Quality evaluation of acetaminophen formulations manufactured in Congo DR

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ABSTRACT

The objective of this work was to study the accelerated stability of Acetaminophen 500mg tablet sold on the Congolese market. Five specialties of Acetaminophen were examined: four locally manufactured generics and the innovator. Two analytical tests were made to study the change during the storage: The dosage of active ingredient by HPLC and dissolution profile by UV / Visible spectrophotometer. The results of this study reveal a problem with the manufacturing processes of Congolese generics. That is caused because they all present an abnormal drop of active ingredient and a release below the limit, from the sixth month of storage at a temperature and relative humidity of 40 °C and 75%.HR as per ICH guidelines.

Keywords: Stability, Acetaminophen, generic, Tablet, DR Congo.

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INTRODUCTION

Acetaminophen, in figure 1, is an analgesic and antipyretic with only weak peripheral anti-inflammatory effect. Analgesia is obtained at a plasma concentration of about 10 µg / ml and antipyretic activity at 4-18 µg / ml [1]. It was widely used since the 1950s, first in the United States shortly after in Europe. Surprisingly, it was only during the 1970s that were published reports on its hepatotoxic effects and the first case of serious and fatal overdose. [2]. Acetaminophen is currently one of the most sold analgesic and antipyretic in the world. In Europe and the United States, it is frequently used for suicide attempts [3]. In the United States, acetaminophen poisoning is a major cause of acute liver failure [4-6]. Every year there are over 100,000 cases of overdose with an average of over 450 deaths [3, 7]. In DR Congo Acetaminophen is on top of the most consumed drugs by the population [8, 9]. Its manufacture is completely local since 2006, following the ban on the import of generic Acetaminophen [10, 11].

In this work, we study the quality of Acetaminophen tablet 500 mg from the Congolese manufacturing, and its innovator from France. In addition we will study the accelerated stability conditions of temperature and relative humidity (40 ° C / 75% RH) recommended by WHO for zone IV [12-14]. During this study, the quality and stability of samples taken from the Congolese market, will be verified by the dosage of the active ingredient and the dissolution test, before incubation for 3 months and after 6 months
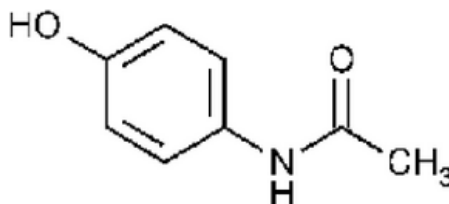
Figure 1: Chemical Structure of Acetaminophen

EXPERIMENTAL SECTION

2.1 Apparatus
UV-Visible spectrophotometer Perkin Elmer Lambda Series 35 made in the USA, the Mettler Toledo scale made in Switzerland, pH meter used was from Schott (Germany). Dissolution Test of Hanson SR8-Plus™ (USA). The chromatographic system consisted of Waters 2695 pump, auto sampler and Waters 2998 photodiode-array detector (PDA). Data acquisition was performed by the Empower Software data registration TM. The enclosure for the accelerated stability BINDER GmbH brand made in Germany.

2.2 Reagents and Materials:
All chemical products were of analytical grade and were supplied by the National Laboratory of Drugs Control (LNCM) Rabat, Morocco.

The acetaminophen standard (99,9 %) was provided by the National Laboratory of Drug Control of Morocco. Methanol was of HPLC grade from Sigma- Aldrich (Germany).

Acetaminophen generics 500 mg tablet made by four pharmaceutical industries in DR Congo, with a duration of four years were collected from the market in Kinshasa and appointed Generic 1, 2, 3, 4. The innovator from France also on the market manufactured was used for comparison.

2.3 Storage conditions:
Blisters containing acetaminophen 500mg tablets were placed in the accelerated stability enclosure set at 40 °C and 75 % relative humidity for a period of six months.

2.4 Chromatographic Conditions
Separation was by isocratic elution with the apparatus Waters, C18 column 5µm 3, 9 mm x 300 mm. The flow rate was 1,5mL/min, the wavelength 243 nm and the injection volume was 10 µL.

The mobile phase consisted of a mixture of methanol with water (3:1) vacuum filtered with a filter of pore size 0.45 microns.

2.5 Standards solutions
The Standard solution for HPLC was prepared with mobile phase and contained 0,01mg/mL.

The phosphate buffer was prepared by dissolving 68.05 g / l of dihydrogen orthophosphate potassium; the pH is adjusted to 5.8 by NaOH 1M

2.6 Samples solutions
The samples were prepared with the mobile phase and contained 0,01mg/mL of acetaminophen, obtained from a mixture of 20 tablets. The solution was sonicated for 10 min.

2.7 Dissolution test:
The USP paddle method (Apparatus2) was used for the dissolution profile. An acetaminophen 500mg tablet is placed in the vessel containing 900ml of phosphate buffer at 37 ° C, turned at the speed of 50 rpm for 30 minutes. 2mL of samples are taken with a syringe at 15, 30, and 45 minutes and filtered with a filter of 0.45 mm to form the profile curve of dissolution. The reading was measured at 243nm with phosphate buffer [15, 16].

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RESULTS AND DISCUSSION

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Dosages of active ingredient and dissolution profiles were made on acetaminophen found on the Congolese market.

Four generics manufactured in the DR Congo and an innovator from France, were subjected to accelerated stability study. The results found before, after three and six months of incubation are summarized as follows:

3.1 Determination of the active ingredient
Before storage in the enclosure at 40°C and 75% RH.

Three generic out of four (1, 2.4) are in terms of the amount of active ingredient with respectively (100.06%, 100.25% and 96.14%) while the generic three is overdosed with 109.2%. The results are presented in Table I.

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Table I. Determination of Acetaminophen in the finished products before incubation

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Finished products (FP)	Concentration in active ingredient (AI)				
	Declared Concentration in mg/tablet	Found concentration in mg/tablet	Found concentration in %	Normes in %	Observation
Innovator	500	500,63	100,12	95 – 105	In normes
Generic 1	500	500,31	100,06	95 – 105	In normes
Generic 2	500	501,28	100,25	95 - 105	In normes
Generic 3	500	546,07	**109,2**	95 – 105	Out of normes
Generic 4	500	480,70	96,14	95 – 105	In normes

The generic 3 overdosed does not meet the standards before incubation at 40 ° C/75% RH and no longer will be in the batch of the accelerated stability study. A strict quality control must be exercised before the AMM to prevent the influx of such generic. For regular use of overdosed Acetaminophen causes liver failure leading to death [17].

After three months of storage:
Subject to accelerated storage conditions of stability (40 ° C/75% RH) the originator and generic three kept the active ingredient content in the standards with 98.51% for the originator, 98.52% for the generic one , regarding the generic 2 and 4, they have 99.05% and 95.03% respectively. These results are presented in Table II.

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Table II. Determination of Acetaminophen in the finished products after three months of incubation

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Finished products (FP)	Concentration in active ingredient (AI)				
	Declared Concentration in mg/tablet	Found concentration in mg/tablet	Found concentration in %	Normes in %	Observation
Innovator	500	492,57	98,51	95 – 105	In normes
Generic 1	500	492,63	98,52	95 – 105	In normes
Generic 2	500	495,27	99,05	95 - 105	In normes
Generic 4	500	475,15	95,03	95 – 105	In normes

The resistance of all pharmaceutical specialties of Acetaminophen with accelerated storage stability conditions (45 ° C/75% RH) shows the stability of the molecule facing the increase in temperature and humidity for three months. Six months after conservation

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Table III. Determination of Acetaminophen in the finished product after six months of incubation

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Finished products (FP)	Concentration in active ingredient (AI)				
	Declared Concentration in mg/tablet.	Found concentration in mg/tablet	Found concentration in %	Normes in %	Observation
Innovator	500	478,46	95,69	95– 105	In normes
Generic 1	500	465,49	**93,09**	95 – 105	Out of normes
Generic 2	500	493,22	98,64	95- 105	In normes
Generic 4	500	468,48	**93 ,69**	95 – 105	Out of normes

After six months of storage at 45 ° C/75% RH, the generic 2 and innovator remained within the range of established limits. The innovator with 95.69%, and 98.6% with generic 2 while generic 1 and 4 were affected by storage conditions and have fallen out of standards with 93.09% respectively, and 93.69%. The results are presented in Table III.

This stability study allowed to see the inability of generic made in DR Congo to keep physic-chemical properties within specified limits during the period of validity. Except the fourth (generic3) in overdose, only the second (generic 2) among the three submitted to the study of stability withstood the storage conditions of 45 ° C/75% RH for 6 months. This difficulty can be attributed to a lack of optimization of the manufacturing process for zone IV. The innovator was unchanged from the beginning to the end of the study.

This result calls into question the validity of 4 years attributed to generic Acetaminophen in DR Congo. A similar study on generic amoxicillin sold in Congo confirms the same thing [19].The most common failure case in countries in development has been mentioned in the study of stability of Iron Pills in Libya [20] and amoxicillin trihydrate-clavulanic acid in Yemen[21].

The dissolution profiles of acetaminophen.
In a study with six acetaminophen tablets , USP states that the minimum percentage of active ingredient released at 30 minutes in the dissolution medium must be 85% (Q +5%) [15, 16].

All five specialties of Acetaminophen before incubation shows dispersion curve as a function of the release of active ingredient, a study of formulation and evaluation of Ranolazine extended release tablets shows a similar result [23].

The two curves for generic 1 and 3 are below 85% in 30 minutes, while those generic 2, 4 and innovator are above with 100.29%, 91.30% and 97.8% respectively.
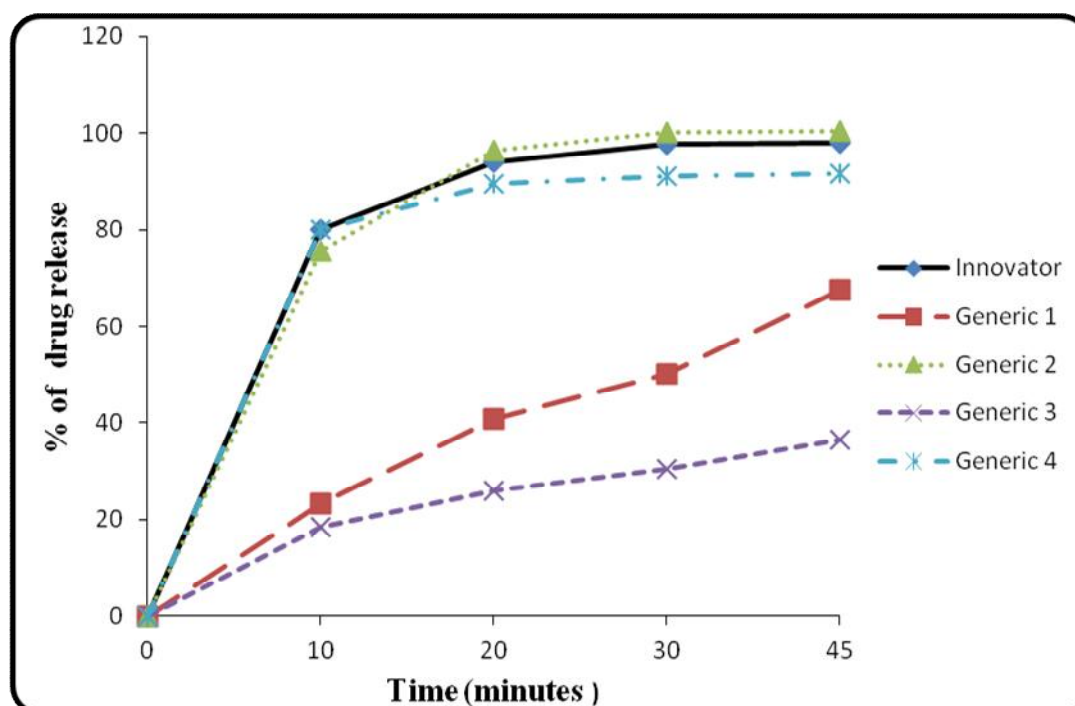

Figure 2: Dissolution profiles before incubation.

Generic 2, 4 and the innovator are in terms of dissolution profiles as shown in Figure 2. After the dissolution profiles, the calculation of F1 and F2 was done to show the similarity between the generics (2, 4) and the innovator.
Similarity factor.
This parameter has two basic functions: 1°) relative difference function (F1). This is a measure of the relative error between two curves studied. Its formula is:

$$f_1 = \frac{\sum_{i=1}^{n}|R_t - T_t|}{\sum_{i=1}^{n}R_t} \cdot 100$$

2°) Similarity function (F2) its structural formula is:

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{i=1}^{n}(R_i - t_i)^2\right]^{1/2} \times 100\right\}$$

Concerning the similarity: F1 is less than or equal to 10 and when F2 is more than or equal to 50. It varies between 50 and 100 [22].

Similarity factor calculation.
Generic 2: F1 = F2 = 2,694 and 82,298.
Generic 4: F1 = F2 = 4,828 and 86,625.
Both generic acetaminophens are therefore consistent with the innovator.

The dissolution profile of acetaminophen after three months of incubation
The generic two did not survive for three months at 45 ° C/75% RH. Although the active ingredient concentration remained within normal limits, the percentage of Acetaminophen released in the dissolution medium (75%) is below 85% in 30 minutes. The result is shown in Figure 3.
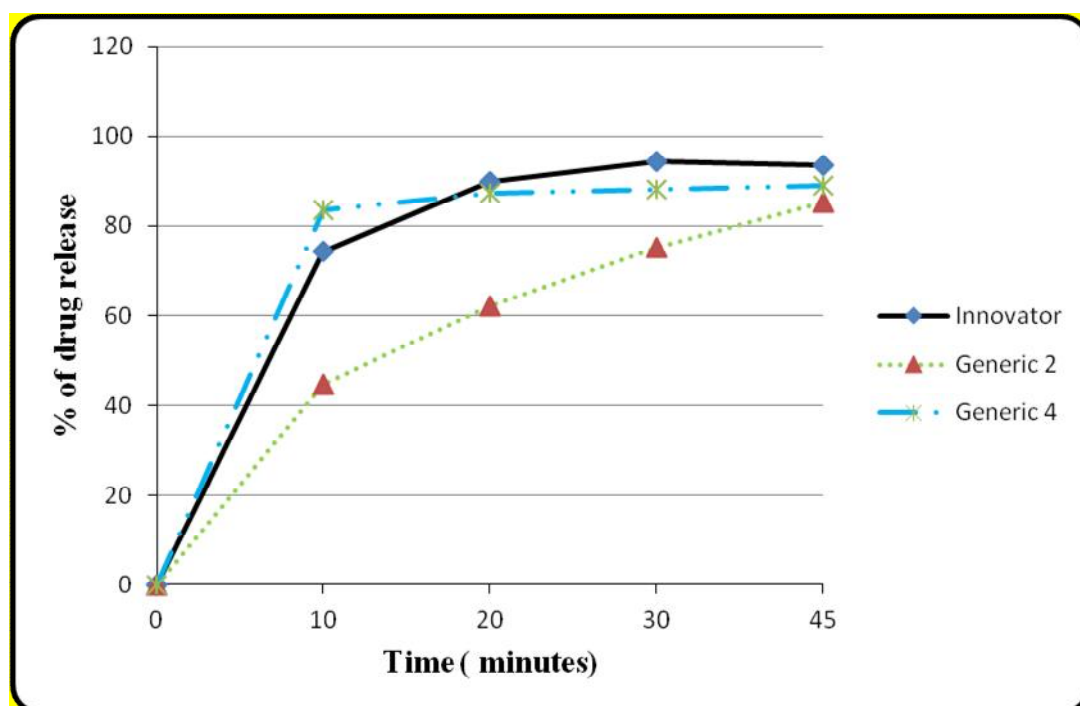

Figure 3: Dissolution profile after three months of incubation

The originator and generic 4 continue to release Acetaminophen in standards with 94.24% and 88.04% respectively.

The dissolution profile of acetaminophen after six months of incubation
No generic manufactured in DR Congo has reached the end of the sixth month of accelerated stability. Generic 4 which had resisted the third month of storage conditions, has lost much of its content of active ingredient to get a percentage of 93.6%. So the dissolution profile will also be out of norm as the release of the active ingredient in the dissolution medium depends on the total concentration in the molecule. The innovator carried out with normal concentration of Acetaminophen and 95.69% release in the dissolution medium 92%.
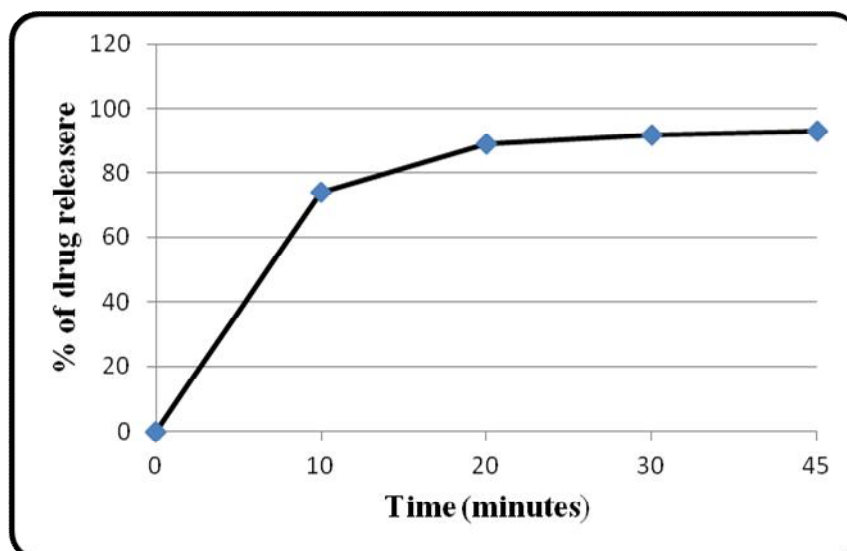
Figure 4: Dissolution profile's innovator after three months of incubation

CONCLUSION

These work shows that the generics of Acetaminophen manufactured in DR Congo are unstable in storage conditions, 45°C/75% RH accelerated stability recommended by WHO for zone IV stimulating tropical climate. The Congolese pharmaceutical factories must please the good manufacturing practices to provide to the population generics that are able to withstand the tropical climate as in the case of the innovator.

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