# CHAPTER IV

## USE OF LASER DRILLED CAPSULES IN DESIGNING SUSTAINED RELEASE CAPSULES

The class of drugs known as β-adrenoreceptor blocking agents have been widely used in the treatment of hypertension and angina. Propranolol hydrochloride was the first -adrenergic blocking agent to give this wide spread acceptance in the clinical practice (1). It has 2-6 hr plasma half-life in man following intravenous or oral administration (2,3), is normally administered two to four times daily and has been shown to be effective for the treatment of hypertension when dosed twice daily (4). Therapy for both hypertensive and anginal patients is long term and it has been shown that compliance for hypertensive patients can be a problem (5,6). A sustained release dosage form of propranolol hydrochloride was therefore, developed to provide simple, acceptable and effective preparation that could be given once or twice daily and produce both a steady propranolol blood level and a steady degree of beta blockade. Of many methods available for formulating sustained release products, a plastic matrix tablet and coated granules were thought appropriate because of relatively high water solubility of propranolol hydrochloride and its rapid absorption throughout the GIT (7).

Laser drilling technique can be successfully employed in designing controlled drug delivery system, and the drug delivery may be controlled by the variation in number and diameter of the laser drilled pores made on the body of the capsule (experimental findings from Chapter II). Drugs with good water solubility, independent of pH are ideal for encapsulation in such a drug delivery system (Chapter III.A & B).

The objectives of this part of the study were to :

i) design a sustained release capsule dosage form capable of delivering the loading dose immediately and then the maintenance dose at a controlled rate;

ii) use the above dosage form designed to prepare propranolol hydrochloride sustained release capsule (Laser Drilled SR capsule) for maintaining the blood level of the drug for 12.0 hr; and

iii) make a comparative evaluation of the <u>in vitro</u> and <u>in vivo</u> performance of the Laser Drilled SR capsule with that of Inderal® LA and Inderal® conventional tablets.

## EXPERIMENTAL

Designing Laser Drilled SR Capsules - The laser drilled SR capsule (Figure IV.1) consisted of an outer Mother capsule with the loading dose and an inner Baby capsule, encapsulating the maintenance dose. The amount of propranolol hydrochloride to be taken as loading dose and the maintenance dose in the preparation of Laser Drilled SR capsule was calculated as follows; based on the reported (8) pharmacokinetic data, Table IV.1 considering the average weight of an individual as 70.0 kg with a view to maintain an average therapeutic blood level concentration of about 52.5 ng/ml of the plasma, for 12.0 hr. Loading dose was calculated based on equation (1) (9),

$$D_t = V_d P_t \qquad \ldots \text{ Equation (1).}$$

where, $V_d$ is the apparent volume of distribution and $D_t$ and $P_t$ represent respectively the total amount of the drug in the body and the concentration of the drug in the blood at some time, t.

Substituting the values of $V_d$ and $P_t$ (Table IV.1)

$$D_t = 3.9 \times 70 \times 52.5 \times 1000$$
$$= 14.33 \text{ mg}$$

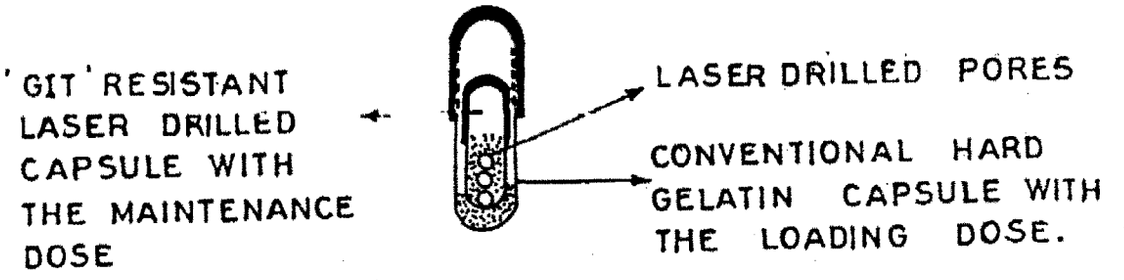


Figure IV.1- Schematic Figure of the Sustained Release Dosage Form Designed.

Table IV. 1 : Pharmacokinetic Data of Propranolol

| Availability (oral) % | Urinary Excretion % | Bound in Plasma % | Clearance ml $min^{-1}$ $kg^{-1}$ |
|---|---|---|---|
| 36±10 | 0.5 | 93.3±1.2 | 12±3 |
| **Volume of Distribution (Vd)** | **Half Life ($t_{0.5}$)** | **Effective Concentration** | **Toxic Concentration** |
| 3.9±0.6 | 3.9±0.4 | 20 ng/ml* | - |

* Effective Concn. Range 15-90 ng/ml, av. = 52.5 ng/ml

Since only 36.0% of the orally administered drug is available, the amount of the drug need to be administered would be :

$$\frac{14.33 \times 100}{36} = 39.89 \text{ mg} \simeq 40.0 \text{ mg}$$

For calculating the maintenance dose, the rate of elimination of propranolol was considered.

Clearance = 12.0 ml $min^{-1}$ $kg^{-1}$ (Table IV.1)

$\therefore$ Rate of elimination = $\frac{52.5 \times 12 \times 60 \times 70}{10^{-6}}$

= 2.65 mg $hr^{-1}$

$\therefore$ In order to maintain the blood level, the amount of drug need to be released as the maintenance dose from the Baby capsule, considering that only 36.0% of the orally administered drug is available, would be :

$$\frac{2.65 \times 100}{36} = 7.36 \text{ mg} \simeq 8.0 \text{ mg hr}^{-1}$$

$\therefore$ To maintain the release of the drug for 8.0 hr, the amount of the drug need to be encapsulated in the Baby capsule as the maintenance dose would be :

$$8.0 \text{ mg hr}^{-1} \times 8 \text{ hr} \simeq 65.0 \text{ mg}$$

The preliminary studies were carried out to optimize the number and diameter of the drilled pores to get the required

release rate, by preparing Laser Drilled SR capsules as per above calculations.

Mother Capsule - The Mother capsule was prepared by encapsulating 40.0 mg of propranolol hydrochloride[1] in conventional No. 0 hard gelatin capsules.[2]

Baby Capsule - Conventional hard gelatin capsules[2] were made GIT resistant by formalin vapour treatment (Chapter II, page 52) and 5, 10 and 15 drilled minute pores were made on the body of the capsules separately, by laser drilling (Chapter II, page 56). The capsules were filled with 65.0 mg propranolol hydrochloride using lactose as the diluent, and band sealed with a suitable GIT resistant material. Based on the results of the preliminary studies the Laser Drilled SR capsules for comparative *in vitro* and *in vivo* studies with the commercial products were then prepared as above, but, with 35.0 mg and 65.0 mg of propranolol hydrochloride taken as the loading and maintenance dose in Mother and Baby capsule respectively.

Commercial Products - The commercial product Inderal® LA[3],

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1. Propranolol Hydrochloride, Sarabhai Research Center, ase, Wadi Wadi, Baroda 390 007 (INDIA).
2. Hard gelatin capsules, Associated Capsules, Kandivali, Bombay 400 067 (INDIA).
3. Inderal LA Capsules 160.0 mg, propranolol hydrochloride B.P., 160.0 mg, long acting capsules, ICI Limited, Pharm. Division, Macclesfield, Cheshire, GREAT BRITAIN.

each containing 160.0 mg of propranolol hydrochloride and Inderal® conventional tablet[4] each containing 40.0 mg of propranolol hydrochloride were procured through proper channels of distribution.

In Vitro Dissolution Assessment - Dissolution studies were carried out in USP XX (10) dissolution apparatus using a basket stirrer assembly at a stirrer speed of 100 rpm and the dissolution medium temperature held at 37±0.5°C. 300.0 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 NF (11), under timed Release Tablets and Capsules In Vitro Test Procedure. 5.0 ml samples were withdrawn at the end of 0.1, 1.0, 2.0, 3.5, 5.0, 6.0, 7.0 and 8.0 hr time intervals, filtered and analysed at 290 nm using a spectrophotometer[5]. Beer's plot of propranolol hydrochloride at 290 nm in different buffer solutions was prepared (Figure IV.2), and was used as the standard curve for the determination of the amount of propranolol hydrochloride in test solutions.

In Vivo Study - A crossover study was carried out with one week washout period in between on six mongrel dogs weighing 6-10 kg as the subjects in three groups of two dogs each. The treatment consisted of Laser Drilled SR

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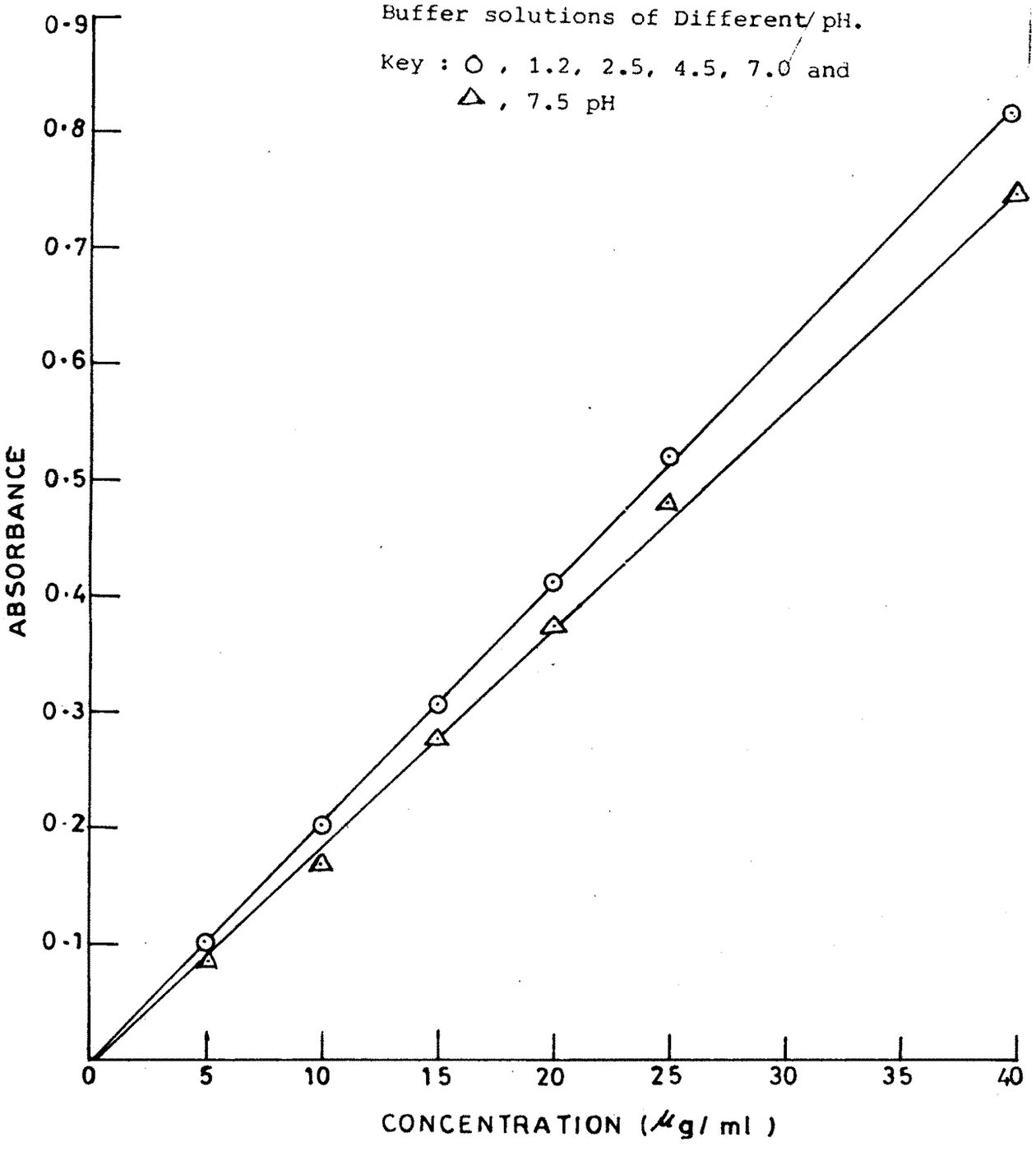
4. Inderal, Propranolol Tablets, I.P. The Aikal Chemical Corporation of India Limited, Ennove, Madras (INDIA).
5. Model VSU 2-P, C.Z. Spectrophotometer, GERMANY.

Figure IV.2- Beer's plot of Propranolol Hydrochloride in Buffer solutions of Different pH.

Key : ○ , 1.2, 2.5, 4.5, 7.0 and
△ , 7.5 pH



capsule (Treatment I) and Inderal® LA capsule (Treatment II). The *in vivo* study of Inderal® conventional tablets (Treatment III) was carried out on six dogs separately. Starting at 8.30 a.m. on the day of the experiment, the dogs were weighed and anaesthetised with pentobarbitone sodium[6] (30 mg/kg i.p. and maintenance dose of i.v. 5 mg/ml solution was administered when necessary). The capsules/tablets were administered orally with 100.0 ml of water after withdrawing zero-time blood samples from femoral vein, which was earlier canulated. 3.0 ml of blood samples were then collected at 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0 and 12.0 hr after administration of each treatment. Sterile normal saline solution[7] was infused prior to and after blood sampling; the blood samples were centrifuged immediately and the plasma was stored frozen until analysed.

Spectro-Fluorimetric Determination of Propranolol - The analytical method employed for the determination of propranolol in the plasma was based on the method reported by Offerhans and Van der Vecht (12). It involves extraction of propranolol in an alkaline medium using hexane containing 1.5% v/v isoamyl alcohol as the extraction fluid.

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6. Pentobarbitone sodium (Nembutol capsules), Abbott Laboratories, Bombay (INDIA).
7. Normal Saline Injection I.P., Parenteral Preparation Department, S.S.G. Hospital, Baroda 390 001 (INDIA).

Propranolol was further extracted from the organic phase to the aqueous phase using 0.01 N HCl as the extraction fluid. The content of propranolol present was then determined by measuring the fluorescence of aqueous phase at excitation and emission wavelength of 290 nm and 350 nm respectively, using a spectrophoto-fluorimeter[8]. Figure IV.3 shows the standard curve for propranolol hydrochloride which was used for calculation of the amount of the drug present in sample solutions.

## RESULTS AND DISCUSSION

The preliminary <u>in vitro</u> dissolution rate study results (Figure IV.4) indicate that the Mother capsule released the drug immediately as expected (within 10 min), while the Baby capsule released the drug slowly, at different rates depending on the number of drilled pores,n on the body of the capsule, following zero-order kinetics, irrespective of the pH of the dissolution media. The Baby capsule with n equal to 5, 10 and 15 released the maintenance dose at a rate of 9.99, 33.23 and 47.82%/hr respectively after releasing the loading dose immediately.

Based on the results of the above preliminary study the number of laser drilled pores which should be made on

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8. Aminco-Bowman Spectrophoto-fluorimeter, American Instrument Co., Silver Spring, Md, U.S.A..

Figure IV.3- Standard Curve for Fluorimetric Determination of Propranolol Hydrochloride.

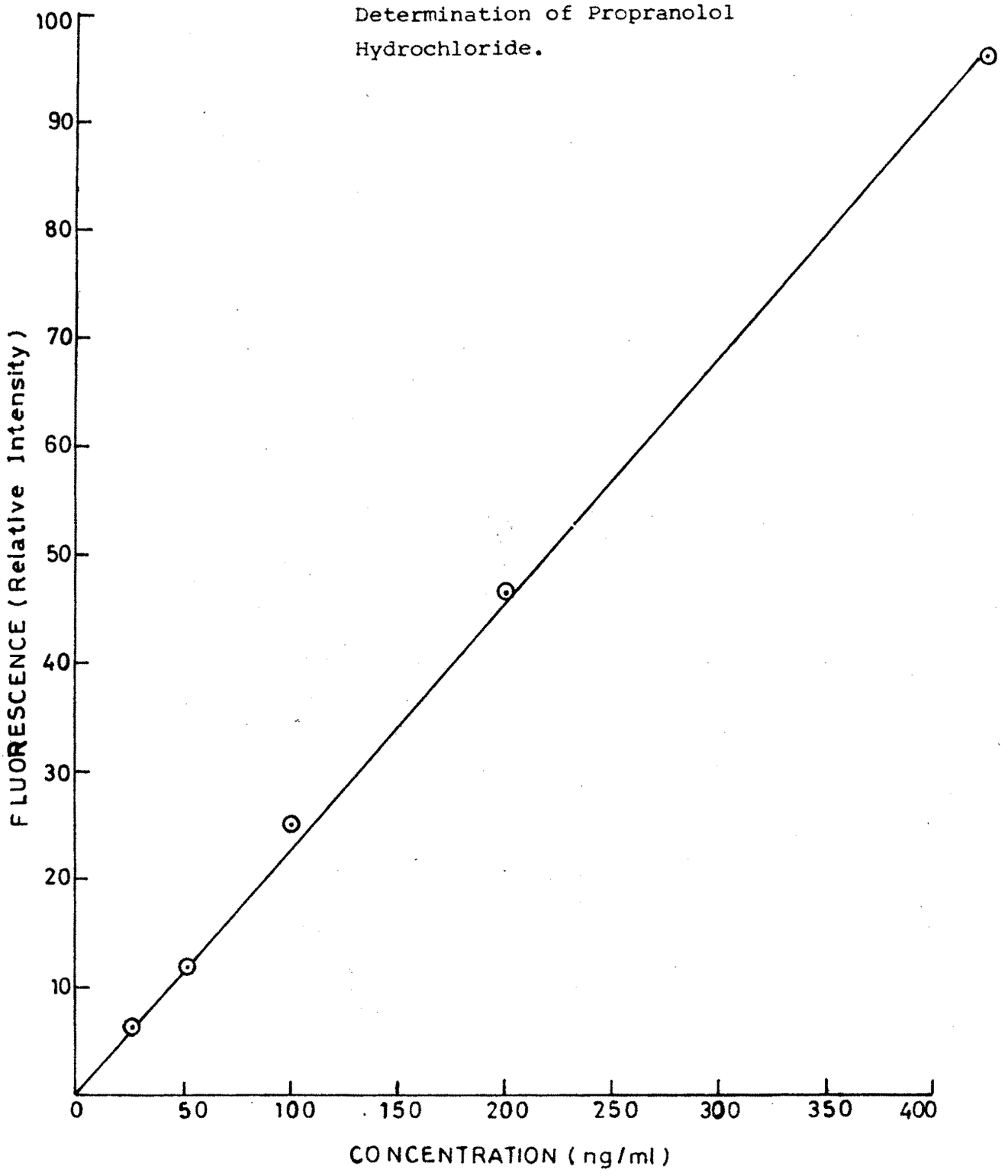
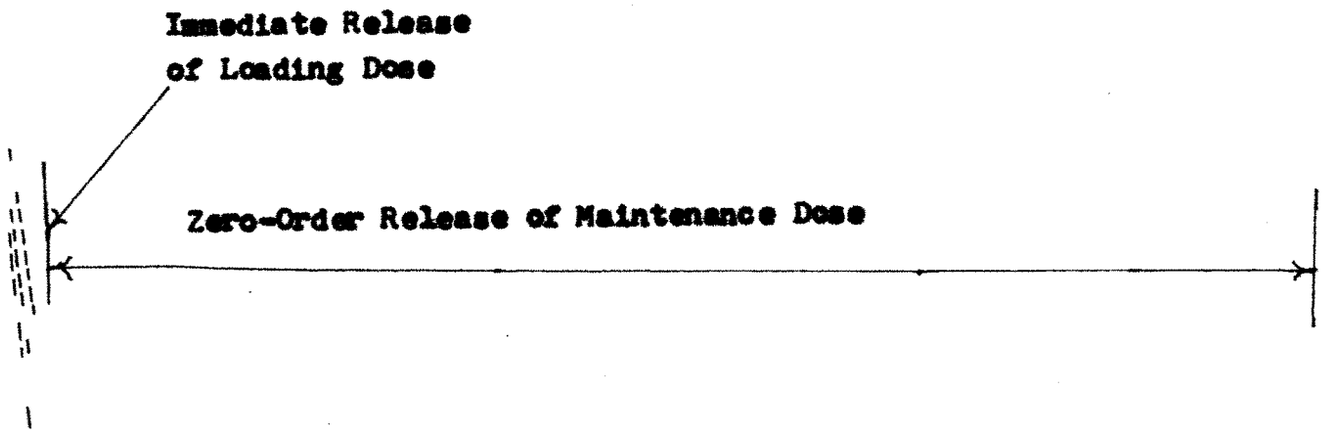
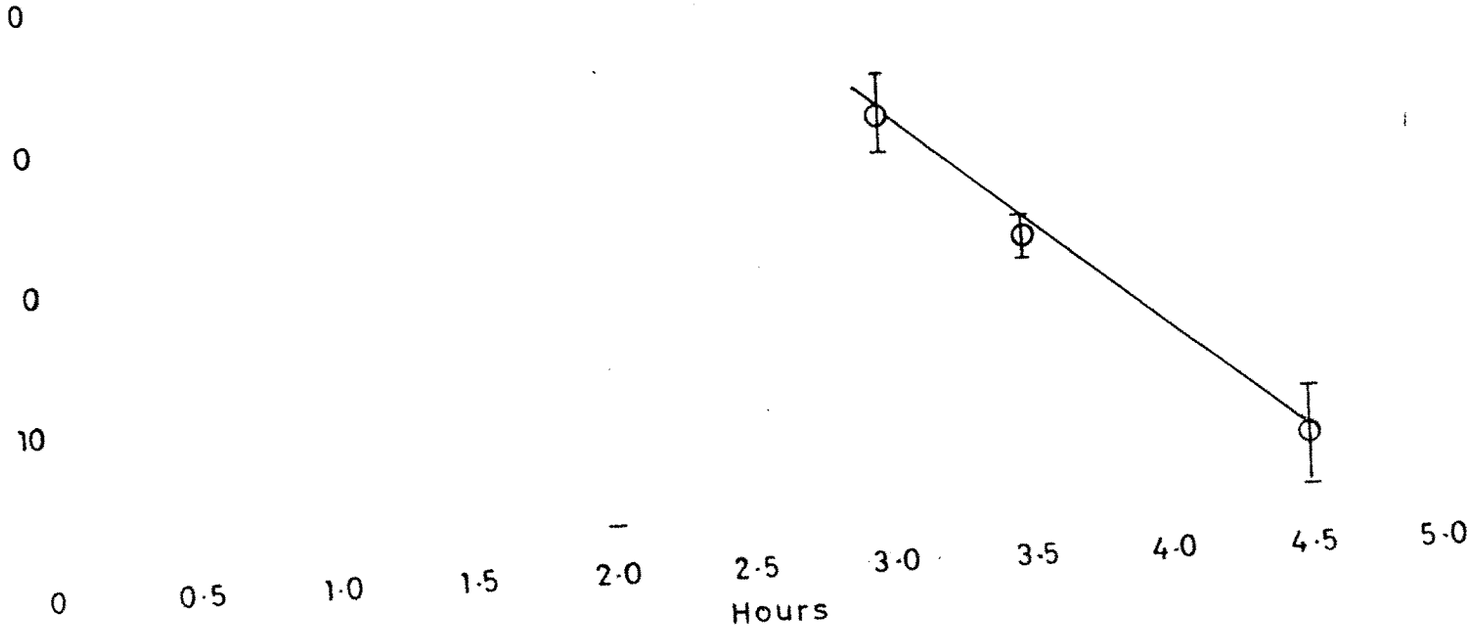


Figure IV.4- Effect of Variation in Number of Drilled Pores, n, on Release of Loading and Maintenance Dose Expressed as Percent Drug Retained vs. Time. Key: ○ n,= 5, ●,n= 10 and △, n= 15.



the body of the Baby capsule, in order to get the desired release rate of the maintenance dose i.e. 8 mg $hr^{-1}$ was calculated and found to be equal to 3 drills of about 100 um average diameter. One more important observation made from the result of the preliminary study (Figure IV.4) is that the Baby capsule also begins to release the maintenance dose after a very short lag period. Robinson and Erikson (13) suggested that in such a case a correction on loading dose is necessary due to contribution from the maintenance portion based on equation (2) (13),

$$D_1^{corr} = D_1 - Rt_p \qquad \text{... Equation (2)}$$

where $D_1$ is the loading dose and $Rt_p$ is the correction on the initial dose necessary due to supply of drug from the maintenance portion over the time period zero to peak time. A trial experiment indicated that a Baby capsule with 3 drilled pores on the body releases about 5.0 mg of propranolol hydrochloride in the first hour. Hence based on equation (2), the loading dose (corr) to be encapsulated in the Mother capsule would be :

$$D_1^{corr} = 40 - 5 = 35.0 \text{ mg}$$

The Laser Drilled SR capsules for the comparative *in vitro* and *in vivo* performance study were prepared based on these calculations.

The comparative in vitro dissolution profile as shown in Figure IV.5 was constructed by plotting percent drug retained versus time. Laser Drilled SR capsules released 34.0% of the drug within 0.1 hr, which corresponds to the loading dose filled in Mother capsule, indicating that Mother capsule disintegrated immediately releasing the loading dose as desired. The inner Baby capsule released the contents slowly at a contrclled rate of 8.31%/hr following zero-order kinetics irrespective of the pH of the dissolution media. Relatively Inderal® LA capsules released the loading dose over a period of 2.0 hr at a rate of 12.64%/hr and the maintenance dose at a rate of 7.69%/hr following zero-order kinetics like laser drilled SR capsules. Inderal® conventional tablet like Mother capsule of Laser Drilled SR capsule released 50.0% of the loading dose in less than 30 min.

Figure IV.6 is a plot of mean propranolol plasma concentration (ng/ml±SE) as a function of time, for the three treatments studied. The mean propranolol plasma concentrations for the three treatments were compared at each sampled time by t-test, with suitable treatment interactions (Table IV.2); Treatment I showed significantly higher mean plasma levels than that of Treatment II ($P < 0.01$)

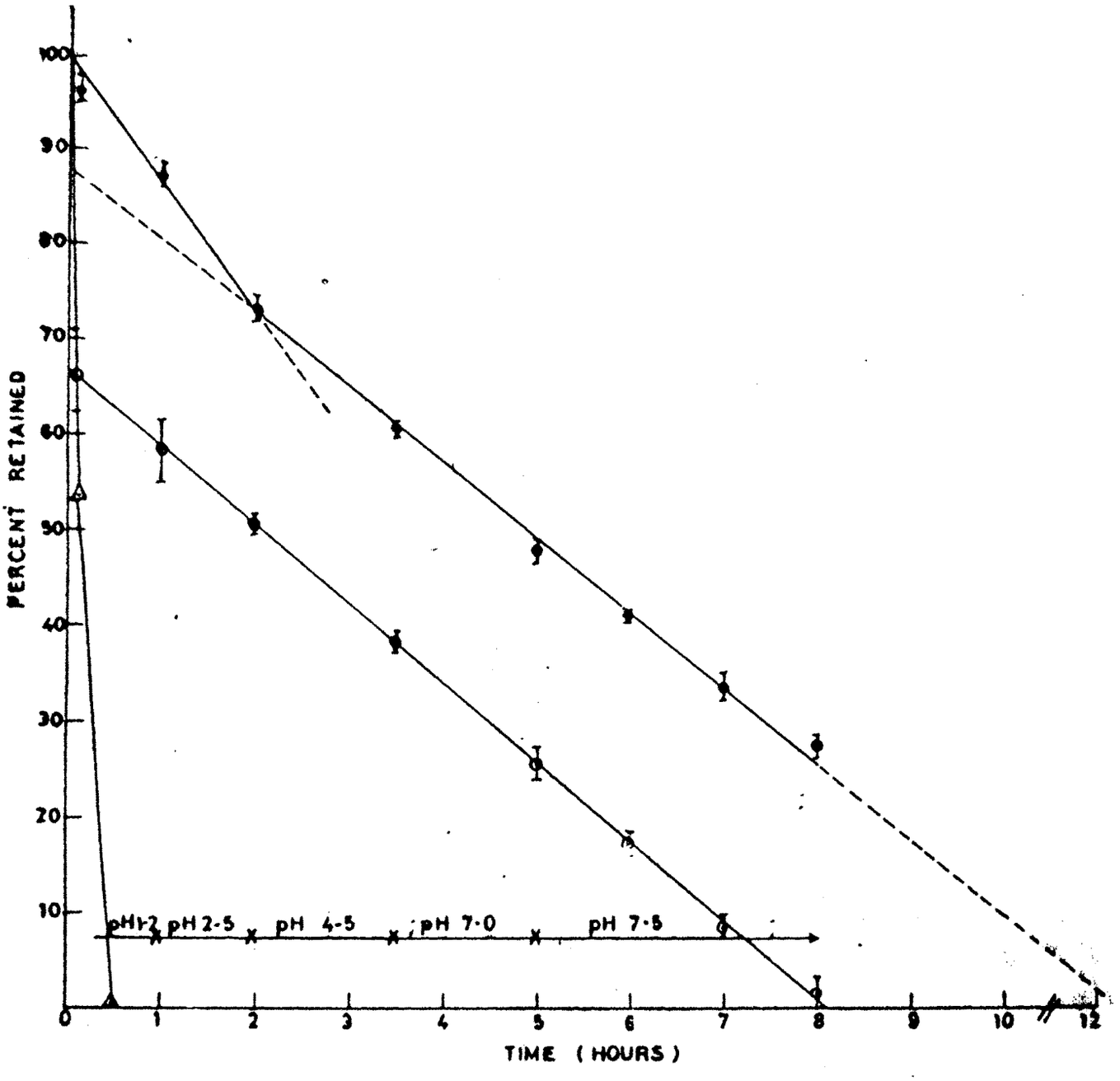



Figure IV.5- Percent Propranolol Hydrochloride Retained, <u>in vitro</u> as a function of time for the Three Products Studied.
Key : ●, Laser Drilled SR Capsule; ○, Inderal® LA and △, Inderal® Conventional Tablet.

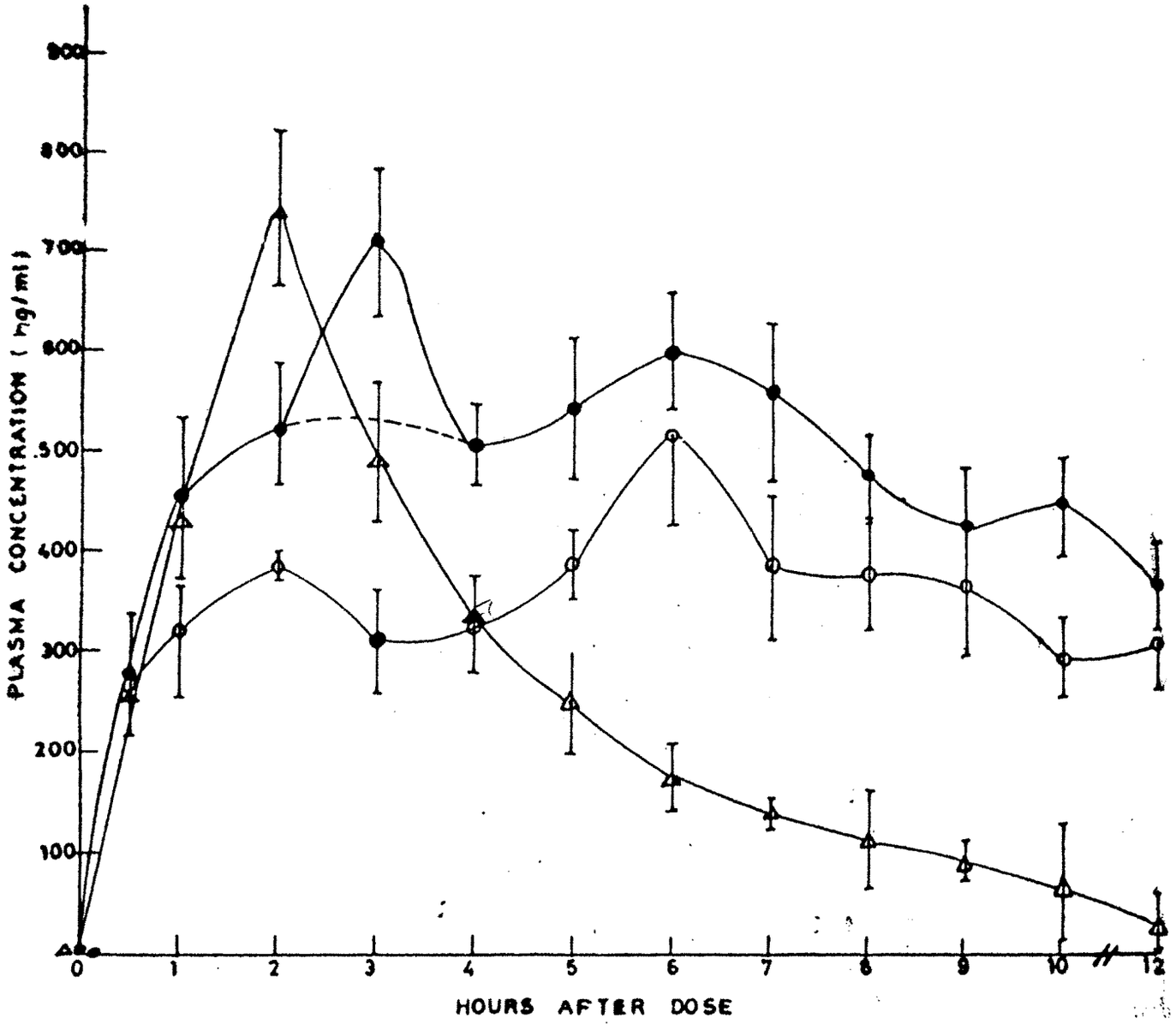



Figure IV.6. Mean(±SE) Propranolol Plasma Concentration as a Function of Time Following Oral Administration of the Three Treatments to Dogs. Key: ● , Laser Drilled SR Capsules; ○ , Inderal® LA and △ Inderal® Conventional Tablet.

Table IV.2 : Mean Propranolol Plasma Levels at Each Sampled Time Compared by t-test, For the Three Treatments Studied.

| Time (hr) | Treatment I and Treatment II[a] | | Treatment II and Treatment III[b] | | Treatment III and Treatment I[b] | |
|---|---|---|---|---|---|---|
| | t value[c] | P | t value[d] | P | t value[d] | P |
| 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 0.5 | 4.13 | $<0.01$ | 0.27 | ns[e] | 0.16 | ns[e] |
| 1.0 | 4.05 | $<0.01$ | 1.44 | ns | 0.29 | ns |
| 2.0 | 7.92 | $<0.01$ | 4.01 | 0.01 | 1.86 | ns |
| 3.0 | 8.60 | $<0.01$ | 2.32 | ns[e] | 2.07 | ns |
| 4.0 | 5.34 | $<0.01$ | 0.05 | ns | 2.84 | ns |
| 5.0 | 4.65 | $<0.01$ | 3.23 | $<0.01$ | 3.01 | ns |
| 6.0 | 4.43 | 0.01 | 3.56 | $<0.01$ | 5.35 | $<0.01$ |
| 7.0 | 2.69 | ns[e] | 3.82 | $<0.01$ | 4.31 | $<0.01$ |
| 8.0 | 2.48 | ns | 3.75 | $<0.01$ | 6.42 | $<0.01$ |
| 9.0 | 3.41 | ns | 5.95 | $<0.01$ | 5.56 | $<0.01$ |
| 10.0 | 3.71 | ns | 5.34 | $<0.01$ | 5.64 | $<0.01$ |
| 12.0 | 4.71 | $<0.01$ | 5.24 | $<0.01$ | 6.63 | $<0.01$ |

a) Treatments compared by paired t-test

b) Treatments compared by unpaired t-test

c) DF = 5, t = 4.032

d) DF = 11, t = 3.106

e) $P > 0.01$

Treatment I = Laser Drilled SR capsule

Treatment II = Inderal® LA capsule

Treatment III = Inderal® conventional Tablet.

at 0.5, 1.0, 2.0, 3.0, 4.0, 5.0 and 6.0 hr time intervals which could be because Laser Drilled SR capsule released the loading dose immediately, followed by the maintenance dose at the initial hours while Inderal® LA released only the loading dose over a period of time in the initial 2 hr as evident from the *in vitro* results (Figure IV.5). The insignificant difference subsequently at 7.0, 8.0, 9.0 and 10.0 hr interval may be attributed to the release of maintenance dose by both the capsules at almost a similar rate. The significant difference at 12.0 hr could be because the Laser Drilled SR capsule being a product designed to release the contents only for 8.0 hr would be empty by this time resulting in subsequent reduction in blood level due to continuous elimination of the drug with no simultaneous replenishment by the dissolved and absorbed drug between 8.0 and 12.0 hr, while Inderal® LA being a 24.0 hr sustained release product continues to release the drug at the same rate for more than 12.0 hr, keeping the blood level relatively high. Interaction between treatment II and III showed significant difference ($P < 0.01$) in mean propranolol concentrations at 2.0 hr possibly because Inderal® conventional tablet released relatively a higher amount of the drug at a faster rate in comparison to Inderal® LA capsule which might have released the loading dose relatively slowly as evident from *in vitro* results

(Figure IV.5). The significant difference further at 5.0, 6.0, 7.0, 8.0, 9.0, 10.0 and 12.0 hr is obviously because the Inderal® conventional tablet being a single dose 40.0 mg tablet, produces low blood levels after 5-6 hr, in comparison to a sustained release product of propranolol hydrochloride, a drug with short half-life of 2-6 hr (2,3). Treatment III showed no significant difference from Treatment I at 0.5, 1.0, 2.0, 3.0, 4.0 and 5.0 hr time intervals, while it showed significant difference at 6.0, 7.0, 8.0, 9.0, 10.0 and 12.0 hr. The insignificant difference at the initial hours may be attributed to the similar rate of release of the loading dose from Laser Drilled SR capsule as compared to Inderal® conventional tablet, while significant difference in the later hours may be for reasons similar to that explained for Treatment interactions II and III.

The $C_{max}$, $t_{max}$ and $AUC_{0-12}$ values for each of the three treatments studied are presented in Table IV.3. Laser Drilled SR capsules gave two peak plasma concentrations 708.78 ng/ml and 599.84 ng/ml at 2.5 and 5.0 hr respectively. The first peak may be attributed to the loading dose which was also similar to the peak plasma concentration obtained with Inderal® conventional tablet; 741.08 ng/ml at 2.2 hr. Mcainsh *et al.* (14) reported peak plasma concentration of propranolol as 23.0 ng/ml after the

Table IV.3 : The $C_{max}$, $t_{max}$ and $AUC_{0-12}$ Values For Each of the Three Treatments Studied.

| Treatment | $C_{max}$ ng/ml±SE | $t_{max}$ hr±SE | $AUC_{0-12}$ ng.hr.ml$^{-1}$±SE |
|---|---|---|---|
| I | 708.72±65.84 | 2.5±0.5 | 5958.56±117 |
| | 599.84±69.6 | 5.4±0.9 | |
| II | 520±100.0 | 5.6±0.51 | 4138.58±141.1 |
| III | 741.68±87.0 | 2.2±0.41 | 1069.28±95.3 |

oral administration of 80.0 mg of propranolol hydrochloride, in the form of a film coated tablet to human of average weight 74.0 kg. The $t_{max}$ value of second peak was similar to the one which is usually obtained with sustained release products of propranolol at 6.0 and 6.2 hr as reported by Dvornik *et al.* (15) and Mcainsh *et al.* (14), respectively. Inderal® LA on the other hand did not show the first peak possibly because of relatively less amount of the drug released in the initial 2.0 hrs, as observed in the *in vitro* dissolution studies (Figure IV.5); however, it gave the second peak, 520 ng/ml at 5.6 hr, significantly similar to the one obtained with Laser Drilled SR capsules (Figure IV.6). The calculated value of $AUC_{0-12}$ for Laser Drilled SR capsules, 5958.56 ng hr/ml was higher than that for both the Inderal®LA capsule, 4138.58 ng hr/ml and Inderal®conventional tablet, 1069.28 ng hr/ml. The higher $AUC_{0-12}$ value obtained in the case of Laser Drilled SR capsule may be attributed to the relatively higher amount of the drug, released at a faster rate, over a period of 8.0 hr by the capsule as evident from *in vitro* dissolution results (Figure IV.5).

## CONCLUSION

The laser drilling technique was successfully employed in designing the sustained release product of propranolol

hydrochloride, capable of releasing the loading dose immediately and then the maintenance dose slowly at a controlled rate for 8.0 hr and maintain the blood level for 12.0 hr like a commercial product, Inderal® LA capsule.

The results also indicate that Laser Drilled SR capsules designed could be used as a sustained release dosage form of propranolol hydrochloride for twice daily administration (every 12.0 hr) after confirming the findings by *in vivo* studies in human subjects.

The pH independent, zero-order *in vitro* and *in vivo* release pattern of propranolol hydrochloride from the Laser Drilled SR capsule indicate that the drugs with pH independent solubility characteristics may be released following zero-order kinetics from the new laser drilled controlled drug delivery system designed, irrespective of the pH of the GIT fluid surrounding the capsule.

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