

Physical profile of counterfeit tablets Viagra® and Cialis®

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The profile of tablets containing an active pharmacological ingredient can be obtained using different sets of properties, including physical and chemical aspects. The first measurements carried out on tablets are the physical characteristics also called post-tabletting batch (post-TB) characteristics. These data may be valuable to assist in the detection of pharmaceutical product forgery and may also be used in a forensic intelligence perspective when inserted into databases. This work is focused on the physical characteristics of Cialis® and Viagra® tablets seized by the Brazilian Federal Police in the Rio Grande do Sul state. Using the F-test (ANOVA), all samples of counterfeit Viagra® (n = 28) and Cialis® (n = 40) were well distinguished from authentic samples by the following post-TB characteristics: length (major and minor), thickness, and mass. Using the exploratory statistical technique of Hierarchical Cluster Analysis (HCA), tablets with similar physical profiles were grouped. This result may indicate a common illicit production. We observed the validity of using post-TB properties to generate – in a fast and reliable manner and with no sample preparation – a technological profile that joins itself to the other analytical methods assisting in routine forensic detection of counterfeit Viagra® and Cialis®.

Uniterms: Counterfeit drugs. Tablets/physical characteristics. Viagra®. Cialis®.

Perfil para medicamentos na forma farmacêutica comprimidos contendo uma substância ativa pode ser obtido usando diferentes conjuntos de propriedades, incluindo aspectos físicos e químicos. As primeiras medições realizadas em comprimidos são de características físicas, também chamadas características pós-compressão. Tais dados podem ser valiosos para auxiliar na detecção de falsificações de medicamentos e ser utilizados em uma perspectiva de inteligência forense, quando inseridos em bancos de dados. Este trabalho está focado nas características físicas dos comprimidos de Cialis® e Viagra® apreendidos pela Polícia Federal no Estado brasileiro do Rio Grande do Sul. Com o emprego do Teste de Fisher (ANOVA), todas as amostras falsificadas de Viagra® (n = 28) e de Cialis® (n = 40) foram diferenciadas das amostras autênticas pelas seguintes características pós-compressão: comprimento (maior e menor), espessura e massa. Utilizando-se a Análise Hierárquica de *Cluster* (AHC), os comprimidos com perfis físicos semelhantes foram agrupados, o que pode indicar uma produção ilícita em comum. Observou-se a validade da utilização das características pós-compressão para gerar, de um modo rápido, confiável e sem preparo de amostra, um perfil tecnológico que se une aos demais métodos analíticos utilizados na rotina forense de detecção de falsificações de Cialis® e de Viagra®.

Unitermos: Medicamentos falsificados. Comprimidos/características físicas. Viagra®. Cialis®.

INTRODUCTION

Studies to obtain chemical or physical profiles of illicit drugs intended to materially prove the existence of a crime or to provide the strategic and operational intel-

ligence services with accurate information. A profile can be defined as a series of specific characteristics selected to provide information about certain clandestine production (Weyermann *et al.*, 2008; Marquis, *et al.*, 2008; UNDCP, 2001).

For samples of synthetic drugs in tablet pharmaceutical dosage form, it is generally assumed that seizures with corresponding characteristics come from the same production batch, while tablets that exhibit differing

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characteristics come from different batches (Weyermann *et al.*, 2008; Marquis, *et al.*, 2008; Milliet, Weyermann, Esseiva, 2009). The main stages of production of tablets may be listed as follows: (A) synthesis of the active pharmacological ingredient, (B) addition of excipients that enable the production of pharmaceutical dosage form – this pharmaceutical complex in powder form is defined in a preliminary study called pre-tabletting batch (pre-TB) (Weyermann *et al.*, 2008) –, and (C) compression of the mixture powder into tablets – a set of tablets produced by compression in a given machine provides properties that define a study called post-tabletting batch (post-TB) (Marquis *et al.*, 2008). These processes can be performed in different locations and should be considered separately during the studies to obtain profiles. The samples submitted to forensic analysis are unchanged from tabletting until consumption or seizure by police forces (Milliet, Weyermann, Esseiva, 2009). Thus, even if distributed by different routes, pre-TB and post-TB properties remain permanent marks of a common origin. The post-TB characteristics – among them weight, thickness, and length – are the first measurements made in tablets and create a physical profile for them.

These definitions imply that the obtaining of profiles can be perfectly used in other forensic problem: counterfeiting drugs. Following a global trend, the highest incidence of counterfeit medicines in Brazil is on the products Viagra® (sildenafil citrate, Pfizer) and Cialis® (tadalafil, Eli Lilly)* (Brasil, 2008). Sildenafil and tadalafil are drugs used to treat male erectile dysfunction because they act as selective inhibitors of phosphodiesterase type-5 (PDE-5) (Brunton, Chabner, Knollmann, 2010).

Counterfeiting detection involves a detailed analysis of different elements in the existing packaging and pharmaceutical dosage form. It generally includes (1) examination of the packaging and drug leaflets – such as printing patterns, including fonts and images, holograms, and the existence of reactive ink, (2) external evaluation of the pharmaceutical dosage form, referring to the visual and technological aspects – for tablets, it includes post-TB measures, and (3) chemical analyzes to characterize the formulation in order to identify or quantify drugs and excipients. These tests are performed chronologically and compare the results against a reference standard or literature data. In the last decade, many works have been published involving the identification of sildenafil and tadalafil in pure form or in pharmaceutical dosage forms – including counterfeits – by different chemical analytical techniques (Vredenburg *et al.*, 2006; Inoue *et al.*, 2008;

Singh *et al.*, 2009; de Veij *et al.*, 2008; Trefi *et al.*, 2008; Holzgrabe, Malet-Martino, 2011; Ortiz, Antunes, Linden, 2010; Sacré *et al.*, 2010). However, there were no reports employing physical profiles of Viagra® and Cialis® tablets for forensic purposes.

This paper proposes to assess the validity of employing post-TB characteristics of genuine and counterfeit Viagra® and Cialis® tablets to generate a physical profile for these products before starting advanced chemical tests, often destructive and costly in time and material resources. This fast, without sample preparation, non-destructive and reproducible physical profile can contribute to the forensic analyst's conclusion by the inauthenticity of these medicines, as well as being a very useful perspective to investigate the manufacture origin of counterfeiting.

MATERIALS AND METHODS

Counterfeit Viagra® tablets (n = 28, six distinct seizures) and Cialis® (n = 40, six distinct seizures) sent to the Rio Grande do Sul Technical and Scientific Division for forensic analysis, as well as authentic tablets of Viagra® (n = 30, nine different batches) and Cialis® (n = 35, six different batches), were used as samples (Figure 1). The post-TB characteristics mass (mg), thickness (mm), shorter length (mm) and longer length (mm) were used as variables in the study. Measurements were performed on an analytical balance (Mettler Toledo XP205, Brazil) and using a micrometer (Mitutoyo, Japan). The data were described in the form of histograms and plots of means and confidence intervals (95%). Subsequently, data were treated with multivariate statistical analysis by the technique of Hierarchical Cluster Analysis (HCA) (STATISTICA, version 7.0, StatSoft®). The images in this article were obtained with a video spectral comparator (VSC 5000 Foster & Freeman Ltd.UK) that provides 20 times magnification with illumination under visible light and automatic settings for focus, brightness and contrast.

RESULTS AND DISCUSSION

Descriptive statistics

The observed results are summarized in Table I. Authentic Viagra® and authentic Cialis® show very low variation in properties from post-TB measurements (RSD [relative standard deviation] < 1.10%). This derives from the application of advanced technologies in the manufacturing process of tablets and a rigid quality control that

*The symbol ® will be used only in reference to the original medicines.



FIGURE 1 – Examples of samples used in the study: counterfeit Viagra® (A-F), authentic Viagra® (V), counterfeit Cialis® (G-L) and genuine Cialis® (T).

discards any product outside its specifications (Gennaro, 2000; Allen *et al.*, 2007). On the other hand, the counterfeit tablet had a higher dispersion of the observed results (until RSD = 6.73%). These values are shown to be in agreement with forensics publications which associated the greater variability found in illicit products with the peculiarities of clandestine modes of production, such as exemption from quality control in the production cycle and absence of homogeneity of powder mixtures (Weyermann *et al.*, 2008; Marquis, *et al.*, 2008; UNODC, 2005; Lociciro *et al.*, 2008; Dujourdy *et al.*, 2008; Andersson *et al.*, 2007).

In counterfeit products, the observed value dispersion for the variables mass and thickness has relatively

higher amplitudes, while greater length and shorter length exhibit closer frequency distribution values (Table I, Figure 2, Figure 4). Probably, this is associated with the success of the falsifiers in obtaining a matrix and punches that mimic the compression chamber which produces authentic tablets. Differences in adjustment to the position of the punches, in the compression force, and especially in the quantity and composition of the pharmaceutical complex to be tableted may be associated with lack of reproducibility in mass and thickness.

Variables histograms for Viagra® tablets are illustrated in Figure 2. We can observe the mean values of mass (316), thickness (4.5), greater length (11.4) and shorter length

TABLE I - Description of the number of samples with values expressed as mean and relative standard deviation (RSD) (NA = not applicable)

	Code	Units seized	Units tested	Mass (mg)	Thickness (mm)	Greater length (mm)	Shorter length (mm)
Authentic Viagra®	V	-	30	316.23 (1.10)	4.47 (1.33)	11.40 (0.16)	8.30 (0.11)
Counterfeit Viagra®	A	132	10	328.07 (2.40)	4.48 (1.41)	11.40 (0.00)	8.30 (0.00)
	B	8	1	356.82 (NA)	4.30 (NA)	11.60 (NA)	8.50 (NA)
	C	3	1	307.60 (NA)	4.40 (NA)	11.40 (NA)	8.30 (NA)
	D	9	7	379.22 (6.71)	4.74 (2.39)	11.63 (0.96)	8.47 (0.58)
	E	9	5	422.86 (2.54)	5.65 (1.66)	11.52 (0.26)	8.38 (0.40)
	F	4	4	362.62 (6.73)	4.38 (6.57)	11.58 (0.83)	8.45 (1.18)
	Z		8	424.92 (3.98)	5.75 (3.98)	11.58 (0.55)	8.41 (0.76)
Authentic Cialis®	T	-	35	364.71 (0.84)	4.97 (0.81)	12.30 (0.25)	7.56 (0.59)
Counterfeit Cialis®	G	6	1	409.98 (NA)	5.10 (NA)	12.40 (NA)	7.40 (NA)
	H	7	1	418.04 (NA)	5.10 (NA)	12.70 (NA)	7.60 (NA)
	I	40	16	419.33 (2.19)	4.96 (1.45)	12.51 (0.20)	7.80 (0.47)
	J	40	10	456.56 (3.15)	5.67 (2.89)	12.65 (0.42)	7.81 (0.73)
	K	40	10	486.91 (3.39)	5.64 (2.08)	12.30 (0.00)	7.70 (0.00)
	L	4	2	457.54 (0.55)	5.60 (0.00)	12.60 (0.00)	7.90 (0.00)
	M		10	468.17 (1.43)	5.79 (0.98)	12.57 (0.38)	7.86 (0.66)
	N		12	424.42 (2.47)	4.98 (1.25)	12.60 (0.00)	7.70 (0.00)

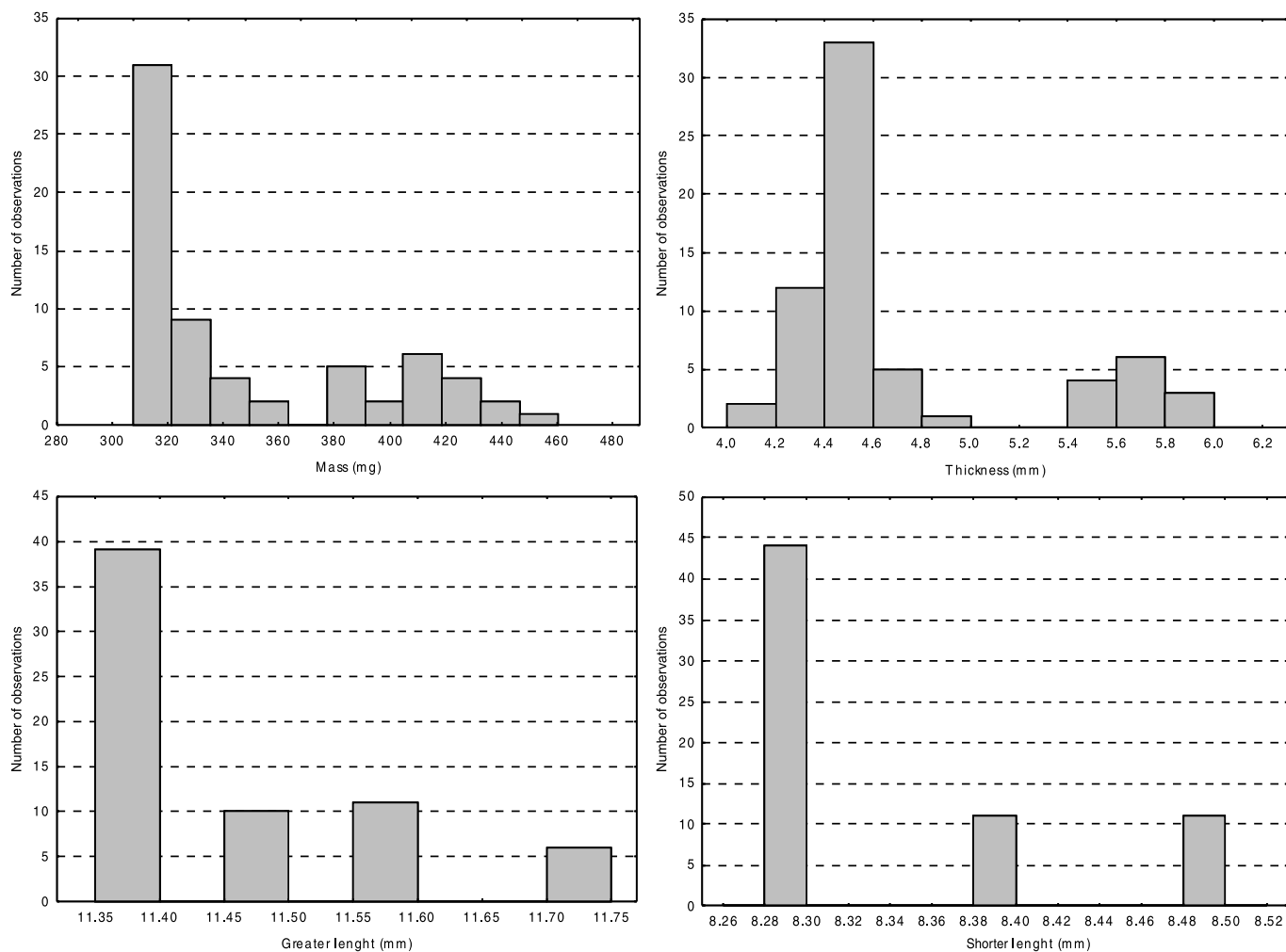


FIGURE 2 - Histograms for variables mass, thickness, greater length and shorter length for counterfeit and genuine Viagra®.

(8.3) of the authentic tablets interpolated to measures of counterfeit products. As seen in the mean and confidence interval graph (Figure 3) for thickness, seizures A and F show overlay of the confidence interval (95%) with the experimental space defined with the original products. It is also observed overlap values of greater length (seizures A and C) and shorter length (seizures A, C and F) with original Viagra®. The F-test (ANOVA) was performed and revealed a significant difference between the sample means for the four variables studied, except for thickness of seizures A and F. Thus, it was shown that these are averages that originate in different populations (F calculated $>$ F critical for a significance level of $\alpha = 0.05$) (Table II).

The mass histogram for Cialis® tablets (Figure 4) shows, in isolation, authentic tablets (35 elements) with a mean value of 364 mg. All counterfeit Cialis® tablets exhibited higher mass than the authentic tablets. In the other properties under evaluation, the means related to genuine Cialis® tablets – 5.0 for thickness, 12.3 to greater

length, and 7.6 to shorter length – are arranged between the values observed for counterfeits. In the mean and confidence interval graph for Cialis® cases (Figure 5), it can be seen that seizures I and N have the ability to replicate the thickness of authentic Cialis® and the seizure K mimics its greater length. Again, the application of the F-test (ANOVA) indicates a significant difference between means at a significance level of 5% (F calculated $>$ F critical), except for thickness of seizures I and N and greater length for the seizure K (Table II).

Briefly, some of the counterfeit tablets can imitate one or another measured post-TB characteristics; however, none of the forgeries evaluated was able to simultaneously present mass, thickness, greater length and shorter length values within the ranges defined for the genuine products. Therefore, in this study, the simultaneous measures of those four proposed post-TB properties corroborated the results of other tests for quality control, detecting all counterfeit samples ($\alpha = 0.05$).

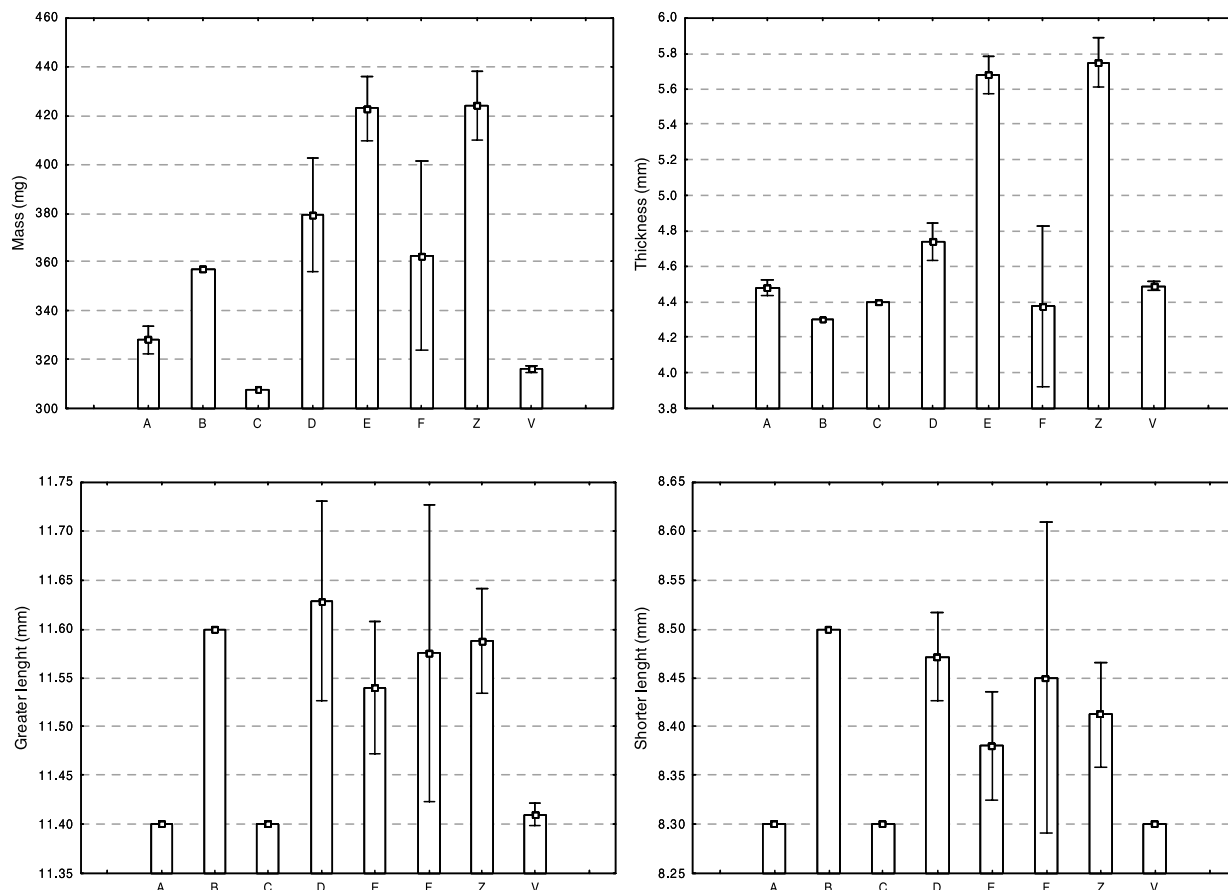


FIGURE 3 - Mean values and confidence intervals (95%) for mass, thickness, greater length and shorter length for counterfeit (A-F and Z) and authentic (V) Viagra®.

TABLE II - *p-values* corresponding to the F-test (ANOVA) performed for means of counterfeit and authentic samples

Product	Seizure	Variables			
		Mass	Thickness	Greater length	Shorter length
Viagra®	A	< 0.0000	0.6782	-	-
	B	-	-	-	-
	C	-	-	-	-
	D	< 0.0000	< 0.0000	< 0.0000	< 0.0000
	E	< 0.0000	< 0.0000	< 0.0000	< 0.0000
	F	< 0.0000	0.544	< 0.0000	< 0.0000
	Z	< 0.0000	< 0.0000	< 0.0000	< 0.0000
Cialis®	G	-	-	-	-
	H	-	-	-	-
	I	< 0.0000	0.3982	< 0.0000	< 0.0000
	J	< 0.0000	< 0.0000	< 0.0000	< 0.0000
	K	< 0.0000	< 0.0000	0.8853	< 0.0000
	L	< 0.0000	< 0.0000	< 0.0000	< 0.0000
	M	< 0.0000	< 0.0000	< 0.0000	< 0.0000
N	< 0.0000	0.9630	< 0.0000	< 0.0000	

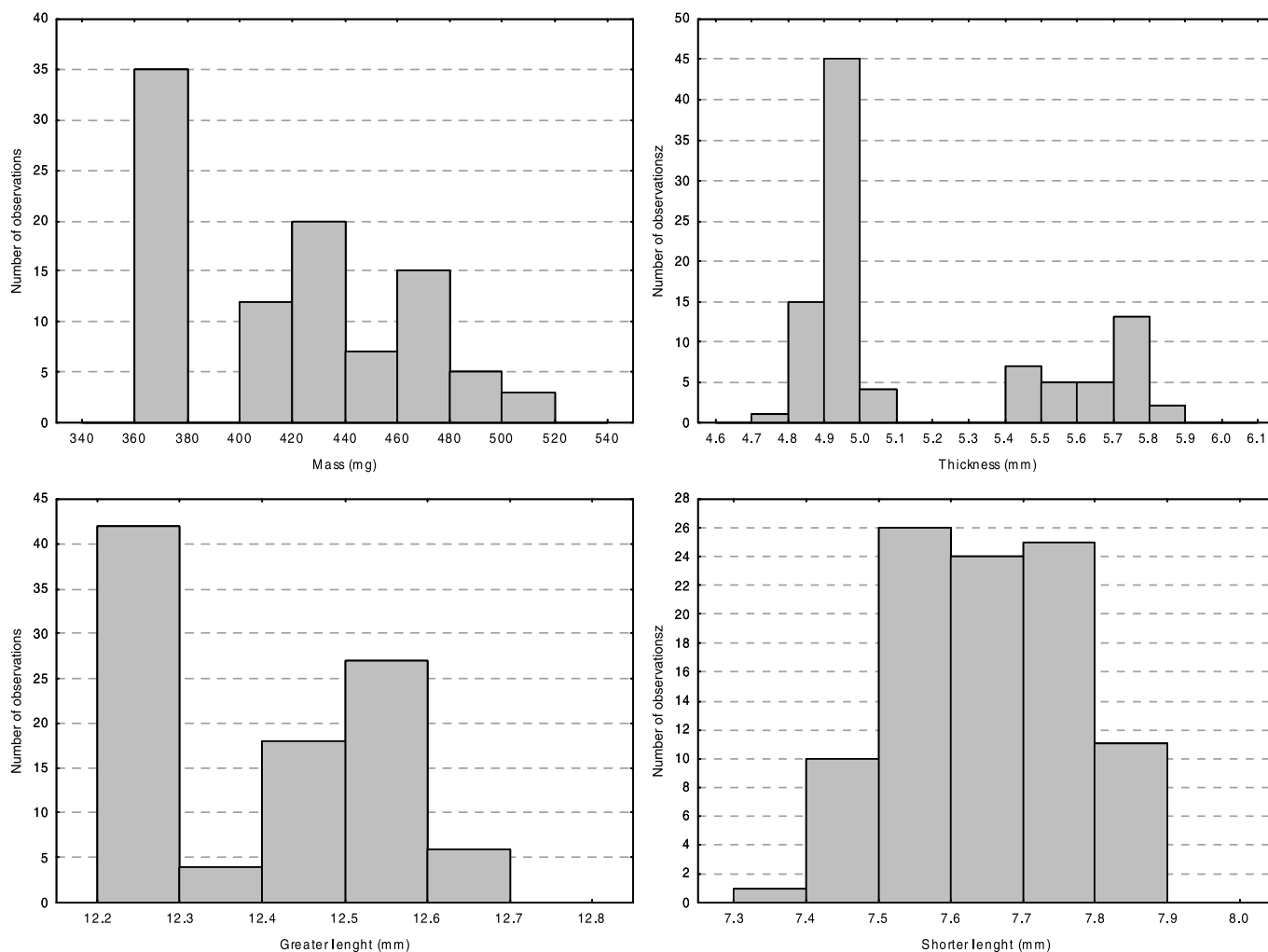


FIGURE 4 - Distributions of variables mass, thickness, greater length and shorter length for counterfeit and authentic Cialis®.

Hierarchical Cluster Analysis (HCA)

HCA is an exploratory classification technique to divide a set of objects into groups in which there is homogeneity within the group and heterogeneity between groups. HCA seeks for objects that are close in the experimental space. The distance between two points in an n -dimensional space is usually calculated using the Euclidean distance obtained by the Pythagorean Theorem in a multidimensional space. Euclidean distance is a similarity measure that expresses the separation between the extremities of two vectors which represent these points or experimental objects (Miller, Miller, 2002; Shaw, 2003).

For this work, the formation of clusters was performed with the single linkage method based on the minimum distance or nearest neighbor rule. The successive stages of grouping performed can be viewed in the form of dendrograms, as seen in Figures 6 and 7. The vertical axis represented the normalized distance in function of the

maximum distance between two points or groups ($[D_{linkage}/D_{maximum}] * 100$).

The Viagra® samples are distributed in two major groups of low similarity between themselves: the *cluster 1* with authentic samples (V) and counterfeits of seizures A, B, C and F, and the *cluster 2* with the counterfeits of seizures D and E (Figure 6). In this graph occur two worse classifications, with one sample of seizure D included in *cluster 1* and one sample of seizure F included in *cluster 2*. Subdividing the groups, we can group in 1A the authentic tablets and seizures A and C, in 1B the seizures B and F, in 2A the seizure D, and in 2B the seizure E.

More clearly for the Cialis® samples, two clusters are formed: all counterfeit samples into *cluster 1* and all authentic samples in *cluster 2* (Figure 7). The cluster 1, with the counterfeits samples, can be subdivided in subgroup 1A, which is composed by seizures G, H and I, and subgroup 1B, which is composed by seizures K and L. At this stage of subdivision, the seizure J is not clearly

TABLE III - Counterfeits paired samples more closely linked by HCA

<i>Samples ([Dlink/Dmáx]*100)</i>	<i>Similarity value for FT-IR spectrum (match)*</i>	<i>Active pharmacological ingredient **</i>
G and I11 (Cialis®) (< 10)	95.34	(SLD/TAD) (SLD/TAD)
G and I13 (Cialis®) (< 10)	95.01	(SLD/TAD) (SLD/TAD)
A7 and D5 (Viagra®) (< 10)	89.32	(SLD/HSD) (SLD/HSD)
B and F1 (Viagra®) (< 10)	79.23	(SLD/HSD) (SLD/HSD)
D6 and F2 (Viagra®) (< 20)	95.81	(SLD/HSD) (SLD/HSD)

SLD, sildenafil; TAD, tadalafil; HSD, homosildenafil. * In preparation paper. ** Submitted paper (Ortiz *et al.*, 2011).

pre-compression batches (with different chemical profiles) (Milliet, Weyermann, Esseiva, 2009). In this work using dendrograms with only counterfeit samples, paired samples of different seizures closely linked, i.e., with lower normalized distance, were identified. Preliminary chemical tests indicated that there was similarity between some of these samples, as can be seen in Table III, which lists the similarity value between their FT-IR spectrum – *match*, on a scale of zero to 100 – and the active pharmacological ingredient identified in the samples - sildenafil (SLD), homosildenafil (HSD), and/or tadalafil (TAD). These results may indicate that these samples have a common origin of mixture powders and tableting cycle (hypothesis A). Therefore, the physical profile data may be useful when added together with results of chemical analysis to database mapping to forgery. No information would be put into the external reports, but for internal use with forensic intelligence purposes.

CONCLUSIONS

The results demonstrate that the post-tabletting characteristics mass, thickness, greater length, and shorter length are reliable and relevant features in the forensic analysis of suspected counterfeit tablets. The mean and confidence interval plots and the F-test (ANOVA) for these variables, analyzed together, corroborated the results of other quality control tests, detecting all samples of counterfeit Viagra® and Cialis® evaluated in this study ($\alpha = 0.05$). The profile of the physical aspects provides important information based on a quick, non-destructive and without sample preparation before the start of chemical analysis.

Using Hierarchical Cluster Analysis, it was possible to classify the samples into groups of homogeneous physical characteristics. We identified paired samples from different seizures closely linked by physical profile, which can be associated with a common origin of mixture powders and tableting cycle. Complementary studies

including more samples will be carried out to evaluate the validity of employing the physical profile information together with chemical analysis results for forensic intelligence purposes.

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