Factors Influencing the Release of a Drug from a Prolonged-Action Matrix

By JACK LAZARUS, MIRIAM PAGLIERY, and LEON LACHMAN

The influence of drug particle size, drug concentration, and granule size on the *in vitro* release rate of the water-soluble drug tripelennamine from a compressed waxy granular matrix was studied. The rate of release is affected to a greater degree by drug concentration and crystal size than by the size of the matrix granules. At a given drug concentration, a faster release rate was observed as the crystal size increased.

THE DESIRED duration of continuous and uniform release from an oral sustained-action dosage form is generally about 8 to 12 hours. The various methods and processes which are employed to accomplish such prolonged release, and the *in vitro* test procedures used, have been the subject of many reports, patents, and reviews (1–8).

In the early development stages of these dosage forms, their *in vitro* release rates of the active substances serve as a guide for further formulation work. Although many of the studies reported on in the literature mention the factors which influence the release of the drug from the dosage form, there are few published investigations describing the effect of the different variables on the release rate, both *in vivo* and *in vitro*.

Sjogren and Fryklof (9) studied the effect of water solubility and concentration of a drug on its release rate from a tablet which was prepared by compressing a granulate containing the active substance and an insoluble plastic material. The plastic formed a coherent and porous matrix in which the active substance was dispersed. They found that the rate of release was directly dependent upon the solubility, as well as the concentration, of the drug. The release of sparingly soluble substances from the matrix was low, and was found to be increased by the addition of physiologically inert but readily soluble material such as sodium chloride, mannitol, urea, and polyethylene glycol 6000. A recent United States patent also recommends the use of water soluble substances to increase the release of a drug dispersed in a compressed plastic tablet (10). Simoons (11) also employed a soluble substance to aid the release of a small quantity of a sparingly soluble drug from a tablet matrix.

From the aforesaid references and information obtained in our laboratory, it seems necessary to have substances present in the matrix which are soluble in the test fluid in order to facilitate the release of the drug. However, in certain instances when the drug itself is soluble and is present in sufficient concentration, soluble additives are generally not required.

The present investigation was designed to determine the influence of the following three major factors on the *in vitro* release of a freely soluble drug: (*a*) particle size of the drug, (*b*) granule size prior to compression, and (*c*) concentration of active substances.

EXPERIMENTAL

Sizing of Material.—The drug substance employed was tripelennamine HCl U.S.P. having a solubility of more than 1 Gm. in 1 ml. of water.

The crystals were sized on 8-inch diameter U. S. sieve series screens set on a Rotap testing sieve shaker and shaken until two successive weighings did not show a variation of more than 0.2% between weighings.

The crystals taken for study were designated as 40-, 80-, and 120-mesh size since they were retained on these screens. The 40-mesh material passed through a 30-mesh screen, the 80-mesh through a 70-mesh screen, and the 120 mesh through a 100-mesh screen.

Fig. 1.—Various fractions of tripelennamine HCl. The linear distance between each white scale line is 100 microns.

Received September 12, 1963, from the Research Department, Ciba Pharmaceutical Co., Summit, N. J.
Accepted for publication October 22, 1963.
Presented at the Fifth Annual National Industrial Pharmaceutical Conference, Land O' Lakes, Wis., June 1963.

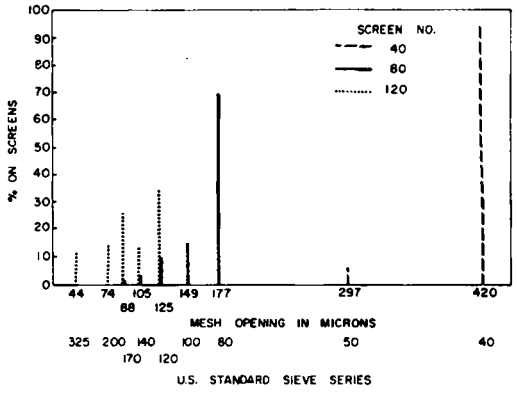

Fig. 2.—Particle size distribution of screened tripelennamine HCl.

A small sample of the sieved crystals was further analyzed on 3-inch diam. stainless steel screens on the vibratory shaker. Photomicrographs of the different crystal fractions were taken to demonstrate the magnitude of the range of particle sizes (Fig. 1). The linear distance between each white scale line is 100 microns. The differences in size should be of value in establishing a mental picture of the pore sizes created in the matrix when the crystals dissolve. Examination of the crystals obtained from each fraction revealed that many fine fragments of crystalline matter clung to the larger particles and further shaking of the screens on the Rotap failed to completely remove these crystals. The data presented in Fig. 2 shows the size distribution of the above crystal fractions.

Core Material.—Equal parts of hydrogenated castor oil (castorwax) and stearyl alcohol were used as the matrix material, since it was considered best in terms of future studies to have a core that was essentially unaffected by pH changes. When stearic acid was used in place of stearyl alcohol, dissolution of the matrix material occurred in simulated intestinal fluid as illustrated in the photograph shown in Fig. 3. The term core is used instead of tablet because, in the commercial tripelennamine HCl prolonged action tablets,[1] it is the core of the compressed coated tablet which provides the prolonged release, while the initial dose is contained in the coating. The coating does not contain any waxy material. The same batch of raw materials was used throughout the tests performed in this study.

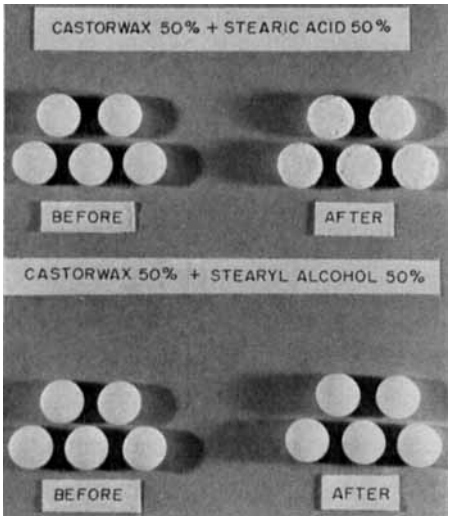

Fig. 3.—Effect on wax cores of 7-hour immersion in simulated intestinal fluid U.S.P. XVI.

The stearyl alcohol and castorwax were melted at 80–85°, and the screened tripelennamine HCl was dispersed in the melt. The liquid dispersion was solidified into flake form by congealing on a chilled stainless steel drum. The flakes were stored at 6° for 16 hours and then passed through a No. 12 mesh screen of the Fitzpatrick comminutor mill. One-third of the granules was mixed with 0.5% magnesium stearate and compressed. The other $^{2}/_{3}$ of the granulation was divided in half and passed through a No. 20 and No. 30-mesh screen on the Fitzpatrick Homoloid mill, respectively. After lubrication of these fractions with magnesium stearate, the granules were compressed. The 12-, 20-, and 30-mesh granules were each prepared to contain 15, 25, and 35% drug.

Fig. 4.—The Stoll-Gershberg apparatus modified to decrease moisture loss by evaporation.

The cores were compressed on a Stokes F machine, using flat-faced $^{12}/_{32}$-inch punches to a thickness of 4.5 to 4.6 mm. and a hardness of 4 to 5 as measured on the Strong-Cobb hardness tester.

For this investigation, the core thickness and hardness were maintained constant while the weight varied somewhat. The surface area was the same for all the tablets.

In Vitro Release Rate.—The release rate of the tablets was determined in a modified U.S.P. tablet disintegration apparatus consisting of baskets fitted with a 30-mesh screen, a glass immersion tube with a coarse fritted glass filter for removing samples of the liquid and a snug-fitting plastic cover to prevent moisture loss as illustrated by Fig. 4.

Purified water (600 ml.) was used as the eluting liquid, since preliminary studies in our laboratories indicated that the release of tripelennamine from a similar core material was the same whether the eluant was water or simulated gastrointestinal fluids. Six cores were used in each test. The disintegration apparatus was maintained at 37 ± 1° in a constant temperature water bath. The test

[1] Marketed as Lontabs by Ciba Pharmaceutical Co.

fluid was sampled at prescribed time intervals over an 8-hour period. Four milliliters of solution was removed at each sampling time and replaced with 4 ml. of purified water. At the end of the tests, the amount of water remaining in the beaker was measured and was found, generally, to exhibit a 5% loss of water over the 8-hour period. Without the plastic covering, a 20–25% loss in water was experienced.

The amount of water lost by evaporation from the beaker was prorated on an hourly basis, and from the amount of eluant in the beaker at sampling time, the total amount of drug present in the solution was calculated. The tripelennamine content of the sample was determined by diluting 1 ml. of solution with methanol and measuring its absorbance in a Beckman model DU spectrophotometer at 246 mμ.

THEORETICAL CONSIDERATIONS

Factors which control the amount of drug released from the matrix are as follows: (*a*) solubility and dissolution rate of drug; (*b*) porosity of tablet, (*c*) hardness of tablet, (*d*) geometry of matrix, (*e*) granule size, (*f*) drug concentration, (*g*) particle size of drug, and (*h*) matrix substances.

Higuchi (12) has indicated that the Eq. 1 relationship holds when the release mechanism from a granular matrix occurs by diffusional movement through porous or intergranular openings.

$$Q = \sqrt{\frac{Dt}{\tau}(2A - \epsilon C_s)C_s} \qquad \text{(Eq. 1)}$$

where Q = the amount of drug released per unit exposed area after time t, D = the diffusivity of the drug in the permeating fluid, τ = the tortuosity factor of the capillary system $\cong 3$, A = the amount of drug present in the matrix per unit volume, C_s = the solubility of the drug in the permeating fluid, and ϵ = the porosity of the matrix.

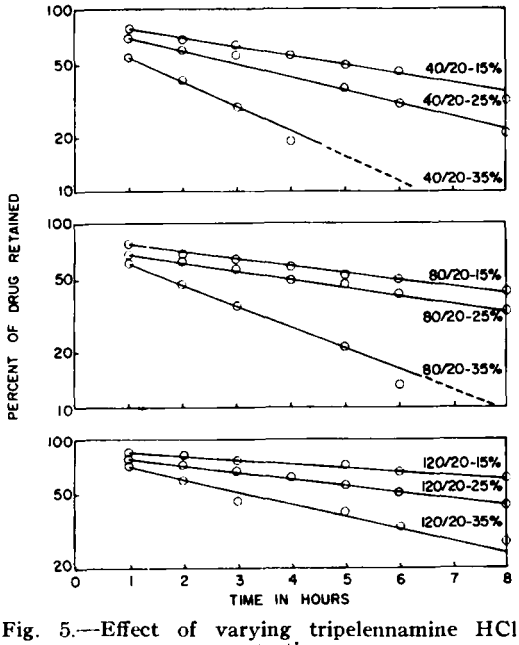

Fig. 5.—Effect of varying tripelennamine HCl concentration.

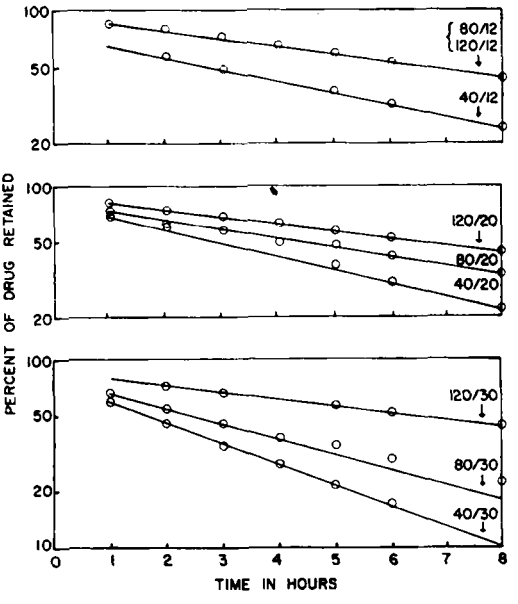

Fig. 6.—*In vitro* release rates of 25% tripelennamine HCl cores.

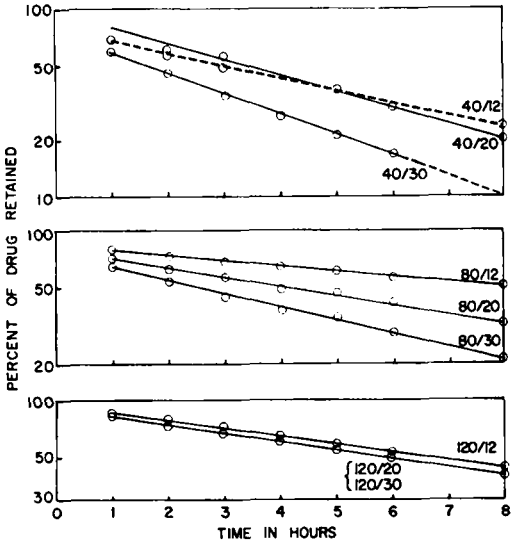

Fig. 7.—*In vitro* release rate of 25% tripelennamine HCl cores.

According to Eq. 1, a reduction of the release rate of a drug from a granular matrix can best be achieved by decreasing those factors which are proportional to the amount released, such as: (*a*) decreasing the solubility and the dissolution rate of the drug results in a decrease of C_s; (*b*) reducing the value of A will tend to decrease the release rate; (*c*) although hardness and porosity of a compressed tablet are related, in the present study, it was necessary to arrive at a predetermined hardness for the tablets since the granules containing the smaller size drug crystals yielded a softer tablet under the application of maximum pressure than the granules with the larger size crystals; and (*d*) the geometry of the tablets will affect the tortuosity factor which has an inverse influence on the release rate.

RESULTS AND DISCUSSION

The logarithm of the per cent drug retained in the cores was plotted against time in evaluating the influence of drug size, granule size, and drug concentration on the release of tripelennamine HCl. The straight lines obtained indicate that the *in vitro* release, for the system under consideration, follows an apparent first-order rate pattern. The *in vitro* release rates were based on the average release from six tablets.

The effect of varying the drug concentration while the granule and the crystal size were maintained constant can be seen from the representative plots in Fig. 5. In each case the release rate increased as the concentration increased. It can be seen from the graph that there was a greater rate increase as the concentration changed from 25 to 35% than for the corresponding increasing from 15 to 25%.

The graphs in Fig. 6 indicate that release obtained when the crystal size was varied while the granule size and concentration were maintained constant. Increasing the crystal size yielded faster release rates for each particular granule size.

When the drug concentration and crystal size are maintained constant, the release rate increases as the granules of the drug dispersion in the wax become smaller as illustrated in Fig. 7. This effect is expected since the grinding action to which the granules are subjected fractures the wax covering exposing more crystal surfaces. No significant effect on the release rate was noted when the size of the granules containing the 120-mesh crystals was varied.

The plots in Figs. 5–7 can be represented by $\log C = -kt/2.303 + \log C_o$, where the release rate is equal to the slope k and C the per cent residual drug concentration at time t.

Table I summarizes the release rate constants in hours^{-1} for the core formulations containing different crystal size, granule size, and drug concentration. The relationships between the three variables can be seen from the table. For the system studied, the drug size and concentration in the core are approximately equivalent in their influence on the rate of release and the granule size showing a lesser over-all effect.

The effect that a droplet of water has on the surface of a placebo wax core and a core containing the drug substance can be seen in Figs. 8–11. The wax cores are hydrophobic in nature, and a droplet of water on them assumes the characteristic shape. The core containing the tripelennamine HCl is readily wetted as seen by the difference in the contact angle of the water droplet to the core surface as illustrated in Fig. 8. The photomicrographs in Fig. 9 show the surface of a placebo core before and after treatment with one drop of water for 1 minute. The droplet was removed from the core by absorption onto filter paper and the core was then air dried. No surface changes were observed and the intergranular spaces or cracks do not appear to be altered.

TABLE I.—*In vitro* RELEASE RATES IN HOURS^{-1} OF TRIPELENNAMINE HCl CORES

Crystal Granule Size	Drug Concn. in Cores 15%	25%	35%
40/12	0.062	0.153	0.290
40/20	0.104	0.167	0.311
40/30	0.157	0.252	0.289
80/12	0.062	0.094	0.110
80/20	0.085	0.107	0.269
80/30	0.106	0.184	0.260
120/12	0.049	0.094	0.083
120/20	0.051	0.101	0.156
120/30	0.057	0.101	0.152

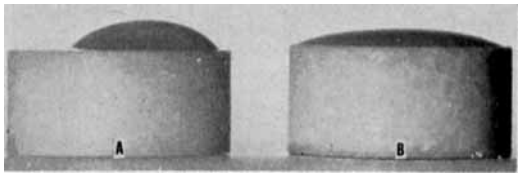

Fig. 8.—Wetting effect of a drop of water on (*A*) placebo compressed granular matrix and (*B*) a compressed granular matrix containing tripelennamine HCl.

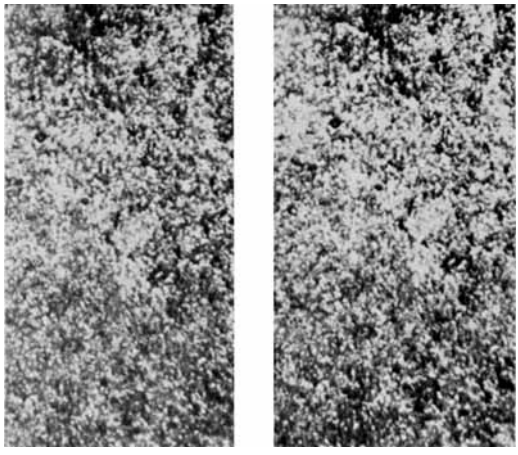

Fig. 9.—Left, surface of a placebo core before treatment with water; and right, same surface after treatment with one drop of water.

The surface appearance of the drug core is approximately the same as the placebo as evidenced by the photomicrograph shown in Fig. 10. Oblique lighting was used to illuminate the tablet and to emphasize the surface defects. When the tripelennamine HCl core is treated with water, porous areas and pitting develop on the surface due to the dissolution of the drug crystals as demonstrated in Fig. 10 (right side). It is obvious from the photomicrographs in Fig. 10 that the test fluid will more readily penetrate the core containing the drug than the placebo. Faster penetration would be due to dissolution of the drug at the exposed surface of the tablet causing pitting and permitting further penetration of fluid more readily. Penetration into the placebo core is by the more limited pathway of capillarity.

The observation of more rapid penetration of fluid into the core containing the drug than into the placebo was substantiated by the use of an indicator, an aqueous solution of sodium fluorescein. The cores were immersed into the solution and were removed periodically, then broken in half for examination under visual and ultraviolet light. With longer immersion the drug cores showed an increasing degree of penetration of the solution

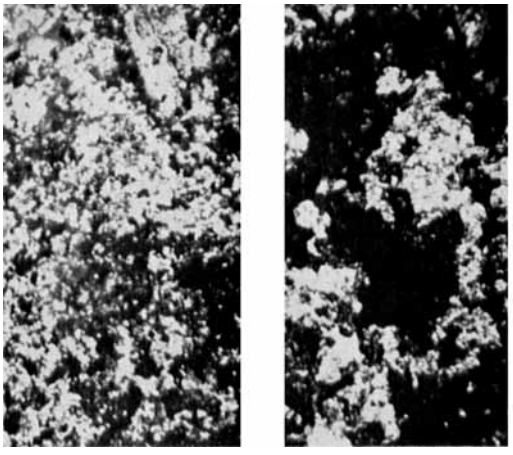

Fig. 10.—Left, surface of core containing tripelennamine HCl before treatment with water; and right, same surface after treatment with one drop of water.

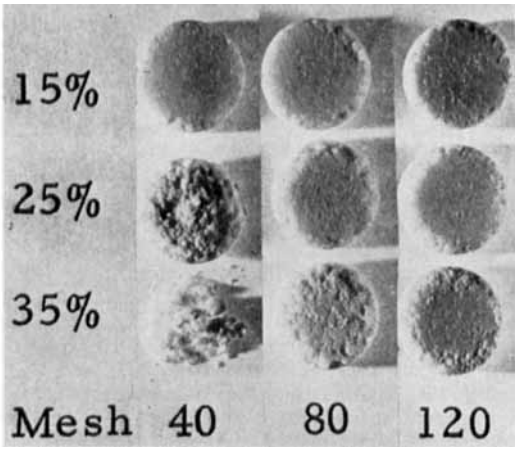

Fig. 11.—Tripelennamine HCl cores after immersion in water.

into the cores together with a gradual increase in the depth of color on the surface of the cores. The placebos, on the other hand, only showed a slight penetration of the solution into the matrix and an insignificant increase in surface color intensity with time.

A possible explanation for the release of a freely soluble drug from the compressed granular wax matrix may now be suggested. As the surface crystals dissolve on contact with the fluid, cavities develop which permit further attack by the fluid. The bonding strength of the granules of the matrix weakens as the pores increase in size and eventually the outer layer of granules slough off and exhibit an eroded appearance.

The effect of an 8-hour immersion in the bathing fluid on the cores is shown in Fig. 11. The matrix with the larger crystals (40 mesh) shows more disintegration than the smaller sized crystals. The small crystals, which are quantitatively more numerous at equivalent concentrations, create small cavities upon dissolution, which appear to be structurally less deleterious to the matrix. As the drug concentration is increased, the proportion of wax to drug decreases, resulting in less protection of the crystals against attack by the fluid and greater erosion occurs.

The data presented in this report represent our initial findings from the investigation that is presently under way to determine the critical physical chemical parameters needed for formulating prolonged action dosage forms with predictable release rates. From this information, it appears that the critical factors which affect the release rate of a drug in a compressed granular matrix of uniform physical properties are drug concentration, drug particle size, and granular size of the matrix.

SUMMARY

In the case studied, the crystal size and drug concentration exerted the greatest influence on the release rate, while the size of the granule as measured prior to compression plays a lesser role.

At the same concentration, the larger crystals gave a more rapid release.

Penetration of the fluid into the matrix appears to be primarily due to the dissolution on the surface of the matrix of water soluble material.

A modification of the *in vitro* U.S.P. tablet disintegration apparatus is described which has resulted in a reduction of the amount of fluid lost from the beaker by evaporation during the test run.

REFERENCES

(1) Lazarus, J., and Cooper, J., THIS JOURNAL, **50**, 715 (1961).

(2) Nelson, E., "Remington's Practice of Pharmacy," 12th Ed., Mack Publishing Co., Easton, Pa., 1961, Chapter 38.

(3) Lazarus, J., and Cooper, J., *J. Pharm. Pharmacol.*, **11**, 257(1959).

(4) Wiegand, R. G., and Taylor, J. D., *Drug Stds.*, **27**, 166(1959).

(5) Wagner, J. G., *ibid.*, **27**, 178(1959).

(6) Munzel, K., *Arch. Pharm.*, **65**, 766(1960).

(7) Blythe, R. H., U. S. pat. 2,738,303(1956).

(8) Cooper, J., U. S. pat. 2,887,438(1959).

(9) Sjogren, J., and Fryklof, L., *Farm. Revy*, **59**, 171 (1960).

(10) Endicott, C. J., U. S. pat. 3,087,860(1963).

(11) Simoons, J. R. A., "Formulation and Experimental Evaluation of Oral Sustained Release Medication Based on the Principle of Delayed Diffusion," Drukkerij Wed. G. Van Soest N. V., Amsterdam, 1962.

(12) Higuchi, T., THIS JOURNAL, **53**, 532(1964).