WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 10, 62-91. Research Article ISSN 2277– 7105

QUALITY VERIFICATION OF SIX MEDICINES IN WHOLES AND HALVES TABLETS, RE-PACKAGED IN INDIVIDUAL PLASTIC COMPARTMENTS DURING SIXTY DAYS

Dr. Olga Baudrit* Eleaneth Baltodano, Luis Jimenez, Jeimy Blanco, Maria-Fernanda Jimenez

INIFAR Institute of Pharmaceutical Research, Faculty of Pharmacy, University of Costa Rica, San Jose, Costa Rica.

Article Received on
15 July 2017,

Revised on 04 August 2017,
Accepted on 25 August 2017

DOI: 10.20959/wjpr201710-9438

***Corresponding Author**
Dr. Olga Baudrit
INIFAR Institute of Pharmaceutical Research, Faculty of Pharmacy, University of Costa Rica, San Jose, Costa Rica.

ABSTRACT

Plastic boxes with individual compartments are often used to improve medication compliance and only a few studies have been done on the stability of the tablet halves after placing them on these devices. In this investigation, wholes and halves tablets of furosemide, hydrochlorothiazide, spironolactone, warfarin sodium and atenolol and levothyroxine sodium were re-packaged and storing for sixty days under normal environmental conditions. The physical characteristics were observed and the quality attributes were verified. There were no changes in physical characteristics of all products. All products, except halves tablets of atenolol, showed accuracy according the test of uniformity of mass. The comparisons of dissolution profiles between whole tablets and tablets halves were adequate for hydrochlorothiazide and atenolol, but not for formulations of furosemide, spironolactone and warfarin sodium. Levothyroxine sodium showed a different dissolution behavior than expected. Whole tablets of atenolol do not meet specifications for uniformity of contents, neither the halves tablets of atenolol and spironolactone. According to the results, it is possible to re-package wholes tablets of furosemide, hydrochlorothiazide, spironolactone and warfarin sodium; but it is not advisable to maintain this practice for whole tablets of atenolol and levothyroxine sodium, neither for the halves of the rest of the products, except hydrochlorothiazide. These findings may become opportunities for improvement for pharmaceutical laboratories, as well as become a study topic for practitioners to advise the use of multi-compartment compliance aids, finally,

these results should not be extrapolated to drugs, manufacturers, lots and conditions other than those used in this study.

KEYWORDS: Repackaging, drug stability, quality assurance, multicompartment compliance aids.

INTRODUCTION

Certain people should follow an appropriate therapeutic regimen, as part their therapy to treat the chronic pathologies that afflict them; however, as time passes they shows a tendency to decrease the compliance.[1-3]

The treatment adherence concept is very broad due to it encompasses behaviors, as lifestyles from the patients regarding to compliance all the recommendations given by the prescriber who play an important role in the adherence achieving, which includes not only pharmacological therapy, especially in complex diseases such as the diabetes mellitus.[4]

In this context, within the services or pharmaceutical practices in which information is provided to people, it is recommended the incorporation of routines that allow the systematic taking of the medication.[5] since it has been detected that forgetfulness is a frequent cause of error to achieve a successful therapy.

For example, the similarity in the form and color of medications taken by older people causes complaints and confusion, which is aggravated when they live alone or have physical limitations, impairment of cognitive function, comorbidities or are polymedicated persons. Therefore, the accompaniment and the development of specific strategies for them can mean an improvement in their life quality.[6,7]

A strategy to improve the evolution of pharmacological therapy in patients from older populations and that is also applicable in children under twelve is to include family caregivers and caregivers in the activities to be developed.[8]

Adherence to treatment in chronic conditions is complex, generally will be for life and often causes fatigue and restlessness. Therefore reinforcements are required to establish habits that remain in the time.[9] Forgetting to take medications is a common problem that tends to improve with mnemonic help, such as the use of portable plastic boxes that contain several compartments identified with the schedules and the respective intake days of intake.[10]

These devices are designed with a certain number of compartments, which is variable; usually they are manufactured with 7 or 28 spaces[11] or with another presentation type[12] and can be purchased in multiple shopping centers. There is also the traditional pill box of a single compartment, which is recommended for short trips. Despite the increasing use of these in outpatients, little is known about changes in physical attributes, quality, and drug stability that may develop if the pharmaceutical formulations are removed from their original container and packaged again in a different container such as the plastic boxes with compartments.

In order to establish habits to achieve a successful adherence to the pharmacological treatment of patients, caregivers must be integrated into the health team. The nurses and people are in charge of medication management sometimes do not have much knowledge about medicines or the care that must be taken during their administration, which is vital in nursing homes.

In the treatment of acute short-term illnesses, lack of adherence rarely occurs, unless adverse effects appear or if there are other reasons, while in hospitals, inpatients generally receive medications for chronic medical conditions and adherence to therapy is critical to improving their diseases. The organization in health services must facilitate the dispensation and to improve the medicines distribution. In some pharmacies it is common to transfer the medicines from the original container to another temporary package (in blister or sachet)[13] that are placed in portables furniture drawers[14] and they are distributed daily to the various services through a system with separate doses per hospitalized patient, known as unit dose system. In this way, every day the treatment is updated and the necessary adjustments are made according to the medical prescription.

In some countries, such as Australia, dose administration aid (DAA) are is as an aid for drug administration, as it provides the patient the possibility of controlling the medication during a day or a week. Blisters or sachets containing various medicines may be placed in a compartment of the DAA (multi-dose pack) or only one product by compartment (unit-dose pack).[15] In other latitudes, this system is offered not only to inpatients, but also to outpatients. The United States Pharmacopoeia (USP) 40th edition, in the general chapter <661> about packaging[16] have regulations for these devices.

Along with the above, another professional practice allows the manipulation of some medicines by the nursing staff due to aspects related to drug stability. In these cases, the pharmacy service does not deliver the medication prepared and ready to administer by nurses. The lack of unification about the criteria regarding the preparation of the medicines make by the nursing service, sometimes led to inaccuracy in doses administered. The preparation, stability and compatibility of medicines are very sensitive issues that are indispensables to know in order to prepare the appropriate doses according needs of sick persons, especially in children.[17]

In addition, physical alteration of a pharmaceutical form, such as breaking a tablet into fractions, spraying the tablets[18] or adding the powder of a capsule to liquid or solid foods may modify the bioavailability of some medicaments.[17]

In that regard, and to meet those needs, it exist a guide that recommends techniques to obtain the prescribed dosage with the required accuracy, thanks to the project Manipulation of Medicines Required in Children (MODRIC) of the United Kingdom.[19]

Another problem to be considered is the professional acts regulation, arguing that the manipulation of pharmaceutical forms may have legal and ethical consequences.[20]

However, professional practice contemplates that the therapeutic decision-making of marketed drugs is also presumably assumed by the prescriber[21] who bases his expert judgment on the best available evidence, clinical experience, references of scientific articles and the risk-benefit balance, to obtain the guidelines to be followed in an individual patient therapy.[22]

The official agency, which regulates medicines in different countries, determines whether the marketing authorization of the products is given, such authorization is specific to indications, doses and population.

In frequently practice, it is possible to use the authorized medicinal product that is marketed, but changing the indication, potency, pharmaceutical form, age and the administration route. These doses are outside the manufacturer's labeling (off-label), for example the use of tablets halves or the drug repackaging in a container other than the original one.

When repackaging pharmaceutical formulations, the preparer is responsible for ensuring product quality during storage and shipment, in addition, the maximum dates for its possible use should be taken into account, based on considerations of the active principle, pharmaceutical formulation and route of administration, among others.[23]

As repackaging a medicinal product, any changes in stability should be assessed, so that the original expiration date reported by the manufacturer will be valid if the storage provides the same conditions specified by the pharmaceutical laboratory on the label.[16]

The original packaging preserves the product integrity and in this context, the World Health Organization (WHO) in 2002 issued a guide for the packaging of pharmaceutical products,[25] which mentions the influence of variations in humidity, light, oxygen, temperature and biological contamination. This guide also identifies damages that may occur due to the inefficiency of the packaging, such as: physical damage, chemical reactions and absorption of undesirable substances.

The USP 40 provides a guidance for conducting stability studies and establishing the expiration date of solid formulations by assessing physical signs of common deterioration and aspects not perceived with the naked eye such as degradation and chemical reactions that could lead to losses in the active pharmaceutical ingredients concentration.[16]

If are not specified storage conditions on the label of the new packaging, storage in a controlled ambient temperature is recommended and avoid places with excessive or variable conditions of heat, cold or light, such as heating or fluorescent lighting.[16]

Other entities linked to the medicines quality, such as the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: ICH (Q1A-Q1F),[26] the European Medicines Agency (EMA)[27] and the WHO[28] issued directives similar to those cited by USP 40.

In Costa Rica there is current legislation on medicinal products stability studies of for human use that must be performed with the control of variables such as temperature, humidity and, if necessary, light.[29]

Stability studies carried out to obtain scientific evidence of the permanence of quality characteristics in pharmaceutical products throughout their useful life and the packaging type

that protects them from external factors influences pharmaceutical formulations. When re-packaging a drug, it is necessary to consider that the new packaging must guarantee stability until it is apply or consumed by the patient.[24]

The medicines re-packaged in customized packages are regulated by the USP 40 general chapter <661> about containers, which establishes an use no longer than 60 days from its preparation.[16]

With respect to solid pharmaceutical formulations, they have the advantage that the medicament tends to decompose less than in a liquid formulation. In general, very stringent conditions for the tablets storage, such as temperatures below 15 degrees or 30% relative humidity, are not required; therefore the manufacturer must indicate on the product label the recommended storage conditions and the expiration date. When the pharmaceutical form of the tablets that are commercially available at the market, are extracted from their original packaging and placed in another reservoir, the manufacturer cannot assure the guarantee about the validity. In this sense, the person in charge of the repackaging is responsible for the maintenance of medicine qualities the during the storage in the determined environmental conditions that are established; these and other considerations must be adhered to by the United States Food and Drug Administration (FDA).[30]

In Costa Rica, there are two climatic seasons a year, one dry and one rainy, so that in each season there are atmospheric changes. A drug storage study depended of these changes and the results cannot be extrapolated to other latitudes, even within the country itself. This investigation taken place in San Pedro de Montes de Oca from December 2014 to November 2015, under an annual 21±1^{o}C (Celsius degree) temperature[31] and a 55±10% relative humidity percentage in the dry season (December-April) and 70±10% the rest of the year (May-November).[32] These is a subtropical zone according to the ICH classification (25 oC to 60% of relative humidity).[20]

Hence, this study aim was to evaluate the doses accuracy and the quality attributes, of wholes and halves tablets, of furosemide, hydrochlorothiazide, spironolactone, warfarin sodium, atenolol and levothyroxine sodium, re-packaged in individual plastic compartments for sixty days. These drugs were selected because they are used for the pharmacological treatment of high relevance pathologies in Costa Rica.

Rather, the study established the usual storage conditions that would be assumed by patients using individual plastic compartments to improve therapeutic compliance. During the bibliographic research, no study was found carried out in Costa Rica under these conditions.

It is important to clarify that this study did not intend to obtain results that solve aspects related to accelerated stability tests, a long time, intermediate or under conditions of forced degradation; neither the consequences of improper storage of re-packaged drugs were not assessed; nor was it known whether the tablets halves met all requirements that are requested by the FDA from manufacturers of functional (and non-decorative) scored tablets.

MATERIALS AND METHODS

Materials

Small multi-dose bottle with 100 tablets for warfarin sodium 5 mg and blister packs of 10 individual units for furosemide 40 mg tablets, hydrochlorothiazide 25 mg, spironolactone 100 mg, atenolol 50 mg and levothyroxine sodium 100 µg whose trade names mark remain anonymous for confidentiality matters. Their acquisition was made in Private Assistance Pharmacies of San José, Costa Rica.

The plastic boxes with 7 or 28 individual compartments, obtained in the national market, for convenience.

The following calibrated analytical equipment was used:

Analytical balance (Accurate LS 120A ± 0.0001g, Switzerland).

UV-VIS Spectrophotometer (Thermo Scientific Orion AquaMate 8000 UV-VIS Spectrophotometer, China).

High Performance Liquid Chromatograph HPLC (Perkin Elmer Flexar series 200; USA).

Disolutor paddle or apparatus 2 (Varian VK7010; USA) with six vessels.

Methods

The methodology is presented according to the order of these activities.

1. Repacking of products the first day and preparation for conduct the quality tests on days 7, 14, 30 and 60 from the start day.
2. Analytical procedures and validation.

3. Quality tests: no changes in physical characteristics of products, tests of uniformity of weight (mass), dissolution profiles and content uniformity.

Repacking of products

The activities developed the starting day were the following:

Fifty whole tablets of each medicament were weighed individually and the masses were scored. They were placed in the assigned compartment.

Twenty-five tablets of each medicament were removed from their original container and were weighed individually. Each tablet was divided in halves and each fragment weighted was placed in the compartment codified corresponding which containing a whole tablet. The masses of the whole tablet and the two halves were scored.

Forty compartments per product were stored in a shelf located in a cool, dry place away from direct sunlight at room temperature. After 7, 15, 30 and 60 day, the content of ten compartments was evaluated.

Analytical procedures and validation

The procedure indicated by BP, 2013 in the case of warfarin sodium was varied since a complete validation was performed.

The tablets of furosemide, hydrochlorothiazide, spironolactone, atenolol were analyzed according to the official British Pharmacopoeia BP, 2013 (BP, 2013)[35] methods and the procedure for levothyroxine sodium was official in USP 40 using an HPLC-UV technique.[16]

The validation of official procedures was partial according to the "Verification of Compendial Procedures", general chapter <1226> of USP 40.[16]

The validations were verified in terms of specificity, precision, accuracy, linearity and linearity range. Those validation were performed according to the recommendations of ICH.[26] The specificity was demonstrated using one of the following two procedures:

a. The comparison of the slopes of the calibration curves and the added dose.

b. The overlap of the absorption spectra of the reference substances and the tablets after applying the test procedure.

Precision and intra-day and inter-day accuracy was evaluated with six replicate samples at low, medium and high concentrations of the calibration curve. The Association of Official Analytical Chemicals (AOAC) considers accuracy in the concentrations of 10 mg/L when DSR% <6% and ± 115% recovery.[16]

Linearity and range were established according to expected concentrations in the dissolution profiles of whole tablets and halves.

The linear adjustment, the intercept with a statistical value equal to zero and the coefficient of determination higher than 0,995 were verified.

Quality tests

Physical characteristics

Color, odor, presence of spots or agglomeration were observed in 10 units at baseline, 7, 15, 30 and 60 days.

Uniformity of weight (mass) Appendices XII C1, BP 2013 The pharmacopeical methodology established this test for 30 tablets.

Because for the storage study a group of 10 units is to be evaluated at any time, the test was modified as follows.

Weighed individually 10 units and determined the average mass. For uncovered or film coated tablets, no more than 1 individual mass was deviated from the average mass by more than the percentages showed in Table 1 and none deviated by more than twice that percentage.

Table 1: Permissible percentage of maximum deviation in mass uniformity

Average mass BP 2013	Deviation (%)
80 mg or less	10
81 to 249 mg	7,5
250 mg or more	5

The average mass of unbroken tablets was obtained from the 50 units weighed on the start day and the percentage of deviation of a whole tablet at each storage time was established by the formula: (individual mass-average mass)*100/average mass.

Because the tablets halves have significant variability with each other, to calculate the percent deviation in half, this formula was used: (mass obtained on the start day-mass on the day of the test)*100/average mass of 50 tablets halves weighted the start day.

Dissolution profiles

The methodologies were based on dissolution tests of pharmacopoeial monographs, but using various sampling times and a calibration curve. For drugs, a stirring speed of 50 o 75 r/min was selected in apparatus 2, according to the specification of the monograph used. The temperature of dissolution medium was 37±5 Celcius degree. Other experimental conditions are shown in Table 2.

Table 2: Experimental conditions tests applied to the dissolution profiles for each drug.

Drugs in tablets	Dissolution medium and volume (mL)	Sampling times (minutes)
Furosemide 40 mg	Phosphate buffer pH 5,8 (900)	5, 10, 15, 20, 30, 45, 60
Hydrochlorothiazide 25 mg	HCl 0,1M (500)	5, 10, 15, 20, 30, 60, 90
Spironolactone 100 mg	HCl 0,1M with sodium laurylsulphate 0,1 % (1000)	5, 10, 15, 20, 30, 60, 90
Warfarin sodium 5 mg	Phosphate buffer pH 6,8 (900)	5, 10, 15, 20, 30, 45, 60
Atenolol 50 mg	Acetate buffer 0,1M pH 4,6 (500)	5, 10, 15, 20, 30, 45, 60
Levothyroxine sodium 100 µg	HCl 0,1M (500)	5, 10, 15, 20, 30, 45, 60

In the six-vessel apparatus, three whole tablets and three halves of tablets were placed randomly. Twelve whole tablets and twelve tablets halves were analyzed for each drug. As a reference, the Q value was set at 70% to 45 minutes, as indicated in BP 2013.[35]

Uniformity of dosage units Appendices XII C4, BP 2013

The uniformity of content or mass variation assays may be applied to demonstrate uniformity of dosage units, according to the dose and proportion of active ingredient (% of mass) in the formulation.

The dose and proportion of active ingredient (% mass) are two parameters that define the assay to evaluate the uniformity of the dosage units.

For tablets with a content ≥ 25 mg and a mass percentage ≥ 25%, the mass variation test was applied. The uniformity of the contents can be used in tablets with a drug content <25 mg or a mass percentage <25%. However, this second test could be applied in all cases.

The table 3 shows the corresponding test applied in the study tablets. The abbreviation CU refers to the test of uniformity of content and MV to the test of variation of mass.

Table 3: Application of content uniformity (CU) and mass variation tests for study tablets.

Active pharmaceutical ingredient	Drug dose per whole tablet (mg)	Percentage of content (% of mass)	Methodology to apply
Furosemide	40	24	CU
Hydrochlorothiazide	25	13	CU
Spironolactone	100	18	MV
Warfarin sodium	5	2	CU
Atenolol	50	25	MV
Levothyroxine sodium	0,1	0	CU

In the uniformity of content, the 10 individual units corresponding to the day of storage were analyzed to determine the individual labeling percentage.

The mass variation test was applied to 10 units. The labeling percentage of each individual unit was obtained by the ratio between the test labeling percentage of tablet samples, the mean mass and the individual mass.

Regardless of the test used, the result was expressed in terms of acceptance value (AV)
The formula of AV included the follow terms:
X = average of individual labeling percentages
k = 2, 4

s = standard deviation
T = 100

M = Reference value having different values depending on the case:

- M = 0 if 98, 5 < X < 101,5
- M = 101,5 if X > 101,5
- M = 98,5 if X < 98,5

The formula for calculating AV was:

$VA = |M - X| + k * s$

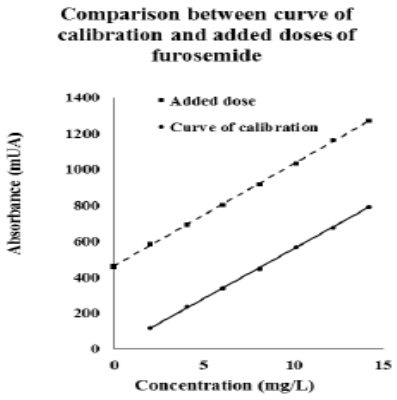
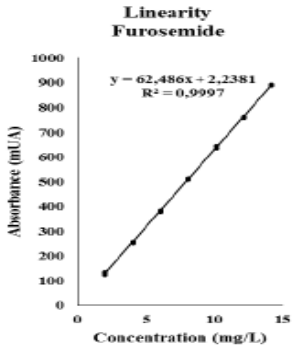
Specification in the uniformity of dosage units: AV ≤ 15, 0.

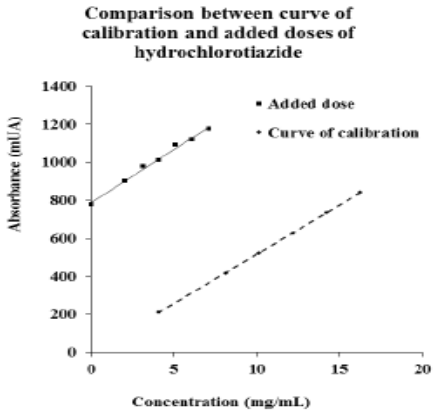
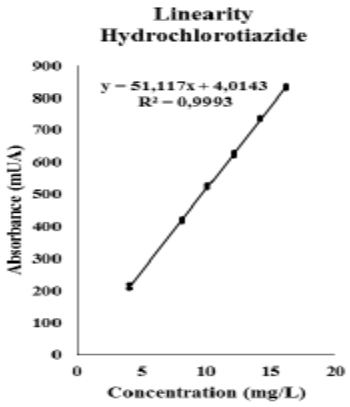
RESULTS AND DISCUSSION

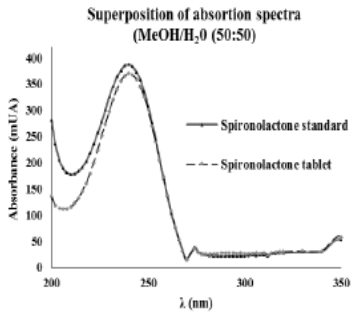
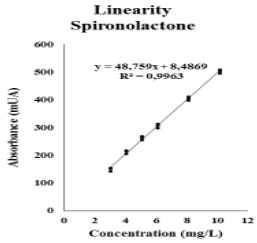
Analytical procedures and validation

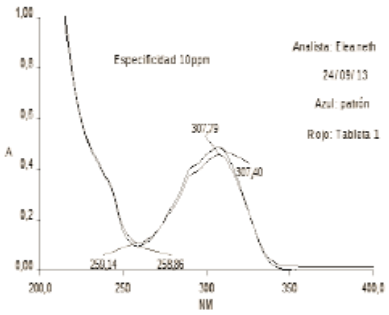
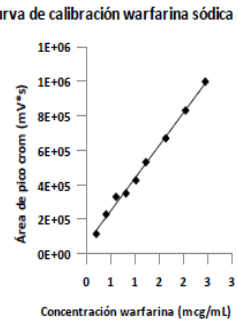
The data of the tests applied to demonstrate the appropriateness of the procedures are showed in the table 4.

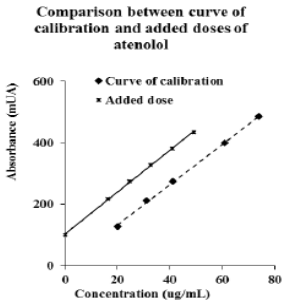
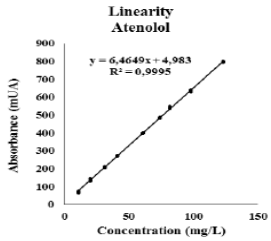
Table 4: Verification of validation parameters of analytical procedures referring to specificity, precision and accuracy (intra-day and inter-day), linearity and range.

Specificity	Precision and accuracy (intraday, inter-day)	Linearity and range
Furosemide		
 There is no significant difference between the slope of both calibration curves: (P> 0.05) y (critical t> experimental t)	Inter-day DSR< 3,6 % ER % -4,6 to 5,0 %	 r > 0,995 Intercept statistically equal to zero Lack of significant deviation with respect to linear Regression. Range: 2 - 14 mg/L

Specificity	Precision and accuracy (intraday, inter-day)	Linearity and range
Hydrochorotiazide		
 There is no significant difference between the slope of both calibration curves: (P> 0.05) y (critical t> experimental t)	Intraday DSR< 3,5 % ER % -6,6 to 2,8 % Inter-day DSR< 2,8 % ER % -4 to 4 %	 r > 0,995 Intercept statistically equal to zero Lack of significant deviation with respect to linear Regression. Range: 4 - 16 mg/L

Specificity	Precision and accuracy (intraday, inter-day)	Linearity and range
Spironolactone		
 There is overlap between the absorption spectra of the spironolactone standard and Tablet solutions (8 mg/L).	Intraday DSR< 1,5 % ER % -2 to 4 % Inter-day DSR< 4,5 % ER % -1,2 to 5,3 %	 r > 0,995 Intercept statistically equal to zero Lack of significant deviation With respect to linear regression. Range: 3 - 10 mg/L

Specificity	Precision and accuracy (intraday, inter-day)	Linearity and range
Warfarin sodium		
 There is overlap between the absorption spectra of the warfarin sodium standard and The tablet solutions.	Intraday DSR< 1 % ER % 0,3 to 1 % Inter-day DSR< 2 % ER % -0,6 to 1,3 %	 r > 0,995 Intercept statistically equal to zero Lack of significant deviation With respect to linear regression. Range: 0,4 – 2,5 mg/L

Specificity	Precision and accuracy (intraday, inter-day)	Linearity and range
Atenolol		
 There is no significant difference between the slope of both calibration curves: (P> 0.05) y (critical t> experimental t)	Intraday DSR< 1 % ER % -0,65 to 3 % Inter-day DSR< 5,2 % ER % -10 to 6 %	 r > 0,995 Intercept statistically equal to zero Lack of significant deviation with respect to linear regression. Range: 20 - 75 mg/L

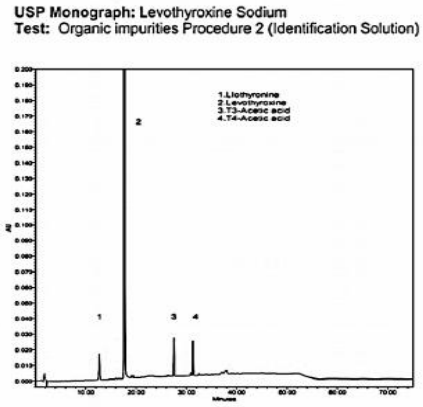
Specificity	Precision and accuracy (intraday, inter-day)	Linearity and range
Levothyroxine sodium		
 The chromatogram of the test of related substances applied to tablets of levothyroxine sodium showed the separation of the chromatographic peak assigned to this active principle and the different Retention times of the other substances.	Intraday DSR< 1,3 % ER % -1,61 to 1,38 %	Only a concentration of 7,75 mg/L was utilized Table

Table 4 presented that the results of procedures validations had values suitable for their use according to the indications of ICH[26] and AOAC[36] in the ranges of concentrations used for all products.

The specificity of the analytical procedures for the tablets was demonstrated by statistically comparing the slopes of the curves of the added doses and the calibration curves or by superposition of the absorption spectra.

The results, with DSR<6% and ±15% relative error, demonstrated the accuracy and the precision in both conditions selected.[16]

The linear adjustment, the intercept with a statistical value equal to zero and the coefficient of determination higher than 0.995 were verified for all analytical procedures.[26]

Physical characteristics

Table 5 provides a summary of the characteristics of the tablets (wholes and halves). Negative signs indicate absence of changes during observations.

Table 5: Physical characterization of tablets (whole and halves) of the drugs under study

Drug	Whole tablet				Tablets halves			
	Color	Odor	Presence of spots	Caking	Color	Odor	Presence of spots	Caking
Furosemide 40 mg	White	-	-	-	White	-	-	-
Hydrochlorothiazide 25 mg	White	-	-	-	White	-	-	-
Spironolactone 100 mg	Light yellow	Mint	-	-	Light yellow	Mint	-	-
Warfarin sódica 5 mg	Light pink	-	-	-	Light pink	-	-	-
Atenolol 50 mg	White	-	-	-	White	-	-	-
Levothyroxine sodium 100 µg	White	-	-	-	White	-	-	-

The results indicated that in the intact tablets or in halves, regardless of drug, no change in color, odor, presence of spots or agglomeration were observed throughout the storage.

However, Pinderfields General Hospital detailed a list of repackaged drugs in multi-compartment compliance aids[37] indicating changes in furosemide tablets that should be monitored. And Church and Smith point out that manufacturers discourage repackaging of furosemide, in plastic boxes with individual compartments, for lack of stability studies.[39]

Uniformity of weight (mass)

The initial mass of whole tablets and halves was obtained and associated in accordance with the test specification. These results are shown in Table 6.

Table 6: Maximum mass deviation (%) assigned with respect to the average mass of products.

	Average mass of ten whole tablets (g)	Deviation (%) for the whole tablet	Deviation (%) for half tablet
Furosemide	0,1691	7,5	10
Hydrochlorothiazide	0,1992	7,5	7,5
Spironolactone	0,5645	5	5
Warfarin sodium	0,2268	7,5	7,5
Atenolol	0,1993	7,5	7,5
Levothyroxine sodium	0,1021	7,5	10

The most common deviation is 7,5% because the tablets had a similar weight. The results of the uniformity of mass for all products are summarized in table 7. The positive sign indicates compliance with the specifications and the negative the non-compliance, followed by the number of units deviated, in parentheses, if applicable.

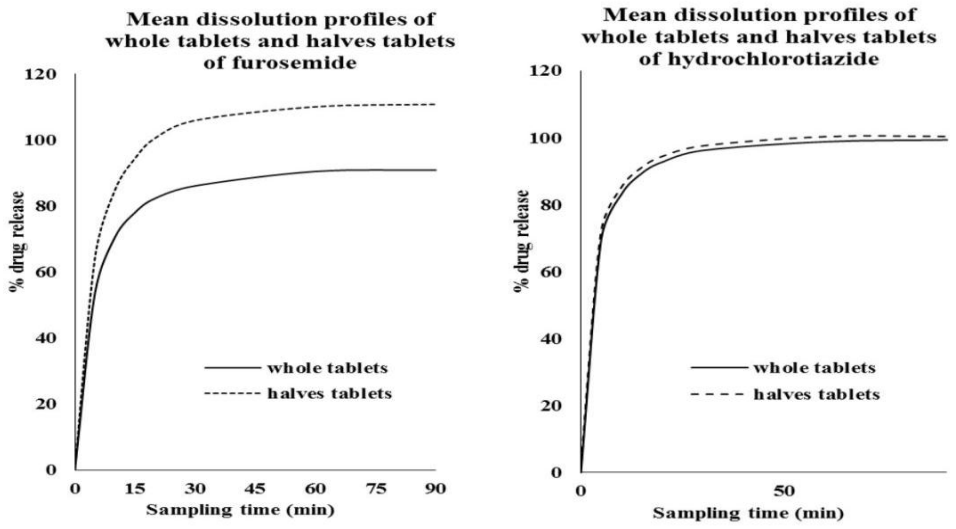
Table 7: Results of mass uniformity test at storage times according to specifications.

	Whole tablets				Halves of tablets			
Days of analysis during storage	**7**	**14**	**30**	**60**	**7**	**14**	**30**	**60**
Furosemide	+	+	+	+	+	+	+	+
Hydrochlorothiazide	+	+	+	+	+	+	+	+
Spironolactone	+	+	+	+	+	+	+	+
Warfarin sodium	+	+	+	+	+	+	+	+
Atenolol	+	+	+	+	+	+	- (2)	- (2)
Levothyroxine sodium	+	+	+	+	+	+	+	+

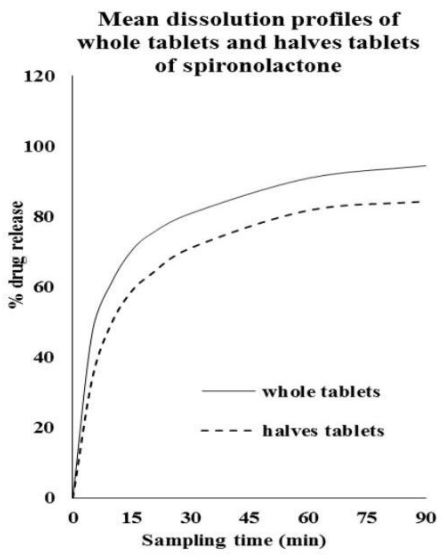
According to Table 7, five drugs meet the specifications for whole tablets and their halves. Atenolol showed the same condition for whole tablets, however, the halves tablets of this drug did not meet the test approval criteria, since there were two units that deviated from the specification at 30 and 60 days, their values exceeded twice the maximum allowed value.

Dissolution profiles

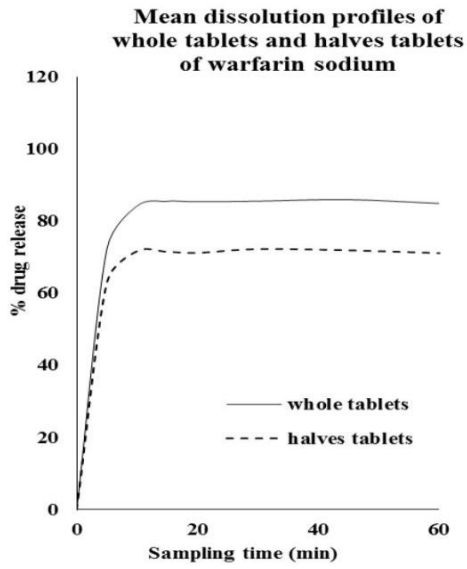
The superposition of dissolution profiles of whole tablets and halves is shown in Figure 1, for each drug: (a) furosemide, (b) hydrochlorothiazide, (c) spironolactone, (d) warfarin sodium, (e) Atenolol. Figure 2 shows only the dissolution profile of the wholes tablets of levothyroxine sodium.



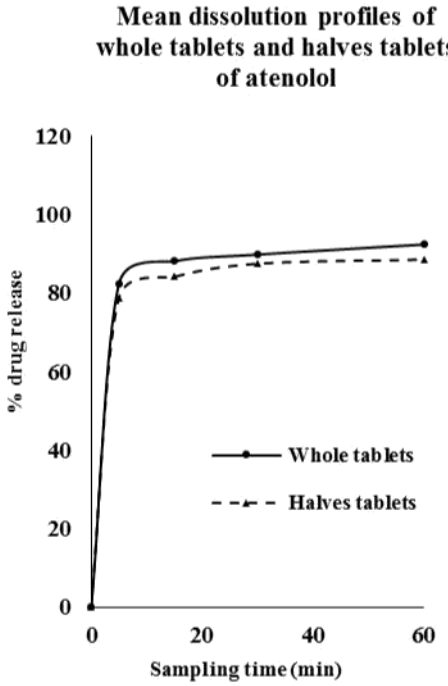
(a) (b)



(c)



(d)



(e)

Figure 1: Overlap of dissolution profiles for whole halves and tablets of (a) furosemide, (b) hydrochlorothiazide, (c) spironolactone, (d) warfarin sodium and (e) atenolol.

In the Figure 1, for all products, the dissolution profiles of whole tablets had shapes illustrating formulations with immediate drug release.

In addition, it is not advisable to repackaging of spironolactone (c), furosemide (a) and warfarin sodium (d) tablet halves in view of the observed difference in the drug release as compared to the whole tablets, although at 45 minutes the units of the three drugs mentioned reach 75% dissolved, with the exception of warfarin sodium.

Although the dissolution profiles are in vitro tests, the behavior of the drug under in vivo conditions is not known with certainty. However, it may be suspected that the behavior of the furosemide moiety of tablets could have a different blood velocity and blood concentration, as evidenced by Zafar *et al*.[39] in a study of crushed tablets of clopidrogel administered via nasogastric tube with faster and greater absorption than that of whole tablets by mouth.

An investigation performed at Pharmacy Department of Pinderfields General Hospital, mentioned that the re-packaging of whole tablets of spironolactone, furosemide, and warfarin sodium was discouraged, although stability studies were not reported.[37]

Atenolol (Figure 1 e) showed adequate overlap of dissolution profiles of whole tablets and tablet halves.

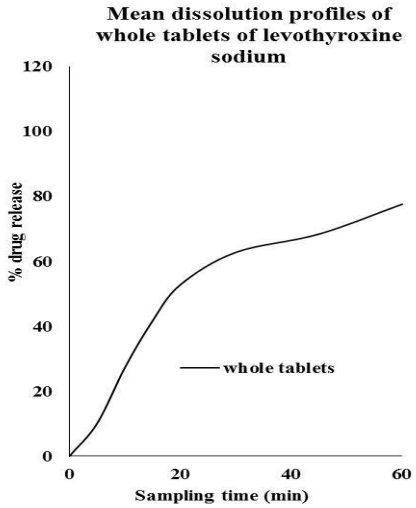


Figure 2: Dissolution profile of the wholes tablets of levothyroxine sodium.

For levothyroxine sodium (Figure 2), data were only obtained for whole tablets, since the detection limit of the HPLC procedure was not sensitive enough to quantify the drug in the dissolution test of the tablet halves.

The dissolution profile of whole tablets of levothyroxine sodium did not show a plateau response, unlike the other products analyzed, and the maximum dissolved percentage of each individual unit did not reach 75% to 45 minutes.

Uniformity of dosage units

The numerical data in Table 8 reflect the results of the tests applied to all dosage units, expressed as acceptance values.

Table 8: Acceptance values for all the products studied in the uniformity of the dosage units.

	Whole tablets					Halves of tablets				
Products	**Starting day**	**7**	**14**	**30**	**60**	**Starting day**	**7**	**14**	**30**	**60**
Furosemide	2,5	9,4	11,1	5,0	7,3	4,1	7,6	7,9	3,1	11,3
Hydrochlorothiazide	4,8	5,2	7,5	11,8	3,5	7,7	2,8	2,9	10,0	2,4
Spironolactone	11,2	3,0	15,2	2,7	4,0	3,0	4,5	5,2	6,6	7,8
Warfarin sodium	6,6	8,2	2,5	4,5	14,7	3,3	3,0	2,8	2,2	3,1
Atenolol	28,5	26,7	4,0	10,0	3,0	38,7	40,9	19,5	15,9	8,3
Levothyroxine sodium	3,5	3,5	3,0	4,5	5,6	5,6	3,9	3,6	3,3	3,7

The halves of tablets of atenolol had values of acceptance greater than 15, 0 during the 60 days of storage, reason why the specifications are not fulfilled. In addition, the results at baseline and day 7 for whole tablets of atenolol had the same situation.

In view of this situation, on the first day, it was decided to perform dissolution profiles with six units of whole tablets and six halves tablets of atenolol, in order to complete the quality tests for this product.

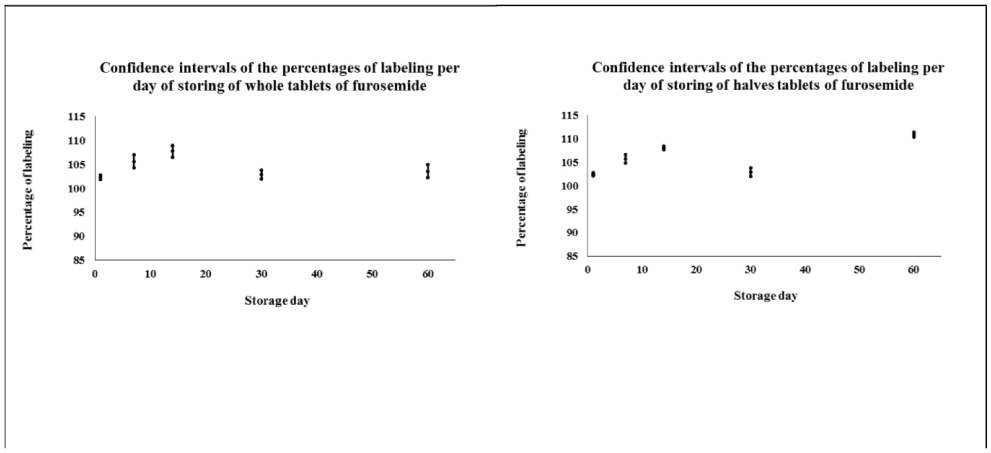
Regardless of the case of atenolol, Table 8 shows that all acceptance values are less than 15, except for the whole tablets of spironolactone 100 mg on day 14, which presented a result of 15.2.

Although almost all drugs presented adequate acceptance values at all storage times.

In order to visualize if there is any tendency towards increasing or decreasing the amount of drug in the dosage units over time, the confidence intervals were elaborated.

The results obtained should not be confused with those of the assay of drug content of the tablets where the analyzed samples are portions of tablets sprayed and not ten samples of individual units.

The analysis of the confidence intervals of the percentages of labeling per group of 10 tablets analyzed, visualized some tendencies regarding the behavior of results during the storage. The confidence intervals of the labeling percentage of each group of 10 units were calculated and can be seen in Figures 3 to 8.



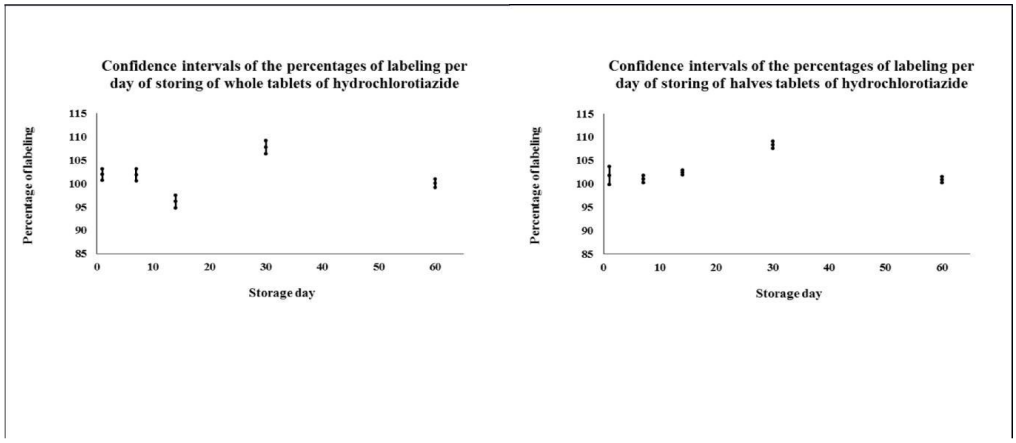
(a) (b)

Figure 3: Confidence intervals of the percentages of labeling per day of storing of (a) whole tablets and (b) halves tablets of furosemide.

At all storage times, the whole furosemide tablets show values between 90,0 and 110,0% as shown in Figure 3 (a). For the tablets halves, an offset was found at 60 days, since that interval has values higher than 110, 0%.

Khan in a furosemide stability study in original packaging and re-packaged (both blister packs) was developed for a long-term year and also under conditions of accelerated stability.[40] It was found that for whole tablets of furosemide 40 mg the quality attributes were not affected by any of the conditions established.

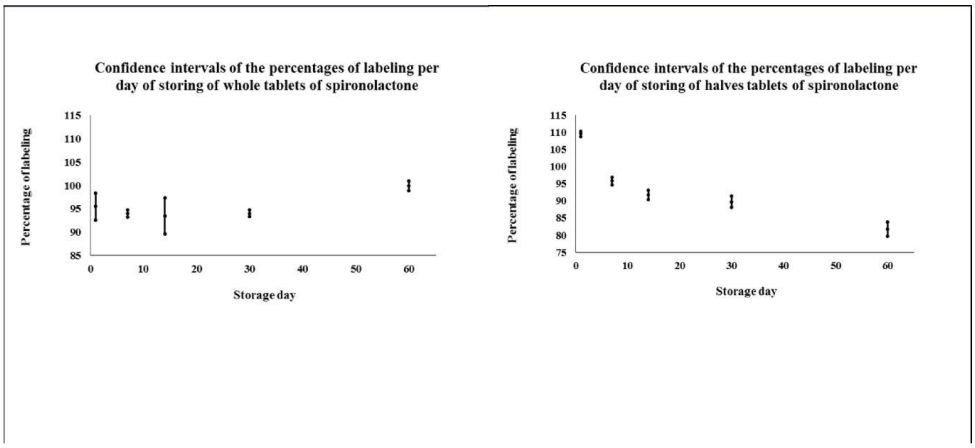
In our study, a similar condition was observed in terms of the results of the furosemide content per tablet, up to two months, but with different environmental characteristics.



(a) (b)

Figure 4: Confidence intervals of the percentages of labeling per day of storing of (a) whole tablets and (b) halves tablets of hydrochlorothiazide.

Figure 4 concerning hydrochlorothiazide showed that at all times the confidence intervals were between 90, 0 and 110,0% of the labeling for whole tablets and halves.



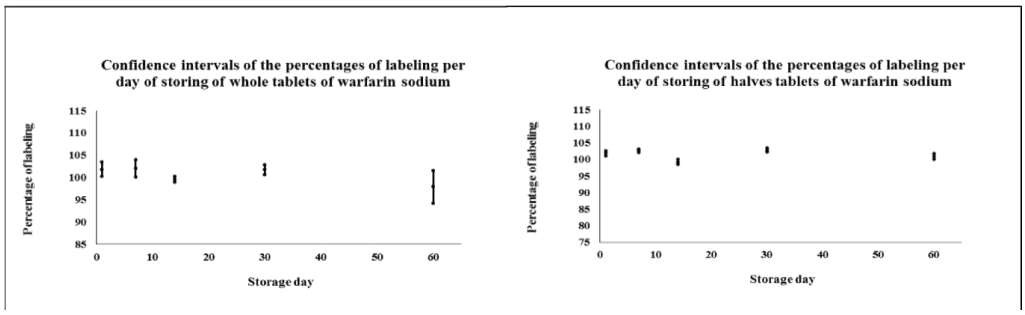
(a) (b)

Figure 5: Confidence intervals of spironolactone labeling percentages per day of storage of (a) whole tablets and (b) halves.

Figure 5 showed for whole spironolactone tablets values between 90,0 and 110,0% at all confidence intervals. However, tablet halves tend to decrease their content as the storage time elapses, with values below 90,0% of the labeling at 30 and 60 minutes.

In an investigation, Margiocco et al evaluated the uniformity of contents for spironolactone tablets. These fractions were re-packaged in plastic containers and stored for 30 days.[41] Their results showed a decrease in the content of active ingredients as time evolved perhaps due to chemical degradation. The results of our study presented a similar tendency for the

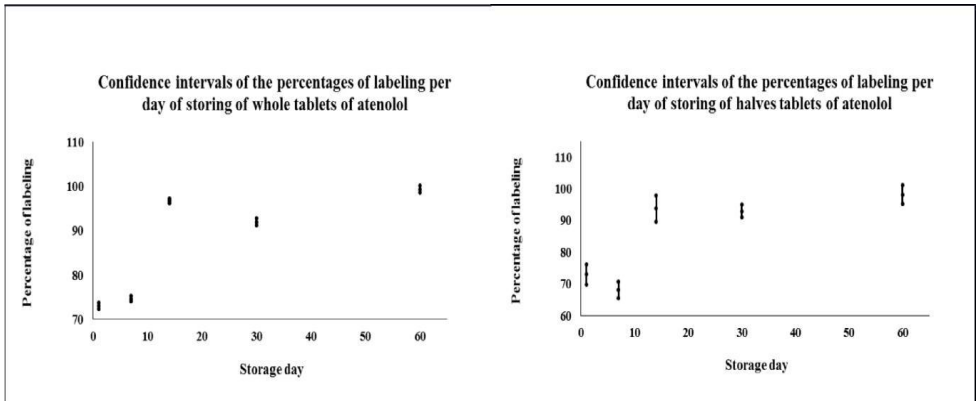
halves of the tablets, but for a longer period of 60 days and under different storage conditions.



(a) (b)

Figure 6: Confidence intervals of warfarin sodium labeling percentages per day of storage of (a) whole tablets and (b) halves.

In the case of warfarin sodium in whole tablets and in halves, Figure 6 shows that for all confidence intervals the limits were found to be between 90,0 and 110,0 percent labeling but more accurate on halves tablets.



(a) (b)

Figure 7: Confidence intervals of the percentages of labeling per day of storing of (a) whole tablets and (b) halves tablets of atenolol.

According to Figure 7, when storage time increases both whole atenolol tablets and halves, they tend to increase the percentage labeling values near 70% in the first two dates to a range of 90-110% on days later.

For whole atenolol tablets, acceptance values of less than 15, 0 were obtained at 14, 30 and 60 minutes, which coincide with the narrow confidence intervals at that time, shown in Figure 7 (a).

For the halves tablets of atenolol, the acceptance values were much higher than 15,0 at the first day, 7, 14 and 30 days as shown in Table 7, which indicates a high variability of the results, a situation can be explained in Figure 6 (b) when is observed wide intervals of confidence, at any moment analyzed.

In view of obvious variations in drug content as storage time increased, the behavior of the release of atenolol was studied using dissolution profiles applied to six units of the two doses. Figure 8 presents the overlap of the dissolution profiles of the whole tablets and the halves of the tablets where the continuous lines correspond to the firsts and the lines with points to the seconds.

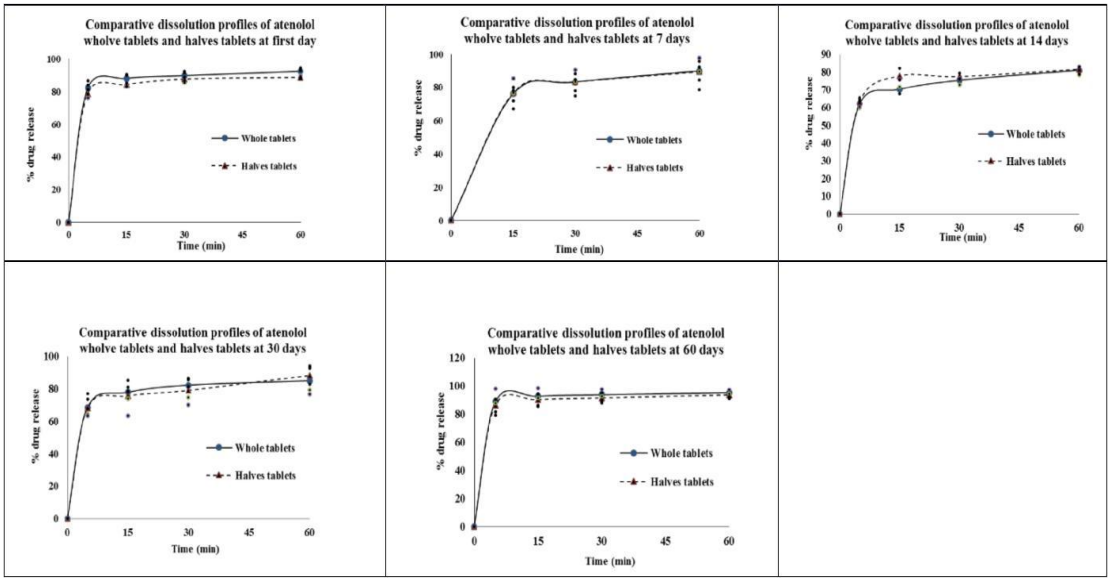


Figure 8: Comparative dissolution profiles of whole tablets and halves of atenolol tablets during storage evaluated at baseline, 7, 14, 30, and 60 days.

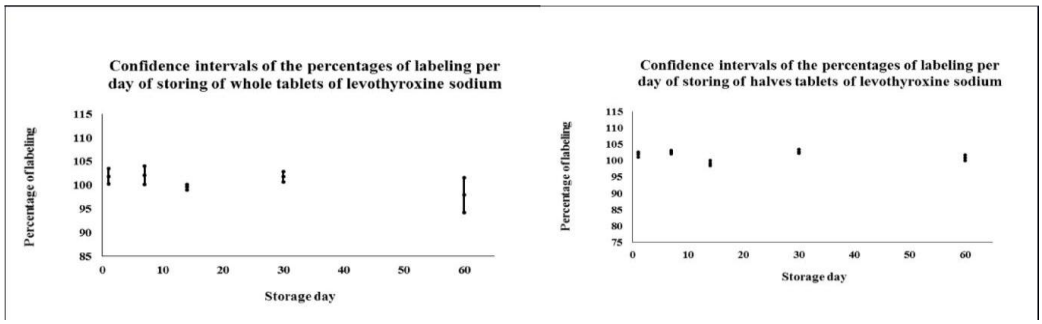
As shown in Figure 8, the whole tablets and tablet halves exhibited a very similar behavior between them at each evaluated moment.

These findings show an adequate release of atenolol in the dissolution medium used during the 60 days of storage. But due to the low labeling rates found up to day 14 of storage, it seems necessary to establish a different quantitative method for analyzing the content of atenolol, particularly in the case of generic medicines, the results of which should coincided with the good performance of the products in the released *in vitro*.

A laboratory manufacturer indicates that in the absence of stability studies, it is preferable not to re-pack atenolol tablets into plastic boxes with individual compartments.[38] Given the

results obtained in our study, atenolol, which can be split in half and stored in plastic boxes with individual compartments.

The final result on the uniformity of the dosage units corresponds to tablets of levothyroxine sodium. A comparison of the dissolution profiles of whole tablets and their halves is shown in Figure 9.



(a) (b)

Figure 9: Confidence intervals of levothyroxine sodium labeling percentages per day of storage of (a) whole tablets and (b) halves.

As shown in Figure 9 the adequate behavior of the whole tablets and their halves, have values between 90 and 100 percent of labeled levothyroxine sodium.

CONCLUSIONS

According to the results, it is possible to re-package wholes tablets of furosemide, hydrochlorothiazide, spironolactone and warfarin sodium; but it is not advisable to maintain this practice for whole tablets of atenolol or levothyroxine sodium, neither for the halves of the rest of the products, except hydrochlorothiazide.

These findings may become opportunities for improvement for pharmaceutical laboratories, as well as become a study topic for practitioners to advise the use of multi-compartment compliance aids, finally, these results should not be extrapolated to drugs, manufacturers, lots and conditions other than those used in this study.

It is recommended that the date of re-packaging of tablets in plastic boxes with individual compartments, the maximum date of use should be noted.

In general, the low dissolution of the tablets halves relative to the whole units should be analyzed by the manufacturing laboratories to verify the critical points of the production and the associated risks.

In the case of treatments with 100 mg of levothyroxine sodium half-tablets, the patient should have greater medical support because of the possibility of a change in the way the drug is released in the specific studied formulation.

ACKNOWLEDGEMENTS

A special thanks to the staff of INIFAR for their cooperation in this study.

Funding

This research was carried out with the financial support of the Research's Vice-rectory of the University of Costa Rica (UCR).

REFERENCES

1. Adherence to pharmacological treatment in chronic pathologies. INFAC Newsletter, 2011; 19(1): 1-6. Availablefrom: http://www.osakidetza.euskadi.eus/contenidos/informacion/cevime_infac/eu_miez/adjuntos/infac_v19_n1.pdf.
2. National Institute for Health and Clinical Excellence. Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. Clinical guideline 76. London. National Institute for Health and Clinical Excellence, 2009. Available from: http://www.nice.org.uk/nicemedia/live/11766/43042/43042.pdf.
3. Umar DM, Makanjuola D, Dayom DW, Sha'aban A, Dafam DG and Dangiwa DA. Assessment of adherence to medication among cardiovascular disease outpatients in Jos University Teaching Hospital, Jos, Nigeria. WJPR, 2017; 6(7): 392-401.
4. Delamater A.M. Improving Patient Adherence. Clinical Diabetes, 2006; 24(2): 71-7.
5. National Institute for Health and Care Excellence. Medicines optimisation. Quality standard. Clinical guideline 14. London. National Institute for Health and Care Excellence, 2016. Available from: https://www.nice.org.uk/guidance/qs120/resources/medicines-optimisation-75545351857861.
6. Medicines and You: A Guide for Older Adults. Council on Family Health. Available from: http://www.fda.gov/downloads/Drugs/ResourcesForYou/UCM163961.pdf.

7. Oboh L. Supporting older people in the community to optimize their medicines including the use of multi compartment compliance aids (MCAs). Medicines Use and Safety. East & South East England Specialist Pharmacy Services. London, 2013. Available from: https://www.sps.nhs.uk/wp-content/uploads/2013/06/MCA20toolkit.pdf.
8. Sino C. Medication Management in Homecare Patients. Thesis. Hogeschool Utrecht University of Applied Sciences, 2013; 67-102. ISBN: 1234567890 Available from: https://dspace.library.uu.nl/bitstream/handle/1874/287124/sino.pdf?sequence=2.
9. Tan JZY, Kwan YH. Stability of chronic medicines in dosage administration aids. How much have been done? SPJ, 2016; 24: 21-8. Available from: http://www.sciencedirect.com/science/article/pii/S1319016414000036.
10. Donyai P. Quality of medicines stored together in multi-compartment compliance aids. J Clin Pharm Ther, 2010; 35: 533–43.
11. Oboh L. Frequently Asked Questions (FAQ) on the use of Multi compartment compliance aids (MCAs) in the community: A resource for community pharmacists and other health and social care professionals involved in medicines management for older people, 2011. Available from: https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Support/toolkit/faqs-on-mcas-nhs-lambeth.pdf.
12. Elliot RA. Appropriate use of dose administration aids. Aust Prescr, 2014; 37(2): 46– 50. Available from: https://www.nps.org.au/australian-prescriber/articles/appropriate-use-of-dose-administration-aids.
13. Brion F, Nunn AJ, Rieutord A. Extemporaneous (magistral) preparation of oral medicines for children in European hospitals. Acta Paediatr, 2003; 92: 480-90.
14. Gilmartin JF, Hussainy SY, Marriott JL. Medicines in Australian nursing homes: a cross-sectional observational study of the accuracy and suitability of re-packing medicines into pharmacy-supplied dose administration aids. Res Social Adm Pharm, 2013; 9(6): 876-83. DOI: 10.1016/j.sapharm.2013.01.002. Available from: http://www.sciencedirect.com/science/article/pii/S1551741113000168.
15. Pharmaceutical Society of Australia. Guidelines and standards for pharmacists. Sidney. Pharmaceutical Society of Australia. 2007. Available from: http://www.psa.org.au/download/community-pharmacy-agreements/dose-administration-aids/dose-administration-service-guidelines.pdf.

16. The United States Pharmacopeia. USP NF the United States Pharmacopeial Convention, Inc, Rockville, MD, 2017; 40-35.
17. Richey RH, Craig JV, Shah UU, Ford JL, Barker CE, Peak M, Nunn AJ, Turner MA. The manipulation of drugs to obtain the required dose: systematic review. J Adv Nurs, 2012; 68(9): 2103-12. DOI: 10.1111/j.1365-2648.2011.05916.x. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2648.2011.05916.x/abstract.
18. Berg C, Ekedahl A. Dosages involving splitting tablets: common but unnecessary? J Pharm Health Serv Res, 2010; 1: 137-41.
19. MODRIC. Manipulations of Drugs Required in Children. London. Available from: http://www.alderhey.nhs.uk/wp-content/uploads/MODRIC_Guideline_FULL-DOCUMENT.pdf.
20. Logrippo S, Ricci G, Sestili M, Ferrara L, Palmieri GF, Bonacucina G and Blas P. Oral drug therapy in elderly with dysphagia: between a rock and a hard place! Clin Interv Aging, 2017; 12: 241–51. Available from: https://www.dovepress.com/oral-drug-therapy-in-elderly-with-dysphagia-between-a-rock-and-a-hard--peer-reviewed-article-CIA.
21. Food and Drug Administration. Guidance for Industry. Prescription requirement under section 503A of the Federal Food, Drug, and Cosmetic Act. Center for Drug Evaluation and Research; 2016. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496286.pdf.
22. American Academy of Pediatrics Committee on Drugs. Off-Label Use of Drugs in Children. Pediatrics, 2014; 133: 563-7. DOI: 10.1542/peds.2013-4060. Available from: http://pediatrics.aappublications.org/content/early/2014/02/18/peds.2013-4060.
23. Stokes JA, Ientile C, Roberts MS. Effectiveness and cost effectiveness of dose administration aids. Final Report Phase, 2006; 3. Available from: http://6cpa.com.au/wp-content/uploads/Effectiveness-and-cost-effectiveness-of-Dose-Administration-Aids-phase-3-DAA-phase-3-Final-Report.pdf.
24. Lagrange F. Déconditionnement et stabilité des formes orales sèches solides : états desconnaissances. Ann Pharm Fr, 2010; 68: 332-58.
25. World Health Organization. Guidelines on packaging for pharmaceutical products. Technical Report Series 902. Annex, 2002; 9: 120-56.
26. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Work products. Quality guidelines. Availablefrom:

http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html.

27. European Medicines Agency. ICH Topic Q 1 E Evaluation of Stability Data. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002649.pdf)y.
28. World Health Organization. WHO working document QAS/05.146 - Stability Studies in a Global Environment. Available from: http://www.who.int/medicines/services/expertcommittees/pharmprep/QAS05_146Stabilitywithcomments.pdf).
29. Central American technical regulation. RTCA 11.01.04: 10. Pharmaceutical products. Stability studies of medicinal products for human use. First update, 2011. Available from: https://www.ministeriodesalud.go.cr/empresas/normativas/DRS_Anexo_resolucion_20256_2010.pdf.
30. Food and Drug Administration. Guidance for Industry. Repackaging of certain human drug products by pharmacies and outsourcing facilities. Center for Drug Evaluation and Research, 2017. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM434174.pdf.
31. National Meteorological Institute Costa Rica. Monthly Bulletins from January to December of the year 2015. ISSN 1654-0465. Available from: https://www.imn.ac.cr/boletin-meteorologico.
32. Weather Online. Percentage of relative humidity (%) retrospective of the year in the Airport Tobías Bolaños in San Jose of Costa Rica to 994 m of altitude. Program Available from: http://www.woespana.es/weather/maps/city, 2015.
33. Monteverde-Verdenelli M, Peranovich-Celton A, Zepeda-Ortega A. Comparación de la prevalencia de discapacidades basada en auto-reportes en países de América Latina. Poblac salud mesoam, 2014; 12(1): 2-11. Available from: http://revistas.ucr.ac.cr/index.php/psm/article/view/15134/14450.
34. World Health Organization. Mortalidad y carga de mortalidad in Noncommunicable diseases country profiles 2014, Costa Rica, Available from: http://www.who.int/nmh/countries/cri_en.pdf?ua=1.
35. British Pharmacopoeia Commission. British Pharmacopoeia, 13th Edition, Stationery Office, Great Britain, 2013.

36. Association of Official Analytical Chemists. Guidelines for Single Laboratory Validation of Chemical Methods for Dietary Supplements and Botanicals, Arlington, Va., USA, 2002. Available from: https://www.aoac.org/aoac_prod_imis/AOAC_Docs/StandardsDevelopment/SLV_Guidelines_Dietary_Supplements.pdf.
37. Stability of Drugs in Compliance Aids. Medicines Information, Pharmacy Department, Pinderfields General Hospital, Wakefield, 2006. Available from: http://www.ub.edu/farmaciaclinica/projectes/webquest/WQ0/docs/ishak.pdf.
38. Church C and Smith J. How stable are medicines moved from original packs into compliance aids? Pharm. J, 2006; 276: 75-81.
39. Zafar MU, Farkouh ME, Fuster V, Chesebro JH. Crushed clopidogrel administered via nasogastric tube has faster and greater absorption than oral whole tablets. J Interv Cardiol, 2009; 22(4): 385–9.
40. Khan MA. Stability of Repackaged Products. In: Huynh-Ba K (Ed.). Pharmaceutical Stability Testing to Support Global Markets: Pharmasp, American Association of Pharmaceutical Scientists, 2010; 129. DOI: 10.1007/978-1-4419-0889-6_17.
41. Margiocco ML, Warren J, Borgarelli M, Kukanich B. Analysis of weight uniformity, content uniformity and 30-day stability in halves and quarters of routinely prescribed cardiovascular medications. J Vet Cardiol, 2009; 11: 31-9.