EVALUATION OF THE FRACTIONATION OF TEN MEDICINES IN TABLETS UNDER THREE METHODS IN COSTA RICA

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ABSTRACT

To obtain the correct dose it was sometimes necessary to split tablets. Some organizations have developed guides in order to verify the quality of the tablets with functional score and their fragments. The objective of this work was to evaluate the fractionation of tablets in halves, performed with three methods and applied to ten medicines used in pathologies of epidemiological relevance in Costa Rica. For each medicine, 60 participants fractionated a tablet once with splitter, knife and hand. The errors produced in the fractionation was determined. The tablet breaking force and the uniformity of mass of whole tablets were verified and the test of uniformity of mass and the percentage of loss of mass was applicable to tablets halves. The results showed that 98% of the whole tablets were in the expected range of Percentage deviation of mass average. No pattern linked the breaking force with the results of tablets halves. A high number of errors in the fractionation were associated with the knife. About tablets halves, the splitter showed the better accuracy for split, and the good results in percentages of loss of mass were evidenced for the fractionation with hand. The fractionation showed a global waste of 46% of 1,800 tablets available for the study. Atenolol and warfarin sodium have the higher levels of waste, which draw attention due to their high consumption associated with to the epidemiological profile of population. These findings should not be extrapolated to other unanalyzed batches and neither to other drugs.

KEYWORDS: Splitting, Tablet, Weight, Uniformity, Pharmacy.
INTRODUCTION

The efficacy, safety and quality of the pharmaceutical drugs are indispensable for successful pharmacological therapy. Achieving dose adjustment is sometimes complex and in some cases it is necessary to divide the tablet to obtain the correct amount of active ingredient.\(^1\text{-}^7\)

Splitting the tablets has caused errors\(^8\) which affects the dose and it was a risky practice, but sometimes necessary. The sources of these errors mainly involved the pharmaceutical formulation (the design, manufacture, the physical characteristics\(^9\text{-}^{10}\) the uniformity of content of the active ingredient\(^11\), and others\(^12\text{-}^{13}\)); also the age, ability and training of the people breaking tablets\(^14\text{-}^{15}\) and the method or instrument used to divide.\(^16\text{-}^{17}\)

There have been many studies evaluating different aspects of tablet fractionation as mentioned by Burnham\(^18\) and also several concerns in international organizations for establish some guidelines or regulations to attained pharmaceutical formulations with better flexibility in dosage, like as the World Health Organization that has issued criteria for some specific children’s preparations.\(^19\)

Similarly, in the last two decades, some pharmacopoeias have included determinations to verify the quality of the tablets with functional score, for example, the European Pharmacopoeia (Eu Ph)\(^20\), the United States Pharmacopeia (USP)\(^21\) and The International Pharmacopoeia.\(^22\) These regulations confirm the need to take special care in the manufacture of tablets having a functional score, in order to obtain the same amount of active ingredient in each half.\(^23\)

In addition, with respect to the clinical part, it is known the existence of pharmacological treatments with low doses or with a stepped dose adjustment, particularly in pathologies of high epidemiological relevance. In the Costa Rican context, there are some examples of these illnesses: arterial hypertension\(^25\), cardio and cerebrovascular\(^26\) and psychotic diseases.\(^24\)

In other hand, the repercussions of the waste caused by dividing tablets may affect the cost of treatment and cause overspending costs for the patient and the health system, as well as several implications for the therapeutic approach to the disease and people's quality of life. In Costa Rica, to date, no published studies have been found on fractionation of tablets.
The objective of this work was to evaluate the fractionation of tablets performed with three methods and applied to ten drugs used in pathologies of high epidemiological relevance in Costa Rica.

MATERIALS AND METHODS

This research was endorsed by the Scientific Ethics Committee of the UCR, which requested the delivery of an information sheet to the people participating in the study.

For the presentation of the methodology, the chronological order of the activities was used, which consisted of:
1. Selection of Active Ingredients for Tablets
2. Fractionation of tablets
3. Physical determinations made on whole tablets and tablets halves

1. SELECTION OF ACTIVE INGREDIENTS FOR TABLETS

A search was made for the medications in tablets halves prescribed by doctors from the following hospitals of the Costa Rican Social Security Fund (CCSS in Spanish), in San José, capital of Costa Rica: National General Geriatric Hospital Dr. Raúl Blanco Cervantes (HNGG in Spanish), San Juan de Dios Hospital, Dr. Rafael Angel Calderón Guardia Hospital and National Children's Hospital Dr. Carlos Sáenz Herrera. The data were obtained thanks to the cooperation of the doctors Sáenz, Montero, Wittingham, Umansor and Carballo, belonging to different Units and Pharmacy Services of the CCSS.

After lifting a list of drugs prescribed in half tablets, it was verified the existence of these aspects
- High frequency of prescriptions
- Use in pathologies of high epidemiological impact
- The active principles of the drugs in relation to the narrow therapeutic index, therapeutic group
- The need to perform studies of therapeutic equivalence
- The existence of first-pass metabolism or metabolism linked to pharmacogenetic conditions, crystalline polymorphism, stability conditions
- Laboratory facilities for physico-chemical and economic feasibility for acquisition.
- Based on these parameters and for convenience, ten active drug principles were chosen for use in three outpatient age groups
Table 1. Active principles and strength of the drugs chosen for the study according to three age groups.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Active ingredient and drug content per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 12</td>
<td>Risperidone 1 mg, Paracetamol 500 mg, Dimenhydrinate 50 mg</td>
</tr>
<tr>
<td>13 - 64</td>
<td>Hydrochlorothiazide 25 mg, Spironolactone 100 mg, Atenolol 50 mg, Furosemide 40 mg</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>Carvedilol 6.25 mg, Levothyroxine sodium 100 µg, Warfarin sodium 5 mg</td>
</tr>
</tbody>
</table>

The active ingredients in Table 1 are used in chronic treatments with the exception of paracetamol 500 mg and dimenhydrinate 50 mg, which are administered in short periods.

After the drugs were selected, the tablets were obtained in two ways, by:

1. Donation in the Pharmacy of the HNGG and the Pharmacy of the Office of Welfare and Health (OBS in Spanish) of the UCR.
2. Acquisition in Private Assistance Pharmacies of San José, Costa Rica, whose names remain anonymous for confidentiality matters.

The conditions of conservation and storage of the tablets were not known before they were obtained. After they being obtained, the tablets were kept in their original packaging and they were stored in a dry place, protected from direct light and in normal conditions (without controlled temperature and humidity).

2. FRACTIONATION OF TABLETS

The instruments used to split the tablets were an Ezy Dose Safety-Shield Pill Splitter (EZYT™ CARE), a blunt knife and the hands. The use of latex gloves were protected the operator and the pharmaceutical product.

Different people participated in the activities of this research. The main actions performed by the assistants are related to the packing process, preparation of a code for the samples under study, selection of the participants and the participation to aid in the sessions of fractionation. The researchers participated in the general organization, recruitment of participants and in the performance of tests and physical determinations.

2. a. PREPARATION OF INPUTS FOR FRACTIONATION SESSIONS

It was counted on the collaboration of students of the career of Pharmacy or Chemistry of the UCR as support personnel. They signed a confidentiality agreement. Each person was trained by the researchers to carry out the required tasks that at this stage were the following:
a) Purchase of supplies such as plastic bags, stickers, pilots pens.

b) Establishment of an alphanumeric and color coding, to avoid biases of appreciation of the researchers after the fractionation and during the weighing. The coding included the active principle, the participant number, the fractionation methods and the sequencing of its ordering on the day of fractionation. An example of the coding is shown in table 2.

Table 2. Coding to identify the samples under study

<table>
<thead>
<tr>
<th>Code</th>
<th>Method position and color code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>R-01</td>
<td>Knife (Pink)</td>
</tr>
<tr>
<td></td>
<td>Splitter (Blue)</td>
</tr>
<tr>
<td></td>
<td>Hand (Green)</td>
</tr>
<tr>
<td>R-02</td>
<td>Knife (Yellow)</td>
</tr>
<tr>
<td></td>
<td>Hand (Pink)</td>
</tr>
<tr>
<td></td>
<td>Splitter (Green)</td>
</tr>
</tbody>
</table>

As can be seen in table 2, it includes:

- The initial letter of the international name of the active substance (R of risperidone)
- The number of participants (01 for the first participant, 02 for the second, etc.)
- The color for each method and the allocation of the ordering method from left to right, to be used on the day of fractionation

For the first participant, the number 01 was assigned. On the day of fractionation, the participant found the instruments in the following order: knife, splitter and empty space for the hand.

For the second participant, the number was 02. From left to right, the organization of the methods was knife, hand and splitter.

It is verified that in the two participants will appear a green color label. And that color is not associated with the same fractionation method

A plastic bag of 20 x 5 cm was sealed in half with heat to have two compartments. On each of them was placed a label with the coding of the active principle, participant number, color of the method plus the letter A or B, to identify each tablet half.

The three bags of each participant were organized according to the position to be followed in the fractionation.

c) Installation of blankets and paper tablecloths used in tables during fractionation of tablets
2. b. SELECTION AND ROLE OF PARTICIPANTS

The number of 60 participants was selected for convenience according to available financial resources.

In each fractionation session, adults of both sexes, aged between 18 and 64, were contacted, listed from minor to major as they were present in the enclosure intended for this purpose. It was observed that they had the required age, adequate motor capacity, good vision and no latex allergy.

To each interested person who fulfilled the above requirements, he was given the information sheet explaining in simple words the following:

- The objective of research and the voluntary participation.
- The absence of consequences if the voluntary is not wanted to participate or if it is accepted to participate but it is decided to retire at any time during the fractionation.
- There will be collaboration of the health personnel of the enclosure to attend any emergency caused by cuts or other eventualities, produced in the session of fractionation.
- There is no time limit to carry out the activity. A tablet will be split in half with each fractionation method: splitter, knife and hand. There will be no indication of how to split, to simulate a real situation. Latex gloves will be worn.
- Do not worry about the result obtained, because the research wants to know if the tablet could be broken or not, or if it split exactly in half, or if many fragments remained or if it was sprayed.
- Part of the study was to know if it was easy or difficult to break the pills. Do not worry about picking up any clutter, as students will pick up and clean the site.
- If the person gives consent, eventually a photograph could be taken for the purpose of illustrating some publication of the results. If the person does not want to be photographed, their decision will be respected.
- After the participation, information will be requested about the sex, age and comments about the fractionation. The information will remain anonymous.
- There will be no economic reward or any compensation for participation.

2. c. TABLET BREAKING SESSIONS

The place chosen for the fractionation sessions had the voluntary collaboration of trained personnel in case of requiring first aid. For convenience, the HNGG Clinical Laboratory
waiting room (for warfarin sodium 5 mg) and a space located opposite the OBS's receipt for
the rest of the pharmaceutical products were chosen as places. There were 10 sessions; one
per active principle, where the population of participants was different each time, for
convenience and each person applied the three methods of fractionation once.

In each session, 60 tablets were cut with a splitter, 60 with a knife and 60 with the hands, for
180 tablets as a total per active drug.

During the sessions, the assistant students supported the following tasks:

a) Place on the screens, clean paper tablecloths, 3 weighing papers with one tablet each,
immediately removed from its primary packaging. For each participant, the instruments were
placed in the order according to the established codification. Latex gloves were used to avoid
contamination due to moisture, foreign particles or cross-contamination.

b) Receive the participants, tell them to use the appropriate size of gloves (small, medium or
large) and remind them not to worry if the operations to be split were not as expected and
leave the fractions untouched. They were told the order in which the tablets were to be
broken. No instructions were given on the best way to split with each method. It is requested
to split the tablet on the weighing paper placed under each instrument and not change the
order arranged for it.

c) After the fractionation, a student only dedicated to this function, recorded in an electronic
sheet of Excel and according to the codification assigned to each participant, the age and the
sex of the participants, besides the appreciations and observations of the fractionation
realized.

d) While the data of the participants were taken, other students placed, in the paper
corresponding to each method, the fractions and the corresponding residues. The weighing
paper was folded in half, closed at the top by a double fold and a single fold on each side to
be held between them at the back.

e) Check the participant's code and the fractionation method and place each folded paper in
one of the compartments of the coded bag. Fold the bag, close it and place it in the desiccator
with silica gel. The bags remained in these conditions for a maximum of three days until the
moment of the respective weighing that would realize the investigators.
f) Shake, dry clean the tablecloth and utensils of the study and prepare the space according to the order and coding of the next participant.

2. d. PARTICIPATION OF RESEARCHERS DURING POST-FRACTION WEIGHING

The researchers were pharmacists specializing in Physicochemical Quality Control of Medicines. Before weighing, the existence or not of fractionation errors was observed. These errors were classified as: occurrence of a single half, presence of three, four and more than four fractions, finding a fraction greater than 75% of the whole tablet and finding the whole tablet without fractionation. These cases were excluded from the weights.

If these errors were not found, the weight of each fraction and the residue was obtained. The total weight or mass of the whole tablet was established by summing the three values obtained. Weights were performed on a calibrated analytical balance (Accurate LS 120A ± 0.0001g, Switzerland), gloves, grippers, additional weighing papers and cleaning brushes were used.

Whole tablets were not weighed before being fractionated to avoid errors due to tablet stability after removal from the original package and to the effect that moisture and temperature on the weight could cause.

Each heavy tablet half was placed on a weighing paper and closed in the same manner as explained above.

A register of alphanumeric, color and letter A and B coding corresponding to the active ingredient, the participant number and the weights of the halves A and B and the tablet residues corresponding to the color of the corresponding sticker were taken.

One half of the tablet packed in the paper was placed in compartment A and the other in compartment B. The compartments were heat sealed and placed in the vacuum desiccator for further studies.

At the end of all the weights the researchers asked the students for the codification to perform the decoding of each carried out and to make the calculations of the ones of the study.
At the end of the study of each active principle of the drugs, the residues of all tablets and other material used were discarded following the procedures established in the UCR, according to each case, and were moved to a suitable place for final disposal.

3. PHYSICAL DETERMINATIONS MADE ON WHOLE TABLETS AND TABLETS HALVES AFTER FRACTIONATION

The procedures for the determinations used by the investigators in the study are described below:

**PHYSICAL CHARACTERIZATION OF THE WHOLE TABLETS OF EACH MEDICINE**

The morphology of the tablets was recorded, the following aspects were considered: color, geometry, presence of central score and dimensions. It was measured with a Vernier caliper handling (Royal, type 6931, ± 0.1 mm, Switzerland).

**STRENGTH OF RUPTURE OF WHOLE TABLETS**

The procedure described in the General Chapter <1217> Tablet Breaking Force of the USP 37[27]. For this, the tablets are oriented with their scores perpendicular to the platen faces of a durometer (ERWEKA®-Apparatebau-GmbH, type TB 24, ± 0.5 N, Germany). A number of 10 tablets were analyzed for each drug and the mean was calculated. This test had no acceptance values for the tablets, therefore only the average of the measurements and the relative standard deviation were reported.

**NUMBER OF FRACTIONATION ERRORS**

The number of tablets that presented errors during fractionation according to each fractionation method was determined according to the following classification:

- Only an a half present
- Three fractions present
- Four fractions present
- More than four fractions present
- A fraction greater than 75% of the whole tablet
- Whole tablet

For each active ingredient, the percentage of errors was calculated according to the 60 tablets fractionated by each method.
UNIFORMITY OF MASS OF WHOLE TABLETS

The procedure was based on the methodology for uncoated tablets and film-coated tablets, formulated to contain 5% or more of the active ingredient, of the General Chapter 5.2 Uniformity of mass for single-dose preparations of the International Pharmacopoeia, sixth edition.[27]

The test acceptance criteria were not applied since the number of tablets in the study was different from 20. For comparison purposes, the data were distributed according to the limits of minimum and maximum percentages stated in the official general chapter. The procedure was as follows:

Weigh the tablets and calculate the average mass. The nominal percentage of content of the active principle per tablet was calculated. If the latter value was equal to or greater than 5%, the percentage of the deviation of each individual mass from the average was obtained.

The number of tablets present in the ranges was obtained depending on the average value of the tablet mass
± 10.0 and ± 20.0% if the mass average <80.0 mg
± 7.5 and ± 15.0% if the mass average is between 80.1 and 250.0 mg
± 5.0 and ± 10.0% if the mean mass ≥ 250.1 mg

The 90% or more of the results in all ranges should be in the first margin and the 10% of the results or less should be in the second margin in each range

UNIFORMITY OF MASS OF THE TABLETS HALVES

The methodology of the general chapter, <705> Quality attributes of tablets labeled as having a functional score of the USP 37[21] was used but with a modifying in the equation of the nominal mass. For this study, it was considered that the mass of the whole tablet corresponding to that fraction divided by two was the nominal mass. In addition, this test was performed on all halves of tablets, not only on 30 halves described by the USP.

Each mass percentage (X) was classified according to 5 categories, namely (where X is the mass percentage of each half)

X <75%
75 <X <85%
85 ≤ X ≤ 115%
115 <X ≥ 124.9%
X > 125%

It is calculated the summation of the number of halves corresponding to each category by the particular method for each drug. These values were relativized into percentage in order to make comparisons between the findings. This is because the number of fractionation errors was not the same neither by drug nor by method.

Although all halves of tablets were used, the following acceptance criteria were maintained:
0 data in the category <75% and in category X > 125%
only a one mass at most in the categories 75 < X < 85% and 115 < X ≥ 124.9%
99 data between the percentages of 85 ≤ X ≤ 115%

PERCENTAGE OF MASS LOSS WHEN FRACTIONATING TABLETS
The effectiveness of fractionation was assessed and the criteria of the FDA guideline regarding the ability to divide tablets “Tablet splitability” were followed.[29]

The mass of the residue produced in the fractionation of each tablet were used and the percentage of residue was calculated in relation to the weight of the corresponding whole tablet. All available data were used and although it was not considered the number of 15 tablets indicated by the FDA, the specification that the percentage of mass loss should be less than 3.0% was conserved.

ESTIMATION OF TABLETS WASTAGE IN THE STUDY OF FRACTIONATION
Due to the existence of multiple variables associated with tablets wastage during fractionation, an actual value of wastage can not be found. Therefore, to estimate the tablets wastage produced in this study, it was taken in account the sum of three factors: the number of tablets with fractionation errors, the tablets with an unacceptable result in the weight uniformity test of the tablet halves, and finally, the tablets with a bad result of percentage of the mass loss. In this calculation, it was considered the participation of 600 people who divided 1800 tablets as a total.
RESULTS AND DISCUSSION
LIMITATIONS OF THE STUDY AND ITS INFLUENCE ON THE RESULTS OBTAINED

Some of the limiting conditions of the study that had to be taken into account to discuss the results obtained. The following were considered as limitations:

The findings of this study should not be extrapolated to unanalyzed batches and drugs. The large interrelation between the variables that intervened in the fractionation of the tablets in half, does not allow independent quantification of each of them because they are multiple and of several types.

The maintenance of the quality of the medicines depends to a large extent on the conditions of storage, conservation, stability and date of expiration. The conditions in which the drugs were found before the study were unknown and the expiration dates were different for the ten products analyzed. Although all tablets were fractionated in dates prior to their expiration, there could be a variability of the results associated with the indicated conditions that were not quantified.

The selection of the active ingredients of the tablets was based on the medical prescription made during two months in four specific hospitals and the duplicate recipes were eliminated per patient. The active principles could have been different from those chosen, if the data collection time had extended to a year or more.

The age and sex distribution of the participants did not show a significant difference between the ten populations of 60 participants, whose ages ranged from 18 to 70 years and the distribution by sex was close to 30 ± 6 males and 30 ± 6 females. There was no relationship between the results obtained in the accuracy and efficiency of the fractionation and the different age groups and sex.

By not giving the participants any indication as to how best to split the tablets, the results of this study could not be compared with those obtained in other studies whose participants had other characteristics such as being students or health personnel, laboratory workers, trained patients, young people and seniors of day centers or hospitals, who would be more careful when breaking down with the three methods used.
The results obtained in this research are influenced by the natural ability of the inexperienced people who voluntarily participated in the fractionation. We did not consider the experience of people to split, nor measured the strength or motor ability before splitting. Therefore, there were no parameters to correlate the number of individual hits with the accuracy and effectiveness of the fractionation with the three methods.

RESULTS OF PHYSICAL TESTS

PHYSICAL CHARACTERIZATION OF TABLETS AND BREAKING STRENGTH

Table 1 summarizes the characteristics of the tablets.

For the tablet shape, C is considered cylindrical, O is oval; on the side, C is convex and P is flat. In the score, the C stands for central, CS is cross and WS, without score, and the number two in parentheses means that a score present on both sides. * Refers to length (mm) and width (mm) instead of diameter.

<table>
<thead>
<tr>
<th>Active substance of medicine</th>
<th>Shape</th>
<th>Side</th>
<th>Score</th>
<th>Diameter (mm)</th>
<th>High (mm)</th>
<th>Volume (cm³)</th>
<th>Tablet breaking force (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone 1 mg</td>
<td>O</td>
<td>C</td>
<td>C</td>
<td>*11.7 x 5</td>
<td>3.0</td>
<td>0.18</td>
<td>70.0 ± 9.0</td>
</tr>
<tr>
<td>Paracetamol 500 mg</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>11.8</td>
<td>5.7</td>
<td>0.62</td>
<td>102.8 ± 6.6</td>
</tr>
<tr>
<td>Dimenhydrinate 50 mg</td>
<td>C</td>
<td>C</td>
<td>CS</td>
<td>8.8</td>
<td>4.0</td>
<td>0.24</td>
<td>56.5 ± 3.2</td>
</tr>
<tr>
<td>Hydrochlorothiazide 25 mg</td>
<td>C</td>
<td>P</td>
<td>C</td>
<td>9.2</td>
<td>3.0</td>
<td>0.20</td>
<td>39.3 ± 8.5</td>
</tr>
<tr>
<td>Spironolactone 100 mg</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>12.4</td>
<td>5.0</td>
<td>0.60</td>
<td>&gt; 150</td>
</tr>
<tr>
<td>Atenolol 50 mg</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>8.9</td>
<td>4.9</td>
<td>0.30</td>
<td>81.8 ± 8.7</td>
</tr>
<tr>
<td>Furosemide 40 mg</td>
<td>C</td>
<td>P</td>
<td>WS</td>
<td>8.7</td>
<td>2.8</td>
<td>0.17</td>
<td>44.3 ± 4.3</td>
</tr>
<tr>
<td>Carvedilol 6.25 mg</td>
<td>C</td>
<td>P</td>
<td>C (2)</td>
<td>7.0</td>
<td>2.2</td>
<td>0.08</td>
<td>36.3 ± 3.2</td>
</tr>
<tr>
<td>Levothyroxine sodium 100 µg</td>
<td>C</td>
<td>P</td>
<td>C (2)</td>
<td>7.3</td>
<td>2.6</td>
<td>0.11</td>
<td>60.7 ± 5.9</td>
</tr>
<tr>
<td>Warfarin sodium 5 mg</td>
<td>C</td>
<td>C</td>
<td>C (2)</td>
<td>9.3</td>
<td>4.4</td>
<td>0.30</td>
<td>41.0 ± 1.3</td>
</tr>
</tbody>
</table>

The tablets of risperidone 1 mg have an oval shape; the others are cylindrical as shown in Table 1. The faces of six medications are convex and the rest are flat. Only furosemide 40 mg does not have a score. Carvedilol 6.25 mg and levothyroxine sodium 100 µg have one score on each side. Only dimenhydrinate 50 mg has scores in cross.

The most of tablets had volumes between 0.17 and 0.3 cm³, and this condition reflects an adequate quality according to the preferences of the participants in surveys applied by Ibrahim et al. [30]
The tablets of risperidone 1 mg have an oval shape; the others are cylindrical as shown in Table 1. The faces of six medications are convex and the other are flat. Only furosemide 40 mg does not have a score. Carvedilol 6.25 mg and levothyroxine sodium 100 µg have a score on each side. Only dimenhydrinate 50 mg has a cross shape score.

The size, oval morphology and functional score of risperidone 1 mg facilitate its division. This finding also agrees with van der Steen et al.\textsuperscript{[12]}

Of the cylindrical tablets, only carvedilol 6.25 mg and levothyroxine sodium 100 µg had diameters less than 8 mm. The rest of tablets with round shape could possibly present difficulties for their ingestion, either by adhesion, or by slow esophageal transit, as warned by the EMA\textsuperscript{[8]} and FDA.\textsuperscript{[31]} The same situation could be occurred for flat tablets, such as hydrochlorothiazide 25 mg and furosemide 40 mg. It does not known the existence of studies that related the transit difficulties in the organism with the physical characteristics of the halves of tablets. Others considerations as the variations in the tablets halves content, weight, disintegration, or dissolution, could change the expected quantity of active principle available to be absorbed, like as was commented by Zhao et al.\textsuperscript{[32]}

**NUMBER OF FRACTIONATION ERRORS**

Figure 2 presents the quantification of the fractionation errors of 1,800 tablets available for this study, without specifying the individual contribution of each drug.

![Percentage of fractionation errors of all tablets under study by method](image)

**Figure 2. Frequency distribution of percentage of errors per drug according to each fractionation method applied**
Figure 2 reveals that the knife and the hand produce the greater errors. With knife there were 234 tablets broken into three fragments. The 16% of 1,800 tablets were intact because they could not be broken by hand.

Adding the errors of the 3 methods showed a 25.5% wastage of the 1,800 tablets acquired for the study, taking into account only the division maneuver, whose results prevented the application of the physical determinations.

None of the participants in the fractionation was voluntarily withdrawn; therefore, the number of 60 persons who fractionated the drugs of each active principle with the three methods was maintained. This allowed comparisons between the results of the drugs studied.

The fractionation pattern of 60 tablets was different for each method, which can be observed in table 2.

Table 2. Percentage of tablets per drug active with fractionation errors according to each method applied

<table>
<thead>
<tr>
<th>Drug Active Principle</th>
<th>Splitter</th>
<th>Knife</th>
<th>Hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone 1 mg</td>
<td>3</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Paracetamol 500 mg</td>
<td>7</td>
<td>47</td>
<td>22</td>
</tr>
<tr>
<td>Dimenhydrinate 50 mg</td>
<td>8</td>
<td>12</td>
<td>63</td>
</tr>
<tr>
<td>Hydrochlorothiazide 25 mg</td>
<td>12</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Spironolactone 100 mg</td>
<td>5</td>
<td>22</td>
<td>45</td>
</tr>
<tr>
<td>Atenolol 50 mg</td>
<td>25</td>
<td>35</td>
<td>55</td>
</tr>
<tr>
<td>Furosemide 40 mg</td>
<td>20</td>
<td>52</td>
<td>5</td>
</tr>
<tr>
<td>Carvedilol 6.25 mg</td>
<td>12</td>
<td>38</td>
<td>32</td>
</tr>
<tr>
<td>Levothyroxine sodium 100 µg</td>
<td>10</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>Warfarin sodium 5 mg</td>
<td>18</td>
<td>92</td>
<td>20</td>
</tr>
</tbody>
</table>

Also, in Table 2 we have that none of the methods was 100% effective for dividing the tablets and the knife turned out to be three times worse than the splitter.

As for drugs, 92% of warfarin sodium 5 mg presented poor fractionation with a knife. The most frequent error in this medication was the fragmentation of tablets into three parts.

In the case of dimenhydrinate 50 mg, atenolol 50 mg and spironolactone 100 mg, it was impossible to carry out the division, leaving whole tablets.

Participants reported these observations, but it was the researchers who defined these criteria. This allowed obtaining a uniformity and avoiding the subjectivity in the appreciation of...
errors, given the high number of fractionated tablets. This way of proceeding contrasts with that reported by Pautas et al\textsuperscript{[33]}, where the correct fractionation was judged by those who split. On the other hand, Hill and collaborators in a research where only the splitter was used\textsuperscript{[34]} and errors were classified according to the minimum, moderate and significant degree of pulverization; but, the number of non-fractionated tablets was not taken into account.

The variation in the number of errors can not be compared with other articles because of the diversity of variables related to the drug, the instruments to be used and the characteristics of the participants.

**UNIFORMITY OF MASS OF WHOLE TABLETS**

When calculating the percent content (mg active principle multiplied by 100 and divided by mg of the mass average per drug), it was found that:

- The tablets of risperidone 1 mg, levothyroxine sodium 100 µg and warfarin sodium 5 mg presented percentages of content below 5%. Values were 0.5; 0.1 and 2% content respectively.
- Therefore, they were not analyzed.

With content percentage above 5%, dimenhydrinate 50 mg, hydrochlorothiazide 25 mg, atenolol 50 mg, furosemide 40 mg, carvedilol 6.25 mg, paracetamol 500 mg and spironolactone 100 mg were found. Of the drugs listed in the second group, the first five had averages of tablet masses greater than 80 mg and less than 250 mg; while the last two medications had averages above 250 mg.

Whole tablets of the seven drugs were analyzed and for the results evaluation, there were two ranges as indicated by the pharmacopoeial methodology.

It was found that more than 90% of the individual tablet masses of these seven drugs are within the narrow margins of the specification. That is ± 7.5 for the first five drugs (80 to 250 mg) and ± 5 for the second (> 250 mg).

With regard to compliance with the second range of ± 10 and ± 5 respectively, it was obtained that dimenhydrinate 50 mg and paracetamol 500 mg presented acceptable values in these lax margins. However, it was not so for hydrochlorothiazide 25 mg, furosemide 40 mg,
carvedilol 6.25 mg and spironolactone 100 mg, instead of finding 10% of values in that lax range, they presented 9.25% instead of 10%. Finally, atenolol 50 mg showed a compliance of 8.20% instead of 10%.

It is to rescue that 98% of the masses of the whole tablets analyzed, of seven medicines, conform to the determination of mass uniformity. And that whole tablets outside the specification globally correspond to 6 tablets, which could be a negligible value given the study conditions, in particular as regards mass losses due to errors in the collection of residual dust, Which was present at the tables, after each participant fractionated the tablets.

1. UNIFORMITY OF MASS OF THE HALVES OF EACH TABLET
There was no 100% effectiveness of fractionation or between methods, nor between drugs. There were some contrasts worth mentioning, for example those between atenolol 50 mg and levothyroxine sodium 100 µg.

According to figure 3, the majority of the data outside the limits of 85 to 115% are mainly presented with atenolol 50 mg. The degree of dispersion of the data is associated from highest to lowest with the splitter, knife and hand methods.

The levothyroxine sodium 100 µg presents values closer to those of the specification, however, it does not meet the acceptance requirements for determination of uniformity of mass of tablets halves.

Figure 3. Determination of uniformity of mass of tablets halves of atenolol 50 mg and levothyroxine sodium 100 µg obtained with each fractionation method.
Zaid and Ghosh proposed a relationship between hardness and mass uniformity for atenolol 100 mg tablets from two different manufacturing laboratories, so that at higher hardness, lower data dispersion in mass uniformity.\textsuperscript{[35]}

If this assumption is extrapolated to different drugs, it is expected that a similar relationship will be maintained. The data obtained, by hand fractionating atenolol 50 mg and levothyroxine sodium 100 \( \mu \)g, follow the pattern of behavior indicated by Zaid and Ghosh.\textsuperscript{[35]} But, for the halves of spironolactone 100 mg and atenolol 50 mg, the relationship is different: the higher the hardness, the greater the dispersion of data in the uniformity of mass. This reflects that it is necessary to take into account other variables, relative to the fractionation, to be able to establish relations between these physical tests.

For the calculation of the percentage in uniformity of mass, the use of the nominal value conditions the results to obtain: it is not equal to take into account half of the average mass of 15 whole tablets, that half of the mass of the corresponding tablet. This makes the results of this study not comparable with others, for example with those found by Hill and colleagues for warfarin sodium 5 mg.\textsuperscript{[34]} In addition, we must consider the difference in the number of tablets halves analyzed in the studies.

1. PERCENTAGE OF LOSS OF MASS WHEN FRACTIONATING THE TABLETS

The comparison of the results of this determination was recorded in Table 3, where the most ineffective method in fractionation, particularly for warfarin sodium 5 mg, is that of the knife with 100\% out-of-specification results. However, for comparative purposes, it should be considered that only 5 tablets of this drug were fractionated in adequate halves, whereas with the other medicines the number of tablets was higher.

| Table 3. Percentage of tablets analyzed with mass loss greater than 3\% |
|-----------------|----|----|----|
| Risperidone 1 mg | 0  | 4  | 2  |
| Paracetamol mg   | 4  | 3  | 0  |
| Dimenhydrinate 50 mg | 0  | 2  | 9  |
| Hydrochlorothiazide 25 mg | 8  | 40 | 2  |
| Spironolactone 100 mg | 0  | 6  | 0  |
| Atenolol 50 mg   | 16 | 15 | 15 |
| Furosemide 40 mg | 4  | 24 | 2  |
| Carvedilol 6.25 mg | 11 | 38 | 2  |
| Levothyroxine sodium 100 \( \mu \)g | 6  | 36 | 2  |
| Warfarin sódica 5 mg | 14 | 100| 6  |
The lack of efficacy of the knife was also given for hydrochlorothiazide 25 mg, carvedilol 6.25 mg, levothyroxine sodium 100 µg and furosemide 40 mg, as shown in table 3. There was no great difference between the fractionation methods for atenolol tablets, which had values of 15, and 16%.

In Table 3, splitter and knife percentages showed a tendency to facilitate splitting of risperidone 1 mg, dimenhydrinate 50 mg and spironolactone 100 mg tablets.

On the other hand, a direct relationship between the results of this test and those of the rupture strength for cylindrical tablets was not demonstrated. However, this ratio did occur in risperidone 1 mg, whose form is oblong.

The pressure exerted on the tablet when trying to divide it into two is different between methods and is a variable to consider when comparing methods with splitter, knife and hand. In this sense, most tablets had better results when fractioned with the splitter, where the pressure is exerted in the groove and not in the edges of the tablet. It would be expected that in the division of a tablet into halves, the force be given at the edges and not over the score.\[^{36}\] This way of departing is indicated by the pharmacopoeial tests\[^{21}\] and some guides of sanitary authorities\[^{29}\] for scored tablets.

The score in the tablets are not always made to achieve the division into equal fragments, sometimes they are markings that serve to stabilize the tablet after its compression with the punch.\[^{37}\] The results of mass loss and its relationship to the tablet scores can not be linked to the results that were obtained because the characteristics established by the manufacturers of the study tablets are unknown.

It is noteworthy that the results showed that furosemide 40 mg without score has few values out of specification with the hand and splitter methods, but not with the knife. It is interesting to note that this divided tablet with the knife presented a 52% loss by fractionation error and barely 5% by hand.

### 1. DISCARDED TABLETS PRODUCT OF THE FRACTIONATION

During this fractionation study of 1,800 tablets in halves, three variables were identified by which tablet wastage was quantified in this experiment. The variables are as follows:

1. Fractionation errors
2. Nonconformities in mass uniformity
Out of specification in % mass loss

The effect of each variable was different for each type of tablet as shown in Table 4.

**Table 4. Effect of the variables associated with the discard of tablets during the study according to each drug active principle.**

<table>
<thead>
<tr>
<th>Variables associated with tablet wastage</th>
<th>Fractionation errors</th>
<th>Nonconformities in mass uniformity</th>
<th>Out of specification in % mass loss</th>
<th>Total tablets discarded per drug substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone 1 mg</td>
<td>12</td>
<td>16</td>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td>Paracetamol 500 mg</td>
<td>45</td>
<td>29</td>
<td>3</td>
<td>77</td>
</tr>
<tr>
<td>Dimenhydrinate 50 mg</td>
<td>49</td>
<td>14</td>
<td>3</td>
<td>66</td>
</tr>
<tr>
<td>Hydrochlorothiazide 25 mg</td>
<td>37</td>
<td>34</td>
<td>22</td>
<td>93</td>
</tr>
<tr>
<td>Spironolactone 100 mg</td>
<td>43</td>
<td>12</td>
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<td>Atenolol 50 mg</td>
<td>69</td>
<td>42</td>
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<td>31</td>
<td>16</td>
<td>19</td>
<td>66</td>
</tr>
<tr>
<td>Warfarin sodium 5 mg</td>
<td>78</td>
<td>19</td>
<td>15</td>
<td>112</td>
</tr>
<tr>
<td>Total tablets per variable</td>
<td>459</td>
<td>245</td>
<td>116</td>
<td>820</td>
</tr>
<tr>
<td>Percentage of tablets of each variable with respect to 1,800 tablets</td>
<td>26</td>
<td>14</td>
<td>6</td>
<td>46</td>
</tr>
</tbody>
</table>

The total number of discarded tablets was 820 which corresponds to 46% of the 1,800 tablets available for this research. The majority of tablet wastage in this study was caused by fractionation errors, as can be seen in Table 4.

In Table 4, atenolol 40 mg was observed as the drug with the highest degree of wastage compared to other pharmaceutical products, followed by warfarin sodium 5 mg.

**CONCLUSIONS**

If we take into account the 1,800 tablets of the study, there were bigger errors when breaking with the hand, then with the knife and finally with the splitter. The product that produced minor fractionation errors was risperidone 1 mg and the greatest errors occurred for warfarin 5 mg, particularly 92% with knife fractionation. It is noteworthy that with this same method, furosemide 40 mg without score presents 52% fractionation errors.

The 98% of the whole tablets analyzed were within the specifications of the mass uniformity determination. This finding is important so that there are no factors that add to variations in the uniformity of mass of the tablet halves.
As for the tablets halves, no analyzed pharmaceutical product remained in the range of 85 to 115 of the expected mass percentage for the halves, there being a greater degree of dispersion of the data for the halves of atenolol 50 mg tablets, independently of the fractionation method. There were no differences between the fractionation methods with respect to the dispersion of the data in the mass uniformity test for tablets halves.

With the hand fractionation method, less mass loss (or greater fractionation efficiency) occurs, followed by the splitter and the knife. It was noted that although spironolactone 100 mg tablets had high percentages of fractionation errors, the tablets that do fractionate produce very little mass loss comparable to that of risperidone 1 mg tablets.

In most medicines, the methods of greatest to least accuracy and efficiency in the fractionation are the splitter, then the hand and finally the knife.

Although furosemide 40 mg tablets do not have a score, it fractionation results do not seem to indicate that the lack of score could induce a major error when splitting by hand, compared to other products whose functional scores are well pronounced.

The fractionation of 1,800 tablets, performed by 600 participants on a voluntary basis, shows a global waste of 46% of tablets available for the study.

Atenolol 50 mg presents a waste of 71% of available tablets and warfarin sodium 5 mg has a 62% of waste, which draw attention due to the high consumption of them as they respond to the epidemiological profile of the Costa Rican population.

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CONFLICT OF INTEREST
The authors state that there is no conflict of interest in the conduct of the research and publication.

REFERENCES


