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The effect of temperature and moisture on the physical and chemical stability of paracetamol tablets (500 mg) marketed in Syria

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□ ABSTRACT □

Stability is an essential factor of quality, safety and efficacy of a drug product. The objective of this study was to investigate the effect of moisture and temperature on paracetamoltablets (500 mg) marketed in Syria. Three commercial brands (A, B, C) were examined.Tablets were exposed to different storage conditions (RH=75%& 40°C) , (RH=75%& 25°C), (RH=60%& 40°C), (RH=60%& 25°C) for 6 months and storage on shelf for 12 months. Changes in physicochemical properties of tablets were determined by hardness, friability tests and assay the content. High humidity and temperature (RH=75%& 40°C) decreased in hardness and content of paracetamol tablets(less than 90%) and increased in friability (more than 1%) in all studied brands. Second condition also caused the same results, but less than the first condition because of normal temperature. The effect of temperature on stability is less than moisture as we saw in the third condition (RH=60%& 40°C).physicochemical properties of tablets remainedwithout changes when stored in (RH=60%& 25°C) condition. The storage of tablets on shelf caused changes in hardness , friability, and content of tablets according to climatic changes during the year.

Key words: moisture, temperature, paracetamol, physicochemical properties, storage, stability.

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تأثير درجة الحرارة والرطوبة على ثباتية الخصائص الفيزيائية والكيميائية لأقراص الباراسيتامول (500 مغ) المسوقة في سوريا

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□ ملخّص □

الثباتية هي عامل أساسي لجودة وسلامة وفعالية المنتج الدوائي و أن الهدف من هذا البحث هو دراسة تأثير الرطوبة ودرجة الحرارة على أقراص الباراسيتامول (500 مغ) التي يتم تسويقه في سورية.

تم فحص ثلاث أصناف تجارية (A، B، C). (درجة رطوبة = 75٪ وحرارة 40 درجة مئوية)، (ودرجة رطوبة = 75٪ وحرارة 25 درجة مئوية)، (درجة رطوبة = 60٪ وحرارة 40 درجة مئوية)، (درجة رطوبة = 60٪ وحرارة 25 درجة مئوية) لمدة 6 أشهر والتخزين على الرف لمدة 12 شهرا.

تم تحديد التغيرات في الخصائص الفيزيوكيميائية للأقراص عن طريق اختبارات القساوة، واختبارات التفتت وفحص المحتوى.

أنقصت الرطوبة العالية ودرجة الحرارة (درجة رطوبة = 75وحرارة 40 درجة مئوية) في قساوة ومحتوى أقراص الباراسيتامول (أقل من 90٪) وزادت في القابلية للتفتت (أكثر من 1٪) في جميع الأصناف التجارية المدروسة. أعطى الشرط الثاني من الرطوبة والحرارة بنفس النتائج، ولكن أقل من الشرط الأول بسبب درجة الحرارة العادية. وكان تأثير درجة الحرارة على الثباتية أقل من الرطوبة كما هو في الشرط الثالث (درجة رطوبة = 60٪ وحرارة 40 درجة مئوية).

بقيت الخصائص الفيزيوكيميائية للأقراص دون تغييرات عند تخزينها في (درجة رطوبة = 60٪ وحرارة 25 درجة مئوية).

وتسبب تخزين الأصناف على الرف في حدوث تغيرات في القساوة، والتفتت، ومحتوى الأقراص وفقا للتغيرات المناخية خلال السنة.

الكلمات المفتاحية : الرطوبة، درجة الحرارة، الباراسيتامول، الخصائص الفيزيوكيميائية، التخزين، الثباتية.

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Introduction

Drug stability means the ability of the pharmaceutical dosage form to maintain the physical, chemical, therapeutic and microbial properties during the time of storage and usage by thepatient [1-3].There are many factors affecting on the drug stability such as [4-8]

(a) temperature:high temperature accelerate oxidation, reduction and hydrolysis reaction which lead to drug degradation.

(b) pH: acidic and alkaline pH influence the rate of decomposition of most drugs.

(c) Moisture: Water catalyses chemical reactions as oxidation, hydrolysis and reduction reaction and promotes microbial growth.

(d) Light: affects drug stability through its energy or thermal effect which lead to oxidation

(e) Pharmaceutical dosage forms: solid dosage forms are more stable than liquid dosage forms for presence of water.

(f) Concentration: rate of drug degradation is constant for the solutions of the same drug with different concentration. So, ratio of degraded part to total amount of drug in diluted solution is bigger than of concentrated solution.

(g) Drug incompatibility: reactions between components of pharmaceutical dosage forms itself or between these components and cover of the container .

(h) Oxygen: exposure of drug formulations to oxygen affects their stability.

The objective of stability study is to determine the shelf life, namely the time period of storage at aspecified condition within which the drugproduct still meets its established specifications.Stability is an essential factor of quality, safetyand efficacy of a drug product. A drug product, which is not of sufficient stability, can result inchanges in physical (like hardness, dissolution rate, phase separation etc) as well as chemical characteristics (formation of high riskdecomposition substances).

The Chemical stability of drug is of great importance since it becomes less effective as it undergoes degradation. Also drug decomposition may yield toxic byproducts that are harmful to the patient. Microbiological instability of a sterile drug

product could also be hazardous. Stability evaluation of drug substance or drug product is the key to drug quality as it determines the efficacy of any drug or dosage form. Stability assessment of drug products and drug substancesare mandated by regulatory agencies across theglobe. In fact, stability-testing issues are responsible for a number of audit findings by regulatory agencies. Stability testing problems are regularly cited in warning letters and sometimes results in costly product recall. Stability testing provides evidence that the quality of drug substance or drug productchanges with time under the influence of variousenvironmental conditions such as temperature, relative humidity etc. The stability study consists of a series of tests in order to obtain an assurance of stability of a drug product, namely maintenance of the drug product packed in it specified packaging material and stored in the established storage condition within the determined time period [9-13].

Paracetamol and acetaminophen are commonly used names for drug that is chemically derived from N-acetyl-para-aminophenol (Figure 1). It is considered the most popular drug in the world and accessible without a prescription. The main use of paracetamol is analgesic and antipyretic. It was discovered since about 100 years ago, but until now the mechanism that it affects in the body is unknown. Its pharmacological effects similarly to NSAIDs, but it doesn't have any anti-inflammatory activity [14]. The

absorption of paracetamol occurs quickly from the Gastrointestinal tract and reaches to its peak plasma after about 30 minutes from oral doses. The distribution happens into most body tissues. Paracetamol is excreted in the urine after the metabolism in the liver by cytochrome p450. The elimination half-life is about 2 hours. Paracetamol traverses the placenta and exhibits in breast milk [15-16].Paracetamol is available in many dosage forms like as tablets, syrups, suppositories, injections, oral drops.

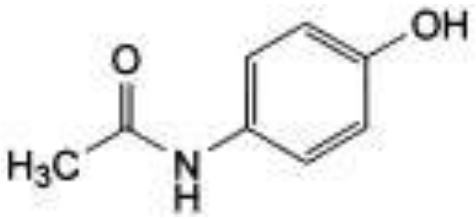

Figure1: structure of paracetamol

The present work is based on a study of the effect storage conditions (temperature and humidity) on the physiochemical stability of different brands of paracetamoltablets (500 mg) marketed in Syria.

Material and methods

Three commercial brands (A, B, C,) of paracetamol were randomly selected. Paracetamol tablets brands having label strength of 500 mg were purchased from registered pharmacies in Lattakia, Syria. All tests wereperformed within product expiration dates. The reagents used were sodium chloride, sodium bromide, sodium hydroxide and Freshly distilled water was used throughout the work.

Storage conditions

paracetamol tablets to be tested were subjected to storage conditions as shown in table(1).samples were withdrawn within periods of time and evaluated for physical and chemical stability.

Table(1): storage conditions

Storage conditions		Storage period
Moisture (RH%)	Temperature(°C)	
75±5	40±2	6 months
75±5	25±2	6 months
60±5	40±2	6 months
60±5	25±2	6 months
Storage on shelf		12 months

Physical stability

Physical stability was evaluated through hardness , friability, and weight variation tests:

a- **Hardness test**:Sample tablets (10) of each brand were taken, a tablet was placed between the spindle of the Erwerka hardness tester machine and pressure was applied by turning the knurled knot just sufficiently to hold the tablet inposition. The pressure was then increased as uniformly as possible until the tablet broke and the pressure required to break the tablet was then read off the machine and recorded.

b- **Friability test**: Sample tablets (20) of each brand were weighed together before transferring them to the Roche friabilator. The friabilator was adjusted to 25 rpm for 4 minutes. After that, the tablets were taken and cleaned from dust and weighed again. By

using this formula % of Friability = [(Wi – Wf)/ Wi] x 100 was calculated. The loss should be less than 1% according to BP.

Chemical stability

chemical stability was evaluated through assay the content of the stored tablets:

a- **Calibration curve of paracetamolin sodium hydroxide 0.1N at 257 nm**: A standard curve was created for paracetamol using pure drug powder diluted to 5 known concentrations (range between 0.12 and 0.3 mg/100ml). These standard curves were established to verify accurate analysis of the drug.

b- Assay the content: 10 tablets were taken from each brand. Each tablet was crushed and dissolved separately using a combination of manual agitation and sonication techniques in 100 ml of distilled water. Then the samples were mixed well before filtration through a membrane filter. The samples of each solution were assayed for drug concentration using spectrophotometer at 257 nm. The drug content was quantified by calculating the concentrationsfrom the absorbance readings obtained through UV analysis.Several measures were calculated in order to assess the amount and acceptability of variations in drug content. The measured drug content expressed as a percent of label claim was calculated for each tablet then the average of the content percentage for 10 tablets was calculated . The average should be in the range of 90-110% forparacetamol(proxy USP specification for drugcontent.

Results and discussion

A-Calibration curve of paracetamolin sodium hydroxide 0.1N at 257 nm

Alinear relationship between the absorbance and the concentration of paracetamolin sodium hydroxide at 257 nm in the concentration range of 0.12-0.3mg/100ml is observed. The regression equation is Y= 2.6515X-0.0104 and the correlation coefficients (r) of the linear regression of the calibration curves is 0.9998.

B- Storage in (RH=75%&40°C)

This study reviews the effect of moisture and temperature on paracetamol(500 mg) tablets. It was stated that the amount of moisture adsorbed by drugs or excipients and increased in temperature influences hardness, friability and content. These changes may alter bioavailability, and therapeutic efficacy, even though the drug potency. The influence of relative humidity and temperature depends on its chemical affinity for tablet and nature of excipient or additive.

High (relative humidity 75% and temperature 40°C) decrease in tablets hardness for all studied brands after 3 days of storage and hardness reached to values less than 3 kp after (three, two, one) months for brands(A, B, C) respectively, as shown in table (2). Also this conditions affected on the friability of tablets and the values of friability in all brands exceeded BP specifications 1% after one month for (A &B) brands and after one week for brand C.

The content of tablets in all studied brands was decreased after 3 days from storage and reached to values less than 90% (USP specifications for drug content) after (three , two) months for A &B brands and after two weeks for brand C. This happened because of the degradation ofparacetamoland the content reached to low values (50.08, 48.87, 35.55) for (A, B, C) brands ,respectively,at the end of storage period.

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Table(2): The results of storage in (RH=75%&40°C) condition.

Time	Hardness(kp)			Friability (%)			Content (%)		
	A	B	C	A	B	C	A	B	C
Fresh	7.12	6.56	5.87	0.76	0.65	0.91	97.11	95.77	91.11
3days	6.85	6.31	5.61	0.79	0.71	0.93	97.09	95.07	90.91
1 week	6.23	6.05	5.09	0.81	0.77	0.98	96.97	94.56	90.68
2weeks	6.09	5.91	4.77	0.85	0.82	1.13	96.86	94.01	90.31
3 weeks	5.83	5.61	4.61	0.92	0.89	1.32	96.73	93.22	89.13
1 month	5.53	5.03	3.05	0.97	0.95	1.46	95.13	92.87	87.09
2 months	4.11	3.11	2.78	1.95	1.34	1.97	92.12	90.13	84.36
3 months	3.09	1.98	1.92	2.23	2.09	2.44	90.34	86.44	80.19
4months	2.12	1.02	0.97	2.97	2.98	3.09	80.87	78.31	71.06
5months	1.08	0.43	0.31	3.11	3.86	3.97	69.54	65.08	54.65
6 months	0.87	0.12	0.11	3.78	4.56	4.55	50.08	48.87	35.55

C- Storage in (RH=75%&25°C)

In this condition the relative humidity is high while the temperature is normal. The high humidity also decrease in tablets hardness for all studied brands and hardness reached to values less than 3 kp after (four, two, one) months for brands(A, B, C) respectively, as shown in table (3). Also this conditions affected on the friability of tablets and the values of friability in all brands exceeded BP specifications 1% after 3 weeks for (A &B) brands and after 3 days for brand C.

The content of tablets in all studied brands was decreased after 2weeks from storage and reached to values less than 90% (USP specifications for drug content) after (three, two, one) months for (A, B, C) brands, respectively. This happened because of the degradation of paracetamoland the content reached to low values (54.34, 50.81, 40.19) for (A, B, C) brands,respectively,at the end of storage period. The effect of this condition is low comparison with the above condition because of normal temperature in this condition.

Table(3): The results of storage in (RH=75%&25°C) condition.

Time	Hardness (kp)			Friability (%)			Content (%)		
	A	B	C	A	B	C	A	B	C
Fresh	7.12	6.56	5.87	0.76	0.65	0.91	97.11	95.77	91.11
3days	7.05	6.11	5.15	0.81	0.82	0.97	97.09	95.16	91.01
1 week	6.94	5.89	4.85	0.86	0.88	1.11	96.87	94.89	90.89
2weeks	6.75	5.55	4.23	0.91	0.95	1.34	96.54	94.45	90.77
3 week	6.35	5.31	3.89	0.97	0.99	1.51	96.13	94.34	90.55
1 month	6.21	4.86	3.05	1.12	1.21	1.89	95.45	93.91	90.11
2 months	5.05	3.05	2.78	1.78	1.97	2.19	93.32	90.03	86.24
3 months	4.14	2.76	1.67	2.13	2.33	2.54	91.92	87.33	81.59
4months	3.04	1.88	0.98	2.88	2.98	3.11	83.76	80.28	74.24
5months	1.78	1.03	0.21	3.12	3.76	3.98	70.12	68.12	56.33
6 months	1.22	0.45	0.11	4.12	4.56	4.71	54.34	50.81	40.19

D- Storage in (RH=60%&40°C)

In this condition the temperature while the relative humidity is normal. The high temperature also decrease in tablets hardness for all studied brands and hardness reached to values less than 3 kpafter (five, four, three) months for brands(A, B, C) respectively as shown in table (4). Also this condition affected on the friability of tablets and the values of friability friability in all brands exceeded BP specifications 1% after (three, two) months for (A &B) brands,respectively, and after two weeks for brand C.

The content of tablets in all studied brands was decreased and reached to values less than 90% (USP specifications for drug content) after(4, 3,2)months for (A, B, C) brands,respectively. This happened because of the degradation of paracetamol. The effect of this condition is low comparison with the above condition (RH=75%&25°C) , so we can say that the effect of humidity on paracetamoltablets stability is larger than temperature.

Table(4): The results of storage in (RH=60%&40°C) condition.

Time	Hardness (kp)			Friability (%)			Content (%)		
	A	B	C	A	B	C	A	B	C
Fresh	7.12	6.56	5.87	0.76	0.65	0.91	97.11	95.77	91.11
3days	7.11	6.51	5.77	0.78	0.69	0.93	97.11	95.75	91.09
1 week	7.02	6.45	5.61	0.79	0.72	0.97	97.05	95.70	91.04
2weeks	6.95	6.34	5.33	0.83	0.79	0.99	96.95	95.45	90.91
3 weeks	6.75	6.06	5.19	0.86	0.86	1.13	96.79	95.12	90.73
1 month	6.67	5.91	4.94	0.91	0.97	1.58	96.63	94.96	90.55
2 months	6.13	5.11	3. 91	0.99	1.64	1.98	94.88	92.92	90.01
3 months	5.22	4.09	3.08	1.23	2.15	2.33	92.96	90.08	86.33
4months	4.33	3.11	2.13	1.93	3.09	2.92	90.11	84.32	80.21
5months	3.02	2.01	1.09	2.78	3.88	3.95	77.54	73.66	62.09
6 months	1.95	1.12	0.67	3.12	4.11	4.53	63.89	55.98	57.14

E- Storage in (RH=60%&25°C)

This condition is the idealism condition for storage.hardness was decreased at the end of the storage, but still above 3 kp for all studied brands as shown in table (5). Also the values of friability in all brands didn't exceed BP specifications 1%. The content of paracetamolin tablets of all studied brands remained above 90% (USP specifications for drug content) during all the storage period.

Table(5): The results of storage in (RH=60%&25°C) condition.

Time	Hardness (kp)			Friability (%)			Content (%)		
	A	B	C	A	B	C	A	B	C
Fresh	7.12	6.56	5.87	0.76	0.65	0.91	97.11	95.77	91.11
3days	7.12	6.56	5.87	0.76	0.65	0.91	97.11	95.77	91.11
1 week	7.12	6.56	5.87	0.76	0.65	0.91	97.11	95.77	91.11
2weeks	7.10	6.56	5.86	0.76	0.65	0.91	97.11	95.77	91.11
3 weeks	6.99	6.55	5.86	0.76	0.65	0.91	97.11	95.77	91.11

1 month	6.97	6.54	5.86	0.77	0.65	0.91	97.11	95.77	91.11
2 months	6.95	6.54	5.82	0.77	0.65	0.93	97.09	95.75	91.09
3 months	6.93	6.48	5.79	0.78	0.65	0.93	97.09	95.75	91.09
4months	6.91	6.35	5.75	0.78	0.67	0.93	97.08	95.75	91.08
5months	6.85	6.21	5.61	0.78	0.67	0.93	97.08	95.73	91.08
6 months	6.77	6.08	5.55	0.78	0.67	0.93	97.08	95.75	91.08

f- Storage on shelf

In this condition the tablets exposed to different values of relative humidity and temperature according to climatic conditions across 12 months. Hardness of tablets was decreased in all studied brands and reached to values less than 3 kpafter (11, 10, 9) as shown in table (6). The friability of tablets in (A, B) brands exceeded BP specifications 1% after (10, 9, 8) months for (A, B,C) brands, respectively.

The content of tablets in all studied brands was decreased to values less than 90% (USP specifications for drug content) after (11, 9, 6) months for (A, B,C) brands, respectively.

Table(6): The results of storage on shelf.

Time	Hardness (kp)			Friability (%)			Content (%)		
	A	B	C	A	B	C	A	B	C
Fresh	7.12	6.56	5.87	0.76	0.65	0.91	97.11	95.77	91.11
1month	7.05	6.51	5.84	0.76	0.67	0.91	97.11	95.77	91.11
2 months	6.91	6.33	5.78	0.78	0.71	0.92	97.02	95.24	91.05
3 months	6.76	6.07	5.66	0.81	0.75	0.93	96.87	95.05	90.94
4months	6.23	5.86	5.49	0.84	0.81	0.93	95.78	94.57	90.33
5 months	6.08	5.45	4.98	0.87	0.85	0.95	94.88	93.81	90.12
6 months	5.56	5.12	4.13	0.91	0.89	0.97	94.11	92.15	90.02
7 months	5.29	4.87	3.95	0.92	0.93	0.97	93.75	91.33	85.09
8months	5.02	4.61	3.56	0.94	0.96	0.99	92.91	90.93	81.22
9months	4.23	4.11	3.02	0.98	0.99	1.11	92.01	90.06	77.89
10 months	3.87	3.08	2.51	1.11	1.12	1.23	91.66	87.22	72.55
11months	3.03	2.19	1.98	1.21	1.24	1.52	90.07	84.67	68.98
12months	2.04	1.98	1.11	1.43	1.52	2.02	85.33	80.55	63.23

Conclusion

From this work we can report that paracetamoltablets, when stored in inappropriate storage conditionespecially in coastal area weather of Syria that usually is in high humidity which cause acceleration changes on the physical and chemical properties leading to less effective drug.

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