RESEARCH ARTICLE

Effects of Non-standard Storage Conditions on the Stability, Safety and Suitability of Drug Consumption

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ABSTRACT

Drugs are distinctive and sensitive products. It should pass specific tests and have specific criteria for human use. The disparity of any of the acceptance criteria will influence the product's effectiveness, despite the product being still in validated expiry date. The stability study and manufacturing of many drugs were done at specific climatic zones, but marketed and sold at different climatic zones. In a hot poor country or country that suffers from a power supply shortage (like in Iraq), it is impossible to provide standard storage conditions as the manufacturer recommends. The research aims to study the effects of non-standard storage conditions on the official and non-official acceptance criteria for stored tablets compared to the same newly manufactured tablets. The results showed that the physical appearance, tablet hardness, friability, disintegration, uniformity of weight, assay was not affected.

On the other hand, the dissolution profile of the stored products showed a change in the solubility behavior. From the results, we can conclude that storage conditions may not affect the content of the active substance. Still, it may affect other characteristics of the active substance, such as solubility. The research recommends the necessity of scrutiny of the storage conditions of drugs and not being lenient with them. Also recommends the necessity to study the dissolution profile and stability of excipients when conducting a drug stability study and determining the expiry date.

Keywords: Dissolution test, Safety, Stability, Storage conditions.

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INTRODUCTION

Drugs are chemical or biological compounds from natural or manufactured sources that use for treatment, prevention, improvement of health status, or modifying physiological systems for the benefit of patients.[1] Most drugs are available in the form of pharmaceutical products in various dosage forms. Any pharmaceutical products have two main parts, the active substance and the inactive additives or excipients.[2] The manufactured drug in its final pharmaceutical form most possesses all the specifications that allow it to be marketed in terms of therapeutic efficacy, safety, and stability during storage.[3]

The physical and chemical properties of the drug can change during storage, which leads to the deterioration and decrease of its therapeutic benefit, and, in some cases, may lead to an increase in the toxicity of the drug.[4] This degradation usually occurs due to a series of chemical reactions involving the active ingredient and other excipients. Additionally, physical changes like changes in color, odor, and taste are usually due to chemical degradation. Physical or chemical changes usually occur due to exposure to improper environmental conditions such as temperature, humidity, sunlight, pH, and oxygen possibly affecting the rate and extent of a drug's degradation.[5] These changes may affect drug bioactivity.[2] Accordingly, the quality of the product must be maintained during manufacturing, transportation, and storage, as well as during handling by patients.[5]

Any pharmaceutical product was subjected to numerous studies before it is ready for human use, including the stability study and expiration date. Drug stability is defined as "the ability of a drug substance or medicinal product to remain within definite specifications to maintain its quality and efficacy throughout the validity period".[4] Stability studies are necessary to decide on the appropriate packaging materials and storage conditions, to determine the proposed shelf-life and verify that there are no changes in the marketed pharmaceutical formula.[6] However, the weakness of the stability study is that it relies heavily on evaluating the concentration of the active ingredient without assessing other parameters such as solubility. Additionally, the stability studies were conducted

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under specified storage conditions of the climatic zone as classified by the International Conference of Harmonization guideline (ICH guideline).[7] Normally, the stability of the drug was studied within a specific climatic region according to the geographical location of the manufacturer while the product is marketed to a different climatic region. This difference in climatic conditions such as temperature, humidity, and sunlight intensity, may affect the stability of the product, especially if the recommended storage conditions are not well adhered to.[8]

Two pharmaceutical products, valsartan 160 mg tablet (Diovan 160 mg tablet®) manufactured by Novartis and propranolol 10 mg tablets (Inderal 10 mg tablet®) manufactured by AstraZeneca were selected. Both of them are used for the treatment of chronic high blood pressure and cardiovascular problems. High blood pressure is a risky and life-threatening condition which should be treat regularly with a correct and usable drug(s) that comply with standard specifications.

The present research aims to assess the extent to which a drug manufactured in a climatic zone I (cold zone), marketed to climatic zone III (hot and dry zone), and stored in non-standard storage conditions effected focusing, among others, on the dissolution profile in addition to other criteria such as the uniformity of weight and uniformity of content of the active ingredient for stored products and comparing to the same newly manufactured products.

MATERIALS AND METHODS

Chemicals and Reagents

Monobasic potassium phosphate; sodium hydroxide, hydrochloric acid (Sichuan- China). Valsartan USP reference standard, Propranolol hydrochloride USP reference standard, and Phosphoric acid (Sigma-Aldrich- Malaysia). Valsartan 160 mg tablet (Diovan 160 mg tablet®, Novartis) and propranolol 10 mg tablets (Inderal 10 mg tablet®, AstraZeneca) were purchased from the local market of Iraq.

Instruments and Equipment

Sensitive balance 4 digits XB220A (Presiza-Germany); Dissolution tester PT-DT7 (Pharma-Germany); and ultraviolet-vis spectrophotometer (Shimadzu- Japan). Monsanto hardness tester (Ajanta type, India). TA-100 Erweka friabilator; Erweka Disintegration testing apparatus type ZT 221 (Germany).

Preparation of Drug Samples

Two pharmaceutical products, valsartan 160 mg tablet, and propranolol 10 mg tablets were selected. The newly manufactured tablets were evaluated for physical appearance, tablet hardness, friability, disintegration, uniformity of weight, assay, and the dissolution profile; then after, stored in a stability chamber at 40°C and 25% relative humidity for 6 months. After the storage period ended, the samples were subjected to the same evaluation tests and the results compared to those of the same tablets before storage.

Methods

The official tests were performed according to the standard specifications of the United State Pharmacopoeia 2020 (USP43-NF35). Other non-official tests, including the hardness, friability, and disintegration tests, were performed as described by Ramu *et al.,* 2014 and Ali *et al.*[2-18]

Physical Appearance

For the detection of any change in the physical appearance, a direct comparison between tablets before and after storage was made. This comparison includes tablet color, odor, thickness, texture quality, and any change in shape. Additionally, a microscopic examination of Inderal 10 mg tablet® (propranolol) and Diovan 160 mg tablet® (valsartan) to inspect the status of the film coat was done.

Hardness Test

Tablets need a certain level of hardness to be able to tolerate shocks from packaging, shipping, and handling. Ten tablets were placed between two jaws, a force was applied, and the force at which the tablet was crushed was documented. The results were expressed as mean ± SD.

Friability Test

Ten tablets were taken separately, dusted, weighed, and placed in the friability. The machine was run for 100 revolutions at a speed of 25 rpm. Then after, the tablets were taken out, dusted, and weighed again. The difference in weight points to the friability. The acceptance criteria are not more than a 1% difference in weight.

Disintegration Test

The six vessels of the disintegration tester were filled with 900 mL distilled water at 37 ± 2°C. In each vessel, one tablet was placed in the basket of the disintegrator, and the machine started. The disintegration time (DT) was recorded when no particle remained on the basket.

Uniformity of Weight

This test was conducted by weighing 10 tablets individually (xi), then the average weight (x) was calculated. By using average weight, the deviation of the weight of each tablet from the average weight was calculated in the form of a percentage using the following equation:

$$wu\% = \frac{x - xi}{x} * 100 \qquad \text{... Eq. (1)}$$

Tablets are accepted in terms of weight uniformity if the percentages of weight variances fall within the range of 1 to 1.3%. The acceptance criteria permit at most two tablets to exceed the allowed percentage variance, and no tablet is allowed to exceed twice the allowed percentage.

Assay of Valsartan 160 mg Tablets

The assay was determined using an HPLC method as described by USP43-NF35. The mobile phase was acetonitrile: water: glacial acetic acid (50:50:0.1); Acetonitrile and water (50:50) was used as diluent. The column was L1 (4.6-mm × 25-cm) with particle size 10 µm packing. The detector was UV 230 nm; Column temperature 30°C; Flow rate at 1.0 mL/min and injection size of 20 µL. Acceptance criteria are 95.0 to 105.0% of the labeled amount of valsartan. The acceptance limits is 90 to 110% of the labeled amount.

Table 1: Hardness test for newly manufactured and stored tablets of valsartan and propranolol tablets (n=10) expressed as mean ± SD

Tablets	*Hardness (kg/cm²)*	
	Valsartan	*Propranolol*
New	6.67 ± 0.089	7.58 ± 0.105
Stored	6.21 ± 0.132	7.35 ± 0.112

Dissolution Test for Valsartan 160 mg Tablet

The test was conducted for six tablets using the dissolution tester according to the conditions specified by the USP for valsartan tablets which are: USP apparatus II, rotation speed: 50 rpm, temperature: 37 ± 2°C, and medium: 1000 mL of buffer solution pH 6.8. The buffer solution was prepared by mixing 54.5 g of monobasic potassium phosphate and 7.14 g of sodium hydroxide with 6 L of distilled water. Samples of 2 mL were withdrawn at specified intervals and replaced with 2 mL of fresh medium pre-heated at 37°C. The samples were filtered using micro-filters, then the absorbance of samples was measured at a wavelength of 250 nm, and then the absorbance against time was drawn.

Assay of Propranolol 10 mg Tablets

The assay was determined using an HPLC method as described by USP43-NF35. Mobile phase was a mixture of 1.6 g sodium dodecyl sulphate and 0.31 g tetra butyl ammonium phosphate in a mixture of 1-mL of sulphuric acid, 550 mL of acetonitrile, and 450 mL of water. Adjust the pH to 3.3 with 2 N sodium hydroxide solution. The standard solution was 0.2 mg/mL of USP propranolol hydrochloride RS in mobile phase. The sample solution was 0.2 mg/mL of propranolol hydrochloride in the mobile phase. The detector was UV-vis at 292 nm, the column was L1 (4.6 mm × 25 cm; 5 µm packing), flow rate was 1.8 mL/min, and injection volume was 20 µL. The acceptance limit is 98 to 102% of the labeled amount.

Dissolution Test of Propranolol 10 mg Tablets

This test was conducted for six tablets using the dissolution tester according to the conditions specified by the USP for valsartan tablets which are: USP apparatus II, rotation speed: 100 rpm, temperature: 37 ± 2°C, medium: 1000 mL of dilute hydrochloric acid (1 in 100), and wavelength: 289 nm. Metal wires in the form of a preservative (basket) were used, and the tablets were placed inside them to avoid floating. Samples of 2 mL were withdrawn at selected intervals with replacement with 2 mL of fresh medium pre-heated at 37°C. The samples were filtered using micro-filters, then the absorbance of samples was measured at a wavelength of 289 nm, and then the absorbance against time was drawn.

RESULTS AND DISCUSSION

Physical Appearance

By directly comparing stored and newly manufactured tablets for valsartan and propranolol, no change in color, odor, thickness, or texture was found.

Tablet Hardness

The results showed a slight decrease in tablet hardness for the stored tablets for both pharmaceutical products compared to newly manufactured tablets (Table 1). Stored valsartan tablets showed a decrease of hardness by 6.89% compared to newly manufactured tablets, while stored propranolol tablets showed a decrease by 3.03%. Being an unofficial test, there are no pharmacopeia acceptance criteria for the hardness test. For orally administered tablet, the acceptable hardness value range is 4–10 kg/cm^2, largely depending on the disintegration test result.[11] The decrease in tablet hardness is possibly due to a decline in activity "aging" and loss of cross-links of the binder.[12]

Friability Test

The results showed a 0.28 and 0.17% for valsartan and propranolol, respectively. Both results were acceptable. Usually, a friability test is applied to the core tablet before coating to measure the ability of the tablet core to withstand collision and tablet sliding towards one another during the handling and coating process.

Disintegration Time

Table 2 showed the results of the disintegration test. Both products showed decreased disintegration time for the stored tablets compared to the newly manufactured ones. There is a direct relation between tablet hardness and disintegration time, i.e. as tablet hardness decreases disintegration time decrease and *vice-versa*.

Any solid dosage form after administration, it needs to disintegrate first, then dissolve in a gastric medium, and be absorbed, then after its medical effect starts. Accordingly, the change in disintegration time possibly affects onset and/or intensity of drug activity.

The results of friability test and disintegration time reveals the film coat's durability and effectiveness, which showed no scraping, peeling, abrasion or presence of micro-cracks due to the preservation of elasticity property (Figure 1).

Uniformity of Weight

Ten tablets for each the newly manufactured tablets and after storage were weighed individually using a sensitive balance and the average was calculated as shown in Table 3. The results showed that all samples were within the acceptable range according to the USP standard specifications of (1–1.3%) weight variation. These results reflect that storage conditions do not affect the weights of the tested tablets. The probable reason is that these products do not contain any volatile or sublimate materials and are stored in a tightly closed blister.

Table 2: Disintegration time for newly manufactured and stored tablets of valsartan and propranolol tablets (n=6) expressed as mean ± SD

Tablets	*Disintegration time (min)*	
	Valsartan	*Propranolol*
New	7.64 ± 0.625	5.68 ± 0.675
Stored	7.18 ± 0.883	5.45 ± 0.902

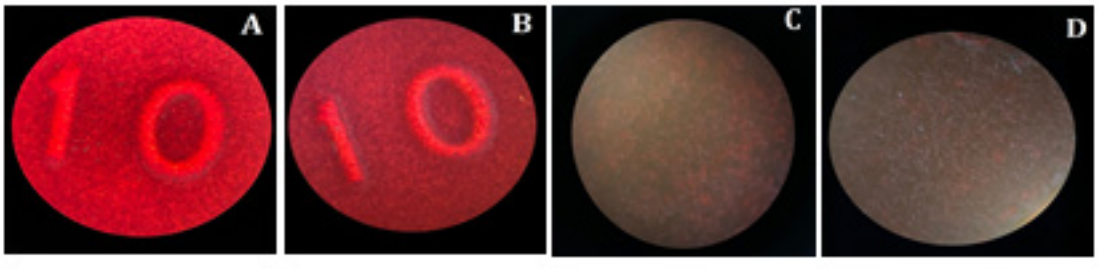

Figure 1: A microscopic images (x4) of Inderal 10 mg tablet® (propranolol) and Diovan 160 mg tablet® (valsartan). A: new propranolol tablet; B: stored propranolol tablet; C: new valsartan tablet; and D: stored valsartan tablet.

Table 3: Uniformity of weight for newly manufactured and stored tablets of valsartan and propranolol tablets (n=10) expressed as average weight.

Tablets	*Average weight (mg)*	
	Valsartan	*Propranolol*
New	311.7	111.8
Stored	313.0	111.7

Assay

The results of assay test showed that the concentration of the active substance in all samples was within the acceptable range according to USP (95–105%) for valsartan and (90–110%) for propranolol (Table 4). This means that the tested products are still valid and usable for human as the concentrations of the active substance is acceptable and within the biologically active range if we relied on the content assay test only.

Effect of Storage Conditions on the Dissolution

Effect of Storage Conditions on the Dissolution of Valsartan

The results of the dissolution test of newly manufactured valsartan tablets showed a stable dissolution profile, where the increase in the concentration of the active ingredient dissolved in the test medium with time up to a time of 90 minutes (Figure 2). On the other hand, stored valsartan tablets showed a fluctuation and instability in solubility. The results of the dissolution test of the stored tablets showed a faster and more intense solubility at minute 5, then a decrease in the solubility at minutes 10 and 30; then after return to the rise until the 90th minute.

This fluctuation in the solubility profile could be due to the effect of non-standard storage conditions on excipients which might be led to losing their impact on the medicinal product. Even though the excipients are pharmacologically inert and biologically ineffective, they have an important role in maintaining the product's standard specifications, leading to its desired and specific therapeutic effect.

Table 4: Assay for newly manufactured and stored tablets of valsartan and propranolol tablets (n=3) expressed as mean ± SD of the labeled amount.

Tablets	*Assay%*	
	Valsartan	*Propranolol*
New	102.47	101.06
Stored	98.33	98.22

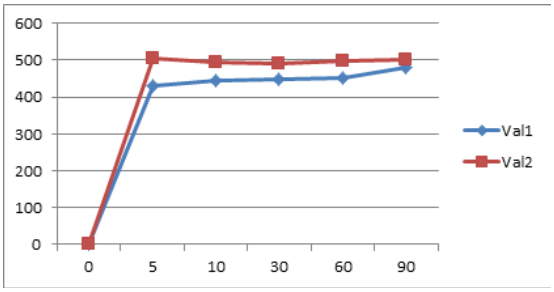

Figure 2: Dissolution profile of Valsartan tablets examined using the specified test conditions according to the US Pharmacopeia (USP43-NF35). Val 1: a sample of newly manufactured valsartan tablets and Val 2: a sample of a stored valsartan tablet.

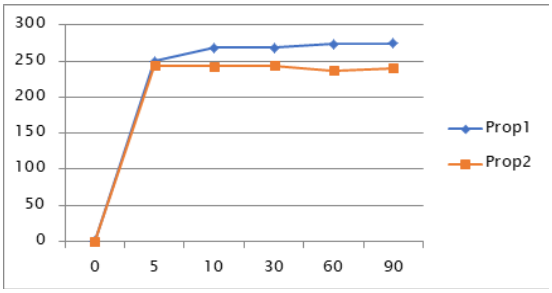

Figure 3: Dissolution profile of propranolol samples in the dissolution medium and test conditions specified according to the US Pharmacopeia (USP43-NF35). Pro1: newly manufactured propranolol tablet sample and Pro2: tablet sample propranolol stored.

The obtained results of a decrease in tablet hardness and disintegration time concomitant to the result of rapid dissolving of stored tablets faster than new manufactured tablets. In a previous study,[13] the researchers found a direct effect of the concentration of excipient hydroxyl propyl methyl cellulose (HPMC) on the solubility profile and a direct relationship between the solubility of the active substance and the concentration of HPMC in the preparation. For Diovan 160, the manufacturer company mentions the use of hypromellose (short name of HPMC) in the formula. The study also showed that the active substance suffered from re-precipitation (or recrystallization) after some time after dissolving in the solvent medium, which could explain the situation for valsartan tablets as well.

Effect of Storage Conditions on the Solubility of Propranolol

The results of the dissolution test of newly manufactured propranolol tablets showed a stable dissolution profile with

time. The stored propranolol tablets also showed a stable dissolution profile but at a lower concentration than the newly manufactured samples (Figure 3). The test for drug content showed a noticeable decline of about 9% in the concentration of the active ingredient of stored tablets compared to newly manufactured tablets, yet still within acceptable limits. The strict recommendation of the manufacturer about storage conditions of not more than 30°C and the sensitivity of propranolol to light explain the decline in the concentration of the active ingredient. The loss of part of the concentration of the active substance as a result of storage as its oxide content; it dissolves and produces basic hydroxide that raises the acidic function and increases its alkalinity. Increase in alkalinity affects the stability of pH-sensitive materials, and this intensifies the active ingredient's degradation rate in addition to the effect of high storage temperature.[14,15]

For any medicinal product to offer biological activity, it must first reach blood circulation. To reach blood circulation, the product must be dissolved adequately and constant rate so the gastrointestinal tract can absorb it. This indicates that the effectiveness of the medicinal product is directly affected by the active ingredient's solubility degree and pattern. Accordingly, any change in the solubility or dissolution profile of the product can lead to a significant change in the therapeutic efficacy of the product although the product contains a concentration of an active ingredient within the constitutionally acceptable limit.

CONCLUSION AND RECOMMENDATIONS

The results showed that relying on the evaluation of the concentration of the active ingredient during the stability study and estimation of the expiry date is insufficient to determine the product's validity for human use. In Diovan® 160 mg tablets, the results of the stored tablets showed that the concentration of the active ingredient was still within the USP acceptable limit, but other specifications, especially the dissolution test altered. These alterations are probably due to the excipients used in the formula. Here the research suggests either the manufacturer needs to re-evaluate the formulation of their pharmaceutical products intended to be exported to hot climatic zones (zones III and IV) or to re-estimate the expiry date to be applicable. For sure pharmaceutical products should be stored in proper storage conditions as recommended by the manufacturer, but in some countries, like Iraq where a shortage in electricity power supply during the extremely hot season, it is difficult to provide the correct storage conditions. Also, we recommend the necessity of adopting the dissolution test in the stability study of pharmaceutical products.

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