As stated earlier, this reduction seems to take place through an intermediate $(BH_2^+)_s$ which disappears quickly with the complete reduction of the double bonds at the potentials at which the polarographic wave is detected. The *p*-chlorophenyl substituent in chloroguanide seems to be transformed into a state of reduced electron delocalization with respect to the other biguanides. Perhaps as is the case in the solid state (14), the monoprotonated molecule-cation, (BH^+), which exists at physiological pH in solution, is present as a result of a certain independence of the guanidine groups, as occurs with other efficient antimalarial drugs which show the independent imine groups (31).

The polarographic method can be applied for the analytical determination of chloroguanide at pH 3-7 in buffered media. The plots of i_d *versus* C give linear calibrations at 10^{-5}–5×10^{-3} M concentrations. For example, at pH 5.01: $i_d(\mu A) = (4.25 \times 10^3) \cdot C\ (\text{mol} \cdot \text{L}^{-1})(SD = 5 \times 10^{-3})$.

The assay is rapid and has great sensitivity. The lowest sensitivity limit recorded is 0.05–0.1 $\mu g \cdot mL^{-1}$. At $\tau = 0.6$ s the limit of detection is less favorable than in conventional DC polarography because the ratio of charging current to faradic current increases when drop time decreases (32).

Any substance having a half-wave potential within the range of ±100 mV with respect to the $E_{1/2}$ of chloroguanide produces an overlapping of both waves. Also, the presence of gelatin, Triton X-100, or another strongly absorbable substance on the DME produces interferences since the chloroguanide electroreduction is a heterogeneous process.

REFERENCES

(1) F. Kurzer and D. Pitchfort, *Fortschr. Chem. Forsch.*, **10,** 759 (1968).

(2) J. M. Tanzer, A. M. Slee, and B. A. Kamay, *Antimicrob. Agents Chemother.*, **12,** 721 (1977).

(3) V. D. Warner, D. M. Lynch, and R. S. Ajemian, *J. Pharm. Sci.*, **65,** 1070 (1976).

(4) V. D. Warner, D. M. Lynch, K. Kwan Kim, and G. L. Grunewald, *J. Med. Chem.*, **22,** 359 (1977).

(5) F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 729 (1946).

(6) M. S. Manku and D. F. Horrobin, *Prostaglandins*, **12,** 789 (1976).

(7) J. P. Famay, J. Fontaine, and J. Reuse, *J. Pharm. Pharmacol.*, **29,** 761 (1977).

(8) D. F. Horrobin and M. S. Maku, *Br. Med. J.*, **1,** 651 (1978).

(9) E. C. Huskisson, *Handb. Exp. Pharmacol.*, **50**(II), 399 (1979).

(10) J. Fontaine, C. O. Quédraogo, J. P. Famay, and J. Reuse, *Arch. Int. Pharmacodyn. Ther.*, **242,** 300 (1979).

(11) W. U. Malik and R. N. Goyal, *Talanta*, **23,** 705 (1976).

(12) F. Vicente, J. Trijueque, F. Tomás, *Quim. Ind. (Biblao)* **29,** 619 (1982).

(13) G. C. Whitnack and S. S. Clair Gautz, *J. Electrochem. Soc.*, **106,** 422 (1952).

(14) C. J. Brown, *J. Chem. Soc., A*, **1,** 60 (1967).

(15) G. Schwarzenbach, R. Gunt, and G. Anderegg, *Helv. Chim. Acta*, **37,** 937 (1954).

(16) R. Ernst and F. W. Cagle, *Acta Crystallogr. B*, **33,** 235 and 237 (1977).

(17) F. Vicente, F. Tomás, and M. A. Nuñez-Flores, IV Reunion de Química (Sanitaria), A.N.Q.E., Vol. II, 57, Madrid (1981).

(18) F. Vicente, Doctoral Thesis, Universidad de Valencia (1981).

(19) F. Vicente, F. Tomás, and J. Vera, Libro de actas de La VI Reunion Latinoamericana de Electroquímica y Corrosion, vol. II, 500, Oaxtopec, México (1983).

(20) F. Vicente, J. Trijueque, and F. Tomás, *J. Pharm. Sci.*, **72,** 565 (1983).

(21) H. E. Stagg, *J. Pharm. Pharmacol.*, **1,** 391 (1949).

(22) S. G. Mairanovskii, "Catalytic and Kinetic Waves in Polarography," Plenum, New York, N.Y. 1968, p. 2.

(23) H. A. Jaffe and M. Orchi, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley, New York, N.Y., 1962, p. 536.

(24) M. Heyrovsky and S. Vavricka, *J. Electroanal. Chem.*, **36,** 203 (1972).

(25) E. Laviron, *Bull. Soc. Chim. Fr.*, 2350 (1961).

(26) J. Trijueque, F. Vicente, and F. Tomás, V Encontro de Química, Communication C. 31.46, S.P.Q., Porto (1982).

(27) J. Heyrovský and J. Kunta, "Principles of Polarography," Academic Press, New York, N.Y., 1966, p. 557.

(28) M. V. Susic, D. A. Markovic, and N. N. Hercigonja, *J. Electroanal. Chem.*, **41,** 122 (1973).

(29) L. Holleck, *Naturwiss.*, **43,** 13 (1956).

(30) R. C. Schultz, *J. Amer. Pharm. Assoc. Sci. Ed.*, **38,** 84 (1949).

(31) A. Burger, "Química Medica," vol. II, Aguilar, Madrid, Spain, 1955, p. 289.

(32) A. J. Bard and L. R. Faulkner, "Electrochemical Methods: Fundamentals and Applications," John Wiley, New York, N.Y., 1982, pp. 147-156.

Design of a Slow-Release Capsule Using Laser Drilling

N. K. JAIN ˣ and S. U. NAIK

Received August 29, 1983, from the *Pharmaceutics Laboratory, Pharmacy Department, Faculty of Technology & Engineering, M. S. University of Baroda, Baroda, India.* Accepted for publication December 13, 1983.

Abstract □ Conventional hard gelatin capsules were made GI-tract resistant by formalin vapor treatment. The residual formalin content was 80 μg/capsule 24 h after treatment, which decreased with increased storage time. An *in vitro* GI-tract resistance test was performed by exposing the capsules to simulated gastric fluid for 4 h and then to simulated intestinal fluid for 4 h at 37°C. The resistance was further confirmed by *in vivo* X-ray studies in human volunteers. Minute pores were drilled on the hardened shells of the capsules with a carbon dioxide gas laser. This permitted the slow passage of the encapsulated tetracycline hydrochloride when subjected to 0.1 M HCl in *in vitro* dissolution studies. *In vitro* drug release from these capsules followed zero-order kinetics after an initial lag period of 30 min. The factors influencing the *in vitro* release rate of tetracycline hydrochloride from these capsules are discussed.

Keyphrases □ Gelatin capsules–drug release, GI-tract resistance, laser-drilled design □ Laser-drilled capsules–drug release, GI-tract resistance, X-ray studies

The potential application of the laser in the fields of communication, industry, military science, chemistry, biology, and medicine has been well established and well documented (1). The possible use of the laser in designing a controlled-release capsule dosage form has been recently reported (2). Theeuwes *et al.* (3) reported the use of automated laser drilling in making exit pores for indomethacin in the design of an elementary osmotic pump.

Conventional hard-gelatin capsules normally disintegrate rapidly and the encapsulated drug exhibits a cube-root dissolution pattern (4). Exposure to formalin vapors causes the cross-linkage of the gelatin molecule, resulting in an unpre-

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dictable decrease in solubility of these capsules (5). The objectives of this study were: (*a*) to prepare GI-tract resistant hard-gelatin capsules by formalin vapor treatment and to confirm their resistance by *in vitro* and *in vivo* studies; (*b*) to make minute pores on the hardened shells of the capsules by laser drilling to allow the contents to release slowly through these minute pores; (*c*) to report on the different factors that are likely to influence the *in vitro* drug release rate from these capsules.

EXPERIMENTAL SECTION

Preparation of GI-Tract Resistant Capsules—The conventional hard-gelatin capsules were exposed to formalin vapor under normal temperature and pressure conditions. After the vapor contact time, the capsules were dried in an oven at 50°C. The formalin vapor contact time and drying time were optimized with respect to GI-tract resistance, residual formalin content, drilling requirements, physical characteristics of the capsules, *etc.*, by trial experiments.

Residual Formalin Content—The analytical procedure used to determine the residual formalin content was based on the method of Macfadyan (6). The method involves the spectrocolorimetric measurement (at 490 nm) of the violet color produced when 1.0 mL of the sample, containing ~2–3 μg of formalin with 9.0 mL of 0.2% (w/v) solution of chromotropic acid[1] in 80% (v/v) sulfuric acid, was heated on a boiling-water bath for 30 min.

The sample was prepared by placing one formalin-treated capsule in each of the three clean, dry, 20.0-mL vials containing 10.0 mL of distilled water. After closing with rubber stoppers and sealing with aluminum seals, the vials were agitated on a mechanical agitator for 1.0 h. The saturation solubility of the formalin capsule in 10.0 mL of distilled water was optimized with respect to agitation time by trial experiments. A sample (1.0 mL) was withdrawn from each vial with a syringe, and the residual formalin content was determined. The average content of the three vials was reported as the residual formalin content.

***In Vitro* GI-Tract Resistance Test**—The studies were carried out by the rotating-basket method (7). A flask containing 900.0 mL of simulated gastric fluid as the dissolution medium (8) was immersed in a constant-temperature bath at 37 ± 0.5°C. The empty formalin-treated capsule (with laser drilled pores on the body) was then inserted, and the basket was rotated at 100 rpm for 4 h. At the end of 4.0 h, 900.0 mL of the simulated gastric fluid was replaced by the same quantity of simulated intestinal fluid (8), and the experiment was repeated for 4.0 h.

***In Vivo* X-ray Studies**—Two human male volunteers (age, 27 and 29 years; weight, 65.5 and 71.5 kg.) were selected for the study. The subjects had no history of GI disease and neither used any medication regularly. Both volunteers were asked to abstain from alcoholic beverages for 48 h preceding each experiment and fasted overnight. At 8:30 a.m. one capsule containing 250.0 mg of barium sulfate (band sealed with a suitable GI-tract resistant material) was administered orally with ~25.0 mL of water. Volunteers were allowed to take food 4.0 h after administration of the capsule. X-ray photographs were taken at 0.5, 1.0, 2.0, 4.0, 6.0, and 8.0 h after capsule administration.

Laser Drilling—A CO_2 (CW/pulsed) laser[2] (Fig. 1) was used to drill small pores into the hardened shells of the capsules. This laser can be operated in continuous or pulsed modes. In the pulsed mode, the pulse width of the laser can be varied from 100 μs to 1 s, and the frequency can be varied from 1 to 1000 pulses/s. Pulse width and frequency variations changed the diameter of the drilled pores and the number of drilled pores, respectively. The laser was internally pulsed through an electronically controlled trigger switch. This type of pulsing provides a power output four to five times the average output, depending on the pulse width selected. This laser system had well-insulated high-voltage terminals and an automatic switch to ground the capacitor bank when switching off or tripping off the power supply; the power supply and the coolant flow were interlocked.

In this investigation, laser-drilled capsules were studied with respect to variation in the number of drilled pores, diameter of the drilled pores, and the drilling pattern of the pores. To vary the number of pores, the capsule was mounted on a linear drive (speed, 2 mm/s). By changing the laser frequency and keeping the power and pulse width (220 μs) constant, 25, 50, 75, and 100 pores with an SD_2 size distribution were drilled on the body of the capsule shell.

[1] P.B. No. 6136; Loba-Chemie, Indoaustranal Co., Bombay, India.
[2] 50W CO_2 Laser model JI.S-C-101; designed and developed by Laser Division, Jyoti Ltd., Baroda, India.

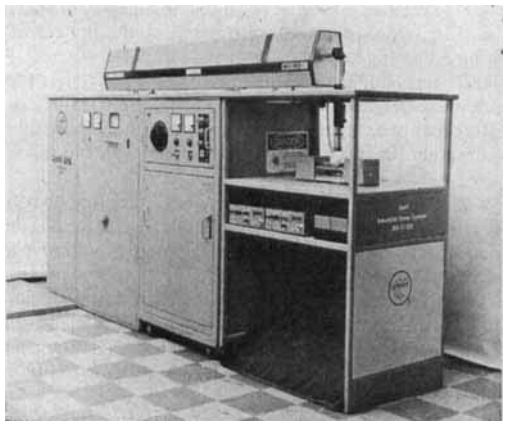

Figure 1—*Carbon dioxide gas laser with a linear drive.*

Table I—Pulse Width Variations with Corresponding Pore Size Distributions and Average Diameters

Pore Size Distribution	Pulse Width, μs	Average Pore Diameter, μm	
		dln[a]	*dg*[b]
SD_1	100	83–88	78.50 ± 1.57
SD_2	220	103.60	100.00 ± 1.41
SD_3	300	160.20	155.00 ± 1.52
SD_4	420	207.80	205.00 ± 1.38

[a] Statistical length-number mean diameter. [b] Geometric mean diameter from the probability plot (±*SD*).

The pores were placed equidistant in three lines with an almost equal number of pores per line.

For the study of diameter variation, 50 drilled pores with size distributions of SD_1, SD_2, SD_3, and SD_4, with an average length-number mean diameter (*dln*) equal to 83.58, 103.60, 160.20, and 207.80 μm, respectively [determined by the optical microscopic method (9)], were obtained by varying the pulse width of the laser and keeping the frequency constant at 1 pulse/s (Table I). The variation in the pore drilling pattern was studied with 50-pore capsules (of SD_2 distribution) on the body only and on both the cap and body. Laser-drilled pores on the hardened shells of the capsules are shown in Fig. 2.

Factors Influencing Release Rate—GI-tract resistant capsules with 50 laser-drilled pores (SD_2 size distribution) on the body, containing tetracycline hydrochloride[3] (as a model drug) and band sealed with GI-tract resistant seals, were used for the study. The average weight of the filled capsules was determined by weighing 10 capsules. Friability testing of the capsules was done on a friabilator[4] (10). The bulk density of the sample was determined by the

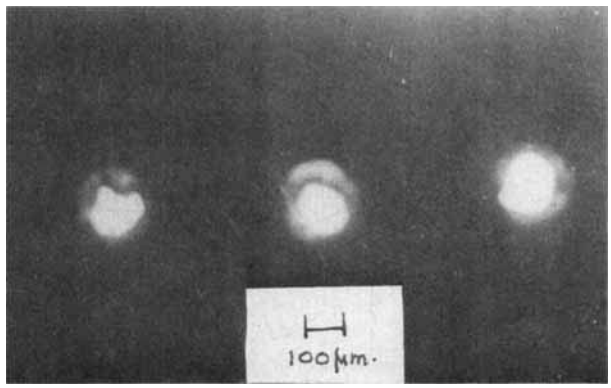

Figure 2—*Different sizes of laser-drilled pores on the hardened capsule shell.*

[3] Synbiotics, Wadi Wadi, Baroda, India.
[4] Roche.

standard three-tap method suggested by Butler and Ransey (11). The particle size and size distribution analyses were made by the optical microscopic method (9), by preparing a suspension of the sample in glycerol.

To study the effect of diluents, capsules containing 250.0 mg of tetracycline hydrochloride were prepared using lactose or microcrystalline cellulose as diluent. Differences in bulk density between the drug and the diluents were taken into consideration when calculating the fill weight of individual capsules.

The effect of powder properties such as particle size and distribution and bulk density were studied by using capsules filled with three powder samples with different characteristics. The original sample of tetracycline hydrochloride (sample I) was screened through a 360-mesh standard sieve; an oversized fraction (sample II), and an undersized fraction, which was pulverized with a pestle and mortar (sample III), were also used for the study. Tetracycline hydrochloride capsules were prepared by filling tetracycline hydrochloride with 2.0% talc or 1.0% magnesium stearate to study the effect of common lubricants.

Saturated solutions of dioctyl sodium sulfosuccinate[5] and polysorbate 80[6] in alcohol were sprayed separately on the tetracycline hydrochloride to give 0.5% (w/w) and 1.0% (w/w) of these wetting agents uniformly distributed in the dried (at 40°C) tetracycline hydrochloride. These samples were used to study the effect of wetting agents.

***In Vitro* Dissolution Rate Studies**—The dissolution rate studies were carried out by a method similar to that used in the *in vitro* GI-tract resistance test. However, the dissolution medium was 0.1 M HCl, 5.0-mL samples were withdrawn at 30-min intervals and the volume of the dissolution medium was maintained by replacing an equal volume of the medium after each withdrawal. The samples were analyzed at 353 nm using a spectrocolorimeter[7].

RESULTS AND DISCUSSION

All the samples tested for *in vitro* GI-tract resistance showed resistance in both simulated gastric and intestinal fluids. The capsules remained intact throughout the GI tract in the X-ray studies, confirming *in vivo* resistance in the subjects tested. Figure 3 shows the position of the capsule in the GI tract at 0.5, 1.0, 2.0, 4.0, 6.0, and 8.0 h after the capsule was administered in one of the subjects. The capsule remained in the stomach for more than 1.0 h; 2.0 h after administration, the capsule was seen in the duodenal area of the small intestine. The capsule was traced intact in the ileum after 4.0 h, in the colon after 6.0 h, and finally in the rectum at 8.0 h. The residual formaldehyde content after 24.0 h of treatment was 80 μg/capsule, which reduced to 68 and 60 μg/capsule after 15 and 30 d of storage, respectively.

The number of drilled pores considerably influenced the release rate of tetracycline hydrochloride from the capsule (Fig. 4). A plot of percentage of

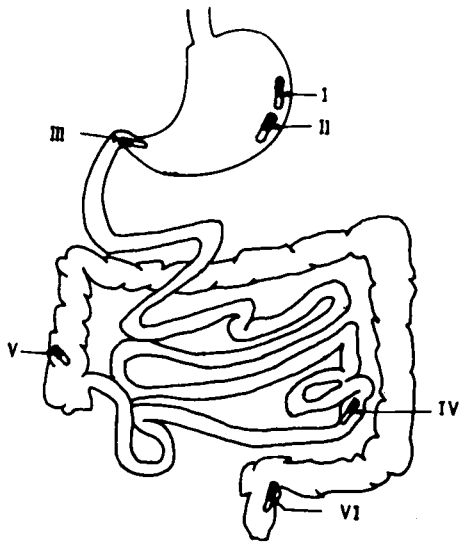

Figure 3—*Schematic representation of the position of the capsule in the GI tract (detected by X-ray photography) after capsule administration. Key: (I) 0.5 h; (II) 1.0 h; (III), 2.0 h; (IV) 4.0 h, (V) 6.0 h; (VI) 8.0 h.*

[5] Doxinate; Hoescht Aktiengeselschaft, Badvilbel, F.R.G.
[6] Tween 80; Atlas Chemical Co., Wilmington, Del.
[7] Model VSU2-P; C.Z. Spectrophotometer, F.R.G.

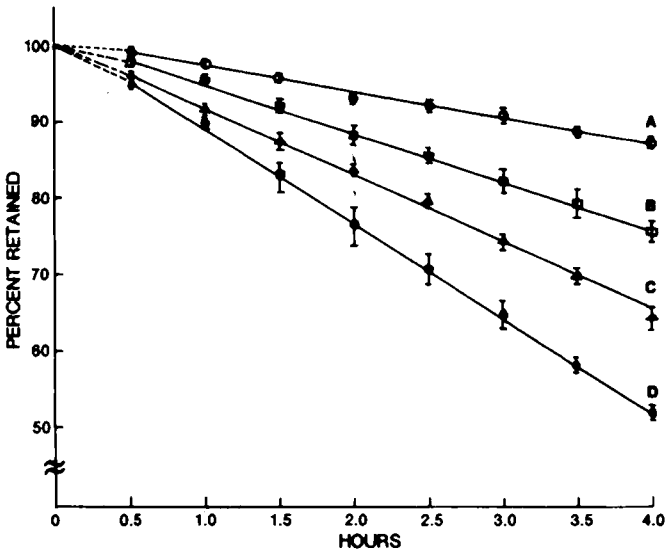

Figure 4—*Effect of variation in number of drilled pores, n (with SD_2 type of size distribution) on percent drug retained as a function of time. Key: (A) n = 25; (B) n = 50; (C) n = 75; (D) n = 100.*

the drug retained against time indicates that the drug release follows a zero-order pattern after an initial lag period of 30 min in all cases. This lag period may be attributed to the time required for the dissolution fluid to penetrate the capsule, wet and dissolve the drug, and finally allow the drug to pass through the pores.

The slope values were calculated by (12):

$$\alpha = \frac{\{\sum xy - (\sum x \cdot \sum y/n)\}}{\{\sum x^2 - [(\sum x)^2/n]\}} \qquad \text{(Eq. 1)}$$

where α is the slope, x is the time (in hours), and y is the percentage drug retained. Since the release follows zero-order kinetics, the slope represents the rate of the release (k_n) and n indicates the number of pores drilled. The calculated values of k_{25}, k_{50}, k_{75}, and k_{100} were 3.30, 6.32, 8.92, and 12.27%/h, respectively. The variations in number of drilled pores were in the ratio of 1:2:3:4; the release rate constant, k_n, showed a similar ratio. This indicates a proportionate increase in the release rate of the drug with an increase in the number of drilled pores (n).

The effect of pore size and size distribution on the release rate constant of tetracycline hydrochloride is shown in Fig. 5 for the size distribution ranges SD_1, SD_2, SD_3, and SD_4. The statistical mean diameter of each size distribution was calculated by (12):

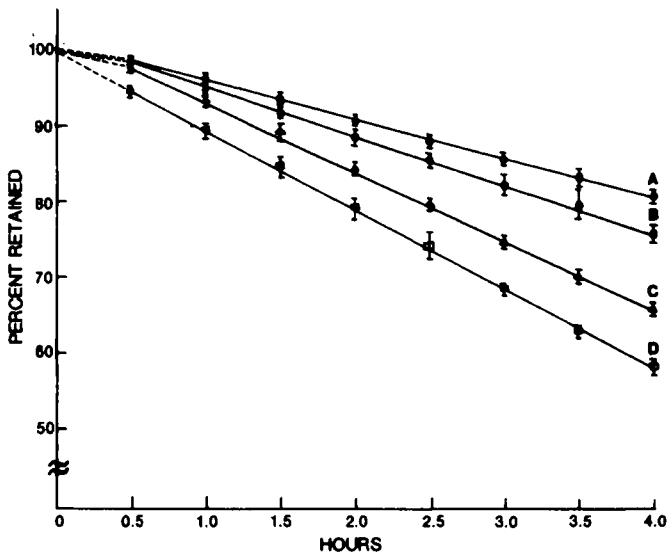

Figure 5—*Effect of variation in size distribution of drilled pores on percent drug retained as a function of time. Key: (A) SD_1; (B) SD_2; (C) SD_3; (D) SD_4.*

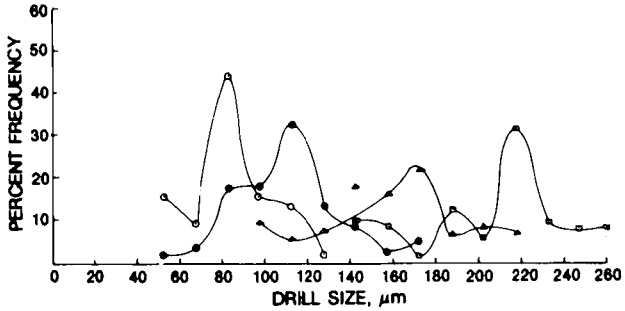

Figure 6—*Frequency distribution plots of different size ranges of drilled pores. Key: (⊙) SD_1; (●) SD_2; (▲) SD_3; (⊡) SD_4.*

$$d_{mean} = \left(\frac{\sum nd^{p+f}}{\sum nd^f}\right)^{1/p} \quad \text{(Eq. 2)}$$

where n is the number of pores in a size range whose midpoint, d, is one of the equivalent arithmetic, geometric, or harmonic mean diameters; p is the index related to size of an individual pore, since d raised to the power $p = 1$ or $p = 2$ is an expression of the pore length or surface, respectively. The frequency with which the pores in a certain size range occur is expressed by nd^f. When the frequency index has values of 0, 1, or 2 the size frequency distribution is expressed in terms of total number, length, or surface of pores, respectively. The frequency distribution and the log probability plots of SD_1, SD_2, SD_3, and SD_4 pore size distributions are shown in Figs. 6 and 7, respectively. The arithmetic length-number mean diameters, *dln*, were calculated by (12):

$$dln = \frac{\sum nd}{\sum n} \quad \text{(Eq. 3)}$$

and were 83.58, 103.60, 160.20, and 207.80 μm. These values correlated well with the corresponding geometric mean diameters of 78.50, 100.00, 155.00, and 205.00 μm obtained from the log probability plot. The respective standard deviations calculated from the slopes of the lines were 1.57, 1.41, 1.52, and 1.38. The total surface area available for the release of the drug with 50 pores on the body of the capsule for each of the four groups was 1.10, 1.68, 4.03, and 6.78 cm^2/capsule. The calculated release rate constants indicate that the drug was released at the rate of 5.04, 6.32, 8.96, and 10.60%/h for the respective release areas. The release rate followed zero-order kinetics after an initial lag period of 30 min in all cases, except the capsules with SD_4 pore size distribution had no lag period. Such a deviation for larger pore sizes may be due to a decrease in the time required for the dissolution fluid to penetrate the capsule with a larger surface area. The capsules with pores of SD_1 and SD_2 size distributions showed a loss of <0.8%/capsule when subjected to friability tests, unlike the capsules with SD_3 and SD_4 distributions, where the loss was >1%/capsule.

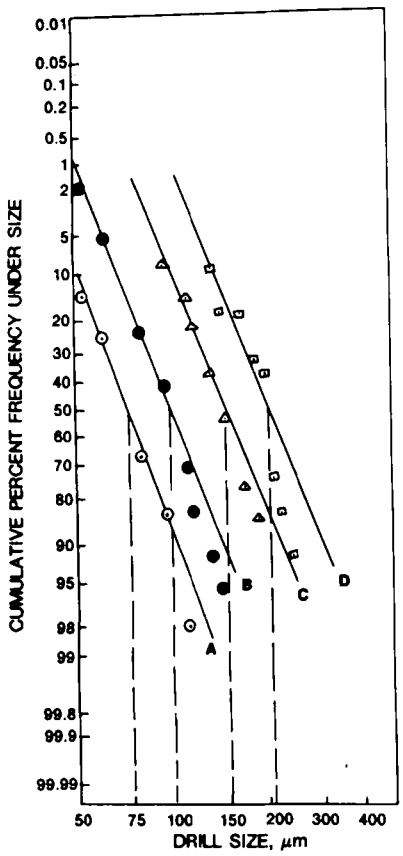

Figure 7—*Log probability plots of different size ranges of drilled pores. Key: (A) SD_1; (B) SD_2; (C) SD_3; (D) SD_4.*

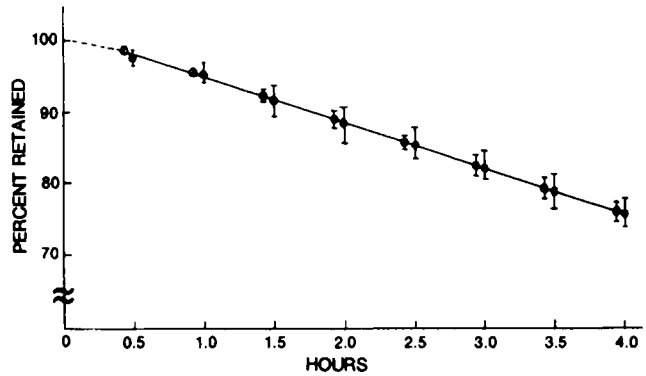

Figure 8—*Influence of variation in pattern of drilling on percent drug retained as a function of time. Key: (○) only body drilling; (●) cap and body drilling.*

The variation in drilling pattern did not show statistically significant differences ($t = 0.037$, $d = 16$, $p < 0.01$) in release rates of the drug (Fig. 8). The higher standard deviations observed in the values for cap and body drilling as compared with body drilling alone may be attributed to incomplete drilling when the comparatively thicker cap and body surface was drilled simultaneously.

The release rate of the drug from the capsule was considerably affected by the powder characteristics, *i.e.*, bulk density and particle size distribution, of the encapsulated drug samples I, II, and III. The bulk densities were 0.61, 0.60, and 0.73 g/cm^3. Average length number mean diameters (*dln*) were 51.20, 95.74, and 23.30 μm and showed release rates of 6.32, 5.00, and 8.11%/h, respectively (Fig. 9). This probably indicates an increase in release rate with decreased particle size of the encapsulated drug. The frequency distributions and log probability plots of the three samples are shown in Figs. 10 and 11, respectively. The aforementioned statistical diameters correlated well with the geometric mean diameters (*dg*) of 48.50, 85.0, and 17.50 μm, respectively, obtained from the log probability plot. The corresponding standard deviations calculated from each slope were 3.03, 1.67, and 2.8.

Figures 12 and 13 show the effect of different additives on the release rate of the drug from the capsules. The use of lactose and microcrystalline cellulose

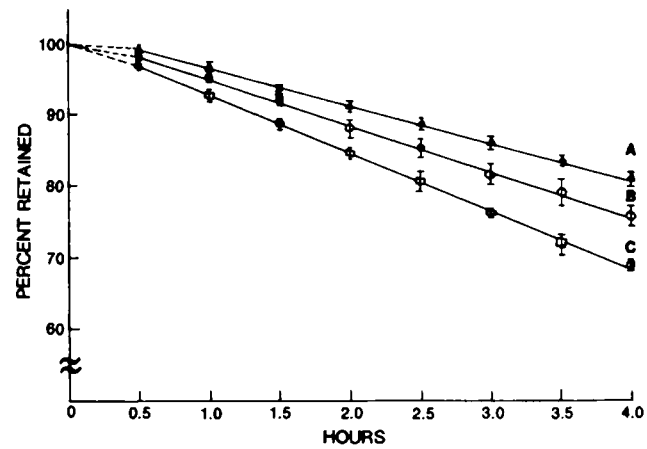

Figure 9—*Effect of particle size and size distribution of the encapsulated drug sample on percent drug retained as a function of time. Key: (A) sample I; (B) sample II; (C) sample III.*

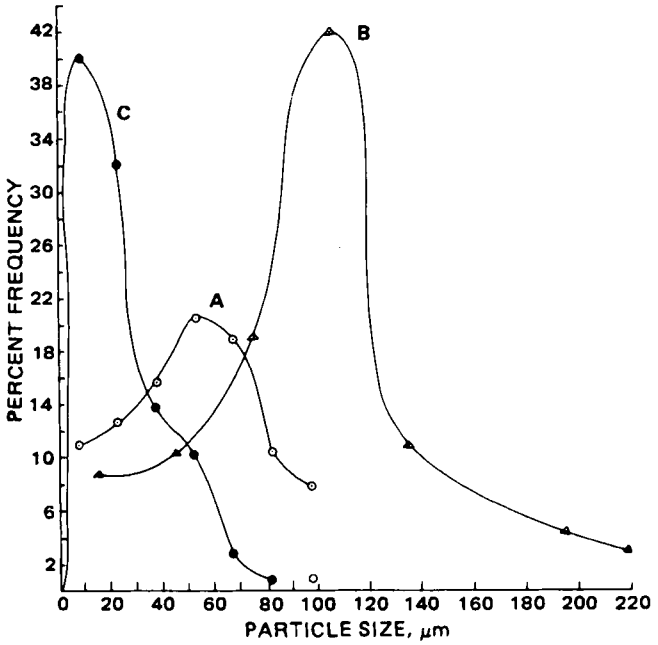

Figure 10—*Frequency distribution plots of different samples of powder. Key: (A) sample I; (B) sample II; (C) sample III.*

as diluents and magnesium stearate and talc as lubricants did not significantly affect the release rate of the drug. Of the two wetting agents used, dioctyl sodium sulfosuccinate showed a statistically significant enhancement of the release rate, unlike polysorbate 80 which showed some enhancement but was not statistically significant. Table II is the analysis of variance (13) to compare the effect of additives on the release rate of the drug. The calculated F ratio is higher than the F value obtained from the table (13) ($f_1 = 6, f_2 = 56, p =$ 0.05) which clearly indicates that the samples do not have the same release rate *i.e.*, they are statistically different. To determine which samples are different from each other, a least-significant procedure (13) was applied; Table III shows the ranked means. The calculated value of 5% allowance is 7.05

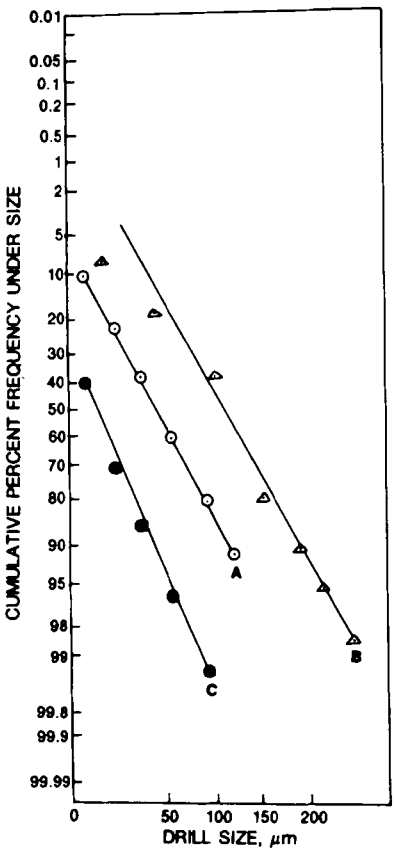

Figure 11—*Log probability plots of different samples of powder. Key: (A) sample I; (B) sample II; (C) sample III.*

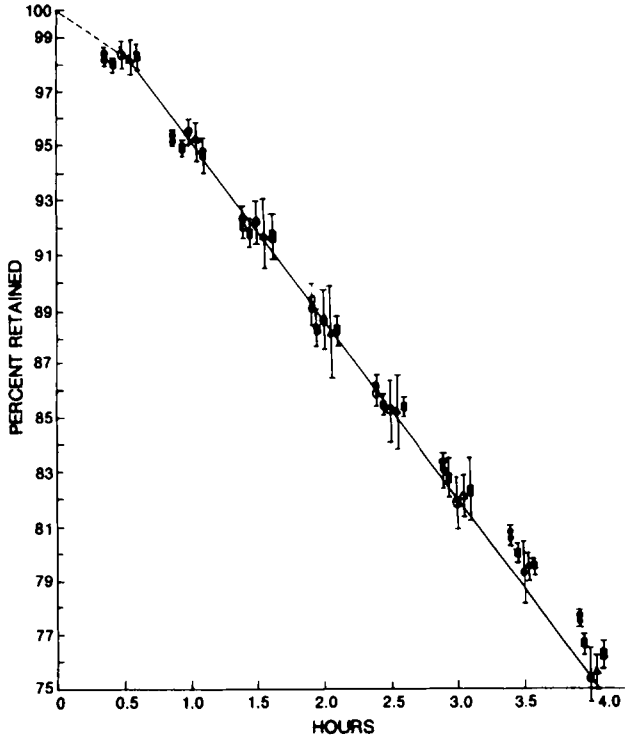

Figure 12—*Effect of common capsule additives on percent drug retained as a function of time. Key: (○) drug only; (△) with microcrystalline cellulose; (□) with lactose; (●) with talc; (⚉) with magnesium stearate.*

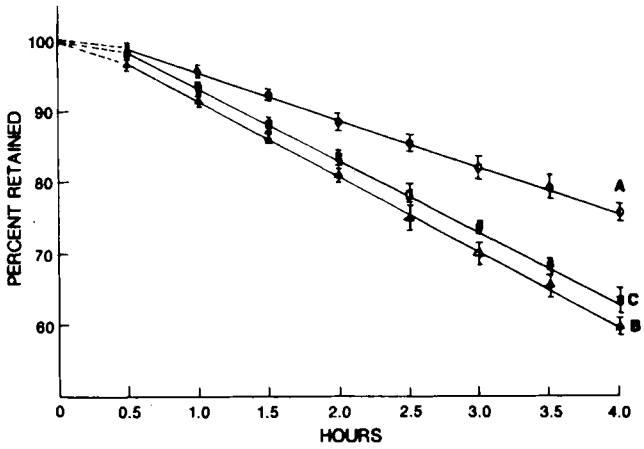

Figure 13—*Effect of wetting agents on percent drug retained as a function of time. Key: (A) drug only; (B) with dioctyl sodium sulfosuccinate; (C) with polysorbate 80.*

Table II—Analysis of Variance

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Squares	F Ratio	F Value[a]
Among the treatments	$t - 1 = 6$	3990.93	665.16	11.88	2.25[b]
Within the treatments	$\Sigma ni - 1 = 56$	3135.68	55.99		
Total	$N - 1 = 62$				

[a] From the tables. [b] F value at $f_1 = 6$, $d_2 = 56$, and $p = 0.05$; $\bar{x} = 5457.87$, $\bar{x}^2 = 479957.48$, $N = 63$, $\Sigma ni - 1 = 56$, and $t = 7$.

Table III—Ranked Means [a]

Drug	Talc	Magnesium Stearate	Microcrystalline Cellulose	Lactose	Polysorbate 80	Dioctyl Sodium Sulfosuccinate
88.48	88.70	89.10	83.54	88.38	82.78	80.53

[a] Any two means not underscored by the same line are statistically significantly different; $t = 2.00$, $S_2 = 55.99$, $ni = 9$, $n = 9$, degrees of freedom = 56, $p = 0.05$, and 5% allowance = 7.05.

which indicates dioctyl sodium sulfosuccinate has a statistically significant difference in release rate than the other additives studied ($p = 0.05$, $t = 2.0$, $S_2 = 55.99$, $n_1 = 9$, degrees of freedom = 56).

CONCLUSIONS

GI-tract resistant hard-gelatin capsules were prepared by formalin treatment. The contents of the capsule were released slowly through minute laser-drilled pores. Variations in number and diameter of drilled pores changed the rate of release of the drug from these capsules. Common additives like lactose, microcrystalline cellulose, magnesium stearate, and talc did not significantly affect the rate of release of the drug; neither did variations in drilling patterns. The presence of dioctyl sodium sulfosuccinate significantly affected the release rate; although polysorbate 80 enhanced the release, the effect was not statistically significant.

The results of the present investigation clearly indicate that the technique of laser drilling could be successfully used in designing slow-release capsule dosage forms. A proportionate increase in release rate with the number of pores drilled and with increased average diameter of the pores suggests the possibility of using the laser technique to design controlled-release capsule dosage forms.

REFERENCES

(1) A. Lytel, "Introduction to Lasers & Masers," Buckinghamshire, England, 1965, p. 103.

(2) *Laser Focus*, **16**(7), 26 (1980).

(3) F. Theeuwes, D. Swanson, P. Wong, P. Bonsen, V. Place, K. Heimlick, and K. C. Kwan, *J. Pharm. Sci.*, **72**, 253 (1983).

(4) J. T. Carstensen, "Pharmaceutics of Solids and Solid Dosage Forms," Wiley, New York, N.Y., 1977, p. 145.

(5) L. Lachman, H. A. Lieberman, and J. L. Kanig, "The Theory and Practice of Industrial Pharmacy," 2nd ed., Lea and Febiger, Philadelphia, Pa., 1976, p. 404.

(6) H. Macfadyan, *J. Biol. Chem.*, **158**, 107 (1945).

(7) "The United States Pharmacopeia," 19th rev., U.S. Pharmacopeial Convention, Rockville, Md., 1975, p. 651.

(8) "The United States Pharmacopeia," 19th rev., U.S. Pharmacopeial Convention, Rockville, Md., 1975, p. 765.

(9) A. N. Martin J. Swarbrick, and A. Cammarata, "Physical Pharmacy," 2nd ed., Lea & Febiger, Philadelphia, Pa., 1970, pp. 468-493.

(10) L. Lachman, H. A. Lieberman, and J. L. Kanig, "The Theory and Practice of Industrial Pharmacy," 2nd ed., Lea and Febiger, Philadelphia, Pa., 1976, p. 347.

(11) A. Q. Butler and J. R. Ransey, Jr., *Drug Standards*, **20**, 217 (1952).

(12) J. T. Carstensen, "Theory of Pharmaceutical Systems," vol. I, Academic Press, New York, N.Y., 1972, p. 16.

(13) "Remington's Pharmaceutical Sciences," 14th ed., Mack Publishing Co., Easton, Pa., 1970, pp. 122-140.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the Laser Division and the management of Jyoti Ltd., Baroda, India, for providing laser facilities and guidance; Dr. O. D. Gulati and Dr. N. A. Dave, Radiology Department, Medical College, Baroda, for providing X-ray facilities and guidance; M/s Sarabhai Chemicals, a Division of Ambalal Sarabhai Enterprises, Baroda, India, for supplying free gift samples of the drug and hard-gelatin capsules; and Professor S. S. Merh, Department of Geology, Faculty of Science, M. S. University of Baroda, Baroda, India, for providing photomicrograph facilities.