dx.doi.org/10.14227/DT220415P38

Comparison of Dissolution Profiles of Commercially Available Lamivudine Tablets

Naile Ozturk[1,2], Mustafa Sinan Kaynak[1], and Selma Sahin[2,*]
[1]*Faculty of Pharmacy, Department of Pharmaceutical Technology, Inonu University, 44280 Malatya, Turkey*
[2]*Faculty of Pharmacy, Department of Pharmaceutical Technology, Hacettepe University, 06100 Ankara, Turkey*
e-mail: sahin.selma@gmail.com

ABSTRACT

The aim of this study was to investigate the influence of dissolution medium on the in vitro release of lamivudine (100 mg) from four commercially available lamivudine tablets (one reference and three generic). Three different buffer solutions (pH 1.2, 4.5, 6.8) and deaerated water were used as the dissolution media (900 mL), and the paddle rotation speed was kept at 50 rpm with twelve replicates. An RP–HPLC method was developed for analysis of lamivudine in samples obtained from dissolution studies. The mobile phase consisted of acetonitrile/water (10:90) pH adjusted to pH 2.5 with o-phosphoric acid, a C_{18} column (Ace 250 × 4.60 mm, 5 µm) was used, and the flow rate was set at 1 mL/min. All the drugs tested were very rapidly dissolving (more than 85% of the labeled amount in 15 min), and the dissolution profiles of the generic tablets were thus considered similar to that of the reference tablet in each of the buffers at pH 1.2, 4.5, and 6.8, and deaerated water. Because of the dissolution results and the high solubility and borderline permeability, a biowaiver can be proposed for lamivudine immediate-release solid oral dosage forms provided that the excipient composition of the test product is the same as or similar to that of the reference product and the excipients that have an effect on bioavailability are qualitatively and quantitatively the same as that of the reference product.

KEYWORDS: Lamivudine; dissolution profile; biowaiver; dissolution.

INTRODUCTION

The dissolution test measures the time required for a given drug in an oral solid dosage form to go into solution under specified conditions (*1*). For an immediate-release (IR) solid dosage form (e.g., tablets, capsules), in vitro dissolution tests are used to (1) determine the batch-to-batch quality of a drug product, (2) guide the development of new formulation, (3) ensure continuing product quality, and (4) support the bioavailability of a new product and the bioequivalence of a generic product (*2, 3*).

The Biopharmaceutics Classification System (BCS) was developed by Amidon et al. (*4*) to classify drug substances according to their aqueous solubility and intestinal permeability. In 2000, FDA published a guidance for industry (*5*) stating that demonstration of in vivo bioavailability or bioequivalence may not be necessary for highly soluble and highly permeable Class I substances in IR solid oral dosage forms that exhibit rapid in vitro dissolution. Also, if the drug substance exhibits high solubility and limited absorption, the EMEA guideline (*3*) allows BCS biowaivers for Class III substances in IR drug products in addition to BCS Class I biowaivers. Although it is not a regulatory organization, the World Health Organization (WHO) suggested that BCS-based biowaivers can be considered for Class I–III drug products under certain conditions. WHO collated a draft proposal (*6*) to waive in vivo bioequivalence requirements for the WHO Model List of Essential Medicines IR, solid oral dosage forms.

Lamivudine, a nucleoside reverse transcriptase inhibitor, is used in combination with other antiretroviral agents to treat human immunodeficiency virus Type 1 (HIV-1) infection in patients with acquired immunodeficiency syndrome (AIDS) and as monotherapy in the treatment of hepatitis B virus infection (*7*). There are conflicting reports regarding the BCS classification of lamivudine. It is classified as both BCS Class I (*6*) and BCS Class III (*8*). Because of its high solubility (300 mg dissolved in less than 75 mL of solution at pH 1–7.5) and borderline permeability (82–88% bioavailability in adults), lamivudine is classified as BCS Class III by Strauch et al. (*7*). According to the Biopharmaceutics Drug Disposition Classification System that categorizes drugs by their extent of metabolism and solubility, lamivudine is classified as Class III compound (*9*). Lamivudine drug products fulfill the criterion of very rapidly dissolving (more than 85% of the labeled amount of the drug dissolved within 15 min in each required medium). Based on solubility, permeability, and dissolution results, the authors concluded that a biowaiver for lamivudine is acceptable under certain conditions (*7*). Furthermore, lamivudine is listed in the WHO Model List

*Corresponding author.

of Essential Medicines (*6*) and is suggested as eligible for BCS-based biowaiver.

Lamivudine was originally formulated as tablets in three strengths (100, 150, and 300 mg). In the Turkish drug market, both original tablets (100 and 150 mg) and several generic formulations (100 and 150 mg) are commercially available. The main objective of this study was to investigate the influence of dissolution medium on the in vitro release of lamivudine (100 mg) from four commercially available lamivudine tablet formulations (one reference and three generic). The dissolution profiles of test and reference tablets were compared according to the dissolution criteria for biowaivers based on the BCS. In addition, a reversed-phase HPLC method was developed and validated for precise and accurate measurement of lamivudine in the samples.

MATERIALS AND METHODS

Chemicals

Lamivudine was received as a gift sample from Sanovel-Turkey. Hydrochloric acid, glacial acetic acid, potassium dihydrogen phosphate, sodium hydroxide, sodium acetate trihydrate, and potassium chloride were all analytical grade, and acetonitrile was HPLC grade. Lamivudine reference (Batch No: UC2760, UE0279) and test (Test A: Batch No. 12M443721; Test B: Batch No. 13114002; Test C: Batch No. 3KJ0003B and 3KJ0004A) 100-mg tablets were obtained from a local community pharmacy.

Dissolution Media and Test Apparatus

Dissolution studies on the test and reference tablets were conducted using a Pharmatest DT-70 USP Apparatus 2 (paddle method) with twelve replicates at 37 ± 0.5 °C. Three different buffer solutions (pH 1.2, 4.5, 6.8) and deaerated water (*10*) were used as the dissolution media (900 mL), and the paddle rotation speed was kept at 50 rpm. In all experiments, 2-mL samples were withdrawn at predetermined time intervals (5, 10, 15, 20, 25, 30, 40, 50, and 60 min) and replaced with an equal volume of fresh medium to maintain a constant total volume. After filtration, the concentrations of lamivudine in samples were determined by a validated HPLC method.

Chromatographic Conditions

Analyses were performed on a Thermo Finnigan Surveyor HPLC system (LC pump, autosampler, UV–vis detector). A C_{18} column (ACE 250 × 4.60 mm, 5-µm) was used, and the mobile phase consisted of acetonitrile and water (10:90 v/v) adjusted to pH 2.5 with o-phosphoric acid. Analyses were run at a flow rate of 1.0 mL/min, and the UV detector was set at 270 nm. The injection volume was 10 µL, and the total run time for an assay was 10 min.

Standard Solution Preparation

Separate calibration curves were constructed for all dissolution media (pH 1.2, 4.5, 6.8, and deaerated water). Stock solutions in each dissolution medium were prepared by transferring 30 mg of accurately weighed lamivudine to separate 50-mL volumetric flasks and bringing each to volume with one of the four dissolution media. From the main stock solutions, secondary stock solutions with concentrations of 10 and 100 µg/mL were freshly prepared every week. The standard solutions were prepared daily by further diluting the secondary stock solutions with mobile phase to 1 mL. Concentrations of the standard solutions used for calibration were in the range of 1–60 µg/mL.

Analytical Method Development and Validation

The determination of lamivudine from dissolution samples was carried out under the chromatographic conditions given above. During method development, different mobile phase combinations were tested, and calibration studies were conducted daily. The developed method was validated for linearity, accuracy, precision, range, and specificity parameters. Linearity of the calibration curves was obtained for each dissolution medium, and the linearity of the method was determined at seven different concentration levels (1–60 µg/mL) by performing six independent repetitions. Accuracy of the method was demonstrated by intra- and inter-day recovery studies. For this purpose, known amounts of lamivudine were added to lamivudine tablet dissolution samples and determined by the developed method. Precision of the method was determined from the results of three independent determinations of lamivudine at three different concentrations (5, 20, and 40 µg/mL) on three different days. Precision was assessed by calculating the relative standard deviation (RSD) of the measurements. To show the specificity of the method, chromatograms of pure lamivudine standard solutions and lamivudine tablet dissolution samples were compared.

RESULTS AND DISCUSSION

Method Development and Validation

Various mobile phase compositions have been reported (*11–15*) for the determination of lamivudine by HPLC. In our study, mixtures of acetonitrile and water in different ratios were tested, and the combination that gave the most favorable retention time was selected. To obtain the optimum chromatographic peak area and retention time, the selected mobile phase combination was tested at different pH values (2.5–5.5). Based on the results, a mixture of acetonitrile/water (10:90) at pH 2.5 was selected as the mobile phase. A flow rate of 1.0 mL/min,

Table 1. Linearity Data in Different Media (n = 6)

	pH 1.2	pH 4.5	pH 6.8	Deaerated Water
Regression equation[a]	$y = 26755x + 10877$	$y = 24415x + 15131$	$y = 26187x + 1358.5$	$y = 26803x - 571.5$
Standard error of slope	349.34	522.60	90.12	133.46
Standard error of intercept	5488.14	1497.59	3774.6	788.71
Determination coefficient (r^2)	0.9995	0.9995	0.9998	1.0000
Linearity range (µg/mL)	1–60	1–60	1–60	1–60
Number of data points	7	7	7	7
LOD (µg/mL)	0.4	0.5	0.5	0.5
LOQ (µg/mL)	1.0	1.0	1.0	1.0

[a] *y = peak area, x = concentration (µg/mL)*

Table 2. Accuracy and Precision Data (n = 3)

Dissolution Medium	Added Amount of Lamivudine (µg/mL)	Intra-day			Inter-day		
		Found[a] (µg/mL)	Accuracy[a] Recovery (%)	Precision[b] (% RSD)	Found[a] (µg/mL)	Accuracy[a] Recovery (%)	Precision[b] (% RSD)
pH 1.2 buffer	5	4.88 ± 0.03	97.5 ± 0.57	0.59	5.01 ± 0.14	100 ± 2.76	2.76
	20	20.1 ± 0.07	100 ± 0.33	0.33	19.9 ± 0.34	99.5 ± 1.70	1.70
	40	40.0 ± 0.03	99.9 ± 0.07	0.07	40.0 ± 0.15	100 ± 0.39	0.39
pH 4.5 buffer	5	4.82 ± 0.03	96.4 ± 0.53	0.54	4.94 ± 0.09	98.7 ± 1.90	1.92
	20	20.2 ± 0.03	101 ± 0.14	0.14	20.1 ± 0.05	101 ± 0.27	0.27
	40	39.9 ± 0.02	99.8 ± 0.05	0.04	40.0 ± 0.14	100 ± 0.36	0.36
pH 6.8 buffer	5	5.17 ± 0.01	103 ± 0.26	0.26	5.21 ± 0.04	104 ± 0.75	0.72
	20	19.8 ± 0.13	98.8 ± 0.67	0.67	20.0 ± 0.40	100 ± 1.99	1.99
	40	40.1 ± 0.07	100 ± 0.17	0.17	40.0 ± 0.20	99.9 ± 0.51	0.51
Deaerated Water	5	4.83 ± 0.01	96.7 ± 0.23	0.29	4.83 ± 0.06	96.5 ± 1.10	1.14
	20	20.4 ± 0.04	102 ± 0.18	0.18	20.3 ± 0.08	102 ± 0.42	0.41
		39.8 ± 0.02	99.6 ± 0.05	0.05	39.9 ± 0.04	99.7± 0.10	0.1

[a] *Mean ± standard deviation*
[b] *Relative standard deviation*

an injection volume of 10 µL, and a detection wavelength of 270 nm were the most suitable conditions for analysis of lamivudine. System suitability tests such as column efficiency (theoretical plates) and peak tailing were estimated from the chromatograms. The peak tailing (1.05) and column efficiency (N = 3821) values show that the method is suitable for the determination of lamivudine. The method was validated according to ICH guidelines (*16*). Validation results demonstrate that the method is linear in the concentration range of 1–60 µg/mL for all dissolution media (Table 1). The values obtained for relative standard deviation (RSD) and recovery of intra- and inter-day studies indicate that the precision and accuracy of the method are satisfactory (Table 2). The chromatograms obtained from standard solutions were identical to those obtained from the tablet dissolution samples containing an equivalent concentration of lamivudine. The representative chromatograms (Figure 1) show that there is no interference from excipient peaks at the retention time of lamivudine and retention times did not change. Based on these results, the proposed method is considered selective.

Dissolution Studies

A BCS-based biowaiver is applicable for an IR drug product of both Class I (FDA, EMEA) and Class III (EMEA) compounds (*3, 4*). For Class I (high solubility and high permeability/complete absorption) drugs, drug products must show either very rapid (>85% within 15 min) or similarly rapid (85% within 30 min) in vitro dissolution characteristics for both test and reference products in pH 1.2, pH 4.6, and pH 6.8 dissolution media. For BCS Class

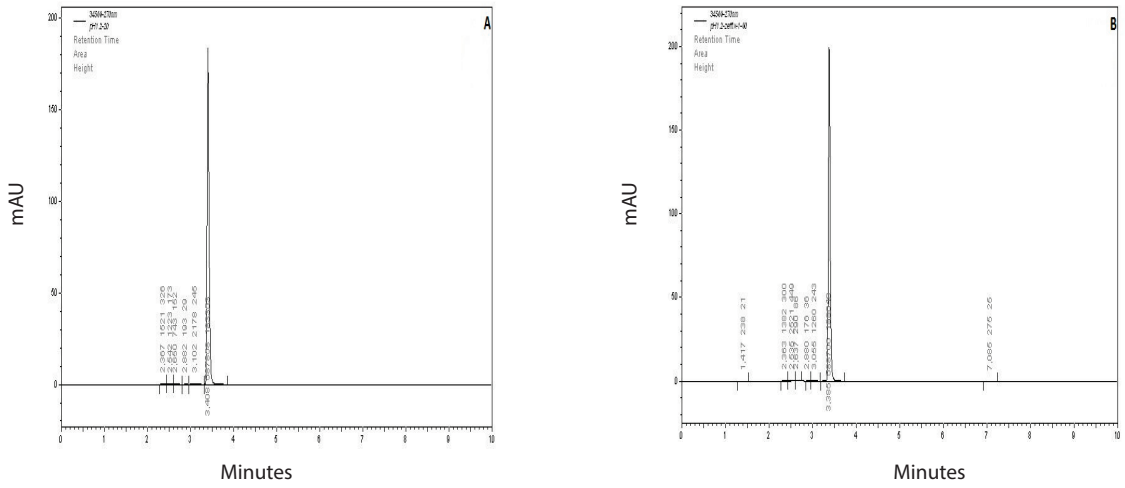

Figure 1. Representative chromatograms obtained from (A) pure lamivudine standard solution and (B) lamivudine containing dissolution sample. Conditions: acetonitrile/water (10:90 v: v, pH 2.5), 1 mL/min flow rate, UV detection at 270 nm.

III drugs (high solubility and low permeability/limited absorption), the drug product must show very rapid (>85% within 15 min) in vitro dissolution for both test and reference in three dissolution media (pH 1.2, 4.5, 6.8).

According to the guidelines, if more than 85% of the labeled amount of drug substance in an IR drug product is dissolved within 30 min, dissolution profiles of test and reference products should be compared by a similarity factor (f_2). The similarity factor is a logarithmic reciprocal square-root transformation of the sum-of-squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. Two dissolution profiles are considered similar if the f_2 value is ≥50. However, when 85% or more of the labeled amount of both test and reference drug products dissolves in ≤15 min using the recommended dissolution media (pH 1.2, pH 4.6, and pH 6.8), dissolution profiles are considered similar without any mathematical calculation (*3, 5*).

In the present study, dissolution was performed on four commercially available lamivudine tablets (one reference and three generic) available in the Turkish drug market. The dissolution profiles of the reference and test drug products of lamivudine (100 mg) are shown in Figure 2. The dissolution of lamivudine from the tablets was pH independent, and more than 85% of the labeled amount dissolved within 15 min in the three dissolution media (pH 1.2, 4.5, and 6.8 media) and in deaerated water. Therefore, a mathematical comparison of the dissolution profiles of lamivudine obtained in pH 1.2, 4.5, 6.8 buffers and deaerated water was not necessary. Based on these results, all the drugs tested are very rapidly dissolving (more than 85% of the labeled amount in 15 min) and dissolution profiles of the generic tablets are considered similar to that of the reference tablet in each of the buffers and deaerated water.

Excipients may have a significant effect on the bioavailability of compounds. It is reported (*17–23*) that commonly used excipients have no significant effect on bioavailability, but excipients such as surfactants, mannitol, polymers, and cyclodextrins have an effect on bioavailability. According to the guidelines, excipients that might affect bioavailability must be qualitatively and quantitatively the same, and other excipients must be qualitatively the same and quantitatively very similar for both BCS Class I and III (*3, 5*) for a BCS-based biowaiver. If the excipients may have an effect on gastrointestinal transit time (e.g., mannitol, sorbitol), absorption (e.g., surfactants), in vivo solubility (e.g., co-solvents), or in vivo stability of the active substance, an in vivo bioequivalence study should be conducted unless the differences in the amounts of these excipients can be adequately justified. For lamivudine, it was reported (*7*) that the excipients (e.g., microcrystalline cellulose, sodium starch glycolate, magnesium stearate) present in lamivudine IR solid oral dosage forms with a marketing authorization in various countries (i.e., EU countries, the United States) seem to be safe and not significantly affect lamivudine absorption when present in amounts typical for IR tablets.

According to the FDA database (*10*), there are two different dissolution methods for lamivudine tablets of different strengths. For 100- and 150-mg lamivudine tablets, dissolution testing should be carried out in a paddle apparatus at 50 rpm using 900 mL of deaerated water. On the other hand, for 300-mg lamivudine tablets,

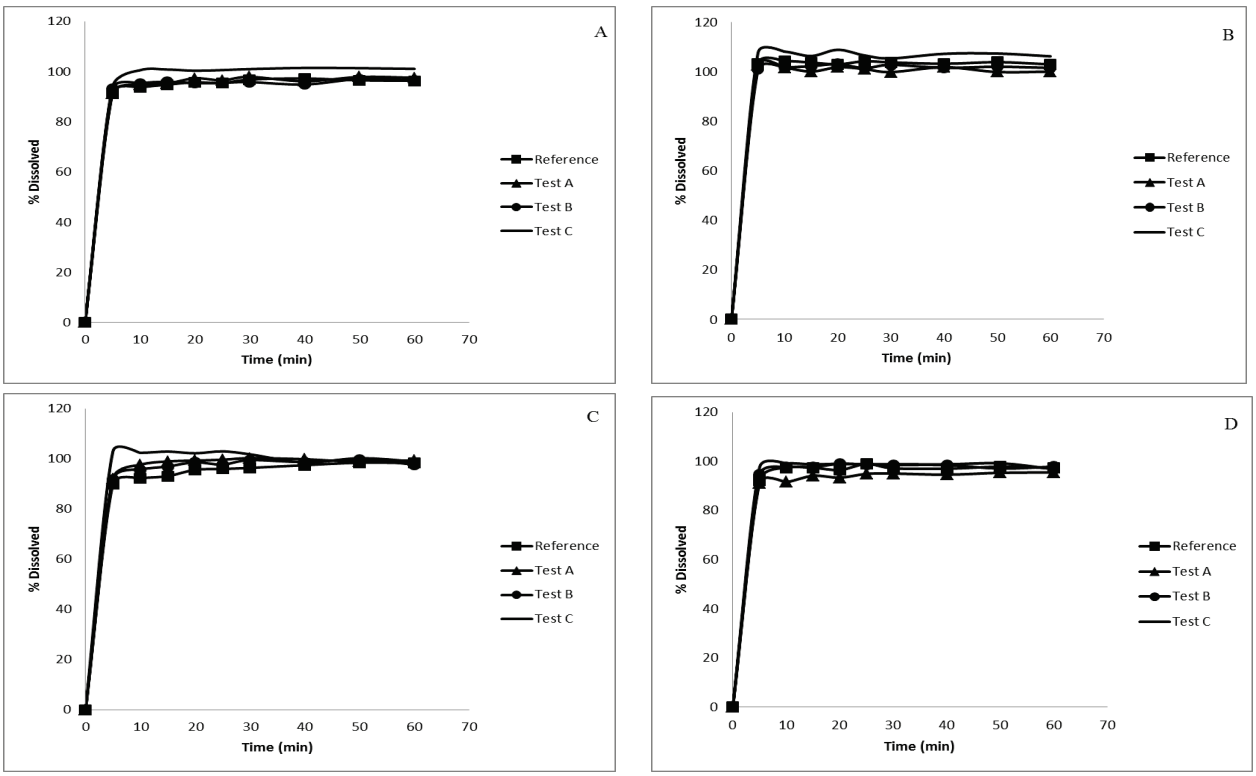

Figure 2. Dissolution profiles of test and reference products in (A) pH 1.2, (B) pH 4.5, (C) pH 6.8 buffer, and (D) deaerated water.

dissolution studies should be carried out in a paddle apparatus at 75 rpm using 900 mL of 0.1 N HCl. Dissolution studies of three different lamivudine tablets (150 mg) were performed according to WHO (*7*) in a paddle apparatus at 75 rpm using three different dissolution media (pH 1.2, 4.5, 6.8). In this study, we examined the dissolution behavior of lamivudine from 100-mg tablet dosage forms (one branded and three generics) in 900 mL of the media deaerated water and pH 1.2, 4.5, and 6.8 buffers with a paddle apparatus at 50 rpm. Although we performed dissolution studies for a different strength (100 mg) using a different rotational speed (50 rpm), the results obtained from pH 1.2, 4.5, and 6.8 dissolution media were similar to those of Strauch et al. (*7*). In addition, all lamivudine tablets were very rapidly dissolving in deaerated water.

CONCLUSIONS

The validation procedure is an integral part of analytical method development. Therefore, the method was validated according to the guidelines. A simple, fast, and reliable HPLC method was developed in the present study. The method showed good performance with respect to linearity, accuracy, precision, and selectivity, and hence, it is suitable for dissolution studies.

All the tested formulations are very rapidly dissolving (more than 85% of the labeled amount in 15 min), and the dissolution profiles of the generic tablets are similar to those of the reference tablet in each of the buffers at pH 1.2, 4.5, and 6.8 and in deaerated water. This, in combination with high solubility and borderline permeability, can justify a biowaiver for lamivudine provided that excipient composition of the test product is the same as or similar to that of the reference product and excipients that have an effect on bioavailability are qualitatively and quantitatively the same as those in the reference product.

CONFLICT OF INTEREST

No conflict of interest has been declared by the authors.

REFERENCES

1. Sayar, E.; Şahin, S.; Cevheroğlu, Ş.; Hincal, A. A. Comparison of Dissolution Profiles of Two Commercially Available Co-Trimoxazole Tablets. *FABAD J. Pharm. Sci.* **2008**, *33*, 87–94.
2. *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.
3. *Guideline on the Investigation of Bioequivalence*; CPMP/EWP/QWP/1401/98 Rev. 1; Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency: London, 2010.

4. Amidon, G. L.; Lennernäs, H.; Shah, V. P.; Crison, J. R. 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), 413–420. DOI:10.1023/A:1016212804288.
5. *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*; 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, 2000.
6. *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate release, solid oral dosage forms*; Working document QAS/04.109/Rev 1; World Health Organization: Geneva, 2006.
7. Strauch, S.; Jantratid, E.; Dressman, J. B.; Junginger, H. E.; Kopp, S.; Midha, K. K.; Shah, V. P.; Stavchansky, S.; Barends, D. M. J. Biowaiver monographs for immediate release solid oral dosage forms: Lamivudine. *J. Pharm. Sci.* **2011**, *100* (6), 2054–2063. DOI:10.1002/jps.22449.
8. Kasim, N. A.; Whitehouse, M.; Ramachandran, C.; Bermejo, M.; Lennernäs, H.; Hussain, A. S.; Junginger, H. E.; Stavchansky, S. A.; Midha, K. K.; Shah, V. P.; Amidon, G. L. Molecular Properties of WHO Essential Drugs and Provisional Biopharmaceutical Classification. *Mol. Pharmaceutics* **2004**, *1* (1), 85–96. DOI:10.1021/mp034006h.
9. Benet, L. Z.; Broccatelli, F.; Oprea, T. I. BDDCS Applied to Over 900 Drugs. *AAPS J.* **2011**, *13* (4), 519–547. DOI:10.1208/s12248-011-9290-9.
10. Dissolution Methods Database. U.S. Food and Drug Administration Web site.
11. Sarkar, M.; Khandavilli, S.; Panchagnula, R. Development and validation of RP–HPLC and ultraviolet spectrophotometric methods of analysis for the quantitative estimation of antiretroviral drugs in pharmaceutical dosage forms. *J. Chromatogr. B* **2006**, *830* (2), 349–354. DOI:10.1016/j.jchromb.2005.11.014.
12. Notari, S.; Bocedi, A.; Ippolito, G.; Narciso, P.; Pucillo, L. P.; Tossini, G.; Donnorso, R. P.; Gasparrini, F.; Ascenzi, P. Simultaneous determination of 16 anti-HIV drugs in human plasma by high-performance liquid chromatography. *J. Chromatogr. B* **2006**, *831* (1–2), 258–266. DOI:10.1016/j.jchromb.2005.12.016.
13. Anandakumar, K.; Abirami, G.; Murugan, S.; Ashok, B. RP–HPLC method for simultaneous estimation of lamivudine, tenofovir, disoproxil fumarate and efavirenz in tablet formulation. *J. Anal. Chem.* **2013**, *68* (9), 815–821. DOI: 10.1134/S1061934813090025.
14. Anbazhagan, S.; Indumathy, N.; Shanmugapandiyan, P.; Sridhar, S. K. Simultaneous quantification of stavudine, lamivudine and nevirapine by UV spectroscopy, reverse phase HPLC and HPTLC in tablets. *J. Pharm. Biomed. Anal.* **2005**, *39* (3–4), 801–804. DOI: 10.1016/j.jpba.2005.04.044.
15. Kapoor, N.; Khandavilli, S.; Panchagnula, R. Simultaneous determination of lamivudine and stavudine in antiretroviral fixed dose combinations by first derivative spectrophotometry and high performance liquid chromatography. *J. Pharm. Biomed. Anal.* **2006**, *41* (3), 761–765. DOI: 10.1016/j.jpba.2006.01.007.
16. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *Validation of Analytical Procedures: Text and Methodology, Q2(R1)*; ICH Harmonised Tripartite Guideline: Geneva, Switzerland, 2005.
17. Takizawa, Y.; Kishimoto, H.; Nakagawa, M.; Sakamoto, N.; Tobe, Y.; Furuya, T.; Tomita, M.; Hayashi, M. Effects of pharmaceutical excipients on membrane permeability in rat small intestine. *Int. J. Pharm.* **2013**, *453* (2), 363–370. DOI: 10.1016/j.ijpharm.2013.05.055.
18. Rege, B. D.; Yu, L. X.; Hussain, A. S.; Polli, J. E. Effect of Common Excipients on Caco-2 Transport of Low-Permeability Drugs. *J. Pharm. Sci.* **2001**, *90* (11), 1776–1786. DOI: 10.1002/jps.1127.
19. Panakanti, R.; Narang, A. S. Impact of Excipient Interactions on Drug Bioavailability from Solid Dosage Forms. *Pharm. Res.* **2012**, *29* (10), 2639–2659.DOI: 10.1007/s11095-012-0767-8.
20. Rege, B. D.; Kao, J. P. Y.; Polli, J. E. Effects of nonionic surfactants on membrane transporters in Caco-2 cell monolayers. *Eur. J. Pharm. Sci.* **2002**, *16* (4–5), 237–246. DOI: 10.1016/S0928-0987(02)00055-6.
21. Goole, J.; Lindley, D. J.; Roth, W.; Carl, S. M.; Amighi, K.; Kauffmann, J.-M.; Knipp, G. T. The effects of excipients on transporter mediated absorption. *Int. J. Pharm.* **2010**, *393* (1–2), 17–31. DOI: 10.1016/j.ijpharm.2010.04.019.
22. Cornaire, G.; Woodley, J.; Hermann, P.; Cloarec, A.; Arellano, C.; Houin, G. Impact of excipients on the absorption of P-glycoprotein substrates in vitro and in vivo. *Int. J. Pharm.* **2004**, *278* (1), 119–131. DOI: 10.1016/j.ijpharm.2004.03.001.
23. Schulze, J. D. R.; Peters, E. E.; Vickers, A. W.; Staton, J. S.; Coffin, M. D.; Parsons, G. E.; Basit, A. W. Excipient effects on gastrointestinal transit and drug absorption in beagle dogs. *Int. J. Pharm.* **2005**, *300* (1–2), 67–75. DOI: 10.1016/j.ijpharm.2005.05.004.