CHAPTER III

FABRICATION, FORMULATION AND IN VITRO EVALUATION

Various techniques are employed to prolong drug action in the biological system, ranging from chemical modification of the drug molecule to the placement of the drug in a rate controlling dosage form. In addition, there are several biological approaches that one can take, such as suppression of drug elimination. However, the biological approach is usually applicable in restricted cases and is not routinely used for prolongation of drug action.

Physical approaches used for controlling drug release from oral dosage form can be classified into four systems based on their mode of controlling drug release. These systems are - diffusional control (1-5), dissolution control (6-10), ion exchange control (11-13) and osmotic pressure control (14) .

In the present investigation an attempt was made to fabricate and formulate controlled drug delivery systems of selected drugs based on diffusional and dissolution control systems. List of matrix and coating materials for the fabrication and formulation of controlled release drug delivery systems of tetracycline hydrochloride and hydralazine hydrochloride includes a wide variety of substances, both of natural and synthetic origin. Few of these materials are water-soluble while others are hydrophobic in nature. Some of these materials have pH dependent solubility while

solubilities of other materials are pH independent (throughout the pH of GI tract fluids). Choice of these materials mainly depends upon desired release rate modification and physico-chemical and biological characteristics of these drugs (15-20). Technique of preparation of dosage form, duration of action and protection against required environment also largely influence the selection of release controlling materials. For selecting these materials for present investigation the pH dependent solubility and other physico-chemical properties of drug and duration of action required have been given due consideration. The following materials, alone or in combination, were used during the present investigation :

a) Lipids and wax :

   i) Glyceryl monostearate
   ii) Glyceryl distearate
   iii) Bees wax

b) Hydrogels :

   Polyvinylpyrrolidone (P.V.P.)

c) Hydrophobic polymers/resins :
   (pH dependant)
   i) Cellulose acetate phthalate
   ii) Shellac
   iii) Eudragit S100 (co-polymers of methacrylic acid and methacrylic esters).

d) Hydrophobic polymers/resins :

(pH independant)

i) Eudragit RL100/RLPM (copolymer of acrylic and methacrylic acid esters with a low content of quarternary ammonium groups (1:40).

ii) Eudragit RS100/RSPM (copolymer of acrylic and methacrylic acid ester with a low content of quarternary ammonium groups (1:20).

Raw Materials

Following raw materials were employed in the present investigation.

Tetracycline hydrochloride oral grade (Synbiotics Ltd., India), Hydralazine hydrochloride (Sarabhai Chemicals, India), Succinic acid I.P. (Sarabhai M. Chemicals, India), Silica gel powder (E. Merck, Darmstadt, West Germany), Magnesium stearate (Chemical Supply Corpn., India), Talc (Chemical Supply Corpn., India), Polyvinylpyrrolidone K-30 (S.D. Fine Chem. Pvt. Ltd., India), Shellac (Chemical Supply Corpn., India), Cellulose acetate phthalate 50 CP (Wilson Bombay, India), Ethyl cellulose 5% 100 CP (Aldrich Chemical Company, Inc., USA), Glyceryl monostearate (Croda Chemicals, U.K.), Glyceryl distearate (Croda Chemicals, U.K.), Eudragits (Rohm Pharma GmbH, West Germany), White bees wax (Chemical Supply Corpn., India), Avicel (Cellulose Products of India, India), Lactose

(Chemicals Supply Corpn., India), Triacetin (Riedel-Dehaen AG Seelze-Hannover), Dibutyl phthate (Riedel-Dehaen A6 Sleelze-Hannover), Sorbiton monoleate (Hico Products Ltd., India), Propylene glycol L.R.(Sarabhai M. Chemicals, India), Ethyl alcohol absolute (Alembic Chemicals, India), Isopropanol (Sarabhai M., Chemicals, India), Methylene chloride pure (Sarabhai M. Chemicals, India), Carbon tetrachloride pure (Sarabhai M. Chemicals, India), Acetone pure (Sarabhai M. Chemicals, India), Sodium chloride G.R. (S.D. Fine Chem. Pvt. Ltd., India), Potassium phosphate monobasic L.R. (Sarabhai M. Chemicals, India), Sodium hydroxide A.R. (S.D. Fine Chem. Pvt. Ltd., India).

A. FABRICATION, FORMULATION AND EVALUATION OF TETRACYCLINE HYDROCHLORIDE PRODUCTS

Following three types of preparations were attempted in the present investigation.

1. Matrix Granules

a. Preparation of Granules :

Tetracycline hydrochloride, succinic acid, silica gel and talc were taken in a planetary mixer attached to Erweka unit (Erweka Apparatebau, West Germany) in following proportion :

Tetracycline hydrochloride 100%	100 g
Succinic acid	15 g
Silica gel	0.5 g
Talc	0.5 g

After thorough mixing, the mix was granulated with a mixture of 27 ml of the 20% w/w solution of polyvinyl-pyrrolidone in isopropranolol and 13 ml of the 40% w/w shellac solution in isopropanol or 10% w/w cellulose acetate phthalate solution in acetone. Wet mass was then passed through a 20 mesh sieve. The granulation was dried at 40°C in a vacuum dryer (Ganson, India) and then sieved using a 16 mesh and retained at 50 mesh. The resulting granules had a yield of 60 to 75%.

b. Coating of Granules :

The above granules were placed in a small coating pan (7.5" diameter) attached to Erweka unit and wetted regularly with a solution of 85 parts of 20% w/w polyvinylpyrrolidone solution and 15 parts of 40% w/w shellac solution or 70 parts of 20% w/w polyvinylpyrrolidone solution and 30 parts of 10% w/w cellulose acetate phthalate solution. After each wetting, homogenous mixture of tetracycline hydrochloride, succinic acid and silica gel was applied in small proportions. Mixture has following composition :

Tetracycline hydrochloride 100%	150 g
Succinic acid	22.5 g
Silica gel	7.5 g

After each application the granules were dried by the introduction of hot air into the pan. During this phase of operation no talc was used, as it would make the granules too heavy. Varying number of such coats were applied in this fashion and then the granules were sieved between 20 mesh and retained on 40 mesh. The granules thus produced were finally covered with coating devoid of active ingredient. The granules were dried through introduction of hot air in the pan so that no special drying was necessary.

Granules equivalent to 500 mg of tetracycline hydrochloride were filled in No. 00 hard gelatin capsules and subjected to *in vitro* dissolution studies.

2. Coated Beads

a. Preparation of beads :

Beads of tetracycline hydrochloride were prepared using pelleter EXDS-60 type (Fuji Paudal Co. Ltd., Osaka, Japan) and marumerizer Q-230 type (Fuji Paudal Co. Ltd., Osaka, Japan). Weighed quantities of tetracycline hydrochloride, succinic acid and other excipients (such as lactose, dicalcium phosphate etc.) were mixed thoroughly and the mix

was wetted with required amount of polyvinylpyrrolidone in isopropanol (25% w/v). Wet mass was passed through pelleter (shaft speed 40 rpm). Care was taken in feeding material into the pelleter to avoid overloading. The pellets so obtained were rotated in marumerizer (30 seconds, thrice) using 4-5 mm size marume plate at the speed of 600 rpm to obtain spherical beads of suitable size. However, tetracycline hydrochloride, succinic acid and avicel mixture wetted with polyvinylpyrrolidone in isopropanol (25% w/v) solution with following composition gave most satisfactory beads.

Tetracycline hydrochloride	100%	650 g
Succinic acid		65 g
Avicel		205 g
Polyvinylpyrrolidone		80 g

After drying, beads were screened and 16/40 mesh portion was used for coating. The resulting beads had a yield of 85-95%.

b. Coating of beads :

About 200 g of beads were placed in a small coating pan (7.5" diameter) attached to Erweka unit and coated differentially with ethyl cellulose, cellulose acetate phthalate, glyceryl monostearate, glyceryl distearate, eudragit S100, eudragit RL100, eudragit RS100 solutions employing a Pilot

spray gun type-59 (Pilot, Manik Mfg. Pvt. Ltd., India). The composition of different coating solutions was as follows :

1. Ethyl cellulose solution

Ethyl cellulose	5 g
Propylene glycol	1 g
Ethyl alcohol absolute to make 100 ml	q.s.

2. Cellulose acetate phthalate solution :

Cellulose acetate phthalate	12 g
Propylene glycol	3 g
Sorbiton monooleate	1 g
Ethyl alcohol	45 ml
Acetone to make 100 ml	q.s.

3. Glyceryl monostearate solution :

Glyceryl monostearate	30 g
Bees wax	2.86 g
Carbon tetrachloride to make 100 ml	q.s.

4. Glyceryl distearate solution :

Glyceryl distearate	25 g
Carbon tetrachloride to make 100 ml	q.s.

5. Eudragit S100 solution :

Eudragit S100	12.5 g
Magnesium stearate	0.5 g
Triacetin	0.2 g
Isopropanol	84 ml
Purified water	3 ml

6. Eudragit RL100 solution :

Eudragit RL100	12.5 g
Magnesium stearate	0.5 g
Dibutyl phthalate	0.5 g
Methylene chloride and Isopropanol (1:1) to make 100 ml	q.s.

7. Eudragit RS100 solution :

Eudragit RS100	12.5 g
Dibutyl phthalate	0.5 g
Magnesium stearate	0.5 g
Methylene chloride and Isopropanol (1:1) to make 100 ml	q.s.

8. Eudragit RL100-RS100 solution :

Eudragit RL100	6.25 g
Eudragit RS100	6.25 g
Magnesium stearate	0.5 g
Dibutylphthalate	0.5 g
Methylene chloride and Isopropanol (1:1) to make 100 ml	q.s.

Quantities of drug, excipients and coating material were altered and effect of these alterations on release of tetracycline hydrochloride was studied. In another set of experiments avicel was partially (10%) replaced with eudragit RSPM and release of the drug was studied after coating of the beads of this composition.

Beads equivalent to 500 mg of tetracycline hydrochloride were filled in capsules and subjected to *in vitro* evaluation.

3. Matrix Tablets

a. Preparation of matrix tablets by coating method :

Weighed quantities of tetracycline hydrochloride, succinic acid, and lactose were thoroughly mixed and granulated with required amount of polyvinylpyrrolidone in isopropanol (25% w/v solution). Wet mass was dried at 40°C and 16/40 mesh fraction was used for further studies. It has resulted in a yield of 75-80%.

Weighed quantity of granules (about 200 g) was placed in a small coating pan (7.5" diameter) attached to Erweka unit and coated differentially with glyceryl monostearate solution or glyceryl distearate solution, having same composition as that used in coating of beads, employing a Pilot spray gun type 59 at a temperature of 70±5° and 55±5°C respectively. Coated granules were lubricated with the talc and compressed into special oblong shape tablets (0.72" x 0.36") using a single punch machine (Kilburn, India) as per following specifications.

Tablet weight	: 1.1 g
Gauge	: 18-19
Hardness	: 21-22 Strong-Cobb unit

Tablets had following composition :

Tetracycline hydrochloride 100%	50 g
Succinic acid	5 g
Polyvinylpyrrolidone	3.3 g
Glyceryl monostearate with bees wax or glyceryl distearate	5-50 g
Talc	1.7 g
Lactose	45-0 g

Tablets were subjected to <u>in vitro</u> dissolution studies.

(b) <u>Preparation of matrix tablets by acetone exposure</u> :

Weighed amount of tetracycline hydrochloride, succinic acid, eudragit RLPM and/or RSPM were mixed thoroughly and wet granulated with polyvinylpyrrolidone in isopropanol (25% w/v solution). Wet mass was dried at 50°C and passed through 16 mesh. Granules after lubrication with talc were compressed into oblong special shape (0.72" x 0.36") tablets using single punch machine as per following specifications :

Tablet weight	: 1.1 g
Gauge	: 24-26
Hardness	: 20-21 Strong Cobb units

Tablets had following composition :

Tetracycline hydrochloride 100%	50 g
Succinic acid	5 g
Polyvinylpyrrolidone	3.3 g

Eudragit RLPM and/or RSPM	5-50	g
Talc	1.7	g
Avicel	45-0	g

Compressed tablets were placed in a small vacuum dryer and a vacuum (29" of Hg) was created inside the dryer chamber with the help of a vacuum pump. About 200 ml of acetone was sucked inside the dryer chamber and vacuum was broken. Temperature of the dryer chamber was adjusted to 40°C and tablets were exposed to acetone vapours for a period sufficient to form uniform matrix (about 2 hours). Finally tablets were dried at 40°C for 24 hours and subjected to in vitro dissolution studies.

DISSOLUTION STUDIES

Dissolution studies were carried out using a basket stirrer assembly of USP XX (21) dissolution test apparatus at a stirrer speed of 100 rpm and the dissolution media temperature was held at 37±0.5°C. 900 ml each of 1.2, 2.5, 4.5, 7.0 and 7.5 pH dissolution media were prepared and changed at different intervals of time as per the method recommended in N.F. XIV (22), under "Timed Release Tablet and Capsules In Vitro Test Procedure". Aliquots of samples were withdrawn at 1.0, 2.0, 3.5, 5.0, 7.0 and 9.0 hr and equal volume of fresh dissolution medium was added. Absorbance of the suitably diluted solution was measured at

maximum of 353 nm on a Hitachi-Perkin Elmer 139 UV visible spectrophotometer after adjusting the pH of the solution to 1.0. Observations on release of the drug from products are recorded in Tables 3-1 to 3-18 and shown graphically in Figures 3-1 to 3-17.

Mathematical Calculations for Loading and Maintenance Doses

A number of investigators have applied rigorous pharmacokinetic principles to design sustained release dosage forms (23-26). Equations, based on the release characteristics of such hypothetical dosage forms, describing the time course of the drug in the plasma following their administration are relatively simple to develop. However, formulation of sustained release preparations which will yield these ideal plasma level-time profiles is considered to be an exceedingly difficult technical problem.

The initial dose in a multiple dosage regimen is usually the dose that provides the desired concentration at the receptor site, and all subsequent doses are intended to more or less maintain this concentration. Reformulation to reduce frequency does not require a significant change in the initial dose, only knowledge of the replacement rate, so that the biological effect can be maintained constant. When the initial dose is estimated from multiple dose data, the dose (D) is the quantity needed to produce B (quantity of

drug that must be maintained at the receptor site). The correction for irreversible binding and/or degradation of drug in depot (1/F) is not required, when D is calculated from multiple dose data.

The amount of tetracycline hydrochloride to be taken as loading dose and maintenance dose in the preparation of controlled release products was calculated based on the reported pharmacokinetic data (27-29) considering the average weight of an individual as 60 kg with a view to maintain an average therapeutic blood level concentration of about 3 µg/ml of the serum at steady state after multiple dosing of the product (250 mg controlled release products). Loading dose was calculated based on equation

$$Dt = Vd \cdot Pt$$

where, Vd is the apparent volume of distribution and Dt and Pt represent respectively the total amount of the drug in the body and the concentration of the drug in the blood at any time, t. Substituting the values of Vd and Pt.

$$Dt = \frac{1.3 \times 1000 \times 60 \times 0.8}{1000} = 62.4 \text{ mg}$$

where Vd = 1.3 litres kg^{-1}; body weight = 60 kg; serum level at 1 hour = 0.8 µg ml^{-1}

Since only 77% of the orally administered drug is available, the amount of the drug needed to be administered

would be

$$\frac{62.4 \times 100}{77} = 81 \text{ mg i.e} 32.4\% \text{ of total dose}$$

For calculating the maintenance dose the rate of elimination of tetracycline hydrochloride at steady state was considered.

$$\therefore \text{ Rate of elimination} = \frac{3 \times 1.9 \times 60 \times 60}{1000}$$

$$= 20.52 \text{ mg hr}^{-1}$$

where Clearance = 1.9 ml $\text{min}^{-1}\text{kg}^{-1}$, serum level at steady state = 3 µg/ml.

Hence in order to maintain the blood level, the amount of drug need to be released as the maintenance dose from the products, considering that only 77% of the orally administered drug is available, would be :

$$\frac{20.52 \times 100}{77} = 26.65 \text{ mg hr}^{-1} \text{ i.e. } 10.66\% \text{ of total drug hr}^{-1}$$

Product is required to release 81 mg as loading dose (i.e. initially) and then 26.65 mg of drug per hour in 2nd and subsequent hours till total drug (250 mg) is released.

For 500 mg tetracycline hydrochloride controlled release products, both loading and maintenance doses were doubled to achieve higher serum levels.

RESULTS AND DISCUSSION

1. Matrix Granules

Products of this type consist of matrix formed of tetracycline hydrochloride, shellac-polyvinylpyrrolidone or cellulose acetate phthalate-polyvinylpyrrolidone, and an organic acid. The resulting granules had a yield of 60-70%.

Observations of the release of the drug from this type of products are recorded in Tables 3-1 and 3-2 and shown graphically in Figures 3-1 and 3-2.

(a) $T_{50\%}$ (time required for dissolution of 50% of the drug) values, as shown in figures, increase with increase in the amount of sustaining material applied.

(b) Following products of the two matrices tried with a release pattern close to the desired one were subjected to *in vitro* dissolution test in triplicate and observations are shown in Table 3-18.

	Product No.
Shellac-P.V.P. matrix capsule	7
Cellulose Acetate phthalate-P.V.P. matrix capsule	10

Results show large inter-capsule variation in the release pattern of the drug (i.e. larger standard deviation).

TABLE 3-1 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM SHELLAC-P.V.P. MATRIX CAPSULES.

PRODUCT No.	AMOUNT OF SHELLAC-P.V.P. 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
1	10.0-12.7	82.5	85.5	101.2	-	-	-
2	20.0-25.4	72.6	95.5	98.2	-	-	-
3	30.0-38.1	68.6	80.6	93.5	99.7	-	-
4	40.0-50.8	56.2	71.7	85.5	101.7	-	-
5	50.0-63.5	49.9	63.8	78.5	94.5	104.6	-
6	60.0-76.2	36.7	58.5	74.6	90.5	90.7	-
7	70.0-88.9	30.6	55.3	70.5	88.2	100.2	-
8	80.0-101.6	28.7	55.8	71.3	85.6	95.3	101.3
9	90.0-114.3	25.5	57.6	68.3	83.5	93.6	98.5
10	100.0-127.0	25.8	52.3	68.5	81.5	92.6	103.2

FIG. 3-1 CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM SHELLAC P.V.P. MATRIX CAPSULES

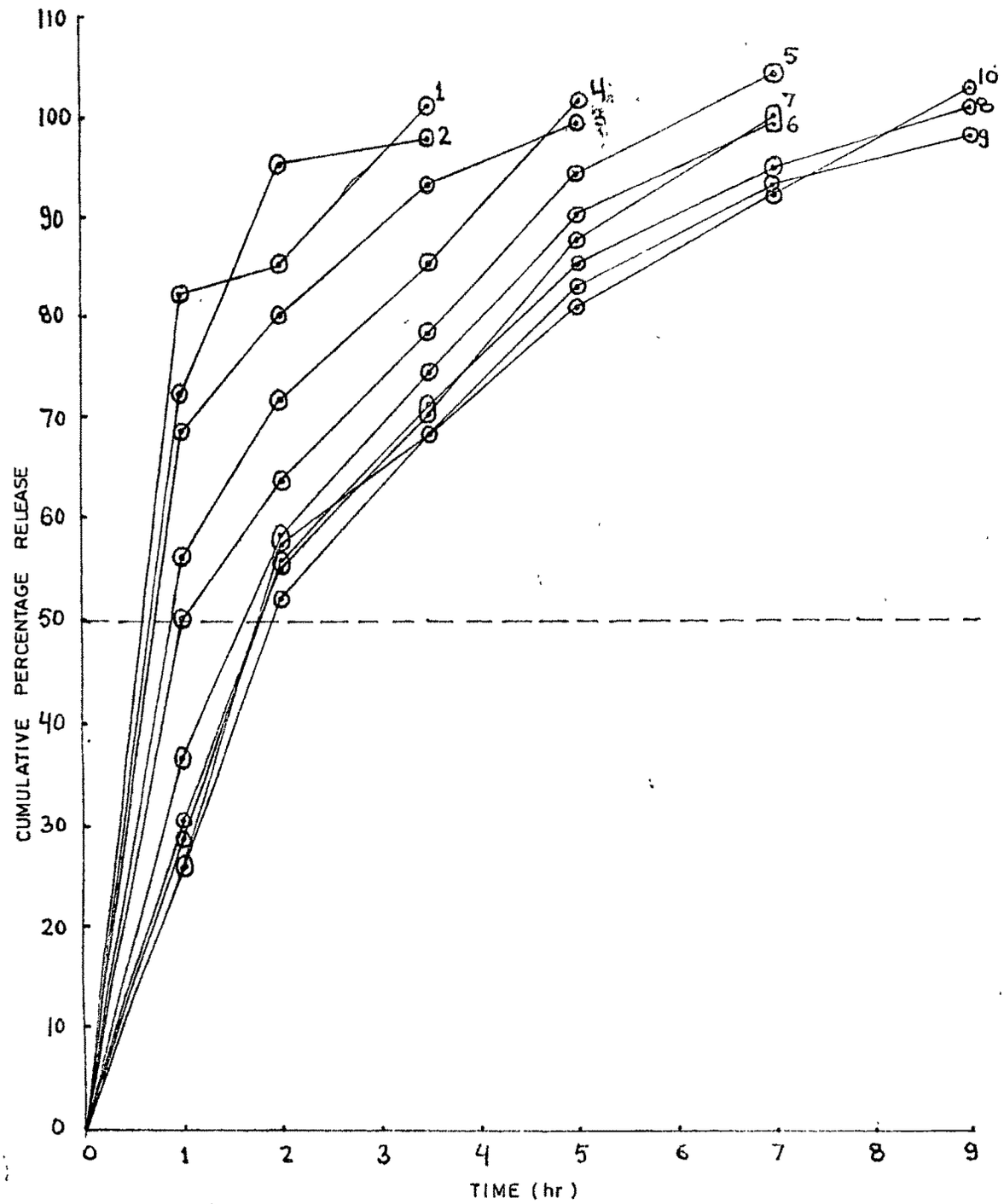
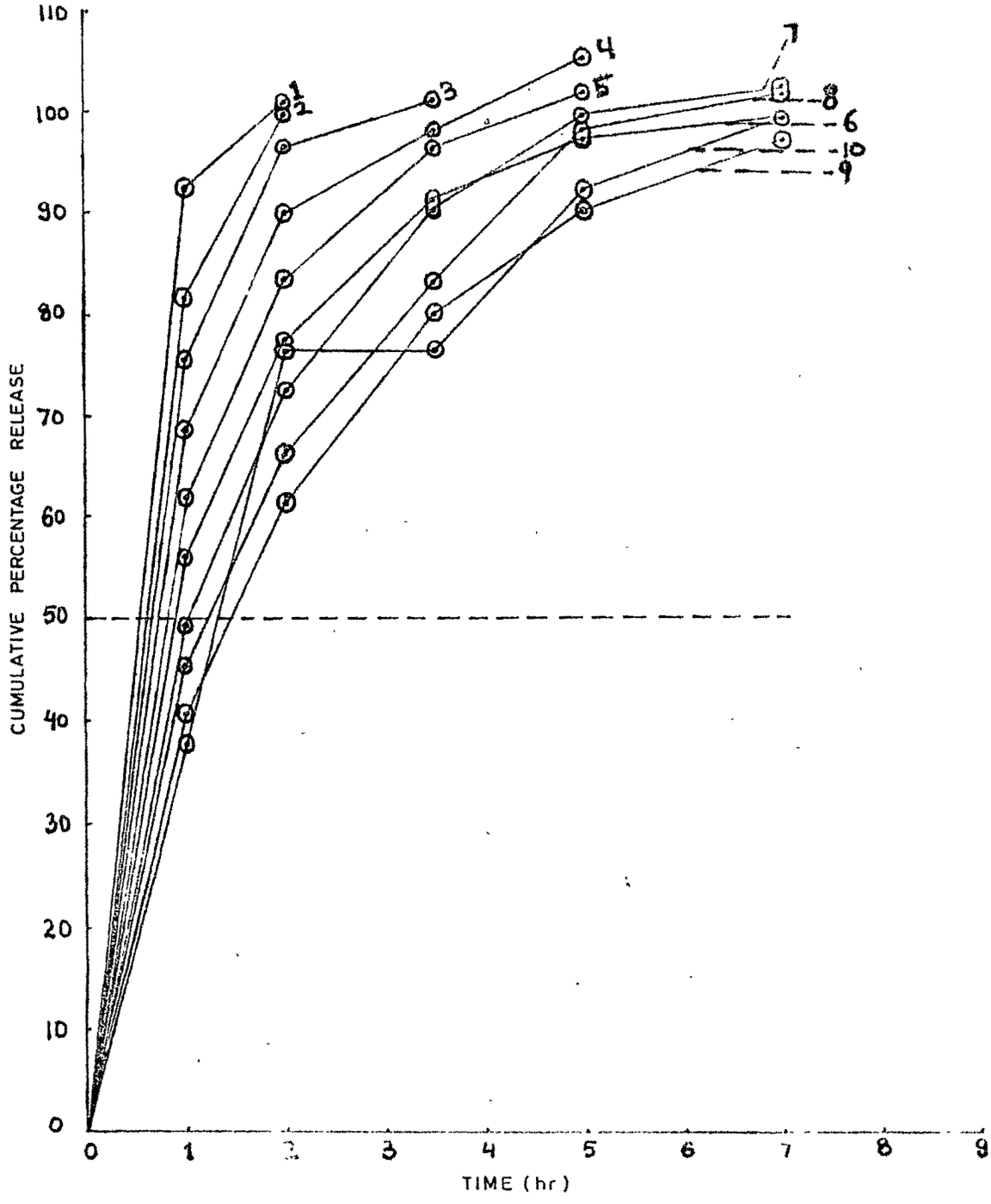


TABLE 3-2 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM CELLULOSE ACETATE PHTHALATE-P.V.P. MATRIX CAPSULE.

PRODUCT No.	AMOUNT OF C.A.P:- P.V.P. 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
1	10-11		92.3	101.2	-	-	-	-
2	20-22		81.5	99.7	-	-	-	-
3	30-33		75.6	96.6	101.3	-	-	-
4	40-44		68.7	90.2	98.3	105.6	-	-
5	50-55		61.5	83.5	96.5	102.1	-	-
6	60-66		55.7	77.5	91.5	97.6	99.5	-
7.	70-77		49.3	72.5	90.5	99.7	102.7	-
8	80-88		45.3	66.7	83.5	98.5	102.1	-
9	90-99		40.3	61.3	80.2	90.5	97.5	-
10	100-110		37.6	56.5	76.5	92.5	99.7	-

FIG. 3-2: CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM CELLULOSE ACETATE PHTHALATE P.V.P. MATRIX CAPSULES



Product of this type consists of matrix formed of tetracycline hydrochloride, succinic acid, sustaining materials and excipients. Succinic acid was included in the matrix to prevent the hydrolysis of tetracycline hydrochloride at pH value of 3 or more (as upon leaving the stomach) and resultant precipitation of the drug as base. This is necessary to make the drug available for absorption throughout the GI tract (30).

Method of preparation of such matrices was found to be tedious and giving a lower yield. Results of release of the drug from the products tested in triplicate show lesser reproducibility. Hence the products of this type were not subjected to further studies.

2. Coated Beads

Tetracycline hydrochloride beads were coated differentially with ethyl cellulose, cellulose acetate phthalate, glyceryl monostearate-bees wax, glyceryl distearate, eudragit S100, eudragit RL100 and eudragit RS100 separately and in combination. Products of this type consist of tetracycline hydrochloride, avicel, an organic acid and excipients in core coated with different coating material. The resulting beads had a yield of 85-95%.

Observations on release of the drug from this type of products are recorded in Tables 3-3 to 3-12 and shown graphically in Figures 3-3 to 3-12.

(a) $T_{50\%}$ values, as shown in figures, increase with an increase in percentage of the coating material applied to beads in each case. However, extent of prolongation vary from one coating material to the other and was found to follow the order : eudragit RS100 > eudragit RL100 > cellulose acetate phthalate > ethyl cellulose > eudragit S100 > glyceryl distearate > glyceryl monostearate - white bees wax.

(b) Following products of different coating materials with a release pattern close to the desired one were subjected to in vitro dissolution test in triplicate and observations are shown in Table 3-18.

		Product No.
Glyceryl monostearate-Bees wax coated beads	mix of	5 and 10 (1:1)
Glyceryl distearate coated beads		5
Cellulose acetate phthalate coated beads	mix of	3 and 5 (1:1)
Eudragit S100 coated beads	mix of	3 and 6 (1:1)
Eudragit RL100-RS100 coated beads	mix of plain beads, 12, and 9 (1:3.6)	

Glyceryl monostearate-bees wax, glyceryl distearate, cellulose acetate phthalate, and ethyl cellulose coated beads show larger inter-capsule

variation (i.e. standard deviation) in release pattern of tetracycline hydrochloride. However, eudragit S100, eudragit RL100 and/or RS100 coated beads show less variation (standard deviation) in release of the drug from capsule to capsule.

(c) Eudragit S100 coated beads show reasonably good sustained action with less inter-capsule variation in release pattern of the drug. This coating material being soluble at pH 7; with increase in percentage of coating of eudragit S100, release of the drug in acidic medium decreases considerably. Release pattern tends to shift to a region having pH value of 7.00 or more.

(d) Eudragit RL100 and eudragit RS100 coated beads show good sustained action with less inter-capsule variation in release of the drug. The release of the drug from these beads was found to be independent of the pH of the dissolution medium.

(e) Replacing part of avicel inside the beads by eudragit RS (as RSPM) incorporated during the preparation of beads followed by coating eudragit RS100 helps in further delay in the release of the drug (Table 3-12). But this requires more amount of eudragit RS to obtain similar results as coating of plain beads. However, the results were found to be reproducible.

TABLE 3-3 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM GLYCERYL MONOSTEARATE COATED BEADS.

PRODUCT No.	PERCENTAGE OF COATING	CUMULATIVE PERCENTAGE RELEASE					
		TIME (hr)	1	2	3.5	5	7	9
		pH	1.2	2.5	4.5	7	7.5	7.5
1	5		90.2	101.2	-	-	-	-
2	10		80.2	99.3	-	-	-	-
3	15		71.2	103.4	-	-	-	-
4	20		57.2	91.5	102.3	-	-	-
5	25		41.3	82.1	99.3	101.5	-	-
6	30		35.7	71.5	90.7	105.6	-	-
7	35		31.5	58.6	85.6	98.6	-	-
8	40		25.7	48.3	78.5	93.2	102.1	-
9	45		21.3	33.7	70.3	92.3	94.3	-
10	50		18.3	30.1	62.3	86.5	105.6	-
11	55		13.3	25.1	51.2	81.5	99.7	101.5
12.	60		8.7	15.7	52.3	78.6	95.3	103.5
13	65		8.3	16.7	45.3	71.5	88.3	98.5
14	70		6.7	10.7	40.3	68.5	81.5	93.2
15	75		5.3	11.5	35.5	55.7	75.6	91.3

FIG. 3-3: CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM GLYCERYL MONOSEARATE COATED BEADS

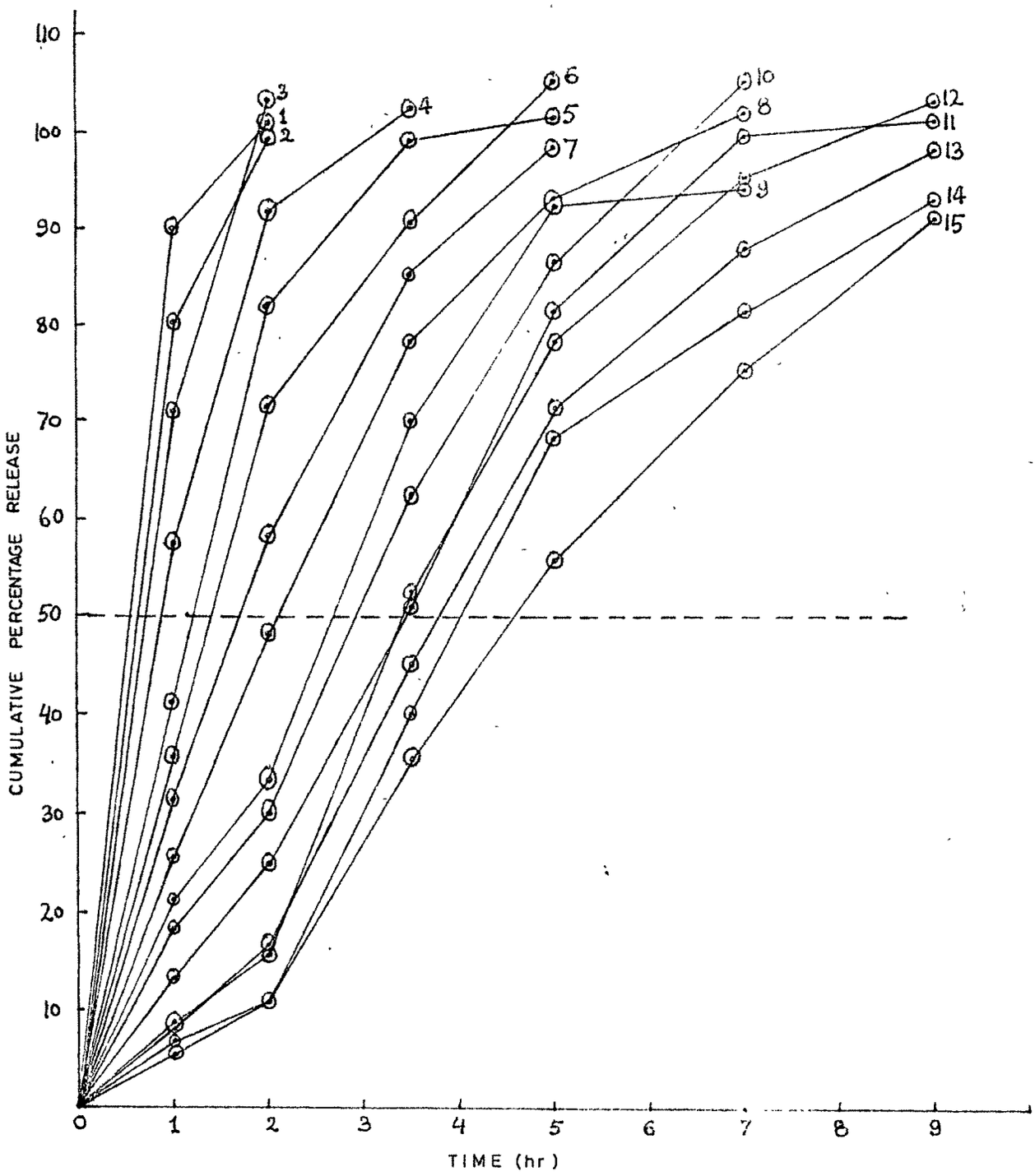


TABLE 3-4 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM GLYCERYL DISTEARATE COATED BEADS.

PRODUCT No.	PERCENTAGE OF COATING	CUMULATIVE PERCENTAGE RELEASE					
		TIME (hr)	1	2	3.5	5	7	9
		pH	1.2	2.5	4.5	7	7.5	7.5
1	5		85.9	100.3	-	-	-	-
2	10		81.6	97.9	99.0	-	-	-
3	15		67.4	95.2	99.3	-	-	-
4	20		47.2	70.3	95.6	100.3	-	-
5	25		30.2	51.4	81.4	102.6	102.9	-
6	30		22.0	41.8	71.9	100.5	102.0	-
7	35		12.4	28.1	61.7	94.8	99.1	-
8	40		11.1	20.7	53.8	89.9	101.9	-
9	45		10.8	15.1	29.2	55.3	100.0	102.1
10	50		6.2	9.2	19.3	49.4	86.5	101.6
11	55		2.4	7.6	15.7	42.9	75.1	102.0
12	60		1.9	6.6	13.8	38.4	66.5	94.2
13	65		1.8	6.5	12.5	36.8	63.9	94.2
14	70		1.7	4.9	10.2	31.8	56.4	87.1
15	75		1.5	5.1	10.1	31.4	52.6	85.1

FIG. 3-4 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM GLYCERYL DISTEARATE COATED BEADS

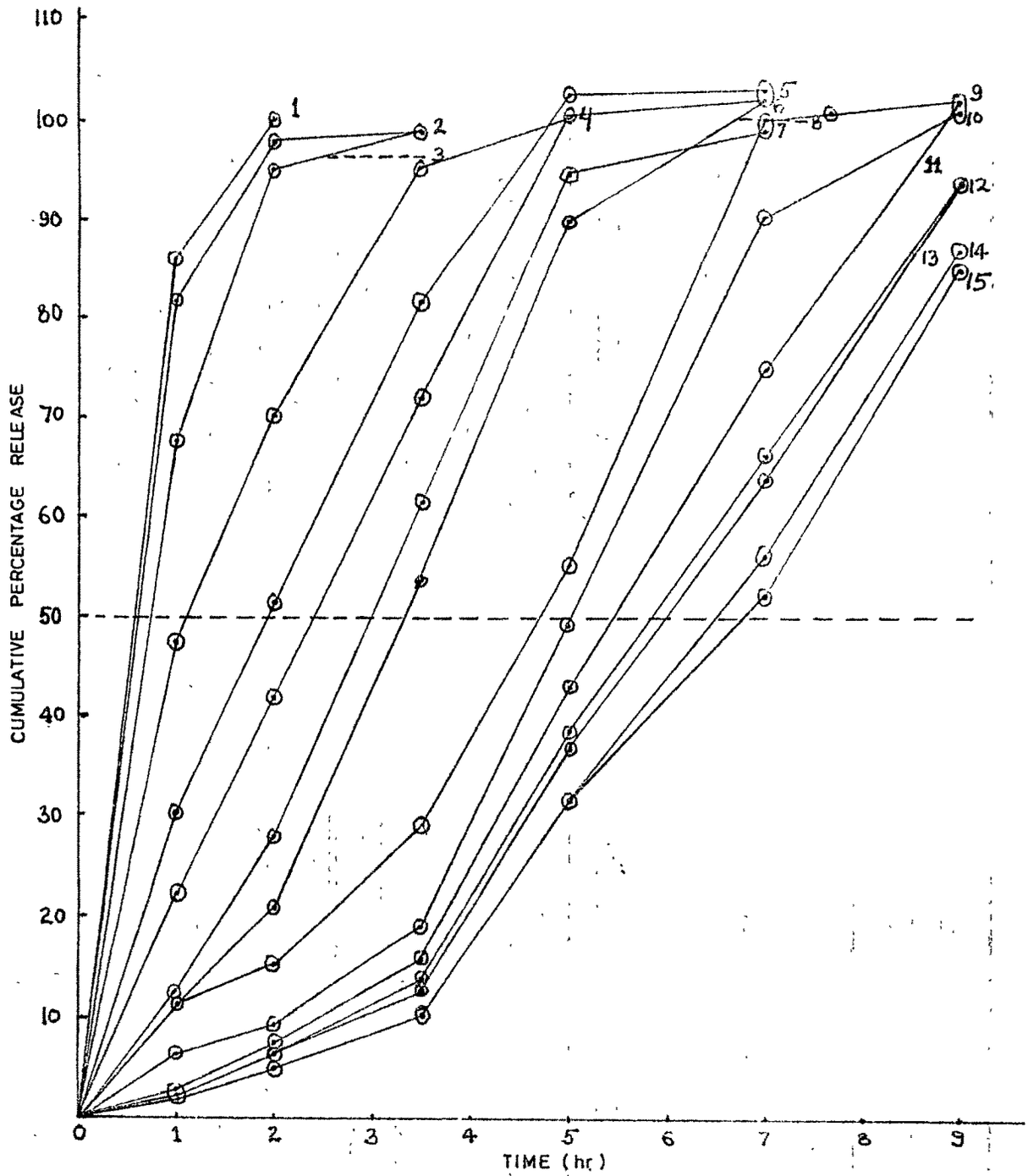


TABLE 3-5 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM CELLULOSE ACETATE PHTHALATE COATED BEADS.

PRODUCT No.	PERCENTAGE OF COATING	CUMULATIVE PERCENTAGE RELEASE					
		TIME (hr)	1	2	3.5	5	7	9
		pH	1.2	2.5	4.5	7	7.5	7.5
1	5		78.5	88.5	99.7	-	-	-
2	10		62.5	84.5	102.3	-	-	-
3	15		41.3	76.3	89.7	103.6	-	-
4	20		21.7	48.3	78.5	96.3	-	-
5	25		13.3	36.4	62.1	84.3	104.6	-
6	30		6.3	25.6	45.3	76.5	99.8	-
7	35		3.1	16.3	36.7	68.5	85.6	101.2
8	40		1.2	11.5	31.5	63.6	81.2	96.7
9	45		-	6.3	20.7	81.2	78.5	91.5
10	50		-	1.5	15.6	43.4	70.6	82.3

FIG. 3-5 CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM CELLULOSE ACETATE PHTHALATE COATED BEADS

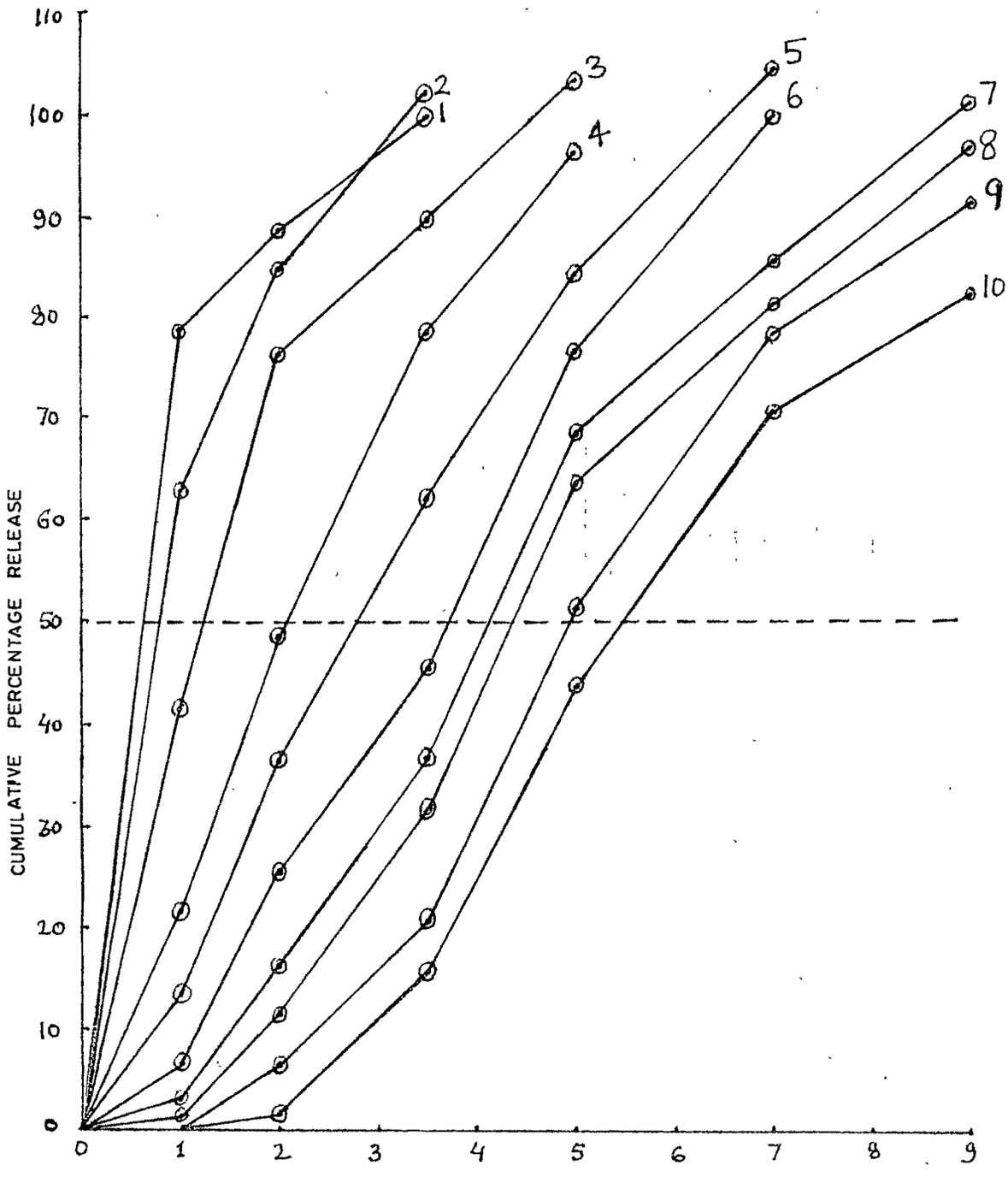


TABLE 3-6 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM ETHYL CELLULOSE COATED BEADS

PRODUCT No.	PERCENTAGE OF COATING	CUMULATIVE PERCENTAGE RELEASE					
		TIME (hr)	1	2	3.5	5	7	9
		pH	1.2	2.5	4.5	7	7.5	7.5
1	2.5		89.6	101.5	-	-	-	-
2	5		82.3	99.7	-	-	-	-
3	7.5		71.7	90.6	101.3	-	-	-
4	10		76.2	87.9	102.5	-	-	-
5	12.5		62.3	78.6	98.3	-	-	-
6	15		50.3	70.0	92.5	106.3	-	-
7	17.5		43.6	61.5	88.5	99.7	-	-
8	20		31.5	55.3	87.5	93.6	101.2	-
9	22.5		37.6	58.3	82.5	95.7	97.3	-
10	25		22.6	49.7	78.6	87.6	93.5	100.3

FIG. 3-6: CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM ETHYL CELLULOSE COATED BEADS

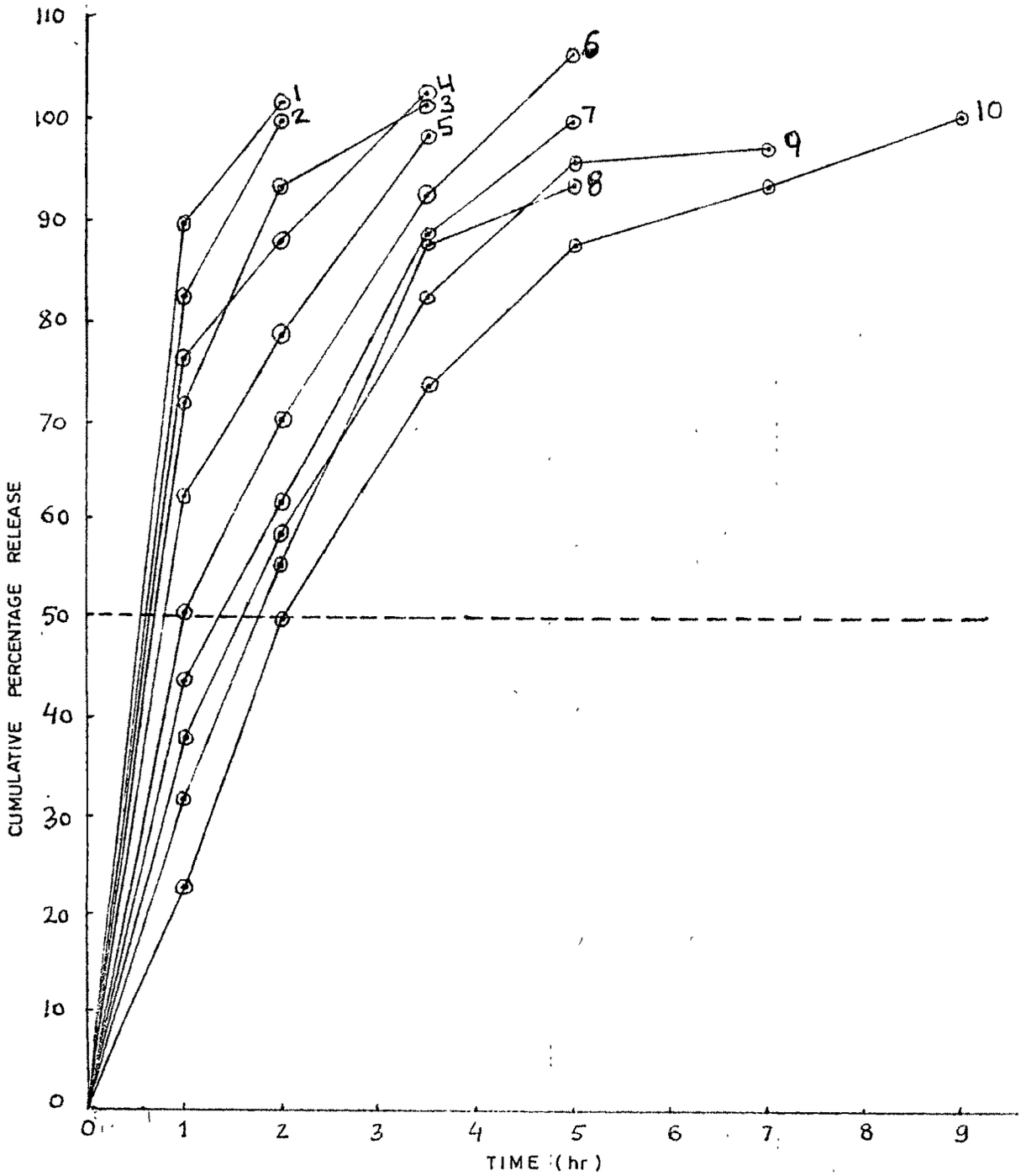


TABLE 3-7 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM EUDRAGIT S100 COATED BEADS.

PRODUCT No.	PERCENTAGE OF COATING	CUMULATIVE PERCENTAGE RELEASE					
		TIME (hr)	1	2	3.5	5	7	9
		pH	1.2	2.5	4.5	7	7.5	7.5
1	5		85.2	103.5	-	-	-	-
2	10		65.6	87.5	97.5	-	-	-
3	15		45.5	68.2	88.6	103.5	-	-
4	20		25.6	58.2	81.4	98.8	-	-
5	25		15.2	43.5	68.3	90.3	101.8	-
6	30		13.2	31.6	55.2	78.5	99.2	-
7	35		6.5	11.8	46.2	68.7	95.3	103.5
8	40		2.1	11.5	35.6	56.8	86.2	99.5
9	45		-	5.6	25.6	48.3	81.5	101.5
10	50		-	2.1	12.3	41.6	74.3	96.7

FIG. 3-7: CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM EUDRAGITS-100 COATED BEADS

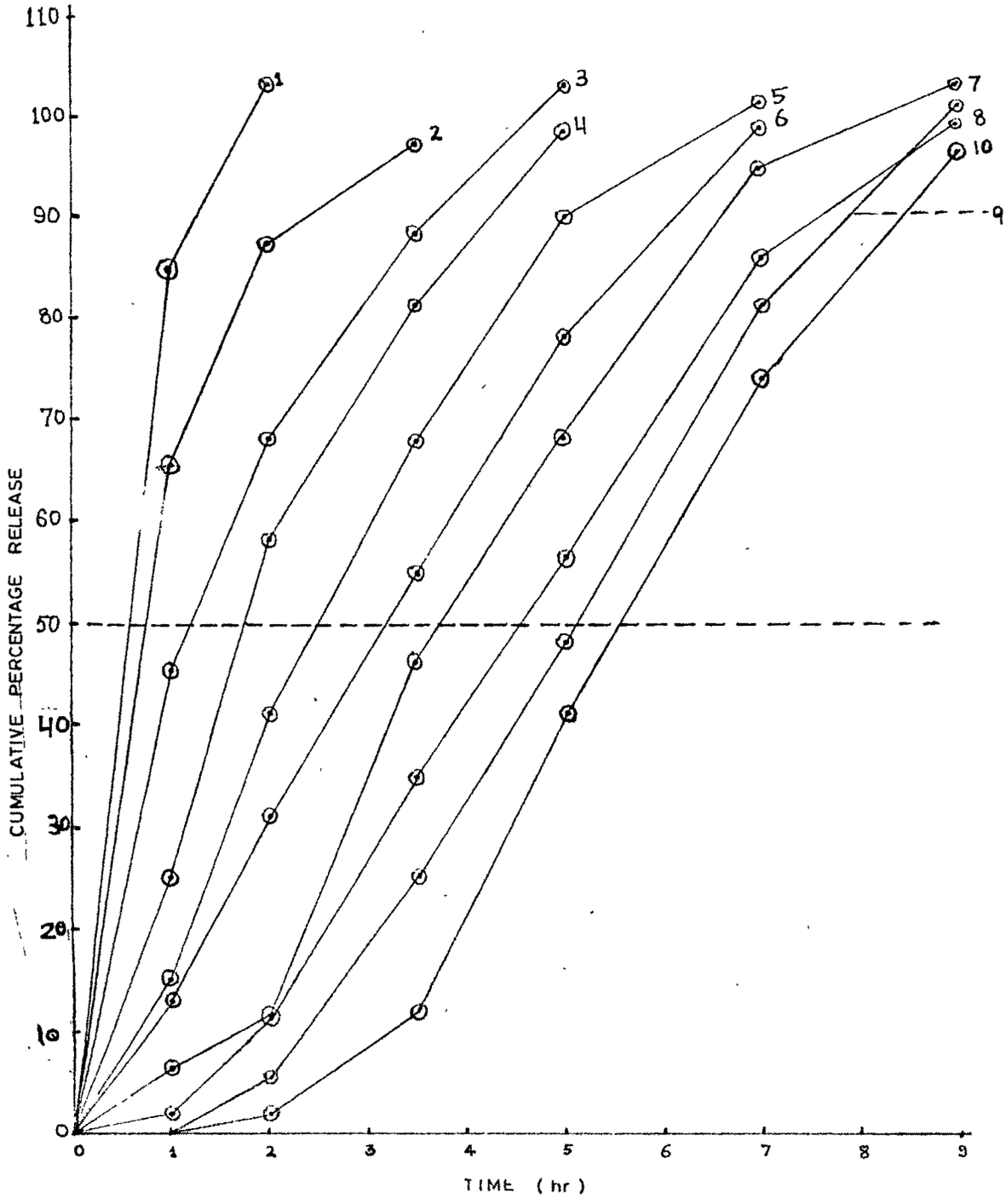


TABLE 3-8 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM EUDRAGIT RL100 COATED BEADS.

PRODUCT No.	PERCENTAGE OF COATING	CUMULATIVE PERCENTAGE RELEASE					
		TIME (hr)	1	2	3.5	5	7	9
		pH	1.2	2.5	4.5	7	7.5	7.5
1	5		76.5	88.2	103.5	-	-	-
2	10		61.6	76.2	101.3	-	-	-
3	15		51.8	70.3	95.7	103.5	-	-
4	20		35.7	62.5	91.5	101.6	-	-
5	25		25.7	48.3	79.6	98.3	103.6	-
6	30		22.5	45.5	70.3	95.7	99.3	-
7	35		13.6	40.2	65.7	85.6	101.6	-
8	40		9.7	31.7	59.3	78.3	95.6	101.2
9	45		8.9	25.6	50.6	72.5	90.3	98.7
10	50		6.5	18.7	43.3	65.3	82.5	93.5

FIG. 3-8: CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM EUDRAGIT RL-100 COATED BEADS

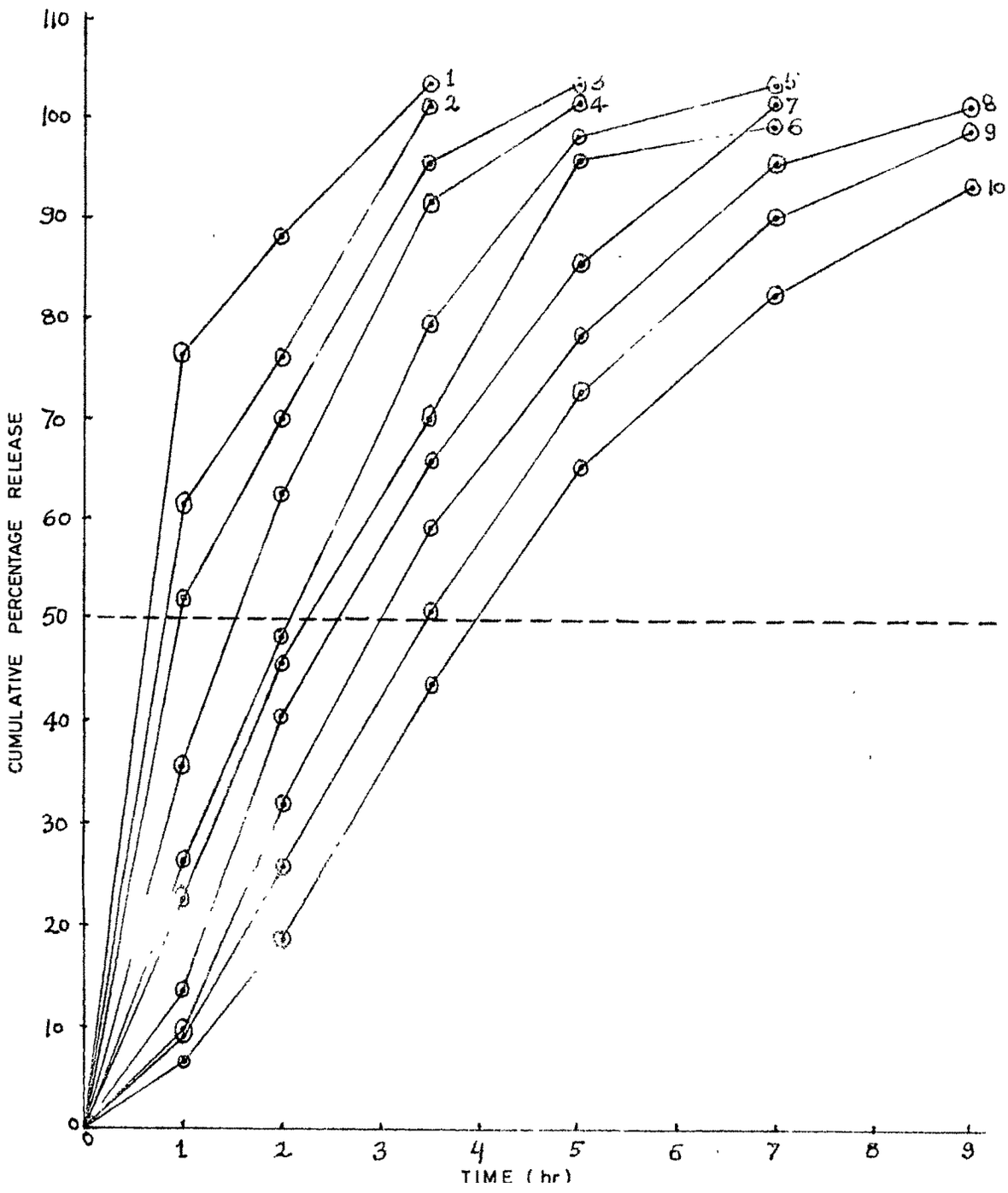


TABLE 3-9 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM EUDRAGIT RS100 COATED BEADS.

PRODUCT No.	PERCENTAGE OF COATING	CUMULATIVE PERCENTAGE RELEASE					
		TIME (hr)	1	2	3.5	5	7	9
		pH	1.2	2.5	4.5	7	7.5	7.5
1	5		50.2	70.3	91.8	97.9	-	-
2	10		41.1	64.6	89.3	99.3	-	-
3	15		30.9	59.0	88.1	100.2	-	-
4	20		20.6	38.1	70.2	98.6	99.4	-
5	25		19.8	36.9	66.2	97.9	99.0	-
6	30		17.3	36.6	63.6	96.3	100.6	-
7	35		9.5	20.3	38.0	62.8	94.9	100.4
8	40		3.1	7.2	19.1	37.0	65.1	83.3
9	45		2.3	6.5	22.5	36.7	58.7	71.3
10	50		1.7	5.8	18.6	31.5	52.6	69.5

FIG. 3-9: CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM EUDRAGIT RS-100 COATED BEADS

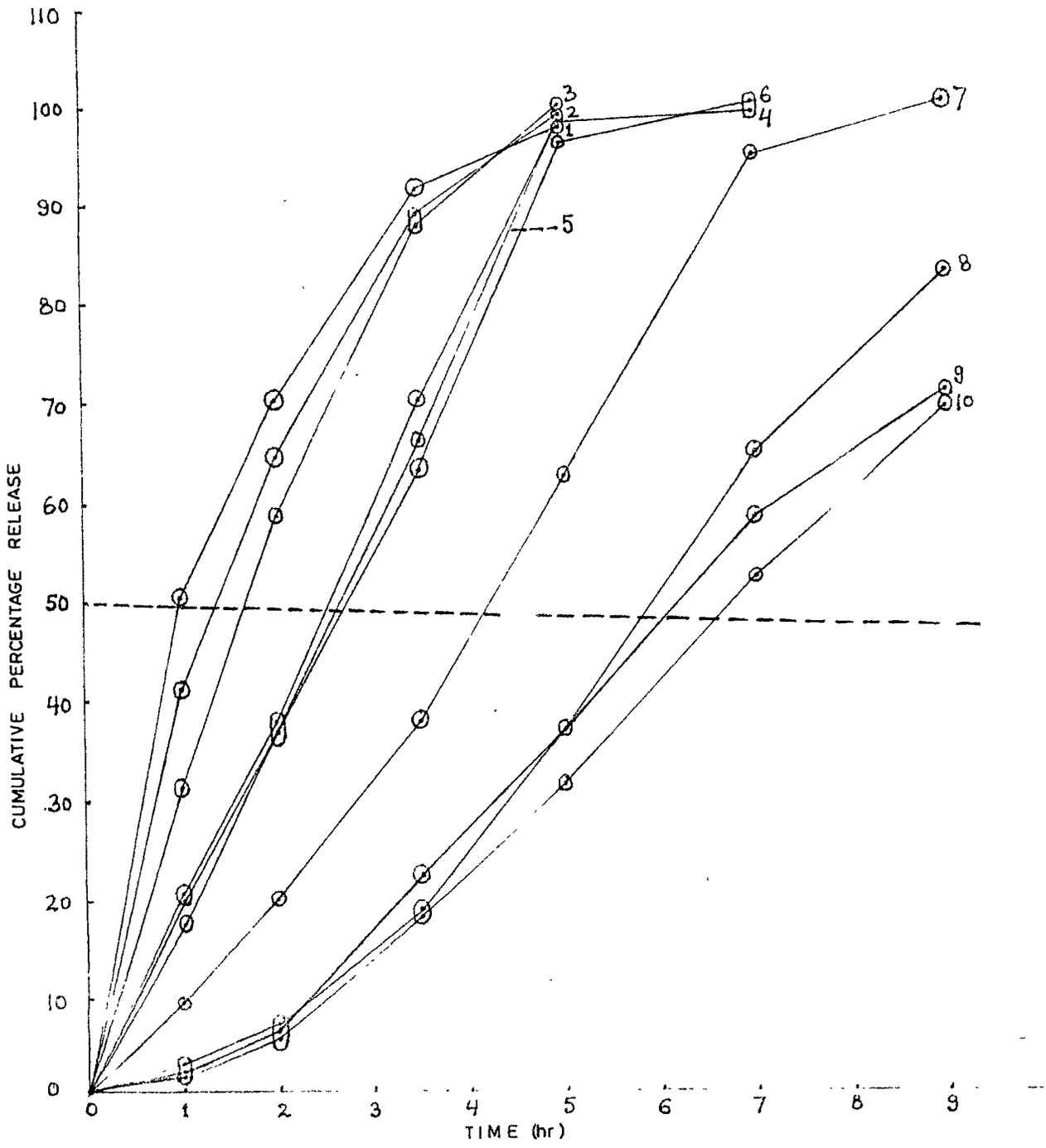


TABLE 3-10 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM EUDRAGIT RL100/RS100 (50:50) COATED BEADS.

PRODUCT No.	PERCENTAGE OF COATING	CUMULATIVE PERCENTAGE RELEASE					
		TIME (hr)	1	2	3.5	5	7	9
		pH	1.2	2.5	4.5	7	7.5	7.5
1	5		65.2	82.4	104.3	-	-	-
2	10		56.5	72.5	99.3	-	-	-
3	15		48.6	63.7	93.1	101.3	-	-
4	20		31.5	52.6	83.4	103.7	-	-
5	25		23.5	41.5	73.8	99.5	-	-
6	30		21.2	37.3	65.2	91.5	100.7	-
7	35		11.7	31.5	59.7	73.5	99.4	-
8	40		8.5	21.5	45.6	64.5	93.4	97.8
9	45		6.5	15.3	36.5	62.3	91.6	102.6
10	50		5.6	11.3	31.1	59.3	80.3	92.3

FIG. 3-10: CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM EUDRAGIT RL 100-RS 100 (50:50) COATED BEADS

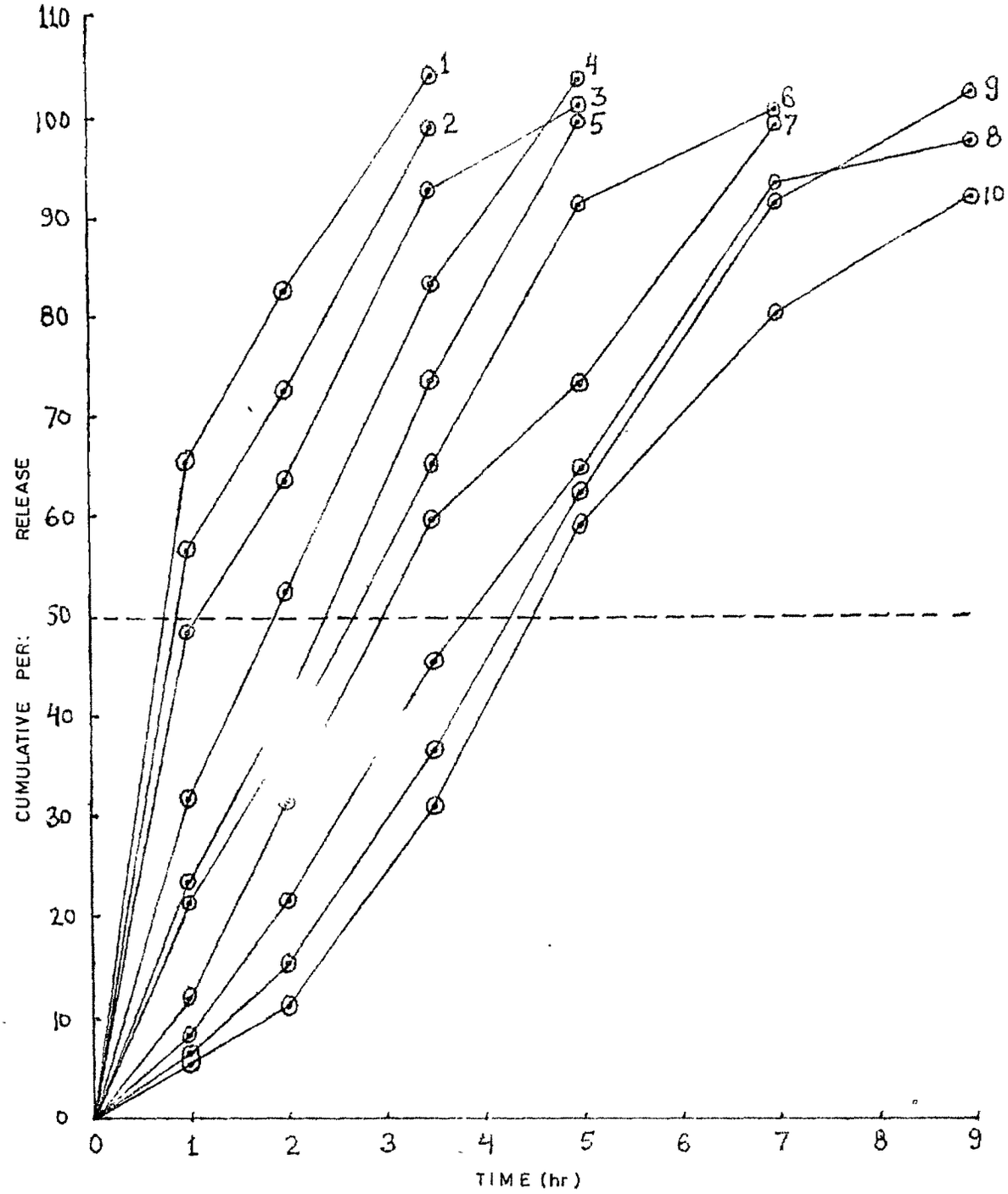
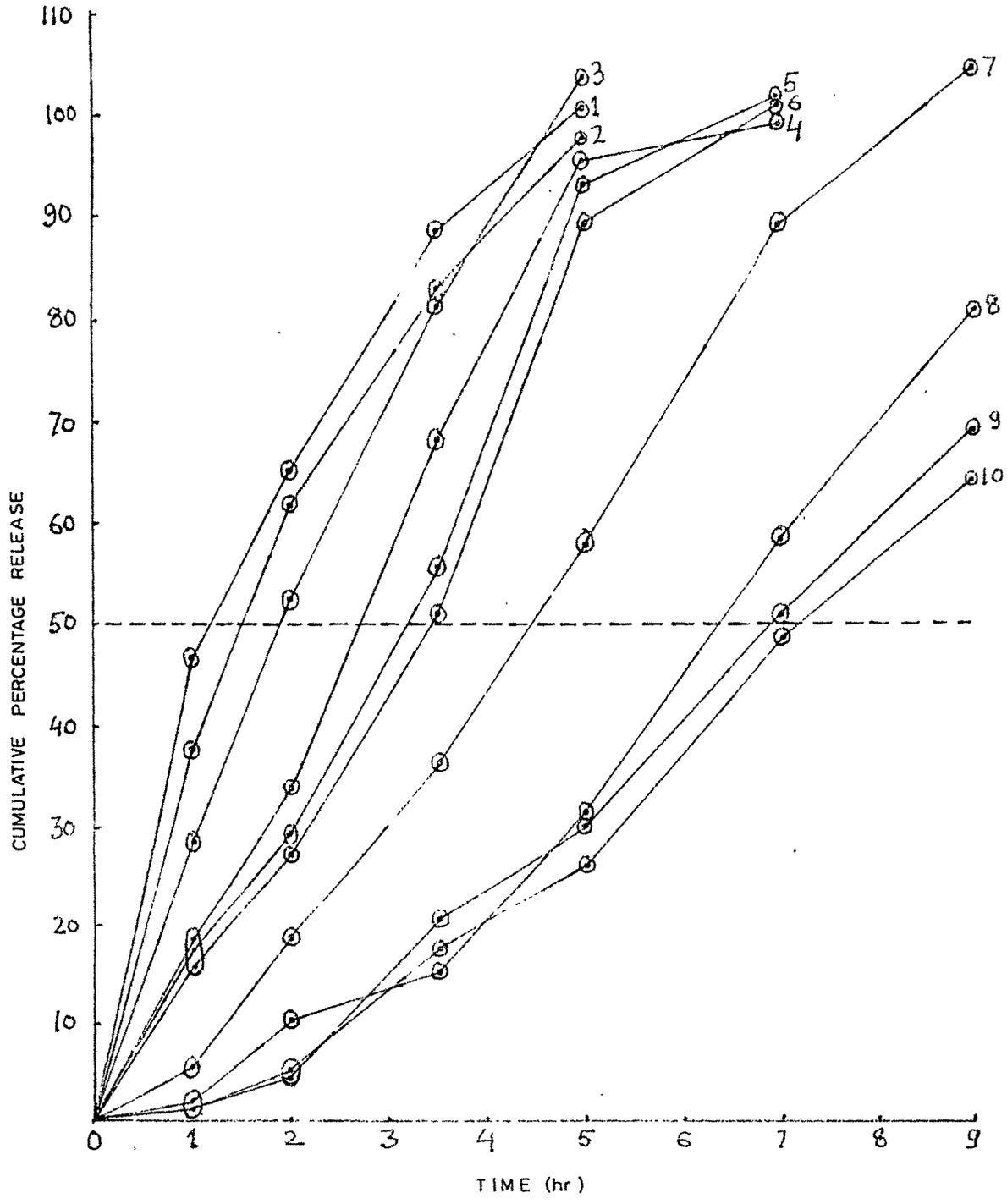


TABLE 3-11 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM EUDRAGIT RS100 COATED BEADS *

PRODUCT No.	PERCENTAGE OF COATING	CUMULATIVE PERCENTAGE RELEASE					
		TIME (hr)	1	2	3.5	5	7	9
		pH	1.2	2.5	5	7	7.5	7.5
1	5		46.5	65.2	88.7	101.2	-	-
2	10		37.6	61.7	83.3	98.2	-	-
3	15		29.5	52.6	81.5	104.2	-	-
4	20		18.3	33.7	68.2	95.7	99.7	-
5	25		17.2	29.5	55.6	93.2	102.5	-
6	30		15.7	27.5	51.3	89.5	101.5	-
7	35		5.6	18.7	36.2	58.3	89.5	105.2
8	40		2.1	10.2	15.2	31.7	58.7	81.3
9	45		1.2	4.5	20.6	30.3	51.3	69.5
10	50		1.1	5.1	17.6	26.3	48.7	64.6

* Plain beads contain higher concentration of tetracycline hydrochloride (75%).

FIG. 3-11: CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM EUDRAGIT RS-100 COATED BEADS *



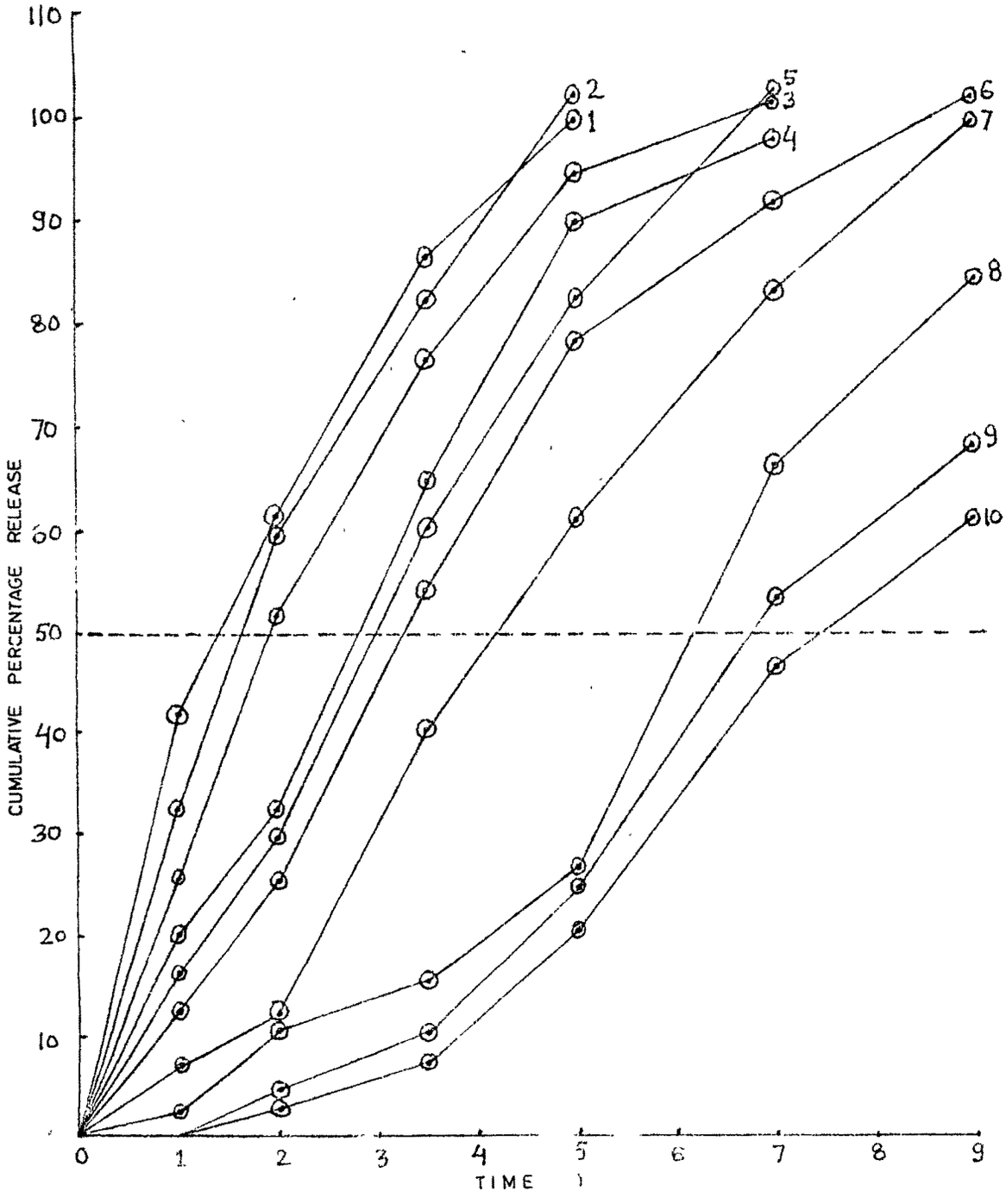
* PLAIN BEADS CONTAIN HIGH CONCENTRATION OF TETRACYCLINE HYDROCHLORIDE (75%)

TABLE 3-12 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM EUDRAGIT RS100 COATED BEADS*

PRODUCT No.	PERCENTAGE OF COATING	CUMULATIVE PERCENTAGE RELEASE					
		TIME (hr)	1	2	3.5	5	7	9
		pH	1.2	2.5	5	7	7.5	7.5
1	5		41.5	61.5	86.5	99.8	-	-
2	10		32.6	59.6	82.3	102.5	-	-
3	15		25.6	51.7	76.5	94.5	101.6	-
4	20		19.9	32.6	64.5	89.7	97.9	-
5	25		16.3	29.4	60.3	82.6	102.7	-
6	30		12.5	25.2	44.6	78.6	91.7	102.3
7	35		7.1	12.3	40.2	61.2	53.2	99.7
8	40		2.6	10.5	15.5	26.7	66.5	84.5
9	45		-	4.8	10.5	24.6	53.6	68.6
10	50		-	2.8	7.6	20.6	46.5	61.5

* 10% Avicel was replaced with eudragit RSPM.

FIG. 3-12: CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM EUDRAGIT R S 100 COATED BEADS *



* 10 % AVICEL WAS F ... WITH EUDRAC ...S PM

(f) Amount of tetracycline hydrochloride in plain beads was increased from 65% by 75% we weight and then beads were coated with eudragit RS100. Observations (Table 3-11) show decrease in the release of the tetracycline hydrochloride even after application of the same amount of eudragit RS100 by coating.

Products of this type contain tetracycline hydrochloride, avicel, organic acid and other excipients in core, coated with different materials. Succinic acid was included for the reasons explained earlier.

Results of release of the drug from products tested in triplicate show that ethyl cellulose, cellulose acetate phthalate, glyceryl monostearate and glyceryl distearate coated beads have larger inter-capsule variation in release of the drug compared to eudragit S100, eudragit RL100 and/or RS100 coated beads. Release pattern of the drug from eudragit RL100 and/or RS100 coated beads was found to be reproducible. Yield of the products was also between 85 to 95%. Photomicrographs of eudragit RL100-RS100 coated beads of tetracycline hydrochloride show nearly spherical beads with uniform coating. Hence the products prepared with eudragit RL100 - RS100 coating were selected for *in vivo* studies.

Effect of alteration in the composition of plain beads was evaluated. Incorporation of part of eudragit RS (as eudragit RSPM) inside the beads core by replacing part of avicel and then coating of beads with eudragit RS100, helped in further delaying the release of tetracycline hydrochloride. But larger amount of eudragit RS in total is required to obtain similar results as that for coating of plain beads. However, the results were found to be reproducible. This procedure can be used when larger amount of eudragit RS is to be applied by coating to obtain desired release pattern and application of that much amount of eudragit RS by coating is not feasible due to problems of sticking, solvent use etc.

Decrease in release of tetracycline hydrochloride was observed with increase in percentage of the drug inside the beads. This may be attributed to reduction in surface area available for diffusion per unit weight due to an increase in the amount of tetracycline hydrochloride.

(3) Matrix Tablets

The tetracycline hydrochloride matrix tablets prepared by the two processes consists of tetracycline hydrochloride, an organic acid, sustaining material and excipients.

Observations on release of the drug from this type of products are recorded in Tables 3-13 to 3-17 and shown graphically in Figures 3-13 to 3-17.

(a) $T_{50\%}$ values, as shown in figures, increase with increase in amount of sustaining material per tablet.

(b) Following products of different sustaining materials with a release pattern close to the desired one were subjected to <u>in vitro</u> dissolution test in triplicate and observations are shown in Table 3-18.

	Product No.
Glyceryl monostearate - bees wax matrix tablets	3
Glyceryl distearate matrix tablets	1
Eudragit RLPM/RSPM matrix tablets (500 mg)	1
Eudragit RLPM/RSPM matrix tablets (250 mg)	2

Glyceryl monostearate and glyceryl distearate matrix tablets show larger inter-tablet variation (standard deviation) in release of the drug from these tablets. Eudragit RLPM-RSPM matrix tablets showed less tablet to tablet variation in release of the drug.

(c) Extent of prolongation in release of the drug varies with the sustaining material. Eudragit RSPM matrix tablets show more prolongation in release of the drug compared to eudragit RLPM matrix tablets. However, the mix of the two gave products with intermediate prolongation in the release of the drug.

TABLE 3-13 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM GLYCERYL MONOSTEARATE MATRIX TABLETS.

PRODUCT No.	Amount of Glyceryl monostea-rate + Bees wax per Tab. (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
1	50		41.1	55.3	65.3	85.7	104.6	-
2	100		32.5	48.7	59.5	80.3	99.4	-
3	150		32.1	43.6	55.2	72.3	95.6	101.6
4	200		28.3	41.2	50.9	67.4	89.6	104.5
5	250		25.6	38.3	51.4	64.8	84.6	102.3
6	300		24.5	33.5	48.7	67.6	81.5	99.7
7	350		25.7	36.7	52.6	61.3	80.2	92.6
8	400		21.5	31.5	48.9	62.6	78.3	97.5
9	450		19.8	28.6	45.8	55.7	77.6	94.6
10	500		20.7	24.5	39.6	51.7	75.7	85.2

FIG.- 3-13 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM GLYCERYL MONOSTEARATE MATRIX TABLETS.

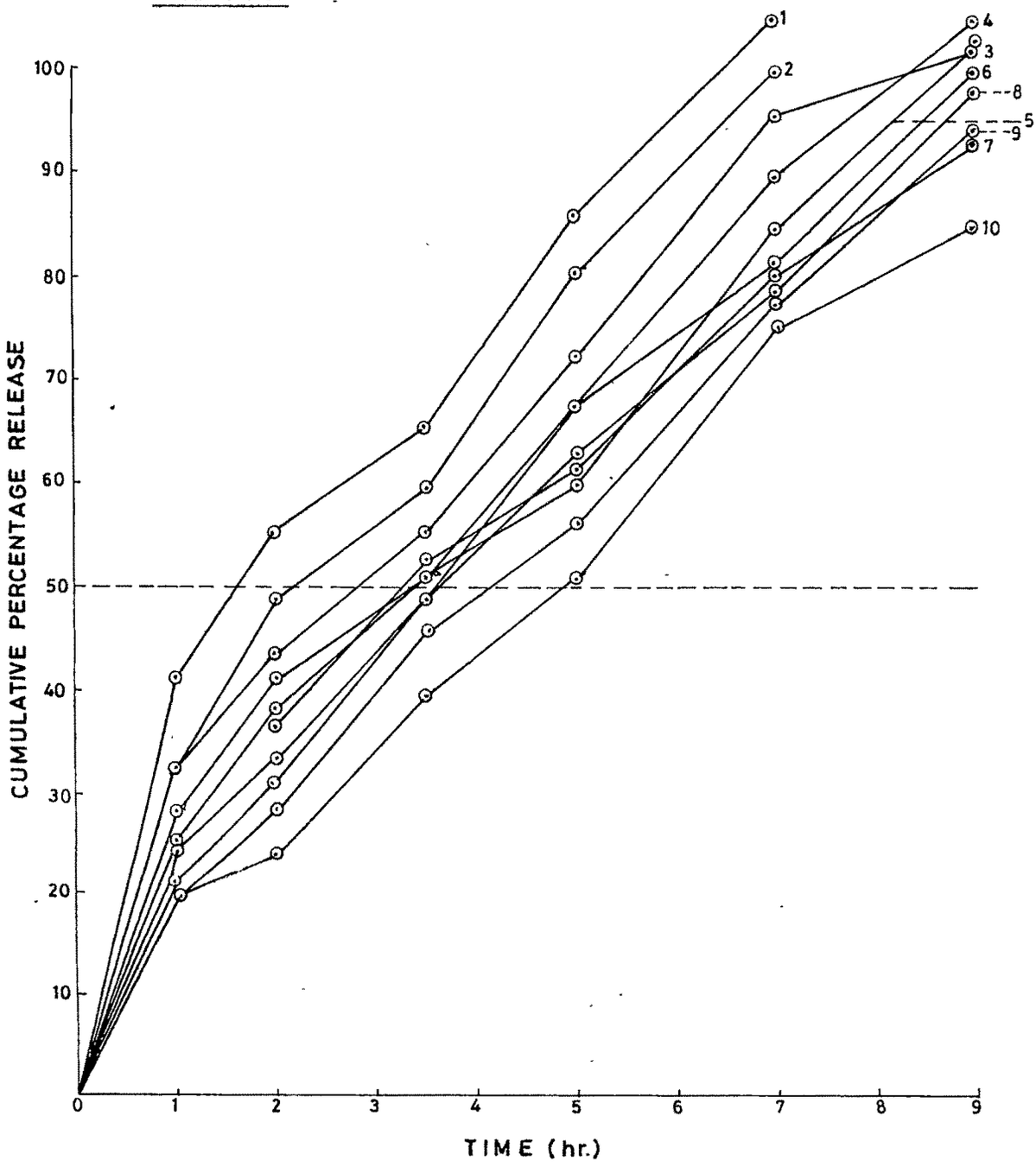


TABLE 3-14 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM GLYCERYL DISTEARATE MATRIX TABLETS.

PRODUCT No.	Amount of Glyceryl distearate per tablet (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
1	50		30.2	48.0	61.7	76.8	93.2	97.2
2	100		25.3	36.9	51.4	67.5	89.4	99.6
3	150		24.1	34.1	51.1	66.1	86.4	103.2
4	200		23.5	33.0	46.6	63.3	68.3	99.0
5	250		22.5	30.6	44.7	59.8	79.9	91.8
6	300		21.8	24.4	30.5	39.2	64.5	77.2
7	350		25.7	28.7	36.9	46.9	72.0	82.5
8	400		19.4	23.4	29.9	41.9	67.6	78.9
9	450		21.6	26.5	33.2	47.3	77.3	85.4
10	500		18.6	22.9	30.2	43.8	69.4	81.1

FIG. 3-14: CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM GLYCERYL DISTEARATE MATRIX TABLETS.

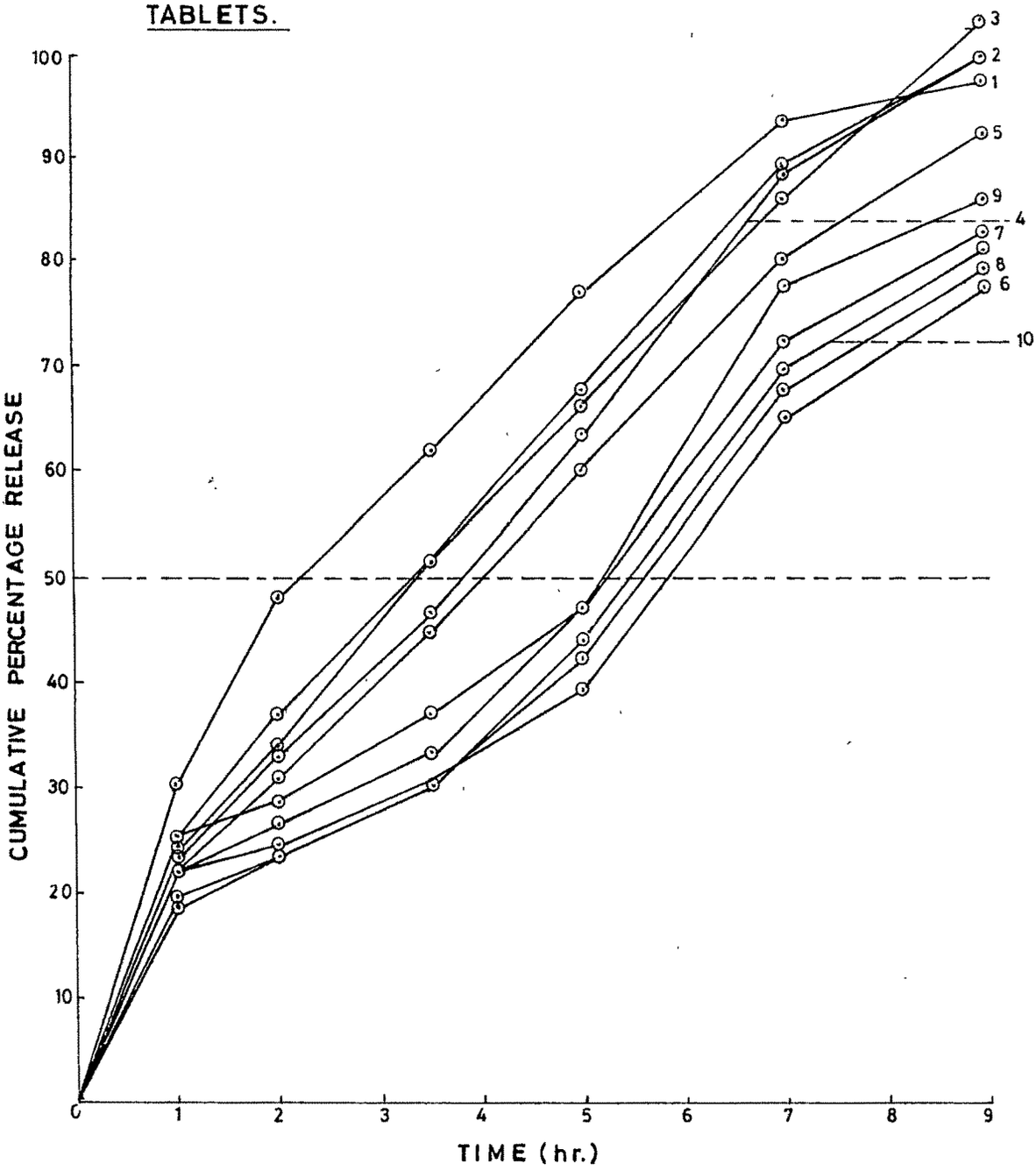
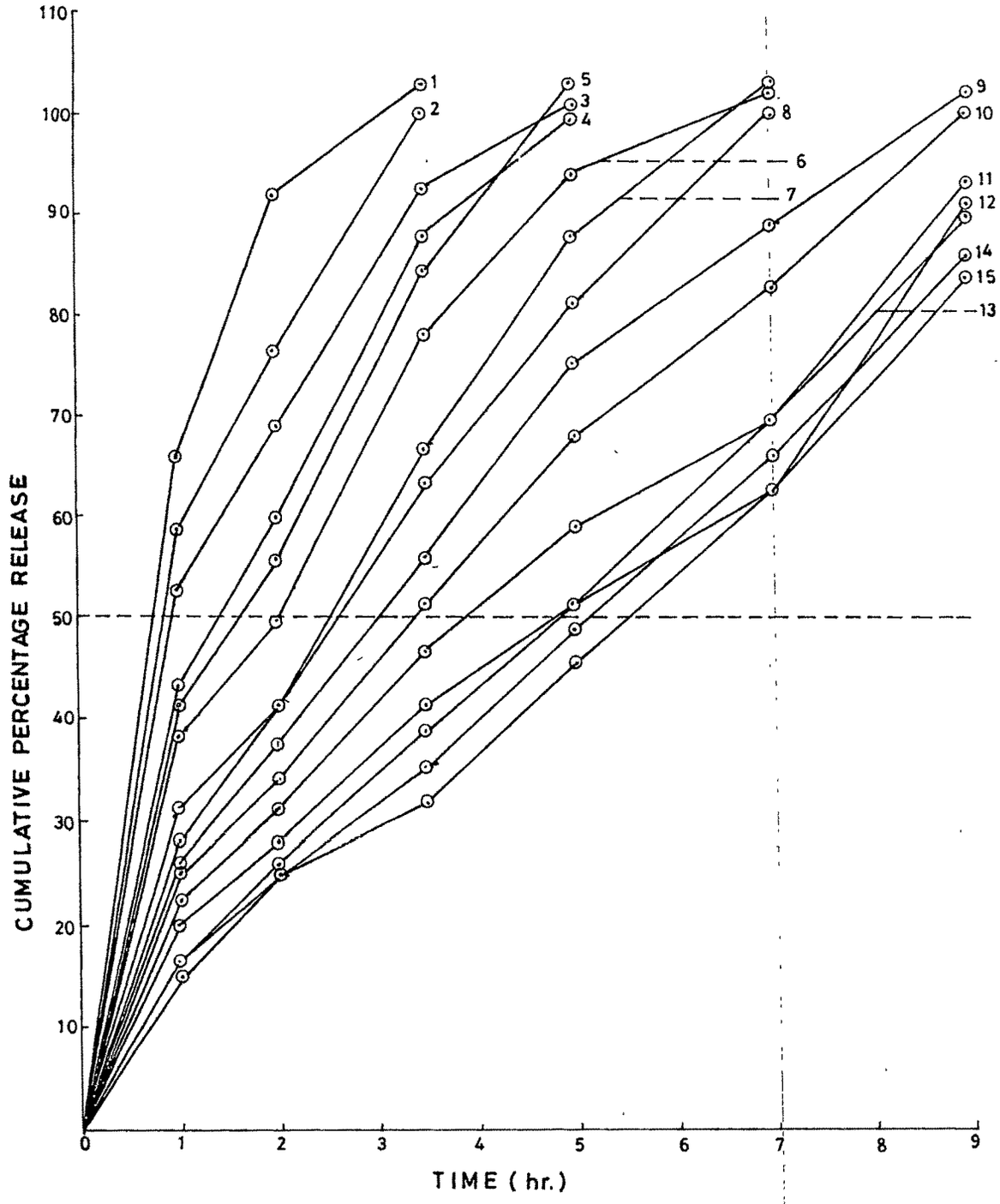


TABLE 3-15 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM EUDRAGIT RLPM MATRIX TABLETS

PRODUCT No.	Amount of eudragit RLPM per Tablet (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
1	50		65.7	91.5	102.5	-	-	-
2	100		58.3	76.3	99.8	-	-	-
3	150		52.6	68.7	92.5	101.7	-	-
4	200		43.2	59.7	87.5	99.2	-	-
5	250		41.3	55.6	84.3	102.5	-	-
6	300		38.2	49.6	78.1	93.8	101.6	-
7	350		31.2	41.3	66.5	87.5	102.5	-
8	400		28.2	41.7	63.2	81.2	99.7	-
9	450		26.2	37.6	55.7	75.2	88.6	101.7
10	500		25.2	33.7	51.2	67.5	82.4	99.7
11*	300		22.5	31.2	46.4	58.7	69.3	92.7
12*	350		20.1	28.1	41.3	51.2	62.3	90.6
13*	400		16.5	26.2	38.7	50.6	68.9	89.5
14*	450		16.5	25.3	35.1	48.7	65.6	85.6
15*	500		15.1	24.8	31.7	45.2	62.7	83.5

* Acetone vapour exposure time = 4 hours.

FIG. 3-15: CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM EUDRAGIT RLPM MATRIX TABLETS.



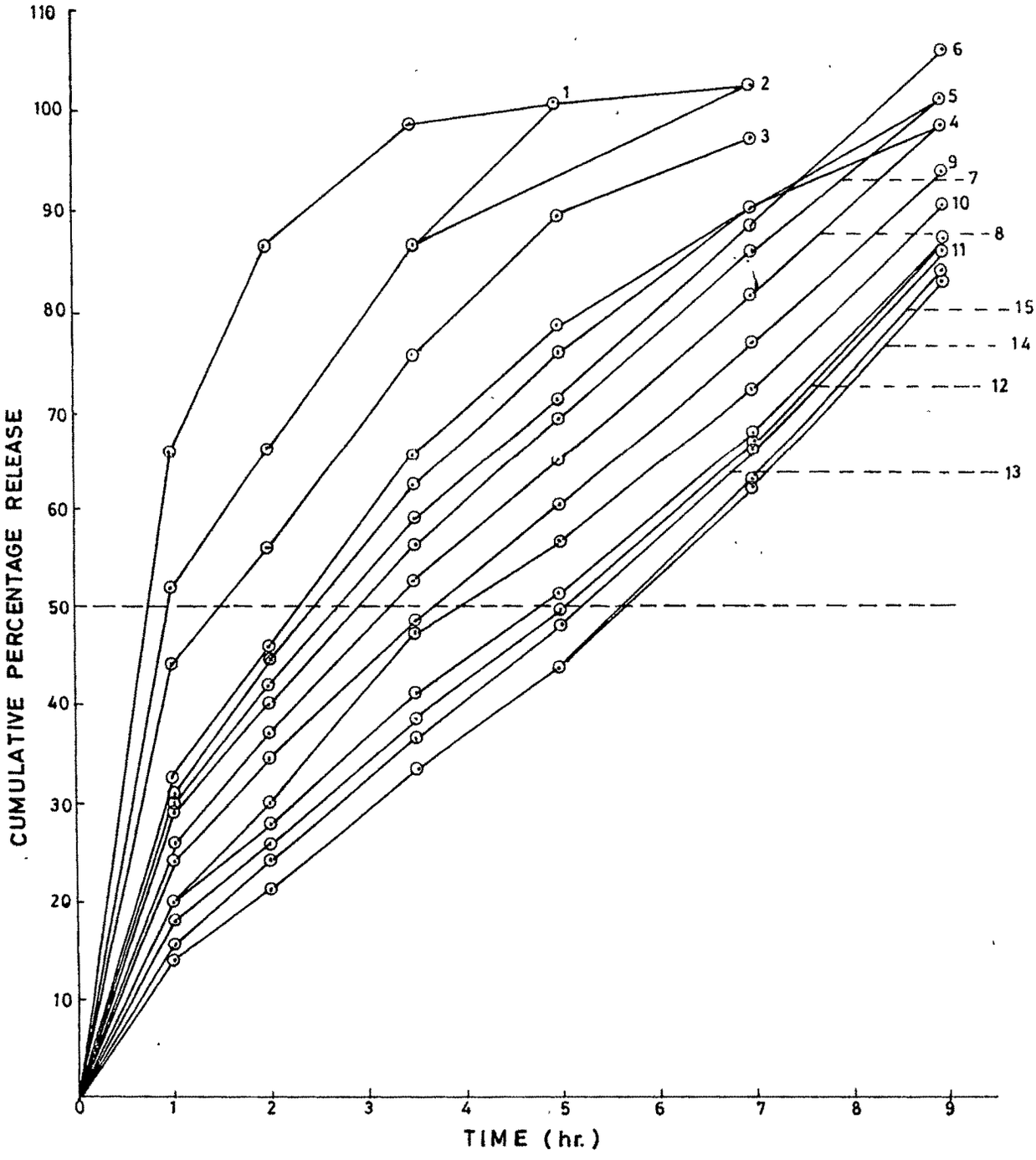
* ACETONE VAPOURS EXPOSURE TIME = 4 hrs FOR No 11-15

TABLE 3-16 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM EUDRAGIT RSPM MATRIX TABLETS.

PRODUCT No.	Amount of Eudragit RSPM per Tablet (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
1	50	66.0	86.5	98.7	100.8	-	-
2	100	52.1	66.2	86.5	100.5	102.4	-
3	150	44.0	56.0	75.8	89.5	97.2	-
4	200	32.4	46.0	65.7	78.8	90.3	98.5
5	250	31.3	44.5	62.4	76.1	90.8	101.0
6	300	30.1	42.1	59.2	71.6	88.4	106.0
7	350	28.9	40.1	56.2	69.4	86.1	101.5
8	400	26.1	37.0	52.7	64.9	81.7	99.0
9	450	24.1	34.5	48.6	60.5	76.7	93.8
10	500	20.1	30.1	46.9	56.6	72.3	90.4
11*	300	19.9	27.9	41.0	51.3	68.0	87.2
12*	350	18.0	26.1	38.5	49.6	66.7	86.5
13*	400	15.7	24.1	36.3	47.9	66.0	85.9
14*	450	14.0	21.3	33.4	43.7	62.2	82.7
15*	500	14.0	21.7	33.6	43.7	62.8	84.0

* Acetone vapour exposure time = 4 hours.

FIG.·3-16: CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM EUDRAGIT RSPM MATRIX TABLETS.



* ACETONE VAPOUR EXPOSURE TIME=4 hrs. FOR NO 11-15

TABLE 3-17 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM EUDRAGIT RSPM/RLPM MATRIX TABLETS.

PRODUCT No.	Amount of Eudragit RSPM/RLPM per Tablet (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
500 mg Tablet							
1	50/250	32.5	43.5	60.2	76.5	96.2	103.6
2	100/200	33.4	45.6	64.1	81.2	97.5	101.2
3	150/150	35.7	47.5	66.7	83.5	99.6	99.7
4	200/100	36.1	47.8	69.7	87.6	98.6	99.3
5	250/ 50	36.5	48.7	75.3	90.7	101.5	-
250 mg Tablet							
1	25/150	28.6	40.6	58.5	70.6	91.7	99.3
2	50/125	30.4	42.3	60.6	75.3	93.7	102.6
3	75/100	33.6	45.6	63.4	78.7	98.3	101.3
4	100/ 75	36.7	48.5	69.7	82.5	99.3	102.2
5	125/ 50	38.5	51.3	72.7	85.3	100.8	-
6	150/ 25	41.2	52.6	75.3	89.5	103.5	-

FIG.-3-17A: CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM EUDRAGIT RSPM/ RLPM MATRIX TABLETS (500 mg.)

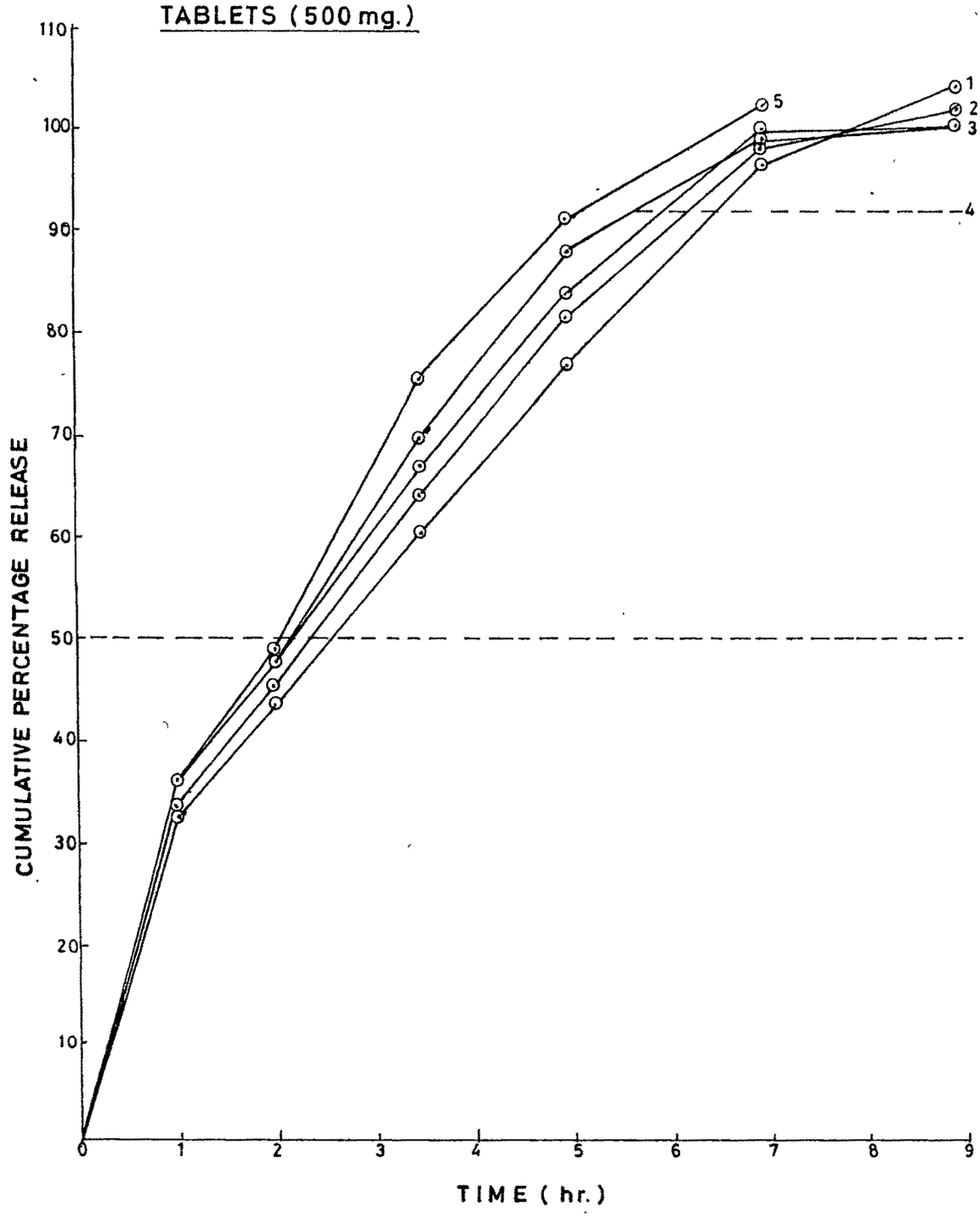
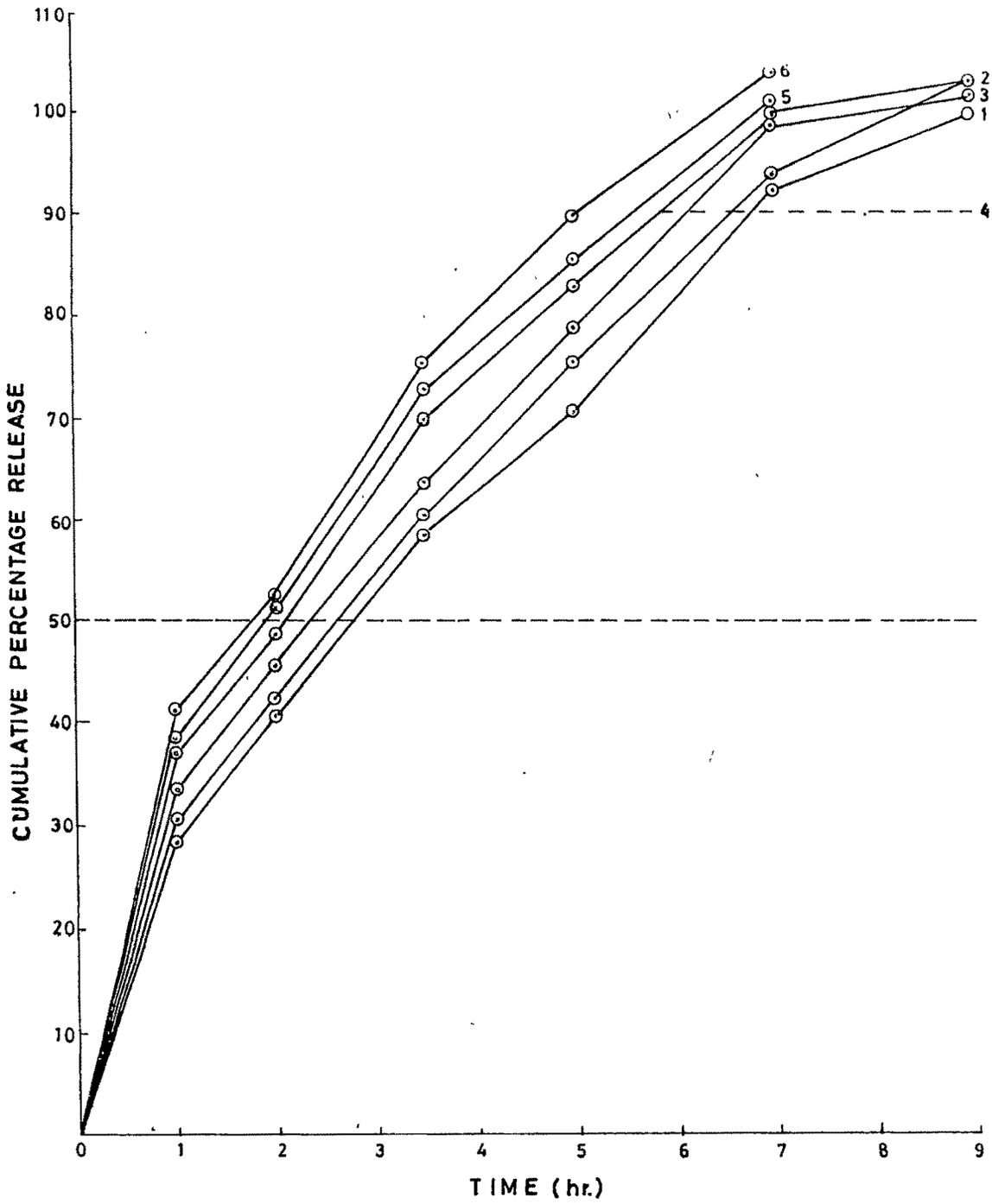


FIG. 3-17B: CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE FROM EUDRAGIT RSPM / RLPM MATRIX TABLETS (250 mg.)



(d) Acetone exposure time was altered and its effect on the release of the drug was seen (Tables 3-15 and 3-16). With increase in exposure time, decrease in release of the drug was observed.

Matrix tablets prepared by the two processes consist of tetracycline hydrochloride, organic acid, sustaining material and excipients. Succinic acid was included in the matrix for reasons mentioned earlier.

Process of glyceryl monostearate-bees wax and glyceryl distearate matrix tablet preparation was tedious, resulted in lower yield and observations on release of the drug from these matrices showed significant variation. Hence the products were not taken up for *in vivo* evaluation.

The procedure adopted to formulate eudragit RLPM and/or RSPM matrices was simple, quick and comparatively more reproducible. Eudragit RSPM matrix tablets had shown more prolongation in release of the drug than eudragit RLPM matrix tablets, mix of the two has shown intermediate prolongation in release of the drug. Release pattern of tetracycline hydrochloride in such type of matrices varies with the amount of drug, eudragit, and avicel. Other important factors controlling release of the drug from this type of matrices are dependent on exposure conditions i.e. time, temperature and vacuum.

TABLE 3-18 : CUMULATIVE PERCENTAGE RELEASE OF TETRACYCLINE HYDROCHLORIDE IN VITRO FROM SELECTED PRODUCTS.

PRODUCT TYPE	PRODUCT No.	CUMULATIVE PERCENTAGE RELEASE					
		TIME (hr)	1	2	3.5	5	7	9
		pH	1.2	2.5	4.5	7	7.5	7.5
Shellac-P.V.P. Matrix capsule	7		30.6	55.3	70.5	88.2	100.2	-
			25.3	48.3	62.3	85.2	105.7	
			28.4	52.7	68.7	92.5	103.8	
			28.1±2.17	52.1±2.89	67.1±3.51	88.63±2.99	103.23±2.28	-
Cellulose Acetate phthalate-P.V.P. Matrix capsule	10		37.6	56.5	76.5	92.5	99.7	-
			30.8	43.7	68.7	90.7	103.4	
			28.1	58.4	69.8	102.5		
			32.16±3.99	52.86±6.52	71.66±3.64	95.23±5.19	101.5±1.85	-
Glyceryl monostearate coated beads capsule	Mix of 5 and 10 (1:1)		29.3	58.9	81.7	90.7	104.7	
			35.7	53.2	71.3	98.7	99.3	
			24.6	46.7	76.4	88.6	101.2	
			29.86±4.54	52.93±4.24	76.46±4.24	92.66±4.35	101.73±2.23	
Glyceryl distearate coated beads capsule	5		30.2	51.4	81.4	102.4	102.6	-
			25.4	60.3	80.4	89.7	103.3	
			36.7	55.2	73.4	92.5	105.7	
			30.76±4.63	55.63±3.64	78.4±3.55	94.93±5.54	103.96±1.23	

Contd..

TABLE 3-18 : Contd.

PRODUCT TYPE	PRODUCT No.	CUMULATIVE PERCENTAGE RELEASE					
		TIME (hr)	1	2	3.5	5	7	9
		pH	1.2	2.5	4.5	7	7.5	7.5
Cellulose acetate phthalate Contd. beads capsule	Mix of 3 and 5 (1:1)		25.8	56.4	75.8	93.4	103.6	-
			33.7	48.7	82.4	89.7	98.7	
			33.8	59.4	83.4	101.2		
			31.1±3.74	54.83±4.50	80.53±3.37	94.76±4.80	101.1±2.45	
Ethyl cellulose coated beads capsule	8		23.6	51.6	81.2	89.7	102.3	
			36.7	46.7	83.7	96.7	105.6	
			31.5	55.3	87.5	93.6	101.3	
			30.6±5.38	51.2±3.52	84.13±2.59	93.33±2.86	103.03±1.83	
Eudragit S100 coated beads capsule	Mix of 3 and 6 (1:1)		29.32	49.6	71.3	89.6	101.3	
			28.6	48.7	69.6	90.6	103.5	
			30.7	48.2	73.4	91.3	98.6	
			29.53±0.87	48.83±0.58	71.45±1.55	90.5±0.69	101.13±2.00	
Eudragit RL100-RS100 coated beads capsule (500mg)	Mix of plain beads, 2 and 9 (1:3.6)		31.5	41.6	57.8	74.4	93.8	101.2
			28.6	42.8	59.7	73.8	94.8	99.7
			30.4	45.3	60.6	71.6	90.4	98.6
			30.16±1.19	43.23±1.54	59.36±1.17	73.26±1.20	93.±1.88	99.83±1.06

Contd...

TABLE 3-18 : Contd.

PRODUCT TYPE	PRODUCT No.	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 bead (250 mg) Capsule	Mix of plain beads 2 and (1:3:6)	28.3	40.7	59.7	71.2	91.7	102.6
		31.2	42.6	58.6	73.6	93.8	103.6
		29.6	43.8	61.6	73.4	90.5	99.8
		29.7±1.18	42.36±1.27	59.9±1.24	72.7±1.08	92.±1.36	102.6±1.60
Glyceryl monostearate Matrix Tablets	3	28.3	41.2	50.9	67.4	89.6	104.5
		25.6	52.6	57.6	68.6	91.7	103.6
		29.7	48.6	53.2	73.4	84.5	98.9
		27.86±1.70	47.46±4.72	53.9±2.78	69.8±2.59	88.6±3.02	102.33±2.45
Glyceryl distearate Matrix Tablets	1	30.2	48.0	61.7	76.8	93.2	97.2
		32.6	53.7	68.4	78.4	98.6	99.7
		25.5	45.7	56.5	79.7	102.3	-
		29.43±2.94	49.13±3.36	62.2±4.87	78.3±1.18	98.03±3.73	98.45±1.25
Eudragit RLPM/RSPM Matrix Tablets (500 mg)	1	32.5	43.5	60.2	76.5	96.2	103.6
		31.7	43.2	62.2	73.6	95.7	99.8
		30.9	45.4	58.7	78.6	94.7	103.2
		31.7±0.65	44.03±0.97	60.36±1.43	76.23±2.04	95.53±0.62	102.2±1.70
Eudragit RLPM/RSPM Matrix Tablets (250 mg)	2	30.4	42.3	60.6	75.3	93.7	99.3
		31.3	40.6	61.5	71.5	94.5	105.6
		29.9	39.2	58.6	72.5	93.6	102.5
		39.53±0.58	40.7±1.26	60.23±1.21	73.1±1.60	93.93±0.40	102.46±2.57

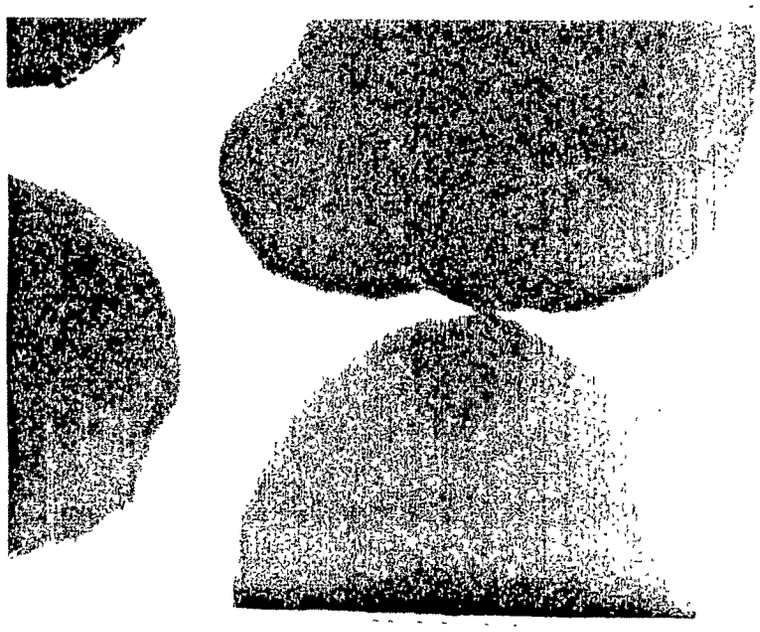


FIG. 3-18 A PHOTOMICROGRAPH OF EUDRAGIT RS 100 – RL 100 COATED BEADS OF TETRACYCLINE HYDROCHLORIDE (X 40)

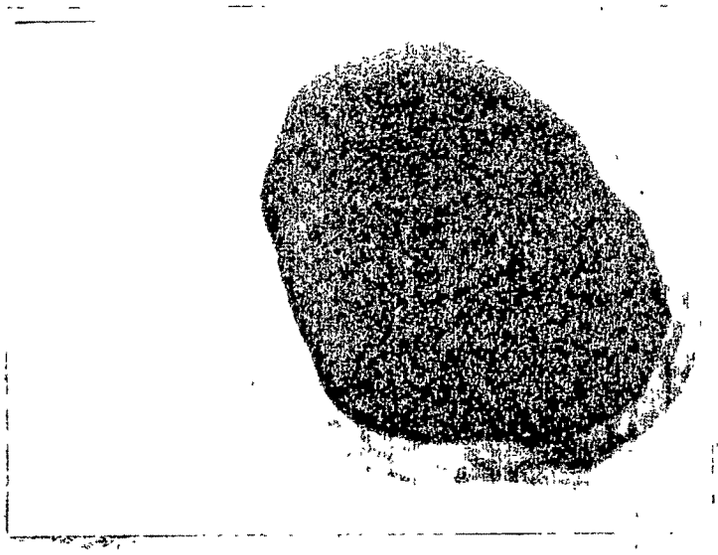


FIG. 3-18 B: PHOTOMICROGRAPH OF EUDRAGIT RS 100 – RL 100 COATED BEADS OF TETRACYCLINE HYDROCHLORIDE SHOWING CORE AND COATING (X 100)

It was also noted that the tablet characteristics like hardness, gauge, friability etc. before acetone exposure do not make significant difference in the release of drug from this type of matrices.

Tablets prepared with combination of eudragit RLPM-RSPM were found most close to the desired release pattern with less inter-tablet variation in release of the drug and hence were selected for in vivo studies.

B. FABRICATION, FORMULATION, AND EVALUATION OF HYDRALAZINE HYDROCHLORIDE PRODUCTS

Following two types of preparations were attempted in the present investigation.

(1) Coated Beads

(a) Preparation of beads :

Beads of hydralazine hydrochloride were prepared using pelleter EXDS-60 type and marumerizer Q-230 type. Hydralazine hydrochloride, avicel and lactose were weighed and taken in a suitable container and mixed thoroughly. The mix was wetted with required amount of coloured starch paste and more water was added if necessary to make the wet mass pelletizable. Wet mass was passed through pelleter (shaft speed - 40 rpm). Care was taken in feeding material

into the pelleter to avoid overloading. Pellets so obtained were rotated in marumerizer (speed of marume plate - 600 rpm; marume plate 4-5 mm size) for 60 seconds - thrice, to obtain spherical beads of suitable size. Beads were dried at 50°C, screened and 16/40 mesh fraction was used for coating. The resulting beads had a yield of 85-90%. Beads had following composition :

Hydralazine hydrochloride	250 g
Tartrazine yellow (F.D. & C yellow No.5)	0.05 g
Corn starch	25 g
Avicel	200 g
Lactose	524.95 g

(b) Coating of beads :

Each time about 500 g of beads were placed in the coating chamber of Uni-Glatt air suspension coating apparatus (Glatt-GmbH, West Germany). Beads were coated differentially with glyceryl monostearate, glyceryl distearate, eudragit S100, eudragit RL100 and/or RS100 coating solutions (composition of solutions was same as used for tetracycline hydrochloride - page 77) as per following specifications.

Inlet air temperature : 30-35°C

Outlet air temperature : open

Spraying pressure : 2 atm (29 psi)

Coating solution pump speed: 5 rpm

Temperatures of the glyceryl monostearate and glyceryl distearate coating solutions were kept respectively at 70±5°C and 55±5°C at the time of coating. 100 ml of the respective pure solvent was sprayed to clean the nozzle after each withdrawal of sample as well as after completion of coating operation. This was followed by a drying period (half an hour) at slow moving speed and an air inlet temperature of 50°C. Finished product was spread in trays for further drying at 40°C for 24 hours.

Beads equivalent to 50 mg of hydralazine hydrochloride were filled in No. 1 hard gelatin capsule and subjected to *in vitro* evaluation.

(2) Matrix tablets

(a) Preparation of matrix tablets by coating method

Weighed quantities of hydralazine hydrochloride and lactose were thoroughly mixed and wet granulated with coloured starch paste using more water if necessary. Wet mass was dried at 50°C and 16/40 mesh fraction was used for further studies. The process yielded 70 to 80% of granules of required size.

Weighed quantity (about 500 g) of granules was taken in coating chamber of Uni-Glatt air suspension coating apparatus and coated with glyceryl monostearate and glyceryl

distearate coating solutions (composition as on page 77) as per following specifications :

Inlet air temperature	: 40°C
Outlet air temperature	: open
Spraying pressure	: 2 atm (29 psi)
Speed of coating solution pump	: 10 rpm
Temperature of coating solutions	
Glyceryl monostearate coating solution	: 70±5°C
Glyceryl distearate coating solution	: 55±5°C

Coated granules were lubricated with magnesium stearate and compressed into round (9 mm) flat face, bevel edge, with bisecting bar on upper side, tablets using single punch machine, as per following specifications :

Tablet weight	: 200 mg
Gauge	: 10
Hardness	: 25 Strong Cobb units

Tablets had following composition :

Hydralazine hydrochloride	50 mg
Tartrazinc yellow (F.D. & C. yellow No. 5)	0.01 mg
Avicel	40 mg

Glyceryl monostearate -	
white bees wax/or glyceryl distearate	5-50 mg
Maize starch	8 mg
Magnesium stearate	3 mg
Lactose	93.99-48.99 mg

These tablets were subjected to in vitro evaluation.

(b) Preparation of matrix tablet by acetone exposure

Weighed quantities of hydralazine hydrochloride, eudragit RLPM and/or RSPM, and avicel were mixed thoroughly and wet granulated with coloured starch paste. Wet mass was dried at 50°C and passed through 16 mesh. Granules after lubrication with magnesium stearate were compressed into round (9 mm), flat face, bevel edge, with bisecting bar on upper side, tablets using single punch machine as per following specifications :

Tablet weight	:	200 mg
Gauge	:	12
Hardness	:	5-7 Strong Cobb units

Compressed tablets were placed in a small vacuum dryer and vacuum (about 29" of Hg) was created inside the dryer chamber with the help of a vacuum pump. About 200 ml of acetone was sucked inside the dryer chamber and vacuum was broken. Temperature of the dryer chamber was adjusted to

40°C and tablets were exposed to acetone vapours for required period (1½ hours). Tablets were dried at 40°C overnight.

Tablets had following composition :

Hydralazine hydrochloride	50 mg
Tatrazine yellow (F.D. & C. Yellow No. 5)	0.01 mg
Avicel	40 mg
Eudragit RLPM and/or RSPM	5-50 mg
Maize starch	8 mg
Magnesium stearate	3 mg
Lactose	93.99-48.99 mg

These tablets were subjected to in vitro evaluation.

DISSOLUTION STUDIES

Dissolution studies were carried out using a basket stirrer assembly of USP XX (21) dissolution test apparatus at a stirrer speed of 100 r.p.m. and the dissolution media temperature was held at 37±0.5°C. 900 ml each of 1.2, 2.5, 4.5, 7.0, and 7.5 pH dissolution media were prepared and changed at different intervals of time as per the method recommended in N.F. XIV (22) under "Timed Release Tablets and Capsules In Vitro Test Procedure". Aliquots of sample were withdrawn from the dissolution medium at 1.0, 2.0,

3.5, 5.0, 7.0 and 9.0 hr and equal volume of fresh dissolution medium was added. Samples were analysed as per the procedure described in Chapter II (page 48). Absorbance was measured at maximum of 510 nm on a Spectronic-20 visible spectrophotometer. Observation on release of the drug from products are recorded in Tables 3-19 to 3-30 and shown graphically in Figures 3-19 to 3-29.

Mathematical Calculations for Loading and Maintenance Doses

The amount of hydralazine hydrochloride to be taken as loading dose and maintenance dose in the preparation of controlled release products was calculated. Based on the reported pharmacokinetic data (31-34) considering the average weight of an individual to be 60 kg with a view to maintain an average therapeutic blood level of about 0.10 to 0.20 µg/ml of the blood at steady state after multiple dosing of the product (50 mg controlled release products). Loading dose was calculated based on equation

$$Dt = Vd.Pt$$

where, Vd is the apparent volume of distribution and Dt and Pt represent respectively the total amount of the drug in the body and the concentration of the drug in the blood at any time t.

Substituting the values of Vd and Pt

$$Dt = \frac{1.6 \times 1000 \times 60 \times 0.08}{1000} = 7.68 \text{ mg}$$

where Vd = 1.6 litres kg^{-1}; body weight = 60 kg;

plasma level at 1 hr = 0.08 $\mu g/ml^{-1}$.

Since only 50% of the orally administered drug is available, the amount of the drug needed to be administered would be

$$\frac{7.68 \times 100}{50} = 15.36 \text{ mg i.e. } 30.72\% \text{ of total dose.}$$

For calculating the maintenance dose the rate of elimination of hydralazine hydrochloride at steady state was considered

$$\text{Clearance} = 10 \text{ ml } min^{-1}kg^{-1}$$

$$\therefore \text{ Rate of elimination} = \frac{10 \times 0.1 \times 60 \times 60}{1000}$$

$$= 3.6 \text{ mg } hr^{-1}$$

Hence in order to maintain the blood level, the amount of drug needed to be released as the maintenance dose from the products, considering that only 50% of the orally administered drug is available would be

$$\frac{3.6 \times 100}{50} = 7.2 \text{ mg } hr^{-1} \text{ i.e. } 14.4\% \text{ of the total dose per hour.}$$

Thus the product is required to release 15.36 mg as loading dose initially and then 7.2 mg per hour in 2nd and subsequent hours till total drug (50 mg) is released.

RESULTS AND DISCUSSION

(1) Coated Beads

Hydralazine hydrochloride beads were differentially coated with different coating materials. The resulting beads had a yield of 85 to 90%.

Observations of release of the drug from this type of products are recorded in Tables 3-19 to 3-24 and shown graphically in Figures 3-19 to 3-24.

(a) $T_{50\%}$ values, as shown in the figure, increase with increase in percentage of the coating material applied to beads in each case. However, extent of prolongation varies from one coating material to the other and was found to be in the following order :
Eudragit RS100 > eudragit RL100-RS100 (50:50) > eudragit RL100 > eudragit S100 > glyceryl distearate > glyceryl monostearate — white bees wax.

(b) Following products of different coating materials with a release pattern close to the desired release pattern were subjected to *in vitro* dissolution test in triplicate and observations are shown in Table 3-30.

	Product No.
Glyceryl monostearate-Bees wax coated beads	mix of 4 and 10 (1:1)
Glyceryl distearate coated beads	mix of 4 and 7 (1:1)

TABLE 3-19 : CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM GLYCERYL MONOSTEARATE COATED BEADS.

PRODUCT No.	PERCENTAGE OF COATING	CUMULATIVE PERCENTAGE RELEASE					
		TIME (hr)	1	2	3.5	5	7	9
		pH	1.2	2.5	4.5	7	7.5	7.5
1	5		93.6	108.2	-	-	-	-
2	10		78.8	101.4	-	-	-	-
3	15		68.5	99.8	-	-	-	-
4	20		55.6	85.7	103.4	-	-	-
5	25		36.7	72.3	105.7	-	-	-
6	30		25.4	42.4	85.7	103.4	-	-
7	35		15.6	36.3	75.8	95.6	101.5	-
8	40		18.6	28.3	61.3	88.3	107.8	-
9	45		10.6	22.7	53.4	75.7	92.5	102.4
10	50		7.8	20.3	43.2	53.6	83.7	98.9

FIG.·3-19: CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM GLYCERYL MONOSTEARATE COATED BEADS.

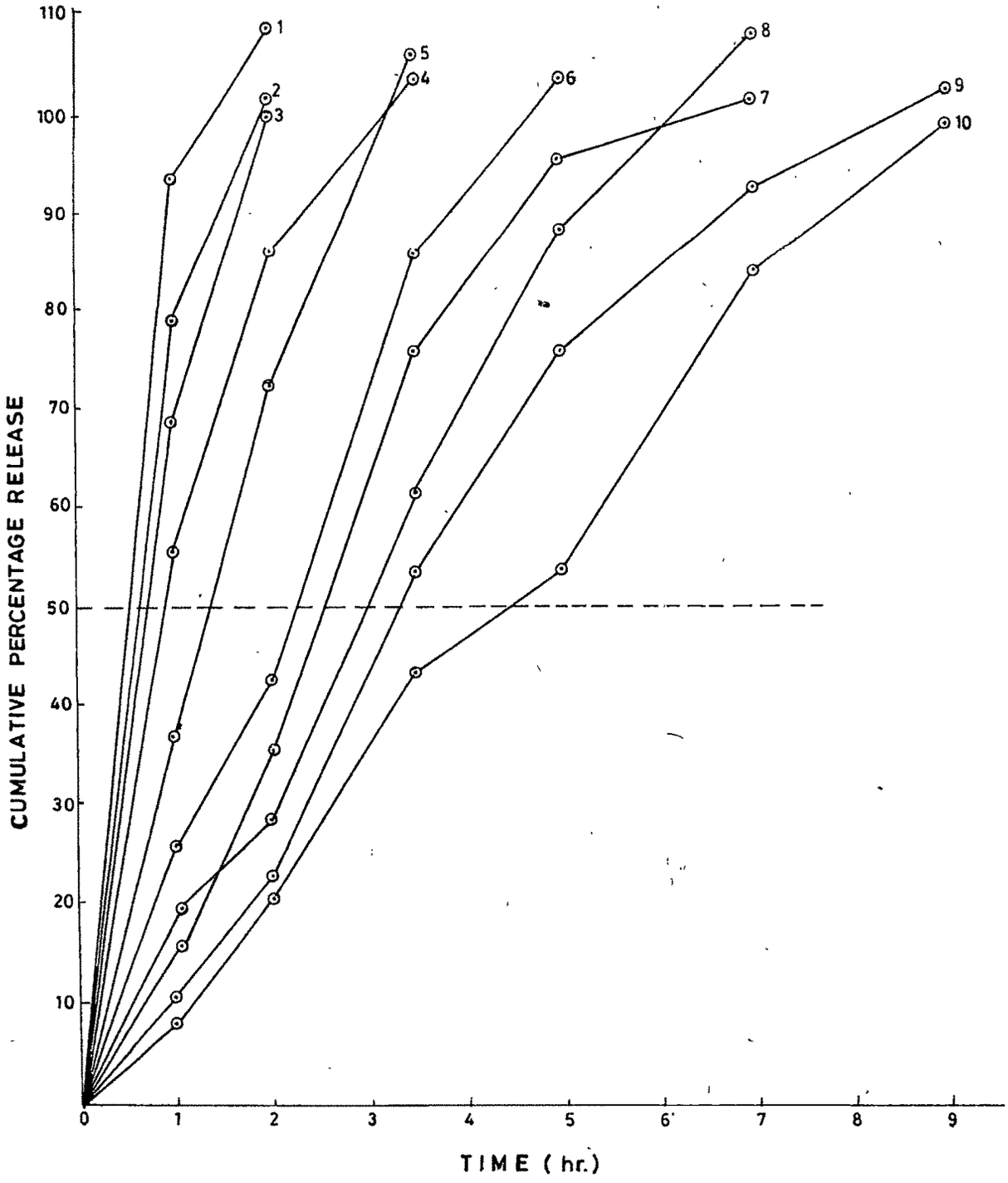


TABLE 3-20 : CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM GLYCERYL DISTEARATE COATED BEADS.

PRODUCT No.	PERCENTAGE OF COATING	CUMULATIVE PERCENTAGE RELEASE					
		TIME (hr)	1	2	3.5	5	7	9
		pH	1.2	2.5	4.5	7	7.5	7.5
1	5		81.2	103.6	-	-	-	-
2	10		76.4	101.8	-	-	-	-
3	15		65.5	95.6	106.9	-	-	-
4	20		45.6	76.5	101.2	-	-	-
5	25		33.5	53.8	82.4	102.3	-	-
6	30		21.7	42.7	73.5	106.2	-	-
7	35		13.5	29.6	68.6	91.2	103.6	-
8	40		10.9	22.4	58.7	72.5	104.8	-
9	45		6.8	15.5	31.4	61.7	94.6	105.6
10	50		8.9	11.7	18.5	48.6	72.5	101.3

FIG.·3-20: CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM GLYCERYL DISTEARATE COATED BEADS.

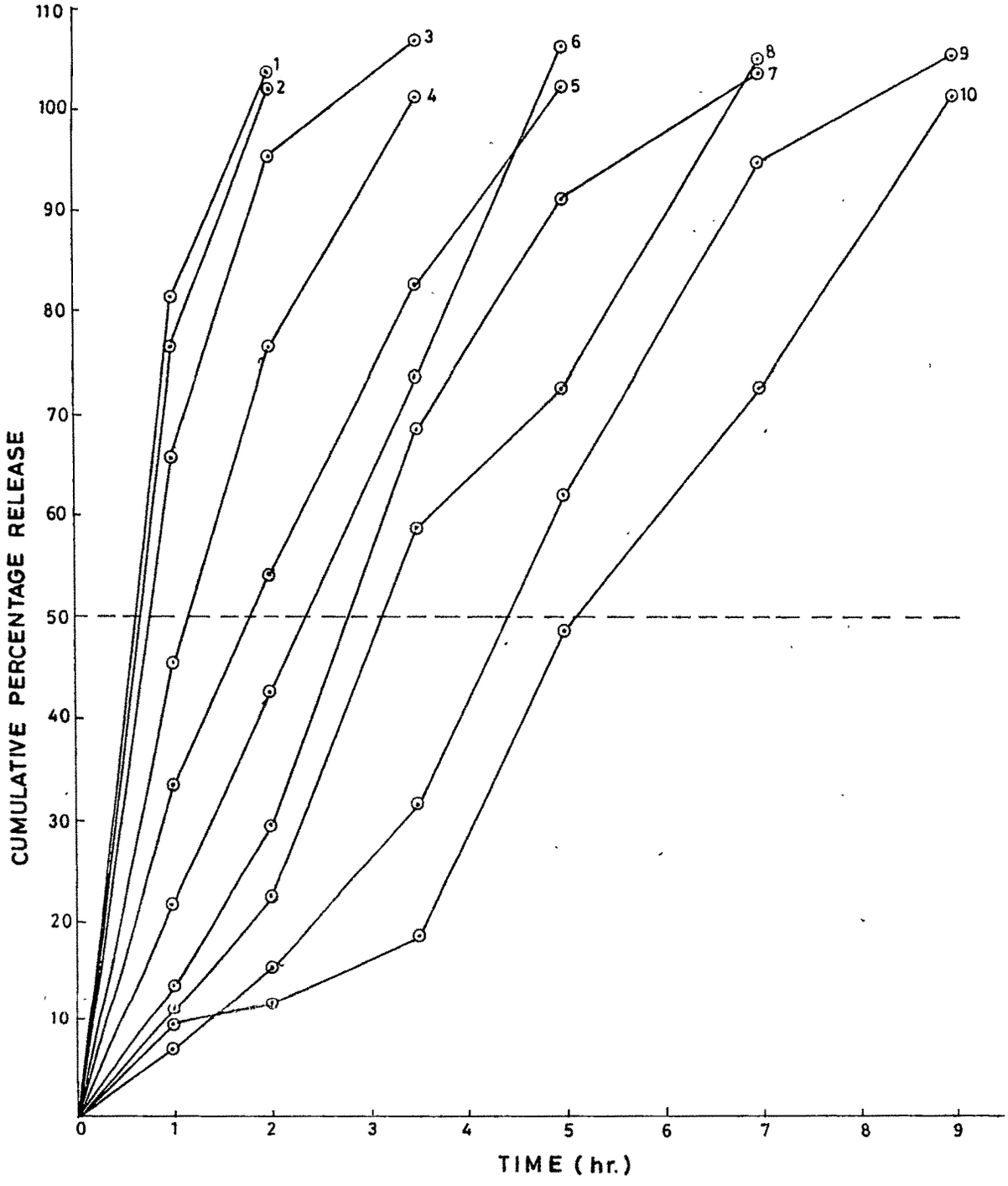


TABLE 3-21 : CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM EUDRAGIT S100 COATED BEADS.

PRODUCT No.	PERCENTAGE OF COATING	CUMULATIVE PERCENTAGE RELEASE					
		TIME (hr)	1	2	3.5	5	7	9
		pH	1.2	2.5	4.5	7	7.5	7.5
1	5		85.7	101.3	-	-	-	-
2	10		62.1	84.6	107.6	-	-	-
3	15		38.6	68.4	101.7	-	-	-
4	20		26.5	63.2	88.6	98.7	-	-
5	25		17.6	39.6	64.8	79.3	89.6	-
6	30		10.5	23.6	52.6	64.5	86.5	101.3
7	35		6.3	15.2	27.6	46.8	68.7	91.3
8	40		3.5	11.5	21.2	40.1	58.7	85.6
9	45		-	8.8	18.7	33.7	48.2	79.1
10	50		-	6.1	12.3	25.2	41.6	72.3

FIG.-3-21: CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM EUDRAGIT S-100 COATED BEADS.

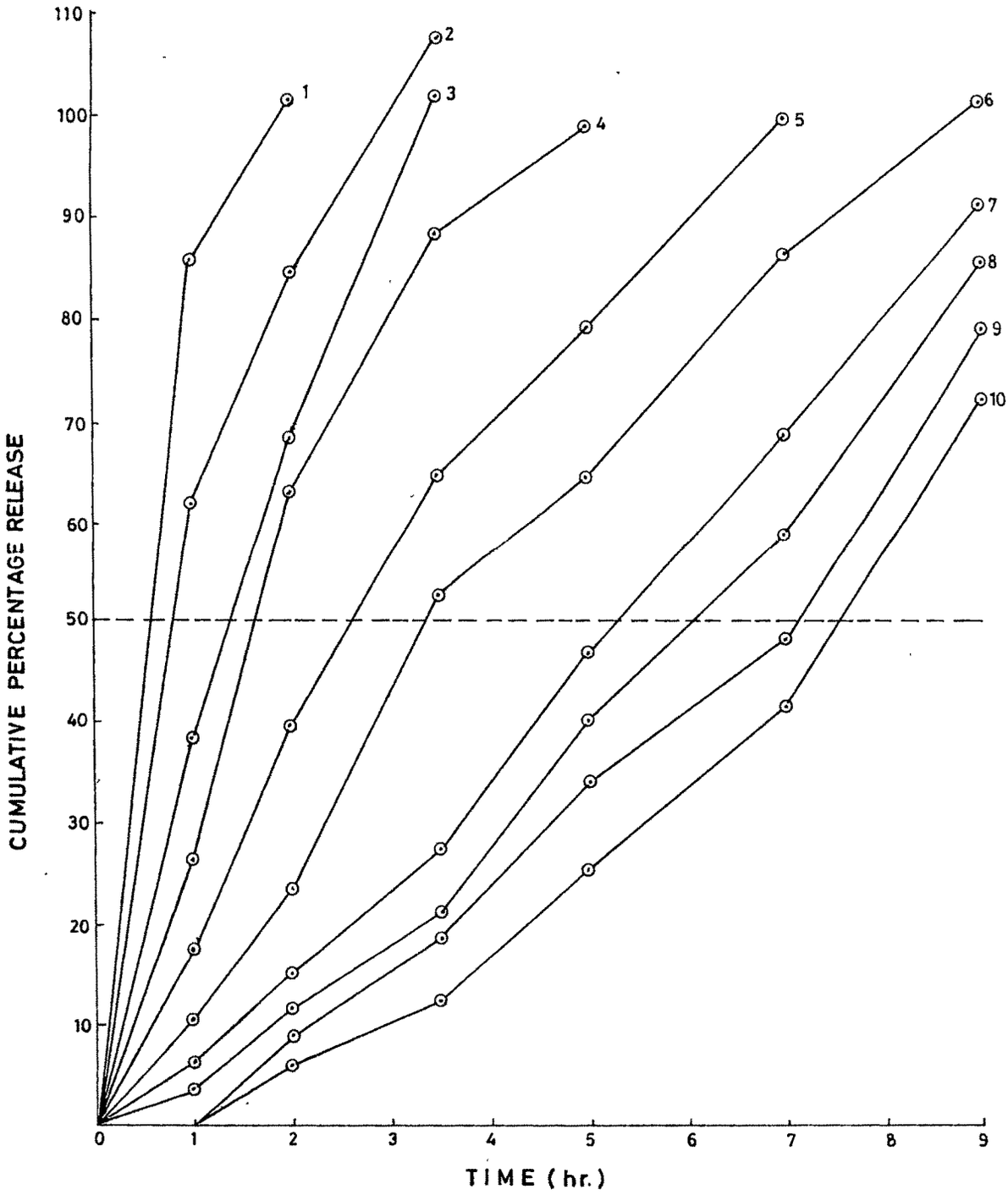


TABLE 3-22 : CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM EUDRAGIT RL100 COATED BEADS.

PRODUCT No.	PERCENTAGE OF COATING	CUMULATIVE PERCENTAGE RELEASE					
		TIME (hr)	1	2	3.5	5	7	9
		pH	1.2	2.5	4.5	7	7.5	7.5
1	5		71.5	89.6	101.2	-	-	-
2	10		60.2	79.6	104.4	-	-	-
3	15		48.6	69.6	94.3	99.8	-	-
4	20		31.5	54.2	89.6	101.2	-	-
5	25		22.8	45.3	78.7	107.3	-	-
6	30		18.7	36.4	69.8	93.2	104.2	-
7	35		15.6	28.2	61.2	83.4	102.6	-
8	40		8.5	18.7	52.1	74.5	93.7	108.2
9	45		7.3	13.7	43.2	61.2	82.3	99.7
10	50		5.7	11.3	34.6	58.6	71.6	91.8

FIG.-3-22: CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM EUDRAGIT RL-100 COATED BEADS.

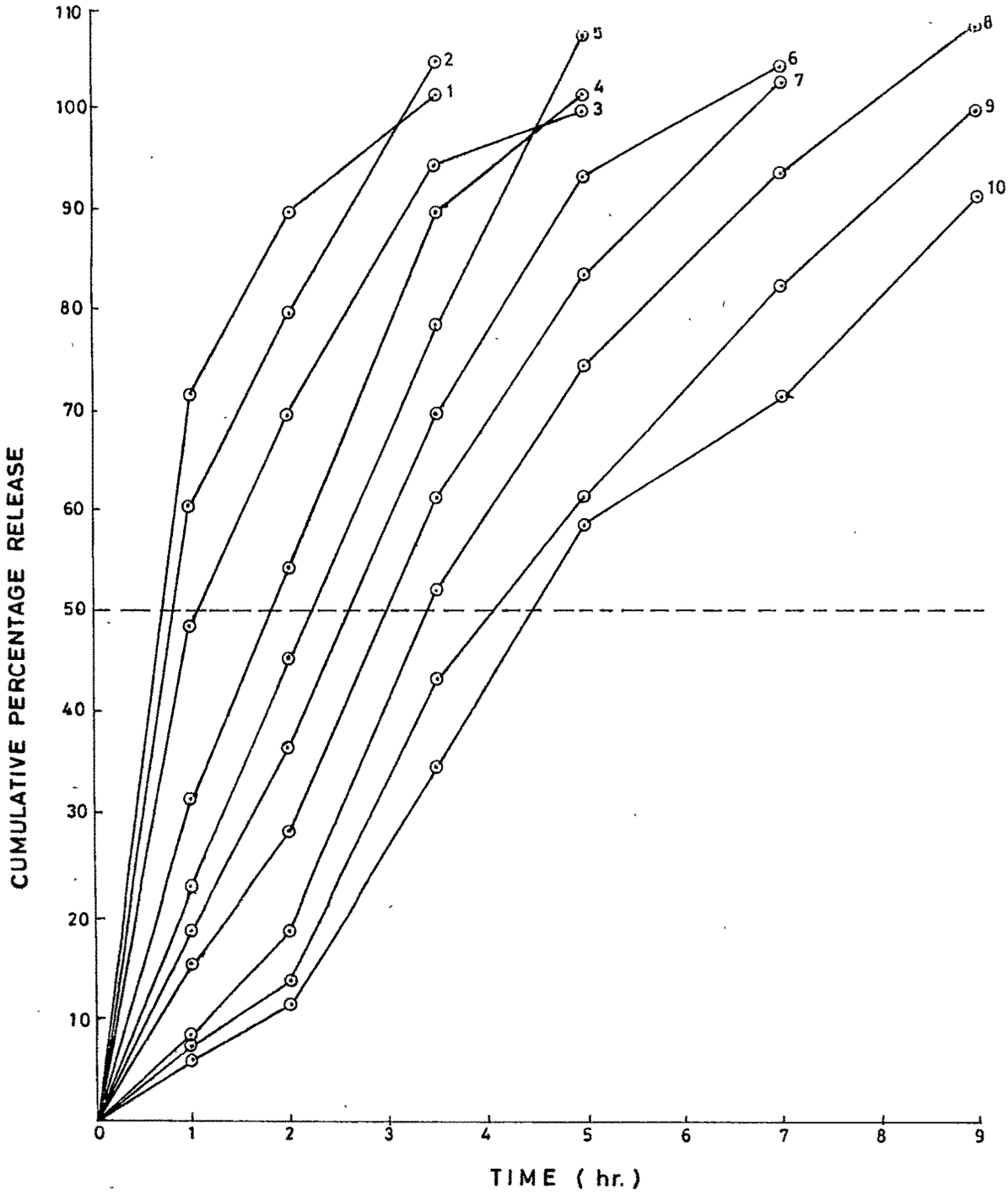


TABLE 3-23 : CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM EUDRAGIT RS100 COATED BEADS.

PRODUCT No.	PERCENTAGE OF COATING	CUMULATIVE PERCENTAGE RELEASE					
		TIME (hr)	1	2	3.5	5	7	9
		pH	1.2	2.5	4.5	7	7.5	7.5
1	5		52.5	71.8	93.6	104.1	-	-
2	10		40.3	65.6	87.5	101.2	-	-
3	15		29.7	58.6	81.4	99.8	-	-
4	20		18.2	40.6	73.5	94.5	101.3	-
5	25		16.7	31.3	64.5	89.6	105.7	-
6	30		15.2	25.6	52.5	83.6	103.7	-
7	35		8.6	18.6	43.4	72.6	95.7	98.7
8	40		6.2	15.2	33.5	59.7	87.5	102.2
9	45		1.8	10.9	25.6	45.6	81.5	100.7
10	50		1.1	5.2	18.7	39.6	72.3	104.5

FIG.·3-23: CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM EUDRAGIT RS-100-COATED BEADS.

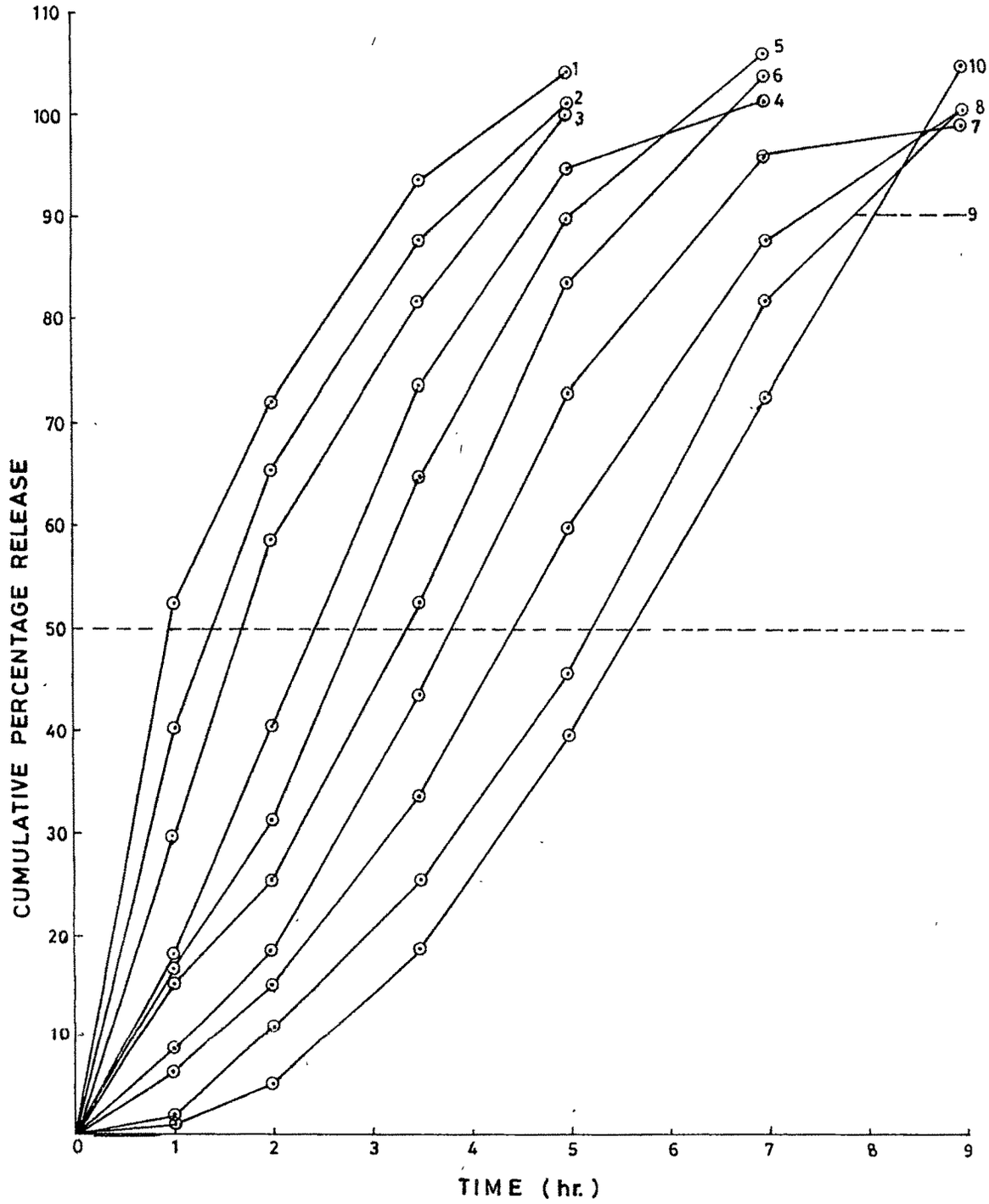
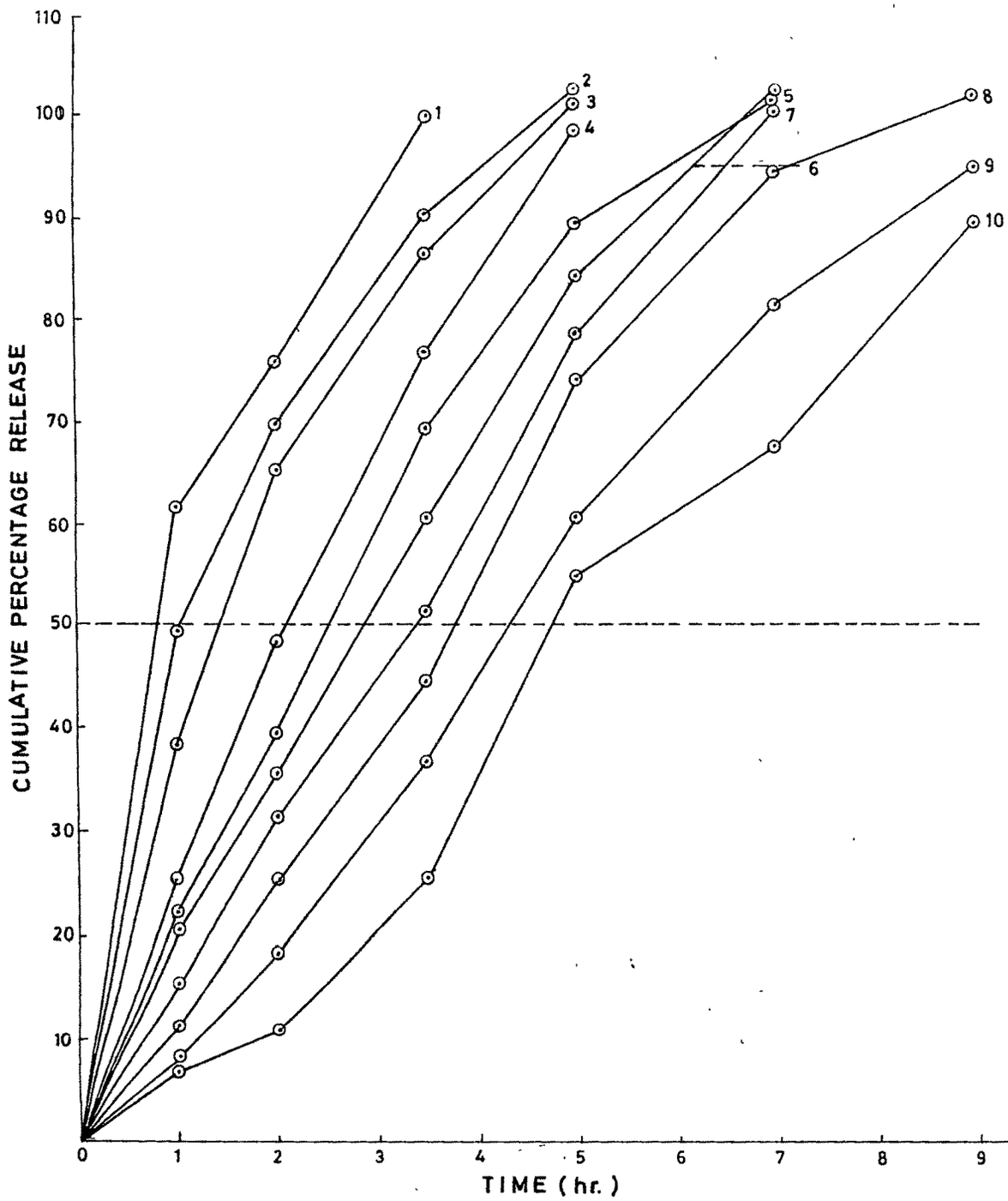


TABLE 3-24 : CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM EUDRAGIT RL100-RS100 (50:50) COATED BEADS.

PRODUCT No.	PERCENTAGE OF COATING	CUMULATIVE PERCENTAGE RELEASE					
		TIME (hr)	1	2	3.5	5	7	9
		pH	1.2	2.5	4.5	7	7.5	7.5
1	5		61.6	75.8	99.7	-	-	-
2	10		49.3	69.8	90.3	102.4	-	-
3	15		38.3	65.3	86.4	101.1	-	-
4	20		25.6	48.3	76.8	98.4	-	-
5	25		22.3	39.4	69.3	89.4	101.6	-
6	30		20.4	35.6	60.4	84.3	102.3	-
7	35		15.6	31.2	51.3	78.6	100.2	-
8	40		11.2	25.6	44.3	73.9	94.6	101.7
9	45		8.2	18.6	36.7	60.4	81.2	94.7
10	50		6.7	10.7	25.6	54.8	67.4	89.6

FIG. 3-24: CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM EUDRAGIT RL 100-RS 100 (50:50) COATED BEADS.



Eudragit S100 coated beads	Mix of plain beads and 6 (2:3)
Eudragit RS100 and RL100-RS100 coated beads	Mix of Eudragit RS100 - 8 Eudragit RL100-RS100 - 1 (6:4)

Glyceryl monostearate-bees wax and glyceryl distearate coated beads show larger inter-capsule variation (standard deviation) in release of hydralazine hydrochloride from the respective products. However, eudragit S100, eudragit RL100 and/or RS100 coated beads show less variation (standard deviation) in release of hydralazine hydrochloride from one capsule to the other.

(c) Eudragit S100 coated beads show good sustaining action with less inter-capsule variation in release of the drug. Eudragit S100 is soluble at pH 7, and hence these beads release most of the drug when beads reach to a region having pH value of 7.0 and above.

(d) Eudragit RL100 and/or RS100 coated beads show good sustaining action with less inter-capsule variation in release of the drug. The release of the drug from these beads was found to be independent of the pH of the dissolution medium.

Products of this type consist of hydralazine hydrochloride, avicel and other excipients in core with different sustaining material in coating.

Results of release of the drug from products of different coating materials tested in triplicate show that glyceryl monostearate-bees wax and glyceryl distearate coated beads have larger inter-capsule variation compared to eudragit S100, eudragit RL100 and/or RS100 coated beads. Release of the drug from these beads was found to be pH independent and reproducible. It has resulted in an yield of 85-90%. Photomicrographs of eudragit RS100 coated beads of hydralazine hydrochloride show nearly spherical beads with uniform coating. Hence product prepared with eudragit RL100 and/or RS100 coating was selected for in vivo studies. The use of the automatic air suspension coating apparatus, Uni-Glatt, might have helped in further reducing the variation in release of the drug from one capsule to the other.

(2) Matrix Tablets

The hydralazine hydrochloride matrix tablets prepared by the two processes consist of hydralazine hydrochloride, sustaining material, avicel and excipients.

Observations on release of the drug from this type of products are recorded in Tables 3-25 to 3-29 and shown graphically in Figures 3-25 to 3-29.

(a) $T_{50\%}$ values, as shown in figures, increase with increase in amount of sustaining material per tablet.

(b) Following products of different sustaining materials with a release pattern close to desired one were

TABLE 3-25 : CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM GLYCERYL MONOSTEARATE MATRIX TABLETS.

PRODUCT No.	Amount of G.M.& B.W. per tablet (mg)	CUMULATIVE PERCENTAGE RELEASE					
		TIME (hr)	1	2	3.5	5	7	9
		pH	1.2	2.5	5	7	7.5	7.5
1	5		41.1	55.3	65.2	85.7	104.6	-
2	10		32.5	48.7	59.7	80.3	99.4	-
3	15		32.1	43.6	55.2	72.3	95.6	101.6
4	20		28.3	41.2	50.9	67.4	89.6	104.5
5	25		25.6	38.3	51.4	64.8	84.6	102.3
6	30		24.5	33.5	48.7	67.6	81.5	99.7
7	35		25.7	36.7	52.6	61.3	80.2	92.6
8	40		21.5	31.5	48.9	62.6	78.3	97.5
9	45		19.8	28.6	45.8	55.7	77.6	94.6
10	50		20.7	24.5	39.6	51.7	75.7	85.2

Key G.M. - Glyceryl monostearate
B.W. - Bees wax

FIG.·3-25: CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM GLYCERYL MONOSTEARATE MATRIX TABLETS.

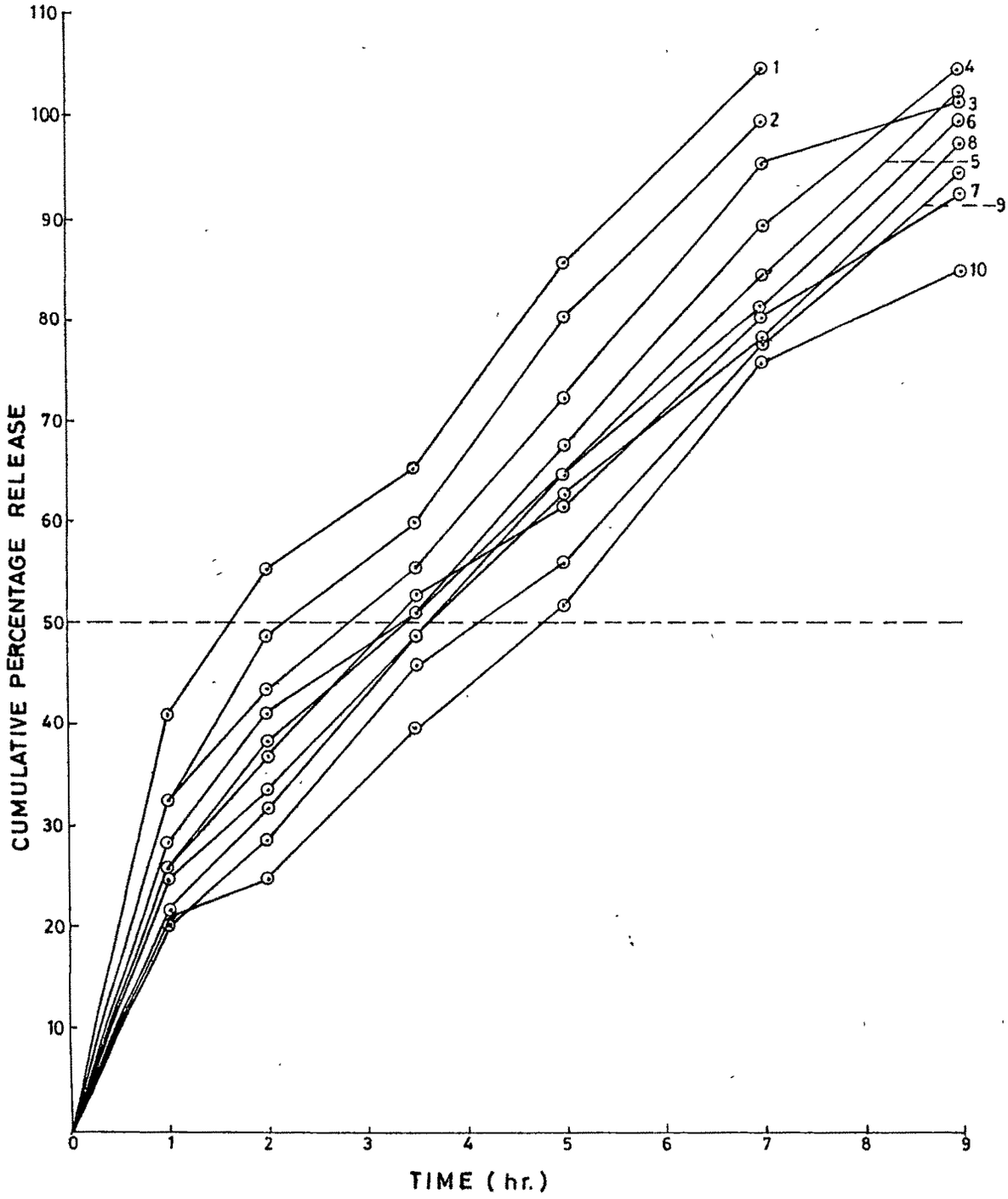


TABLE 3-26 : CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM GLYCERYL DISTEARATE MATRIX TABLETS

PRODUCT No.	Amount of G.D.per Tablet (mg)	CUMULATIVE PERCENTAGE RELEASE					
	TIME (hr)	1	2	3.5	5	7	9
	pH	1.2	2.5	5	7	7.5	7.5
1	5	32.7	51.8	63.4	78.3	95.7	101.5
2	10	30.3	47.6	61.2	74.4	91.6	97.6
3	15	27.7	41.5	55.4	69.7	84.3	101.5
4	20	24.5	36.7	53.2	64.3	85.6	103.6
5	25	23.5	31.5	47.2	61.5	81.5	95.7
6	30	20.3	27.6	41.3	55.7	75.3	89.6
7	35	22.3	25.6	39.7	46.9	70.3	81.5
8	40	18.7	25.7	38.4	45.7	67.6	83.5
9	45	19.3	20.3	35.4	41.5	61.2	73.6
10	50	15.3	21.3	31.7	42.5	60.6	71.1

Key G.D. - Glyceryl distearate

FIG.·3-26: CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM GLYCERYL DISTEARATE MATRIX TABLETS.

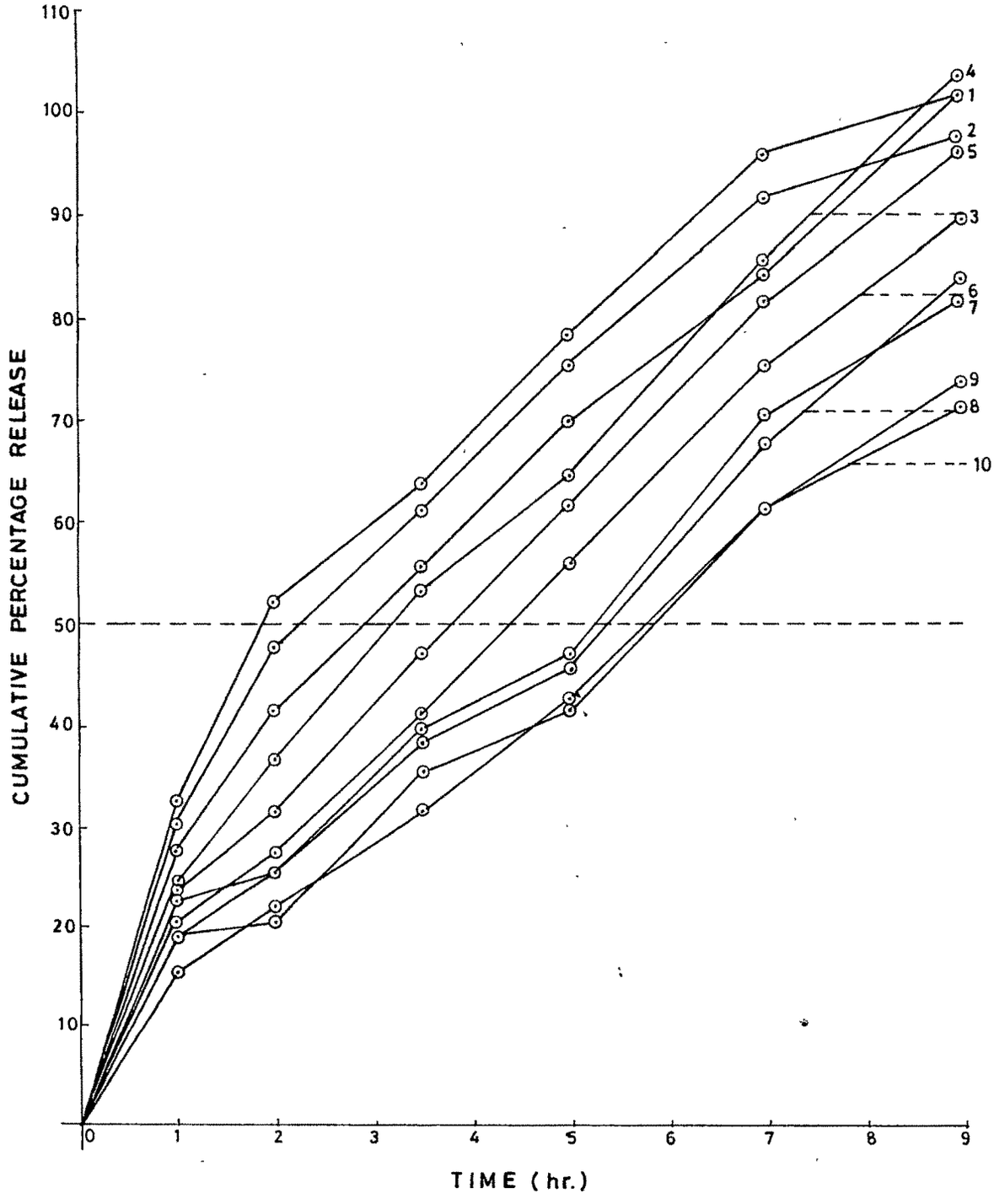


TABLE 3-27 : CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM EUDRAGIT RLPM MATRIX TABLETS.

PRODUCT No.	Amount of eudragit RLPM per Tablet (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
1	5	99.2	101.3	-	-	-	-
2	10	82.7	104.9	-	-	-	-
3	15	73.5	93.7	96.7	-	-	-
4	20	63.5	84.7	102.3	-	-	-
5	25	65.8	72.4	93.5	101.6	-	-
6	30	48.3	61.7	75.7	89.7	101.2	-
7	35	41.2	54.7	71.2	84.6	96.8	-
8	40	33.7	47.6	65.4	78.6	93.6	103.2
9	45	27.5	40.3	61.3	74.2	91.3	101.7
10	50	26.9	37.6	55.2	69.7	87.5	101.7

FIG. 3-27: CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM EUDRAGIT RLPM MATRIX TABLETS.

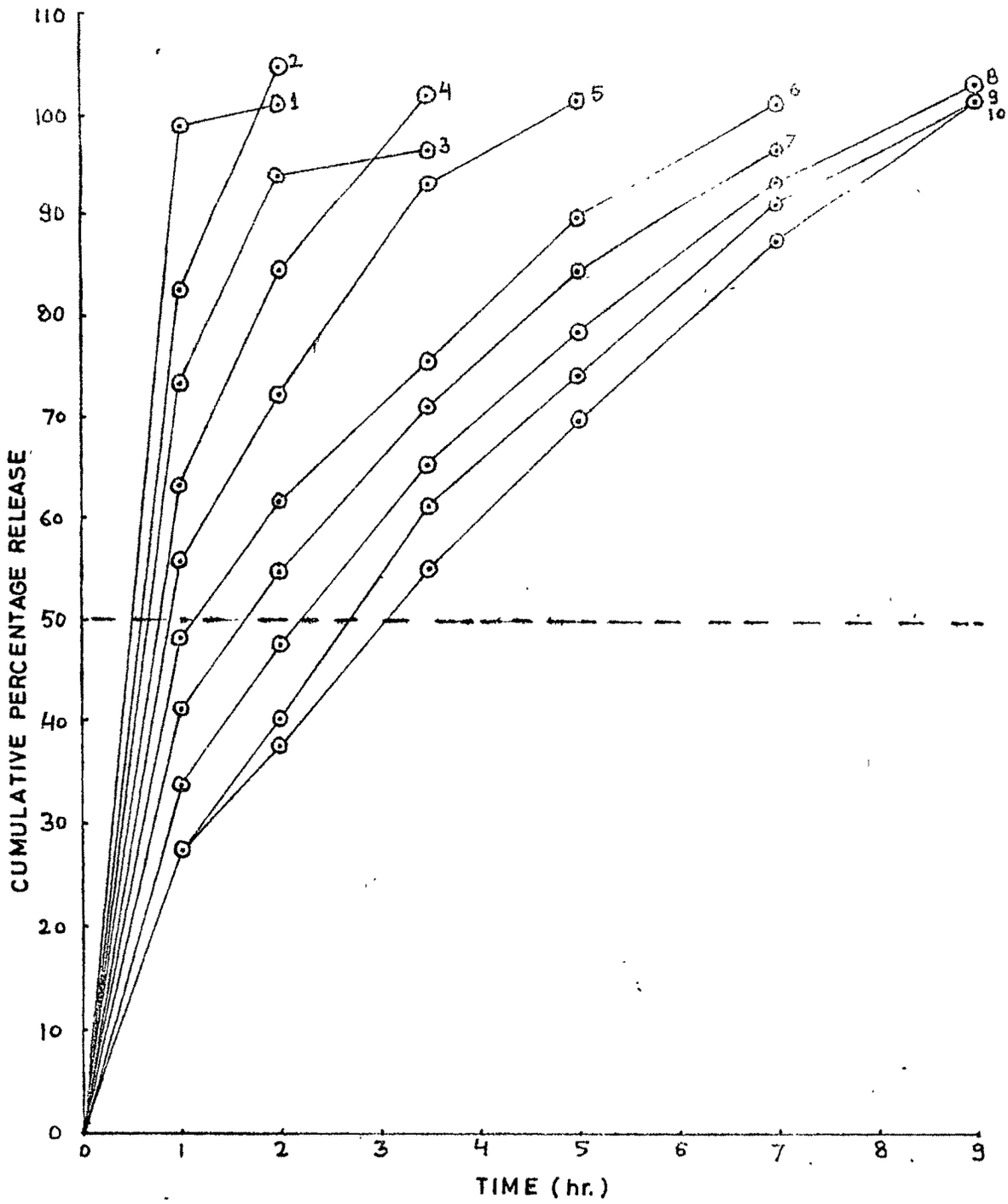


TABLE 3-28 : CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM EUDRAGIT RSPM MATRIX TABLETS.

PRODUCT No.	Amount of Eudragit RSPM per Tablet (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
1	5		85.2	101.6	-	-	-	-
2	10		60.1	85.2	103.5	-	-	-
3	15		52.3	69.7	83.5	99.1	-	-
4	20		45.6	62.5	78.3	90.2	106.2	-
5	25		33.6	45.3	67.3	85.6	101.3	-
6	30		29.7	41.4	63.5	78.6	92.5	105.3
7	35		24.4	34.8	59.7	72.5	87.5	99.9
8	40		20.1	30.3	56.7	65.3	81.7	102.5
9	45		18.3	26.5	50.3	62.2	76.4	94.7
10	50		15.3	21.7	48.9	61.7	73.5	91.5

FIG.·3-28: CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM EUDRAGIT RSPM MATRIX TABLETS.

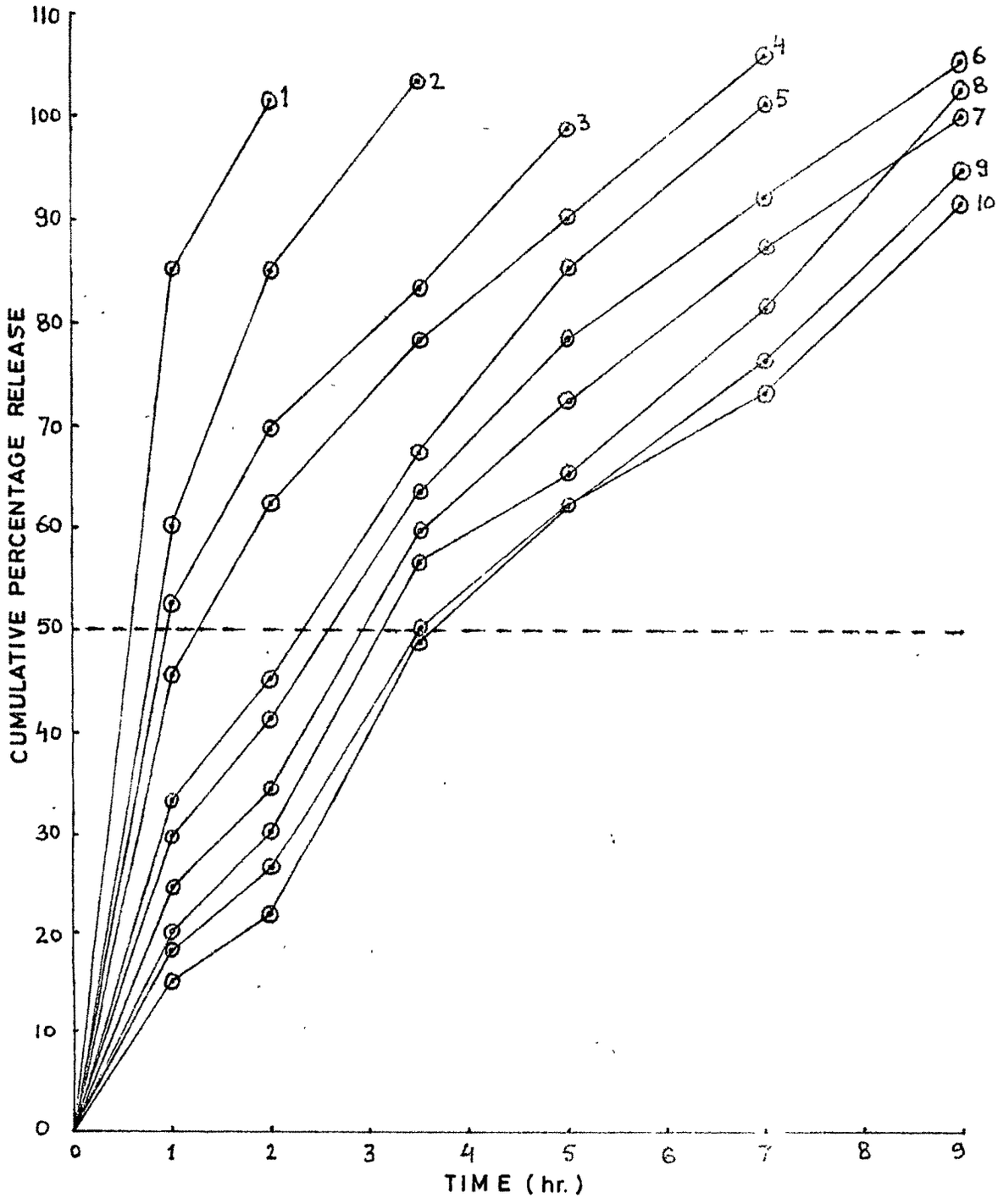


TABLE 3-29 : CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM EUDRAGIT RLPM-RSPM MATRIX TABLETS.

PRODUCT No.	Amount of Eudragit RLPM-RSPM per Tablet (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
1	30/ 5		25.4	36.7	58.7	73.7	94.6	101.3
2	25/10		28.3	39.8	59.7	76.4	98.4	102.4
3	20/15		32.7	43.8	63.5	81.3	99.3	-
4	15/20		36.8	49.7	66.4	85.7	102.5	-
5	10/25		38.2	51.2	69.3	88.3	101.3	-
6	25/ 5		30.6	43.1	67.9	81.6	95.6	101.2
7	20/10		33.2	45.3	68.7	88.5	102.5	-
8	15/15		38.5	53.5	73.6	91.7	104.3	-
9	10/20		40.6	59.5	76.3	97.6	99.7	-
10	5/25		45.7	63.7	81.5	101.3	-	-

FIG.·3-29: CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE FROM EUDRAGIT RL PM-RSPM MATRIX TABLETS.

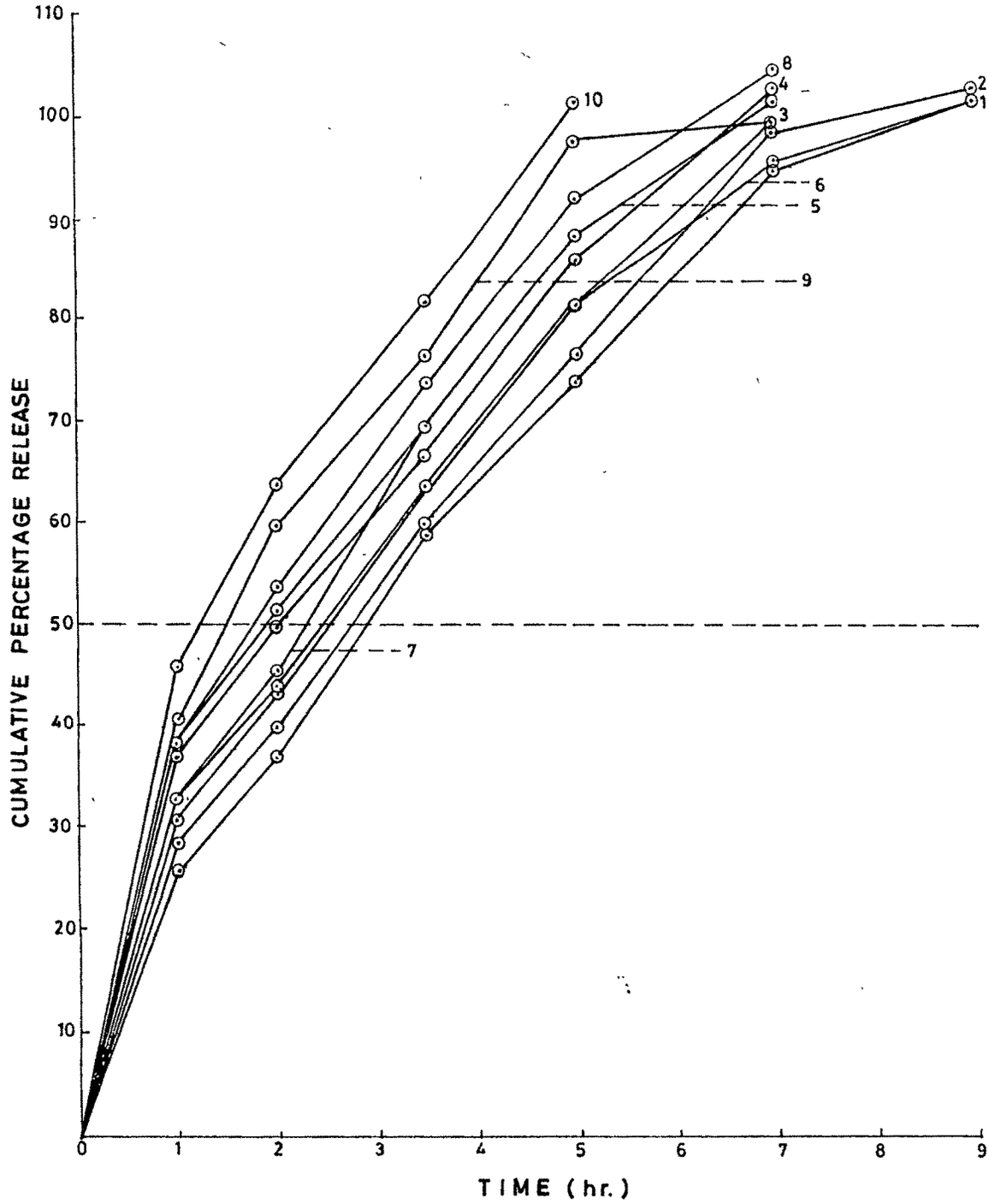


TABLE 3-30 : CUMULATIVE PERCENTAGE RELEASE OF HYDRALAZINE HYDROCHLORIDE IN VITRO FROM SELECTED PRODUCTS.

PRODUCT TYPE	PRODUCT No.	CUMULATIVE PERCENTAGE RELEASE					
TIME (hr)		1	2	3.5	5	7	9
pH		1.2	2.5	4.5	7	7.5	7.5
Glyceryl monostearate coated beads capsule	Mix of 4 and 10 (1:1)	31.7	51.6	71.6	81.7	93.6	101.2
		28.6	48.6	68.7	83.8	99.7	102.3
		35.6	52.3	65.7	78.2	89.8	104.1
		31.9±2.86	50.8±1.60	68.6±2.40	81.2±2.30	94.4±4.07	102.5±1.19
Glyceryl distearate coated beads capsule.	Mix of 4 and 7 (1:1)	30.6	51.4	81.2	85.7	102.7	-
		28.3	48.6	75.6	88.6	103.2	-
		25.7	55.7	73.5	82.5	98.3	-
		28.2±2.00	51.9±2.92	76.8±3.24	85.6±2.49	101.4±2.20	-
Eudragit S100 coated beads capsule	Mix of plain beads 2 and 6 (2:8)	32.6	44.2	65.5	70.5	89.2	101.2
		28.6	43.5	66.7	72.8	87.3	103.0
		31.6	41.7	68.4	71.6	90.4	102.1
		30.93±1.70	41.3±1.05	66.8±1.19	71.6±0.94	88.97±1.28	102.1±0.73

TABLE 3-30 : Contd.

PRODUCT TYPE	PRODUCT No.	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 &/or RS100 coated beads Capsules.	Mix of Eudragit RS100- 8 and Eudragit RL100-RS100-1 (6:4)	30.4	41.1	58.7	73.4	96.2	101.2
		32.7	40.3	59.2	72.9	93.9	103.4
		29.9	38.8	58.6	74.2	93.7	99.8
		31.1±1.21	40.0±0.95	58.8±0.26	73.5±0.53	94.6±1.13	101.4±1.48
Glyceryl monostearate Matrix Tablets	3	32.1	43.6	55.2	72.3	95.6	101.6
		31.6	48.3	59.6	69.1	90.3	101.5
		28.7	42.5	61.3	75.2	93.7	102.0
		30.8±1.50	44.8±2.51	58.7±2.57	72.2±2.50	93.2±2.19	101.7±0.21
Glyceryl distearate Matrix Tablets	2	30.3	47.6	61.2	75.4	94.6	97.6
		32.6	43.4	63. 4	73.2	94.5	101.3
		29.2	45.7	59.7	78.1	98.4	103.6
		30.7±1.41	45.5±1.71	61.4±1.52	75.5±2.00	96.2±1.81	100.8±2.47
Eudragit RLPM/RSPM Matrix Tablets	2	28.3	39.8	59.7	76.4	98.4	102.4
		30.3	41.6	58.6	73.5	95.7	101.5
		31.2	41.2	57.5	75.8	98.5	102.3
		29.9±1.21	40.8±0.77	58.6±0.89	75.23±1.25	97.53±1.29	102.1±0.40

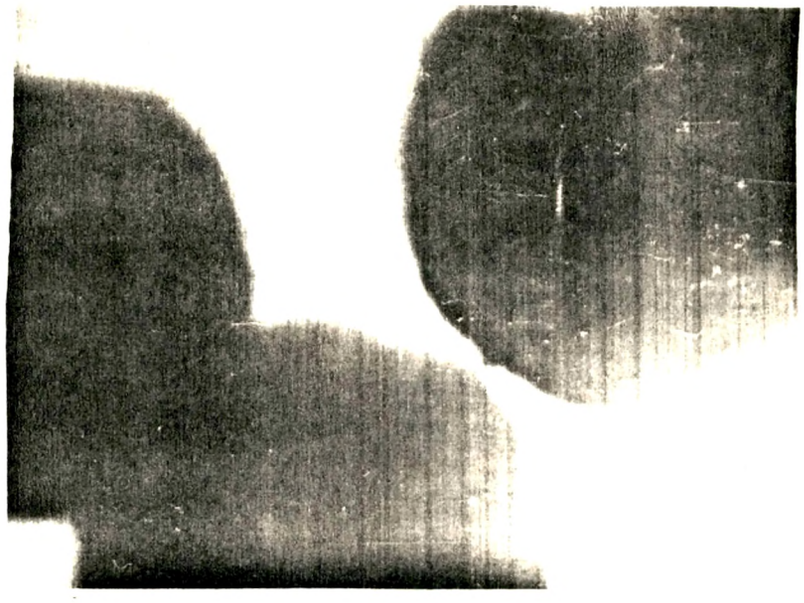


FIG. 3-30 A: PHOTOMICROGRAPH OF EUDRAGIT RS 100 COATED BEADS OF HYDRALAZINE HYDROCHLORIDE (X 40)

FIG. 3-30 B: PHOTOMICROGRAPH OF EUDRAGIT RS 100 COATED BEAD OF HYDRALAZINE HYDROCHLORIDE SHOWING CORE AND COATING (X 100)

subjected to *in vitro* dissolution test in triplicate and observations are shown in Table 3-30.

	Product No.
Glyceryl monostearate-bees wax matrix tablets	3
Glyceryl distearate matrix tablets	2
Eudragit RLPM and/or RSPM matrix tablets	2

Glyceryl monostearate and glyceryl distearate matrix tablets show larger inter-tablet variation (standard deviation) in release of the drug from these tablets. Eudragit RLPM and/or RSPM matrix tablets show less inter-tablet variation in release of the drug.

(c) Eudragit RSPM matrix tablets show more prolongation in release of the drug as compared to eudragit RLPM matrix tablets. However, mix of the two gave tablets with intermediate prolongation in release of the drug as desired.

Process for glyceryl monostearate-bees wax and glyceryl distearate matrix tablet preparation was tedious, gave less yield and less reproducible results as compared to eudragit RLPM and/or RSPM matrices. Tablets made with combination of eudragit RLPM-RSPM were found most close to the desired release pattern with less inter-tablet variation in release of the drug were selected for *in vivo* studies.

* * * * *

REFERENCES

1. Borodkin, S. and Tucker, F.E., J. Pharm. Sci., 1974, 63, 1359.
2. Donbrow, M. and Friedman, M., ibid., 1975, 64, 76.
3. Coletta, V. and Rubin, H., ibid., 1964, 53, 953.
4. Sjogren, J. and Ostholm, I., J. Pharm. Pharmacol., 1961, 13, 496.
5. Lapidus, H. and Lordi, N.G., J. Pharm. Sci., 1966, 55, 840.
6. Rosen, E. and Ellison, T., Tannenbaum, P., Free, S.M., and Crosley, A.P., ibid., 1967, 56, 365.
7. Rosen, E. and Polk, A., Free, S.M., Tannenbaum, P.J., and Crosley, A.P., ibid., 1967, 56, 1285.
8. Royal, J., Drug Standards, 1958, 26, 41.
9. Khalil, S.A.H., and Elgamal, S.S., J. Pharm. Pharmacol., 1971, 23, 72.
10. Royal, J., Drug Standards, 1959, 27, 1.
11. Chaudhry, N.C. and Saunders, L., J. Pharm. Pharmacol., 1956, 8, 975.
12. Wulff, O., J. Pharm. Sci., 1965, 54, 1058.
13. Schlichting, D.A., ibid., 1962, 51, 134.
14. Theeuwes, F., ibid., 1975, 64, 1987.

15. Hamlin, W.E., Northam, J.I., Wagner, J.G., ibid., 1965, 54, 1651.

16. Martin, B.K., Nature, 1965, 207, 274.

17. Martin, B.K., ibid., 1965, 207, 959.

18. Fincher, J.H., J. Pharm. Sci., 1968, 57, 1825.

19. Gibaldi, M., Nagashima, R. and Levy, G., ibid., 1969, 58, 193.

20. Evans, G.H., Nies, A.S. and Shand, D.G., J. Pharmacol. Exp. Ther., 1973, 186, 114.

21. "The United States Pharmacopoeia, 20th rev., U.S. Pharmacopeial Convention, Inc., Rockville, Md., U.S.A., 1980, p. 959.

22. "The National Formulary" 14th Ed., American Pharmaceutical Association, Washington, DC., U.S.A., 1975, p. 985.

23. Nelson, E., J. Amer. Pharm. Assoc. (Sci. Ed.), 1957, 46, 572.

24. Rowland, M. and Beckett, A.H., J. Pharm. Pharmacol., 1964, 16, 156T.

25. Kruger-Thiemer, E., and Eriksen, S.P., J. Pharm. Sci., 1966, 55, 1249.

26. Robinson, J.R. and Eriksen, S.P., ibid., 1966, 55, 1254.

27. Bennett, J.V., Mickelwait, J.S., Barrett, J.E., Brodie, J.L., and Kirby, W.M.M., "Antimicrob. Agents Chemother.", 1965, p. 180.

28. Doluiso, J.T. and Dittert, L.W., Clin. Pharm. Ther., 1969, 10, 690.

29. Davis, C.M., Vandersarl, J.V., Kraus, E.W., Amer. J. Med. Sci., 1973, 265, 69.

30. Corn, M.E., U.S.3, 499, 959, 1970; through Colbert, J.C., "Controlled Action Drug Forms", Noyes Data Corporation, New Jersey, 1974, p. 217.

31. Talseth, T., Eur. J. Clin. Pharmacol., 1976, 10, 395; through C.A., 1977, 86, 100742n.

32. Talseth, T., ibid., 1976, 10, 183; through C.A., 1976, 85, 186459q.

33. Lesser, J.M., Israili, Z.H., Davis, D.C., Dayton, P.G., Drug Metab. Dispos., 1974, 2, 351.

34. Talseth, T., Fauchald, P., Pape, J.F., Curr. Ther. Res., 1977, 21, 157.

* * * * *