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In Silico Simulation of Dissolution Profiles for Development of Extended-Release Doxazosin Tablets

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ABSTRACT

Developing extended-release (ER) formulations with appropriate release characteristics can be challenging for formulation scientists. The aim of this study was to demonstrate the use of computer-simulated dissolution profiles associated with statistical experimental design in the development of doxazosin ER tablet formulations. Experimental doxazosin ER tablets were prepared and tested using USP Apparatus 2 with 900 mL of simulated gastric fluid without enzyme at 37 ± 0.5 °C and 75 rpm for 960 minutes. The results were used to optimize calibration constants for the ingredients in the simulation software, DDDPlus. Design Expert software 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 identified, manufactured, and tested for comparison with the predicted profile. A correlation coefficient 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 with design of experiments can save time and reduce costs in the development of ER formulations.

KEYWORDS: Doxazosin, DDDPlus, Design Expert, computer simulation, dissolution, extended-release (ER) tablets, experimental design

INTRODUCTION

Extended-release (ER) tablets are solid oral dosage forms formulated with excipients to extend drug release over a prolonged period after oral administration (*1*). Developing ER dosage forms is a challenge for formulation scientists given that tablets must be designed to release drugs slowly in the gastrointestinal (GI) tract; the control of drug release can be achieved mainly by formulation approaches like coatings, compressed coated tablets, osmotic pump systems, or hydrophilic polymers (*2–6*).

In coated systems, drug release is controlled by a polymer film. Aqueous media penetrates the dosage form and dissolves the drug, which then diffuses out of the dosage form (*7*). Compressed coated tablets are obtained by precompression into core tablets followed by other compression with coating powder containing polymers for pulsatile drug controlled release (*3*). In osmotic pumps, an excipient expands when in contact with water and presses the active pharmaceutical ingredient (API) in a controlled manner through an orifice. Such systems can be obtained by compressing an API and excipients into a tablet that is then coated with a semipermeable polymeric membrane, permitting water to penetrate the dosage form, forming a saturated solution, which is released through an orifice on the top of the tablet (*8, 9*). Push–pull osmotic pump systems are two-chamber devices that consists of a compressed bilayer tablet containing a push compartment composed of a swellable polymer and a drug layer. This tablet is surrounded by a semipermeable membrane that is penetrated by water, leading to hydration of drug and push layers. A hydrodynamic pressure is formed by swelling of the push layer, which allows the drug suspension to be delivered through an orifice (*10*).

Hydrophilic matrix tablets made with polymers, such as hydroxypropyl methylcellulose (HPMC), are primarily used for ER systems. Such polymers swell and form a gel layer that controls water and drug diffusion and surface erosion, a process called anomalous transport

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(*11, 12*). Commercially available polymers exhibit different degrees of polymerization, leading to higher or lower swelling properties and erosion rates (*13*).

Using appropriate amounts of HPMC, including different viscosity grades in matrix formulations, is essential for the desirable drug release pattern (*14*). Statistical planning, including design of experiment (DOE), reduces the number of laboratory experiments necessary for development of ER dosage forms (*15*). This approach is an essential part of modern pharmaceutical development and ties into Quality by Design approaches. Optimal knowledge and control of the drug release mechanisms from the formulation will define the design space (*16*).

A useful tool in defining a design space and the reduction of laboratory work on a trial and error basis is the estimation of drug dissolution using computer simulations (*17–19*). The software Dose Disintegration and Dissolution Plus (DDDPlus, Simulations Plus, Inc.) simulates in vitro dissolution of pharmaceutical dosage forms and intrinsic dissolution of APIs using United States Pharmacopeia (USP) apparatuses (*20*).

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

MATERIAL AND METHODS

Materials

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

Determination of Dissociation Constant (pKa) and Solubility

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

Doxazosin was dissolved in a mixture of 10 mM dimethyl sulfoxide solution, linear buffer solution, and methanol solution containing deionized water and methanol (20:80) with 0.15 M KCl (*21*). Turbidity was monitored at 500 nm during titration with 0.5 M HCl and 0.5 M KOH. The pKa values were obtained by titration at different methanol solution ratios. Resulting pKa values were extrapolated using the Yasuda–Shedlovsky method in the software, Sirius T3Refine, version 1.1.2.0 (Sirius Analytical Instruments Ltda) (*22*).

For solubility determination, three samples of doxazosin (1.11, 2.50, and 5.41 mg) were previously dissolved in methanol solution (10%, 20%, and 30%, respectively) containing deionized water and methanol (20:80) with 0.15 M KCl. After sample ionization, a base titration was conducted at a pH range of 2–12 by adding 0.5 M KOH, using the Cheqsol method (*23*).

Formulation

Experimental doxazosin ER formulation was prepared using a hydraulic press (American Lab., São Paulo, Brazil), in which 11-mm-diameter tablets were obtained by compression at 1500 psi for one minute. Drug and excipients were accurately weighted and mixed using a mortar and pestle. Formulation composition was doxazosin mesylate (4.86 mg, corresponding to 4.00 mg of doxazosin), lactose (45.07 mg), HPMC K100M (200 mg), and magnesium stearate (2.5 mg).

Dissolution Test

Experimental doxazosin ER tablets (n = 3) were submitted to dissolution in a 708-DS Dissolution Apparatus (Agilent Technologies, USA) coupled with a 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 (*24*). 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.) spectrophotometer at 246 nm using 10.0-mm quartz cuvettes (*1*).

Computer Simulations

DDDPlus, version 4.0 (Simulations Plus Inc., Lancaster, CA, USA) was used to simulate in vitro dissolution tests to optimize the quantity of each component to develop a doxazosin ER formulation. Drug solubility and pKa values were obtained as described above and were used as input data in the formulation tab in DDDPlus, as well as the following parameters: molecular weight (451.47 g/mol), tablet radius (r = 0.55 cm), and table height (h = 0.2 cm).

Polymer matrix (swellable) was selected as the dosage form in the same Tab. DDDPlus contains a database of excipients to create formulations. Excipients of the experimental doxazosin ER formulation were recorded in the database and were also used as input data in formulation tab. Dissolution test conditions described above were used in the experimental tab in DDDPlus.

DDDPlus has an optimization module that adjusts selected parameters of any given formulation, including experimental, processing, and drug characteristics, for the observed dissolution data to minimize differences between predicted and observed values. For formulations with a swellable polymer matrix, DDDPlus applies the mass transfer model given by eq 1 (*20*).

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

where M_U and M_D are amounts of undissolved and dissolved drug, respectively, 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 for calculation of the release exponent (*n*), which is an indicator of drug release mechanism (*20*). Thus, the in vitro dissolution profile of experimental doxazosin ER formulations 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 to compare it to the observed dissolution profile from the experimental doxazosin ER formulation.

Formulation Development

A seven-run, two-factor, simplex lattice, mixture experimental design using Design Expert, version 10.0 (Stat-Ease, Inc., MN, USA) was applied for lactose (x_1) and HPMC K100M (x_2), with constraints at $0.2 \le xi \le 0.8$ (i = 1 and 2; $\sum xi = 1$) 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, are shown in Table 1.

Table 1. Composition of Formulations F1–F7 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)

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 in the software (Table 1). Values of k for each component and *n* obtained as described above were applied to formulations. Single simulations of dissolution tests using the conditions previously described were performed.

Plots of simulated percentage of doxazosin dissolved versus time for formulations F1–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) (Table 2). Such data are hypothetical examples that serve to illustrate the use of DDDPlus prediction associated with DOE. Based on the Design Expert optimization, an optimized doxazosin ER formulation was produced and submitted to in vitro dissolution testing, and the results were compared to the predicted dissolution profile obtained in DDDPlus for the same formulation.

Table 2. Drug Dissolved 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

Resources Used

The amount of resources used was calculated for analyst working hours, equipment usage time, and medium volume consumed during tests with simulation (two formulations) and without simulations (nine formulations).

RESULTS

The pKa values obtained were 6.81, 6.75, 6.70, and 6.65 for different methanol solution (containing deionized water and methanol 20:80 with 0.15 M KCl) ratios 15.50%, 22.85%, 29.11%, and 37.44%, respectively. 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. (*25*).

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

Dissolution tests were performed at pH 1.2 (SGF without enzyme) according to the US Food and Drug Administration (FDA) recommendation for doxazosin ER tablets (*24*). The 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 1A.

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 0.80. Dissolution simulations were performed to evaluate the closeness between observed (in vitro) and predicted profiles (Fig. 1B).

Seven drug records (F1–F7) were created considering k values calculated by the 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 1). Dissolution profiles were simulated for all formulations under test conditions described above. Predicted dissolution profiles are shown in Figure 1C.

The amounts of drug dissolved at each time point for simulated formulations were used as responses for statistical analysis in Design Expert. 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 for the experimental design were calculated as well as the percent of drug dissolved in the composition, as shown in Figure 2 and Table 2.

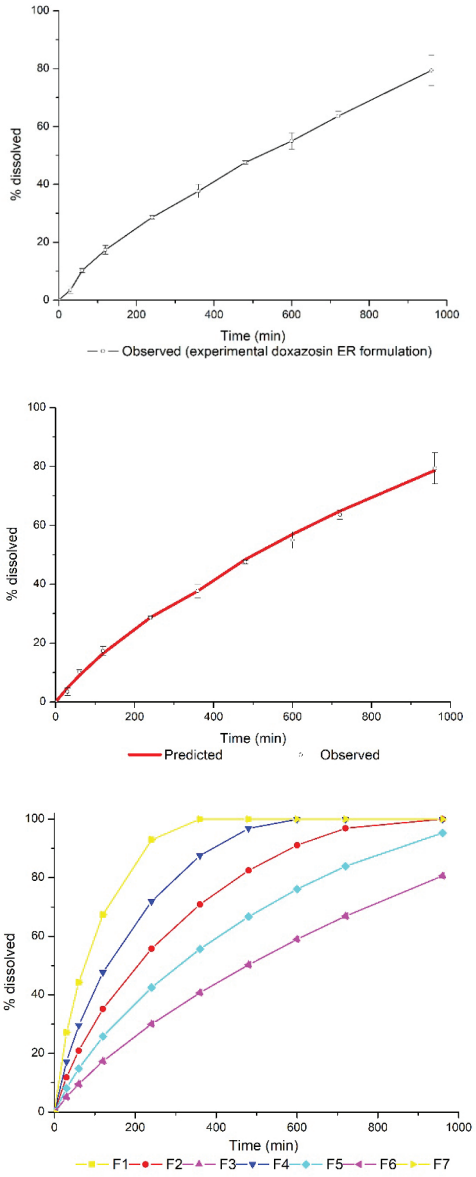

Figure 1. (A) In vitro dissolution profile of experimental doxazosin ER formulation obtained with USP Apparatus 2 (paddle), 900 mL of SGF without enzyme at 37 ± 0.5 °C and 75 rpm for 960 minutes. Error bars represent standard deviation (n = 3). (B) Predicted versus observed (experimental doxazosin ER formulation) dissolution profiles of doxazosin ER formulation. (C) Predicted dissolution profiles of doxazosin ER formulations F1–F7 obtained with USP Apparatus 2, 900 mL of SGF without enzyme at 37 ± 0.5 °C and 75 rpm for 960 minutes (two formulations are replicates: F1 = F7 and F3 = F6, so there is overlap of the dissolution profiles).

Using the range 0.20–0.80 for lactose and HPMC K100M, component proportions calculated were 0.27 and 0.73, respectively. The percent of drug dissolved showed desirability of 0.968 (Fig. 2).

Tablets were produced considering the optimized doxazosin ER formulation containing 27% lactose and 73% HPMC K100M and submitted to dissolution tests under

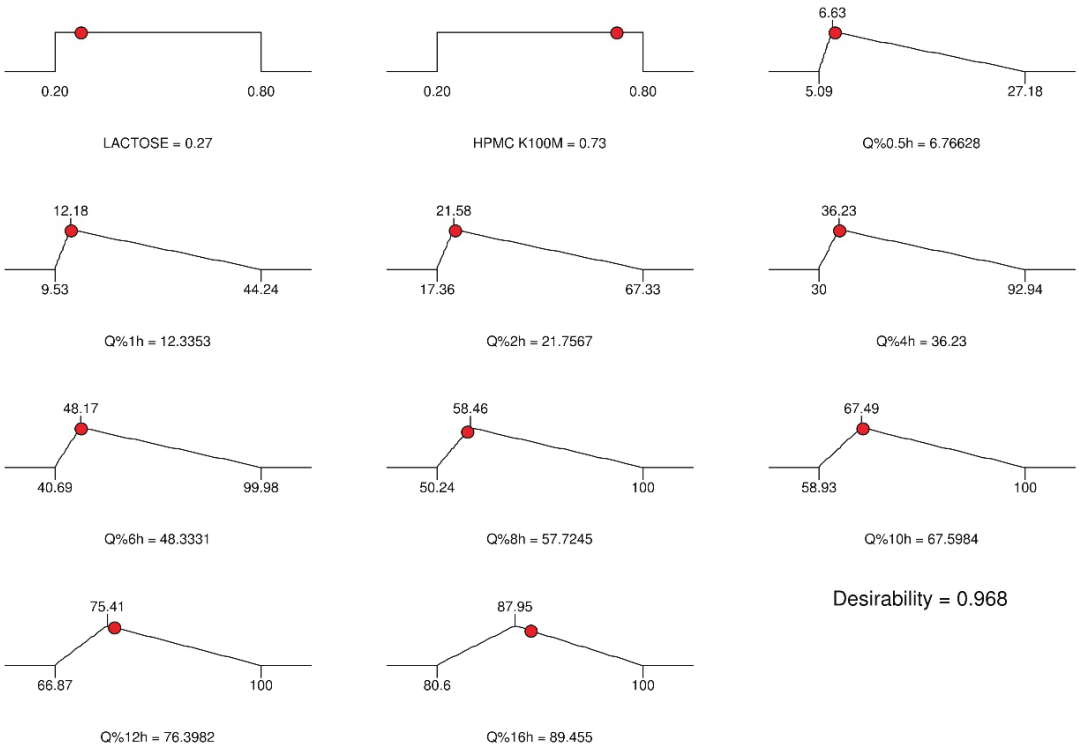

Figure 2. Plot for optimized composition, percent of drug dissolved (Q%) at different time points (red circles,) and desirability predicted using Design Expert.

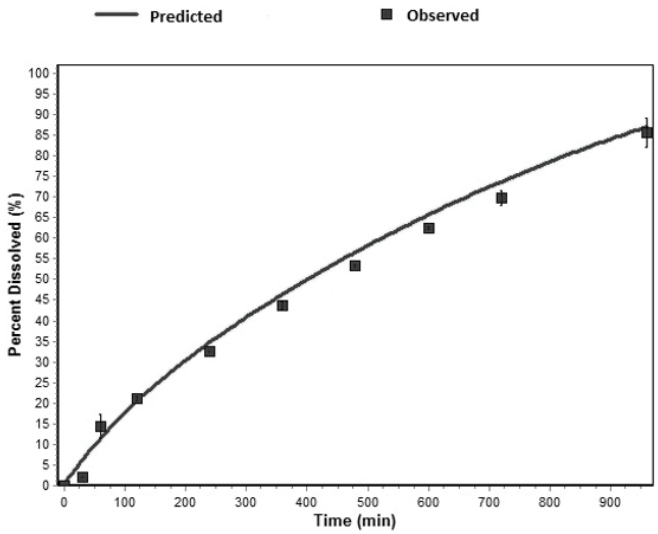

Figure 3. Predicted versus observed dissolution profiles of optimized doxazosin extended-release formulation; error bars represent standard deviation for observed plot.

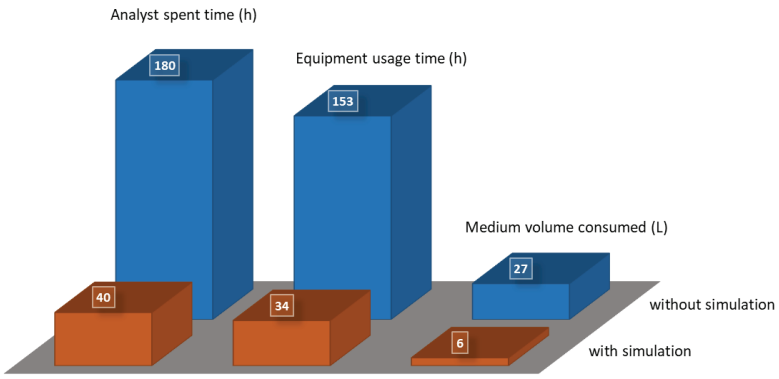

Figure 4. Resources consumed during tests with simulation (two formulations) and without simulation (nine formulations).

test conditions described above. In vitro dissolution results were compared to predicted dissolution profile created in DDDPlus and the obtained R^2 was 0.99 (Fig. 3). The similarity factor ($f2$) for predicted and observed dissolution profiles calculated by DDDPlus was 76.

In this work, pharmaceutical development of doxazosin ER tablets was carried out considering nine formulations. Tablets of two formulations were prepared and tested via dissolution testing, whereas dissolution results from the other seven formulations were obtained by simulations using DDDPlus. Each in vitro dissolution test lasted 960 minutes (16 h). Considering the time spent preparing tablets and analyzing dissolution test samples, the total analysis time for each formulation was about 20 hours. Equipment usage time and medium volume used for each testing condition were also considered when evaluating resources consumed in this work (Fig. 4). Analyst time was reduced by 66.67%, and both equipment usage and volume of dissolution media needed were reduced by 77.78% when using simulations.

DISCUSSION

Doxazosin mesylate is a BCS class I (high solubility and high permeability) drug (*26*). The obtained pKa value and higher solubility at a low pH is due to its weak basic characteristic, showing pH-dependent solubility. Similar solubility behaviour was also suggested by Cha and colleagues, who evaluated solubility of doxazosin mesylate in simulated gastric fluid at pH 1.2 without pepsin (solubility = 0.237 mg/mL), acetate buffer pH 4.0 (solubility = 4.277 mg/mL), and simulated intestinal fluid (pH 6.8) without pancreatin (solubility = 0.0139 mg/mL) (*27*).

The doxazosin ER dosage form is commercially available as a push–pull osmotic pump system in 4- and 8-mg tablets (*28*, *29*). Several strategies have been applied to develop modified release doxazosin formulations (e.g., using carrageenan matrices, pellets, and compression coated tablets) (*30*–*32*, *3*).

Dissolution tests are a standard tool in the development of pharmaceutical oral dosage forms (*33*). Dissolution test conditions for doxazosin as recommended by FDA are 900 mL of pH-1.2 SGF without enzyme at 37 ± 0.5 °C and 75 rpm for 960 minutes (*24*). These test conditions were applied to our experimental doxazosin ER tablets and to simulate the dissolution profiles.

Predicted versus observed dissolution profiles are shown in Fig. 1B for doxazosin ER formulations with a high correlation (R^2 = 1). The simulated dissolution profile was obtained after optimization using k values for the drug and excipients, and the release exponent, n. Such results indicate that by defining the amount of ingredients and their in silico constants in a formulation, it is possible to predict dissolution profiles for other formulations with different excipient ratios, aiding in developing an ER dosage form with desirable drug release.

The predicted dissolution profiles for formulations F1–F7 (Fig. 1C) showed the fastest drug release in formulations F1 and F7, which contained the same composition (80% lactose and 20% HPMC K100M), due to less polymer and more solubility (i.e., lactose). Formulations F3 and F6, containing the opposite composition (20% lactose and 80% HPMC K100M), showing the lowest amount of drug dissolved due to the quantity of HMPC K100M,

which forms a high viscosity gel layer, leading to greater drug retention. Intermediate dissolution profiles were found for the other formulations (F2, F4, and F5).

After optimization of the drug release pattern as shown in Table 2 using Design Expert, a plot for the optimized composition (Fig. 2) was obtained with high predictability (0.968). Predictability can be expressed as the correlation coefficient, R^2, which is a mathematical function that measures the closeness between observed values and predicted ones within a defined range (*34*).

R^2 was 0.99 with respect to predicted and observed dissolution profiles for optimized doxazosin ER formulations (Fig. 3). High correlation between percent of drug dissolved observed in dissolution tests and simulated values predicted by DDDPlus was also found by Almukainzi et al. for drugs glyburide and montelukast sodium (*17*). Additionally, the *f*2 value calculated by DDDPlus in our study for predicted and observed dissolution profiles was between 50 and 100, indicating that dissolution profiles are similar (*35*).

According to Figure 4, simulation of dissolution tests using DDDPlus led to a great reduction in analyst time, equipment usage, and volume of dissolution media needed. These are very promising results regarding the time savings and costs reduction due to less wet lab work.

CONCLUSION

Dissolution simulations using DDDPlus in combination with experimental design can be successfully applied to the pharmaceutical development of ER formulations of doxazosin tablets. Moreover, DDDPlus simulations can help companies save time and reduce laboratory costs by reducing the number of experiments to be conducted. Furthermore, predictive models of formulation design can be used to set a suitable design space for drug release patterns.

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CONFLICT OF INTEREST

The authors disclosed no conflicts of interest related to this article.

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