oral administration (USP, 2011). Developing ER dosage forms is a challenge for formulation scientists given that tablets must be designed to release drugs slowly during dissolution; the control of drug release can be achieved mainly by formulations with hydrophilic polymers (SIEPMANN; PEPPAS, 2012), coated process (ZHOU et al., 2010) or osmotic pump systems (RABTI et al., 2014).

Matrix tablets with hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) are the most widely employed strategy for ER systems. Such polymers swell and form a gel layer that controls water uptake by drug diffusion or a diffusion/erosion phenomenon called anomalous transport (SIEPMANN; PEPPAS, 2001; SIEPMANN; SIEPMANN, 2008). Commercially available polymers exhibit different degrees of polymerization, leading to higher or lower swelling properties (WEN; NOKHODCHI; RAJABI-SIAHBOOMI, 2010).

Using appropriate amounts of HPMC of different viscosity grades in matrix formulations is an important step in obtaining the desirable drug release (MOURÃO et al., 2010). Statistical planning, including design of experiments (DOE), reduces the number of laboratory experiments necessary for developing ER dosage forms. This approach can improve formulation scientists' knowledge on how drug release occurs and help to evaluate the influence of polymers on drug dissolution (DUQUE et al., 2013).

Another useful tool to reduce laboratory work and avoid experimenting based on trial and error is the estimation of drug dissolution using computer simulations (ALMUKAINZI et al., 2015). The software DDDPlus™ (Dose Disintegration and Dissolution Plus) simulates *in vitro* dissolution of pharmaceutical dosage forms and intrinsic dissolution of active pharmaceutical ingredients using United States Pharmacopeia (USP) apparatuses (SIMULATIONS PLUS, 2011).

The objective of this study was to demonstrate the use of computer simulations of *in vitro* dissolution associated to DOE in the development of ER tablets using doxazosin as model drug.

2 MATERIAL AND METHODS

2.1 Material

Doxazosin mesylate was kindly donated by EMS Pharma (Hortolândia, São Paulo, Brazil). Hydroxypropyl methylcellulose Methocel® K100M (HPMC K100M) (Colorcon, Cotia, São Paulo, Brazil), lactose and magnesium stearate were of pharmaceutical grade. Sodium chloride (Synth, Diadema, São Paulo, Brazil), hydrochloric acid P.A. 37% (Synth, Diadema, São Paulo, Brazil), methanol HPLC grade (J.T. Baker, Hexis, Jundiaí, São Paulo, Brazil), potassium chloride (Synth, Diadema, São Paulo, Brazil), 1 mol/L potassium hydroxide standard solution (Sigma-Aldrich, Steinheim, Germany) and dimethyl sulfoxide P.A. (Synth, Diadema, São Paulo, Brazil) were of analytical grade.

2.2 Determination of pKa and solubility

Potentiometric measurement at 37 °C using a Sirius T3 instrument (Sirius Analytical Instruments Ltda., East Sussex, UK) was conducted to obtain pKa and solubility values for doxazosin.

Doxazosin was dissolved in a mixture of 10 mM dimethyl sulfoxide solution, linear buffer solution (BOX et al., 2003) and methanol solution containing deionized water and methanol (20:80) with 0.15 M KCl. Turbidity was monitored at 500 nm during titration with 0.5 M HCl and 0.5 M KOH. Resulting pKa values were extrapolated using the Yasuda-Shedlovsky method (AVDEEF, 2001) in the software Sirius T3Refine version 1.1.2.0 (Sirius Analytical Instruments Ltda., East Sussex, UK).

Solubility determination was conducted by dissolving 1.11 mg, 2.50 mg and 5.41 mg of the drug in 10%, 20% and 30%, respectively, of methanol solution containing deionized water and methanol (20:80) with 0.15 M KCl.

For each assay, basic titration at pH range 2-12 using the Cheqsol method (BOX et al., 2006) was conducted.

2.3 Formulation

Experimental doxazosin ER formulation was prepared using a hydraulic press (American Lab., São Paulo, Brazil) in which tablets were obtained by compression at 1500 psi for one minute. Drug and excipients were accurately weighted and mixed using a mortar and pestle before processing. Formulation composition is shown in Table 1.

Table 1 – Composition of experimental doxazosin extended-release formulation

Ingredients	Amount (mg)
Doxazosin mesylate	4.86*
Lactose	45.07
HPMC K100M	200
Magnesium stearate	2.5

*Corresponding to 4.00 mg of doxazosin.

2.3.1 Dissolution test

Experimental doxazosin ER tablets (n = 3) were submitted to dissolution in a 708-DS Dissolution Apparatus (Agilent Technologies, USA) equipment coupled with VK 8000 (Varian® Inc. Palo Alto, CA, USA) automatic sampler. Dissolution tests were conducted using USP Apparatus 2 (paddle) with 900 mL of simulated gastric fluid (SGF) without enzyme at 37 ± 0.5 °C and 75 rpm for 960 minutes (FDA, 2016). Aliquots of 5.0 mL were withdrawn at 30, 60, 120, 240, 360, 480, 600, 720 and 960 minutes and quantified in a UV-VIS Cary 50 (Varian® Inc., Palo Alto, CA, USA) spectrophotometer at 246 nm using 10.0-mm quartz cuvettes (USP, 2011).

2.4 Computer simulations

The software DDDPlus™ version 4.0 (Simulations Plus Inc., Lancaster, CA, USA) was used to simulate *in vitro* dissolution of doxazosin ER formulations and to optimize component amounts for development of an optimized doxazosin ER formulation. Doxazosin solubility and pKa values were obtained according to item 2.2 and used as input data in Formulation Tab, as well as the following parameters: molecular weight (451.47 g/mol), tablet radius (r = 0.55 cm) and height (h = 0.2 cm). Polymer matrix (swellable) was selected as dosage form in the same Tab. DDDPlus™ contains a database of excipients in order to create formulations. Excipients of the experimental doxazosin ER formulation (Table 1) are recorded in the database and were also used

as input data in Formulation Tab. Dissolution test conditions described in item 2.3.1 were used in Experimental Tab.

DDDPlus™ has an optimization module that adjusts selected parameters of any given formulation, including experimental, processing and drug characteristics, to observed dissolution data in order to minimize differences between predicted and observed values. For formulations with swellable polymer matrix, DDDPlus™ applies the Mass Transfer Model given by Equation 1 (SIMULATIONS PLUS, 2011).

$$\frac{dM_U}{dt} = -\frac{3k\gamma}{\rho r}\left(C_S - \frac{M_D}{V}\right)M_U \quad \text{(Equation 1)}$$

where M_U and M_D are amounts of non-dissolved and dissolved drug, k is a coefficient of mass transfer (calibration constant), ρ is ingredient density, r is particle radius, C_S is solubility on particle surface, and V is the volume of dissolution medium. The parameter γ is a property-enhancing constant that was not used in simulations in this work.

DDDPlus™ optimization module also allows calculating release exponent (n) which is an indicator of drug release mechanism (SIMULATIONS PLUS, 2011).

Thus, *in vitro* dissolution profile of experimental doxazosin ER formulation was used to optimize k values for formulation components doxazosin, lactose, HPMC K100M and magnesium stearate used in the Mass Transfer Model, as well as to calculate n. After optimization, coefficient of determination (R^2) for dissolution test simulation of doxazosin ER formulation was obtained.

2.5 Formulation development

A seven-run, two-factor, simplex lattice, mixture experimental design using the statistical software Design Expert® version 10.0 (Stat-Ease, Inc., MN, USA) was applied for lactose (x_1) and HPMC K100M (x_2), with constraints at $0.2 \leq x_i \leq 0.8$ ($i = 1$ and 2; $\sum x_i = 1$) considering two replicates. The mixture of lactose and HPMC K100M generated by the software and calculated amounts of these excipients for each formulation, considering 100% of the mixture as 245.07 mg, is shown in Table 2.

Table 2 – Composition of formulations F1 to F7 defined using mixture experimental design

Formulation	Lactose (%)	HPMC K100M (%)	Lactose (mg)	HPMC K100M (mg)
F1	80	20	196.06	49.01
F2	50	50	122.54	122.54
F3	20	80	49.01	196.06
F4	65	35	159.30	85.77
F5	35	65	85.77	159.30
F6	20	80	49.01	196.06
F7	80	20	196.06	49.01

HPMC K100M, hydroxypropyl methylcellulose Methocel® K100M

2.5.1 Dissolution simulations

Drug records for each formulation (F1, F2, F3, F4, F5, F6 and F7) were created in DDDPlus™. Doxazosin mesylate (4.86 mg) and magnesium stearate (2.5 mg) were also added to each formulation composition (Table 2) in the software. Values of *k* for each component and *n* obtained as described in item 2.4 were applied to formulations. Single simulations of dissolution tests using the conditions previously described were performed.

Plots of simulated percent of doxazosin dissolved versus time for formulations F1, F2, F3, F4, F5, F6 and F7 were used as responses in Design Expert®. These responses were analyzed and optimal numerical values for drug release at each time point were defined (setting values): 30 min (6.63%), 60 min (12.18%), 120 min (21.58%), 240 min (36.23%), 360 min (48.17%), 480 min (58.46%), 600 min (67.49%), 720 min (75.41%) and 960 min (87.95%). Such data are a hypothetical example that serves to illustrate the use of DDDPlus™ prediction associated to DOE. Based on the statistical software optimization, an optimized doxazosin ER formulation was produced and submitted to *in vitro* dissolution test, and the results were compared to the predicted dissolution profile obtained in DDDPlus™ for the same formulation.

2.6 Resources use

Resources use was calculated for analyst working hours, equipment usage time and dissolution medium volume spent during tests with simulation (two formulations) and without simulations (nine formulations).

3 RESULTS AND DISCUSSION

Table 3 shows pKa values for different methanol solution (containing deionized water and methanol 20:80 with 0.15 M KCl) ratios used during the potentiometric assay.

Table 3 – Values of pKa obtained by titration at different methanol solution ratios

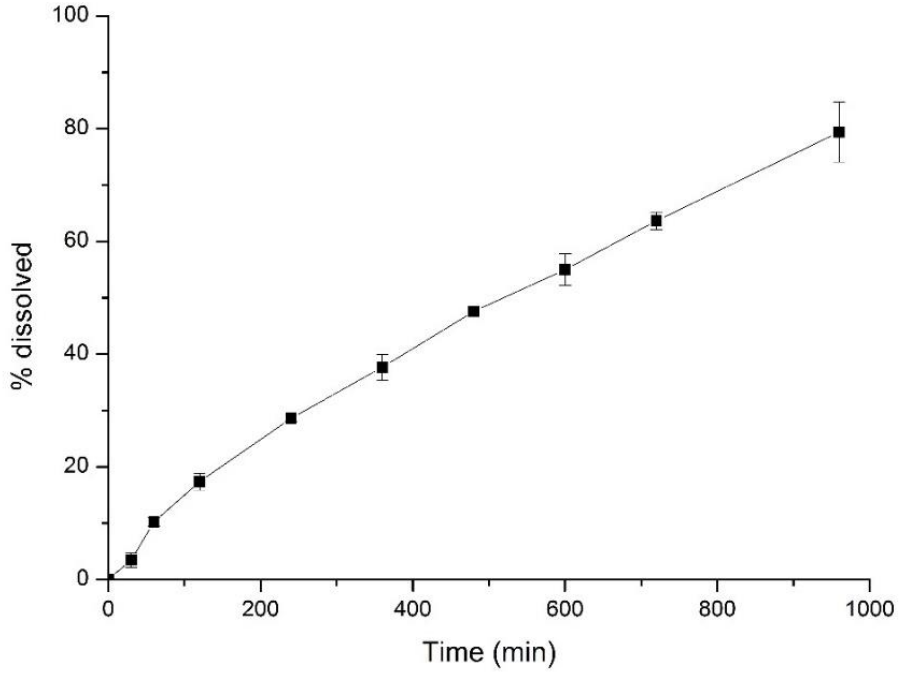
Methanol Solution (%)	pKa
15.50	6.81
20.65	6.75
22.85	6.75
27.79	6.70
29.11	6.70
37.44	6.65

Considering these results, the pKa value obtained by extrapolation for 0% of methanol solution was 6.87, which is close to pKa 6.93 reported by Erceg et al. (2012).

Doxazosin solubility obtained by potentiometry was 2.216 mg/mL (pH 2.0), 0.222 mg/mL (pH 3.0), 0.396 mg/mL (pH 5.8) and 0.079 mg/mL (pH 6.8) at 37 °C. For simulation purposes, solubility was set at 0.079 mg/mL at pH 6.8 and pKa 6.87.

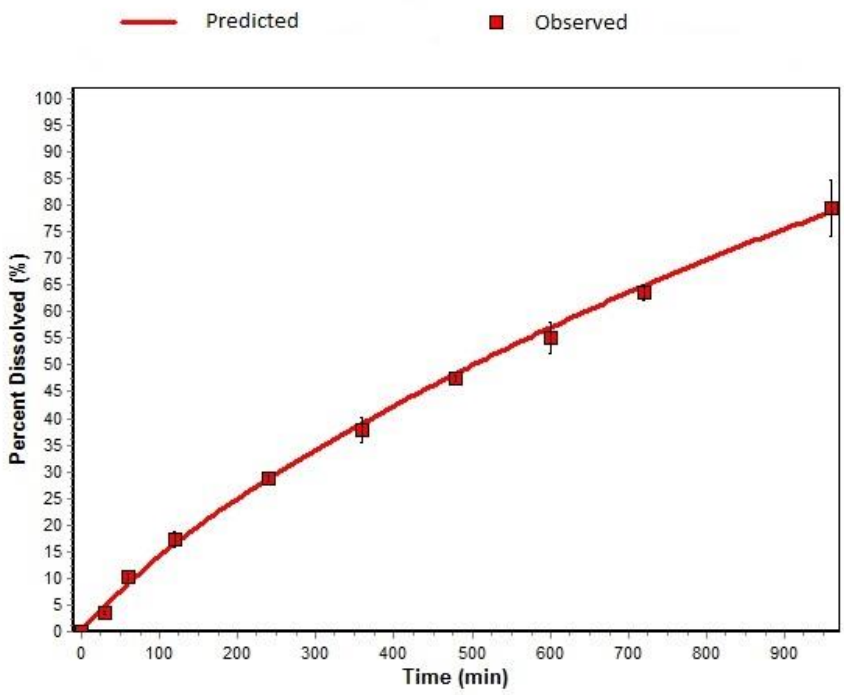
Dissolution test was performed at pH 1.2 (SGF without enzyme) according to the Food and Drug Administration (FDA) recommendation for doxazosin ER tablets (FDA, 2016). *In vitro* dissolution profile of experimental doxazosin ER formulation used in DDDPlus™ to optimize drug and excipient *k* values and *n* is shown in Figure 1.

Figure 1 – *In vitro* dissolution profile of experimental doxazosin extended-release formulation obtained with USP Apparatus 2 (paddle), 900 mL of SGF without enzyme at 37 ± 0.5 °C and 75 rpm for 960 minutes; error bars represent standard deviation (n = 3 ± SD)



After optimization, *k* values were set for doxazosin (0.6815), lactose (0.5427), HPMC K100M (3.2723) and magnesium stearate (0.0012), and *n* was 0.64. Dissolution simulations were performed to evaluate the closeness between observed (*in vitro*) and predicted profiles (Figure 2).

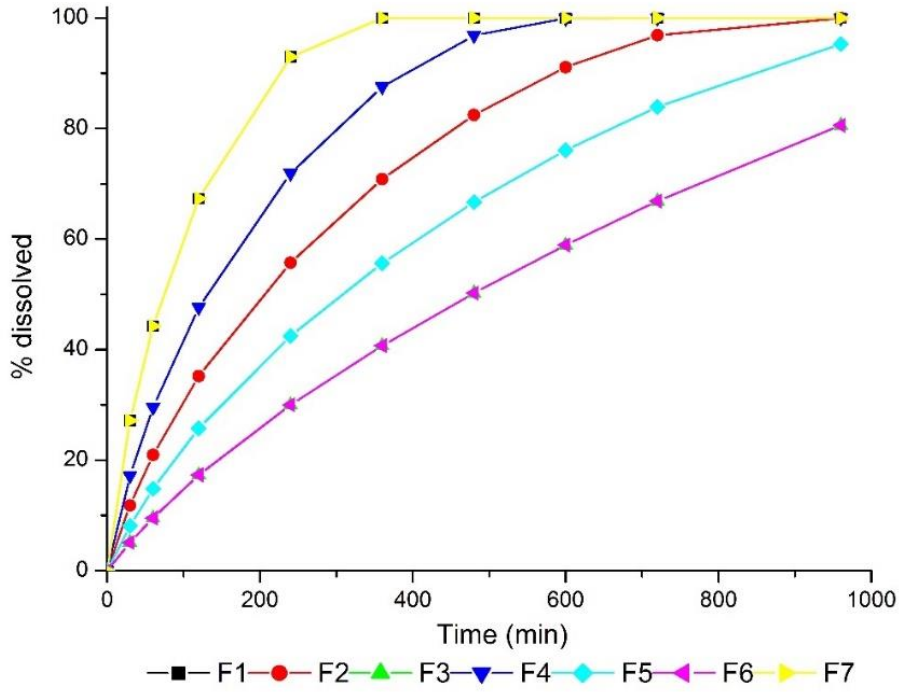
Figure 2 – Predicted versus observed dissolution profiles of doxazosin extended-release formulation; error bars represent standard deviation for observed plot (n = 3 ± SD)



Predicted versus observed dissolution profiles showed in Figure 2 for doxazosin ER formulation had high correlation ($R^2 = 1$). Such results indicated that by changing amounts of ingredients in this formulation, it is possible to simulate dissolution profiles for other formulations with different excipient ratios, helping the development of an ER dosage form with desirable drug release.

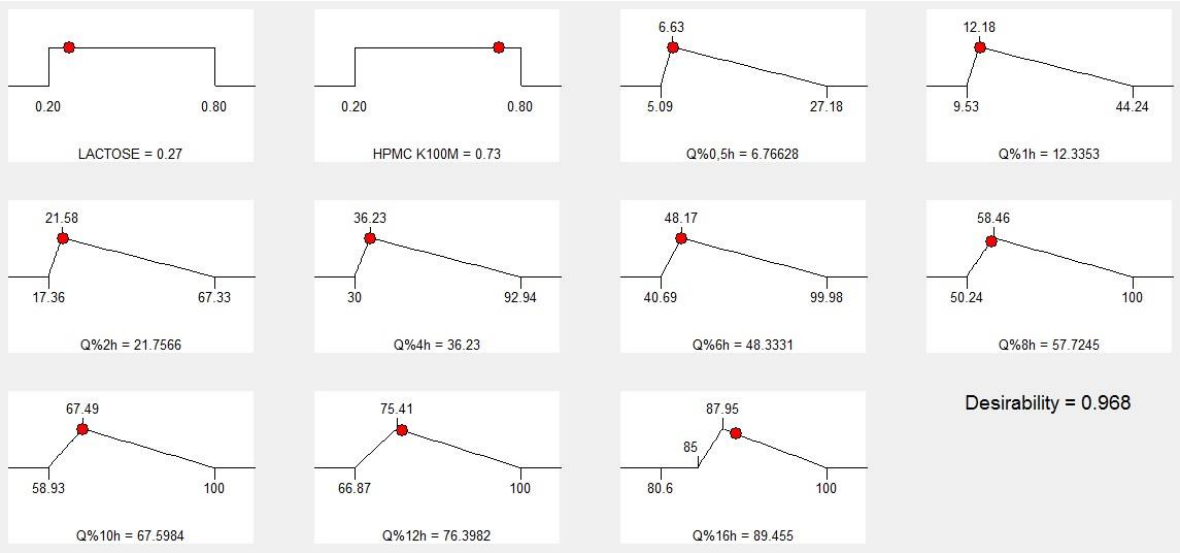
Seven drug records (F1, F2, F3, F4, F5, F6 and F7) were created considering *k* and *n* values calculated by DDDPlus™ optimization module for the experimental doxazosin ER formulation. The amounts of lactose and HPMC K100M were varied according to the mixture experimental design (Table 2). Dissolution profiles were simulated for all formulations under test conditions described in item 2.3.1. Predicted dissolution profiles are shown in Figure 3.

Figure 3 – Predicted dissolution profiles of doxazosin extended-release formulation F1, F2, F3, F4, F5, F6 and F7 obtained with USP Apparatus 2 (paddle), 900 mL of SGF without enzyme at 37 ± 0.5 °C and 75 rpm for 960 minutes



The amounts of drug dissolved at each time point for simulated formulations were used as responses in the software Design Expert® for statistical analysis. By choosing the numerical optimization tab in this software, it is possible to set the desirable amount of drug dissolved at each time point within the range of drug dissolved from F1 to F7. Based on these values, component proportions (lactose and HPMC K100M) in the mixture experimental design are calculated as well as the % of drug dissolved for this composition that is closer to setting values, as shown in Figure 4 and Table 4.

Figure 4 – Plot for optimized composition, percent of drug dissolved (Q%) at different time points and desirability predicted using Design Expert®



HPMC K100M, hydroxypropyl methylcellulose Methocel® K100M

Table 4 – Setting values for % of drug dissolved and corresponding optimized values obtained using Design Expert®

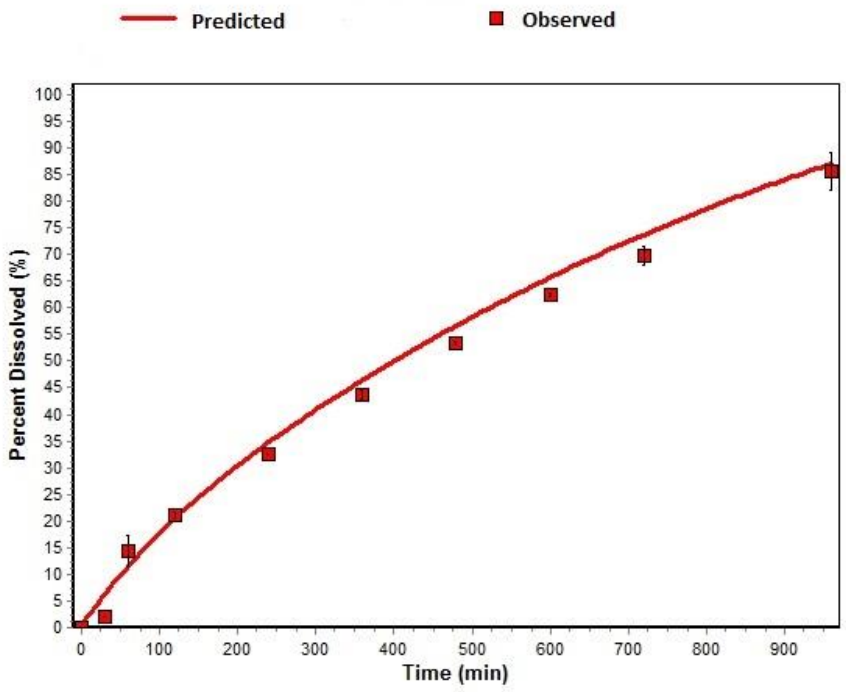
Time (min)	Setting values for drug dissolved (%)	Optimized values for drug dissolved (%)
30	6.63	6.76
60	12.18	12.34
120	21.58	21.75
240	36.23	36.23
360	48.17	48.33
480	58.46	57.72
600	67.49	67.59
720	75.41	76.39
960	87.95	89.46

Using the range 0.20 to 0.80 for lactose and HPMC K100M, component proportions calculated were 0.27 and 0.73, respectively. The % of drug dissolved showed desirability of 0.968. Desirability is a mathematical function that measures the closeness between setting values to optimized ones within a defined range. A desirability near to 1 means a good approximation between setting and optimized values within the range of drug dissolved (ISSA et al., 2013).

Tablets were produced considering the optimized doxazosin ER formulation containing 27% lactose and 73% HPMC K100M as described in item 2.3 and then submitted to dissolution tests under test conditions reported in item 2.3.1. *In vitro*

dissolution results were compared to predicted dissolution profile obtained in DDDPlus™ (Figure 5).

Figure 5 – Predicted versus observed dissolution profiles of optimized doxazosin extended-release formulation; error bars represent standard deviation for observed plot

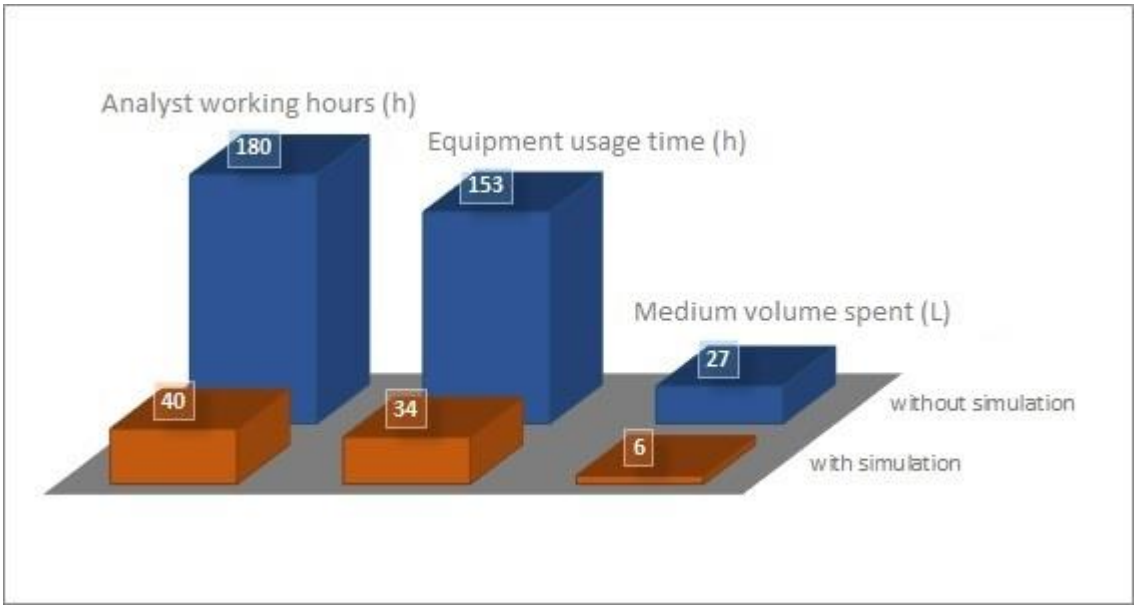


R^2 was 0.99 with respect to predicted and observed dissolution profiles for optimized doxazosin ER formulation. High correlation between % of drug dissolved observed in dissolution tests and simulated values predicted by DDDPlus™ was also found by Almukainzi et al. (2015) for drugs glyburide and montelukast sodium. Additionally, similarity factor (f_2) for predicted and observed dissolution profiles was 76. An f_2 value between 50 and 100 indicates that dissolution profiles are similar (FDA, 1997).

In this work, the resources use in the development of the formulations was also evaluated, considering nine formulations. Tablets of two formulations were prepared and submitted to dissolution tests whereas dissolution results from the other seven formulations were obtained by simulation in the software DDDPlus™. Each *in vitro* dissolution test lasted 16 hours; considering the time spent preparing tablets and analyzing aliquots from dissolution test, total testing time for each formulation was about 20 hours. Equipment usage time and medium volume spent for each testing

condition were also considered when evaluating resources spent in this work (Figure 6).

Figure 6 – Resources spent during tests with simulation (two formulations) and without simulation (nine formulations)



According to Figure 6, simulation of dissolution tests using the software DDDPlus™ lead to a 66.67% reduction in analyst working hours and 77.78% reduction in both equipment usage time and dissolution medium volume spent. These are very interesting data regarding the reduction of time and costs for research laboratories that can serve as basis for cost/time reduction approaches in pharmaceutical companies.

4 CONCLUSION

Dissolution simulations using DDDPlus™ associated to mixture experimental design can be successfully applied to the pharmaceutical development of ER formulations with the model drug doxazosin, with the additional advantage of reduced experimentation resources in research laboratories. Moreover, DDDPlus™ simulations can help companies to save time and reduce costs by reducing the number of laboratory experiments to be conducted.

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RABTI, H.; SALMANI, J. M. M.; ELAMIN, E. S.; LAMMARI, N.; ZHANG, J.; PING, Q. Carbamazepine solubility enhancement in tandem with swellable polymer osmotic pump tablet: a promising approach for extended delivery or poorly water-soluble drugs. **Asian Journal of Pharmaceutical Sciences**, v. 9, p. 146-154, 2014.

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UNIVERSIDADE DE SÃO PAULO
Faculdade de Ciências Farmacêuticas
Secretaria de Pós-Graduação

Informações para os Membros de Bancas Julgadoras de Mestrado/Doutorado

1. O candidato fará uma apresentação oral do seu trabalho, com duração máxima de trinta minutos.

2. Os membros da banca farão a argüição oral. Cada examinador disporá, no máximo, de trinta minutos para argüir o candidato, exclusivamente sobre o tema do trabalho apresentado, e o candidato disporá de trinta minutos para sua resposta.

2.1 Com a devida anuência das partes (examinador e candidato), é facultada a argüição na forma de diálogo em até sessenta minutos por examinador.

3. A sessão de defesa será aberta ao público.

4. Terminada a argüição por todos os membros da banca, a mesma se reunirá reservadamente e expressará na ata (relatório de defesa) a aprovação ou reprovação do candidato, baseando-se no trabalho escrito e na argüição.

4.1 Caso algum membro da banca reprove o candidato, a Comissão Julgadora deverá emitir um parecer a ser escrito em campo exclusivamente indicado na ata.

4.2 Será considerado aprovado o aluno que obtiver aprovação por unanimidade ou pela maioria da banca.

5. Dúvidas poderão ser esclarecidas junto à Secretaria de Pós-Graduação: pgfarma@usp.br, (11) 3091 3621.

São Paulo, 23 de maio de 2014.

Prof. Dr. Adalberto Pessoa Junior
Presidente da CPG/FCF/USP

Currículo Lattes

English

Dados gerais Formação Atuação Produções Eventos Bancas +

Marcelo Dutra Duque

Endereço para acessar este CV: http://lattes.cnpq.br/7085580900560038

Última atualização do currículo em 04/02/2016

Graduado em Farmácia e Bioquímica (2005) pela Universidade Federal de Juiz de Fora, com as habilitações em Análises Clínicas e em Indústria. Possui experiência na área de farmacotécnica, no desenvolvimento e avaliação de formas farmacêuticas sólidas, líquidas e semissólidas. Mestre em Ciências (2009), pelo Programa de Pós-graduação em Fármaco e Medicamentos na Área de Produção e Controle Farmacêuticos da Faculdade de Ciências Farmacêuticas da Universidade de São Paulo. Aluno de Doutorado no mesmo Programa de Pós-graduação, sendo colaborador no DEINFAR (Laboratório de Desenvolvimento e Inovação Farmacotécnica) da Faculdade de Ciências Farmacêuticas da Universidade de São Paulo. Trabalha como farmacêutico, servidor técnico-administrativo em educação na Universidade Federal de São Paulo. **(Texto informado pelo autor)**

Identificação

Nome

Marcelo Dutra Duque

Nome em citações bibliográficas

DUQUE, MD;DUQUE, M. D.;Duque, Marcelo Dutra

Endereço

Endereço Profissional

Universidade Federal de São Paulo, Campus Diadema.
Rua São Nicolau, 210
Centro
09913030 - Diadema, SP - Brasil

Formação acadêmica/titulação

2014

Doutorado em andamento em Fármaco e Medicamentos.
Universidade de São Paulo, USP, Brasil.
Título: Determinação das curvas de absorção, perfis de dissolução e estabelecimento de correlação in vitro-in vivo por métodos in silico utilizando o GastroPlus e o DDDPlus,
Orientador: Humberto Gomes Ferraz.
Coorientador: Raimar Löbenberg.

2007 - 2009

Mestrado em Fármaco e Medicamentos.
Universidade de São Paulo, USP, Brasil.
Título: Otimização da liberação de difosfato de primaquina em comprimidos de liberação controlada,Ano de Obtenção: 2009.
Orientador: Profa. Dra. Vladi Olga Consiglieri.
Bolsista do(a): Conselho Nacional de Desenvolvimento Científico e Tecnológico, CNPq, Brasil.

2000 - 2005

Graduação em Faculdade de Farmácia e Bioquímica.
Universidade Federal de Juiz de Fora, UFJF, Brasil.

Formação Complementar

2013 - 2013

Dissol. Form. Farm. Sól. - Interpretando a RDC 31. (Carga horária: 16h).
Faculdade de Ciências Farmacêuticas - FCF-USP, FCF-USP, Brasil.

2013 - 2013

Workshop Cap. Métodos Estatísticos Multivariados. (Carga horária: 40h).
Faculdade de Ciências Farmacêuticas - FCF-USP, FCF-USP, Brasil.

2012 - 2012

Workshop Powder Flow. (Carga horária: 6h).
Universidade Federal de São Paulo, UNIFESP, Brasil.

2012 - 2012

Determinação da solubilidade na ind. farmacêutica. (Carga horária: 4h).
Faculdade de Ciências Farmacêuticas - FCF-USP, FCF-USP, Brasil.

2011 - 2011

VI FÓRUM DE DIRETRIZES CURRICULARES. (Carga horária: 8h).
Conselho Regional de Farmácia do Estado de São paulo, CRF-SP, Brasil.

2009 - 2009

Semin. de Tecnologias de Formulação e Revestimento. (Carga horária: 8h).
COLORCON, COLORCON, Brasil.

2008 - 2008

Latin American Modified Release Forum 2008. (Carga horária: 9h).
COLORCON, COLORCON, Brasil.

2006 - 2006

Pharmaceutical Tablet Technology -by Dr. Adel Sakr. (Carga horária: 30h).
Universidade de São Paulo, USP, Brasil.

2005 - 2005

Extensão universitária em Monitoria em Tecnologia Farmacêutica. (Carga horária: 400h).
Universidade Federal de Juiz de Fora, UFJF, Brasil.

2005 - 2005

Assistência e Atenção Farmacêutica. (Carga horária: 30h).
Universidade Federal de Juiz de Fora, UFJF, Brasil.

2004 - 2005

Extensão universitária em Estágio em Análises Clínicas com plantões. (Carga horária: 450h).
Hospital Universitário/UFJF, HU/UFJF, Brasil.

2003 - 2005

Extensão universitária em Treinam. Profissional/Farmácia Universitária. (Carga horária: 1260h).
Universidade Federal de Juiz de Fora, UFJF, Brasil.

2003 - 2003

Formas Farmacêuticas de Liberação Modificada. (Carga horária: 6h).
Conselho Federal de Farmácia, CFF, Brasil.

2003 - 2003

IXEscola de Verão Quim. Farmacêutica e Medicinal. (Carga horária: 45h).
Universidade Federal do Rio de Janeiro, UFRJ, Brasil.

2003 - 2003

Estrat. Racionais Desenvolv. de Novos Fármacos. (Carga horária: 15h).
Universidade Federal do Rio de Janeiro, UFRJ, Brasil.

2003 - 2003

Introdução à Química Farmacêutica e Medicinal. (Carga horária: 15h).
Universidade Federal do Rio de Janeiro, UFRJ, Brasil.

2001 - 2002

Farmácia Hospitalar. (Carga horária: 163h).
Hospital Universitário/UFJF, HU/UFJF, Brasil.

2001 - 2001

Estágio no Laboratório de Produção Farmacêutica. (Carga horária: 31h).
Faculdade de Farmácia e Bioquímica/UFJF, FFB/UFJF, Brasil.

2000 - 2000

Síntese Orgânica. (Carga horária: 2h).
Universidade Federal de Juiz de Fora, UFJF, Brasil.

2000 - 2000

Controle da Dor. (Carga horária: 9h).
Universidade Federal de Juiz de Fora, UFJF, Brasil.

2000 - 2000

Aplicação de Injetáveis e Aferição de P. Arterial. (Carga horária: 9h).
Universidade Federal de Juiz de Fora, UFJF, Brasil.

2000 - 2000

Compostos Solúveis e Insolúveis. (Carga horária: 2h).
Universidade Federal de Juiz de Fora, UFJF, Brasil.

2000 - 2000

Fitoquímica. (Carga horária: 2h).
Universidade Federal de Juiz de Fora, UFJF, Brasil.

2000 - 2000

Nutrição Parenteral. (Carga horária: 6h).
Universidade Federal de Juiz de Fora, UFJF, Brasil.

Atuação Profissional

Universidade Federal de São Paulo, UNIFESP, Brasil.

Vínculo institucional

2013 - Atual

Vínculo: Servidor Público, Enquadramento Funcional: Farmacêutico, Carga horária: 40

Outras informações

Assumiu o cargo de Farmacêutico, tomando posse em 02/09/2013, habilitado em Concurso Público para Pessoal Técnico Administrativo em Educação, homologado pelo Edital nº 606, de 22/07/2013, publicado no D.O.U. de 23/07/2013.

23/07/2013.

Atividades

12/2013 - 12/2014

Direção e administração, Campus Diadema, .

Cargo ou função
Vice-coordenador do Núcleo de Apoio Técnico ao Ensino e Pesquisa (NATEP).

Universidade de São Paulo, USP, Brasil.

Vínculo institucional

2014 - Atual

Vínculo: Aluno de pós-graduação, Enquadramento Funcional: Doutorado

Vínculo institucional

2007 - 2009

Vínculo: Aluno de pós-graduação, Enquadramento Funcional: Mestrado

Atividades

10/2014 - Atual

Conselhos, Comissões e Consultoria, Faculdade de Ciências Farmacêuticas, Departamento de Farmácia.

Cargo ou função
Suplente da representação discente na CCP - Comissão Coordenadora do Programa de Pós-graduação em Fármacos e Medicamentos.

07/2014 - Atual

Pesquisa e desenvolvimento , Faculdade de Ciências Farmacêuticas, Departamento de Farmácia.

Linhas de pesquisa

Desenvolvimento de sistemas multiparticulados de liberação prolongada

07/2007 - 12/2009

Pesquisa e desenvolvimento , Faculdade de Ciências Farmacêuticas, .

Linhas de pesquisa
Desenvolvimento e obtenção de dispersões sólidas
Desenvolvimento de sistemas matriciais de liberação controlada

02/2008 - 07/2008

Estágios , Faculdade de Ciências Farmacêuticas, .

Estágio realizado
Programa de Aperfeiçoamento de Ensino (PAE) - disciplina FBF 0341 - Farmacotécnica.

Universidade Federal de Juiz de Fora, UFJF, Brasil.

Vínculo institucional

2000 - 2005

Vínculo: Aluno, Enquadramento Funcional: Aluno de graduação em Farmácia e Bioquímica

Atividades

09/2003 - 06/2005

Estágios , Faculdade de Farmácia e Bioquímica, .

Estágio realizado
Estágio extracurricular em manipulação de medicamentos e produtos cosméticos na Farmácia Universitária com carga horária de 1260 horas..

08/2001 - 06/2005

Pesquisa e desenvolvimento , Faculdade de Farmácia e Bioquímica, .

Linhas de pesquisa
Quantificação de vitamina C em comprimidos e em frutos de acerola
Desenvolvimento de formulações de suspensões
Avaliação da estabilidade de fármaco em cremes e xampus

Universidade Paulista, UNIP, Brasil.

Vínculo institucional

2010 - 2013

Vínculo: Professor universitário, Enquadramento Funcional: Professor adjunto, Carga horária: 24

Vínculo institucional

2009 - 2010

Vínculo: Professor universitário, Enquadramento Funcional: Professor assistente, Carga horária: 24

Atividades

02/2011 - 08/2013

Conselhos, Comissões e Consultoria, Setor de Estágios - Campus Alphaville, .

Cargo ou função
Supervisor de Estágio do Curso de Farmácia - noturno.

08/2010 - 08/2013

Ensino, Farmácia e Bioquímica, Nível: Graduação

Disciplinas ministradas
Fundamentos de Tecnologia Farmacêutica e de Cosméticos

02/2010 - 08/2013

Ensino, Farmácia e Bioquímica, Nível: Graduação

Disciplinas ministradas
Controle de Qualidade Físico-químico
Farmacotécnica e Tecnologia Farmacêutica
Farmacotécnica Geral
Tecnologia de Cosmético
Tecnologia Farmacêutica e de Cosméticos

02/2009 - 08/2013

Ensino, Farmácia e Bioquímica, Nível: Graduação

Disciplinas ministradas
Controle de Qualidade de Produtos Farmacêuticos e Cosméticos
Farmacotécnica Especial
Fundamentos de Controle de Qualidade de Produtos Farmacêuticos e Cosméticos
Tópicos de Farmacotécnica

08/2012 - 12/2012

Ensino, Farmácia, Nível: Graduação

Disciplinas ministradas
Farmácia Homeopática

Drogaria São Paulo S.A., DSP, Brasil.

Vínculo institucional

2005 - 2007

Vínculo: Farmacêutico substituto, Enquadramento Funcional: Farmacêutico, Carga horária: 40

Linhas de pesquisa

1.

Desenvolvimento de sistemas multiparticulados de liberação prolongada

2.

Desenvolvimento e obtenção de dispersões sólidas

3.

Desenvolvimento de sistemas matriciais de liberação controlada

4.

Quantificação de vitamina C em comprimidos e em frutos de acerola

5.

Desenvolvimento de formulações de suspensões

6.

Avaliação da estabilidade de fármaco em cremes e xampus

Revisor de periódico

2010 - 2010

Periódico: Drying Technology

2013 - Atual

Periódico: Journal of Forensic Toxicology and Pharmacology

2013 - Atual

Periódico: Drug Development and Industrial Pharmacy

2014 - Atual

Periódico: AAPS PharmSciTech

2015 - Atual

Periódico: International Journal of Nanomedicine (Online)

2015 - Atual

Periódico: Brazilian Journal of Pharmaceutical Sciences (Impresso)

Idiomas

Inglês

Compreende Razoavelmente, Fala Razoavelmente, Lê Razoavelmente, Escreve Razoavelmente.

Espanhol

Compreende Razoavelmente, Fala Pouco, Lê Razoavelmente, Escreve Pouco.

Produções

Produção bibliográfica

Artigos completos publicados em periódicos

Ordenar por

Ordem Cronológica ▼

1.

PEZZINI, B. R. ; ISSA, M. G. ; **DUQUE, M. D.** ; FERRAZ, H. G. . Applications of USP apparatus 3 in assessing the in vitro release of solid oral dosage forms. Brazilian Journal of Pharmaceutical Sciences (Online) JCR, v. 51, p. 265-272, 2015.

2.

ISSA, M. G. ; **DUQUE, M. D.** ; SOUZA, F. M. ; FERRAZ, H. G. . Evaluating the impact of different variables in the intrinsic dissolution of metronidazole. International Journal of Pharmacy and Engineering, v. 1, p. 17-29, 2013.

3.

Duque, Marcelo Dutra; Kreidel, Rogério Nepomuceno ; Taqueda, Maria Elena Santos ; Baby, André Rolim ; Kaneko, Telma Mary ; Velasco, Maria Valéria Robles ; Consiglieri, Vladi Olga . Optimization of primaquine diphosphate tablet formulation for controlled drug release using the mixture experimental design. Pharmaceutical Development and Technology JCR, v. 18, p. 1247-1254, 2013.

Citações: SCOPUS 1

4.

ISSA, MICHELE GEORGES ; **Duque, Marcelo Dutra** ; QUEIROS, ALINE ROTILDES DE ; FRANÇOSO, JULIANA BUONO ; Ferraz, Humberto Gomes ; RODRIGUES, LETICIA NORMA CARPENTIERI . Development of a dissolution test method for enrofloxacin tablets using factorial design. International Journal of Experimental Design and Process Optimisation, v. 3, p. 435-446, 2013.

5.

DUQUE, M. D.; SOUZA, D. H. ; GONÇALVES, L. M. ; BERNARDO, R. S. ; PINHO, J.J.R.G. . Estudo das propriedades físico-químicas de preparações farmacêuticas contendo cetoconazol para uso tópico. HU Revista, v. 39, p. 45-49, 2013.

6.

Takahashi, Andrea Ikeda ; Lourenço, Felipe Rebello ; **DUQUE, MD** ; Consiglieri, Vladi Olga ; Ferraz, Humberto Gomes . Using fluid bed granulation to improve the dissolution of poorly water-soluble drugs. Brazilian Archives of Biology and Technology (Impresso) JCR, v. 55, p. 477-484, 2012.

Citações: WEB OF SCIENCE℠ 2 | SCOPUS 2

7.

KREIDEL, R. N. ; **DUQUE, M. D.** ; SERRA, C. H. R. ; VELASCO, M. V. R. ; BABY, A. R. ; KANEKO, T. M. ; CONSIGLIERI, V. O. . Dissolution Enhancement and Characterization of Nimodipine Solid Dispersions with Poloxamer 407 or PEG 6000. Journal of Dispersion Science and Technology JCR, v. 33, p. 1354-1359, 2012.

Citações: WEB OF SCIENCE℠ 3 | SCOPUS 3

Resumos publicados em anais de congressos

1.

KAKUDA, B. A. S. ; RODRIGUES, L. N. C. ; **DUQUE, M. D.** ; ISSA, M. G. ; FERRAZ, H. G. ; SOUZA, N. V. . Intrinsic dissolution of pyrimethamine for evaluation of solubility as the biopharmaceutics classification system (BCS). In: XVII Congresso Paulista de Farmacêuticos, 2013, São Paulo. Brazilian Journal of Pharmaceutical Sciences, 2013, v. 49, p.

Congresso Paulista de Farmacêuticos, 2013, São Paulo. Brazilian Journal of Pharmaceutical Sciences, 2013. v. 49. p. 59-59.

2.

ISSA, M. G. ; QUEIROS, A. R. ; SOUZA, N. V. ; **DUQUE, MD** ; FERRAZ, H. G. . Improving dissolution of hydrochlorothiazide by coating extruded granules. In: XVII Congresso Paulista de Farmacêuticos, 2013, São Paulo. Brazilian Journal of Pharmaceutical Sciences, 2013. v. 49. p. 54-54.

3.

GUEOGJIAN, K. ; ISSA, M. G. ; FORTES, A. C. ; **DUQUE, M. D.** ; FERRAZ, H. G. . HPTLC method for quantification of metoprolol succinate in matrix containing polyurethan resin from castor oil. In: XVII Congresso Paulista de Farmacêuticos, 2013, São Paulo. Brazilian Journal of Pharmaceutical Sciences, 2013. v. 49. p. 52-52.

4.

ISSA, M. G. ; SOUZA, N. V. ; **DUQUE, M. D.** ; FERRAZ, H. G. . Dissolution profile evaluation of mebendazole suspensions containing different polymorphs. In: XVIII Pharmaceutical Science and Technology Meeting of the Faculty of Pharmaceutical Sciences, 2013, São Paulo. Brazilian Journal of Pharmaceutical Sciences, 2013. v. 49. p. 20-20.

5.

ISSA, M. G. ; PROTAZIO, N. V. ; SOUZA, N. V. ; **DUQUE, M. D.** ; FERRAZ, H. G. . Development of controlled release multiparticulate system containing metoprolol succinate. In: XVIII Pharmaceutical Science and Technology Meeting of the Faculty of Pharmaceutical Sciences, 2013, São Paulo. Brazilian Journal of Pharmaceutical Sciences, 2013. v. 49. p. 30-30.

6.

ISSA, M. G. ; **DUQUE, M. D.** ; FRANCOSO, J. B. ; QUEIROS, A. R. ; RODRIGUES, L. N. C. ; FERRAZ, H. G. . Development of a dissolution test method for enrofloxacin tablets using factorial design. In: XVII Semana Farmacêutica de Ciência e Tecnologia, 2012, São Paulo. Brazilian Journal of Pharmaceutical Sciences, 2012. v. 48. p. 94-94.

7.

ISSA, M. G. ; **DUQUE, MD** ; SOUZA, F. M. ; FERRAZ, H. G. . Evaluation of the impact of different variables in the intrinsic dissolution test for metronidazole. In: XV Semana Farmacêutica de Ciência e Tecnologia, 2010, São Paulo. Brazilian Journal of Pharmaceutical Sciences (Impresso), 2010. v. 46. p. 81-81.

8.

DUQUE, MD; KREIDEL, R. N. ; TAQUEDA, M. E. S. ; SERRA, C. H. R. ; PORTA, V. ; KANEKO, T. M. ; VELASCO, M. V. R. ; CONSIGLIERI, V. O. . Optimization of primaquine diphosphate controlled release tablets produced with different viscosity grades of HPMC. In: Simpósio Anual de Pesquisas em Ciências Farmacêuticas, 2009, São Paulo. Brazilian Journal of Pharmaceutical Sciences, 2009. v. 45. p. 22-22.

9.

DUQUE, MD; KREIDEL, R. N. ; TAQUEDA, M. E. S. ; SERRA, C. H. R. ; PORTA, V. ; KANEKO, T. M. ; VELASCO, M. V. R. ; CONSIGLIERI, V. O. . Desenvolvimento de comprimidos de liberação prolongada de difosfato de primaquina. In: XIII Semana Farmacêutica de Ciência e Tecnologia da FCF - USP, 2008, São Paulo. RBCF. Revista Brasileira de Ciências Farmacêuticas (Cessou em 2008. Cont. ISSN 1984-8250 Brazilian Journal of Pharmaceutical Sciences). São Paulo: Hermano Editoração, 2008. v. 44. p. 39-39.

10.

DUQUE, MD; KREIDEL, R. N. ; CONSIGLIERI, V. O. ; POLLACHAGRA, N. A. . Desenvolvimento de nanocápsulas contendo

DUQUE, MD; KREIDEL, R. N. ; CONSIGLIERI, V. O. ; BOU-CHACRA, N. A. . Desenvolvimento de nanocápsulas contendo nimodipino para formulação de produto inovador. In: XIII Semana Farmacêutica de Ciência e Tecnologia da FCF - USP, 2008, São Paulo. RBCF. Revista Brasileira de Ciências Farmacêuticas (Cessou em 2008. Cont. ISSN 1984-8250 Brazilian Journal of Pharmaceutical Sciences). São Paulo: Hermano Editoração, 2008. v. 44. p. 64-64.

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