

In Vitro Comparative Quality Evaluation of Non-Expired and 10 Years-Expired Lamotrigine Immediate-Release Tablet Formulations – Pilot Study

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ABSTRACT

This study aimed to compare the different physical parameters and dissolution profiles of 10 years-expired with non-expired lamotrigine (LTG) immediate-release tablet formulations. Dissolution tests were conducted using a validated high-performance liquid chromatography method. Dissolution characteristics of the tablet formulations were evaluated at three points spanning the physiological pH range (pH 1.2, pH 4.5, pH 6.8). Physical characteristics of LTG tablets were determined according to the *European Pharmacopoeia*. The dissolution profile comparison was carried out using model-independent (statistical) and model-dependent (kinetic) methods to provide detailed information about dissolution data. The t-test was applied to investigate differences between expired and non-expired tablets, and the differences were considered statistically significant if $p \leq 0.05$. The results demonstrated no statistical differences in physical characteristics between expired and non-expired tablets; however, there were differences in the dissolution profiles, which could cause different pharmacokinetic profiles. The results of this investigation showed that the drug content did not change significantly. Therefore, the lower dissolution rate for expired LTG tablets is due to an interaction of LTG with one or more excipients in the tablet formulation during aging.

KEYWORDS: Lamotrigine, expiration, dissolution, quality, interaction

INTRODUCTION

Drug stability is a quality control attribute for pharmaceutical dosage forms that describes the ability of the drug to maintain the physical, chemical, therapeutic, and microbial properties during the time of storage (1). The expiration date specifies the time period during which the product is known to remain stable, which means the manufacturer guarantees the drug retains its quality and purity when it is stored according to its labeled storage conditions (2). The United States Food and Drug Administration (US FDA) requires stability data from pharmaceutical companies submitting new drug applications to establish shelf-life specifications (1). Stability studies are designed to provide confidence that the product will meet the applicable requirements for quality, safety, and efficacy throughout the shelf-life (1). The FDA verifies that an applicant's proposed expiration date is supported by appropriate studies conducted by the applicant.

Expired pharmaceutical products have not necessarily lost potency, because the expiration date is only an assurance

that the labeled potency will last at least until that time. Most pharmaceutical products continue to be effective and safe for a time after the expiration date (3–6).

Many studies have shown that most active pharmaceutical ingredients (APIs) retain their pharmacological potency far beyond the expiration date. A study conducted by the US FDA evaluated over 100 pharmaceutical dosage forms and showed that about 90% of them were safe and effective as long as 15 years past their expiration dates (5). Another other study had similar results, showing that many drugs stored under reasonable conditions retain 90% of their potency for at least 5 years after the expiration date on the label and sometimes much longer (3). Also, it is determined that four products, namely captopril tablets, flucloxacillin capsules, cefoxitin injection, and theophylline tablets, when stored under ambient temperatures maintained at least 98% of label claim for drug content for 18–170 months past the labeled expiration dates (6).

Consequently, the FDA and the United States

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Pharmacopeia (USP) in cooperation with pharmaceutical industry recommended to determine the benefits and risks associated with lengthening expiration dates and to subsequently conduct longer stability testing. The initial expiration date is based on the amount of real-time stability data for the pharmaceutical product available at the time of approval of the FDA. This initial date can be extended contingent upon the receipt of acceptable supporting data from the manufacturer based on accelerated stability studies. Generally, the marketed pharmaceutical products have a labeled shelf life of 12–60 months.

Regarding the expired medications, most studies have focused on degradation of active pharmaceuticals, so the knowledge of the pharmaceutical performance is limited. There are not many studies on the pharmaceutical quality of expired products; only a few studies have addressed the long-term stability of pharmaceutical dosage forms.

Lamotrigine (LTG) is indicated in the treatment of different types of epilepsy and in bipolar disorder, effective as an add-on therapy in the management of simple and complex partial seizures and secondarily generalized tonic-clonic seizures resistant to multiple-drug therapy (7).

LTG is in class II according to the Biopharmaceutical Classification System (BCS), a lipophilic, weak base poorly soluble in water with a log octanol/water partition coefficient of 1.19 at pH 7.6 (8). However, its poor aqueous solubility (0.17 mg/mL) confines its absorption and dissolution rate and hence delay onset of action (9). In general, dissolution of BCS class II drugs is dependent on a wide variety of physiological factors like pH, ionic strength, and buffer capacity, which are three major characteristics of the gastrointestinal (GI) fluids that can affect the rate of drug release (9). Thus, drug dissolution may be the rate-limiting step for drug absorption, and an in vivo-in vitro correlation may be expected. The FDA guidelines recommend analysis of dissolution profiles of BCS class II drugs in multiple dissolution media with a pH range 1.2 to 6.8 (1). Factors that influence drug dissolution from tablet forms, albeit physicochemical properties of the active ingredients, are the nature and quantity of excipients and their interactions, compression pressure, speed of compressions, condition of storage, and age of the tablet (10–12).

The ability of a drug to have an extended shelf life would be dependent upon the actual drug ingredients, presence of excipients, and storage conditions. For drugs of BCS class 2, a two-point dissolution specification, one at 15

minutes to include a dissolution range and the other at a later point (30, 45, or 60 minutes) to ensure 85% dissolution, is recommended to characterize the quality of the product. The pH of the GI tract influences the dissolution rate of a drug (13). Weakly basic BCS class II drugs such as LTG tend to have a slower dissolution rate at the higher pH of GI fluid during transition from the stomach to the intestine (14–16).

The aim of this pilot study is to determine the quality of LTG immediate-release tablets 10 years after the expiration date with those that are not expired. The tablets were subjected to various post-production tests such as determination of hardness, weight, friability, disintegration time, content determination, and dissolution testing.

MATERIALS AND METHODS

Two tablets containing LTG were tested: tablet A (reference, non-expired tablets), which was commercially available and randomly chosen, and tablet B (test, expired tablets), which was produced by the same manufacturer but 10 years past the expiration date and returned to the local pharmacy by the patient. The labeled amount of drug substance was 100 mg per tablet.

Chemicals and Reagents

LTG (99% purity) standard was provided by Alakloid (Skopje, Macedonia) and chloramphenicol from Galenika (Belgrade, Serbia). Acetonitrile and methanol were high-performance liquid chromatography (HPLC) grade and obtained from CarloErba (Milano, Italy). Orthophosphoric acid 85% (Lanchema a.s., Czech Republic) and potassium dihydrogen phosphate (POCH, Poland) were analytical reagent grade.

Excipients added in formulation of these tablets were lactose monohydrate, microcrystalline cellulose, povidone K30, sodium starch glycolate (type A), iron oxide yellow (E172), and magnesium stearate.

High-Performance Liquid Chromatography (HPLC) analyses

The HPLC system (Agilent Technology Series 1100, Wilmington, DE, USA) used was equipped with degasser, binary pump, automatic injector, and diode array detector (DAD) detector G1315B, with software for data processing (Agilent ChemStation). Chromatographic separation was performed on a C18 guard column (4.6 x 12.5 mm, 5 µm, Zorbax) and C18 analytical column (4.6 x 250 mm, 5 µm, Zorbax). The assay of active substance was performed according to a previously published HPLC method for determination of LTG in dissolution medium and tablet

formulation (17). The mobile phase was a mixture of 0.05 M ammonium dihydrogen phosphate (adjusted pH = 2.68 with 40% ortho-phosphoric acid) and acetonitrile (68:32, v/v). All separations were performed isocratically at a flow rate of 1.2 mL/min, and column temperature was maintained at room temperature (25 °C). For quantitative determination, the peak areas were determined using a calibration curve and external standard (chloramphenicol) with DAD detector set at wavelength 265 nm.

Tablet Quality Characteristics

The quality of LTG tablets was determined according to the 9th *European Pharmacopoeia (EP)* (18). The content uniformity test was performed with 10 tablets from each series that were weighed individually and each of the 10 tablets finely powdered and dissolved in the mobile phase. A standard solution was prepared by dissolving pure LTG in mobile phase. The concentrations of prepared solutions were determined by HPLC method mentioned above. According to the *EP*, content uniformity should be between 85% and 115% of the average content value. Also, 20 tablets were randomly selected from each series and weighed individually and together with an electronic balance for calculation of weight variation. The average weight was noted, and relative standard deviation (RSD) was calculated. The limit of RSD for weight variation in case of tablets of 100 mg mass is $\pm 7.5\%$ (18).

The disintegration test was carried out using the disintegration tester for six tablets. The basket was immersed in a bath of water at 37 °C in a 1-L beaker until the tablet was disintegrated, according to the *EP*. The *EP* does not have a requirement for the hardness of the tablet; however, some researchers state that the crushing force of immediate-release tablets should be between 50–100 N (or 120 N) (19). The hardness test was applied with a hardness tester (Erweka, Heusenstamm, Germany) on 10 tablets for each examined series.

Friability test was performed with 10 tablets from each series, which were weighed and put into the friabilator (Erweka). Tablets were rotated at 25 rpm for 5 minutes six times, and the friability percentage was calculated for each tablet. A maximum weight loss (obtained from a single test or from the mean of three tests) of not more than 1.0% is considered acceptable.

Dissolution Testing

Dissolution profiles were evaluated according to the *United States Pharmacopoeia* (USP paddle method (apparatus 2) (20). The dissolution test was performed on a tablet dissolution tester (CD800, Erweka). The dissolution profile of LTG tablets was evaluated in pH 1.2

hydrochloric acid (HCl) buffer, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer.

Mathematical Models and Statistical Analyses

The t-test was applied to investigate differences between expired and non-expired tablets and the differences were considered statistical if $p \leq 0.05$. The dissolution profile comparison was carried out using model independent statistical, and model dependent methods to evaluate the dissolution data. The model-independent method used the difference (f_1) and similarity factors (f_2), recommended by the FDA Guidance for Industry to compare dissolution profiles of both LTG tablets (2). Generally, f_1 values up to 15 (0–15) and f_2 values greater than 50 (50–100) ensure sameness or equivalence of the two curves of compared products.

The model-dependent method included several kinetic models in which the dissolved amount of drug is a function of time, are used to describe drug dissolution from solid dosage forms (21). The kinetics of the dissolution process were studied through the analysis dissolution data using five kinetic models: first-order, Hixson-Crowell's cube root law, Higuchi's square root equation, Weibull's distribution, and the logistic model (22–26). The best fitting equation uses coefficient of determination (R^2), Akaike information criterion (AIC), and model selection criterion (MSC) (22). The drug release kinetics and mechanism were computed using DDSolver (menu-driven add-in program for Microsoft Excel written in Visual Basic for Applications) (27).

RESULTS AND DISCUSSION

The results of our study are presented in Table 1, including analysis of drug content, physical characteristics (weight, hardness, friability, disintegration time), and estimation of dissolution profiles of non-expired (A) and 10 years-expired (B) LTG tablet formulations. The average weight deviation of 20 tablets taken from each formulation was less than $\pm 3\%$, and all the formulations met the requirement (Table 1).

Table 1. Physical Characteristics of Non-Expired (A) and Expired(B) Lamotrigine Tablets

	Tablet A	Tablet B	p value
Content uniformity (%)	100.02 \pm 7.65	98.72 \pm 5.81	> 0.05
Weight (g)	0.3989 \pm 0.0027	0.3995 \pm 0.0018	> 0.05
Disintegration time (min)	2.21 \pm 0.04	1.76 \pm 0.10	> 0.05
Hardness (kg/mm ²)	8.4 \pm 0.5	7.6 \pm 0.9	> 0.05
Friability (%)	0.572	0.574	> 0.05

Data are expressed as mean \pm SD.

The tested LTG tablets showed no differences in hardness test results. Since tablet hardness is not a perfect index to evaluate the strength of the tablets, friability was also used to test the hardness of tablets. For the both tablet series, friability percentage was less than 1%, which is in the acceptable range (18). Content uniformity test results showed that both LTG tablets fit the criteria of EP and were in accordance with the claimed value (100 mg) by manufacturer. Both LTG tablets contain at least 92.5% and not more than 107.5% of the labeled amount of the active drug.

All analyzed tablets disintegrated in 15 minutes, according to 9th EP test of uncoated tablets (18). A paired t test showed no statistically significant difference of the physical characteristics of expired and non-expired tablet series (Table 1).

Though the physical characteristics of tablets and content could remain the same, aging of tablets could lead to alteration in dissolution profiles and kinetics of release. Thus, the absence of dissolution changes would provide assurance that the bioavailability for therapeutic efficiency remained unchanged 10 years after the expiration date. Significant changes in vitro release could affect therapeutic efficiency and, in the case of LTG, epileptic seizure relapse could occur.

Dissolution profiles of the two examined tablets are showed in Figures 1–3. As expected, the fastest in vitro drug release rate was obtained in more acidic pH, which is a reflection of the highest solubility of the drug in pH 1.2 HCl buffer (Fig. 1). Therefore, in the dissolution medium pH 1.2, tablet A showed almost complete release after 15 min (97%), contrarily the tablets with expired date showed much slower drug release, only 45.07 % at 15 min. The reason for differences in dissolution profile between the investigated tablets could be interaction with excipients. Physical interactions between excipients are very difficult to detect because there are no chemical changes involved (28). One example of a physical interaction is interactive mixing. This is specific for smaller particles of pharmaceuticals that interact with the surface of larger particles of ingredients in the drug formulation, usually excipients (29).

As shown in Figure 2, the rate of LTG tablet B release in acetate buffer (pH 4.5) was after 35 minutes faster than tablet A. For tablet B, 47.43% of drug released within 5 min in acetate buffer, and 65.43% (incompletely dissolved) within the first 15 min. Expired tablets of LTG (B) have faster release in pH 4.5 than pH 1.2.

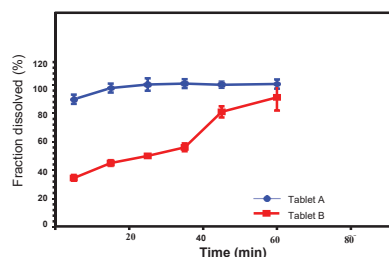


Figure 1. Dissolution profiles of non-expired (tablet A) and 10 years-expired (tablet B) lamotrigine tablets in pH 1.2 dissolution medium.

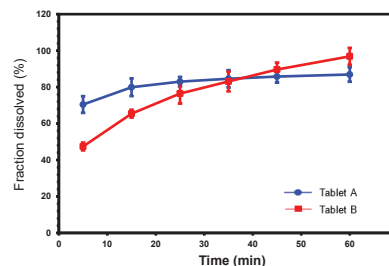


Figure 2. Dissolution profiles of non-expired (tablet A) and 10 years-expired (tablet B) lamotrigine tablets in pH 4.5 dissolution medium.

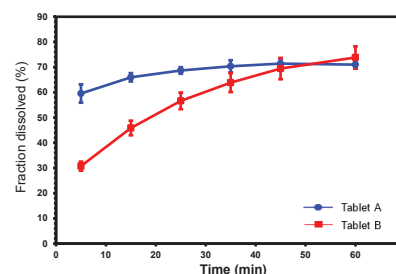


Figure 3. Dissolution profiles of non-expired (tablet A) and 10 years-expired (tablet B) lamotrigine tablets in pH 6.8 dissolution medium.

Magnesium stearate is a common lubricant used for solid pharmaceutical formulations (30). Because of its hydrophobicity, during aging magnesium stearate can also delay tablet dissolution (30–31). The presence of magnesium stearate in a formulation with aging can increase the micro-environmental pH of the formulation, creating an alkaline condition and cause delay of tablet dissolution. Thus, by using this phenomenon when magnesium stearate was added, the tablet tended to float on the surface of pH 1.2 or pH 4.5 dissolution media; however, it dispersed in the pH 6.8 buffer. The slowest rate of release was obtained in pH 6.8 phosphate buffer, which is a consequence of the low solubility in alkaline medium (Fig. 3).

Dissolution from the tablet dosage form involves liberation of the drug from the formulation matrix (disintegration) followed by the dissolution of the drug (solubilization of the drug particles) in the liquid medium. Because the release of LTG from tablets with expired date (B) is slower from the start compared to unexpired tablets (A), the characteristics of the disintegrator could be connected with this delay of release. The ionic nature of the drugs

and superdisintegrants and their potential interactions have been reported to affect dissolution stability (32). Consequently, accelerated release of expired tablets after 35 min of dissolution has been noticed and could be the moment when disintegration of tablets is finished. In the first step of dissolution, the cohesive properties of the formulated drug play a key role. Also, it has been reported that aging decreases the dissolution efficiency of super disintegrants in wet granulated tablets, which confirms the previous theory (33, 34).

In Table 2, results of dissolution profile comparison are shown. The similarity factor (f_2) is more sensitive in finding dissimilarity between dissolution curves than the difference factor (f_1), and the values of fit factors are dependent on the number of sampling time points chosen (35, 36). According to the FDA guidelines, f_1 values up to 15 and f_2 values greater than 50 should ensure equivalence of the dissolution curves, indicating an average difference of no more than 10% at the sample time points. Based on these guidelines, the tablets showed dissolution curve equivalence only in the pH 4.5 acetate buffer medium.

Table 2. Dissolution Data for Calculation of Similarity (f_2) and Difference (f_1) Factors for Expired (B) versus Non-Expired (A) Lamotrigine Tablets

Variable	Dissolution Medium		
	pH 1.2	pH 4.5	pH 6.8
f_1	39.27	12.08	17.76
f_2	18.59	45.55	40.50
5 min	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
10 min	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
15 min	$p < 0.0001$	$p < 0.05$	$p < 0.0001$
30 min	$p < 0.0001$	$p < 0.05$	$p < 0.0001$
45 min	$p < 0.0001$	$p < 0.05$	$p < 0.05$
60 min	$p < 0.05$	$p < 0.05$	$p < 0.05$

Further, it is shown in Table 2 that there are statistically significant differences in dissolution profiles ($p < 0.0001$ and < 0.05) between tablets A and B in multiple dissolution media (pH 1.2, pH 4.5, pH 6.8). To understand the mechanism of drug release, data were fitted to different kinetic models (Table 3). This method presents an acceptable model-based approach in finding the true relationship between percent dissolved and time variables of the two dissolution profiles. Selection of the best and most accurate models should be based on appropriate criteria such as R^2 , AIC, and MSC. The

best-fit model may be considered with lesser AIC and higher MSC and R^2 adjusted values. According to previously established criteria for choosing the best kinetic model, Table 3 clearly depicted that tablet A in the pH 1.2 dissolution medium followed Weibull's model. The correlation coefficient values of the Weibull's model are found to be slightly higher when compared to the first order, logistic, and Korsmeyer-Peppas release models. In the same medium, tablets with expired date (B) followed the Korsmeyer-Peppas model. This model is generally used to analyze the release of pharmaceutical exponents, which indicate the drug release from polymeric dosage forms when the release mechanism is not well known or when more than one type of release phenomena is involved. Also, tablet B had slightly lower correlation coefficient values of the Higuchi's model ($R^2 = 0.9477$, AIC = 41.5736, MSC = 2.0131), which is significantly different than the correlation coefficient values for tablet B ($R^2 = 0.3898$, AIC = 61.7639, MSC = -1.3898).

In the pH 4.5 dissolution medium, the Weibull model was the predominant release mechanism for tablet A, but tablet B predominantly followed the Korsmeyer-Peppas model. Release kinetics of tablet A in pH 6.8 dissolution medium best fit the Korsmeyer-Peppas model, which was the same as tablet B. Consequently, kinetic modeling of the dissolution profiles indicated different models of release for expired and non-expired LTG tablets of the same brand.

CONCLUSIONS

This pilot study found no differences in physical characteristics between expired and non-expired tablets of LTG; however, there were differences in the dissolution profiles. Expired LTG tablets had lower release than non-expired LTG tablets; hence the expired tablets are expected to have lower effectiveness. The dissolution profiles clearly showed that pH plays an important role in the dissolution of aging tablets. Similar content uniformity indicates that no degradation of the active ingredient occurred 10 years after expiration date. The results of this investigation showed that the drug content did not change significantly. Therefore, the lower dissolution rate for expired LTG tablets is due to an interaction of LTG with one or more excipients in the tablet formulation during aging. Significant changes in the in vitro release profiles of a drug product during storage may alter its bioavailability. Further studies are essential to verify the clinical efficiency of expired LTG immediate-release tablet formulations stored under unsuitable conditions.

Table 3. Kinetic Parameters Obtained from Dissolution Data for Non-Expired (A) and 10 Years-Expired (B) Lamotrigine Tablets

Kinetic model	Parameters	pH 1.2		pH 4.5		pH 6.8	
		Tablet A	Tablet B	Tablet A	Tablet B	Tablet A0	Tablet B
First Order	R^2	0.9993	0.8830	0.8046	0.9294	0.3488	0.8763
	k	0.457	0.033	0.194	0.07	0.049	0.031
	AIC	14.2753	47.2158	51.3665	45.0235	57.1357	45.5301
	MSC	5.1089	1.2071	-0.4281	1.3148	-1.6619	0.9299
Hixon Crowel	R^2	0.5413	0.7017	0.5782	0.8744	0.1482	0.8076
	k	0.026	0.009	0.023	0.018	0.012	0.008
	AIC	59.7633	41.4565	56.7531	49.0506	59.0154	48.6222
	MSC	-1.3898	0.8762	-1.1976	0.7395	-1.4262	0.4882
Higuchi	R^2	0.3898	0.9477	0.4735	0.9123	0.4856	0.9613
	k	19.911	11.266	14.15	13.972	11.770	10.515
	AIC	61.7639	41.5736	0.3034	46.5411	55.4856	37.3929
	MSC	-1.6752	2.0131	147.3	1.0980	41	2.0924
Weibull	R^2	0.9997	0.9335	1.0000	0.9939	0.9685	0.9990
	k	1.958	3.562	0.152	0.585	0.135	0.539
	AIC	12.0149	36.4478	-19.7698	31.9003	11.0012	15.4534
	MSC	5.4318	1.7110	9.7342	3.1895	2.7908	5.2266
Logistic	R^2	0.9996	0.8907	0.9999	0.9861	0.9746	0.9966
	k	4.526	2.135	0.972	2.240	0.513	1.749
	AIC	12.2815	48.7384	1.6122	35.6611	9.7165	22.2765
	MSC	5.3937	0.9896	6.6796	2.6523	3.0049	4.2518
Korsmeyer-Peppas	R^2	0.9984	0.9481	0.9961	0.9999	0.9989	0.9980
	k	4.526	11.996	0.972	30.195	53.617	17.944
	AIC	22.2205	43.5307	1.9533	3.4336	14.2339	18.6361
	MSC	3.9739	1.7335	4.8870	7.2562	4.4669	4.7719

R^2 , coefficient of determination; AIC, Akaike's information criterion; MSC, model selection criterion.

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CONFLICT OF INTEREST

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

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