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Article

Statistical process control of manufacturing tablets for antiretroviral therapy

Statistical process control for antiretroviral therapy

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In this study, the manufacturing process of lamivudine (3TC) and zidovudine (AZT) tablets (150 + 300 mg respectively) was evaluated using statistical process control (SPC) tools. These medicines are manufactured by the Fundação para o Remédio Popular "Chopin Tavares de Lima" (FURP) laboratory, and are distributed free of charge to patients infected with HIV by the Ministry of Health DST/AIDS national program. Data of 529 batches manufactured from 2012 to 2015 were collected. The critical quality attributes of weight variation, uniformity of dosage units, and dissolution were evaluated. Process stability was assessed using control charts, and the capability indices Cp, Cpk, Pp, and Ppk (process capability; process capability adjusted for non-centered distribution; potential or global capability of the process; and potential process capability adjusted for non-centered distribution, respectively) were evaluated. 3TC dissolution data from 2013 revealed a non-centered process and lack of consistency compared to the other years, showing Cpk and Ppk lower than 1.0 and the chance of failure of 2,483 in 1,000,000 tablets. Dissolution data from 2015 showed process improvement, revealed by Cpk and Ppk equal to 2.19 and 1.99, respectively. Overall, the control charts and capability indices showed the variability of the process and special causes. Additionally, it was possible to point out the opportunities for process changes, which are fundamental for understanding and supporting a continuous improvement environment.

Keywords: Capability indices. Control charts. HIV treatment. Manufacturing process. Quality tools.

INTRODUCTION

Despite the Brazilian government's efforts to control acquired immunodeficiency syndrome (AIDS), the number of infected patients has increased. Between 1980 and June 2019, 966,058 cases were reported in the country. Although the new HIV infections index has been decreasing in the previous five years, with a national detection rate of 0.18 cases per 1,000 population in 2018 (Brazil, 2019a); globally, this index has remained stable in the same period with nearly 0.23 per 1,000 uninfected population (WHO, 2019).

Fighting HIV requires the combination of at least three antiretrovirals, being two from different classes. The most common antiretroviral therapy is the combination of zidovudine (AZT), a reverse transcriptase inhibitor, and lamivudine (3TC), a nucleic acid synthesis inhibitor. AZT and 3TC are prodrugs and must be metabolized to their triphosphates metabolites for pharmacologic activity (Anderson, Rower, 2010).

3TC and AZT (150 + 300 mg respectively) immediate-release tablets are manufactured using a direct compression method by Fundação para o Remédio Popular "Chopin Tavares de Lima" (FURP)

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in Brazil. The medicines are distributed free of charge through the Health Ministry DST/AIDS program (Brazil, 2019b). One of the features of this therapy is the significant intersubject variability of treatment (Flynn *et al*., 2007). AZT has been associated with hematologic toxicity, including neutropenia and severe anemia, these effects being concentration-dependent. Additionally, the highest prescribed dose should be administered in patients with an average weight above 40 kg, aiming to minimize these adverse effects (Fauchet *et al*., 2013). Thus, the product quality consistency is critical to minimize unacceptable *in vivo* variability and, consequently, therapeutic drug failure.

The current Good Manufacturing Practices (GMP) from the FDA requires statistical process control (SPC) quality tools to measure and analyze variability of the manufacturing process. They are also recommended by other pharmaceutical regulatory guidelines, such as the ICH Pharmaceutical Quality System Q10 guideline (ICH, 2008; FDA, 2011a). The manufacturers must gain enough process knowledge by detecting sources, variability amplitude, and their impact on product quality attributes. This is a paradigm shift in process evaluation towards a rational scientific-based approach, in contrast with the standard practice, which covers a mere comparison of the data collected with the critical quality attributes (CQA) specification (Samohyl, 2009; de Souza Botelho, 2011).

Among the statistical tools, the control charts and the capability indices Cp, Cpk, Pp, and Ppk (process capability; process capability adjusted for non-centered distribution; potential or global capability of the process; and potential process capability adjusted for non-centered distribution, respectively) allow evaluating the process consistency. It is considered stable if only common causes of variation are present, revealed by the control charts (Dudek-Burlikowska, 2005; Kotz, Johnson, 2002) in which the values are distributed in random order. In contrast, when special causes of variation are present (non-random distribution), the process is considered unpredictable. The process capability indices measure the ability to manufacture products that meet specifications. These indices are a ratio of variability and the CQA specification, and they can be applied to estimate the probability of producing out-of-specification (OOS) products. The capability indices Cp and Cpk calculation requires normally distributed data and a stable (stochastic) variation. These tools can be introduced at any time in the product's lifecycle, following a quality by design (QbD) approach, and may support continued process verification and annual product quality review (FDAa, 2011; FDAb, 2011).

To the best of our knowledge, this study shows an unprecedented effort to evaluate five years production of 3TC and AZT industrial batches. The present study aimed to provide insights into tablet manufacturing process variability by retrospective data analysis of 529 batches manufactured by FURP between 2012 and 2015. For this purpose, the following CQA were evaluated: weight variation, uniformity of dosage units, and dissolution.

MATERIAL AND METHODS

Material

FURP kindly provided the retrospective data of 529 batches of 3TC and AZT tablets manufactured between 2012 and 2015. Weight variation, uniformity of dosage units, and dissolution were the CQA selected. Table I shows the number of batches by year.

TABLE I - 3TC and AZT tablet batches manufactured between 2012 and 2015, by year

Lamivudine + zidovudine (150 + 300 mg)	
Year	**Nº batches**
2012	249
2013	88
2014	110
2015	82
Total	**529**

Methods

FURP performed the manufacturing process, and all CQA quality control testing and the methods are summarized below:

3TC and AZT tablets (150 + 300 mg respectively) manufacturing process

The direct compression process was used to manufacture the tablets. The drug substances and excipients were previously sieved, transferred to a 200.0 kg capacity V-blender (Treu® São Paulo), with later blend homogenization for 15 minutes at 13 rpm cycles. Magnesium stearate was also sieved and added to the other components of the formulation in the V-blender and mixed for an additional five minutes. The powder blend was manually transferred to the gravity feeder, and compression was performed in a 25-station rotary tableting machine, model N25 (Neuberger® São Paulo). The speed was 35,000 tablets/hour. After the end of the compression, the tablet cores were transferred to a coating pan machine (150.0 kg) (Lawes Cota 150® São Paulo). An aqueous suspension sprayed the cores for film coating. The parameters used on coating step were: spray gun nozzle of 1.2 mm diameter, a gun-to-bed distance of 25 cm, atomizing air pressure of 36 psi, 8 rpm pan coating rotation speed, 65 ºC inlet air temperature, 45 to 48 ºC tablet bed temperature, and coating time between 45 and 60 minutes.

Critical Quality Attributes (CQA)

Weight variation. The weight variation of 3TC and AZT tablets was performed according to the Brazilian Pharmacopoeia 5th ed. chapter 5 (general methods) (ANVISA, 2010). Briefly, a total of 20 tablets per batch were weighted using a digital balance (Mettler Toledo® Model AL204). The criteria are met when no more than two tablets differ from the mean by ±5 %, and no unit differs in weight more than ±10 % of the mean.

Uniformity of dosage units. The uniformity of dosage units of 3TC and AZT tablets was accessed according to the Brazilian Pharmacopoeia 5th ed. chapter 5 (general methods) (ANVISA, 2010). Briefly, for each batch, ten tablets were weighed individually (Mettler Toledo® Model AL204). The results were expressed as the amount of drug per tablet. The acceptance value (AV) was calculated using the equation: $AV = (M - X) + ks$, where M is the reference batch, X is the mean batch for batch assay, k is the acceptability constant, and s is the standard deviation. The specifications were (90-110 %) (ANVISA, 2010). The high performance liquid chromatography (HPLC) method parameters for 3TC and AZT quantification were: HPLC LC-20AT, Shimadzu®, Phenomenex C18 250 x 4.6 mm column, 0.1 M ammonium acetate buffer, methanol and acetic acid (65:35:0.1) mobile phase, 270 nm wavelength.

Dissolution. Dissolution tests of the 3TC and AZT tablets were performed according to the Brazilian Pharmacopoeia 5th ed (ANVISA, 2010). Briefly, the conditions were: USP apparatus 2, 50 rpm, 900 mL, and 37.0 ± 0.5 ˚C purified water, using DTS, and an Ethik Technology® dissolution system. After 60 minutes, 5 mL aliquots of the dissolution medium were withdrawn and diluted with the mobile phase. The quantification was performed as described in the uniformity of dosage units method. The values were expressed as a percentage of the declared drug content. The first stage's tolerance limit is not less than 80 % (Q + 5 %) of 3TC and AZT.

Statistical analysis

Process stability and process capability of the CQA of the 3TC and AZT tablets were performed using control charts and capability indices respectively (Shah, Shridhar, Gohil, 2010; Chatterjee, Chakraborty, 2016). Histogram evaluation, Anderson-Darling (AD), and Kolmogorov-Smirnov (KS) tests were performed to evaluate normal data distribution. Process stability was evaluated using individual observations with moving range charts, the tool stage in temporal sequence, considering one year as a subgroup. These charts are created using the difference of consecutive batches. Process capability was evaluated by the capability charts and the capability indices: Cp, Cpk, Pp, and Ppk (Kashif *et al*., 2017). The capability indices are calculated as follows (Boyles, 1991):

$$Cp = (USL-LSL)/6\sigma$$
$$Cpk = \text{Min } \{(USL-\mu)/3\sigma, (\mu-LSL)/3\sigma\}$$

and

Pp = (USL-LSL)/6s
Cpk = Min {(USL-μ)/3s, (μ-LSL)/3s}

Where USL = upper specification limit, LSL = lower specification limit, μ = mean, σ = within standard deviation, and s = overall standard deviation.

Accordingly, Cp and Cpk express the capacity of a short-term or the real process picture, and Pp and Ppk a long-term or the desired process scenario (Pereira, 2021). The within and global standard deviations were compared to verify the process capability, the sources of variation, and the variation within subgroups (Chatterjee, Chakraborty, 2016; Chopra *et al.*, 2012; Kovářík, Sarga, 2014). Statistical analysis of data was performed using Minitab 18 software (Minitab, State College, PA).

RESULT AND DISCUSSION

Weight variation evaluation

Assumption of data normality

The histogram evaluated the normality of the data. The data distribution in Figure 1 revealed a symmetrical, bell-shaped, and unimodal curve (Gaussian curve). These features and the mean (666.48 mg) close to the median (666.50 mg) suggest data normality. Moreover, the standard deviation can be evaluated to assume a normal distribution. The 68-95-99.7 empiric rule is another method to assess data normality. This study revealed 69.26 % of data within the limits of one standard deviation (σ), 95.46 % within two σ, and 99.73 % within three σ (Chatterjee, Chakraborty, 2016).

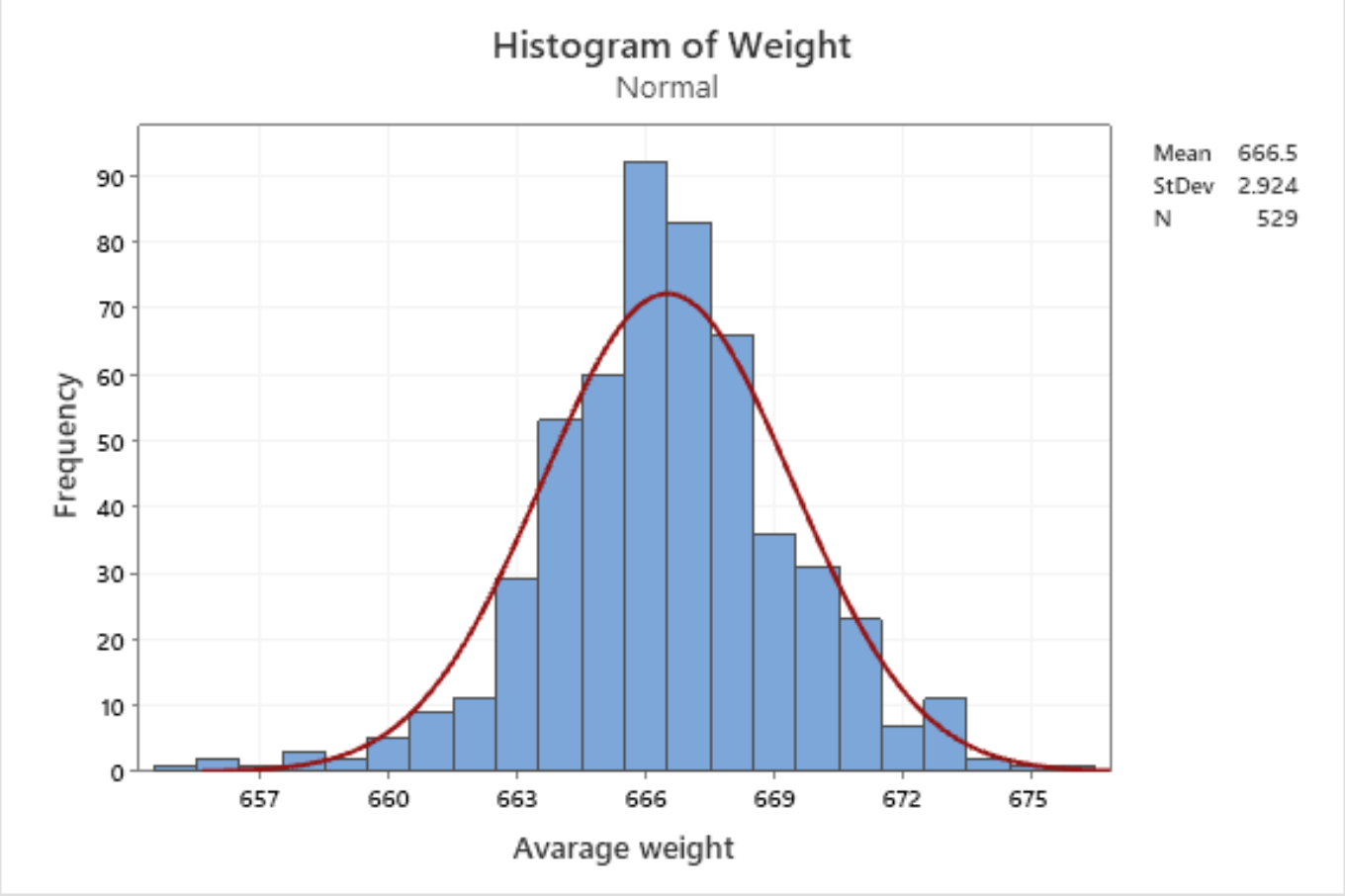

FIGURE 1 - Histogram with the normal curve of the weight variation of 3TC and AZT tablets (150 + 300 mg respectively) manufactured between 2012 and 2015.

The weight variation data by year is described in Table II. The analysis for each year revealed that the values were close to the target (666.5 mg).

TABLE II - Mean, median, and standard deviation of the weight variation from 3TC and AZT tablets (150 + 300 mg respectively) manufactured from 2012 to 2015

	Year	Number of batches	Mean (mg)	Median (mg)	Standard deviation
Target 666.5 mg	2012	249	666.70	667.00	3.12
	2013	88	666.80	667.00	2.78
	2014	110	665.90	666.00	2.51
	2015	82	666.50	666.00	2.99
	Total	529	666.48	666.50	

In addition to the histogram (Figure 1), the normal distribution of the weight variation data was assessed using the AD test (Montgomery, 2015; Anderson, Darling, 1954). In addition, the KS test was also performed, being an alternative normality test. The results of these tests are presented in Figure 2 and Table III. The p-values were below the significance level ($\alpha = 0.05$) for all years and both tests. This implies the rejection of the null hypothesis (H0: the data follow a normal distribution). Consequently, the alternative hypothesis H1 (H1: the data does not follow a normal distribution) was accepted. Therefore this test suggests that the weight variation data does not follow a normal distribution (Montgomery, 2015).

The AD test compares the sum of squares' differences between the empirical data and the hypothetical distribution. AD uses the data without grouping, which means that the test is sensitive to inconsistencies at the distribution tails rather than near the median. Thus, it accentuates the discrepancies in the tails (Anderson, Darling, 1954; Yap, Sim, 2011). Hence, the batches' weight tablet values in the tails significantly influence the assumption of normality (Figure 2). The data normality was assumed despite the AD test result due to histogram evaluation, mean and median comparison, and the standard deviation 68-95-99.7 empiric rule (Figure1).

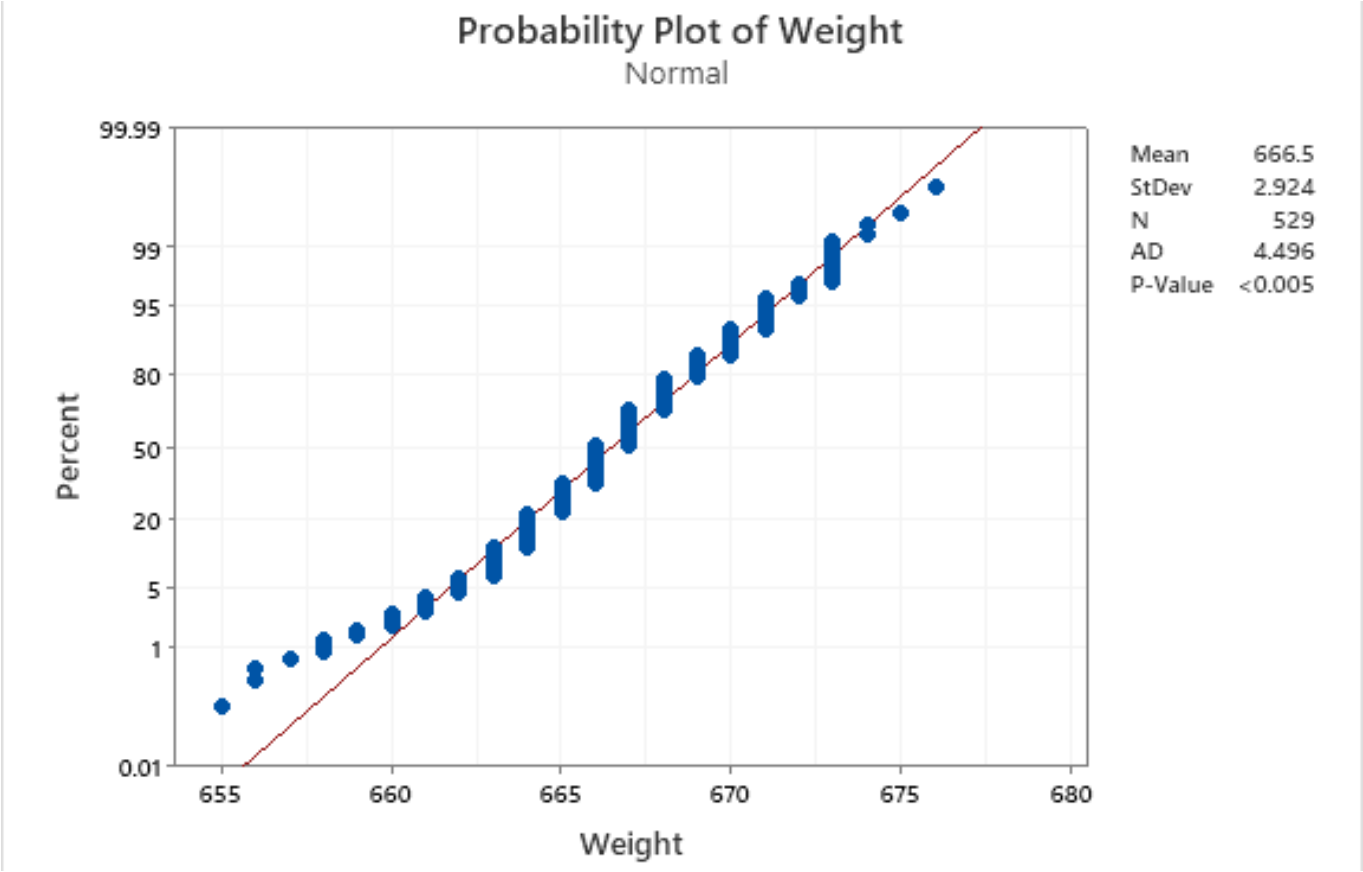

FIGURE 2 - Weight variation normal probability plot of 3TC and AZT tablets (150 + 300 mg respectively) manufactured between 2012 and 2015.

TABLE III - AD and KS normality test p-values of 3TC and AZT tablets (150 + 300 mg respectively) (weight variation data)

	p-values				
	2012	**2013**	**2014**	**2015**	**Overall**
AD	2.659	1.050	0.948	0.854	4.496
p -batch	< 0.005	0.009	0.016	0.027	< 0.005
KS	0.109	0.133	0.093	0.133	0.099
p -batch	< 0.010	< 0.010	0.027	< 0.010	< 0.010

Process stability evaluation

The control chart of weight variation (Figure 3) was performed using the tool stages, which allows the data evaluation in a historical ordered way (by year). Lower (LCL) and upper (UCL) control limits (657.82 and 675.16 mg, respectively) were calculated considering three standard deviation intervals (Figure 3). The Brazilian Pharmacopoeia 5th ed (ANVISA, 2010) sets up the variation limits of ± 5 % for coated tablets weighing more than 300 mg, which means values between 633 and 700 mg. However, in the present study they were 650 and 683 mg (variation ± 2.5 %), respectively. The tight specification is an internal manufacturer procedure implemented to ensure product effectiveness, safety, and quality.

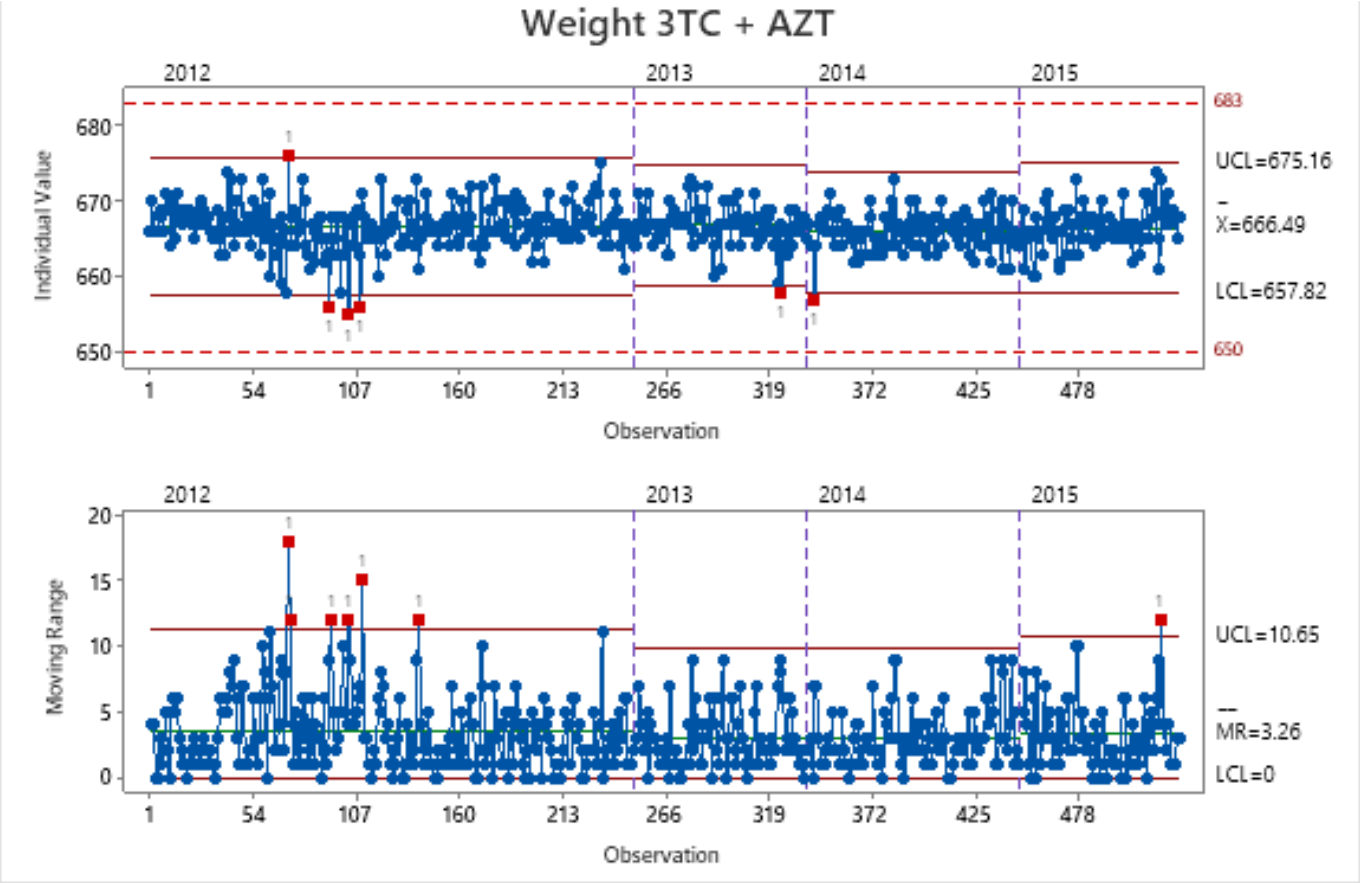

FIGURE 3 - Control chart of individual observations and moving range of weight variation data of 3TC and AZT tablets (150 + 300 mg respectively) manufactured between 2012 and 2015 (n=529).

Six batches were detected out of the control limits (OCL) (individual values chart), known as special causes, being four in 2012, one in 2013, and one in 2014. No OCL was observed in 2015. Five of the six batches were found below the LCL. However, these batches met the internal specification limits. In the moving range chart, the OCL showed high variability between successive batches, mostly in 2012. No OCL was detected in 2013 and 2014, and only one event was detected in 2015 (Figure 3). However, it is essential to point out that the six detected OCL comprises only 1 % of the 529 batches manufactured in the four-year period, which shows the weight variation's practical stability.

A possible explanation for the observed OCL can be related to operator performance and manufacturing issues, including equipment and pharmaceutical inputs. The tablet machine used is hand-fed equipment, making this step a potential source of variability. Moreover, the observed variability might justify the implementation of more advanced technology, for example, a forced feeder machine. Additionally, the detected variability may be due to powder flow characteristics, the components' cohesiveness, and the particles' irregular shape. Thus, forced feeding using suitable blade-containing equipment is recommended. In this case, a 45 degree angle blade can be selected for powders with reduced density for moving the powder downwards. This configuration can improve the matrix's filling for formulations with low powder flow, resulting in standard deviation minimization up to 75 % (Kirsch, 2015).

Process capability evaluation

The process capability indices describe the ability of the process of manufacturing products within the specification limits. These indices are accurate when

the data follows a normal distribution. The indices Cp and Pp do not consider whether the mean is close to the target. Cpk and Ppk are defined as the rate between the unilateral process capability index and the specification limit (upper or lower) closest to the average. Overall, Cp measures the potential capability of the process, while Cpk measures effective capability. The capability indices Cpk and Ppk are calculated with different standard deviations, respectively σ **(**within) and **s** (overall). The σ is used to calculate the control limits and calculate Cp and Cpk, also called short-term process performance indices or potential capability (Chatterjee, Chakraborty, 2016). The ***s*** is used to calculate Pp and Ppk, which are indices of long-term process performance or global capability.

When the values of Cp and Cpk are similar, the process is centralized, which means that the process average is close to the target and under statistical control (only common causes of variability are present). The process is considered capable of manufacturing within specification limits when Cpk > 1.0, being an ideal Cpk ≥ 2.0. When it is between 1.34 and 1.99, the process is considered suitable; values between 1.0 and 1.33 show that the process requires corrective action, and values less than 1.0 denote a non-capable process. If it is equal to 1.0, then 99.73 % of the values lie within the specification limits (Dal Curtivo *et al.*, 2015). Thus, 0.27 % of the units manufactured may be out of specification (example: in 1,000,000 units manufactured, 2,700 units OOS). Figure 4 shows the process capability evaluation for the four years with values of both Pp and Ppk of 1.88 (***s*** = 2.92) and Cp and Cpk of 1.89 and 1.92, respectively (σ = 2.86). This result revealed process centralization and its consistency under the statistical control for this CQA. The process failure probability, in the four years, was two tablets in 100,000,000 manufactured units.

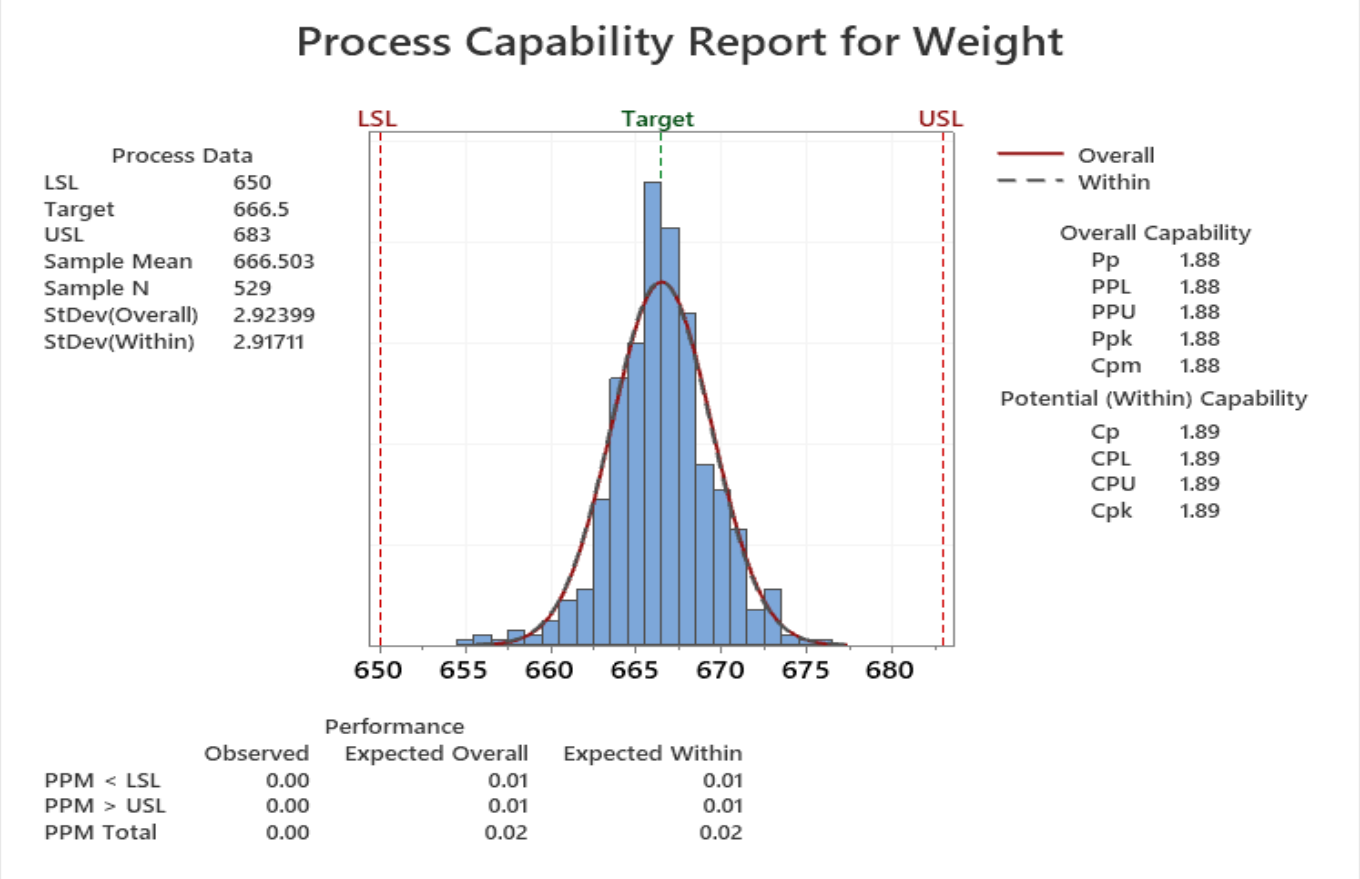

FIGURE 4 - Process capability evaluation for the weight variation of 3TC and AZT tablets (150 + 300 mg respectively) manufactured between 2012 and 2015.

The capability indices were also calculated by year, as shown in Table IV. Cpk ranged from 1.79 to 2.03, and Ppk from 1.75 to 2.11. Standard deviations σ were in the range of 2.65 to 3.04, and 2.51 to 3.12 for ***s***. However, only 2015 showed Cp = Cpk and Pp = Ppk and Cpk = Ppk, showing process consistency. Botelho, R.S. et al. (de Souza Botelho *et al.*, 2011) revealed Cp and Cpk of 1.00 and 0.98, respectively, for the weight variation data of three consecutive batches of furosemide (40 mg) tablets. These values showed a high probability of process failure (2,751 PPM). In this study, the probability of obtaining results outside the specification limits was substantially lower (0.02 PPM).

When the indices were calculated with overall data (no year stage), Cp and Cpk indices were equal, 1.89, and Cpk was almost equal to Ppk (1.89 and 1.88, respectively). This result showed a centralized and under statistical control process. Thus, the analysis by year can expose the opportunities for process improvement. These opportunities are the centralization of the process, special causes investigation, and even technology modernization.

TABLE IV - Weight variation capability indices of 3TC and AZT tablets (150 + 300 mg respectively) manufactured between 2012 and 2015

Indices	2012	2013	2014	2015	Overall
Pp	1.76	1.98	2.19	1.90	1.88
Ppk	1.75	1.94	2.11	1.90	1.88
Cp	1.81	2.08	2.07	1.90	1.89
Cpk	1.79	2.03	2.00	1.90	1.89
Standard Deviation (S)	3.12	2.78	2.51	2.90	2.92
Standard Deviation (σ)	3.04	2.65	2.65	2.89	2.92
Performance PPM	0.13	0.00	0.00	0.01	0.02

Uniformity of dosage units evaluation

Assumption of data normality

Histogram, AD, and KS tests were evaluated as previously described in weight variation analysis (Figure SI and Table SI). Histograms with unimodal distribution and bell-shaped symmetry were observed for both drug substances. The mean and median values were similar, with the maximum difference for 3TC of 0.39 mg, in 2015 (Table SII). The mean and median difference of AZT data was only 0.14 mg in 2012. Reduced values for AZT standard deviations (SD) were detected from 2012 to 2014. In 2015, SD was similar to the two previous years, respectively, 1.94 and 1.96.

In addition to the histogram, the data were evaluated for their distribution using the 2 normality tests (Figure S2 and Table SI). The p-values for both drug substances were lower than the level of significance (α = 0.05), except for AZT in 2014 and 2015. These results indicated that the data do not follow a normal distribution. However, it is possible to observe that the extreme values (from tails) for AZT are closer to the adjusted distribution line (Figure S2). Figures S1, and S2, and Tables SI, and SII can be found in the supplementary material.

Process stability evaluation

Figure 5 shows the control charts for individual observations. The 3TC UCL and LCL were 94.27 and 104.12 % respectively. For AZT, the UCL and LCL were 95.49 and 103.58 %, respectively. For this CQA, the specification limits are 90 and 110 % (ANVISA, 2010).

Ten batches above the UCL (102.94 %) and six below the LCL (96.24 %) were found (Figure 5). In 2012, nine OCL were found, being six above the UCL and three below the LCL. Five OCL batches were observed in 2013, two above the UCL and three below the LCL. In 2014, only two batches were observed below the LCL. In 2015, no OCL was observed. However, all of them are within the specification limits. Figure 5 also shows a lower variability in 2013 when compared with other years.

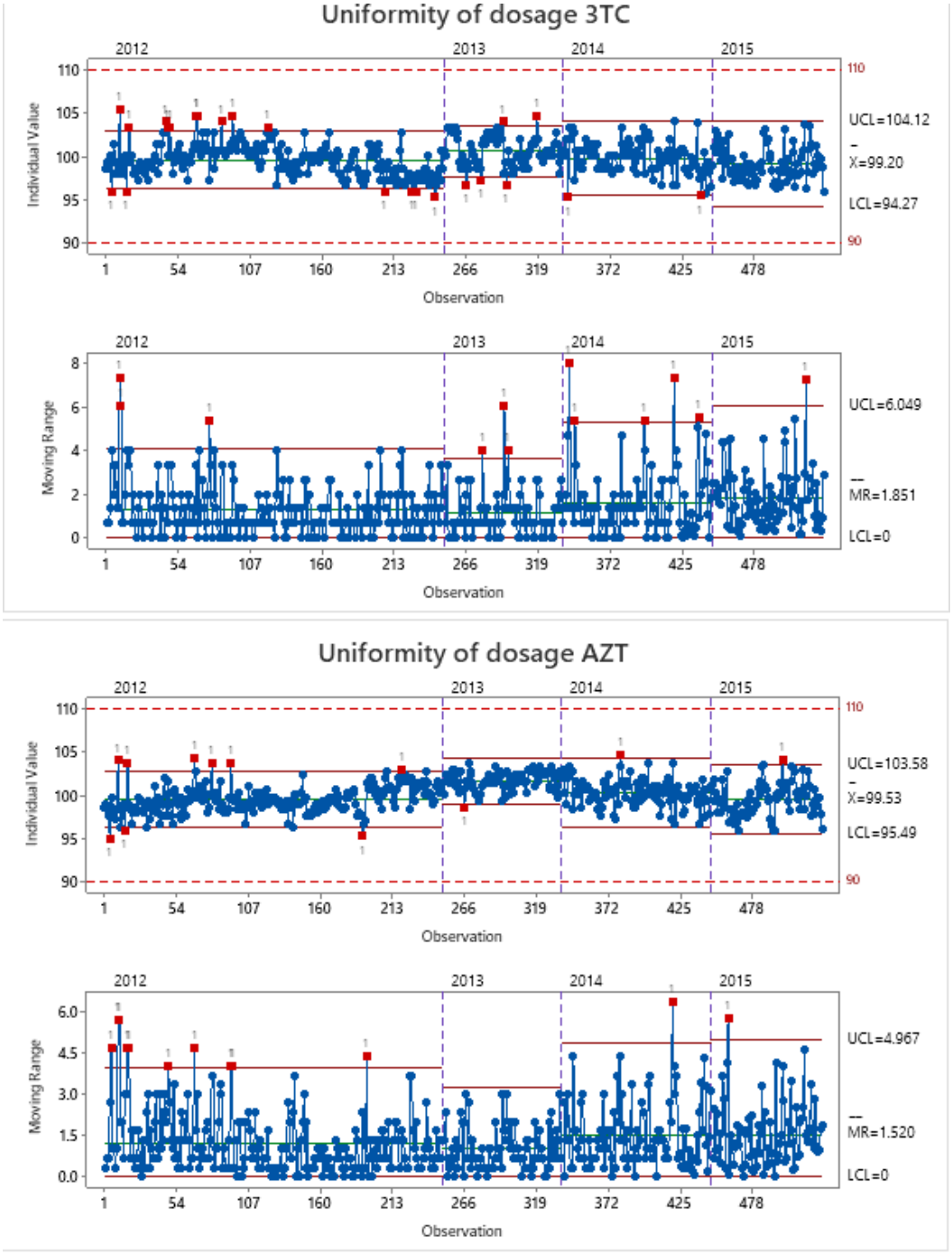

FIGURE 5 - Uniformity of dosage units control charts of 3TC and AZT tablets (150 + 300 mg respectively) manufactured between 2012 and 2015.

The special causes mentioned above could be easily detected using these control charts. Consequently, this tool can be used to support a search for the source of variation and apply corrective actions. Control charts can help in the prevention of non-conforming units when a variability increase trend is found. Thus, this tool can support process variability elimination or its reduction as much as possible (Shah, Shridhar, Gohil, 2010).

Figure 5 shows the moving range (MR). The highest UCL was detected in 2015, with 6.0 and 5.0 % for 3TC and AZT respectively. The most substantial variability in the MR was detected in 2014; batch 419 showed higher values for both drugs, 3TC and AZT, with 6.3 and 7.3 %, respectively. Twenty-three OCL of 3TC make up only 4.3 % of the 526 batches, and for AZT, twelve OCL are only 2.2 % of the total.

Process capability evaluation

Table V shows the process capability indices for uniformity of dosage units. Since 3TC indices are not very close, they revealed the need for process centralization. The minor difference between Cp and Cpk was 0.05 in 2014, and a significant difference was observed in 2013 (0.44). In contrast, the best values for process consistency were observed in 2015, when the difference between Cpk and Ppk was only 0.29. The worst value was found in 2013, with a difference of 1.38. The Cpk and Ppk divergences indicated that the manufacturing process was not operated predictably over time. Considering the worst index (Ppk: 1.58), the probability of process failure was 116 tablets in 100,000,000 units manufactured in 2015 for 3TC.

TABLE V - Process capability indices of uniformity of dosage units of 3TC and AZT tablets (150 + 300 mg respectively) manufactured between 2012 and 2015

Indices	2012		2013		2014		2015		Overall	
	3TC	AZT	3TC	AZT	3TC	AZT	3TC	AZT	3TC	AZT
Pp	1.80	2.15	1.91	3.07	1.88	2.15	1.71	1.69	1.78	1.91
Ppk	1.73	2.04	1.79	2.57	1.84	2.08	1.58	1.62	1.73	1.91
Cp	2.99	3.10	3.38	3.77	2.33	2.53	2.03	2.47	1.82	2.14
Cpk	2.87	2.93	3.17	3.16	2.28	2.45	1.87	2.36	1.77	2.14
St Dev (**S**)	1.85	1.55	1.75	1.08	1.77	1.55	1.94	1.97	1.88	1.74
St Dev (α)	1.11	1.07	0.98	0.88	1.43	1.32	1.64	1.35	1.83	1.56
Performance PPM	0.12	0.00	0.04	0.00	0.02	0.00	1.16	0.68	0.13	0.01

The Cp, Cpk, Pp, and Ppk of AZT (Table V) also revealed the need for process centralization when the process is observed by year. The lowest difference between Cp and Cpk was 0.08 in 2014, while the highest difference was in 2013 (0.61). Considering the lower Ppk (1.62), the probability of failure of the process was 68 tablets in 100,000,000 units manufactured in 2015. Although in 2015, the 3TC Ppk was close to AZT, the probability of failure in the uniformity of the dosage units for 3TC is 1.7 times greater than AZT . Likewise, the Cp and Cpk indices from the uniformity of dosage units of furosemide tablets (40 mg) and captopril (25 mg) also revealed a non-centralized process. Cp and Cpk were 1.43 and 1.27 and 1.69 and 1.83, respectively (de Souza Botelho *et al.*, 2011; Dal Curtivo *et al.*, 2015).

The 3TC and AZT tablets comprise 67.5 % of drug substances (22.5 % of 3TC and 45 % of AZT). Therefore, differences in the powder densities and particle size distribution of drug substances may cause segregation of the powder blend from the feeding to the compression

chamber. This potential failure must be investigated and avoided by controlling the particle size distribution in the blend, flow time evaluation, and morphological analysis of the particles. Crowley (2018) used multivariate models to evaluate the negative impact of non-uniform moisture on compaction performance. Furthermore, the variability between four batches of microcrystalline cellulose prepared from different wood pulp was analyzed, revealing a considerable influence of the excipient's origin on the compaction ability (Crowley, 2018).

Dissolution evaluation

Assumption of data normality

Histogram, AD, and KS tests were evaluated to access data normality as previously described (Figure S3, S4, and Table SIII of the supplementary material). The histogram showed curves with unimodal data distribution and bell-shaped symmetry for both drug substances and cores and coated tablets (Figure S3 and Figure S4). 3TC and AZT dissolution data showed close means and medians for all years (Table SIV). A reduction trend in the standard deviation of 3TC was detected in 2014. Minor values were found in 2015 for both drug substances (2.74 for 3TC and 2.38 for AZT).

Data normality was also evaluated using the AD and KS tests (Figure S5 and Table SIII). The values for both drug substances were lower than the level of significance ($\alpha = 0.05$). These results show that the data do not follow a normal distribution. Similarly, the tablet cores did not show normal data distribution (Figure S6). However, as in earlier evaluations, the data was assumed normally distributed. Figures S3, S4, S5, and Tables SIII and SIV can be found in the supplementary material.

Process stability evaluation

Figure 6a shows the control chart of 3TC. In 2012, five batches presented values below the LCL. No batches were detected above the UCL as expected due to the uniformity of dosage units results. In 2013, higher variability was found compared to other years, with results tending to be lower than the mean, signaled by the LCL below the lower specification limit (LSL). For 2014, two batches were below the LCL and none in 2015. Similar behavior was observed for the 3TC cores (Figure S7).

Figure 6b shows the control chart from 3TC in 2013, with a monthly stage. This chart shows the batches in detail for coated tablets. Between February and November 2013, 88 batches were manufactured. The first 15 batches showed the highest process variability. From batches 16 to 62, 3TC dissolution was close to the target. This means a centralized process with reduced variability. The variability increased from batches 63 to 74, and from batches 75 to 88, the variability decreased.

For the same drug, two batches were found below the LCL in 2014. In 2015, no OCL was found. The LCL and UCL of coated tablets were, respectively, 87.0 % and 103.5 % (2012), 78.1 % and 105.9 % (2013), 87.3 % and 103.6 % (2014), and 88.8 % and 103.8 % (2015). For the tablet cores, these values were very close (LCL= 89.29 % and UCL= 102.3 %) (Figure S7). These values, except the UCL in 2013, are within the limit of specification (ANVISA, 2010).

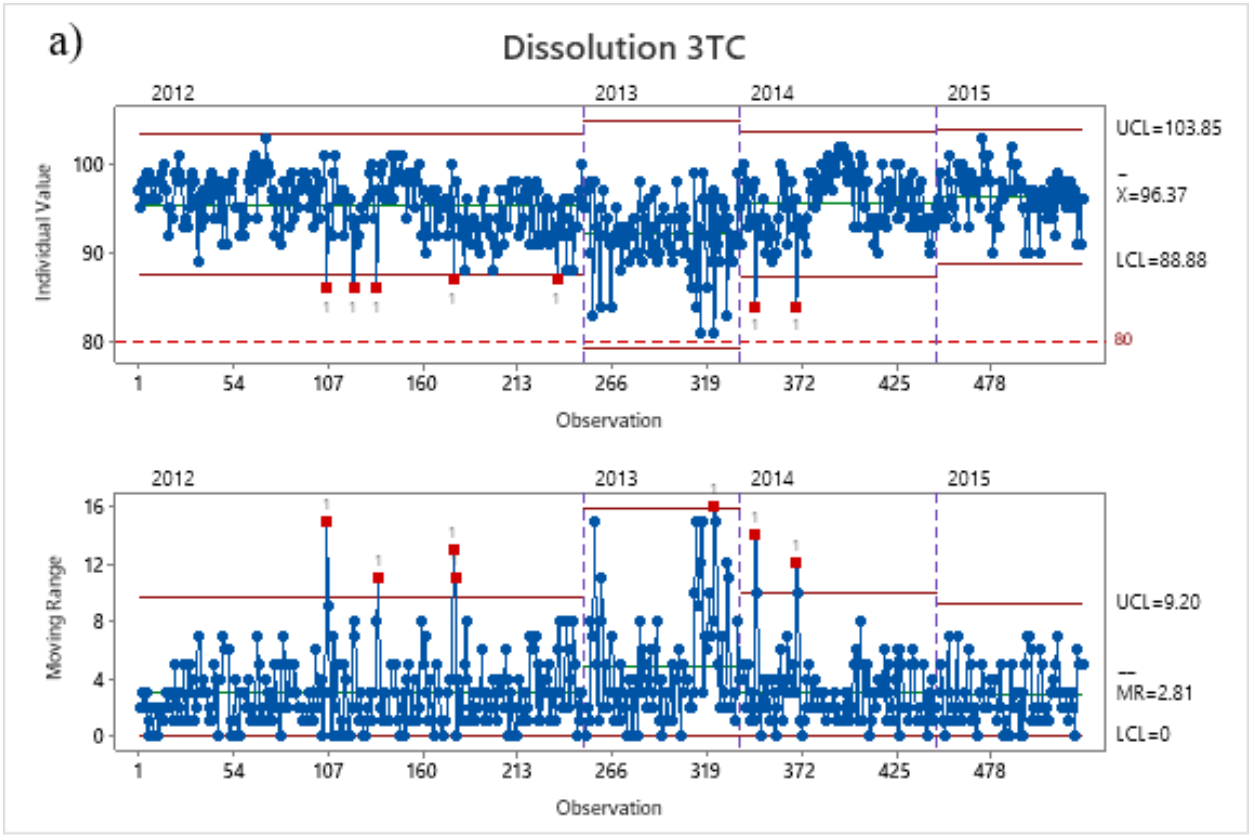

FIGURE 6 - (a) Dissolution control chart of 3TC in tablets manufactured between 2012 and 2015 and (b) manufactured in 2013.

Figure 7 shows the control chart of AZT for coated tablets. In 2012, a more significant number of lots presented OCL results in comparison to other years: four below the LCL and one above the UCL. Even so, this quantity was considerably low regarding the entire batches produced in the period (n=249). Interestingly, in the same period, the cores showed only one result below the LCL and one above the UCL (Figure S8). It is necessary to reinforce that even though some results have shown OCL values, all meet the specification.

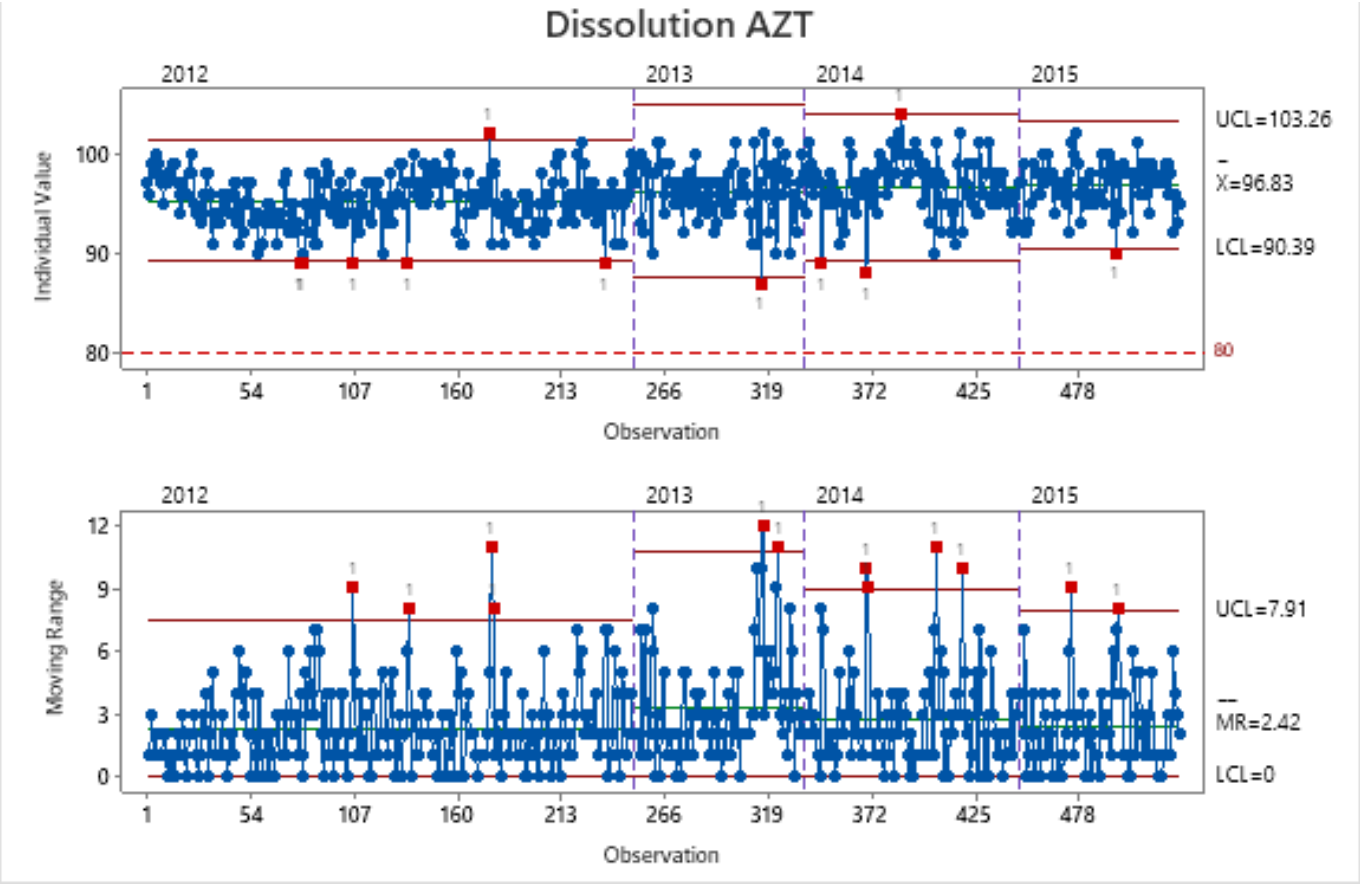

FIGURE 7 - Dissolution control chart of AZT batches in tablets manufactured between 2012 and 2015.

Figures 6a, 6b, 7, S7, and S8 show the moving range charts. The highest UCL was found in 2013 for 3TC and AZT. The moving range values above the UCL showed high variability between successive batches.

Process capability evaluation

Table IV summarizes the dissolution (3TC and AZT) capability process for the period 2012-2015. The process capability of 3TC shows that the process is not centralized for coated tablets or cores (Table VI and SV). Ppk and Cpk, were: 1.63 and 1.96 (2012); 1.00 and 0.94 (2013); 1.45 and 1.91 (2014); and 1.99 and 2.19 (2015) respectively for coated tablets. These indices showed a minimum difference of 0.06 in 2013. The differences between Cpk and Ppk indicated that the process was not operated predictably during the evaluated period. The lowest 3TC Cpk index for coated (0.94) revealed the probability of failure of 1,339 tablets in 1,000,000 units manufactured in 2013. This probability of failure suggests urgent improvement of process centralization and special causes elimination.

TABLE VI - Dissolution process capability indices of 3TC and AZT tablets (150 + 300 mg respectively) manufactured between 2012 and 2015

Indices	2012		2013		2014		2015		Overall	
	3TC	AZT	3TC	AZT	3TC	AZT	3TC	AZT	3TC	AZT
Ppk	1.63	2.02	1.00	1.86	1.45	1.92	1.99	2.36	1.40	1.92
Cpk	1.96	2.50	0.94	1.86	1.91	2.28	2.19	2.62	1.50	1.98
St Dev (***s***)	3.17	2.52	4.02	2.90	3.56	2.89	2.74	2.38	3.55	2.73
St Dev (σ)	2.63	2.03	4.28	2.90	2.72	2.43	2.49	2.14	3.32	2.65
Performance PPM	0.53	0.00	1,339	0.01	6.36	0.00	0.00	0.00	13.91	0.00

According to Tables VI, SV, and Figures 8 and S9, the process capability of AZT shows that the process is also not centered. For coated tablets, the Ppk and Cpk indices were: 2.02 and 2.50 (2012); 1.86 and 1.86 (2013); 1.92 and 2.28 (2014); and 2.36 and 2.62 (2015) respectively. These indices were equal in 2013 (1.86) and had a maximum difference of 0.48 in 2012. The differences between Cpk and Ppk indicated that the process was not operated consistently. Considering the lowest index (Ppk = 1.86), the probability of failure of the process was 1 in 100,000,000 units manufactured in 2013.

The overall Cpk values for coated tablets were 1.50 for 3TC and 1.98 for AZT, denoting AZT's better performance. Even for the evaluation by year, the AZT Cpk values are higher than 3TC, confirming the difference between the drug substances. Significant variability for both drugs on coated tablets was observed in 2013, with the total variation (***s***) of 4.02 and 2.90 for 3TC and AZR, respectively. The within subgroup variation (σ) was also elevated in 2013 (4.28 for 3TC and 2.90 for AZT). In parallel, the lowest variation was observed in 2015 for both drug substances.

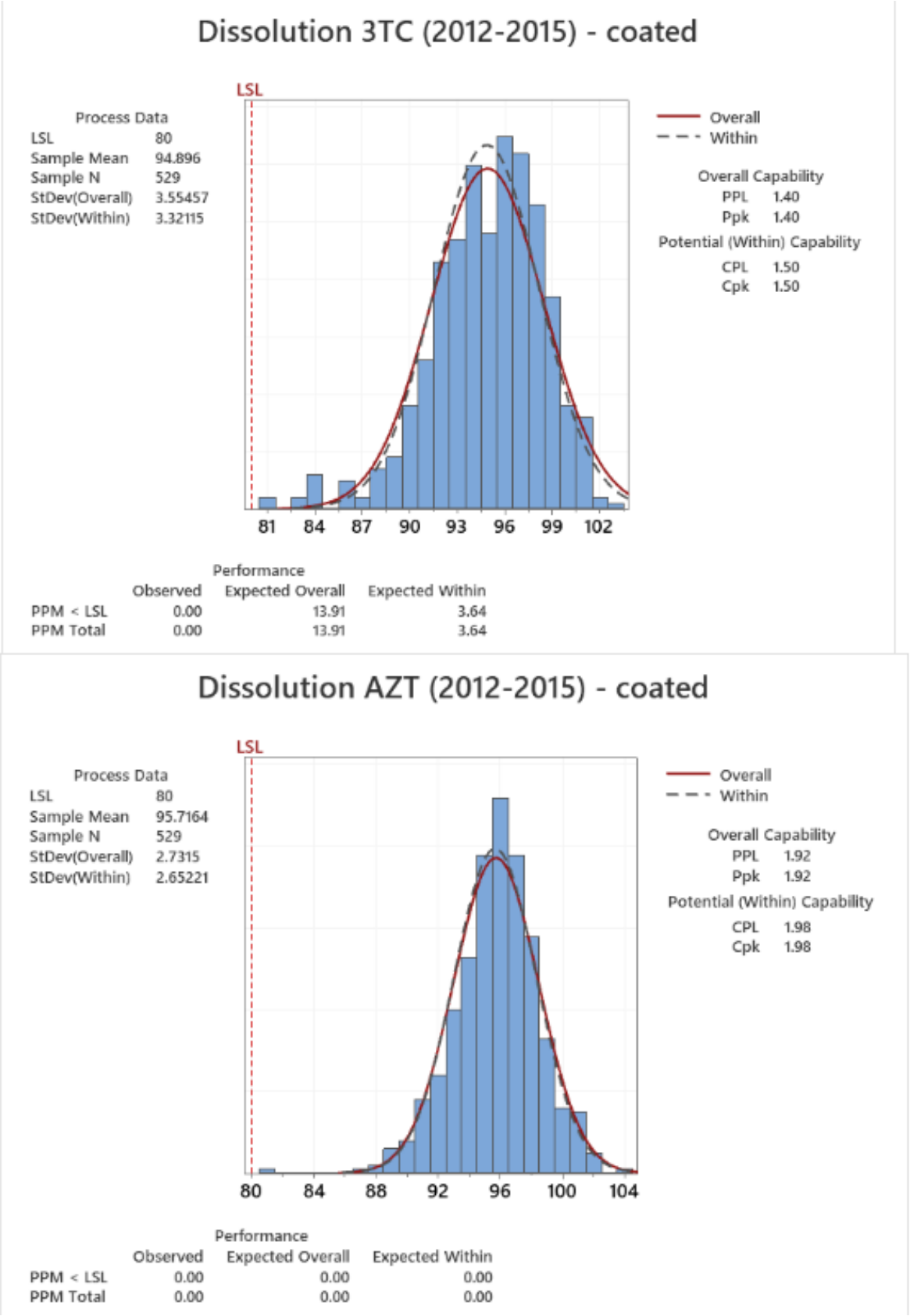

FIGURE 8 - Dissolution process capability of 3TC and AZT (150 + 300 mg respectively) in tablets manufactured between 2012 and 2015.

As the statistical analysis of the dissolution of the coated tablets and the 3TC and AZT cores (150 + 300 mg respectively) showed virtually no difference in results (Tables VI and SV), the higher variability of 3TC from dissolution might be related to the uniformity of dosage units results. However, this CQA showed a lower variability in the year 2013 (Table V, Figure 5). The capability indexes of uniformity of dosage showed high Cp and Cpk, and Pp and Ppk, all above 1.58. This performance reinforced that the uniformity of dosage units did not influence 3TC and AZT dissolution variability in 2013.

Regarding the cores' coating, a slight difference between the results before and after the coating process was expected. This behavior may be explained by the function of the dry film used in the coating process. The excipient Opadry II was hypromellose-based, and its function is to mask the unpleasant taste of 3TC and AZT (Schiffman *et al*., 1999; Nishiyama, Ogata, Ozeki, 2016). Therefore, in this case, the coating did not influence the dissolution of the coated tablets.

The excipients croscarmellose sodium, microcrystalline cellulose, silicon dioxide, hypromellose, and magnesium stearate represent only 32.5 % of the total tablet mass. Considering the higher amount of drug substances in the formulation, differences in 3TC or AZT particles' physical characteristics such as size, shape, density, and polymorphism may contribute to drug dissolution failures and increase the process variability (Kirsch, 2015).

CONCLUSION

This study allowed understanding the 3TC and AZT tablet manufacturing process variability by retrospective data analysis of 529 batches considering the following CQA: weight variation, uniformity of dosage units, and dissolution. The analysis of weight variation highlighted a better understanding of the process performance over time. For this CQA, the manufacturing process stability was revealed, presenting low process failure probability. Nevertheless, some opportunities for improvement can be pointed out. Corrective actions such as the training of operators can be applied immediately. Furthermore, implementing a forced feeder machine may improve matrix filling during direct compression, minimizing its variability.

For uniformity of dosage units, the 3TC and AZT capability indices revealed the need for process centralization. Special causes were progressively eliminated over the years and were not detected in 2015. If process refinements are still desired, it is recommended to investigate the impact of powder density, particle morphology, and origin of excipients on the uniformity of dosage units. Moreover, controlling the particle size during the blend and the flow time through a forced feeder machine implementation may centralize the process.

The dissolution process capability allowed discriminating the performance of the two drug substances. This difference permits the drive of the efforts towards 3TC improvements. Moreover, the dissolution results showed no significant difference before and after the coating process. Also, the large amount of drug substances in the tablet and their physical characteristics may be further investigated to mitigate the process variation.

3TC and AZT AIDS treatment requires product quality consistency to minimize intersubject variability, and consequently, therapeutic drug failure. Control charts and capability indices allowed variation detection, understanding, and assessing their sources on product attributes. Therefore, this approach revealed opportunities for process improvement, aiming to reduce risks to the patients.

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DECLARATION OF INTEREST STATEMENT

No potential conflict of interest was reported by the author(s).

ABBREVIATIONS

3TC: lamivudine; AZT: zidovudine; AD test: Anderson Darling test; AM: average moving range; Cp:

process capability; Cpk: process capability based on unilateral dispersion; CPL: process capability based on lower control limit; CPU: process capability based on upper control limit; KS: Kolmogorov-Smirnov; LCL: lower control limit; LSL: lower specification limit; OCL: out of control limits; Pp: global capability of the process, Ppk: global process capability based on unilateral dispersion; PPL: global process capability based on lower control limit; PPM: parts of failure per million of manufactured units; PPU: global process capability index based on upper control limit; UCL: upper control limit; USL: upper specification limit;

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