Light re-emission utilized in some drugs color analysis

Reemisión de la luz aplicada en la investigación del color de los medicamentos

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ABSTRACT

Measurements of the white, blue and green light re-emission at the level of some white drug powders smooth surface were performed. The "white degree", defined as the blue light re-emission power, has been proposed for the white drugs color quantitative evaluation. The investigation of many different drug batches, both at the date of the preparation and later, during the validity time interval, indicated that the "white degree" may be useful in products ageing surveying. A convenient graphic method was applied for the comparison of the "white degree" distribution curves.
Key words: White degree. Drug. Light re-emission

RESUMEN

Se han efectuado medidas de re-emisión de la luz blanca, azul y verde a la altura de la superficie plana de los polvos medicamentosos blancos. "El grado de blanco", definido como poder de re-emision de la luz azul, ha sido propuesto para una evaluación cuantitativa del color de los medicamentos, tanto inmediatamente después de la fabricación como dentro del tiempo de validez, ha mostrado que "el grado de blanco" puede ser útil en el seguimiento de la vejez de los productos. Un método gráfico adecuado ha sido aplicado para comparar las curvas de distribución del "grado de blanco".
Palabras clave: Grado de blanco. Medicamento. Re-emisión de la luz.

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INTRODUCTION

Physical methods used for the investigation of intrinsic problems in medicine and pharmacy have led to the emphasizing of new cellular and

molecular phenomena, on a hand and to the quantitative expression of biological material characteristics, on the other hand. Spectrophotometric methods for the measurement of electromagnetic wave flow absorption and transmission underground many tests and assay techniques for human body biological liquids analysis as well as for pharmaceutical agents quality quantification. The reflection or the so called re-emission of light can also be a source of information upon a certain sample features. In the next it is presented an example with regard to the study of some crystalline drug substances, by the means of quantitative evaluation of the rate between the reflected light flow F_r and the incident one, F_i: the re-emission power:

$$R=F_r/F_i$$

The value of R for the blue test light (R_B) is taken as the white degree.

MATERIAL AND METHOD

More than a thousand fabrication drug batches, mainly penicillins, have been assayed from the point of view of light re-emission, using a C. Zeiss-Jena (Germany) Leukometer, working with white but also with Balzer broad band (40 nm) transmission filters, adapted to the original set-up. The crystalline or microcrystalline powders were pressed in a cylindrical cell having a 5 mm height and a 3 cm cross diameter, until a flat smooth surface, able of uniform reflection of incident light flow, was obtained. The measurement device was adjusted using a standardized white glass sample having the next characteristics: R_W=85.13%, R_B=85.83%, R_G=85.57%, R_R=79.87% (R_W, R_B, R_G and R_R have the meaning of light re-emission power for white, blue, green and respectively red light). The standard was periodically verified at the National Metrology Institute. The work samples were Romanian products such as: penicillin-potassium salt (712 batches),erythromycin-base (117 batches), streptomycin-sulfate (101 batches) and efitard-mixture of potassium penicillin and procaine-penicillin, Romanian patent (230 batches). During the study the drugs were in good agreement with the quality tests and assays stipulated in the international norms (1).

In order to determine the light (l=420 nm) transmission in penicillin aqueous solutions (0.18 %) a Specord UV-VIS, C. Zeiss-Jena (Germany) spectrophotometer, having an accuracy of about 100 cm^{-1} was used.

For the comparison of the experimental data a modern graphic method, named "box-plot", was utilized. Proposed and successfully used by Simpson (2), Donnelly (3), Wilson (4) and others (5,6,7,8) this method requires the transformation of the absolute frequency curve (i.e. the frequency of a certain value appearance within a data points series) in the relative cumulated frequency

curve and then, the defining of one principal interval as well as of other three secondary intervals into the initial data range.

The principal interval, the "box length", limited by the values corresponding to the cumulated frequency values of 25% (the "box left edge") and respectively 75% ("the box right edge") contains about 50% from the total data points. The width of this box is taken as proportional to the square root from the total number of data points.

The first secondary interval is limited by the "left tail" (drawn from the "box left edge" to the value given by the "box left edge" minus the "box length" multiplied by 1.5) and the "right tail" (drawn from the "box right edge" to the value given by the "box right edge" plus the "box length" multiplied by 1.5). An amount of minimum 80% of the data can be contained between the tails.

The exceptional small or large values are grouped in the other two secondary intervals. The middle outliers, drawn as black circles, for instance, are situated between the "left tail" and "the left edge" minus the "box length" multiplied by 3 or/and between the "right tail" and the "right edge" plus the "box length" multiplied by 3. The extreme outliers are values smaller than the "left edge" minus the "box length" multiplied by 3 and/or the values larger than the "right edge" minus the "box length" multiplied by 3. In this paper they are drawn as black circles. An inside line, parallel to the box edges marks the "median", corresponding to a cumulated frequency value of 50%. Only for symmetrical curves this line is overlapping the average value; in other cases it is able to indicate the curve asymmetry.

In the classical manner of a distribution representation, a little number of points, such as the outliers, could not have a significant influence on the average value or upon the standard deviation. In the box-plot representation they can indicate the existence of cases of deep interest because in life sciences exceptions are not avoided but on the contrary, scientists are often looking for them. In contrast with the interval defined by the standard deviation, which is always symmetrical for any shape of the distribution curve, the box-plot intervals can easily emphasize the distribution asymmetry, if the case. More, the box-plot parameters are able to mark the weights of different size data points into the series to which they belong. And, finally, the total number of points required by this method may be of only some decades. In the next it is presented one of this graphic technical applications.

RESULTS

In the preliminary experimental study 20 penicillin batches, recently yielded, were used for the evaluation of R_W, R_B, R_G values.

Though the relatively high values of the correlation coefficients (0.825, 0.734, 0.739) between the three data points series indicate that any of the three expressions of the light re-emission power can be used in a linear approximation for the white drug color evaluation, we focused on the blue light measurements. In agreement with the National Metrology Institute the conventional name of "white degree" (R_B) was established.

The penicillin white degree (R_B) evolution within a sixteen months interval, (the samples being kept in suitable containers, in could, dry and dark place) is given in Figure 1. In Figure 2 some penicillin batches were randomly chosen to present more in detail their evolution in time: some batches, intended for another final product, the acid 6-amino penicilloic, were not especially purified as the batches for injection are. In Figure 3 is given the white degree situation at the fabrication time, 6 months later and 12 months later, for some efitard batches. A comparison between the powder white degree and the solution color is accomplished in Figure 4.

The "box-plot" representation is used for the statistical comparison between penicillin and other antibiotics white degree (Figure 5).

DISCUSSION AND CONCLUSION

In Figure 1 one can see that during the time the penicillin box shifted to smaller values:

—the "left edge" is equal to 93.7% at the fabrication date (t=0), then decreases to 89.5% after 8 months and after 16 months became equal to 83.5%;

—the "median" shifted from 94.7% to 87.5%;

—the "right edge" decreases from 95.5% to 89.5%.

The box length and "tails" enhanced, i.e. the homogeneity within the analyzed batches series reduced while the asymmetry became more pronounced:

—at the fabrication time approximately half of the total batches ranges in a 6 percent width interval (between 88.5% —the smallest outlier— and 94.7% —the "median"—) but 16 months later the interval had a width of 14 percent (the corresponding values being 73.5% and 87.5%);

—the other half of the total data points, containing the larger R_B values, occupied an interval of 3 percent width at the fabrication time which enhanced to a 5 percent width, 16 months later.

Other physical, chemical and biological parameters, tested in specialized pharmaceutical laboratories, though decreased because of ageing, remained

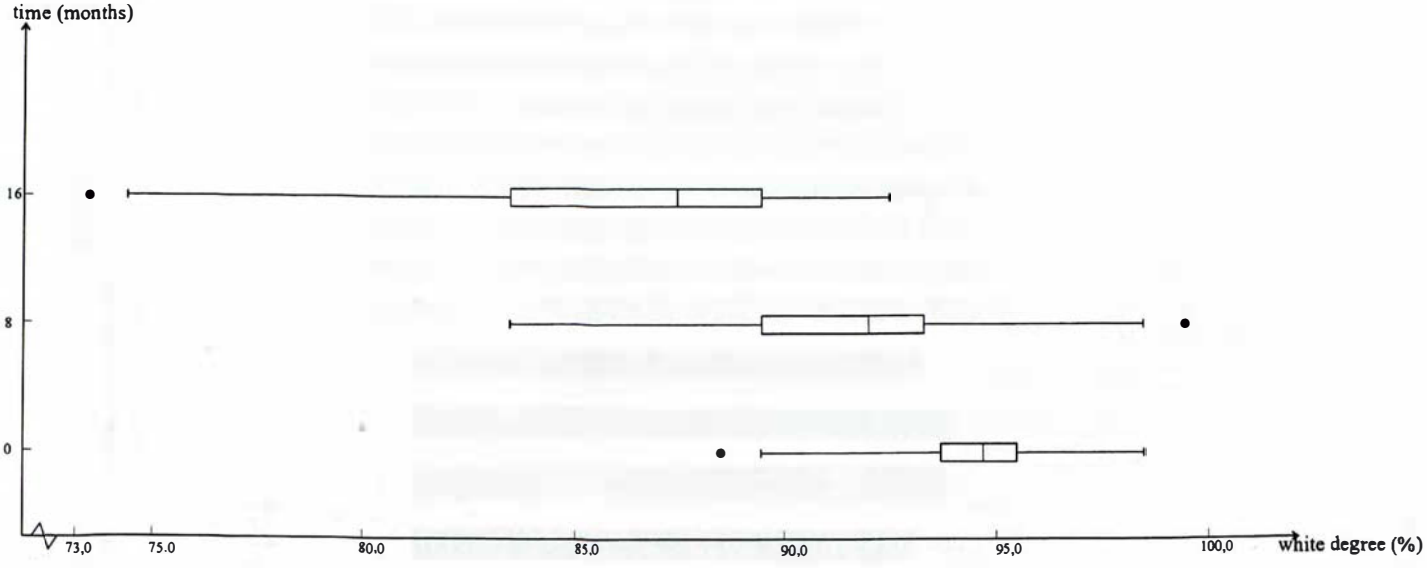

Fig. 1.—The white degree diminution in time for penicillin. The box-plot representation.

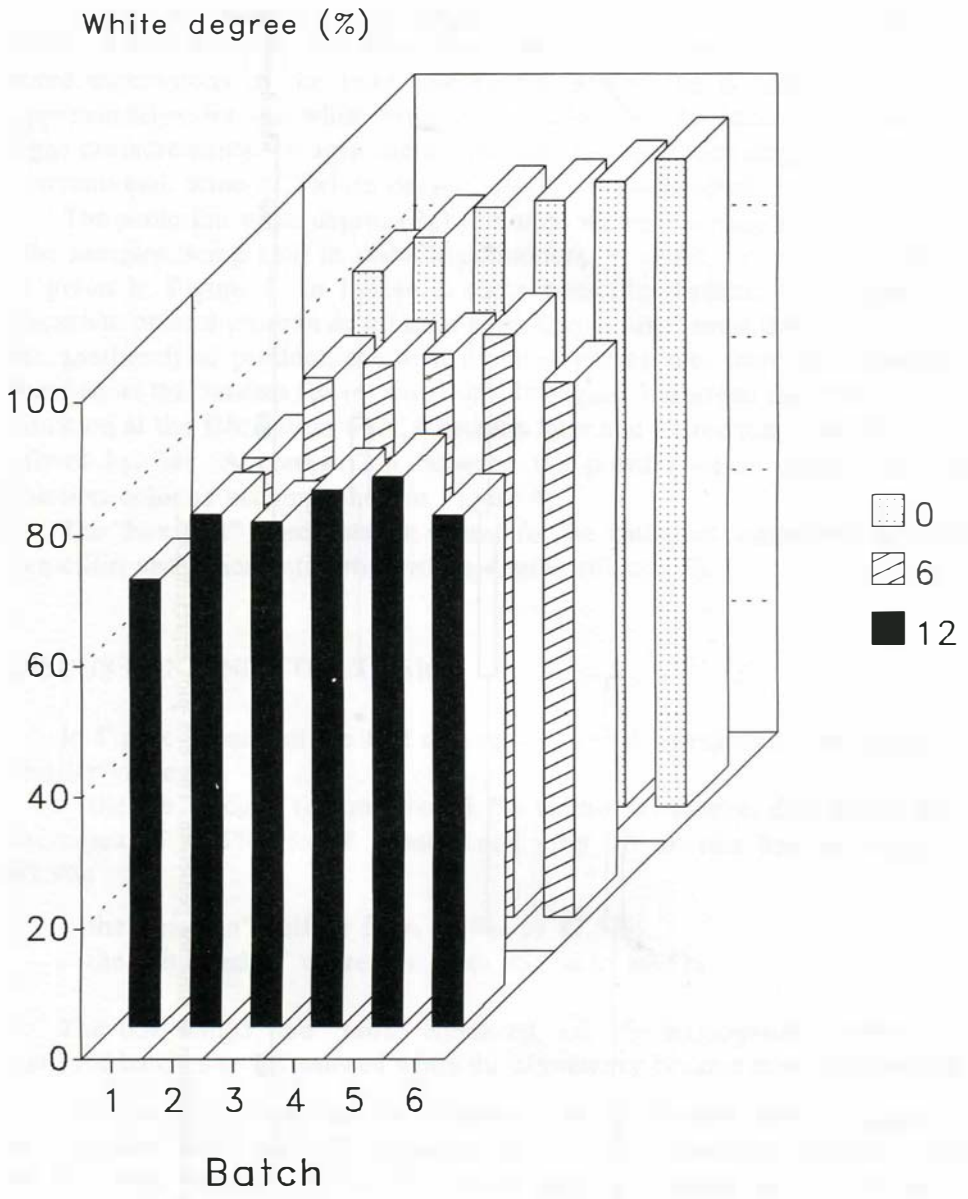

Fig. 2.—The evolution of the penicillin white degree (R_B) in time. Beginning from the background, the three sets of blocks represent the situation at the time equal to: zero, eight and sixteen months. The symbol* designs the non-purified batches.

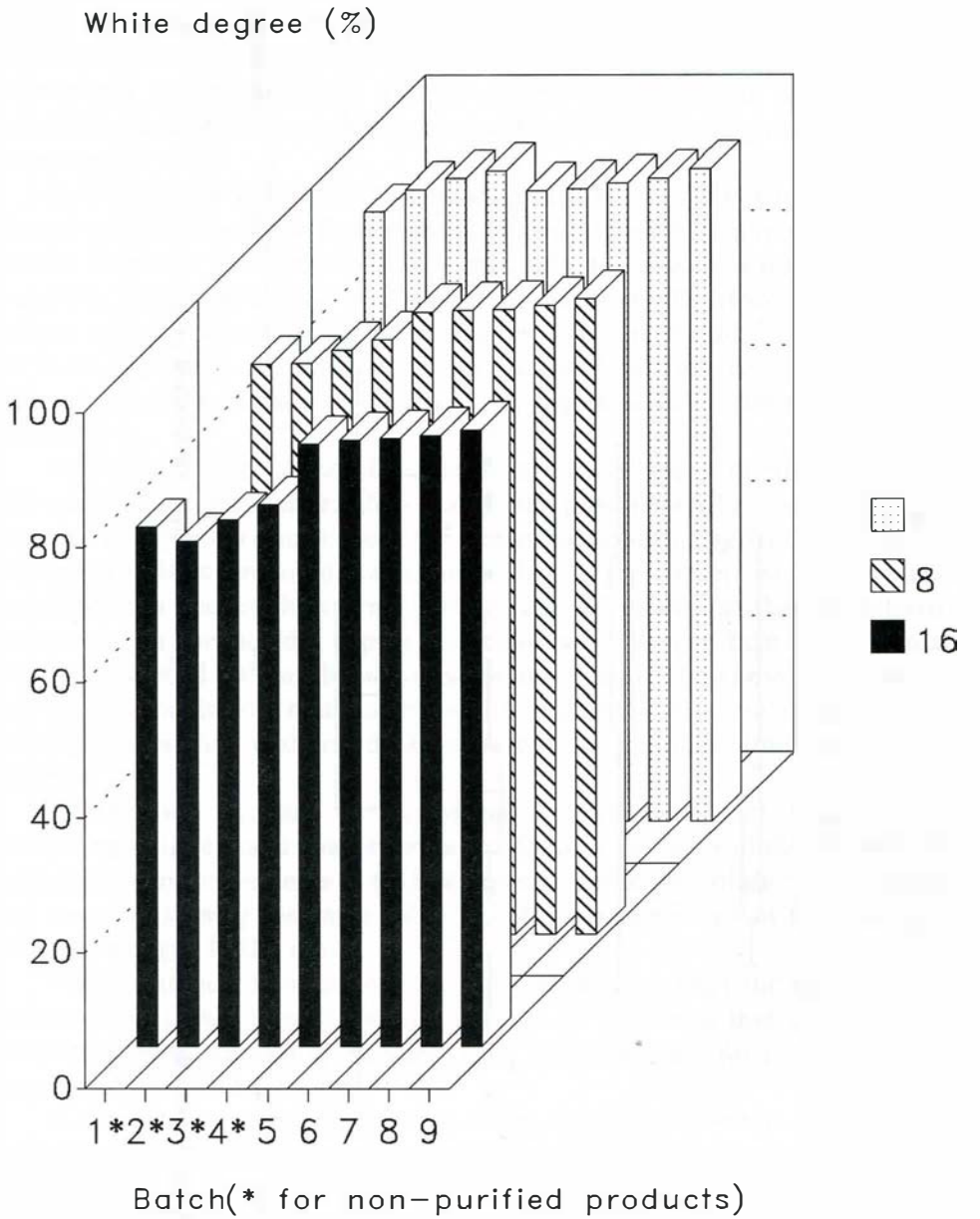

Fig. 3.—The evolution in time of some efitard batches white degree Beginning from the background the three sets of blocks represent the situation at the time equal to: zero, six and twelve months.

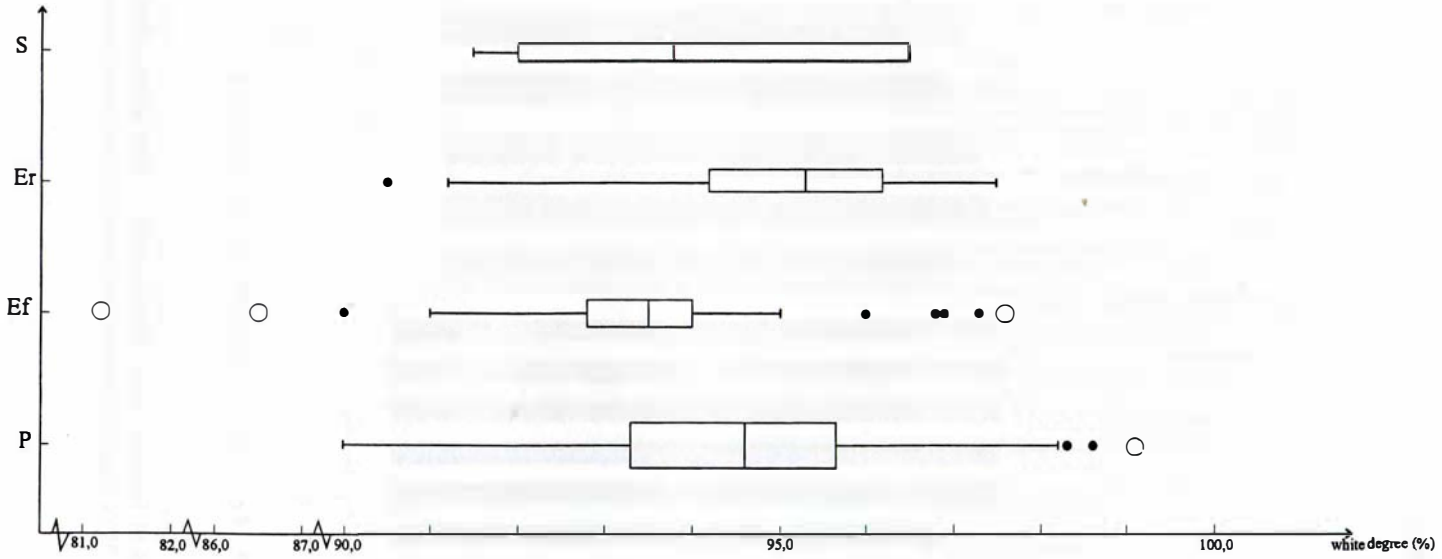

Fig. 4.—The comparison between the penicillin blue light re-emission (R_B) and blue light transmission (T%).

within the ranges required by the international quality norms (1): microbiological potential no less than 1500 units/mg, pH between 5.0 and 7.5, penicillin G content no less than 89 %, loss on drying no more than 1.5%. A first conclusion is that the box-plot representation is suitable for penicillin ageing comparative study.

In Figure 2 is visible that the less purified batches, though having quite similar initial values, are finally characterized by much smaller white degree values than the pure batches. It is possible that some residual chemical reactives (which are very carefully removed from the injection products) induce a higher instability in these samples. It is not excluded also that some of these impurities are involved in the betalactamic ring degradation in the same way as the solvolise (favored by a higher moister content) reactions are (9).

In Figure 3 one can see that the instability of the penicillin mixture is obviously more pronounced than that of the pure penicillin, suggesting that the procaine presence influences the penicillin stability, by still not clarified phenomena. It is important to mention that in the present study the same container was opened three times during 12 or 16 months so that the external influences on the powder aspect and color were deeper than for a similar container opened only at the administration moment. The above observations led to the conclusion that the penicillin instability may be related to the powder interaction with residual impurities or to other drug presence in mixture.

Taking into account the Romanian Pharmacopoeia (10), where the benzylpenicillin content evaluation is provided on the basis of ultraviolet light transmission measurements in 0.18 % aqueous penicillin solutions, we carried out some tests using the same solution but the transmission of the blue light (the wavelength l=420 nm).

The correlation between the blue light re-emission (R_B) and the blue light transmission (T%), though non-linear (Fig. 4), indicated that this radiation interaction with white drug powder is the most adequate for the quantitative expression of "white degree".

A comparative study of the white degree values distributions in penicillin, efitard, streptomycin and erythromycin is presented in Figure 5. The box-plot method emphasized that streptomycin has the lower white degree because the about 80% of the utilized data, situated between the box tails, ranged at the smallest white degree values in comparison to the other antibiotics. It is visible that the values of the "box left edge" (92.8%), the "median" (93.5%) and the "box right edge" (94.0%) in the case of efitard are lower than in the case of penicillin (93.3%, 94.6%, 95.6%) while the values for the erythromycin box-plot parameters are the highest (94.2%, 95.3%,96.2%). The efitard white degree range is the largest, then follows that of the penicillin (which is

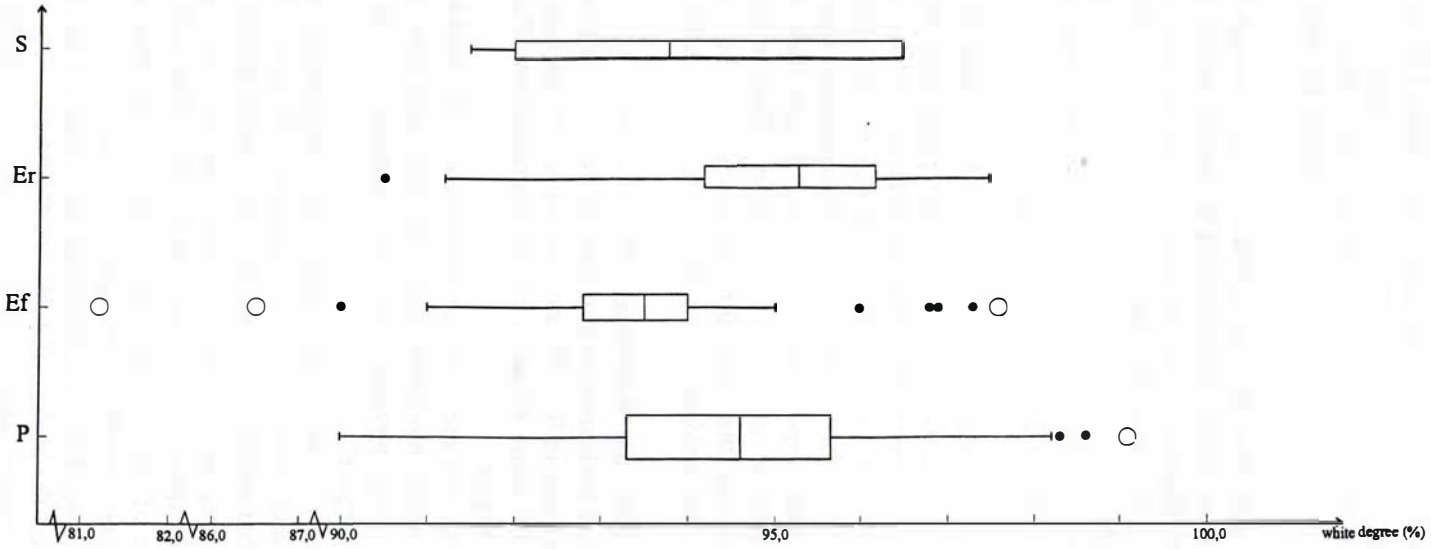

Fig. 5.—The comparison between the white degree distribution in some antibiotic drugs: penicillin (P), erythromycin (Er), streptomycin (S) and efitard (Ef).

definitely the most symmetric) while the streptomycin range is the smaller. The efitard presents the both types of outliers (the white and the black circles) and its distribution asymmetry is the most pronounced. The conclusion is that streptomycin is the most uniform of the four investigated products, from the point of view of the powder white degree while the efitard is the most heterogeneous. Certain limits can be established for the internal use in the case of such white powder drugs fabrication and administration, though the international norms require only large values categories, designed by "white or almost white powder", for example, (1), (10)). In comparison to the verbal values, the numerical values present also the advantage of a quantitative surveying during the product ageing.

Taking into account that the stability problem for the pharmaceutical products has been studied a lot and many investigations were performed concerning the principal degradation reactions (solvolise, isomerisation, oxidation, etc.) as well as regarding the influence of the storage conditions (temperature, humidity, container quality, etc.) on the product, perhaps the study presented above will be able to suggest another method useful for this purpose.

Resuming the above conclusions, the utility of the experimental study presented in this paper, may be related mainly to the adequability of the blue light in the white drug color quantitative estimation, the suitability of the "white degree" measurements for the products ageing monitoring as well as for different white drugs comparison, the advantages of the box-plot graphic method in the direct, visual estimation of some distributions.

The most significant features of the distribution curves representation by the box-plot method (in comparison to the classical one, based on the average value and the interval, always symmetric, determined by the standard deviation), are: the total data points numbers can be of thousands, hundreds or only decades, the total values range is divided in three new intervals (the "box length", the "box tails", the outliers) able to give more intrinsic information on the curves symmetry, on the weight of different size data and on the exceptional data point values.

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