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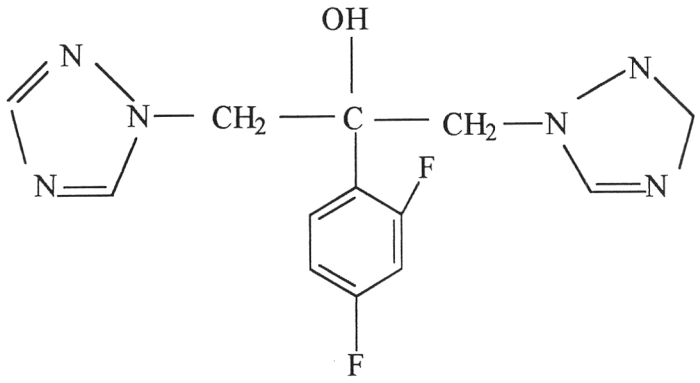
APPENDIX I

Details of fluconazole

Details of fluconazole

Physical properties



Fluconazole

Empirical Formula	:	$C_{13}H_{12}F_2N_6O$
Molecular Weight	:	306.27
Chemical Name	:	2-(2,4-Difluorophenyl) – 1, 3- bis (1H-1,2,4-triazole-1-yl) propan-2-ol
Description	:	A white crystalline powder.
Melting Range	:	138-140°C
pka	:	1.9

Mechanism of action.

The antifungal effects of the azoles are targeted primarily at ergosterol, the main sterol in the fungal cell membrane. The azoles inhibit ergosterol synthesis through an interaction with C-14 alpha demethylase, an enzyme dependent on cytochrome P-450 that is necessary for the conversion of lanosterol to ergosterol

(Joly, Bolard and Yeni, 1992). The depletion of ergosterol alters membrane fluidity, thereby reducing the activity of membrane-associated enzymes and leading to increased permeability and inhibition of cell growth and replication (Van den Bossche et al., 1983). Other antifungal effects of azoles include the inhibition of endogenous respiration, a toxic interaction with membrane phospholipids, and the inhibition of the morphogenetic transformation of yeasts to the mycelial form (Van den Bossche et al., 1983).

Pharmacokinetics

Absorption

Fluconazole is absorbed from the gastrointestinal tract. Peak plasma concentrations in humans are reached two to four hours after oral administration and range from 1.4 μg/ml after a 50-mg dose to 2.82 μg/ml after a 150-mg dose. Seven bone marrow transplant recipients who received fluconazole 100 mg orally achieved peak serum concentrations that were not different from valves in 12 healthy volunteers given a similar dose of fluconazole. It appears that the amount of fluconazole absorbed is linearly proportional to the dose, while urinary excretion data indicate that the oral bioavailability of fluconazole is greater than 90% . This is in distinct contrast to older azole compounds, such as clotrimazole, micronazole, and econazole, which are characterized by poor oral bioavailability and low concentrations in plasma. Unlike ketoconazole, which has limited solubility at high gastric pH, fluconazole, because of its greater water solubility, appears to be minimally affected by gastric pH. In addition, studies comparing peak concentrations and systemic exposure after the administration of oral fluconazole capsules to human volunteers indicate that food has little effect on fluconazole absoption (Kowalsky and Dixon, 1991).

Distribution

Once absorbed, fluconazole has a volume of distribution of 0.6 to 0.8 L/kg. Steady-state pharmacokinetic values were measured in 10 healthy male volunteers given a daily 30-minute intravenous infusion of fluconazole for seven days. A two-compartment analysis showed no substantial change in half-life, total body or renal clearance, or volume of distribution from day 1 to day 7. Terminal elimination half-life ranged from 28 to 32 hours, total body clearance ranged from 20 to 24 ml/min, renal clearance ranged from 15 to 19 ml/min, and volume of distribution ranged from 600 to 820 ml/kg. These data agree with the single dose studies (Kowalsky and Dixon, 1991).

Elimination

The kidneys play a major role in the elimination of unchanged fluconazole. The percentage of the dose recovered in the urine in 48 hours is closed to 60% . Concentrations in the urine are high and the half-life (t1/2) is long (37.2$\pm$5.5 h) in patients, mainly those with AIDS, which is not significantly different from the t1/2 (31.4$\pm$4.7 hours) in healthy individuals. The mean total clearance is 1.073$\pm$0.473 l/h and renal clearance is 72% of the total clearance. Since fluconazole is eliminated primarily by renal excretion, dose modification is recommended for patients with renal failure. A 50% reduction of dose is recommended in those with a creatinine clearance of 21 to 50 ml/min, and a 75% reduction of dose with a creatinine clearance < 21 ml/min (Lyman and Walsh, 1992).

Tolerability

Fluconazole has been well tolerated with very few dose-limiting side effects. Nausea, other gastrointestinal symptoms and elevations in hepatic transaminases have been reported in < 5% of patients receiving the drug. The incidence of asymptimatic hepatic transaminase elevations may be as high as 12% in children. Exfoliative skin reactions have been reported in patients with AIDS. although the exact role of fluconazole in these reactions is unclear. In animal studies, the only histopathological changes were observed in the liver, fibroadenomas and mild hepatic steatosis. Fluconazole does not appear to affect the synthesis of steroid hormones (Lyman and Walsh, 1992).

Indications

Fluconazole has been demonstrated to be active in suppressive therapy and primary treatment of cryptococcal meningitis in patients with AIDS who are at low risk for treatment failure. It may also be useful in primary treatment of coccidiodal meningitis. However, caution must be exerted in the use of fluconazole in patients with altered mental status, as these patients may further deteriorate. Fluconazole is active in the treatment of mucosal candidiasis, including oropharyngeal and oesophageal candidiasis. There are limited data currently available to support its use in primary treatment of deepyl invasive candidiasis ; however, well-designed clinical trials are currently being pursued to investigate fluconazole for such uses. It has also been used for patients with persistent hepatosplenic candidiasis or those unable to tolerate amphotericin B. The most favourable responses were observed in patients extensively pretreated with amphotericin B, suggesting a beneficial interaction between fluconazole and high concentrations of amphotericin B in hepatic tissue.

Fluconazole is also a potential candidate for prevention and early treatment of disseminated candidiasis in granulocytopenic patients. Preliminary reports from a randomised trial of adult marrow transplant recipients demonstrated a significant reduction of invasive candidiasis in patients receiving fluconazole. A randomised trial is currently being pursued in high risk neutropenic children in order to investigate the role of fluconazole in preventive therapy in this pharmacokinetically distinct population. The availability of a parenteral formulation of fluconazole has greatly facilitated its use in cancer patients unable to tolerate oral medications. Finally, fluconazole is also currently being studied for primary treatment of histoplasmosis and sporotrichosis (Lyman and Walsh, 1992).

APPENDIX II

Solubility data of fluconazole

Table 32 Observed solubilities of fluconazole in pure solvents at 30°C (24 hours).

Solubility	Solubility of Fluconazole (mg/ml)			
	n_1	n_2	n_3	Average ± SD
Water	6.59	6.60	6.59	6.59 ± 0.00
Ethanol	107.75	107.77	107.76	107.76 ± 0.01
Propylene glycol	173.75	173.76	173.75	173.75 ± 0.01
Polyethylene glycol 400	115.00	115.23	115.45	115.23 ± 0.23

Table 33 Observed solubilities of fluconazole in pure solvents at 30°C (48 hours).

Solvents	Solubility of Fluconazole (mg/ml)			
	n_1	n_2	n_3	Average ± SD
Water	6.59	6.58	6.61	6.59 ± 0.01
Ethanol	107.73	107.76	107.79	107.76 ± 0.03
Propylene glycol	173.50	173.59	173.40	173.50 ± 0.10
Polyethylene glycol 400	114.50	114.52	114.46	114.50 ± 0.03

Table 34 Observed solubilities of fluconazole in cosolvent (ethanol-water) at 30°C (24 hrs).

Ethanol (% v/v)	Solubility of Fluconazole (mg/ml)			
	n_1	n_2	n_3	Average ± SD
10	11.63	11.29	11.54	11.49 ± 0.18
20	20.32	18.98	19.95	19.75 ± 0.69
30	37.20	37.14	37.15	37.16 ± 0.03
40	77.85	77.44	77.69	77.66 ± 0.21
50	131.94	131.92	131.90	131.92 ± 0.02

Table 35 Observed solubilities of fluconazole in cosolevnt (ethanol-water) at 30°C (48 hrs).

Ethanol (% v/v)	Solubility of Fluconazole (mg/ml)			
	n_1	n_2	n_3	Average ± SD
10	11.54	11.29	11.53	11.45 ± 0.14
20	18.88	19.94	20.32	19.71 ± 0.75
30	37.20	37.13	37.15	37.16 ± 0.04
40	78.02	76.94	77.65	77.54 ± 0.55
50	130.95	132.92	131.45	131.77 ± 1.02

Table 36 Observed solubilities of fluconazole in cosolevnt (PG – water) at 30°C (24 hrs).

Polylene glycol	Solubility of Fluconazole (mg/ml)			
(% v/v)	n_1	n_2	n_3	Average ± SD
10	8.45	8.55	9.14	8.72 ± 0.37
20	11.64	12.74	11.00	11.79 ± 0.88
30	16.72	16.98	17.16	16.96 ± 0.22
40	26.53	26.33	26.17	26.34 ± 0.19
50	47.22	52.00	49.59	49.60 ± 2.39

Table 37 Observed solubilities of fluconazole in cosolevnt (PG- water) at 30°C (48 hrs).

Polylene glycol	Solubility of Fluconazole (mg/ml)			
(% v/v)	n_1	n_2	n_3	Average ± SD
10	8.56	8.48	9.19	8.74 ± 0.39
20	11.75	11.00	12.64	11.80 ± 0.82
30	17.37	16.99	16.82	17.06 ± 0.28
40	25.09	25.67	28.01	26.26 ± 1.55
50	47.20	48.09	53.08	49.46 ± 3.17

Table 38 Observed solubilities of fluconazole in cosolevnt (PEG 400-water) at 30°C (24 hrs).

Polylene glycol 400	Solubility of Fluconazole (mg/ml)			
(% v/v)	n_1	n_2	n_3	Average ± SD
10	8.62	8.40	8.50	8.51 ± 0.11
20	12.00	10.10	11.17	11.09 ± 0.95
30	16.03	15.10	15.43	15.53 ± 0.47
40	22.25	22.00	22.91	22.39 ± 0.47
50	32.55	33.00	32.50	32.69 ± 2.39

Table 39 Observed solubilities of fluconazole in cosolevnt (PEG 400–water) at 30°C (48 hrs).

Polylene glycol 400	Solubility of Fluconazole (mg/ml)			
(% v/v)	n_1	n_2	n_3	Average ± SD
10	8.72	8.40	8.50	8.54 ± 0.16
20	12.05	10.12	11.17	11.11 ± 0.97
30	15.82	15.10	15.43	15.45 ± 0.36
40	22.10	21.87	22.86	22.28 ± 0.52
50	32.41	32.55	33.01	32.65 ± 0.31

Table 40 Observed solubilities of fluconazole in cosolevnt (PEG 4000–water) at 30°C (24 hrs).

(% v/v)	Solubility of Fluconazole (mg/ml)			
	n_1	N_2	n_3	Average ± SD
1	6.52	6.48	6.52	6.51 ± 0.02
2	6.40	7.03	6.31	6.58 ± 0.39
3	6.55	6.11	6.70	6.79 ± 0.29
4	6.91	7.11	6.93	6.98 ± 0.11
7	7.82	7.61	7.42	7.62 ± 0.20

Table 41 Observed solubilities of fluconazole in cosolevnt (PEG 4000–water) at 30°C (48 hrs).

(% v/v)	Solubility of Fluconazole (mg/ml)			
	n_1	n_2	n_3	Average ± SD
1	6.50	6.50	6.46	6.49 ± 0.03
2	6.40	6.30	7.01	6.57 ± 0.39
3	7.10	6.66	6.55	6.77 ± 0.29
4	6.93	7.10	6.90	6.98 ± 0.11
7	7.81	7.42	7.61	7.61 ± 0.20

Table 42 Observed solubilities of fluconazole in cosolvent (PEG 4000 - ethanol - PG water) at 30°C (24 hrs).

% Cosolvent	Solubility of Fluconazole (mg/ml)			
	n_1	n_2	n_3	Average ± SD
1 - 2 - 2 - 95	6.81	6.84	6.83	6.83 ± 0.02
1 - 4 - 4 -91	7.86	7.92	7.88	7.89 ± 0.03
1 - 7 - 7 –85	8.02	8.00	8.45	8.16 ± 0.25
2 –2 - 2 – 94	7.28	7.29	7.26	7.27 ± 0.01
2 - 4 -4 – 90	8.02	8.03	8.01	8.02 ± 0.01
2 - 7 - 7 – 84	9.14	9.12	9.13	9.13 ± 0.01
3 - 2 - 2 – 93	7.88	7.82	7.76	7.82 ± 0.06
3 - 4 - 4 – 89	8.70	8.72	8.71	8.71 ± 0.01
3 – 7 - 7 - 83	9.89	9.95	9.78	9.87 ± 0.09
4 - 2 - 2 - 92	7.59	7.95	7.77	7.77 ± 0.18
4 4 - 4 - 88	8.01	8.62	8.31	8.31 ± 0.30
4 - 7 -7-82	9.35	9.76	10.11	9.74 ± 0.38

Table 43 Observed solubilities of fluconazole in cosolvent (PEG 4000 - ethanol - PG - water) at 30°C (48 hrs).

% Cosolvent	Solubility of Fluconazole (mg/ml)			
	n_1	n_2	n_3	Average ± SD
1 - 2 - 2 - 95	6.82	6.70	6.90	6.81 ± 0.10
1 - 4 – 4 - 91	7.86	7.92	7.89	7.89 ± 0.03
1 - 7 – 7 - 85	8.02	8.00	8.45	8.16 ± 0.25
2 - 2 – 2 - 94	7.26	7.26	7.26	7.26 ± 0.00
2 - 4 – 4 - 90	8.22	8.03	8.13	8.12 ± 0.10
2 - 7 – 7 – 84	9.14	9.11	9.12	9.13 ± 0.01
3 - 2 – 2 - 93	7.86	7.82	7.76	7.81 ± 0.05
3 - 4 – 4 - 89	8.60	8.61	8.59	8.60 ± 0.01
3 – 7 – 7 - 85	9.88	9.80	9.49	9.72 ± 0.21
4 – 2 2 92	7.58	7.96	7.77	7.77 ± 0.19
4 - 4 – 4 - 88	8.31	8.62	8.02	8.31 ± 0.30
4 - 7 – 7 - 84	9.76	9.36	10.12	9.75 ± 0.38

APPENDIX III

Correlation coefficient of fluconazole syrups

Table 44 The correlation coefficient (r) of fluconazole syrups stored in the presence of light.

Antioxidant added	Correlation coefficient (r)		
	Zero order	First order	Second order
None	0.950	0.960	0.967
Propyl gallate (0.001%w/v)	0.878	0.878	0.878
Propyl gallate (0.005%w/v)	0.904	0.895	0.885
Propyl gallate (0.01%w/v)	0.908	0.901	0.895
Sodium bisulfite (0.05%w/v)	0.930	0.922	0.912
Sodium bisulfite (0.075%w/v)	0.880	0.873	0.865
Sodium bisulfite (0.100%w/v)	0.936	0.932	0.927
Disodium edetate (0.005%w/v)	0.868	0.854	0.840
Disodium edetate (0.01%w/v)	0.921	0.911	0.899
Disodium edetate (0.05%w/v)	0.935	0.926	0.914

Table 45 The correlation coefficient (r) of fluconazole syrups stored in the absence of light.

Antioxidant added	Correlation coefficient (r)		
	Zero order	First order	Second order
None	0.963	0.957	0.958
Propyl gallate (0.001%w/v)	0.899	0.895	0.891
Propyl gallate (0.005%w/v)	0.875	0.858	0.842
Propyl gallate (0.01%w/v)	0.912	0.906	0.898
Sodium bisulfite (0.05%w/v)	1.00	1.000	0.999
Sodium bisulfite (0.075%w/v)	0.982	0.987	0.990
Sodium bisulfite (0.10%w/v)	0.939	0.937	0.932
Disodium edetate (0.005%w/v)	0.967	0.966	0.964
Disodium edetate (0.01%w/v)	0.932	0.932	0.908
Disodium edetate (0.05%w/v)	0.942	0.936	0.895

APPENDIX IV

Stability data of fluconazole

Table 46 Stability data of fluconazole syrup stored at 60 ^{o}C

(Absence of light, formulation 1; no antioxidant)

Time (Day)	pH	Color of Syrup	Concentration of fluconazole remaining (mg/ 5ml)			
			No. 1	No. 2	No. 3	Average conc ±SD
0	5.07	Clear	50.49	49.33	50.81	50.21 ± 0.78
6	4.97	Yellow	51.00	50.11	49.22	50.11 ± 0.89
15	4.76	Yellow	48.12	48.98	47.66	48.25 ± 0.67
30	4.25	Red brown	47.80	47.78	47.80	47.79 ± 0.08
44	4.37	Red brown	48.94	47.46	48.20	48.20 ± 0.74
74	4.02	Dark brown	44.41	43.76	45.06	44.41 ± 0.65
107	3.64	Dark brown	37.48	38.47	40.97	38.97 ± 1.80

Zero - order : conc = 50.71 - 9.79 x 10^{-2} time r= 0.963

First - order : ln conc = 3.93 - 2.20 x 10^{-3} time r= 0.957

Second - order : 1/conc = 0.02 + 5.25 x 10^{-5} time r= 0.958

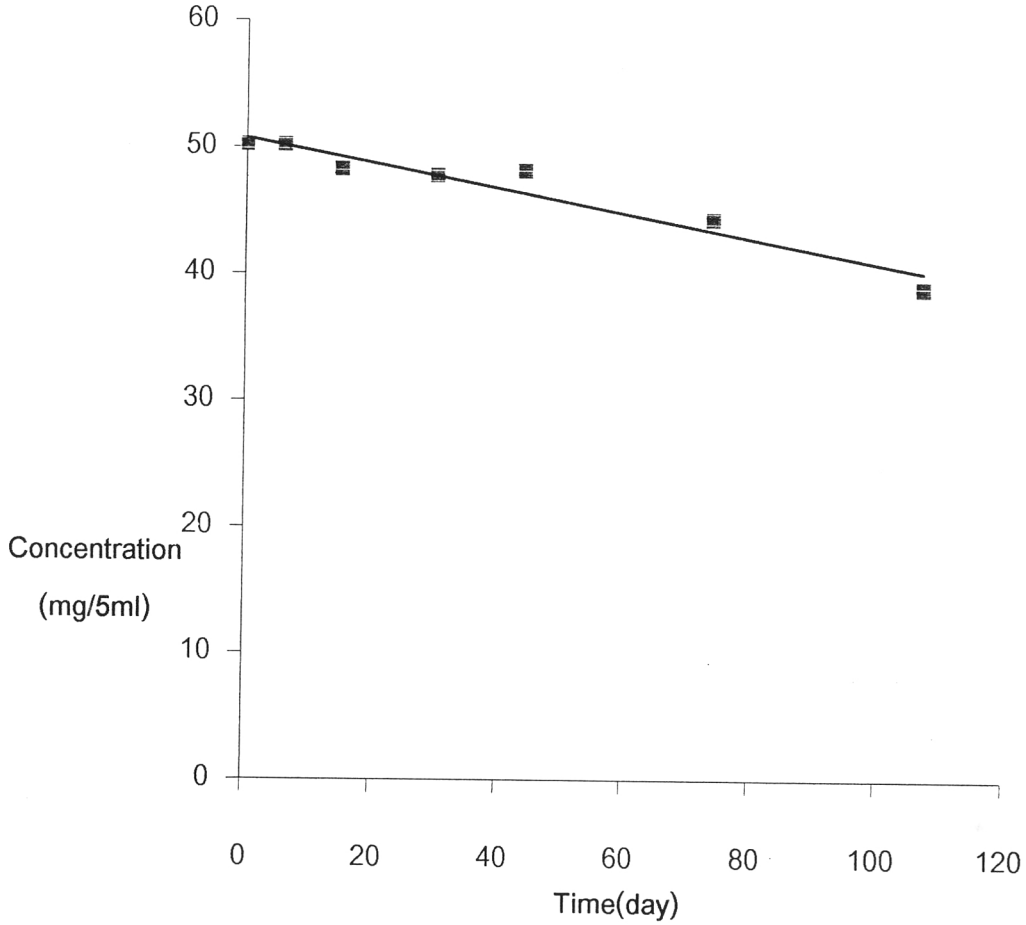


Figure 21 Linear plot of drug concentration remaining vs. time of fluconazole syrup (no antioxidant) in the absence of light at 60°C.

Table 47 Stability data of fluconazole syrup stored at 60 ^{o}C

(Absence of light, formulation 2; propyl gallate 0.001% w/v)

Time	pH	Color of	Concentration of fluconazole remaining (mg/ 5ml)			
(Day)		Syrup	No. 1	No. 2	No. 3	Average conc ± SD
0	5.09	Clear	52.32	51.26	52.46	52.01 ± 0.66
6	4.93	Yellow	51.07	49.44	51.07	50.53 ± 0.94
15	4.80	Yellow	49.89	50.80	49.22	49.97 ± 0.79
30	4.56	Brown	49.02	50.01	52.47	50.50 ± 1.78
44	4.33	Brown	51.15	45.80	50.84	49.26 ± 3.00
74	4.29	Dark brown	49.25	49.26	49.27	49.26 ± 0.01
107	3.92	Dark brown	45.17	43.24	43.80	44.07 ± 0.99

Zero - order : conc = 51.66 - 5.81 x 10^{-2} time r = 0.899

First - order : ln conc = 3.95 - 1.20 x 10^{-3} time r = 0.895

Second - order : 1/conc = 0.02 + 3.00 x 10^{-5} time r = 0.891

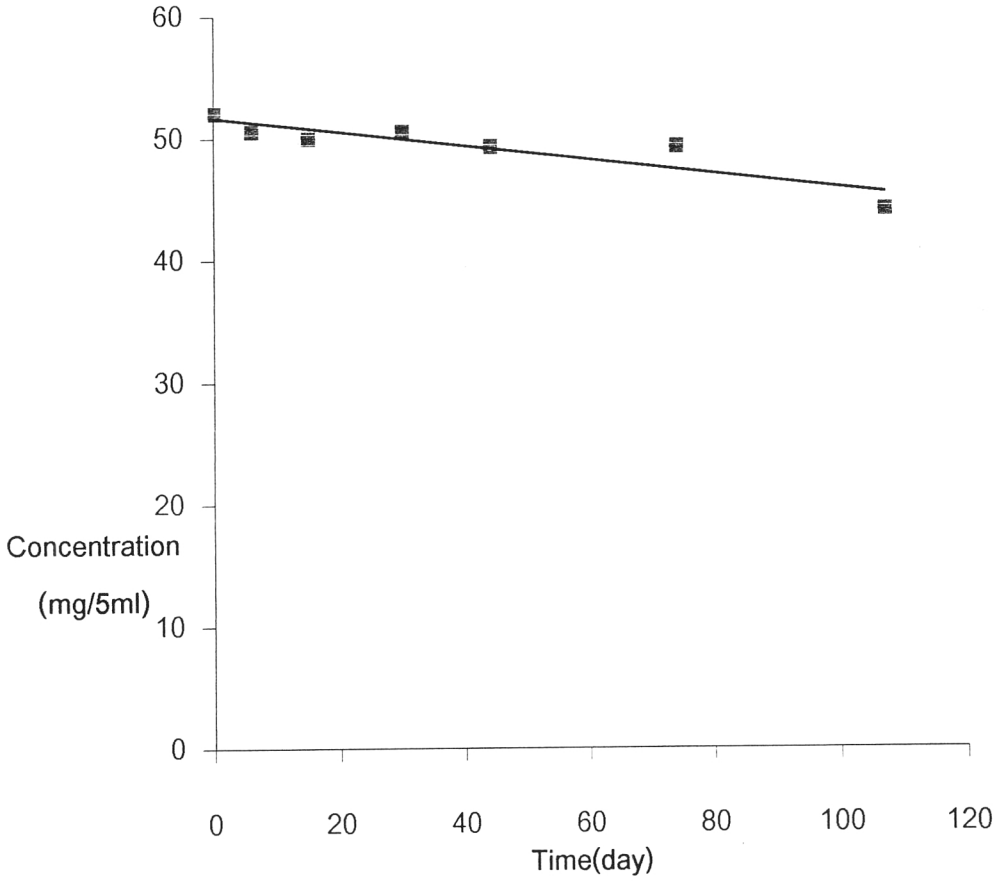


Figure 22 Linear plot of drug concentration remaining vs. time of fluconazole syrup (propyl gallate 0.001 %w/v) in the absence of light at 60°C.

Table 48 Stability data of fluconazole syrup stored at 60 ^{o}C

(Absence of light, formulation 3; propyl gallate 0.005% w/v)

Time	pH	Color of	Concentration of fluconazole remaining (mg/ 5ml)			
(Day)		Syrup	No. 1	No. 2	No. 3	Average conc $\pm$ SD
0	5.09	Clear	50.79	51.20	50.44	50.81 $\pm$ 0.38
6	4.88	Yellow	49.33	51.36	49.94	50.21 $\pm$ 1.04
15	4.70	Yellow brown	49.18	51.17	49.93	50.09 $\pm$ 1.00
30	4.31	Brown	46.12	48.20	50.33	48.22 $\pm$ 2.11
44	4.01	Dark brown	48.92	48.76	49.07	48.92 $\pm$ 0.16
74	3.89	Dark brown	45.01	45.69	49.83	46.84 $\pm$ 2.61
107	3.68	Dark brown	31.83	33.16	32.49	32.49 $\pm$ 0.66

Zero - order : conc = 52.50 - 1.45 x 10^{-1} time r = 0.875

First - order : ln conc = 3.97 - 3.50 x 10^{-3} time r = 0.858

Second - order : 1/conc = 0.02+ 9.00 x 10^{-5} time r = 0.842

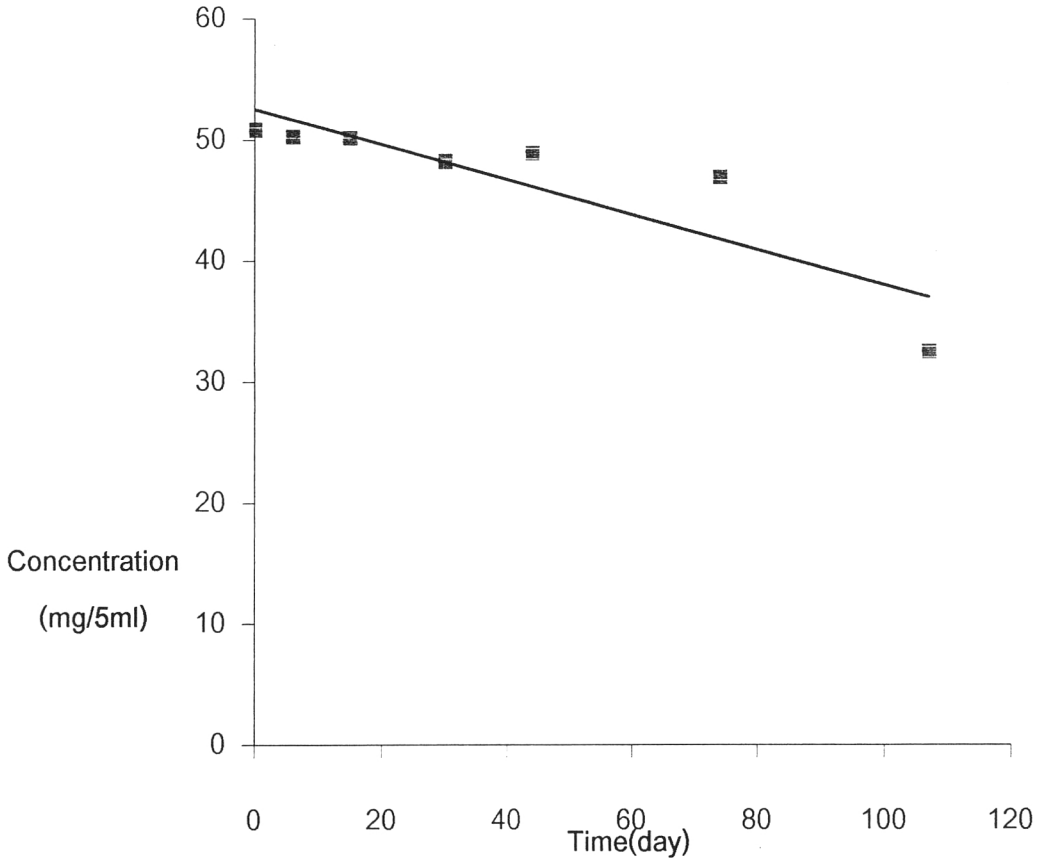


Figure 23 Linear plot of drug concentration remaining vs. time of fluconazole syrup(propyl gallate 0.005 %w/v) in the absence of light at 60°C.

Table 49 Stability data of fluconazole syrup stored at 60 °C

(Absence of light, formulation 4; propyl gallate 0.01% w/v)

Time	pH	Color of	Concentration of fluconazole remaining (mg/ 5ml)			
(Day)		Syrup	No. 1	No. 2	No. 3	Average conc ± SD
0	5.07	Clear	49.18	51.18	50.57	50.31 ± 1.03
6	4.92	Yellow	53.49	52.24	53.54	53.09 ± 0.74
15	4.74	Yellow	50.92	49.18	50.99	50.36 ± 1.02
30	4.51	Brown	49.46	49.61	49.55	49.54 ± 0.08
44	4.42	Brown	50.90	49.53	49.58	50.00 ± 0.78
74	4.22	Dark brown	48.82	47.61	44.44	46.96 ± 2.26
107	3.73	Dark brown	39.37	36.30	42.00	39.22 ± 2.85

Zero - order : $conc = 52.61 - 1.00 \times 10^{-1}\ time$ $r = 0.912$

First - order : $\ln conc = 3.97 - 2.30 \times 10^{-3}\ time$ $r = 0.906$

Second - order : $1/conc = 0.02 + 5.00 \times 10^{-5}\ time$ $r = 0.898$

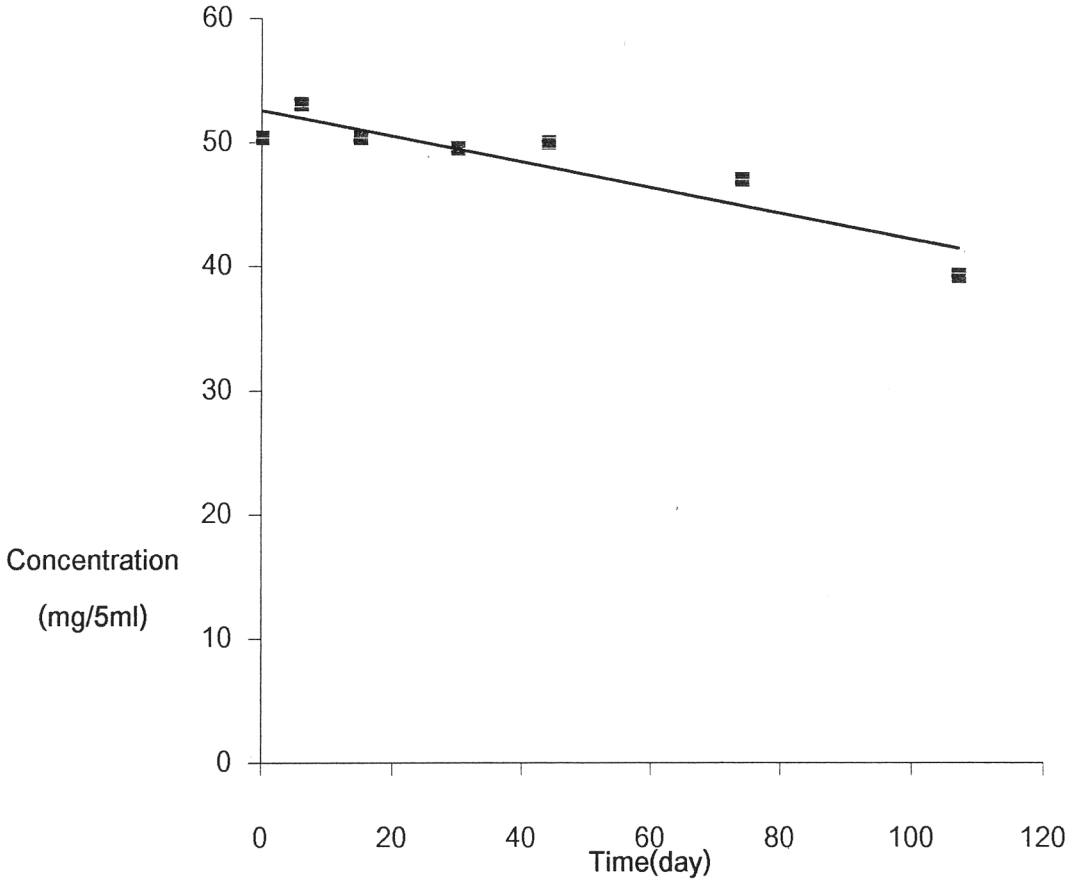


Figure 24 Linear plot of drug concentration remaining vs. time of fluconazole syrup(propyl gallate 0.01 %w/v) in the absence of light at 60°C.

Tabl 50 Stability data of fluconazole syrup stored at 60 ^{o}C

(Absence of light, formulation 5; sodium bisulfite 0.05% w/v)

Time (Day)	pH	Color of Syrup	Concentration of fluconazole remaining (mg/ 5ml)			
			No. 1	No. 2	No. 3	Average conc ± SD
0	5.08	Clear	51.02	51.70	53.14	51.95 ± 1.08
6	4.81	Yellow	49.15	53.15	52.25	51.51 ± 2.10
15	4.52	Yellow	50.09	49.81	52.75	50.88 ± 1.62
30	4.27	Brown	49.84	49.80	49.94	49.86 ± 0.07
44	4.25	Brown	48.71	48.95	48.89	48.84 ± 0.12
74	3.99	Dark brown	47.69	47.79	44.79	46.76 ± 1.70
107	3.80	Dark brown	46.51	45.78	41.10	44.46 ± 2.94

Zero - order : $conc = 51.94 - 6.99 \times 10^{-2}\ time$ $r = 1.000$

First - order : $\ln conc = 3.95 - 1.50 \times 10^{-3}\ time$ $r = 1.000$

Second - order : $1/conc = 0.02 + 3.00 \times 10^{-5}\ time$ $r = 0.999$

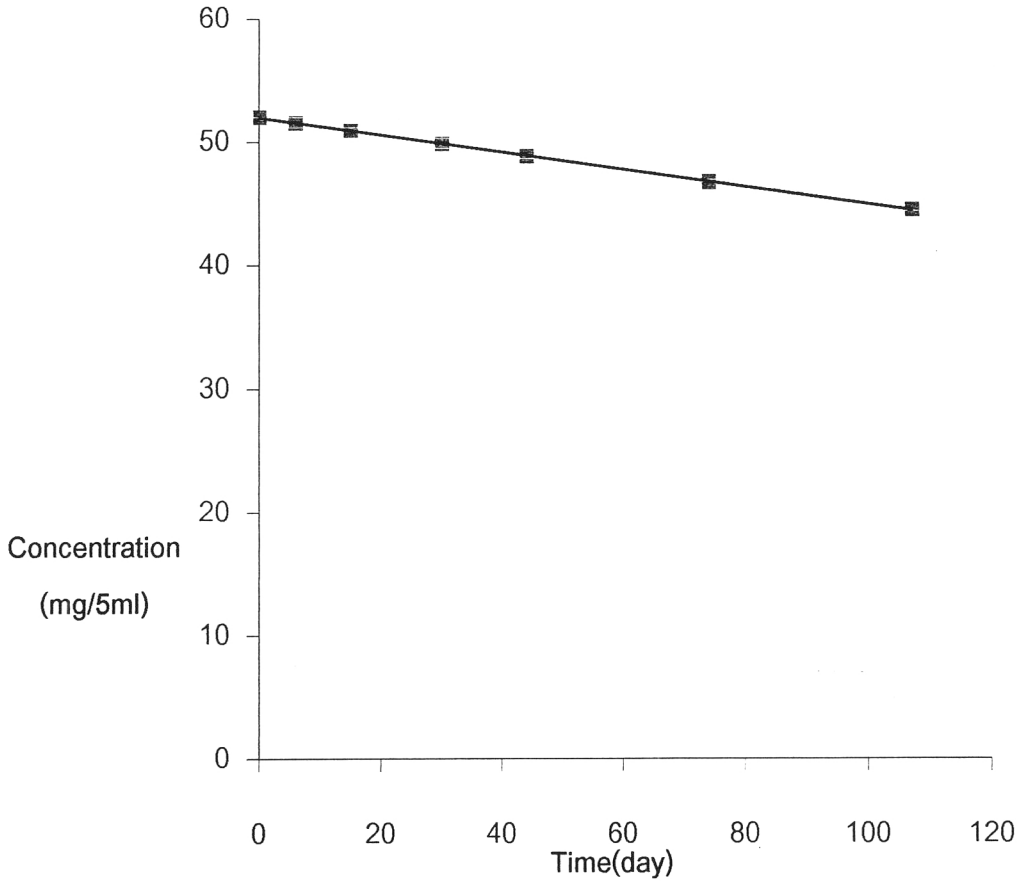


Figure 25 Linear plot of drug concentration remaining vs. time of fluconazole syrup (sodium bisulfite 0.05 %w/v) in the absence of light at 60°C.

Table 51 Stability data of fluconazole syrup stored at 60 ^{o}C

(Absence of light, formulation 6; sodium bisulfite 0.075% w/v)

Time	pH	Color of	Concentration of fluconazole remaining (mg/ 5ml)			
(Day)		Syrup	No. 1	No. 2	No. 3	Average conc + SD
0	5.09	Clear	53.07	53.75	54.41	53.75 $\pm$ 0.67
6	4.76	Yellow	52.27	51.29	52.86	52.14 $\pm$ 0.79
15	4.49	Yellow	50.19	49.91	49.07	49.73 $\pm$ 0.59
30	4.02	Brown	49.56	49.61	49.59	49.59 $\pm$ 0.03
44	3.95	Dark brown	47.65	47.86	47.45	47.65 $\pm$ 0.20
74	3.77	Dark brown	44.43	47.38	43.77	45.19 $\pm$ 1.93
107	3.56	Dark brown	40.70	44.13	41.02	41.95 $\pm$ 1.90

Zero - order : conc = 52.58 - 1.01x 10^{-1} time r = 0.982

First - order : Inconc = 3.96 - 2.10 x 10^{-3} time r = 0.987

Second - order : 1/conc = 0.02 + 5.00 x 10^{-5} time r = 0.990

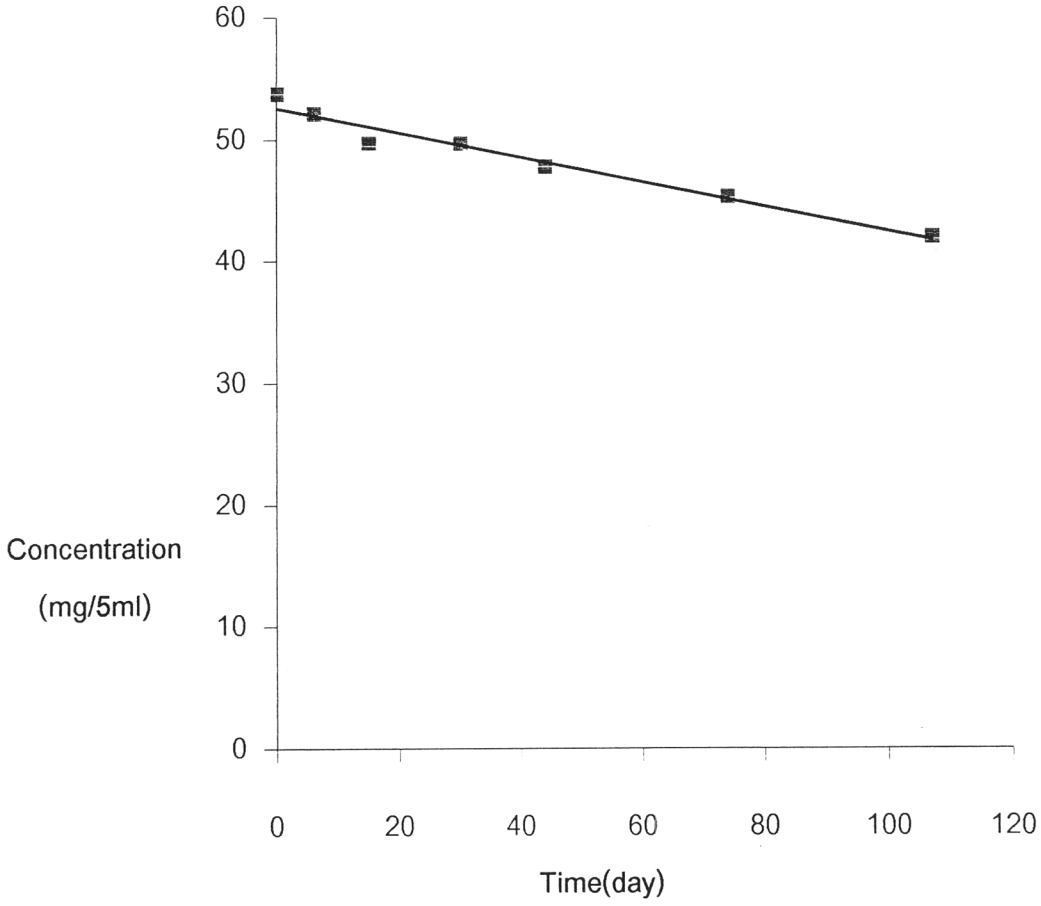


Figure26 Linear plot of drug concentration remaining vs. time of fluconazole syrup(sodium bisulfite 0.075 %w/v) in the absence of light at 60°C.

Table 52 Stability data of fluconazole syrup stored at 60 ^{o}C

(Absence of light, formulation 7; sodium bisulfite 0.100% w/v)

Time	pH	Color of	Concentration of fluconazole remaining (mg/ 5ml)			
(Day)		Syrup	No. 1	No. 2	No. 3	Average conc + SD
0	5.07	Clear	51.47	53.34	53.46	52.76 ± 1.12
6	4.78	Yellow	49.57	51.42	53.79	51.59 ± 2.12
15	4.54	Yellow	48.34	47.63	49.82	48.59 ± 1.12
30	4.18	Yellow	49.13	50.14	48.13	49.13 ± 1.00
44	4.15	Yellow	47.73	47.57	47.65	47.65 ± 0.08
74	3.98	Dark brown	48.87	45.57	47.21	47.22 ± 1.65
107	3.52	Dark brown	36.28	43.97	42.24	40.83 ± 4.03

Zero - order : conc = 51.90 - 9.26 X 10^{-2} time r = 0.939

First - order : ln conc = 3.95 - 2.00 x 10^{-3} time r = 0.937

Second - order : 1/conc = 0.02 + 4.00 x 10^{-5} time r = 0.932

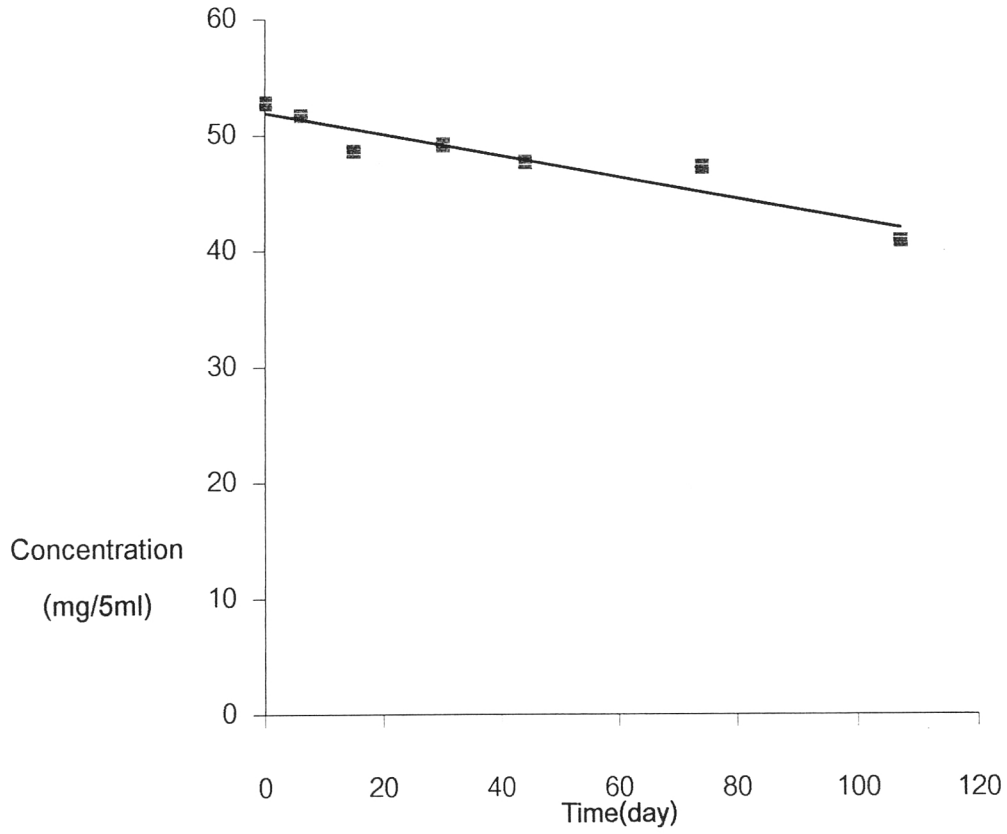


Figure 27 Linear plot of drug concentration remaining vs. time of fluconazole syrup (sodium bisulfite 0.1 %w/v) in the absence of light at 60°C.

Table 53 Stability data of fluconazole syrup stored at 60 ^{o}C

(Absence of light, formulation 8; disodium edetate 0.005% w/v)

Time	pH	Color of	Concentration of fluconazole remaining (mg/ 5ml)			
(Day)		Syrup	No. 1	No. 2	No. 3	Average conc ± SD
0	5.06	Clear	52.40	49.89	53.83	52.04 ± 2.00
6	4.99	Yellow	50.42	51.83	51.37	51.21 ± 0.72
15	4.80	Yellow	49.66	50.02	50.06	49.92 ± 0.22
30	4.39	Yellow	50.79	48.79	49.79	49.79 ± 1.00
44	4.38	Yellow	51.19	43.57	50.95	48.57 ± 4.33
74	4.29	Dark brown	48.75	47.54	48.15	48.15 ± 0.61
107	3.96	Dark brown	41.06	47.48	44.96	44.50 ± 3.24

Zero - order : conc = 51.58 - 6.11 x 10^{-2} time r = 0.967

First - order : ln conc = 3.94 - 1.30 x 10^{-3} time r = 0.966

Second - order : 1/conc = 0.02 + 3.00 x 10^{-5} time r = 0.964

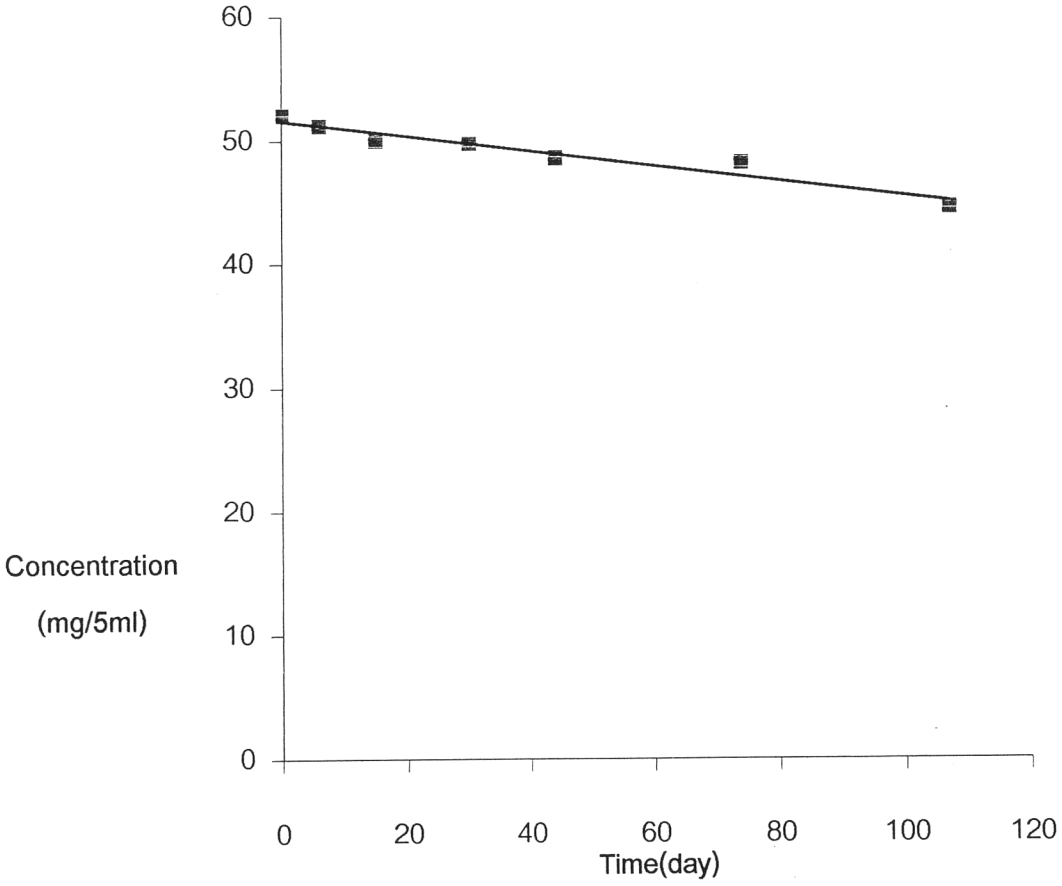


Figure 28 Linear plot of drug concentration remaining vs. time of fluconazole syrup (disodium edetate 0.005 %w/v) in the absence of light at 60°C.

Table 54 Stability data of fluconazole syrup stored at 60 ^{o}C

(Absence of light, formulation 9; disodium edetate 0.01% w/v)

Time (Day)	pH	Color of Syrup	Concentration of fluconazole remaining (mg/ 5ml)			
			No. 1	No. 2	No. 3	Average conc ± SD
0	5.03	Clear	47.02	48.47	51.17	48.89 ± 2.11
6	4.93	Yellow	50.17	52.17	51.17	51.17 ± 1.00
15	4.58	Yellow brown	47.67	51.04	49.56	49.42 ± 1.69
30	3.99	Red brown	46.85	50.85	48.85	48.85 ± 2.00
44	3.88	Dark brown	48.97	49.32	49.21	49.17 ± 0.18
74	3.75	Dark brown	43.79	45.04	44.85	44.56 ± 0.68
107	3.62	Dark brown	37.54	41.47	42.21	40.41 ± 2.51

Zero - order : $conc = 50.99 - 8.86 \times 10^{-2}\ time$ $r = 0.933$

First - order : $\ln conc = 3.93 - 2.00 \times 10^{-3}\ time$ $r = 0.932$

Second - order : $1/conc = 0.02 + 4.45 \times 10^{-5}\ time$ $r = 0.908$

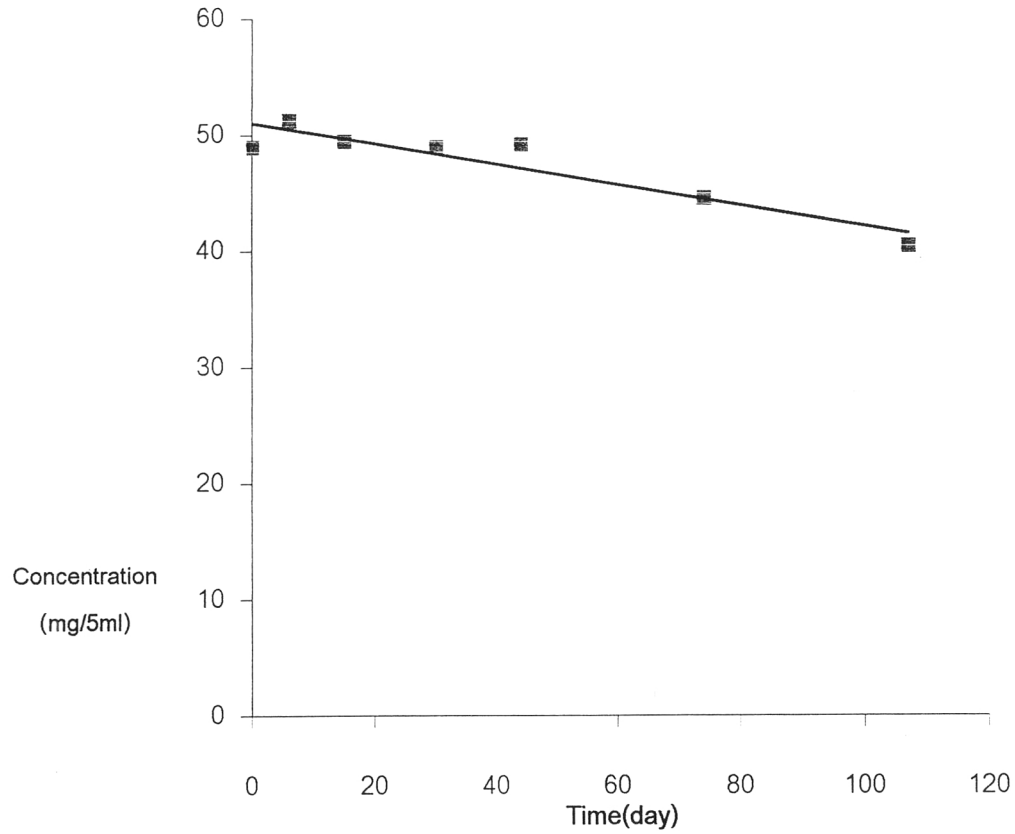


Figure 29 Linear plot of drug concentration remaining vs. time of fluconazole syrup (disodium edetate 0.01 %w/v) in the absence of light at 60°C.

Table 55 Stability data of fluconazole syrup stored at 60 ^{o}C

(Absence of light, formulation 10; disodium edetate 0.05% w/v)

Time (Day)	pH	Color of Syrup	Concentration of fluconazole remaining (mg/ 5ml)			
			No. 1	No. 2	No. 3	Average conc±SD
0	5.06	Clear	50.22	51.52	51.35	51.03 ± 0.71
6	4.99	Yellow	49.10	49.90	46.97	48.66 ± 1.52
15	4.83	Yellow	47.18	47.52	47.94	47.55 ± 0.38
30	4.39	Red brown	47.08	47.17	46.98	47.07 ± 0.10
44	4.24	Red brown	45.14	47.30	43.04	45.16 ± 2.13
74	400	Dark brown	45.16	45.46	44.86	45.16 ± 0.30
107	3.55	Dark brown	37.07	39.17	36.26	37.50 ± 1.50

Zero - order : $conc = 50.13 - 1.03 \times 10^{-1}\ time$ $r = 0.942$

First - order : $\ln conc = 3.92 - 2.40 \times 10^{-3}\ time$ $r = 0.936$

Second - order : $1/conc = 0.02 + 5.30 \times 10^{-5}\ time$ $r = 0.895$

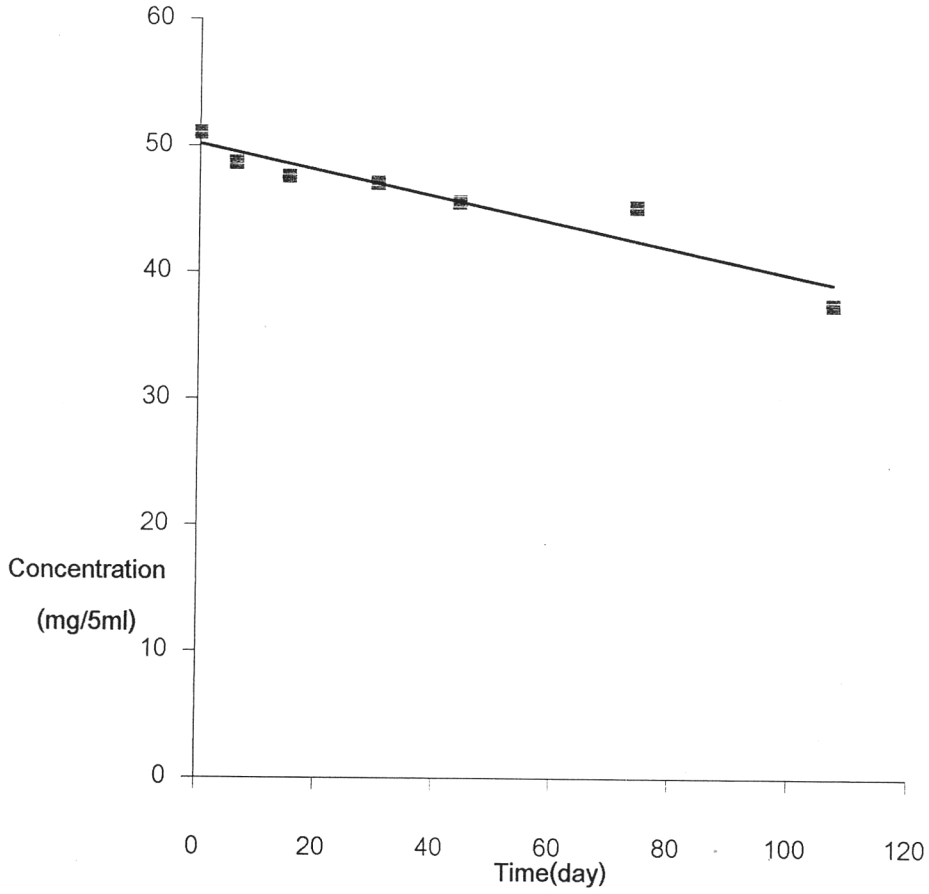


Figure 30 Linear plot of drug concentration remaining vs. time of fluconazole syrup (disodium edetate 0.05 %w/v) in the absence of light at 60°C.

Table 56 Stability data of fluconazole syrup stored at 60 ^{o}C

(Presence of light, formulation 1 ; no antioxidant)

Time	pH	Color of	Concentration of fluconazole remaining (mg/ 5ml)			
(Day)		Syrup	No. 1	No. 2	No. 3	Average conc ±SD
0	5.07	Clear	50.49	49.33	50.80	50.21 ± 0.78
6	4.91	Yellow	46.82	46.05	46.11	46.33 ± 0.43
15	4.79	Yellow	46.64	46.17	45.53	46.11 ± 0.56
28	4.85	Red brown	45.60	45.95	44.95	45.50 ± 0.51
43	3.83	Dark brown	44.32	44.30	44.35	44.32 ± 0.02
73	3.90	Dark brown	41.36	41.51	40.82	41.23 ± 0.36
100	3.89	Dark brown	40.51	37.23	41.81	39.85 ± 2.36

Zero - order : conc = 48.15 - 8.86 x 10^{-2} time r = 0.950

First - order : ln conc = 3.88 - 2.00 x 10^{-3} time r = 0.960

Second - order : 1/conc = 0.02 + 5.00x10^{-5} time r = 0.968

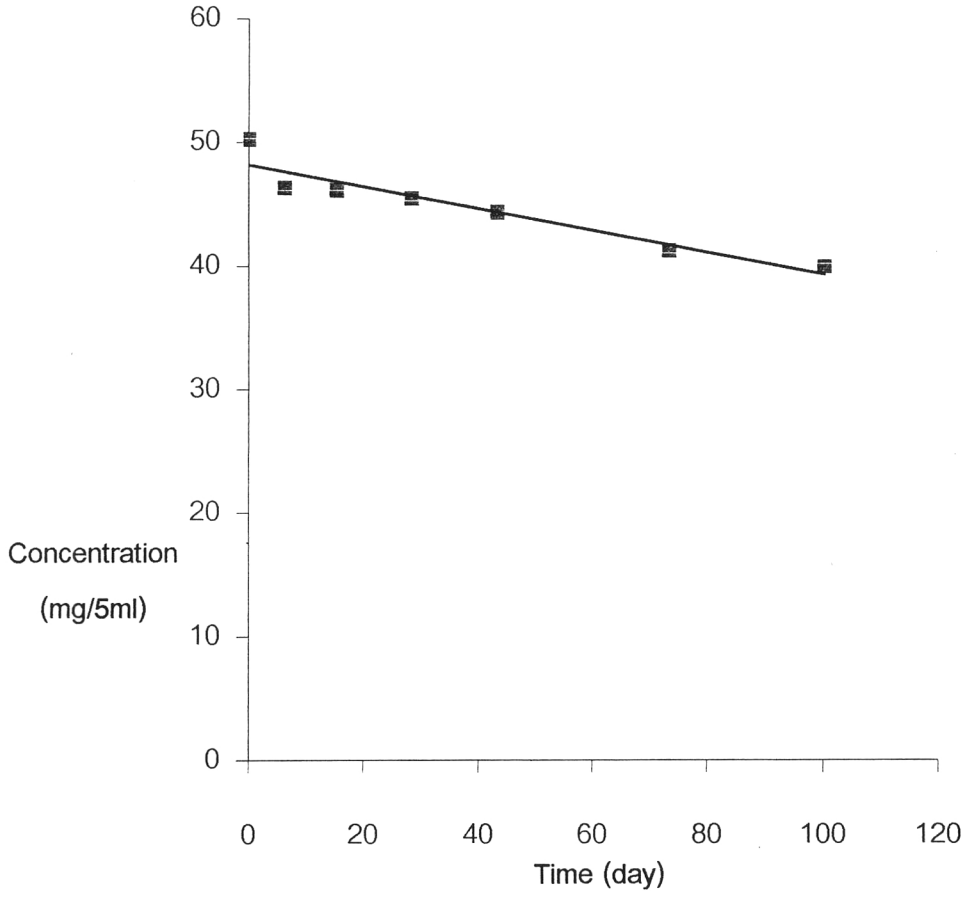


Figure 31 Linear plot of drug concentration remaining vs. time of fluconazole syrup (no antioxidant) in the presence of light at 60 $^{\circ}$ C.

Table 57 Stability data of fluconazole syrup stored at 60 $^{\circ}$C

(Presence of light, formulatio 2; propyl gallate 0.001% w/v)

Time (Day)	pH	Color of Syrup	Concentration of fluconazole remaining (mg/ 5ml)			
			No. 1	No. 2	No. 3	Average conc +SD
0	5.09	Clear	52.32	51.26	52.46	52.01 $\pm$ 0.66
6	5.05	Yellow	50.59	49.81	52.04	50.81 $\pm$ 1.13
15	4.78	Yellow	51.01	49.44	50.24	50.23 $\pm$ 0.79
28	4.42	Yellow	49.03	50.73	47.27	49.01 $\pm$ 1.73
43	4.34	Yellow	51.09	51.36	50.09	50.85 $\pm$ 0.67
73	3.90	Dark brown	48.88	47.57	50.19	48.88 $\pm$ 1.31
100	3.85	Dark brown	44.62	45.46	46.82	45.63 $\pm$ 1.11

Zero - order : $conc = 51.50 - 4.93 \times 10^{-2}$ time $r = 0.878$

First - order : $\ln conc = 3.94 - 1.00 \times 10^{-3}$ time $r = 0.878$

Second - order : $1/conc = 0.02 + 2.00 \times 10^{-5}$ time $r = 0.878$

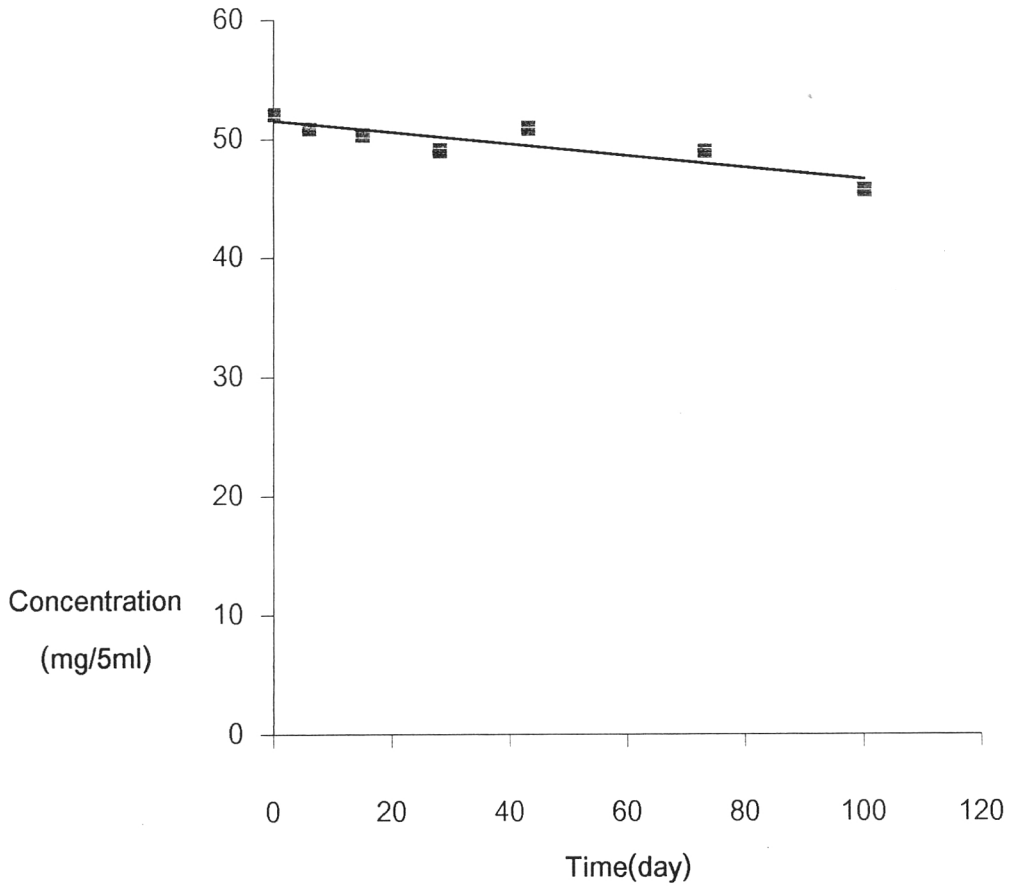


Figure 32 Linear plot of drug concentration remaining vs. time of fluconazole syrup (propyl gallate 0.001 % w/v) in the presence of light at 60 ^{o} C.

Table 58 Stability data of fluconazole syrup stored at 60 °C

(Presence of light, formulation 3; propyl gallate 0.005% w/v)

Time (Day)	pH	Color of Syrup	Concentration of fluconazole remaining (mg/ 5ml)			
			No. 1	No. 2	No. 3	Average conc ±SD
0	5.09	Clear	50.79	51.20	50.44	50.81 ± 0.38
6	5.02	Yellow	50.12	52.14	51.13	51.13 ± 1.01
15	4.73	Yellow brown	49.72	50.75	50.59	50.35 ± 0.56
28	4.24	Red brown	49.17	48.13	51.07	49.46 ± 1.49
43	4.00	Dark brown	45.21	47.32	48.75	47.09 ± 1.78
73	3.95	Dark brown	47.78	48.24	48.01	48.01 ± 0.23
100	3.74	Dark brown	39.34	40.60	40.25	40.06 ± 0.65

Zero - order : $conc = 51.70 - 9.42 \times 10^{-2}\ time$ $r = 0.904$

First - order : $\ln conc = 3.95 - 2.10 \times 10^{-3}\ time$ $r = 0.895$

Second - order : $1/conc = 0.02 + 5.00 \times 10^{-5}\ time$ $r = 0.885$

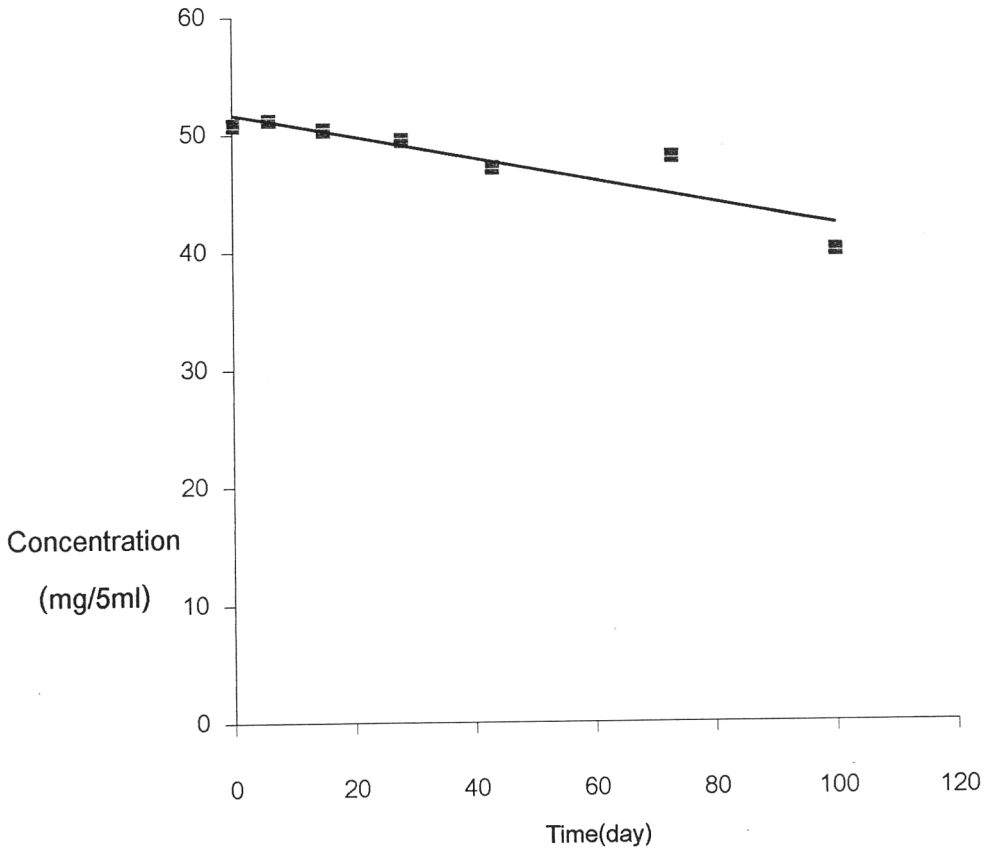


Figure 33 Linear plot of drug concentration remaining vs. time of fluconazole syrup(propyl gallate 0.005 % w/v) in the presence of light at 60 ^{o} C.

Table 59 Stability data of fluconazole syrup stored at 60 ^{o}C

(Presence of light, formulation 4; propyl gallate 0.01% w/v)

Time	pH	Color of	Concentration of fluconazole remaining (mg/ 5ml)			
(Day)		Syrup	No. 1	No. 2	No. 3	Average conc ±SD
0	5.07	Clear	49.18	51.18	50.57	50.31 ± 1.03
6	5.07	Yellow	48.72	50.21	49.33	49.42 ± 0.75
15	4.67	Yellow	49.34	50.10	48.57	49.34 ± 0.77
28	4.26	Red brown	48.41	49.89	48.62	48.97 ± 0.80
43	4.10	Dark brown	45.69	47.47	51.98	48.38 ± 3.24
73	3.91	Dark brown	46.34	47.96	49.58	47.96 ± 1.62
100	3.77	Dark brown	43.94	40.74	45.13	43.27 ± 2.27

Zero - order : conc = 50.39 - 5.69 x 10^{-2} time r = 0.908

First - order : ln conc = 3.92 - 1.20 x 10^{-3} time r = 0.901

Second - order : 1/conc = 0.02 + 3.00 x10^{-5} time r = 0.895

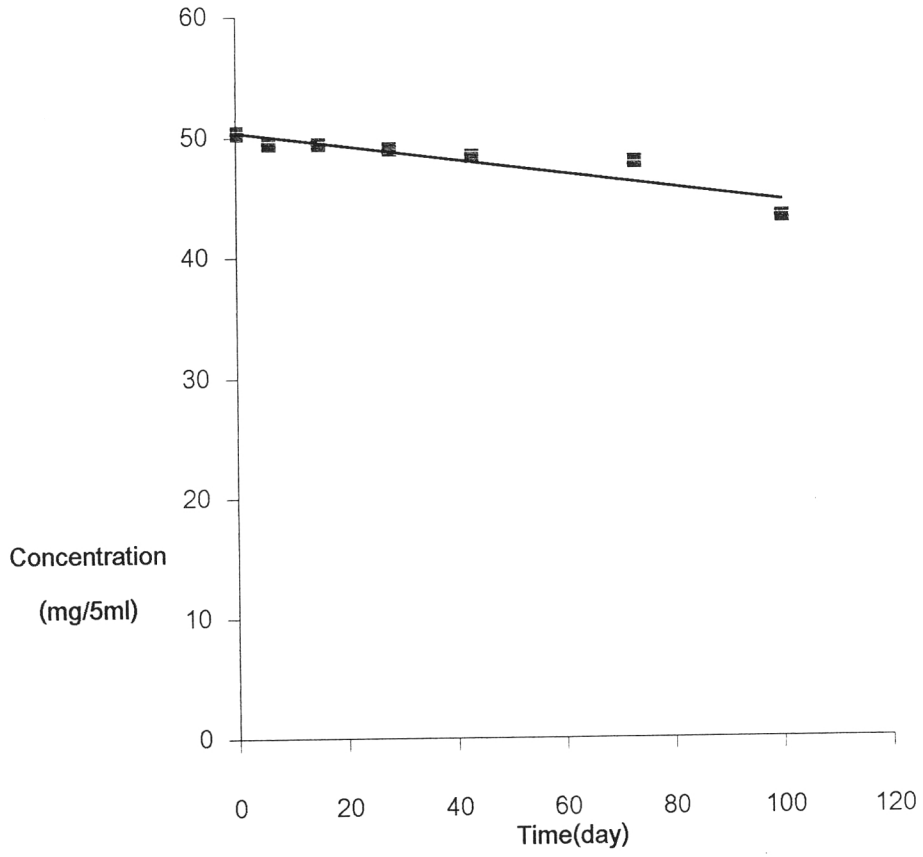


Figure 34 Linear plot of drug concentration remaining v.s time of fluconazole syrup (propyl gallate 0.01 % w/v) in the presence of light at 60 $^{\circ}$ C.

Table 60 Stability data of fluconazole syrup stored at 60 °C

(Presence of light, formulation 5; sodium bisulfite 0.05% w/v)

Time	pH	Color of	Concentration of fluconazole remaining (mg/ 5ml)			
(Day)		Syrup	No. 1	No. 2	No. 3	Average conc ±SD
0	5.08	Clear	51.02	51.70	53.14	51.95 ± 1.08
6	4.97	Yellow	51.43	50.16	50.60	50.73 ± 0.65
15	4.61	Yellow	49.93	51.33	48.27	49.84 ± 1.53
28	4.09	Red brown	46.90	50.94	49.76	49.20 ± 2.08
43	4.00	Dark brown	47.69	52.40	46.55	48.88 ± 3.11
73	3.85	Dark brown	46.85	47.25	48.95	47.68 ± 1.11
100	3.64	Dark brown	41.36	40.49	42.08	41.31 ± 0.79

Zero - order : $conc = 51.81 - 8.70 \times 10^{-2}\ time$ $r = 0.930$

First - order : $\ln conc = 3.95 - 1.90 \times 10^{-3}\ time$ $r = 0.922$

Second - order : $1/conc = 0.02 + 4.00 \times 10^{-5}\ time$ $r = 0.9123$

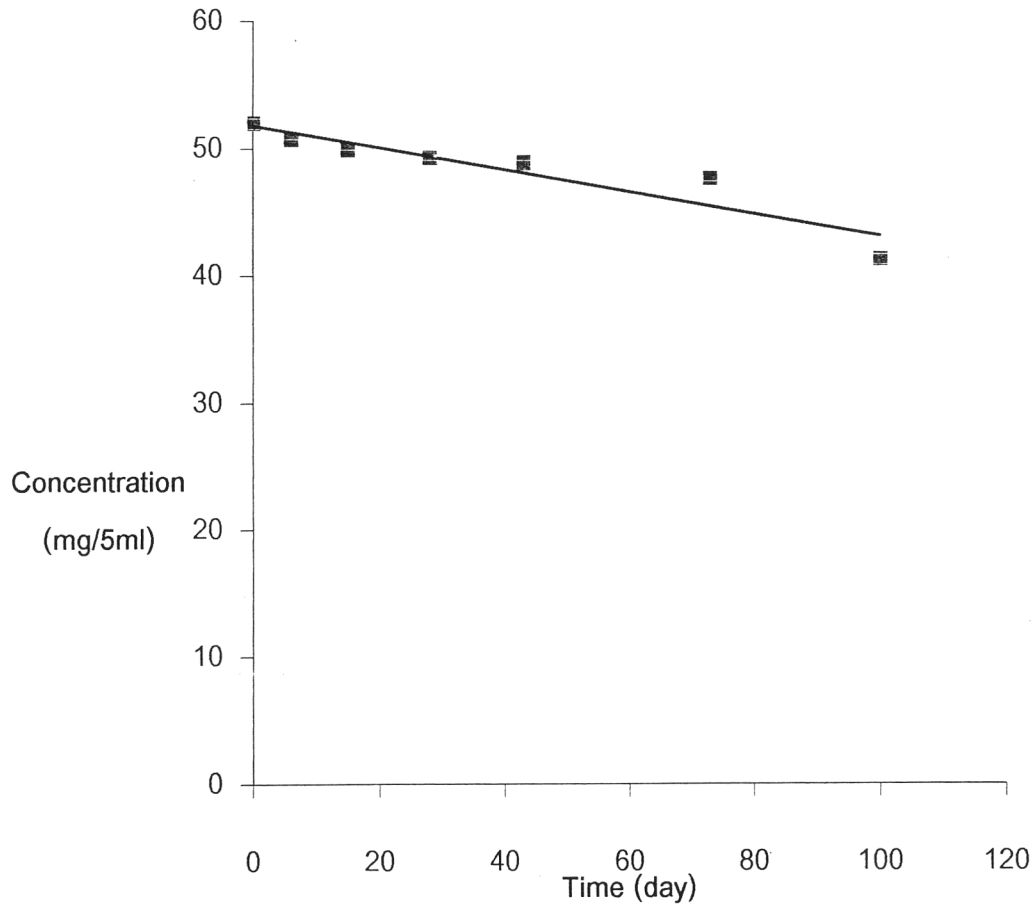


Figure 35 Linear plot of drug concentration remaining vs. time of fluconazole syrup (sodium bisulfite 0.05 %w/v) in the presence of light at 60 ^{o} C.

Table 61 Stability data of fluconazole syrup stored at 60°C

(Presence of light, formulation 6; sodium bisulfite 0.075 %w/v)

Time (Day)	pH	Color of Syrup	Concentration of fluconazole remaining (mg/ 5ml)			
			No. 1	No. 2	No. 3	Average conc ±SD
0	5.09	Clear	53.07	53.75	54.41	53.75 ± 0.67
6	4.77	Yellow	48.76	48.43	50.10	49.10 ± 0.89
15	4.52	Yellow brown	52.90	49.65	49.59	50.71 ± 1.90
28	3.88	Red brown	50.50	49.49	48.48	49.49 ± 1.01
43	3.78	Dark brown	49.85	47.76	49.43	49.01 ± 1.10
73	3.63	Dark brown	47.58	46.49	49.43	47.83 ± 1.49
100	3.57	Dark brown	39.09	39.01	38.69	38.93 ± 0.21

Zero - order : $conc = 52.53 - 1.09 \times 10^{-1}\ time$ $r = 0.880$

First - order : $\ln conc = 3.97 - 2.40 \times 10^{-3}\ time$ $r = 0.873$

Zero - order : $1/conc = 0.02 + 5.00 \times 10^{-5}\ time$ $r = 0.865$

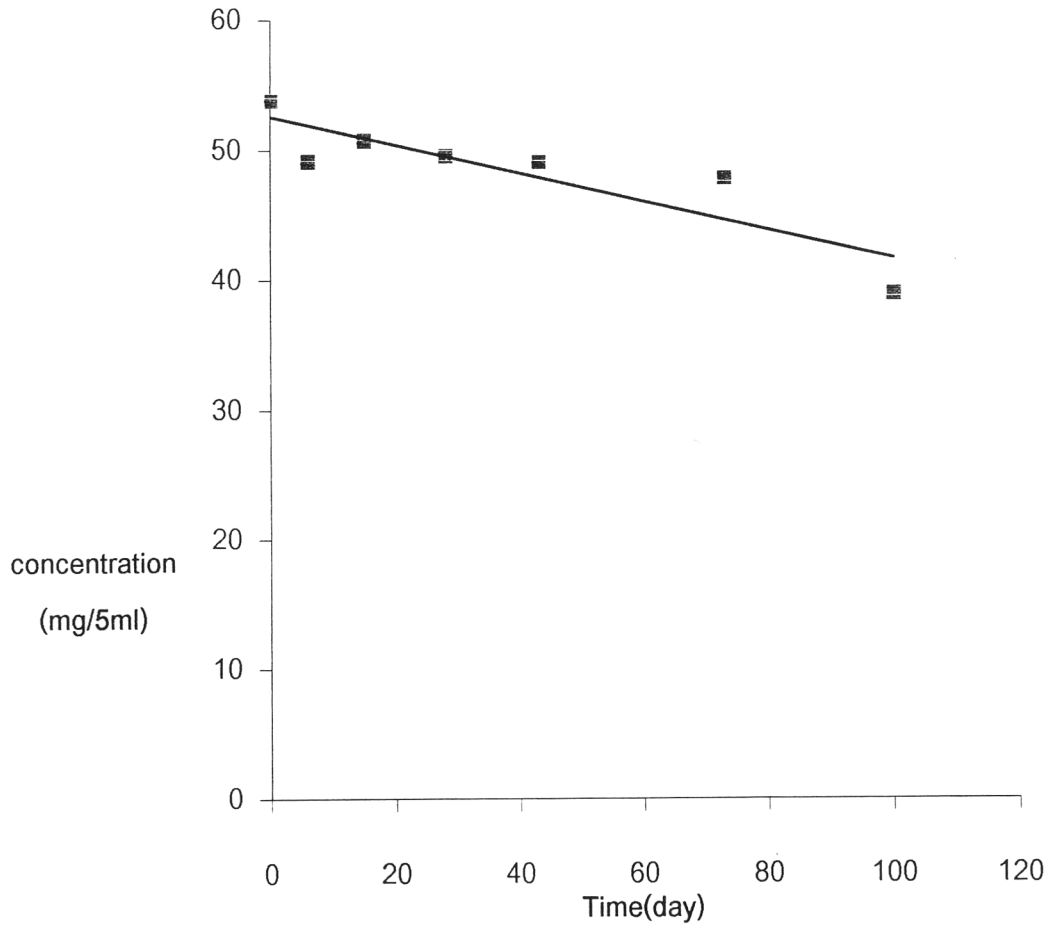


Figure 36 Linear plot of drug concentration remaining v.s time of fluconazole syrup (sodium bisulfite 0.075 %w/v) in the presence of light at 60 °C.

Table 62 Stability data of fluconazole syrup stored at 60 ^{o}C

(Presence of light, formulation 7; sodium bisulfite 0.100% w/v)

Time	pH	Color of	Concentration of fluconazole remaining (mg/ 5ml)			
(Day)		Syrup	No. 1	No. 2	No. 3	Average conc ±SD
0	5.07	Clear	51.47	53.34	53.46	52.76 ± 1.12
6	4.76	Yellow	50.51	49.29	51.19	50.33 ± 0.96
15	4.46	'ellow brow	51.58	49.60	50.59	50.59 ± 0.99
28	3.91	Red brown	47.84	49.71	49.31	48.95 ± 0.99
43	3.87	Dark brown	47.73	49.72	46.27	47.90 ± 1.73
73	3.73	Dark brown	51.80	46.85	44.55	47.74 ± 3.71
100	3.57	Dark brown	40.89	41.21	43.38	41.83 ± 1.35

Zero - order : conc = 51.90 - 8.75 x 10^{-2} time r = 0.936

First - order : ln conc = 3.95 - 1.90 x10^{-3} time r = 0.936

Second - order : 1/conc = 0.02 + 4.00 x10^{-5} time r = 0.927

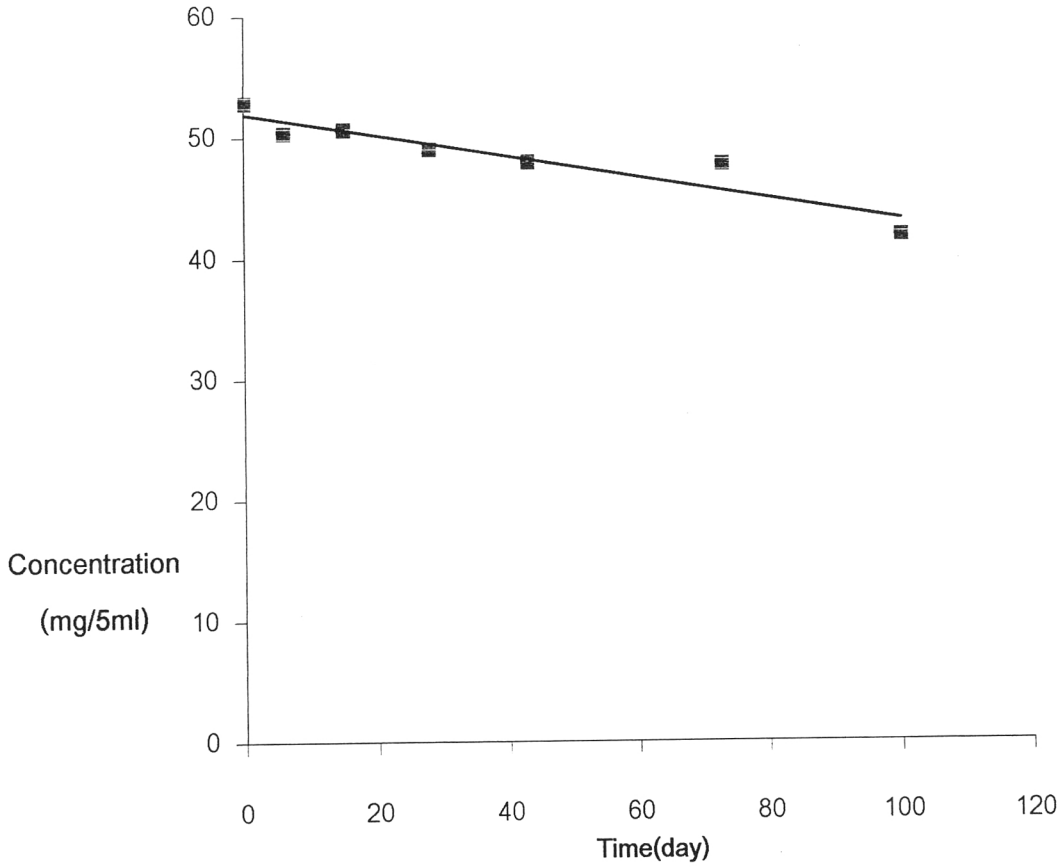


Figure 37 Linear plot of drug concentration remaining vs. time of fluconazole syrup(sodium bisulfite 0.1 %w/v) in the presence of light at 60 $^{\circ}$ C.

Table 63 Stability data of fluconazole syrup stored at 60 °C

(Presence of light, formulation 8; disodium edetate 0.005% w/v)

Time (Day)	pH	Color of Syrup	Concentration of fluconazole remaining (mg/ 5ml)			
			No. 1	No. 2	No. 3	Average conc ±SD
0	5.06	Clear	52.40	49.89	53.83	52.04 ± 2.00
6	5.03	Yellow	52.57	52.57	52.57	52.57 ± 0.00
15	4.94	Yellow	50.42	51.11	49.03	50.19 ± 1.06
28	4.40	Brown	49.61	49.42	49.51	49.51 ± 0.09
43	4.31	Dark brown	49.43	49.82	51.15	50.13 ± 0.90
73	4.02	Dark brown	47.45	48.06	49.76	48.42 ± 1.20
100	3.90	Dark brown	35.69	37.77	36.04	36.50 ± 1.12

Zero - order : $conc = 53.34 - 1.29 \times 10^{-1}\ time$ $r = 0.868$

First - order : $\ln conc = 3.98 - 2.90 \times 10^{-3}\ time$ $r = 0.854$

Second - order : $1/conc = 0.02 + 7.00 \times 10^{-5}\ time$ $r = 0.840$

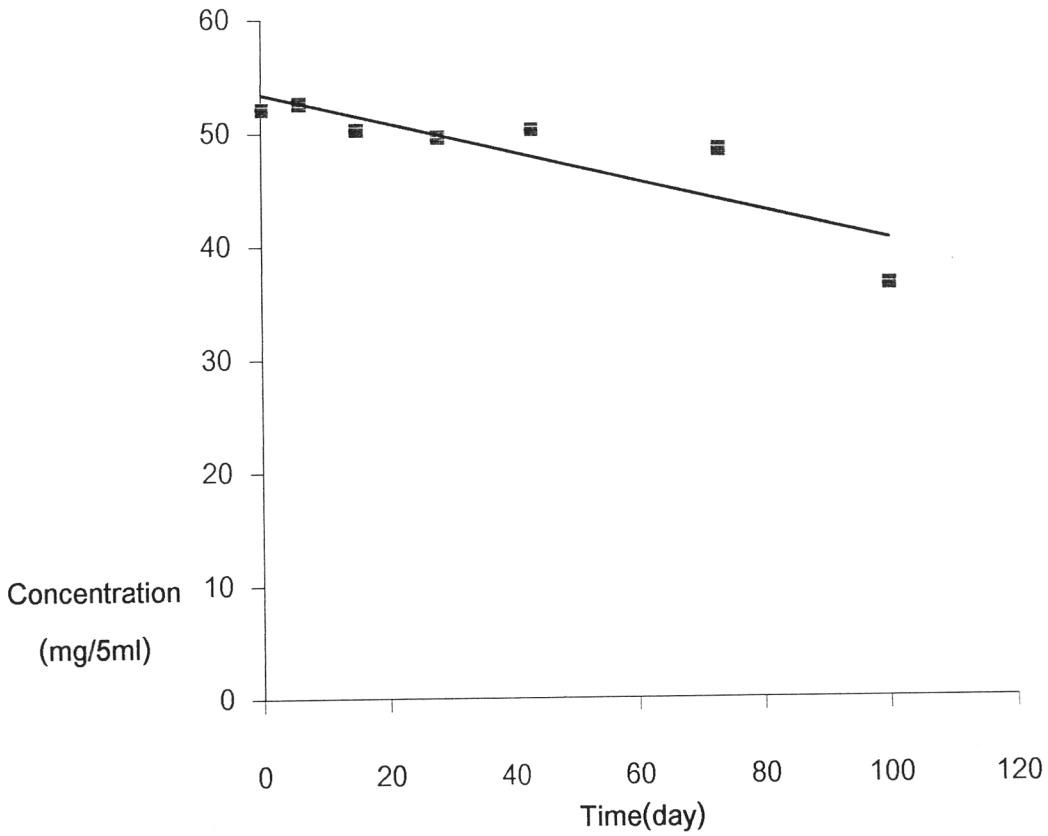


Table 38 Linear plot of drug concentration remaining vs. time of fluconazole syrup (disodium edetate 0.005 %w/v) in the presence of light at 60° C.

Table 64 Stability data of fluconazole syrup stored at 60 ^{o}C

(Presence of light, formulation 9; disodium edetate 0.010% w/v)

Time	pH	Color of	Concentration of fluconazole remaining (mg/ 5ml)			
(Day)		Syrup	No. 1	No. 2	No. 3	Average conc ±SD
0	5.03	Clear	47.02	48.47	51.17	48.89 ± 2.11
6	4.92	Yellow	48.98	49.48	49.18	49.21 ± 0.25
15	4.70	Brown	48.98	49.85	50.28	49.70 ± 0.66
28	4.05	Red brown	46.41	46.42	46.40	46.41 ± 0.01
43	3.94	Dark brown	45.40	45.49	45.45	45.44 ± 0.05
73	3.72	Dark brown	44.39	46.08	44.45	44.97 ± 0.96
100	3.59	Dark brown	35.41	36.42	37.21	36.35 ± 0.90

Zero -order : conc = 50.20 - 1.15 x 10^{-1} time r = 0.921

First -order : ln conc = 3.92 - 2.70 x 10^{-3} time r = 0.911

Second -order : 1/conc = 0.02 + 6.00x10^{-5} time r = 0.899

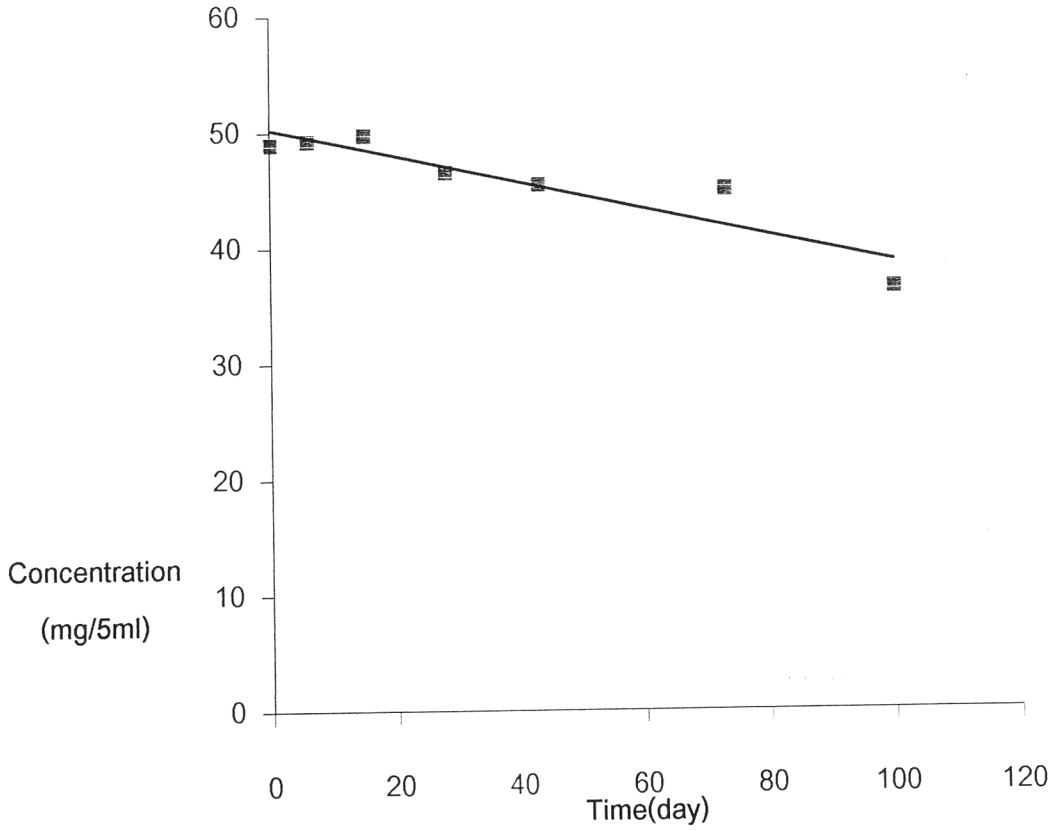


Figure 39Linear plot of drug concentration remaining vs. time of fluconazole syrup (disodium edetate 0.01 %w/v) in the presence of light at 60 °C.

Table 65 Stability data of fluconazole syrup stored at 60 $^{\circ}$C

(Presence of light, formulation 10; disodium edetate 0.050% w/v)

Time	pH	Color of	Concentration of fluconazole remaining (mg/ 5ml)			
(Day)		Syrup	No. 1	No. 2	No. 3	Average conc ± SD
0	5.06	Clear	50.22	51.52	51.35	51.03 ± 0.71
6	4.87	Yellow	49.10	49.90	46.97	48.66 ± 1.52
15	4.53	Brown	45.70	48.38	46.64	46.91 ± 1.36
28	3.95	Red brown	46.80	47.11	46.96	46.96 ± 0.15
43	3.84	Dark brown	46.83	47.94	44.58	46.45 ± 0.79
73	3.81	Dark brown	46.18	44.83	41.41	44.14 ± 2.46
100	3.75	Dark brown	37.78	34.81	36.21	36.27 ± 1.49

Zero - order : conc = 50.27 - 1.19 x 10^{-1} time r = 0.935

First - order : ln conc = 3.92 - 2.80 x 10^{-3} time r = 0.926

Second - order : 1/conc = 0.02 + 6.00x10^{-5} time r = 0.914

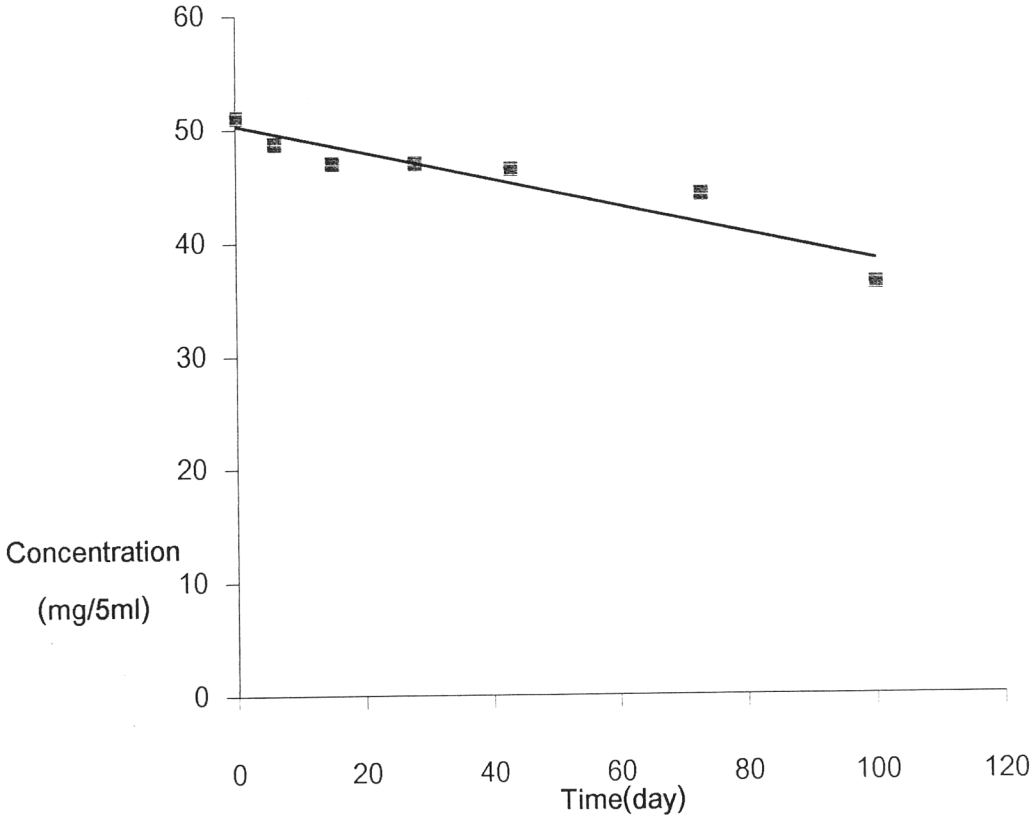


Figure 40 Linear plot of drug concentration remaining vs. time of fluconazole syrup(disodium edetate 0.05 %w/v) in the presence of light at 60 $^{\circ}$ C.

APPENDIX V

Kinetic data of fluconazole

Table 66 Stability data of fluconazole syrup containing propyl gallate 0.001 %w/v

At room temperature

Time (Day)	Color of syrup	Concentration of fluconazole remaining (mg/ 5ml)			
		No. 1	No. 2	No. 3	Average conc ±SD
0	clear	52.62	53.63	53.11	53.12 ± 0.50
31	clear	49.80	50.68	57.78	52.75 ± 4.38
74	clear	51.53	52.63	53.72	52.63 ± 1.10

Zero - order : $conc = 53.06 - 6.40 \times 10^{-3}$ time $r = 0.933$

First - order : $\ln conc = 3.97 - 1.216 \times 10^{-4}$ time $r = 0.933$

Second - order : $1/conc = 0.02 + 2.21 \times 10^{-6}$ time $r = 0.925$

Table 67 Stability data of fluconazole syrup containing propyl gallate 0.001 %w/v

In hot air oven at 45 ^{o}c

Time	Color of syrup	Concentration of fluconazole remaining (mg/ 5ml)			
(Day)		No. 1	No. 2	No. 3	Average conc ±SD
0	Clear	52.62	53.63	53.11	53.12 ± 0.50
13	clear	49.38	55.47	54.15	53.00 ±3.20
74	Yellow	51.24	54.13	50.45	51.94 ± 1.94

Zero - order : conc = 53.16 -1.64 x 10^{-2} time r = 0.997

First - order : ln conc = 3.97 -3.00 x 10^{-4} time r = 0.997

Second - order : 1/ conc = 0.02 + 6.00 x 10^{-6} time r = 0.997

Table 68 Stability data of fluconazole syrup containing propyl gallate 0.001 %w/v

In hot air oven at 55 °c

Time	Color of syrup	Concentration of fluconazole remaining (mg/ 5ml)			
(Day)		No. 1	No. 2	No. 3	Average conc ±SD
0	Clear	52.62	53.63	53.11	53.12 ± 0.50
13	Clear	51.05	57.16	47.05	51.75 ± 5.09
31	Clear	51.07	52.13	50.05	51.08 ± 1.04
38	Yellow	52.81	48.49	52.73	51.34 ± 2.47
54	Yellow	49.36	48.91	49.13	49.13 ± 0.23
74	Yellow	50.57	50.67	50.62	50.62 ± 0.05

Zero - order : $conc = 52.53 - 3.88 \times 10^{-2}$ time r = 0.795

First - order : $\ln conc = 3.96 - 8.00 \times 10^{-4}$ time r = 0.791

Second - order : $1/conc = 0.02 + 1.00 \times 10^{-5}$ time r = 0.787

Table 69 Stability data of fluconazole syrup containing propyl gallate 0.001 %w/v

In hot air oven at 65 °c

Time (Day)	Color of syrup	Concentration of fluconazole remaining (mg/ 5ml)			
		No. 1	No. 2	No. 3	Average conc ±SD
0	Clear	52.62	53.63	53.11	53.12 ± 0.50
13	Clear	48.88	50.92	50.80	50.20 ± 1.15
31	Yellow	49.63	49.85	49.40	49.63 ± 0.23
38	Yellow	48.42	47.23	49.61	48.42 ± 1.19
54	Brown	48.82	46.79	49.17	48.26 ± 1.29
74	Brown	48.02	48.65	50.40	49.02 ± 1.23

Zero order : $conc = 51.59 - 5.20 \times 10^{-2}\ time$ $r = 0.780$

First order : $\ln conc = 3.94 - 1.00 \times 10^{-3}\ time$ $r = 0.781$

Second order : $1/conc = 0.02 + 2.00 \times 10^{-5}\ time$ $r = 0.782$

Table 70 Stability data of fluconazole syrup containing propyl gallate 0.001 %w/v

In hot air oven at 70 °c

Time (Day)	Color of syrup	Concentration of fluconazole remaining (mg/ 5ml)			
		No. 1	No. 2	No. 3	Average conc ± SD
0	Clear	52.62	53.63	53.11	53.12 ± 0.50
13	Yellow	46.51	45.22	47.80	46.85 ± 1.18
31	Yellow	49.68	49.66	49.66	49.67 ± 0.01
38	Brown	49.68	44.00	40.42	44.70 ± 4.67
54	Dark brown	46.61	48.13	45.80	46.85 ± 1.18
74	Dark brown	38.96	44.97	51.90	45.28 ± 6.47

Zero - order : conc = 50.63 - 8.26 x 10^{-2} time r = 0.705

First - order : ln conc = 3.92 - 1.70 x 10^{-3} time r = 0.704

Second - order : 1/conc = 0.02+ 3.00 x 10^{-5} time r = 0.702

APPENDIX VI

Calculation

Table 71 Example for calculation C_o , k , r

X	Y	X^2	Y^2	XY
0	50.206	0.000	2520.642	0.000
6	46.327	36.000	2146.191	277.962
15	46.112	225.000	2126.317	691.680
28	45.500	784.000	2070.250	1274.000
43	44.324	1849.000	1964.617	1905.932
73	41.229	5329.000	1699.830	3009.717
100	39.852	10000.000	1588.182	3985.200

$\Sigma X = 265$ $\Sigma Y = 313.550$ $\Sigma X^2 = 18223$ $\Sigma Y^2 = 14116.029$ $\Sigma XY = 11144.491$

X = time (day) , Y = concentration (mg/5ml) ,

a = C_o = initial concentration (mg/5ml) , b = k = degradation rate constant

$\overline{X} = 37.857$ day , $\overline{Y} = 44.793$ (mg/5ml)

$Y = a + b X$

$$b = \frac{n\Sigma XY - (\Sigma X)(\Sigma Y)}{n\Sigma X^2 - (\Sigma X)^2}$$

$$b = \frac{7(11144.491) - (265)(313.55)}{7(18223) - (265)^2}$$

$k = b = -0.0886$ $(mg/5ml)(day)^{-1}$

$$a = \overline{Y} - b\,\overline{X}$$

$$a = 44.7929 + 0.08859\ (37.8571)$$

$$a = 44.793 + 3.3537$$

$$C_o = a = 48.1466 \quad mg/5ml$$

$$r = \frac{n\Sigma XY - (\Sigma X)(\Sigma Y)/n}{[(\Sigma X^2 - (\Sigma X)^2/n)(\Sigma Y^2 - (\Sigma Y)^2/n)]^{1/2}}$$

$$r = \frac{11144.491 - [(265)(313.55)/7]}{[18223 - (265)^2/7]\,[14116.029 - (313.55)^2/7]^{1/2}}$$

$$r = -0.9500$$

Equation for calculation shelf life

For a zero-order rate reaction the equation is:

$y = mx+b$

y = concentration at any time

b = concentration at time zero

x = time

m = zero-order rate constant

$$m = \frac{\sum_{i=1}^{n} (x_i - \bar{x})(y_i - \bar{y})}{\sum (x_i - \bar{x})^2}$$

$$b = \bar{y} - m\bar{x}$$

$$s_y^2 = \frac{\sum (y_i - y_i)^2}{n-2}$$

y_i = predicted value at t_i

$s_{y=}$ standard error of regression

y_i = actual value at t_i

It is not acceptable to base an expiration date on this line, since this would be too short in about half the causes; instesd, the line above which 95 % of the products would fall is used. The line is given by :

$y_{i=} = m x_i + b - g(x_i)$

where

$$g(x_i) = t\ 0.05, n\text{-}2 \times sy\,x \left(1 + \frac{(x - \bar{x})^2}{n \sum_{i=1}^{n} (x_i - \bar{x})^2}\right)^{1/2}$$

$$\text{The shelf – life } (x_{90\%}) = (y_i - b) / m$$

APPENDIX VII

Statistically data of fluconazole

Analysis of Covariance (ANCOVA) was used for comparing the degradation rate constants of the formulations studied and performed by using SPSS ® 7.5 program. A null hypothesis, i.e. there is no difference in the slopes or degradation rate constants compared, was tested against an alternative hypothesis, i.e. at least one pair of the slopes is not equal (a significance level, $\alpha = 0.05$).

The assumption of equality of regression slopes calculated from the plots of concentration of drug remaining and time can be tested by fitting a model containing main effects of formulation no. (NO) and time (day), as well as the NO * TIME interaction.

Table 72 Test of the effect of storage condition on the degradation rate of fluconazole syrup without antioxidant.

Tests of Between-Subjects Effects

Dependent Variable: CONC

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power[a]
Corrected Model	166.770[b]	3	55.590	40.047	.000	120.142	1.000
Intercept	15493.48	1	15493.48	11161.59	.000	11161.595	1.000
NO	10.416	1	10.416	7.504	.021	7.504	.695
TIME	150.323	1	150.323	108.293	.000	108.293	1.000
NO * TIME	.377	1	.377	.272	.614	.272	.076
Error	13.881	10	1.388				
Total	29574.74	14					
Corrected Total	180.651	13					

a. Computed using alpha = .05

b. R Squared = .923 (Adjusted R Squared = .900)

Table73 Tests of the effect of propyl gallate on the degradation rate of fluconazole syrups stored at 60 ° C, presence of light.

Tests of Between-Subjects Effects

Dependent Variable: CONC

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power[a]
Corrected Model	272.104[b]	7	38.872	22.283	.000	155.983	1.000
Intercept	32011.75	1	32011.75	18350.63	.000	18350.629	1.000
NO	25.058	3	8.353	4.788	.011	14.364	.833
TIME	171.128	1	171.128	98.099	.000	98.099	1.000
NO * TIME	12.389	3	4.130	2.367	.101	7.102	.507
Error	34.889	20	1.744				
Total	64009.03	28					
Corrected Total	306.993	27					

a. Computed using alpha = .05

b. R Squared = .886 (Adjusted R Squared = .847)

Table74 Tests of the effect of propyl gallate on the degradation rate of fluconazole syrups stored at 60 ° C, absence of light.

Tests of Between-Subjects Effects

Dependent Variable: CONC

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power[a]
Corrected Model	442.853[b]	7	63.265	13.604	.000	95.231	1.000
Intercept	34388.27	1	34388.27	7394.873	.000	7394.873	1.000
NO	7.443	3	2.481	.534	.665	1.601	.140
TIME	374.594	1	374.594	80.553	.000	80.553	1.000
NO * TIME	34.391	3	11.464	2.465	.092	7.395	.525
Error	93.006	20	4.650				
Total	64721.83	28					
Corrected Total	535.859	27					

a. Computed using alpha = .05

b. R Squared = .826 (Adjusted R Squared = .766)

Table 75 Tests of the effect of sodium bisulfite on the degradation rate of fluconazole syrups stored at 60 ° C, presence of light.

Tests of Between-Subjects Effects

Dependent Variable: CONC

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power[a]
Corrected Model	358.698[b]	7	51.243	18.998	.000	132.983	1.000
Intercept	32857.87	1	32857.87	12181.64	.000	12181.638	1.000
NO	37.452	3	12.484	4.628	.013	13.885	.819
TIME	283.612	1	283.612	105.145	.000	105.145	1.000
NO * TIME	2.818	3	.939	.348	.791	1.045	.106
Error	53.947	20	2.697				
Total	63783.77	28					
Corrected Total	412.644	27					

a. Computed using alpha = .05

b. R Squared = .869 (Adjusted R Squared = .824)

Table 76 Tests of the effect of sodium bisulfite on the degradation rate of fluconazole syrups stored at 60 ° C, absence of light.

Tests of Between-Subjects Effects

Dependent Variable: CONC

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power[a]
Corrected Model	325.639[b]	7	46.520	44.503	.000	311.521	1.000
Intercept	34271.98	1	34271.98	32786.05	.000	32786.054	1.000
NO	5.822	3	1.941	1.857	.170	5.570	.408
TIME	299.590	1	299.590	286.600	.000	286.600	1.000
NO * TIME	5.554	3	1.851	1.771	.185	5.313	.391
Error	20.906	20	1.045				
Total	65431.40	28					
Corrected Total	346.546	27					

a. Computed using alpha = .05

b. R Squared = .940 (Adjusted R Squared = .919)

Table 77 Tests of the effect of disodium edetate on the degradation rate of fluconazole syrups stored at 60 ° C, presence of light.

Tests of Between-Subjects Effects

Dependent Variable: CONC

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power[a]
Corrected Model	466.287[b]	7	66.612	13.859	.000	97.014	1.000
Intercept	34134.40	1	34134.40	7101.906	.000	7101.906	1.000
NO	44.397	3	14.799	3.079	.051	9.237	.629
TIME	406.981	1	406.981	84.675	.000	84.675	1.000
NO * TIME	6.935	3	2.312	.481	.699	1.443	.130
Error	96.127	20	4.806				
Total	60391.64	28					
Corrected Total	562.414	27					

a. Computed using alpha = .05

b. R Squared = .829 (Adjusted R Squared = .769)

Table 78 Tests of the effect of disodium edetate on the degradation rate of fluconazole syrups stored at 60 ° C, absence of light.

Tests of Between-Subjects Effects

Dependent Variable: CONC

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power[a]
Corrected Model	326.649[b]	7	46.664	28.898	.000	202.288	1.000
Intercept	33053.81	1	33053.81	20469.68	.000	20469.677	1.000
NO	3.461	3	1.154	.714	.555	2.143	.174
TIME	280.842	1	280.842	173.921	.000	173.921	1.000
NO * TIME	9.514	3	3.171	1.964	.152	5.892	.429
Error	32.295	20	1.615				
Total	63261.66	28					
Corrected Total	358.944	27					

a. Computed using alpha = .05

b. R Squared = .910 (Adjusted R Squared = .879)

From table 72, the interaction term (NO * TIME) shows acception of the equal slopes assumption (p-value >0.05). Therefore, there is no significant differences in the degradation rate of fluconazole syrup without antioxidant in difference storage conditions. The interaction terms (NO * TIME) presented in tables 73, 74, 75,76,77, and 78 respectively, show that propyl gallate, sodium bisulfite, disodium edetate do not significantly affect the degradation rate of fluconazole syrups in all storage conditions(p-value >0.05).

VITA

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