BJPS

Brazilian Journal of
Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902024e23633

Review

Review of the dissolution tests in the Brazilian Pharmacopeia

Nathalia Maria Guedes[1], José Geneilson Silva[1], Leandro Luiz Gomes de Miranda Mesquita[1], Whocely Victor de Castro[2], Ednalva de Sousa Pereira Lima[2], Davi Pereira de Santana[1], Danilo Cesar Galindo Bedor[1]*

[1]Department of Pharmaceutical Science, Center of Health Sciences, Federal University of Pernambuco, Recife, PE, Brazil, [2]Graduate Program in Pharmaceutical Sciences, Federal University of São João del-Rei, Divinópolis, MG, Brazil

Dissolution tests evaluate the release of therapeutic agents in various dosage forms, acting as quality control tools to secure batch–batch equivalence and guides for formulation development and *in vivo* drug bioavailability prediction for pharmaceutical scientists. In this article, dissolution tests described in the Brazilian Pharmacopeia 6th ed. were systematically reviewed using the following descriptors: drug, dosage forms, apparatus, rotational speed, dissolution media, sampling time, quantitative procedure, and the value of *Q*. Test conditions were compared with those described in the United States Pharmacopeia (USP) dissolution database. In September, 2023, dissolution tests were required for 127 monographs, accounting for only 10% of those listed in the USP database. Paddles were used in 80 monographs (63.5%) at various rotation speeds. Basket apparatus was recommended for 47 products, including tablets, capsules, and gastro-resistant granules with variable speed ranges. The simulated gastric fluid was described in four monographs. Moreover, pH of the dissolution media for 29 products was adjusted in the physiological range of 2–7.5. Twenty-eight monographs are exclusively listed in the Brazilian Pharmacopeia. Among the 99 products listed in both compendiums, dissolution tests were only harmonized for 69 monographs.

Keywords: Brazilian Pharmacopeia. Dissolution methods. Review. Solid dosage forms. USP dissolution database.

INTRODUCTION

Dissolution is a phenomenon in which a solid substance is dissolved in a liquid to form a solution. Dissolution of a therapeutic agent leading to its change from a dosage form into a biological fluid is a crucial step that precedes its absorption, as only molecules in solutions can cross the biological barriers (Dressman *et al*., 1998). I*n vitro* dissolution tests are required by most regulatory agencies worldwide not only for new drugs but also to secure batch–batch equivalence. Additionally, these tests provide important information to assist formulation scientists in selecting the adequate excipients as they facilitate the measurement of the extent and rate of drug release from a dosage form under specific and controlled conditions mimicking its performance *in vivo* (Dressman *et al*., 1998).

During drug dissolution, solvent interacts with the exposed structure of the solute. At the solute–solvent interface, an unstirred solvent boundary layer is formed, where the concentration saturation is achieved. Fickian diffusion of solute molecules across this stagnant layer towards the bulk solution occurs until the entire particle is dissolved or the solvent solubility concentration is achieved (Dressman *et al*., 1998). This phenomenon is depicted by the Noyes and Whitney (1897) equation, modified by Nernst (1904) and Brunner (1904):

***Correspondence:** D. C. G. Bedor. Departmento de Ciências Farmacêuticas. Centro de Ciências da Saúde. Universidade Federal de Pernambuco. CEP 50.740-520, Recife, PE, Brasil. Phone: (55)81 997824140. E-mail: danilo.bedor@ufpe.br. ORCID: https://orcid.org/0000- 0002-3901-9126

$$\left(\frac{dm}{dt} = \frac{DA_{(t)}}{L} \times (C_s - C_b)\right)$$

where *dm/dt* is the total dissolved mass of the drug per unit time, *D* is the diffusion coefficient of the drug in the solvent, *A* is the total exposed area of the dissolving drug particle, *L* is the thickness of the unstirred solvent layer around the particle, and C_s and C_b are the solubility and concentration of the drug in the bulk solvent, respectively. Notably, *L* value is affected by the fluid viscosity and hydrodynamic properties of the surrounding dissolution medium (Siepmann, Siepman, 2013).

Dissolution test requirement was first listed in the United States Pharmacopeia (USP) 13th ed., with the incorporation of 6 monographs using a basket apparatus in 1970 and paddle method in 1977 (Dokoumetzidis, Macheras, 2006). Currently, the test is requireds for more than 1,770 monographs, and seven distinct apparatuses can be applied according to the dosage forms (Mohite *et al*., 2022). It was officialized by the Brazilian and British Pharmacopeias in 1988, the only methods described in both compendiums are those using the basket or paddle apparatus.

Due to globalization, unpacked medicines produced in one country are commonly exported to other countries. Hence, drug products must comply with the regulatory requirements of each market. Harmonization of the quality parameters and tests described in distinct pharmacopeias is desirable and a focus of The International Council for Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH; https://www.ich.org/). In 2010, based on the ICH guideline Q4B annex 7 (R2), the European Medicines Agency (EMA) recommended the interchangeable use of the official dissolution tests with the basket, paddle, and flow-through cell apparatuses from The European, Japanese, and USP Pharmacopeias within the ICH regions, except when enzymes are used in the media (EMA, 2010).

This article aimed to review and summarize the dissolution tests described in the Brazilian Pharmacopeia, 6th Edition (FB6) (ANVISA, 2019). All test conditions were compared with those currently listed in the USP Dissolution Database (The United States Pharmacopeial Convention, 2023; https://www.usp.org/resources/dissolution-methods-database).

MATERIAL AND METHODS

Methods

All dissolution tests officially adopted by the Brazilian Pharmacopeia in 2023 were reviewed and summarized in this article. This review encompasses the following parameters: type of drug, dosage form, apparatus, rotational speed, dissolution medium, sampling time, quantitative procedure, and the value of *Q*. Additionally, test conditions for each monograph were compared with those described in the USP dissolution database, which was updated on September 20, 2023 (The United States Pharmacopeial Convention, 2023).

RESULTS AND DISCUSSION

Dissolution tests required by FB6 for 2023 are summarized in Table I. The tests is required in 127 monographs for 118 different drugs. Among them, five monographs referred to the following associated drugs: amiloride hydrochloride + hydrochlorothiazide, amoxicillin + clavulanate potassium, atenolol + chlortalidone, levonorgestrel + ethinyl estradiol, sulfamethoxazole + trimetoprim, and zidovudine + lamivudine. Nine drugs had monographs for more than one type of dosage form: amitriptyline hydrochloride (tablet and capsule), ampicillin (tablet and capsule), ampicillin trihydrate (tablet and capsule), cefadroxil (tablet and capsule), ibuprofen (tablet and oral suspension), nitazoxanide (tablet and powder for suspension), pantoprazole sodium (capsule and gastro-resistant granules), levonorgestrel + ethinylestradiol (tablet and dragee), and simvastatin (tablet and capsule). For prednisone tablets, the dissolution method depended on the dose (< 10 or > 10 mg). However, the number of products for which a dissolution test is required by the Brazilian Pharmacopeia is less than 10% of those for which a dissolution test is required by the USP database. Therefore, future studies should focus on developing and validating the dissolution tests for drug products

marketed in Brazil but not listed in the Brazilian Pharmacopeia.

Notably, monographs for 28 products for which the dissolution tests are mandatory in FB6 are not included in the USP database. Moreover, among the 99 monographs listed in both compendiums for 69 dissolution tests were identical (70%). For the other 30 products, some divergence was found, including in the type of dissolution medium, apparatus, speed, and sampling time, as summarized in Table I. This lack of harmonization can affect the Brazilian pharmaceutical market, as products intended for export or import should comply with distinct regulatory tests. However, such differences do not mean that a particular method is not adequate. Official dissolution tests reflect the quality differences among pharmaceutical products but do not necessarily predict the *in vivo* performance of the formulations (Manadas, Pina, Veiga, 2002; Medina-López *et al.*, 2020).

TABLE I - Dissolution dataset from Brazilian Pharmacopoeia 6ed and comparison with the FDA dissolution database (2023)

Monograph	Dosage Form	Medium	Volume (mL)	Apparatus	Speed (rpm)	Time (min)	Q (%)	Quantitative procedure (λ nm)	Harmonization with FDA database (Y/N)
Acetaminophen	Tab	Phophate buffer pH 5.8	900	Paddle	50	30	80	UV (243)	Y
Acyclovir	Tab.	HCl 0.1 M	900	Paddle	50	45	80	UV (255)	Y
Albendazole	Tab.	HCl 0.1 M	900	Paddle	50	30	80	UV (308;350)	Y
Allopurinol	Tab.	HCl 0.01 M	900	Paddle	75	45	75	UV (250)	Y
Amiloride Hydrochloride +Hydrochlorotiazide	Tab	HCl 0.1 M	900	Paddle	50	30	80/75	UV(363/270)	Y
Aminophylline	Tab.	Water	900	Paddle	50	45	75	UV (269)	Y
Amitriptyline Hydrochloride	Tab/ Cap.	HCl 0.1 M	900	Basket	100	45	75	UV (239)	Y/N[1]
Amoxicillin + Clavulanate	Tab.	Water	900	Paddle	75	30	85/80	HPLC (220)	Y
Amoxicillin . $3H_2O$	Cap.	Water	900	Basket	100	90	80	UV(272)	N[1]
Ampicillin	Tab/Cap	Water	900	Basket	100	45	75	UV (320)	Y
Ampicillin . $3H_20$	Tab/Cap	Water	900	Basket	100	45	75	UV (320)	N[1]
Ascorbic Acid	Tab.	Water	900	Paddle	50	45	75	Titration	Y
Aspirin	Tab.	Acetate buffer 0.05 M; pH 4.5	500	Basket	50	30	80	UV (265)	Y
Atenolol	Tab.	Water	900	Paddle	50	30	80	HPLC (226)	N[2]
Atenolol + Chlorthalidone	Tab	HCl 0.01M	900	Paddle	50	45	80	HPLC (275)	Y

Tab: Tablets; Cap: Capsules; [1]: Not included on the FDA database; [2]: acetate buffer 0.1 N, pH 4.6.

Table I - Continued

Monograph	Dosage Form	Medium	Volume (mL)	Apparatus	Speed (rpm)	Time (min)	Q (%)	Quantitative procedure (λ nm)	Harmonization with FDA database (Y/N)
Azathioprine	Tab	Water	900	Paddle	50	30	75	UV (280)	Y
Biperiden Hydrochloride	Tab	HCl 0.01M	500	Paddle	50	45	75	HPLC (205)	N[1]
Bromazepam	Tab	Fluid gastric simulated with enzyme	900	Paddle	50	20	80	UV (239)	N[1]
Bromopride	Tab	HCl 0.1M	500	Basket	50	30	80	UV (274)	N[1]
Captopril	Tab	HCl 0.1M	900	Basket	50	20	80	UV (212)	N[3]
Carbamazepine	Tab	Water (SLS 1%, *w/v*)	900	Paddle	75	15/60	45/75	UV (285)	Y
Cefadroxil	Tab/Cap	Water	900	Paddle/ Basket	50/100	30	75/80	UV (263)	Y
Cephaclor	Cap	Water	900	Basket	50	30	80	UV (264)	Y
Cephalexin	Tab	Water	900	Basket	100	30	80	UV (265)	Y
Cephalexin Hydrochloride	Tab	Water	900	Basket	100	45	75	UV (265)	N[4]
Clopidogrel Bisulfate	Tab	HCl buffer, pH 2.0	1000	Paddle	50	30	80	UV (240)	Y
Chloroquine Diphosphate	Tab	Water	900	Paddle	100	45	75	UV (343)	Y
Chlorpropamide	Tab	Water	900	Paddle	50	60	75	UV (230)	Y
Chlorthalidone	Tab	Water	900	Paddle	75	60	70	UV (275)	Y
Cimetidine	Tab	Water	900	Basket	100	15	75	UV (218)	N[3]
Ciprofloxacin Hydrochloride	Tab	Water	900	Paddle	50	30	80	UV (272)	N[3]

SLS: Sodium lauryl sulfate; [3]: HCl 0.01 N; [4]: 150 rpm;

Table I - Continued

Monograph	Dosage Form	Medium	Volume (mL)	Apparatus	Speed (rpm)	Time (min)	Q (%)	Quantitative procedure (λ nm)	Harmonization with FDA database (Y/N)
Citalopram	Tab	HCl 0.1M	900	Basket	50	30	80	HPLC (239)	N[5]
Clarithromycin	Tab	Acetate buffer 0.1 M pH 5.0	900	Paddle	50	30	80	HPLC (210)	Y

Table I - Continued

Monograph	Dosage Form	Medium	Volume (mL)	Apparatus	Speed (rpm)	Time (min)	Q (%)	Quantitative procedure (λ nm)	Harmonization with FDA database (Y/N)
Clonazepam	Tab	Water	900	Paddle	75	60	75	HPLC (254)	N[6]
Clopidogrel Bisulfate	Tab	HCl buffer pH 2.0	1000	Paddle	50	30	80	UV (240)	Y
Clozapine	Tab	Acetate buffer pH 4.0	900	Basket	100	45	85	UV (290)	Y
Colchicine	Tab	Water	500	Basket	100	30	75	HPLC (254)	Y
Cyclobenzaprine Hydrochloride	Tab	HCl 0.1M	900	Basket	50	30	75	UV (290)	Y
Dexchlorpheniramine Maleate	Tab	Water	500	Paddle	50	45	75	HPLC (262)	Y
Diazepam	Tab	HCl 0.1M	900	Basket	100	45	75	UV (284)	N[7]
Diclofenac Potassium	Tab	Phosphate buffer pH 6.8	900	Paddle	40	60	80	UV (276)	N[8]
Digoxin	Tab	HCl 0.1 M	500	Basket	120	60	80	Fluorimetry (λ_{exc}: 372; λ_{em}: 485)	Y
Diltiazem Hydrochloride	Tab	Water	900	Paddle	75	30/180	60/75	UV (237)	Y
Diphenhydramine Hydrochloride	Tab	HCl 0.1 M	900	Basket	100	45	75	UV (254)	N[1]
Dipyrone.H_2O	Tab	HCl 0.1 M	500	Paddle	50	45	70	UV (258)	N[1]
Duloxetine Hydrochloride	Cap	HCl 0.1 M/ Phosphate buffer pH 6.8	1000	Basket	100	120/60	10*/75	HPLC (230)	Y

[5]: buffer pH 1.5, 800 mL,100 rpm; [6]: 45 min.; [7]: 30 min; [8]: simulate intestinal fluid without enzyme, 50 rpm; * no more than

Table I - Continued

Monograph	Dosage Form	Medium	Volume (mL)	Apparatus	Speed (rpm)	Time (min)	Q (%)	Quantitative procedure (λ nm)	Harmonization with FDA database (Y/N)
Efavirenz	Tab	Water (SLS 1%, *w/v*)	900	Paddle	100	45	80	UV (247)	N[9]
Enalapril Maleate	Tab	Phosphate buffer pH 6.8	900	Paddle	50	30	80	HPLC (215)	Y
Entacapone	Tab	Acetate buffer pH 5.3	900	Paddle	50	30	80	HPLC (305)	N[10]

Table I - Continued

Monograph	Dosage Form	Medium	Volume (mL)	Apparatus	Speed (rpm)	Time (min)	Q (%)	Quantitative procedure (λ nm)	Harmonization with FDA database (Y/N)
Epinastine Hydrochloride	Tab	HCl 0.1 M	900	Paddle	60	45	75	HPLC (207)	N[1]
Ethambutol Hydrochloride	Coated Tab	Water	900	Basket	100	45	75	HPLC (270)	N[11]
Ethionamide	Tab	HCl 0.1M	900	Paddle	100	45	75	UV (274)	Y
Fexofenadine Hydrochloride	Tab	HCl 0.1M	900	Basket	100	45	70	HPLC (250)	N[12]
Fluconazole	Cap	HCl 0.1M	900	Basket	100	30	80	UV (261)	N[1]
Flunitrazepam	Tab	Fluid gastric simulated	900	Paddle	50	45	85	HPLC (279)	N[1]
Fluoxetine Hydrochloride	Tab	HCl 0.1 M	900	Paddle	50	45	70	UV (227)	N[13]
Flurazepam Hydrochloride	Tab	Water	900	Basket	100	20	80	UV (270)	N[1]
Flutamide	Tab	Water (SLS 3%, *w/v*)	900	Paddle	75	45	75	UV (306)	N[1]
Folic acid	Tab	Water	500	Paddle	50	45	75	HPLC (283)	Y
Furosemide	Tab	Phosphate buffer pH 5.8	900	Paddle	50	60	80	UV (271)	Y
Gemifloxacin Mesylate	Tab	Phosphate buffer pH 6.0	900	Paddle	50	60	70	HPLC (272)	N[2]

[9]: SLS 2.0% (*w/v*) in water, 1000 mL, 50 rpm, 30 min; [10]: pH 5.5, UV (313 nm); [11]: VIS (415 nm); [12]: HCl 0.001 N, 50 rpm, 30 min; [13]: 1000 mL, 100 rpm, 15 min, HPLC

Table I - Continued

Monograph	Dosage Form	Medium	Volume (mL)	Apparatus	Speed (rpm)	Time (min)	Q (%)	Quantitative procedure (λ nm)	Harmonization with FDA database (Y/N))
Glibenclamide	Tab	Phosphate buffer pH 7.3	900	Paddle	75	60	70	HPLC (230)	N[14]
Haloperidol	Tab	Fluid gastric simulated	900	Basket	100	60	80	HPLC (254)	Y
Hydralazine Hydrochloride	Tab	HCl 0.01 M	900	Basket	100	30	60	UV (260)	N[6]
Hydrochlorothiazide	Tab	HCl 0.1 M	900	Basket	100	30	60	UV (272)	N[15]

Table I - Continued

Monograph	Dosage Form	Medium	Volume (mL)	Apparatus	Speed (rpm)	Time (min)	Q (%)	Quantitative procedure (λ nm)	Harmonization with FDA database (Y/N))
Ibuprofen	Tab	Phosphate buffer pH 7.2	900	Basket	150	30	60	UV (221)	N[16]
Ibuprofen	Oral Susp.	Phosphate buffer pH 7.2	900	Paddle	50	60	80	HPLC (220)	Y
Imipramine Hydrochloride	Tab	HCl 0.01 M	900	Basket	100	45	75	UV (250)	Y
Indomethacin	Cap	Phosphate buffer pH 7.2: Water (1:4)	750	Basket	100	20	80	UV (318)	Y
Isoniazid	Tab	HCl 0.01 M	900	Basket	100	45	80	UV (265)	Y
Ketoconazole	Tab	HCl 0.1 M	900	Paddle	50	30	80	UV (270)	Y
Lamivudine	Tab	Water	900	Paddle	50	30	80	UV (270)	Y
Leflunomide	Tab 10 or 20 mg	Water	1000	Paddle	100	30	80	UV (260)	Y
Levonorgestrel + Ethinyl Estradiol	Tab	Polysorbate 80 (0.0005%, *w/v*)	500	Paddle	75	60	80/75	HPLC (274/ λ_{exc}: 285; λ_{em}: 310)	Y

[14]: the test conditions depends if the drug is micronized or not; [15]: 60 min; [16]: paddles, 100 rpm, 15 min, Q= 80%

Table I - Continued

Monograph	Dosage Form	Medium	Volume (mL)	Apparatus	Speed (rpm)	Time (min)	Q (%)	Quantitative procedure (λ nm)	Harmonization with FDA database (Y/N)
Levonorgestrel + Ethinyl Estradiol	Dragee	Polysorbate 80 (0.0005%, *w/v*)	500	Paddle	75	60	60/60	HPLC (274/ λ_{exc}: 285; λ_{em}: 310)	N[1]
Loratadine	Tab	HCl 0.1 M	900	Paddle	50	60	80	UV (280)	Y
Mebendazole	Tab	HCl 0.1 M (SLS 1%, *w/v*)	900	Paddle	75	120	75	UV (248)	N[17]
Mefloquine Hydrochloride	Tab	HCl 0.1 M	900	Paddle	100	60	80	UV (283)	N[18]
Metformin Hydrochloride	Tab	Phosphate buffer pH 8.6	900	Basket	100	45	75	UV (233)	Y
Methyldopa	Tab	HCl 0.1 M	900	Paddle	50	20	80	UV (280)	Y
Metoclopramide Hydrochloride	Tab	Water	900	Basket	50	30	75	UV (309)	Y

Table I - Continued

Monograph	Dosage Form	Medium	Volume (mL)	Apparatus	Speed (rpm)	Time (min)	Q (%)	Quantitative procedure (λ nm)	Harmonization with FDA database (Y/N)
Metoprolol Tartrate	Tab	Fluid gastric simulated	900	Basket	100	30	75	UV (275)	Y
Metronidazole	Tab	HCl 0.1 M	1000	Basket	100	60	85	UV (274)	N[19]
Morphine Sulphate	Tab	Phosphate buffer pH 6.5	50	Paddle	50	45	70	HPLC (284)	N[1]
Mycophenolate Mofetil	Tab	HCl 0.1 M	900	Paddle	50	15	80	UV (250)	N[20]
Mycophenolate Sodium	Tab	HCl 0.1 M + NaOH 0.1 M/ Phosphate buffer pH 6.8	750/1000	Paddle	50/50	120/45	75	UV (250)	N[1]
Nalidixic Acid	Tab	Phosphate buffer pH 8.6	900	Paddle	60	30	80	UV (334)	N[1]

[17]: HPLC (254);[18]: 50 rpm, 30 min, UV (285); [19]: 900 mL; [20]: 5 min and 15 min, Q=75/85

Table I - Continued

Monograph	Dosage Form	Medium	Volume (mL)	Apparatus	Speed (rpm)	Time (min)	Q (%)	Quantitative procedure (λ nm)	Harmonization with FDA database (Y/N)
Nifedipine	Cap	Fluid gastric simulated	900	Basket	50	20	80	UV (340)	N[1]
Nimesulide	Tab	Phosphate buffer pH 7.4/ polysorbate 80 (2%, *v/v*)	900	Paddle	75	45	80	VIS (392)	N[1]
Nitazoxanide	Tab	Phosphate buffer pH 7.5/ cetrimonium bromide (6%, w/*v*, 25° C)	900	Paddle	75	45	80	HPLC (240)	N[1]
Nitazoxanide	Powder, for Susp	Phosphate buffer pH 7.5/ cetrimonium bromide (6%, w/*v*, 25° C)	900	Paddle	100	45	80	HPLC (240)	N[1]
Nitrofurantoin	Tab	Phosphate buffer pH 7.2	900	Basket	100	60/120	25/85	VIS (375)	Y

Table I - Continued

Monograph	Dosage Form	Medium	Volume (mL)	Apparatus	Speed (rpm)	Time (min)	Q (%)	Quantitative procedure (λ nm)	Harmonization with FDA database (Y/N)
Pantoprazole sodium	Cap	HCl 0.1 M/ Phosphate buffer pH 6.8	500/900	Basket	100/100	60/60	80	HPLC (290)	N[21]

[21]: Tab, Paddles, HCl 0.1 N(1000 mL, 120 min)/ Phosphate buffer pH 6.8 (1000 mL, 45 min)

Table I - Continued

Monograph	Dosage Form	Medium	Volume (mL)	Apparatus	Speed (rpm)	Time (min)	Q (%)	Quantitative procedure (λ nm)	Harmonization with FDA database (Y/N)
Pantoprazole sodium	Gastro-resistant granules	HCl 0.1 M / Phosphate buffer pH 11.0 (475/425, *v/v*, final pH 6.8)	900	Basket	100	60	80	HPLC (290)	N[1]
Phenobarbital	Tab	Water	900	Paddle	50	45	75	UV (240)	Y
Phenytoin	Tab	Tris buffer 0.05M, pH 9,0	900	Paddle	100	120		HPLC (254)**	N[1]
Piroxicam	Cap	HCl 0.1M	900	Basket	100	45	70	UV (242)	N[1]
Praziquantel	Tab	HCl 0.1 M (SLS 1%, *w/v*)	900	Paddle	50	60	75	UV (263)	N[22]
Prednisone, ≤ 10 mg	Tab	Water	500	Paddle	50	30	80	UV (242)	Y
Prednisone, > 10 mg	Tab	Water	900	Paddle	50	30	80	UV (242)	Y
Primaquine Diphosphate	Tab	HCl 0.1 M	900	Paddle	100	45	80	HPLC (254)	N[23]
Promethazine Hydrochloride	Tab	HCl 0.01 M	900	Basket	100	45	75	HPLC (249)	Y
Propranolol Hydrochloride	Tab	HCl 1% (*v/v*)	1000	Basket	100	30	75	UV (289)	Y
Pyrazinamide	Tab	Water	900	Paddle	50	45	75	UV (268)	Y
Pyridoxine Hydrochloride	Tab	HCl 0.1 M	900	Paddle	50	45	75	UV (290)	Y
Pyrimethamine	Tab	HCl 0.1 M	900	Paddle	50	45	75	UV (272)	Y

** Conditions for chewable tablet for USPharmacopeia; [22]: HPLC (263); [23]: 50 rpm. 60 min

Table I - Continued

Monograph	Dosage Form	Medium	Volume (mL)	Apparatus	Speed (rpm)	Time (min)	Q (%)	Quantitative procedure (λ nm)	Harmonization with FDA database (Y/N)
Rabeprazole sodium	Tab	HCl 0.1 M/ Borate buffer pH 9.0	900/900	Paddle	75/75	120/30	85	HPLC (282)	N[1]
Ranitidine Hydrochloride	Tab	Water	900	Paddle	50	45	80	UV (314)	Y
Rifampicin	Cap	HCl 0.1 M	900	Basket	100	45	75	VIS (475)	Y
Ritonavir	Cap	Water (SLS 0.7%, *w/v*)	900	Coated Paddle	25	60/120	40/75	HPLC (210)	N[24]
Salbutamol Sulfate	Tab	Water	500	Paddle	50	30	80	HPLC (276)	N[1]
Sertraline Hydrochloride	Tab	Acetate buffer pH 4.5	900	Paddle	75	45	75	UV (274)	Y
Sibutramine Hydrochloride.H_2O	Tab	HCl 0.1 M	500	Basket	75	45	75	HPLC (223)	N[1]
Simvastatin	Cap	Phosphate buffer 0.01M pH 7.0/SLS (0.5%, *v/v*)	900	Paddle	75	45	75	HPLC (238)	N[1]
Simvastatin	Tab	Phosphate buffer 0.01M pH 7.0/SLS (0.5%, *v/v*)	900	Paddle	50	30	75	UV (248)	Y
Sulfadiazine	Tab	HCl 0.1 M	900	Paddle	75	90	70	UV (254)	Y
Sulfamethoxazole + Trimethoprim	Tab	HCl 0.1 M	900	Paddle	75	60	70	HPLC (254)	Y

[24]: HCl 0.1 N with 25 mM of polyoxyethylene 10 lauryl ether, 50 rpm, 20 min, and 120 min, sinkers.

Table I - Continued

Monograph	Dosage Form	Medium	Volume (mL)	Apparatus	Speed (rpm)	Time (min)	Q (%)	Quantitative procedure (λ nm)	Harmonization with FDA database (Y/N)
Tetracycline Hydrochloride 250/500 mg	Cap	Water	900	Paddle	75	60/90	80	UV (276)	Y
Thiamine Hydrochloride	Tab	Water	900	Paddle	50	45	75	UV (246)	N[7]
Verapamil Hydrochloride	Tab	HCl 0.1 M	900	Paddle	50	30	75	UV (278,300)	N[3]

Table I - Continued

Monograph	Dosage Form	Medium	Volume (mL)	Apparatus	Speed (rpm)	Time (min)	Q (%)	Quantitative procedure (λ nm)	Harmonization with FDA database (Y/N)
Warfarin Sodium	Tab	Water	900	Paddle	50	30	80	HPLC (280)	Y
Zidovudine	Cap	Water	900	Paddle	50	45	75	HPLC (265)	Y
Zidovudine and Lamivudine	Tab	Water	900	Paddle	50	60	80	HPLC (270)	Y

Dosage forms

Tablets encompassed 83.5% of all dosage forms (106/127), followed by capsules (13.4%, 17/127). Other dosage forms included oral suspensions (ibuprofen), dragees (levonorgestrel + ethinyl estradiol), powders for suspension (nitazoxinide), and gastro-resistant granules (pantoprazole sodium). Each represented less than 1% of the monographs for which a dissolution test was required (1/127). In comparison, from the 1,793 products listed in the USP database, including those for veterinary use, a dissolution test was required for 1,508 (1,536) monographs, including tablets (74.6.0%), capsules (23.6%), and suspensions (1.45%), as shown on Figure 1.

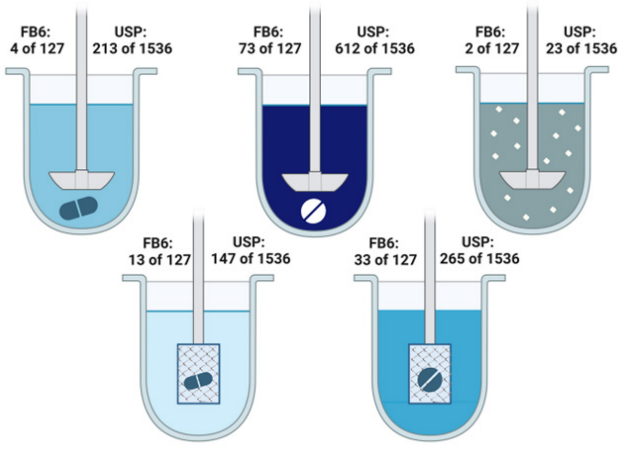

FIGURE 1 - Comparison of the dissolution tests described in the Brazilian Pharmacopeia and USP database.

Apparatus

Compendial apparatus is preferred for dissolution methods to ensure batch–batch quality, consistency, and performance of drug products. Basket and paddle apparatuses were developed in the 60s and are the main choices for immediate-release solid oral dosage forms. For non-floating and disintegrating products, a paddle is recommended as it promotes a well-mixed hydrodynamic environment, whereas a basket or sinker is used as an alternative for floating formulations. Conversely, for non-disintegrating dosage forms, a basket is more suitable as it allows the medium to freely access the dosage form. For other drug release technologies and non-oral products, a different USP apparatus may be chosen (Bredael, Liang, Hahn, 2015).

Although the Brazilian Pharmacopeia describes three dissolution methods, namely Method 1 (basket), Method 2 (paddle), and Method 3 (reciprocal cylinder device), in its general chapter, only the first two are employed. Paddle is required for 80 monographs (63.0%), mainly for tablets (96.8%), whereas the basket is recommended for 47 (37%) products, including 33 tablets, 13 capsules, and 1 gastro-resistant granules; no sinker was prescribed. In contrast, all USP dissolution apparatuses (Apparatuses 1–7) are listed in the USP dissolution methods database (The United States Pharmacopeial Convention, 2023). Paddle is recommended in 69.8% of the monographs (1052/1508) mostly to evaluate the immediate-release solid dosage forms (tablets: 600; capsules: 145; oral suspension: 12). Basket is required for 25.8% of the products (389/1508), including tablets (134), extended-release tablets (104), and capsules (84).

Rotation Speed

As shown in Figure 2, the rotational speed of the basket method varies between 50 and 150. For 36 monographs (24 tablets, 11 capsules, and 1 gastro-resistant granules), the rotation was set at 100 rpm. The highest rotation speed (150 rpm) was used only for the ibuprofen tablets, whereas 50 rpm was required for eight monographs (six tablets and two capsules). Spin values of 75 and 120 rpm were applied to the sibutramine hydrochloride and digoxin tablets, respectively.

In the paddle method, the rotation speed was in the range of 25–100 rpm, with a common speed of 50 rpm (47 monographs, 46 for tablets, and 1 for capsules). The fastest spin value (100 rpm) was cited in seven monographs, whereas the slowest speed (25 rpm) was only required for ritonavir capsules. The rotation speed was set at 75 rpm for 20 products, 17 of which were tablets and two were capsules.

Speed ranges for the paddle and basket methods were within the same range as those listed in the Brazilian Pharmacopeia. Similarly, the most common rotation speeds for the basket and paddle devices were 100 and 50 rpm, respectively.

Rotation is an important factor for the hydrodynamic flow around the dosage form and reflects the different dissolution behaviors (Morihara *et al*., 2002). Generally, rotation speed and dissolution rate exhibit a negative correlation (Bruner, Tolloczko, 1900). This relationship was demonstrated by comparing the effects of stirring on the dissolution profiles of immediate-release tablets containing distinct strengths of propranolol hydrochloride (BCS I), carbamazepine (BCS II), ranitidine hydrochloride (BCS III), and metronidazole (BCS IV). (Medina-López *et al*., 2020). The time required to dissolve 63.2% of the dose (td), derived from the data fitted to the Weibull function, was inversely related to the augmentation of the medium agitation (50, 75, and 100 rpm). Similar behavior was observed when comparing the dissolution profiles of immediate- and extended-release carbamazepine tablets (Qureshi, 2004).

The choice of a specific rotation partly depends on the drug solubility. For a highly soluble compound, the typical conditions may involve 900 mL of 0.1 N HCl, pH 4.5 or pH 6.8 medium, and paddles at 50 rpm (Bradel, Liang, Hahn, 2015). For tablets sticking to the vessel wall, 75-rpm spindle speed should be tested, whereas 100-rpm should be initially investigated for baskets (FDA, 1997).

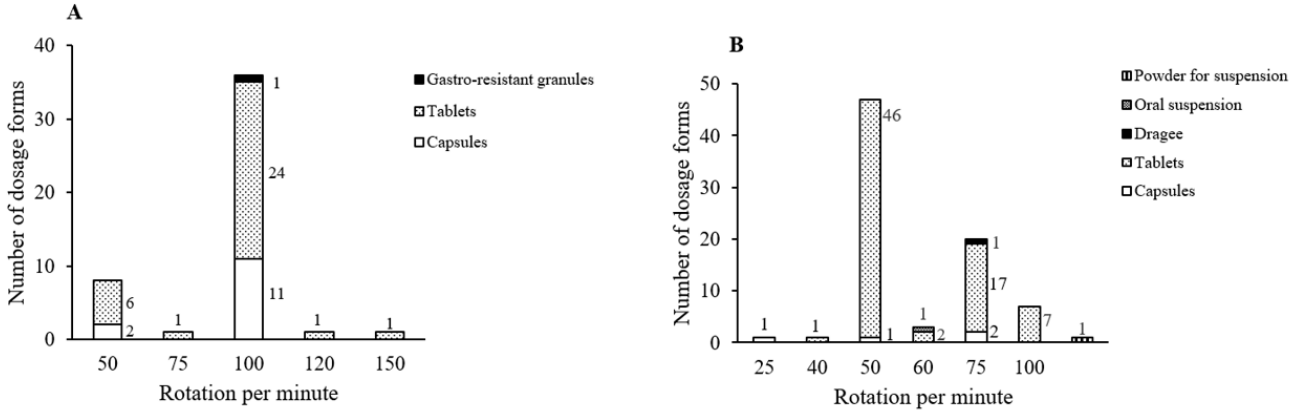

FIGURE 2 - Distribution of the dissolution tests required by the Brazilian Pharmacopeia according to the apparatus, dosage forms, and rotation speed. A: Basket method; B: Paddle method.

Dissolution Media

The composition of the dissolution medium is a critical parameter influencing the quality of the dissolution method. It seeks to discriminate important critical quality attributes and characteristics of drug release from the dosage form, as well as to predict its performance *in vivo* (Dressman *et al.*, 1998).

In the Brazilian Pharmacopeia, different types of media have been described. The deaerated or degassed water has been mentioned in 40 monographs, whereas the hydrochloric acid (0.1 and 0.01 M) is required for 48 products, corresponding to 31.5 and 37.8% of the total number of the dissolution tests, respectively. One should be aware of the lack of water buffering capacity and that the pH value and surface tension can vary according to the water source; therefore, pH monitoring is always recommended in these cases (Shohin *et al.*, 2016),

In five monographs (duloxetine hydrochloride capsules; pantoprazole sodium capsules and gastro-resistant granules; mycophenolate sodium and rabeprazole sodium tablets), the dissolution medium involved acidic and buffered stages.

Dissolution media consisting of buffered solutions were used in 28 monographs, corresponding to 22% of the total number of tests. The most common was the phosphate buffer used in 22 products, and the use of acetate, borate, and Tris buffers were also recommended. Simulated gastric fluid was indicated in four monographs, but the enzyme was required only for ibuprofen and bromazepam tablets.

The pH of the dissolution medium for the 29 products was mostly adjusted within the physiological range of 2–7.5, mainly at pH 6.8. For nalidixic acid tablets, the recommended pH of the dissolution media was 8.6, for rabeprazole sodium and phenytoin tablets was 9.0. The non-physiological pH value of the dissolution media for the nalidixic acid tablets was able to discriminate the dissolution profiles of distinct lots of formulations and also provided linear *in vitro-in vivo* correlations between the cumulative amount of drug excreted at 24 h by healthy volunteers and the log of the amount dissolved at 30 min, and between the log of the cumulative amount excreted up to 24 h and the log of the amount dissolved at 45 min., respectively (Jung, Gonzales, Rodrigues, 1993). The pH of 9.0, which is required for rabeprazole, can be justified by the higher stability of the drug under alkaline conditions, as previously demonstrated (Garcia et al., 2006), whereas for phenytoin, this pH is due to the low solubility of the drug at pH < 8.4, which is its pKa. At lower pH values, it was not possible to discriminate the dissolution profiles of distinct formulations, as clearly demonstrated by Chiang and Wong (2013) via physiologically based pharmacokinetic modeling and pre-clinical studies.

Regarding the media volume, it varied between 500 and 1000 mL, but the most common was 900 mL, corresponding to 82% of the total. The solubility and the dose strength should be taken into account when selecting the volume of the dissolution media, which should be able to guarantee the sink condition. For most drugs, this condition is achieved when a volume of 900 mL (Bredael, Liang, Hahn, 2015).

The use of surfactants in dissolution media is one of the main methods to increase the aqueous solubility of insoluble or poorly soluble drugs (Amidon *et al.*, 1995). This prevents agglomeration and nucleation of the drug and reduces the recrystallization rate in the dissolution medium (Kim *et al.*, 2011). Three types of surfactants were employed in 13 monographs: sodium lauryl sulfate (SLS; 0.5–3%, *w/v*), polysorbate 80 (0.005–2%, *w/v*), and cetrimonium bromide (6%, *w/v*).

SLS is an anionic surfactant with a hydrophilic–lipophilic balance (HLB) of 40 (Wade, Weller, 1994). It was used as additive in the dissolution media of the following drugs: carbamazepine, efavirenz, flutamide, mebendazole, praziquantel, ritonavir, and simvastatin. Except for simvastatin, all of these were weak bases. The non-ionic surfactant, Polysorbate 80 with an HBL value of 15 (Wade, Weller, 1994) was used for the products levonorgestrel + ethinyl estradiol (Tablets and Dragee) and nimesulide (tablets). In contrast, cetrimonium bromide, a hydrophobic cationic surfactant with an HLB of 7.3 (Federation International Pharmaceutique, 2012) was indicated for nitazoxanide capsules.

Of the eleven drugs requiring the use of surfactants, 10 were Class 2 according to the Biopharmaceutical Classification System (Samineni, Chimakurthy, Konidala, 2022). Therefore, these drugs have low solubility and high

permeability, which justify the use of such additives in dissolution media, as they enhance solubility by reducing the surface tension of the medium, increasing the wetting of the drug, and by micellar solubilization (Cherkashina *et al*., 2020). It can be speculated that basic drugs dissociate into a cationic form before solubilization into micelles formed by the anionic surfactant SLS (Park, Choi, 2006). Conversely, nitazoxanide is acidic due to the presence of a nitro moiety, justifying the use of cationic cetrimonium bromide (Valladares-Méndez *et al.*, 2016).

The USP database recommends more diverse and physiologically similar dissolution media, such as simulated fluid (90 monographs) and intestinal fluid (31 monographs). The use of pepsin was mandatory for nine monographs, all of them capsules dosage forms, (cyclophosphamide, doxepin hydrochloride, duloxetine delayed-release, dutasteride + tamsulosin hydrochloride, imipramine hydrochloride, isotretinoin, loratadine, and metyrosine). For tacrolimus capsules the hydroxypropylcellulose was used as an additive. For orlistat capsules, is recommend to add two drops of n-octanol into the dissolution medium. The use of distinct buffers is required throughout the USP database as elicited herein: phosphate buffers are cited in 308 monographs, acetate buffer is required in 31 methods, borate in 3 cases, 20 methods have described the use of citrate buffer, 9 media compositions including tris-buffer, phthalate buffer was cited in 6 methods, and ascorbate was mentioned in 1 method. However, water or HCl 0.1 N are by far the most common medium employed in the USP database (43.28% of the methods).

Sampling Time Points

One key parameter scored by the Brazilian Pharmacopeia in the dissolution tests was the collection time at which aliquots were taken to quantify the drug in the dissolution media.

For very rapid dissolution rate drugs, the dosage form should release 85% of the active substance in 15 min, whereas for rapid dissolution drugs, 85% of the active substance should be released within 30 min (ANVISA, 2010). The sampling time points among the monographs listed in the Brazilian Pharmacopeia varied from 15 to 180 min. The shortest time points were required for the monographs of cimetidine and mycophenolate mofetil tablets. For both, the acceptance criteria were 75 and 80% of the dose within 15 min, respectively; therefore, both did not have a very fast dissolution rate. Diltiazem hydrochloride tablets required the longest collection time (180 min).

The most common collection times were 30 and 45 min, listed in 30 and 39% of the total monographs, respectively. In eight monographs, the tests required two collection times for products with modified-release dosage forms or drugs with very low dissolution rates, such as diltiazem hydrochloride, carbamazepine, nitrofurantoin, and ritonavir.

In the USP database, there are time points ranging from 5 min (rizatriptan benzoate orally disintegrating tablets) to 24 h for extended-release tablets, such as pentoxifylline, and up to 168 h for clonidine transdermal systems. The most frequent collection time points were 30, 45, and 60 min with 412, 251, and 117 methods, respectively. For 509 methods, more than one collection time was required.

Tolerance (*Q*)

Acceptance criteria for the dissolution tests listed in the Brazilian Pharmacopeia varied from not more than 10% to not less than 85% of the dose. The first criterion is required during the acidic stage of products designed for intestinal drug release. The most common minimum values of tolerance were 75 and 85% of the labeled amount, representing 40 and 42.5% of the monographs, respectively. In addition, 10 monographs described more than one tolerance limit for the amount of dissolved drug.

Quantification Methods

Quantification methods are used to measure the percentage of the drug dissolved in the dissolution medium after a certain period of sample collection. For the monographs listed in the Brazilian Pharmacopeia, two major methods were used: spectrophotometry (85 monographs) and high-performance liquid chromatography (40 monographs). Fluorometric

and titrimetric methods are recommended for the quantification of digoxin and ascorbic acid.

CONCLUSION

Among the distinct and important tests and assay procedures described in the Brazilian Pharmacopeia, this review focused on the dissolution tests.

This article summarizes all dissolution tests in a simple and objective manner, with detailed descriptions of various parameters, such as the drug, pharmaceutical dosage form, dissolution medium, apparatus, rotation speed, sampling time, acceptance criteria, and quantitative procedures.

In this review, we found that the predominant apparatuses for tablets and capsules were paddles and baskets at rotation speeds of 50 and 100 rpm, respectively. Water or hydrochloric acid was used as the main dissolution medium. The most common sampling time and acceptance criterion were 45 min and 75–85%, respectively. However, configurations for transdermal devices and extended-release formulations are still lacking.

Harmonization of pharmacopeial tests is essential for the global pharmaceutical market, and efforts are being made to achieve interchangeability among the dissolution methods described in different regulatory compendiums. This review can aid in the development and validation of new tests and facilitate their comparison with the dissolution tests described in the Brazilian Pharmacopeia.

Lack of harmonization between FB6 and the most relevant official compendiums worldwide, such as the British, European, and American pharmacopeias, limits the international trade of Brazilian pharmaceutical products, as pharmaceutical products must comply with distinct regulatory quality tests worldwide. Moreover, new drugs approved abroad may require a long time for commercialization in Brazil, with the need for additional tests affecting the final cost. This may also impact the efforts of Brazilian pharmaceutical companies that are attempting to reach international markets.

Monographs in pharmacopeias can be used as relevant reference materials and starting points for new studies. Future studies should focus on the specific characteristics of analyzed drugs for effective results.

FUNDING

Nathalia Maria Guedes was supported by the Foundation for the Support of Science and Technology of the State of Pernambuco (FACEPE). All opinions, interpretations, conclusions, and recommendations are those of the author and not necessarily endorsed by the funding agency.

This article was partially supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, Brazil; finance code: 001), National Council for Scientific and Technological Development (CNPq; grant: 305133/2021-7), and Fundação de Amparo a Pesquisa de Minas Gerais (FAPEMIG; grant: APQ-0855-19).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

Amidon GL, Lennernäs H, Shah VP, Crison JR. A Theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12(3):413–20.

ANVISA, Farmacopeia Brasileira. 6th ed., vol. 1 & 2. 2019, Ministério da Saúde.

ANVISA, Resolução RDC Nº 31, de 11 de Agosto de 2010. 2010, Ministério da Saúde: Brasília.

Bredael GM, Liang S, Hahn D. A strategy for quality control dissolution method development for immediate-release solid oral dosage forms. Dissolution Technol. 2015;22(3):10–16.

Bruner L, Tolloczko S. Uber die Auflosungsgeschwindigkeit Fester Korper. Z Phys Chem. 1900;35(1):283–290.

Brunner E. Reaktionsgeschwindigkeit in heterogenen systemen. Z Phys Chem. 1904;47:56-102.

Cherkashina K, Voznesenskiy M, Osmolovskaya O, Vakh C, Bulatov A. Effect of surfactant coating of Fe_3O_4 nanoparticles on magnetic dispersive micro-solid phase extraction of tetracyclines from human serum. Talanta. 2020;214: 120861.

Chiang PC, Wong H. Incorporation of physiologically based pharmacokinetic modeling in the evaluation of solubility

requirements for the salt selection process: A case study using phenytoin. AAPS J. 2013;15(4):1109–18.

Dokoumetzidis A, Macheras P. A century of dissolution research: From Noyes and Whitney to the biopharmaceutics classification system. Int J Pharm. 2006;321(1-2):1-11.

Dressman JB, Amidon GL, Reppas C, Shah VP. Dissolution testing as a prognostic tool for oral drug absorption: Immediate release dosage forms. Pharm Res. 1998;15(1):11-22.

EMA, ICH guideline Q4B annex 7 (R2) to note for evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on dissolution test – general chapter, I.C.o. Harmonization, Editor. 2010, EMEA: London.

FDA. Dissolution Testing of Immediate Release Solid Oral Dosage Forms; Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), U.S. Government Printing Office: Washington, DC, 1997.

Federation International Pharmaceutique (FIP). Biowaver monographs 2004-2012. 2012. Available from: https://www.fip.org/file/1377. Date of access: July 10th, 2023.

Garcia CV, Paim CS, Steppe M, Schapoval EES. Development and validation of a dissolution test for rabeprazole sodium in coated tablets. J Pharm Biomed Anal. 2006;41(3):833–7.

Jung H, Gonzalez H, Rodriguez JM. Bioequivalence study of nalidixic acid tablets: In vitro–in vivo correlation. Biopharm Drug Dispos. 1993;14(5):381–8.

Kim MS, Kim JS, Park HJ, Cho WK, Cha KH, Hwang SJ. Enhanced bioavailability of sirolimus via preparation of solid dispersion nanoparticles using a supercritical antisolvent process. Int J Nanomed. 2011;6:2297–3009.

Manadas R, Pina ME, Veiga F. Dissolution studies in vitro as a prognostic tool for oral absorption of modified release pharmaceutical dosage forms. Rev Bras Ciênc Farm. 2002;38(4):375–99.

Medina-López R, Arregui EE, Aranda EJ, Moreno-Rocha LA, Hurtado M, Jung-Cook H, et al. Logic of selecting suitable dissolution parameters in drug formulations based on a BCS approach. Iran J Pharm Res. 2020;19(1):465–86.

Mohite RN, Kapse V, Shinde M, Gore A. A systemic and complete review on dissolution test apparatus. IJSREM. 2022;6(5):1–8.

Morihara M, Aoyagi N, Kaniwa N, Katori N, Kojim S. Hydrodynamic flows around tablets in different pharmacopeial dissolution tests. Drug Develop Ind Pharm. 2002;28(6):655–62.

Nernst W. Theorie der Reaktionsgeschwindigkeit in heterogenen systemen. Z Phys Chem. 1904;47:52–5.

Noyes AA, Whitney WR. The rate of solution of solid substances in their own solutions. J Am Chem Soc. 1897;19(12):930–4.

Park, SH, Choi, HK. The effects of surfactants on the dissolution profiles of poorly water-soluble acidic drugs. Int J Pharm. 2006;321(1-2):35–41.

Qureshi SA. Choice of rotation speed (rpm) for bio-relevant drug dissolution testing using a crescent-shaped spindle. Eur J Pharm Sci. 2004;23(3):271–5.

Samineni R, Chimakurthy J, Konidala S. Emerging Role of Biopharmaceutical Classification and Biopharmaceutical Drug Disposition System in Dosage form Development: A Systematic Review. Turk. J. Pharm. Sci., 2022. 19(6): 706-713.

Shohin IE, Grebenkin DYu, Malashenko EA, Stanishevskii YaM, Ramenskaya GV. A brief review of the FDA dissolution methods database. Dissolution Technol. 2016;23(3):6–10.

Siepmann J, Siepmann, F. Mathematical modeling of drug dissolution. Int J Pharm. 2013;453(1):12–24.

The United States Pharmacopeial Convention. USP Dissolution Methods Database. The United States Pharmacopeial Convention, Maryland. 2023. Available at https://www.usp.org/resources/dissolution-methods-database. Date of access: October 25th, 2023.

Valladares-Méndez A, García-Flores M, Navarrete-Vázquez G, Orozco-Castellanos LM, Hernandez-Nuñez E, Rivera-Leyva JC. Physicochemical characterization of two new nitazoxanide analogs with antiparasitic activity. Med Chem Res. 2016;26:9–18.

Wade A, Weller PJ. Handbook of Pharmaceutical Excipients. 2nd ed. 1994. Washington London: American Pharmaceutical association; The Pharmaceutical Press.

Received for publication on 24th August 2023
Accepted for publication on 03rd March 2024