

STABILITY OF PARACETAMOL IN PACKAGED TABLET FORMULATIONS

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ABSTRACT

A study of the influence of various temperature and humidity conditions on the stability of a number of commercial paracetamol tablet formulations in original packagings has been conducted over a period of six months. Paracetamol degradation in tablets follows apparent first-order kinetics and the shelf-lives (t_{90}) range from 9.8 to 23.0 months. PVC/PVDC/AI foil and polycoated paper packagings offer better protection to the tablets compared to that of viscose film.

Introduction

Paracetamol (acetaminophen) is extensively used as an analgesic and antipyretic in tablet dosage form. It is available in several nonprescription forms and is also an ingredient of many proprietary preparations containing aspirin and caffeine (Moffat, 1986; Reynolds, 1989). Under adverse storage conditions, paracetamol tablets may degrade to give 4-aminophenol (Koshy and Lach, 1961; Connors *et al*, 1986; Racz, 1989) due to faulty or ineffective packaging. Several studies of the effects of temperature and humidity conditions on the stability of aspirin, ascorbic acid and other pack-aged tablets have been conducted to evaluate the efficacy of packaging materials (Lee *et al*, 1965; Clifford *et al*, 1977; Gyeszly, 1980; Nakabayashi *et al*, 1980a, 1980b, 1980c, 1981a, 1981b; Kentala *et al*, 1982; Fulcoly and Liebe, 1983; Wang, 1985; Yonemochi *et al*, 1991). Lachman *et al*. (1986) have dealt with the applications of kinetic principles in stability testing and Hanna (1982) has discussed the mechanisms of drug degradation reactions that affect tablet stability.

In view of the sensitivity of pharmaceutical compounds to various stimuli (Wadke and Jacobson, 1980) it is essential to make a thorough evaluation of the influence of packaging material on the stability of the product and of the effectiveness of the material in protecting the product during extended storage under varying environmental conditions of temperature, humidity and light. The object of this work is to study the influence of a

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variety of temperature — humidity conditions on the stability of different brands of packaged paracetamol tablets stored for a period of six months.

Materials and Methods

Paracetamol (acetaminophen) of BP grade was obtained from Rhone Poulenc (France) and was found to be chromatographically pure, R_f 0.45 (butyl acetate-chloroform-85% formic acid, 60:40:20, v/v) [Lit. (Zarnak and Pfeifer, 1964) R_f 0.46]. It was stored in a refrigerator protected from light. 4-Aminophenol was obtained from Aldrich Chemical Company and was used as such. All reagents and solvents were analytical grade or of the purest form available from Merck/BDH.

The details of fresh stocks of commercial paracetamol tablets procured directly from various manufacturers are given in Table 1. An appropriate quantity of each brand of tablets in original packaging (sample A-E) was stored in a Hot Pack climatic chamber (Model 434304, USA.) for six months under the following conditions of temperature and relative humidity.

Temperature (C)	Relative Humidity ($\pm$ 1%)	
25°	75%,	100%
37°	75%,	100%
45°	75%,	100%

Samples were withdrawn at suitable intervals and subjected to the following tests.

Thin-layer chromatography (TLC)

TLC of the methanolic (50%) extracts of stored samples was carried out on silica gel G 250 μ m plates to detect the degradation products using solvent systems S1: chloroform-acetone (4:1, v/v), and S2: ethyl acetate-methanol-strong ammonia solution (85:10:5, vlv) (Stead *et al*, 1982). The spots were located by spraying with 5% ferric chloride solution.

Assay

The assay of paracetamol content of the stored samples was carried out according to the BP (1993) method by extraction with 0.1M sodium hydroxide and measurement of absorbance at the maximum at 257 nm. The contents of $C_8H_9NO_2$ were calculated taking 715 as the value of A (1% 1cm) at 257 nm. All the assays were run in duplicate and the results were averaged. When the duplicate results showed a variation of more than 5%, the assays were repeated until satisfactory data obtained.

Results and Discussion

Degradation of paracetamol

Paracetamol is affected by moisture and the major route of degradation is its hydrolysis to 4-aminophenol and acetic acid (Cannors *et al.*, 1986). In order to confirm the degradation of paracetamol in tablets stored under various conditions of temperature and humidity, it was necessary to check the presence of 4-aminophenol in the samples. Therefore, the methanolic extracts of tablets were subjected to TLC using solvent systems S_1 and S_2 and 4-aminophenol was detected in all the samples (A-E) at the end of the storage period. The R_f values of 4-aminophenol in solvent systems S_1 and S_2 are 0.20 and 0.59 respectively.

Temperature-humidity effects

The influence of temperature at 75% and 100% relative humidity (RH) on the percent loss of paracetamol over a period of six months is shown in Fig.1 and the shelf-lives of paracetamol tablets (sample A-E) in decreasing order of stability are presented in Table 3. At 75% RH an increase in temperature from 25 to 45° shows least effect on sample E, followed by sample C, D, A and B. at 100% RH the increase in temperature from 25 to 45° gives the same order of stability except for a slight change in the position of sample C and D. Thus sample E, D and C (500 mg) appear to be less affected by both temperature and humidity compared to sample A and B (200 mg) indicating that PVC/PVDC/Al foil and polycoated paper offer better protection to both 500 mg and 200 mg tablets (Table 1).

Table 1

Commercial paracetamol tablets used in the present investigation

Sample No.	Labelled amount per tablet	Mode of packaging
A	200 mg	Polycoated paper
B	200 mg	Viscose film (Cellophane)
C	500 mg	Polycoated paper
D	500 mg	PVC/AC/Aluminium foil
E	500 mg	PVC/PVDC/Aluminium foil

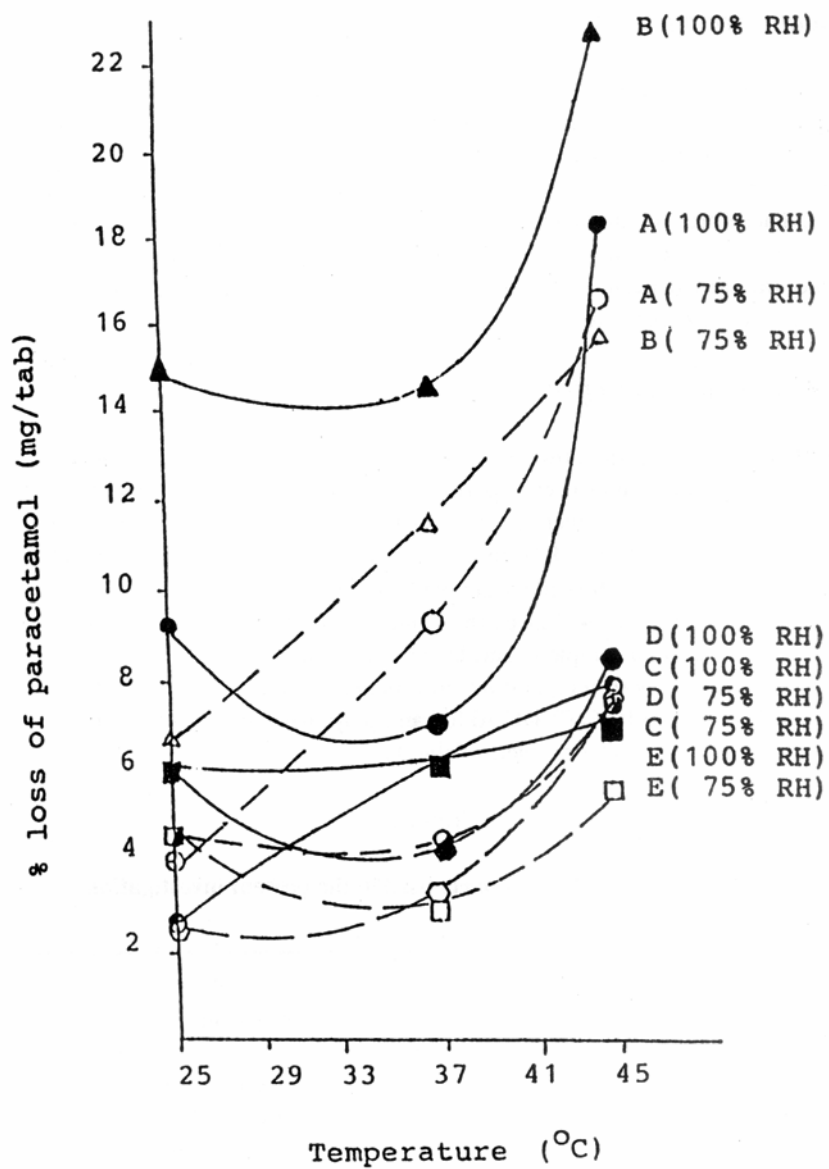


Figure 1: Plots of % loss of acetaminophen vs temperature at 75% and 100% RH.

Table 2
Apparent first-order rate constants for the degradation of paracetamol tablets
stored under various conditions of temperature and humidity

Sampe No.	Temperature °C	Relative Humidity	k, x 10 ⁻⁴ day ⁻¹	Shelf-life t ₉₀ , months
A	25	75	1.92	18.2
B			2.04	17.1
C			1.53	22.9
D			1.83	19.1
E			1.52	23.0
A	25	100	2.56	13.7
B			2.32	15.1
C			1.70	20.6
D			2.01	17.4
E			1.69	20.7
A	37	75	2.17	16.1
B			2.21	15.8
C			1.67	20.9
D			2.04	17.2
E			1.63	21.5
A	37	100	2.81	12.4
B			2.55	13.7
C			1.92	18.2
D			2.21	15.8
E			1.82	19.2
A	45	75	2.42	14.5
B			2.42	14.5
C			1.99	17.6
D			2.11	16.5
E			1.92	18.2
A	45	100	3.45	10.1
B			3.58	9.8
C			2.53	13.8
D			2.42	14.5
E			2.12	16.5

Table 3

Shelf-lives (months) of paracetamol tablet samples A-E with decreasing order of stability at various combinations of temperature and humidity

25°/75%	37°/75%	45°/75%	25°/100%	37°/100%	45°/100%
E(23.0)	E(21.5)	E(18.2)	E(20.7)	E(19.2)	E(16.5)
C(22.9)	C(20.9)	C(17.6)	C(20.6)	C(18.2)	D(14.5)
D(19.1)	D(17.2)	D(16.5)	D(17.4)	D(15.8)	C(13.8)
A(18.2)	A(16.1)	A(14.5)	B(15.1)	B(13.7)	A(10.1)
B(17.1)	B(15.8)	B(14.5)	A(13.7)	A(12.4)	B (9.8)

Table 4

Percent decrease in shelf-lives (months) of paracetamol tablet samples A-E stored at various combinations of temperature and humidity

25°/75% to 37°/75%	25°/75% to 45°/75%	25°/100% to 37°/100%	25°/100% to 45°/100%	25°/75% to 37°/100%	25°/75% to 45°/100%
E(6.5)	D(13.6)	E(7.2)	D(16.7)	E(16.5)	D(24.1)
B(7.6)	B(15.2)	D(9.2)	E(19.5)	D(17.3)	E(28.3)
C(9.1)	E(20.9)	B(9.3)	A(26.3)	B(19.9)	C(39.7)
D(9.9)	A(20.9)	A(9.5)	C(33.7)	C(20.5)	B(42.7)
A(11.5)	C(23.1)	C(11.7)	B(35.1)	A(31.9)	A(44.5)

The percent decrease in shelf-lives of sample A-E stored at various combinations of temperature and humidity is given in Table 4. It appears that there is no definite pattern of change in shelf-lives of the samples with either an increase in temperature or humidity. The samples showing a relatively little change in shelf-lives on increasing the temperature from 25 to 37° (75% RH) show a different pattern on increasing the temperature from 25 to 45° (75% RH). A similar behaviour is observed on increasing the temperature from 25 to 37° or 45° (100% RH) (Fig.1). It may, however, be concluded that

the packaging material of sample E, D and C could withstand temperature-humidity changes and provide better protection to these samples from environmental stress conditions.

The difference in the stability behaviour of commercial paracetamol samples towards specific temperature-humidity conditions may be due to a variable response of tablet excipients of the individual brands. The moisture sorption and retention properties of the samples would largely depend upon the moisture barrier characteristics of the packaging materials as well as the compositional variations of the tablet matrices. The stability of solid dosage forms at constant temperature is considered as a function of equilibrium moisture content (EMC) which, in turn, is dependent on relative humidity (Wang, 1985; Liebe, 1990). The packaging material controls water permeation to achieve EMC and hence the rate of loss of a moisture sensitive drug under specified storage conditions.

As a rule, tablet products should have at least two-years expiration date (Seitz *et al*, 1986) and they should conform to all standards of performance and potency for at least two-years after manufacture. The packaging components play an important role in providing adequate protection to the drug to meet the expiration date and should be thoroughly evaluated under the proposed storage conditions. The oxygen and water vapour transmission characteristics of commonly used packaging materials have been discussed by Hanlon (1984) and may provide useful information in the selection of packaging components for moisture and heat sensitive solid dosage forms.

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