Sustained Release from Inert Wax Matrixes II: Effect of Surfactants on Tripelennamine Hydrochloride Release

ADNAN DAKKURI *, HANS G. SCHROEDER ‡, and PATRICK P. DeLUCA ˣ

Received July 9, 1976, from the *College of Pharmacy, University of Kentucky, Lexington, KY 40506.* Accepted for publication August 3, 1977. *Present address: School of Pharmacy, Ferris State College, Big Rapids, MI 49307. ‡Present address: The Upjohn Co., Kalamazoo, MI 49001.

Abstract □ The influence of several surfactants on the *in vitro* release of tripelennamine hydrochloride from a wax matrix was investigated. The congealed mass, obtained by dispersing the drug and surfactant in a molten mixture of carnauba wax and stearyl alcohol, was granulated and compressed into cores. While controlling particle-size distribution, tablet hardness, and weight, dissolution in simulated intestinal fluid was measured with the rotating-basket method. Water-insoluble surfactants such as glyceryl monostearate had no effect on the dissolution rate; slightly soluble or slowly soluble agents, such as sodium stearate, ammonium stearate, triethanolamine, and dioctyl sodium sulfosuccinate moderately increased dissolution. However, the water-soluble hydrophilic polyoxyethylene 23 lauryl ether considerably increased the dissolution rate; *i.e.*, about 80% of drug was released by a zero-order process over 4 hr. Since only a few surfactants were investigated, it is difficult to explain the difference in dissolution rate on the basis of ionic character. The profound effect of polyoxyethylene 23 lauryl ether could be attributed to both its hydrophilic nature and wetting action in an aqueous environment at the liquid–solid interface. Only with polyoxyethylene 23 lauryl ether was more than 50% released over 8 hr. With no surfactant present, approximately 38% was released, and release in the 1st hr was most rapid. The data suggest that a surfactant may make more channels available for the dissolution fluid to leach out the drug. Thus, the effective porosity of the matrix is increased. Furthermore, wetting is an important factor that controls matrix permeability.

Keyphrases □ Wax matrixes, inert—release of tripelennamine hydrochloride, effect of various surfactants □ Tripelennamine hydrochloride—release from inert wax matrixes, effect of various surfactants □ Surfactants, various—effect on release of tripelennamine hydrochloride from inert wax matrixes □ Antihistaminics—tripelennamine hydrochloride, release from inert wax matrixes, effect of various surfactants □ Tablets—tripelennamine hydrochloride in inert wax matrixes, effect of various surfactants on drug release □ Dosage forms—tablets of tripelennamine hydrochloride in inert wax matrixes, effect of various surfactants on drug release

A method of rapidly achieving and adequately maintaining a desired plasma drug level involves fabrication of a core tablet in which the instantly available portion of the drug is contained in an outer coating and the maintenance dosage is incorporated in a sustained-release wax matrix or core (1, 2). If it is assumed that the drug is readily available from the coating to achieve sufficient absorption to produce a rapid therapeutic response, the release of the balance of the drug from the core is dependent on drug particle size and solubility and core hardness and composition. Since the first three factors have been studied extensively, this investigation focused on the composition of the core. Many compositions have been suggested for sustaining drug release over a long period (3–5).

BACKGROUND

Surfactants have been used successfully as binders in solid formulations; they also function as lubricants during tablet compression. Although these functions are believed to have little connection with surface activity, it is this wetting action that promotes the drug release from the matrix (6). Therefore, surfactant incorporation into the matrix should give rise to two distinct phenomena: (*a*) a wetting action that promotes uniform distribution of the drug in the substrate, and (*b*) a wetting action in an aqueous environment at the liquid–solid interface that promotes uniform release of the drug from the substrate.

The role of wetting on the drug release rate from inert matrixes was emphasized by Singh *et al.* (6), who found that matrix permeability and permeation rates of the matrix by the solvent individually limit drug release. The determining factors were the pore-size distribution of the matrix and the permeation pressure of the contacting fluid defined by its surface tension and contact angle.

The purpose of this investigation was to study the effect of several surfactants individually incorporated in an inert solid matrix on drug release in an *in vitro* system; it is believed that drug distribution will be improved and that the drug release will be controlled more easily. Since drug solubility influences the release rate, drugs of varying solubility in water will be selected for eventual study with cationic, anionic, and nonionic surfactants. This report is limited to tripelennamine with several surfactants.

The surfactants were selected on a somewhat arbitrary basis, but all are pharmaceutically accepted compounds and have been used principally as dispersing and emulsifying agents in topical preparations. The stearates were selected because of their lubricant characteristics and their slight or slow solubility in water. Dioctyl sodium sulfosuccinate, polyoxyethylene 23 lauryl ether, and triethanolamine were selected as representatives of anionic, nonionic, and cationic agents, respectively.

EXPERIMENTAL

Materials—Tripelennamine hydrochloride, carnauba wax, and stearyl alcohol were used as received[1]. The surfactants were glyceryl monostearate[2], sodium stearate[2], ammonium stearate[3], dioctyl sodium sulfosuccinate[4], triethanolamine[5], and polyoxyethylene 23 lauryl ether[6].

Core Preparation—Three methods of incorporating the drug and surfactant into the matrix were explored:

1. The drug and surfactant were physically dispersed into the molten wax matrix.
2. The drug and surfactant were dissolved in a vehicle, the solution was incorporated into the molten wax phase, and the solvent was subsequently evaporated.
3. The ingredients were dry blended and compressed into a slug and then granulated and compressed into a core.

The first method was selected because it produced a more uniform matrix.

The granulations for compression into cores were prepared by melting the carnauba wax to approximately 90° and adding the stearyl alcohol. When a homogeneous melt was attained, the surfactant was added. Stirring was continued until an even distribution was reached. Then tripelennamine hydrochloride was added in small portions while the mass was mixed. With constant stirring, the mixture was allowed to cool slowly to about 75°, and the entire mass was then immediately poured onto cold glass plates and allowed to congeal. The solid mass was then granulated.

Equal quantities of carnauba wax, stearyl alcohol, and tripelennamine were used to prepare the surfactant-free formulation. In the other for-

[1] Supplied by Ciba-Geigy Corp., Summit, N.J.
[2] Fisher Scientific, Fair Lawn, N.J.
[3] Matheson, Coleman and Bell, Rutherford, N.J.
[4] Aerosol OT, Fisher Scientific, Fair Lawn, N.J.
[5] Ransdell Co., Louisville, Ky.
[6] Brij 35, J. T. Baker Chemical Co., Phillipsburg, N.J.

Table I—Tripelennamine Hydrochloride Content, Hardness, and Weight of Cores

Formulation	Tripelennamine Hydrochloride in Granulations[a], %	Hardness[b]	Weight[c], mg	Tripelennamine Hydrochloride Core[d], mg
Experimental control[e]	35.7 ± 1.1	9.6	202.6	71.17
Commercial control	—	10.5	199.6	67.22
Glyceryl monostearate, 2 mg	35.1 ± 0.6	9.9	216.7	71.42
Glyceryl monostearate, 5 mg	33.5 ± 0.7	10.1	205.4	71.68
Glyceryl monostearate, 10 mg	35.1 ± 0.5	9.4	212.0	74.43
Sodium stearate, 5 mg	33.8 ± 0.6	9.8	207.6	67.58
Ammonium stearate, 5 mg	35.5 ± 0.8	9.4	197.0	71.42
Triethanolamine, 5 mg	34.4 ± 0.5	8.9	198.0	66.24
Dioctyl sodium sulfosuccinate, 5 mg	34.3 ± 0.6	10.0	207.3	71.74
Polyoxyethylene 23 lauryl ether, 5 mg	32.7 ± 0.4	9.6	196.7	64.83

[a] Average of six determinations of 1-g samples. Theoretical = 33.3%. [b] Pfizer hardness tester (lb/in.^{2}). Average of 10 determinations. [c] Average of 10 determinations. [d] Average of three determinations from powder obtained from 10 cores. [e] No surfactant present.

mulations, equal quantities of carnauba wax and stearyl alcohol were replaced with the amount of surfactant added.

The granulation was screened and separated into four fractions: >1200, 750–1200, 300–750, and <300 μm. The particle-size distribution of the granulation was held constant for all formulations and was controlled by recombining a fixed amount of granules in each size range: 20, 30, 30, and 20% (w/w) for the four size ranges, respectively.

Magnesium stearate, 1%, was added to the granulation, which was then compressed[7] into 200-mg cores using 9.5-mm (0.38-in.) punches and die. Considerable effort was expended to ensure a uniform tablet weight and a consistent tablet hardness. Every effort was made to make the cores comparable to the commercial cores[8]. It was necessary to compress the cores to the same hardness as the commercial cores, which had been subjected to double compression: first when the cores were prepared and then when the outer coating was applied.

Since the purpose was the determination of drug release from the sustained-release portion, the outer coating of the tablet was washed off with water and the resultant cores were used as controls in the preparation of the experimental cores, as previously mentioned. Therefore, the results should be equally valid when applied to the slow-release core of timed-release tablets.

Dissolution Procedure—The USP XIX rotating-basket method (7) was employed for investigating drug release from the cores. Three tablets were placed in the basket, which was immersed in 600 ml of simulated intestinal fluid[9] previously warmed to 37°. The basket was rotated at 50 rpm, and the water bath was maintained at 37 ± 0.5° for 8 hr.

At 1-hr intervals, a 2-ml sample was withdrawn from the vessel for assay with a pipet fitted with a glass wool prefilter and immediately replaced with an equivalent volume of dissolution medium. The remaining portions of the tablets were assayed at the termination of each dissolution experiment to determine the amount of drug remaining. Duplicate runs were made on each batch.

Tripelennamine Hydrochloride Assay—Aliquots of the dissolution medium were assayed for tripelennamine hydrochloride content by diluting to an appropriate volume with methanol, filtering the sample, and measuring its absorbance[10] at 244 nm against a methanol blank containing the same volume of dissolution medium as the sample. A standard Beer's law plot was constructed, and an absorptivity of 52.08 ml/mg (1-cm cell) was calculated. This factor was used to determine the tripelennamine concentration in the sample. The cumulative drug released was computed from the sample assays using the Wurster and Taylor equation (8).

The presence of the surfactants did not interfere with the drug assay. Intact cores, remains of cores, and granulations were analyzed by extracting the tripelennamine with methanol in a blender[11]. An aliquot was removed and diluted to an appropriate volume with methanol, and the absorbance was read at 244 nm using a methanol blank.

RESULTS AND DISCUSSION

Table I shows the values for tripelennamine hydrochloride contents in the granulations and intact cores as well as the hardness and weight of the cores of all batches. The consistency of the drug percentage in the various granulations indicates that the drug was uniformly distributed, and the lower standard deviations for the surfactant-containing granulations suggest improved drug distribution.

Since the outer coating of commercial tablets readily disintegrates and releases tripelennamine hydrochloride in the gastric fluid, this study was concerned only with drug release from the slow-release wax matrix designed to resist attack in gastric fluid. However, preliminary studies showed that some dissolution occurred within 20 min in simulated gastric fluid. This dissolution can be attributed to surface drug. Any additional drug release was negligible until the core was transferred to the intestinal fluid.

In Fig. 1, tripelennamine release from commercial cores[8] is plotted along with the release from the prepared surfactant-free cores. The two release patterns are similar. Therefore, all comparisons should be valid, and the results obtained using surfactants in the formulations should be representative of what would be expected if such surfactants were incorporated into the commercial cores. The lower initial drug release from these cores can be attributed to the lower concentration of surface drug as a result of washing off the outer coating. Nevertheless, this release can be ignored because the similarity between the two release patterns is clearly evident.

Commercial cores (no outer coating) subjected to single compression only were much softer (5–6 lb/in.^{2}) than the cores obtained by removing the outer coating of the commercial tablet. The increased hardness in the latter cores was due to the second compression step in adding the coating. While the incremental drug release was much faster (between 2 and 5 hr) for the single-compression cores, the incremental release of drug before and after this period was similar to the other two cores (Fig. 1). The abrupt drug release was due to core disintegration, which increased the surface area significantly, particularly in the 2–3-hr interval. This result emphasizes the need for controlled core disintegration. The desired drug dissolution from the sustained-release portion over 10 hr, assuming no initial release, is depicted by the dotted line in Fig. 1.

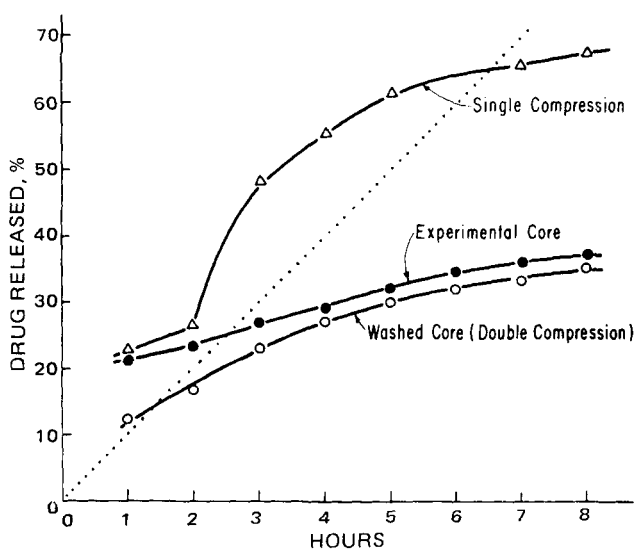

Figure 1—*Tripelennamine hydrochloride release from a wax matrix in the absence of surfactants. Key: △, commercial single-compression cores; ●, experimental cores (no surfactant present); and ○, cores obtained by washing off the outer coating of commercial tablets.*

[7] Stokes model E single-punch tablet press.
[8] Cores of Pyribenzamine Lontabs, Ciba Pharmaceutical Co., Summit, N.J.
[9] Pancreatin NF, 7.44 g; sodium bicarbonate, 120.0 g; and distilled water, sufficient quantity to make 8000 ml; pH 8.0 ± 0.1.
[10] Gilford model 240 spectrophotometer.
[11] Waring.

Table II—Incremental Release (Milligrams) of Tripelennamine Hydrochloride from Cores [a]

Formulation	First 20 min	1st hr	2nd hr	3rd hr	4th hr	5th hr	6th hr	7th hr	8th hr	Remains	Total Recovered mg	Total Recovered %
Commercial control	—	8.93	3.17	4.60	2.97	1.60	1.50	1.40	1.39	40.99	65.55	97.5
Experimental control [b]	—	15.39	1.00	3.03	1.59	2.01	1.56	1.23	1.12	38.06	64.99	91.3
Glyceryl monostearate, 2 mg	—	13.93	1.85	2.95	1.56	2.11	1.19	1.58	2.22	43.56	70.95	99.3
Glyceryl monostearate, 5 mg	—	12.57	2.56	2.81	1.84	0.94	1.30	1.26	1.32	41.20	65.80	91.7
Glyceryl monostearate, 10 mg	8.27	12.86	4.00	3.00	2.60	1.21	1.05	0.95	1.39	42.96	70.02	94.1
Sodium stearate, 5 mg	8.98	14.24	3.52	4.75	2.69	2.25	2.87	2.96	0.57	33.28	67.13	99.3
Ammonium stearate, 5 mg	8.93	13.31	3.84	3.38	2.62	2.77	1.97	2.30	2.09	32.52	64.80	90.7
Triethanolamine, 5 mg	8.29	13.11	3.66	3.62	3.08	2.08	2.49	1.84	0.84	32.36	63.08	95.2
Dioctyl sodium sulfosuccinate, 5 mg	8.36	12.82	4.62	3.70	2.72	2.37	1.51	2.28	2.72	32.56	65.30	91.0
Polyoxyethylene 23 lauryl ether, 5 mg	9.40	19.08	14.86	9.30	8.79	3.65	0.17	0.56	—	6.11	62.52	96.3

[a] Values reported are the average of duplicate samples, three cores each. [b] No surfactant present.

The effect of glyceryl monostearate on the tripelennamine release rate is shown in Fig. 2; the data for three levels of surfactant are plotted. There was very little difference from the release pattern without surfactant present. The fact that glyceryl monostearate did not affect the drug dissolution rate can probably be attributed to its water insolubility.

However, as shown in Fig. 3, when sodium stearate or ammonium stearate was used, the release pattern was improved; sodium stearate gave better results when compared with ammonium stearate. Between 1 and 8 hr, there was a strong ($r = 0.988$) and statistically highly significant correlation ($p < 0.001$) between the amount of drug released and time. The linearity of the relationship and the resulting high correlation coefficient suggest that the drug was released by a zero-order process within the specified time period. Sodium stearate dissolves slowly in water but is more readily soluble in intestinal fluid; this property is probably the reason for it having a greater effect on the dissolution rate than either glyceryl monostearate or ammonium stearate. The latter surfactant is slightly soluble in water and, consequently, the dissolution rate obtained with it lies between the rates obtained with sodium stearate and glyceryl monostearate.

Figure 4 illustrates the effect of three different surfactants on the dissolution rate. While both the cationic surfactant triethanolamine and the anionic agent dioctyl sodium sulfosuccinate increased the release rate, the nonionic agent polyoxyethylene 23 lauryl ether showed a profound effect. Over 4 hr, about 80% of the drug appeared to be released by a zero-order process, as suggested by the linear relationship between the amount of drug released and time. However, very little additional tripelennamine was released thereafter, and less than 90% was in solution following 8 hr.

It is difficult to explain the difference in the dissolution rate on the basis of ionic type since only a few surfactants were investigated. The greater rate with the core containing polyoxyethylene 23 lauryl ether could be attributed, in addition to surface activity, to greater water solubility and hydrophilicity. Triethanolamine is a good wetting agent and shows good miscibility with water, while dioctyl sodium sulfosuccinate is slowly soluble in water.

The incremental drug release with various surfactants is shown in Table II. Only with polyoxyethylene 23 lauryl ether did more than a 50% release occur over 8 hr. With no surfactant present, only 38% was released over the same period, and half of that occurred in the 1st hr.

The desired situation for the tripelennamine core would be the release of its entire content in 10 hr. To maintain sustained release and subsequently to attain a constant blood drug level over such a period, an average of 6.67 mg (66.7 mg/200-mg core) of drug should be released each hour. While polyoxyethylene 23 lauryl ether, sodium stearate, and triethanolamine show promise in improving the release profile, an *in vivo* study is needed to correlate with the *in vitro* dissolution method. The dissolution method utilized is by no means indicative or predictive of the attainable blood levels, and some correlation between *in vitro* drug release and *in vivo* performance is required.

Drug release is principally *via* a leaching mechanism, and drug diffusion through the matrix is either nonexistent or insignificant (4). Either the core must be slowly and continually eroding so that new surfaces are being exposed or channels must be continually forming in the core so that the intestinal fluid penetrates the core and leaches out the drug. Spontaneous core disintegration has a deleterious effect because it only provides an instantaneous drug release and any further release from the resultant small particles is negligible.

The data in Table II show that total release is not possible. A certain percentage of drug will always be coated very effectively with a wax film impermeable to the dissolution fluid. Consequently, total release may be difficult to achieve. The same phenomenon was observed with slowly eroding, timed-release tablets prepared with a swellable gum, carbomer 934P (9). The lubricant magnesium stearate might exert a slight retardant

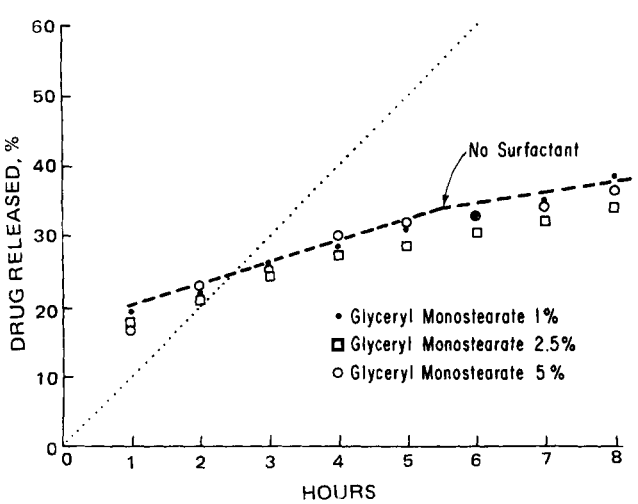

Figure 2—*Tripelennamine hydrochloride release from a wax matrix containing different levels of glyceryl monostearate. Key: ●, 1%; □, 2.5%; and ○, 5%. The broken line represents drug release from a surfactant-free core.*

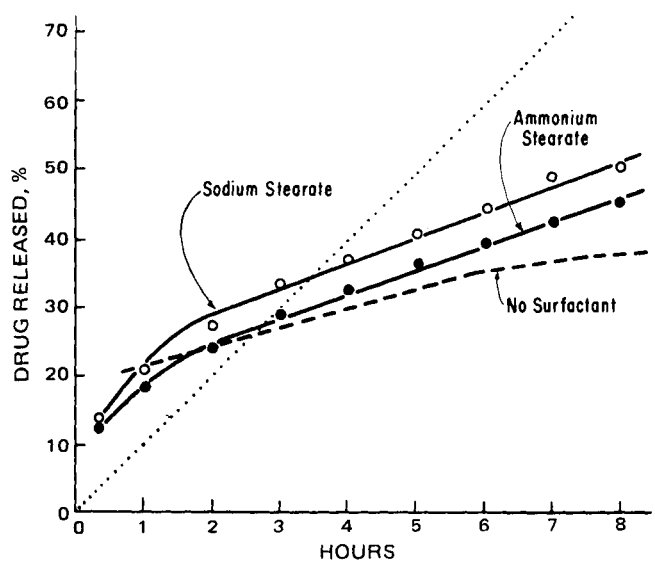

Figure 3—*Effect of stearates on the release of tripelennamine hydrochloride from a wax matrix. Key (surfactant in cores): ●, 2.5% ammonium stearate; and ○, 2.5% sodium stearate. The broken line represents drug release from a surfactant-free core.*

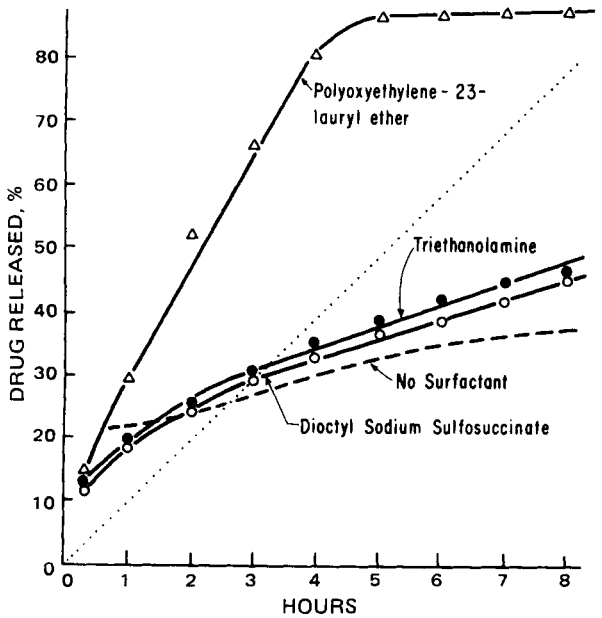

Figure 4—*Effect of surfactants of varying types on tripelennamine hydrochloride release from a wax matrix. The cores contained 2.5% surfactant. The broken line represents drug release from a surfactant-free core.*

effect on core dissolution; it possibly can be replaced with magnesium lauryl sulfate, but its toxicity has not yet been established (10).

The data suggest that a surfactant may make more channels available for the dissolution fluid to leach out the drug. Thus, the effective porosity of the matrix is increased. Wetting is an important factor that controls matrix permeability. It may be of interest to measure the degree of wetting of the various surfactants selected for this study.

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ACKNOWLEDGMENTS

Presented at the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, New Orleans meeting, April 1976.

Sustained Release from Inert Wax Matrixes III: Effect of Povidone on Tripelennamine Hydrochloride Release

ADNAN DAKKURI *, L. DAVID BUTLER, and PATRICK P. DeLUCA ˣ

Received October 13, 1976, from the *College of Pharmacy, University of Kentucky, Lexington, KY 40506.* Accepted for publication February 16, 1977. *Present address: School of Pharmacy, Ferris State College, Big Rapids, MI 49307.

Abstract □ The utilization of povidone as a channeling agent in the formulation of a sustained-release tripelennamine hydrochloride core significantly influenced drug release over 10 hr. Povidone was incorporated into a mixture of carnauba wax and stearyl alcohol by fusion and subsequent congealing in concentrations of 5, 10, and 20% (w/w); the stearyl alcohol concentration was altered to maintain a constant tripelennamine content. Tablet hardness and weight were also held constant. With the povidone-free formulation as a control, the addition of 5% of the channeling agent increased the release by 37% over 8 hr; at the 20% level, the increase was 55%. Between 0.5 and 8 hr, the drug appeared to be released by a zero-order process and a plateau was then approached. Over this interval, the dissolution pattern approached the optimum situation of 10% release/hr with 10–20% povidone. The results obtained from cores made by double compression of the dry-blended ingredients indicated that fusion is essential for channel formation. There was no evidence of complexation between tripelennamine and povidone. A decrease in the release rate was obtained when the polymer was included in the dissolution medium. It appears that channel formation is the mechanism underlying the increase in the drug dissolution rate from cores containing the polymer.

Keyphrases □ Povidone—effect on tripelennamine hydrochloride release from inert wax matrix tablets □ Wax matrixes, inert—effect of povidone on tripelennamine hydrochloride release, tablets □ Tripelennamine hydrochloride—release from inert wax matrix tablets, effect of povidone □ Polymers—povidone, effect on tripelennamine hydrochloride release from inert wax matrix tablets □ Antihistaminics—tripelennamine hydrochloride, release from inert wax matrix tablets, effect of povidone □ Tablets—containing inert wax matrix, effect of povidone on tripelennamine hydrochloride release □ Dosage forms—tablets containing inert wax matrix, effect of povidone on tripelennamine hydrochloride release

The mechanism of drug release from the wax matrix-type core involves leaching by the intestinal fluid that contacts the imbedded drug. In addition to dissolving "surface" drug, the fluid can enter the core through pores, cracks, and intergranular spaces and dissolve the drug. Drug diffusion through the matrix is either nonexistent or insignificant (1).

Higuchi (2) theoretically treated the matrix model and showed that the porosity and degree of tortuosity (a measure of diffusional path) in the capillary system influence the dissolution rate. Since the amount of drug per unit of matrix volume decreases with time as dissolution occurs, the porosity should increase and tortuosity should decrease to maintain a constant dissolution rate, in ac-