CHAPTER V

STABILITY STUDIES

The determination of stability characteristics of the pharmaceutical dosage forms over extended time periods projects the concept of total quality control to the consumer. Laboratory analysis, manufacturing techniques, and quality control procedures prior to market release attempt to insure product purity, identity, strength, and quality at the completion of the manufacturing processes. Stability studies demonstrate that the necessary critical characteristics present at the time of production and release can be expected to be present when the dosage form is administered (1).

Stability of pharmaceutical product is the capability of a particular formulation, in a specific container, to remain within its physical, chemical, microbiological, therapeutic, and toxicological specifications. Assurance that the packed product will be stable during its anticipated shelf life must come from an accumulation of the data on the packed drug. These stability data involve selected parameters which, taken together, form the stability profile, 90% of the labelled potency of active ingredient(s) is generally recognised as the minimum acceptable potency level. Expiration dating is the time in which the preparation will remain stable under the recommended conditions of storage.

The prediction of stability of a drug product depends on quantitative mathematical expressions. These expressions permit calculation of degradation rate taking into account the factors such as concentration, temperature and time. The basic concepts of kinetics and their application in understanding degradation of pharmaceutical systems have been described by several authors (2-7). Higuchi *et al.* (8,9) were the first to publish rigorous kinetic studies including reaction and heat of activation. Garrett (10) described a method for prediction of degradation rate from elevated temperature data. While studying degradation of a drug at elevated temperature, the degree of instability of the active ingredient in a stressed preparation is monitered by specific assay procedure. This approach although not very accurate, is quite satisfactory for comparison. The degradation of the drug is expressed as a linear function of time and degradation rate is computed.

Stability Studies of Selected Controlled Release Products

Controlled release capsules and tablets, found satisfactory in *in vivo* studies, were subjected to stability studies. Both tetracycline hydrochloride and hydralazine hydrochloride products were assayed and packed in amber coloured vials and stored at air condition (20±2°C, 45±5% R.H.), room temperature, 37°C, 65% R.H. and

50°C for 90 days. Samples were withdrawn at the end of 15, 30, 60 and 90 days and subjected to both physical and chemical examination. Tetracycline hydrochloride products were assayed by the method described in USP XX (11), under determination of 4-epianhydrotetracycline and anhydrotetracycline in tetracycline hydrochloride dosage forms. Hydralazine hydrochloride products were assayed as per the method described in Chapter II (page 48). Each sample was also evaluated for in vitro dissolution rate as per the method described in Chapter III (pages 81, 118). The observations are recorded in Tables 5-1 to 5-6 and shown graphically in Figures 5-1 to 5-3.

RESULTS AND DISCUSSION

A. Tetracycline hydrochloride

Selected controlled release products of tetracycline hydrochloride were kept on stability at different conditions for 90 days. The observations are recorded in Tables 5-1 to 5-3 and shown graphically in Figures 5-1 and 5-2.

(1) In capsules, colour of beads darkens at 37°C, 65% R.H. and 50°C in three months. However, no change was observed at room temperature.

(2) In tablets, colour darkens and mottling increases at

TABLE 5-2A: DATA OF STABILITY STUDIES AND RELEASE PATTERN OF SELECTED CONTROLLED RELEASE PRODUCTS OF TETRACYCLINE HYDROCHLORIDE ON STORAGE

Product	Time (days)	Condition of storage	Assay per capsule (mg)	Cumulative Percentage Release					
				Time (hr)1	2	3.5	5	7	9
				pH 1.2	2.5	4.5	7	7.5	7.5
EUDRAGIT RL100-RS100 COATED BEADS CAPSULE (500 mg) (A)		Initial	505.4						
	15	I	505.0	30.6	40.8	58.1	75.2	92.8	101.2
		II	504.2	31.8	41.7	57.6	78.1	91.8	99.8
		III	503.1	32.1	42.3	58.7	76.2	93.7	98.9
		IV	501.9	30.1	41.2	56.3	75.9	93.3	102.3
	30	I	504.4	31.7	40.2	59.4	76.3	91.2	100.6
		II	502.3	30.8	39.6	57.8	77.5	92.5	101.7
		III	499.7	32.3	39.8	58.2	75.2	93.6	103.8
		IV	497.8	29.8	42.6	56.7	74.4	90.9	99.8
	60	I	500.8	32.6	41.7	59.2	77.1	92.5	102.1
		II	498.3	29.7	42.5	56.4	75.8	93.8	104.1
		III	492.7	28.9	42.4	58.4	76.7	91.4	103.6
		IV	488.1	30.6	39.3	57.2	74.2	93.3	101.7
	90	I	498.8	30.1	40.8	56.7	76.9	92.8	102.5
		II	498.2	31.8	41.4	58.1	78.1	91.7	99.7
		III	487.3	32.1	39.8	58.2	77.6	94.3	101.7
		IV	482.6	31.7	39.6	59.1	75.8	95.1	101.1

Contd..

TABLE 5-2A: Contd.

Product	Time (days)	Condition of storage	Assay per capsule (mg)	Cumulative Percentage Release					
				Time (hr) 1 pH 1.2	2 2.5	3.5 4.5	5 7	7 7.5	9 7.5
EUDRAGIT RL100-RS100 COATED BEADS CAPSULE (250 mg) (B)		Initial	252.6						
	15	I	252.7	28.6	40.2	59.3	75.6	93.8	101.3
		II	252.1	29.8	41.3	59.2	77.5	91.2	102.5
		III	251.4	30.6	40.9	56.4	76.7	92.5	101.7
		IV	251.1	29.4	39.8	58.5	74.3	94.3	98.6
	30	I	252.2	28.8	41.2	57.2	75.2	91.9	99.4
		II	251.4	27.8	43.7	59.8	76.7	92.8	102.5
		III	249.8	29.3	40.5	58.3	75.4	93.2	101.7
		IV	249.9	30.2	41.3	59.8	78.1	94.1	100.2
	60	I	250.4	31.0	42.6	56.8	77.1	93.2	98.7
		II	249.1	30.2	43.1	59.1	76.5	91.8	101.3
		III	246.2	29.7	39.7	57.6	74.8	94.7	99.7
		IV	244.1	28.3	39.8	58.5	75.3	95.2	101.4
	90	I	249.5	29.7	40.1	57.2	76.7	91.6	100.6
		II	249.0	28.6	42.6	58.3	77.5	95.6	103.6
		III	243.5	29.5	41.8	58.7	75.8	93.8	102.5
		IV	242.3	28.9	40.6	59.3	76.9	92.9	101.4

Key : I - A.C. (20±2°C, 45±5% R.H.), II - Room Temperature; III - 37°C, 65 R.H.; IV - 50°C.

TABLE 5-2B : DATA OF STABILITY STUDIES AND RELEASE PATTERN OF SELECTED CONTROLLED RELEASE PRODUCTS OF TETRACYCLINE HYDROCHLORIDE ON STORAGE.

Product	Time (days)	Condition of storage	Assay per tablet (mg)	Cumulative Percentage Release					
			Time (hr) 1	2	3	5	7	9
			pH 1.2	2.5	3.5	7	7.5	7.5
EUDRAGIT RLPM-RSPM MATRIX TABLETS (500 mg) (C)		Initial	503.6					
	15	I	503.2	30.8	44.5	61.4	75.1	93.6	102.5
		II	502.8	31.3	46.5	62.5	76.5	91.6	101.3
		III	501.4	32.5	45.7	61.8	76.2	92.6	102.3
		IV	500.2	33.6	44.2	63.3	78.1	94.1	98.6
	30	I	502.6	34.5	43.6	62.4	76.2	93.8	101.8
		II	500.8	31.4	45.6	63.6	75.8	94.5	98.7
		III	498.0	30.2	42.5	61.7	76.3	95.1	103.6
		IV	496.8	32.8	44.8	63.2	75.1	93.4	102.3
	60	I	499.2	31.5	42.6	61.8	76.3	91.7	101.5
		II	496.8	34.7	43.2	62.5	74.6	93.4	102.3
		III	491.1	30.5	42.5	63.6	75.8	92.9	101.7
		IV	486.4	32.5	44.6	62.1	76.3	93.6	98.4
	90	I	497.1	29.8	41.8	63.6	76.1	91.8	98.4
		II	496.6	30.6	44.3	62.1	75.4	94.5	101.3
		III	485.8	32.5	42.8	61.7	75.8	93.1	103.5
		IV	481.8	31.7	42.3	60.3	78.1	92.5	102.5

Contd..

TABLE 5-2B : Contd.

Product	Time (days)	Condition of storage	Assay per tablet (mg)	Cumulative Percentage Release					
			Time (hr) 1	2	3	5	7	9
			pH 1.2	2.5	3.5	7	7.5	7.5
EUDRAGIT RLPM-RSPM MATRIX TABLETS (250 mg) (D)		Initial	251.2					
	15	I	251.0	29.6	41.2	59.7	76.2	97.6	101.3
		II	250.8	28.7	39.8	61.8	75.2	96.8	102.5
		III	250.1	29.4	41.5	60.3	74.6	97.2	99.8
		IV	249.6	30.6	38.7	58.7	75.8	95.6	102.4
	30	I	250.7	31.2	41.4	58.9	75.5	96.5	101.8
		II	249.8	28.6	38.9	62.7	78.3	98.3	99.6
		III	248.5	29.7	41.3	61.4	77.3	98.1	103.1
		IV	242.6	30.6	39.5	63.8	76.5	97.3	101.4
	60	I	249.1	29.8	42.5	61.2	78.2	96.5	102.5
		II	248.0	28.9	41.7	59.8	76.5	95.2	102.5
		III	244.9	29.1	43.6	60.3	77.8	98.6	101.7
		IV	242.6	30.2	40.8	62.5	75.9	97.1	100.3
	90	I	248.2	31.7	42.1	61.7	76.3	97.8	101.2
		II	247.7	33.8	40.3	63.4	78.1	96.8	103.4
		III	242.4	29.8	41.6	60.8	77.8	98.4	102.5
		IV	240.1	28.7	39.8	62.6	75.8	97.2	99.2

Key : I - A.C. (20±2°C; 45±5% R.H.); II - Room temperature; III - 37°C, 65% R.H.; IV - 50°C.

FIG. 5-1A: STABILITY STUDIES OF TETRACYCLINE HYDROCHLORIDE CONTROLLED RELEASE CAPSULE (500 mg.)

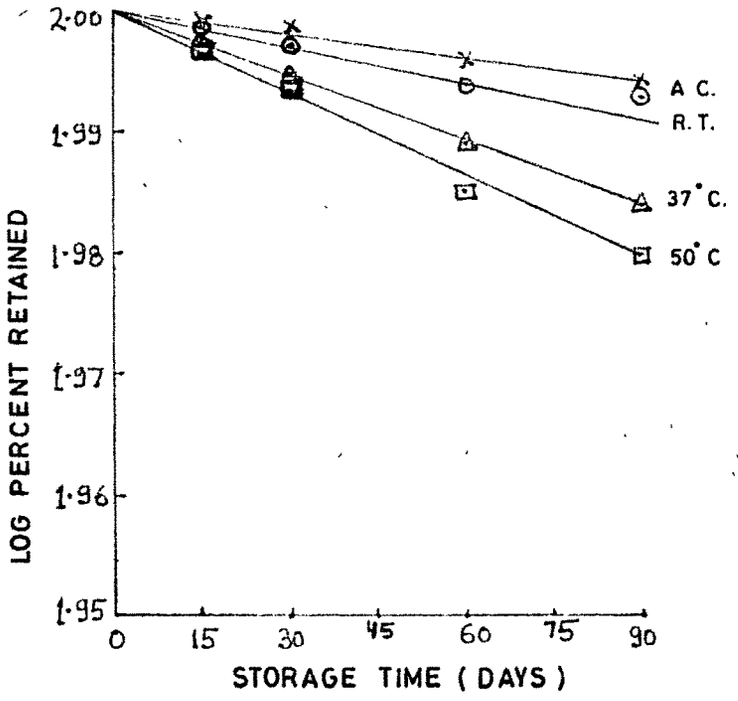

FIG. 5-1B: STABILITY STUDIES OF TETRACYCLIN HYDROCHLORIDE CONTROLLED RELEASE CAPSULE (250 mg.)

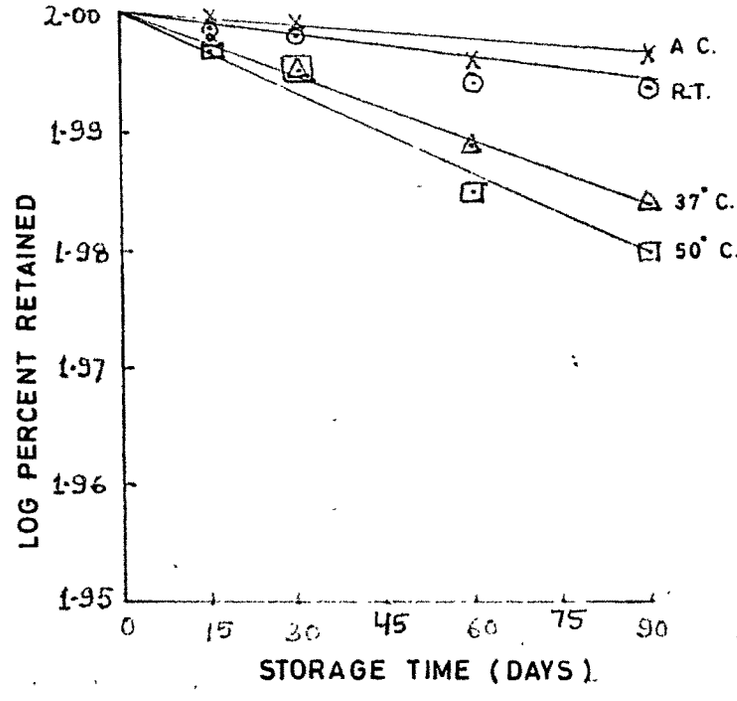

FIG. 5-2A: STABILITY STUDIES OF TETRACYCLINE HYDROCHLORIDE CONTROLLED RELEASE TABLET (500 mg.)

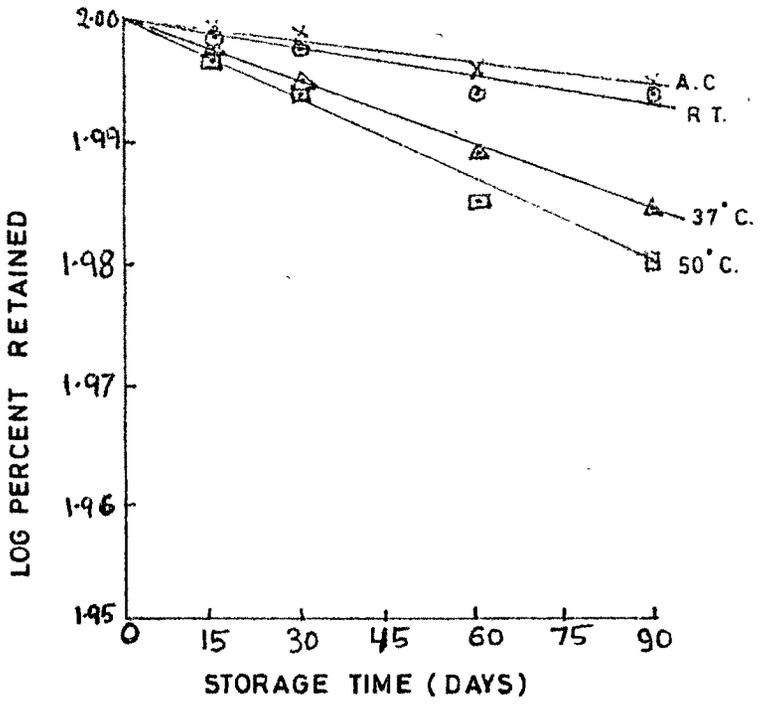

FIG. 5-2B: STABILITY STUDIES OF TETRACYCLINE HYDROCHLORIDE CONTROLLED RELEASE TABLET (250 mg.)

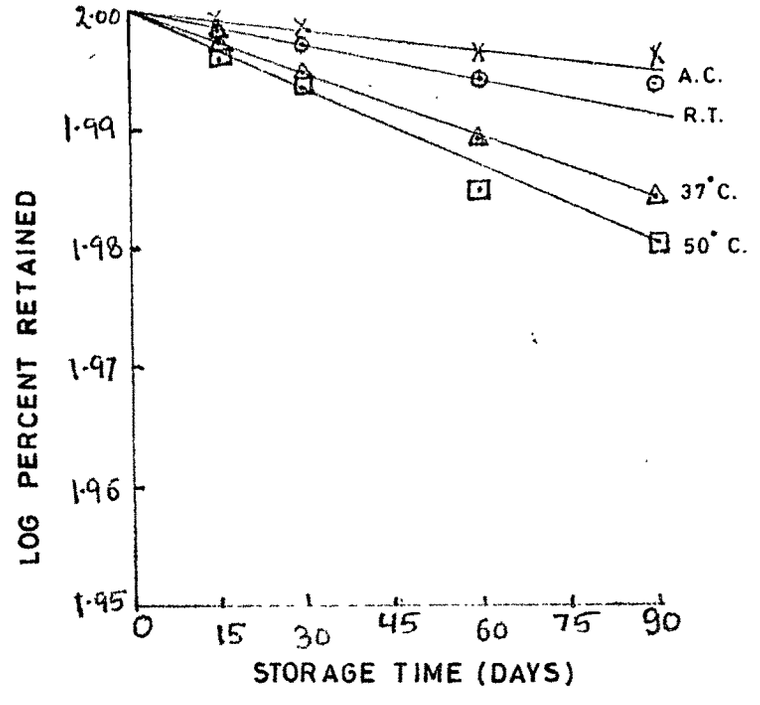

TABLE 5-3 : DEGRADATION RATE CONSTANT (K) AND SHELF LIFE OF SELECTED CONTROLLED RELEASE PRODUCTS OF TETRACYCLINE HYDROCHLORIDE AT VARIOUS CONDITIONS OF STORAGE.

Product		Condition of storage	Degradation rate constant (mg day^{-1})	Shelf life (days)
EUDRAGIT RL100-RS100 COATED BEADS CAPSULES (500 mg)	(A)	I	1.407×10^{-4}	739
		II	1.637×10^{-4}	635
		III	4.068×10^{-4}	256
		IV	5.092×10^{-4}	204
EUDRAGIT RL100-RS100 COATED BEADS CAPSULES (250 mg)	(B)	I	1.305×10^{-4}	797
		II	1.563×10^{-4}	665
		III	4.100×10^{-4}	253
		IV	5.560×10^{-4}	187
EUDRAGIT RLPM-RSPM MATRIX TABLETS (500 mg)	(C)	I	1.407×10^{-4}	739
		II	1.612×10^{-4}	645
		III	4.017×10^{-4}	259
		IV	4.989×10^{-4}	208
EUDRAGIT RLPM-RSPM MATRIX TABLETS (250 mg)	(D)	I	1.305×10^{-4}	797
		II	1.950×10^{-4}	542
		III	3.915×10^{-4}	266
		IV	4.989×10^{-4}	208

Key
I A.C. (20±2°C, 45±5% R.H.)
II Room temperature
III 37°C, 65% R.H.
IV 50°C.

37°C, 65% R.H. and 50°C in three months. However, no change was observed at room temperature.

(3) Plots of log percentage drug retained versus time show that all products follow first order degradation kinetics.

(4) Degradation rate constant (K) was calculated for each product at different conditions of storage from graphs plotted for different products and was found to be highest at 50°C and lowest at A.C. conditions.

(5) No significant change was observed in release pattern of tetracycline hydrochloride from the products kept on stability.

The controlled release capsules of tetracycline hydrochloride show little change in colour of beads at 37°C, 65% R.H. and 50°C in three months. However, the change is not exactly visible, the capsule shell being opaque. As mottling of the controlled release tablets increases at 37°C, 65% R.H. and 50°C in three months, it will be desirable to sugar- or film coat the tablet for making the product more elegant. All products of tetracycline hydrochloride have shelf life of more than $1\frac{1}{2}$ years at room temperature and at other stress conditions also they have adequate shelf life. However, there is no

need of incorporating excess of the drug to enhance shelf life of product. No significant change was observed in release pattern of tetracycline hydrochloride from products kept on stability at different conditions.

The studies show that all controlled release products have sufficiently high stability at room temperature and other stress conditions. It will be better to coat controlled release tablets to enhance elegancy of the product.

B. Hydralazine hydrochloride

Selected controlled release products of hydralazine hydrochloride were kept on stability at different conditions for 90 days. The observations are recorded in Tables 5-4 to 5-6 and shown graphically in Figure 5-3.

(1) There was no marked change in physical characteristics of the controlled release products.

(2) Plots of log percentage drug retained versus time show that both the products follow first order degradation kinetics.

(3) Degradation rate constant (K) was calculated for each product at different conditions of storage from graphs plotted for both the products and it was found highest at 50°C and lowest at A.C. conditions.

TABLE 5-5 : DATA OF STABILITY STUDIES AND RELEASE PATTERN OF SELECTED CONTROLLED RELEASE PRODUCTS OF HYDRALAZINE HYDROCHLORIDE ON STORAGE

Product	Time (days)	Condition of storage	Assay per capsule/ (mg)	Cumulative Percentage Release					
			Time (hr)	1	2	3	5	7	9
			pH	1.2	2.5	3.5	7	7.5	7.5
EUDRAGIT RL100-RS100 COATED BEADS CAPSULE		Initial	51.3						
	15	I	51.1	30.2	41.6	57.8	74.7	95.2	101.2
		II	51.0	29.7	40.3	56.3	72.5	96.7	100.8
		III	50.9	29.8	42.3	58.1	75.6	95.3	102.4
		IV	50.8	30.9	40.8	56.2	74.5	95.6	101.6
	30	I	51.0	31.6	41.3	57.6	75.3	94.6	102.3
		II	50.8	30.2	40.6	56.2	76.2	95.6	101.2
		III	50.6	28.9	41.8	58.2	74.2	94.2	103.6
		IV	50.3	29.6	42.3	55.3	75.7	95.7	102.5
	60	I	50.7	30.2	40.3	56.8	73.8	97.8	101.6
		II	50.4	31.7	41.5	57.2	75.6	96.2	102.5
		III	49.8	28.6	42.3	57.6	74.8	95.3	100.6
		IV	49.4	29.6	43.7	58.1	74.5	96.3	103.2
	90	I	50.5	31.4	41.2	58.2	76.2	95.8	102.5
		II	50.3	30.7	42.6	57.6	74.3	97.1	101.6
		III	49.3	32.8	42.8	56.3	75.6	96.3	101.2
		IV	48.8	28.6	40.6	57. 8	73.9	95.1	100.3

Contd..

TABLE 5-5 : Contd.

Product	Time (days)	Condition of storage	Assay per tablet (mg)	Cumulative Percentage Release					
			Time (hr)	1	2	3	5	7	9
			pH	1.2	2.5	3.5	7	7.5	7.5
EUDRAGIT RLPM-RSPM MATRIX TABLETS		Initial	52.1						
	15	I	51.9	28.4	40.1	58.7	77.4	97.2	101.2
		II	51.8	29.4	40.1	56.2	76.2	96.3	101.5
		III	51.6	30.1	39.6	57.2	77.2	95.7	106.7
		IV	51.6	30.2	41.5	58.3	78.3	98.1	102.5
	30	I	51.8	29.6	42.6	58.3	77.8	98.6	101.5
		II	51.6	29.7	41.5	59.8	76.5	97.5	101.4
		III	51.4	27.8	42.1	56.3	75.4	96.8	103.5
		IV	51.1	29.7	40.3	59.2	78.3	95.7	99.7
	60	I	51.4	28.5	40.6	56.9	75.8	97.8	102.6
		II	51.3	29.7	40.2	58.8	76.8	98.1	97.6
		III	50.6	28.2	41.7	58.2	77.6	99.7	101.3
		IV	50.2	27.3	42.3	59.3	76.5	98.2	103.5
	90	I	51.2	29.6	41.3	58.9	76.3	99.7	103.2
		II	51.0	27.8	42.1	57.6	77.6	97.6	101.7
		III	50.1	28.4	40.6	59.7	75.9	96.3	100.8
		IV	49.6	29.7	41.5	57.9	75.8	95.3	102.9

Key : I - A.C. (20±2°C; 45±5% R.H.); II - Room temperature; III - 37°C, 65% R.H.; IV - 50°C.

FIG.- 5-3A: STABILITY STUDIES OF HYDRALAZINE HYDROCHLORIDE CONTROLLED RELEASE CAPSULE (50 mg.)

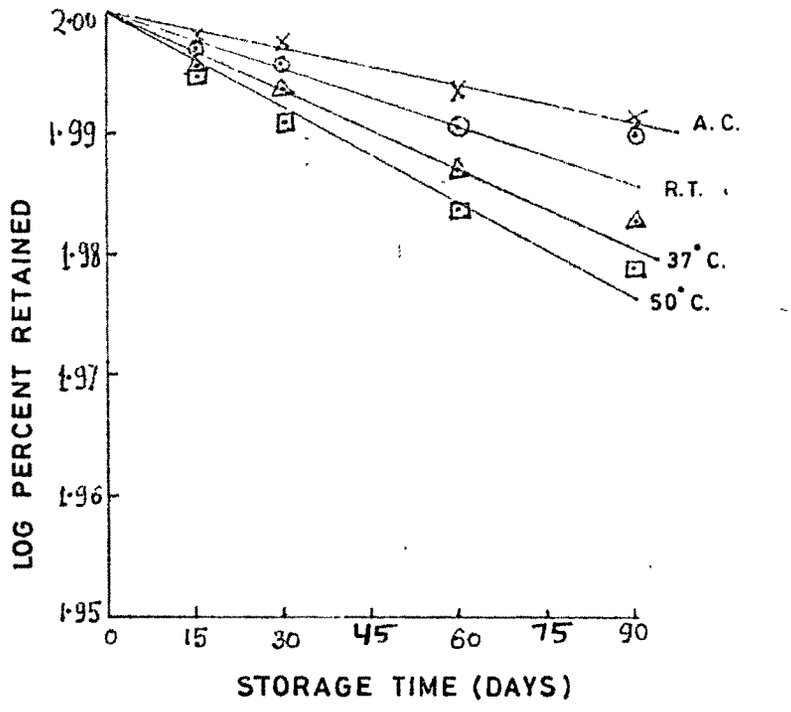

FIG.-5-3B: STABILITY STUDIES OF HYDRALAZINE HYDROCHLORIDE CONTROLLED RELEASE TABLET. (50mg)

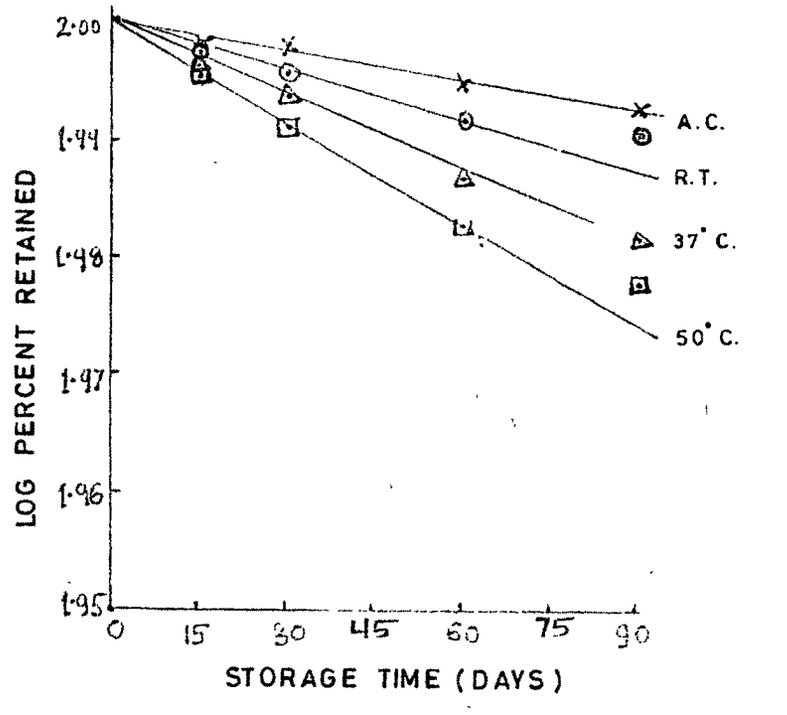

TABLE 5-6 : DEGRADATION RATE CONSTANT (K) AND SHELF LIFE OF SELECTED CONTROLLED RELEASE PRODUCTS OF HYDRALAZINE HYDROCHLORIDE AT VARIOUS CONDITIONS OF STORAGE

Product	Condition of storage	Degradation Rate constant ($mg\ day^{-1}$)	Shelf life (days)
EUDRAGIT RL100-RS100 COATED BEADS CAPSULE (50 mg) (A)	I	1.940×10^{-4}	537
	II	2.010×10^{-4}	514
	III	4.350×10^{-4}	239
	IV	5.424×10^{-4}	192
EUDRAGIT RLPM-RSPM MATRIX TABLETS (50 mg) (B)	I	1.957×10^{-4}	531
	II	1.987×10^{-4}	523
	III	4.720×10^{-4}	220
	IV	6.026×10^{-4}	173

Key : I A.C. (20±2°C, 45±5% R.H.)

II Room temperature

III 37°C, 65% R.H.

IV 50°C.

(4) No significant change was observed in release pattern of hydralazine hydrochloride from the products kept on stability at different conditions.

The controlled release capsule as well as tablet of hydralazine hydrochloride show no significant change in physical characteristics of these products. Both the products have shelf life of over a year at room temperature and for increasing shelf life to two years, it will be necessary to incorporate 5% excess of the drug. At other stress conditions, both the products have sufficient shelf life. There is no significant change in release pattern of hydralazine hydrochloride from the products kept on stability at different conditions.

The studies show that both the controlled release products need incorporation of 5% excess to enhance the shelf life of the products to two years.

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