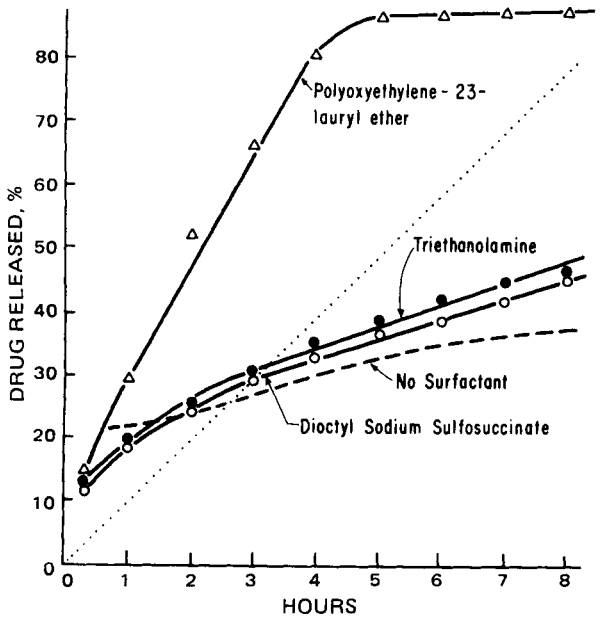

Figure 4—*Effect of surfactants of varying types on tripelennamine hydrochloride release from a wax matrix. The cores contained 2.5% surfactant. The broken line represents drug release from a surfactant-free core.*

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

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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-

Table I—Formulas (in Milligrams) per Core

Ingredient	I Concentration 0%	5%	10%	20%
Tripelennamine hydrochloride	66.7	66.7	66.7	66.7
Carnauba wax	66.7	66.7	66.7	66.7
Stearyl alcohol	66.7	56.7	46.7	26.7
Povidone	—	10.0	20.0	40.0
Magnesium stearate	2.0	2.0	2.0	2.0

Table II—Hardness and Weight of Dry-Blended Cores Containing Various Amounts of I (mol. wt. 10,000)

I, %	Weight[a], mg	Hardness[b], kg. (lb)/in.^{2}
0	204	4.1 (9.1)
5	201	4.3 (9.5)
10	205	4.4 (9.6)
20	210	4.3 (9.5)

[a] Average of 12 determinations. [b] Average of six determinations.

cordance with the Higuchi equation.

Drug dissolution from time-released tablets results from slow and continuous core erosion in which new surfaces are being exposed (3), or channels must be continually forming in the core so that the intestinal fluid penetrates the core and leaches out the drug. A polymer like povidone (I) might fulfill the requirement as a channeling agent to improve the release from a wax matrix core.

This investigation studied the effect of two types of I, individually incorporated in an inert solid matrix, on drug release in an *in vitro* system. The effects of the core preparation method and the influence of I in the dissolution medium on drug release from polymer-free cores also are evaluated.

EXPERIMENTAL

Materials—Tripelennamine hydrochloride, stearyl alcohol, and carnauba wax were used as received[1], except that the first two materials were passed through a 40-mesh screen. Two types of povidone USP, having average molecular weights of 10,000 and 40,000, were employed[2].

Core Preparation—Two methods of incorporating the drug and I into the matrix were explored, *i.e.*, double compression and fusion. In the first method, the materials were blended in a rotary mixer[3]. The mixture was compressed[4] into slugs, which were then passed through an oscillating granulator[5] using a No. 14 screen. The tablets were finally compressed[4] utilizing a 0.95-cm (3/8-in.) standard concave punch and die set.

In the fusion method, the granulations to be compressed into cores were prepared by melting carnauba wax to approximately 90° and adding stearyl alcohol. When a homogeneous melt was attained, I was added; stirring was continued until an even distribution was obtained. 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 75–85°, depending on the concentration and type of I. The entire mass was then immediately cast on cold glass plates and allowed to congeal. Subsequently, the mass was granulated (14 mesh); 1% magnesium stearate was added before compression into cores.

Equal quantities of tripelennamine hydrochloride, carnauba wax, and stearyl alcohol were used to prepare the polymer-free formulation (Table I). In the other formulations, the stearyl alcohol concentration was reduced to accommodate polymer addition (Table I). Considerable effort was expended to ensure a uniform tablet weight (200 mg) and a consistent tablet hardness of 4.1–4.5 kg[6] (9–10 lb)/in.^{2}.

Dissolution Procedure—The USP rotating-basket method (4) was used to investigate drug release from the cores at 37°. Three tablets were placed in the basket, which was immersed in 600 ml of simulated intestinal fluid USP. The basket was rotated at 50 rpm for 10 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. Two to four runs were made on each batch.

Table III—Effect of Method of Preparation, Concentration, and Type of I on Disintegration Time of Tripelennamine Hydrochloride Cores[a]

I, %	Disintegration Time, min
Double Compression, I mol. wt. 10,000	
0	60
5	48
10	42
20	31
Fusion, I mol. wt. 10,000	
0	284
5	164
10	152
20	86
Fusion, I mol. wt. 40,000	
0	284
5	230
10	128
20	93

[a] Average of six determinations in simulated intestinal fluid USP.

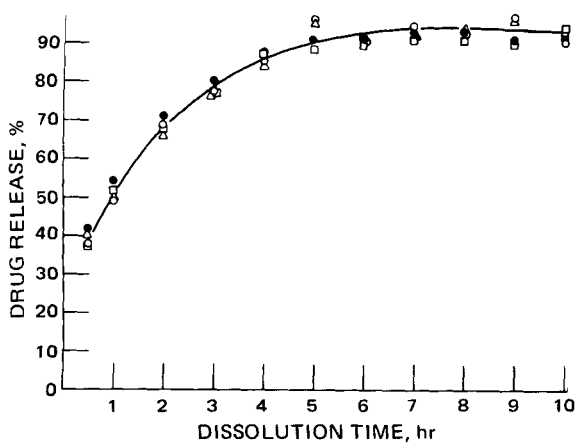

Figure 1—*Effect of I (mol. wt. 10,000) on tripelennamine hydrochloride release from cores prepared by double compression. Key (polymer concentration): ○, 0%; △, 5%; □, 10%; and ●, 20%.*

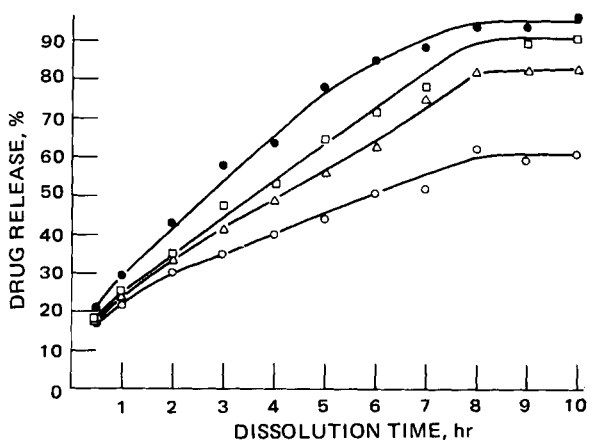

Figure 2—*Effect of I (mol. wt. 10,000) on tripelennamine hydrochloride release from fused cores. Key (polymer concentration): ○, 0%; △, 5%; □, 10%; and ●, 20%.*

[1] Supplied by Ciba-Geigy Corp., Summit, N.J.
[2] Plasdone C-15 and Plasdone C-30, GAF Corp., New York, N.Y.
[3] Model C-100, Hobart Manufacturing Co., Troy, Ohio.
[4] Stokes model E single-punch tablet press.
[5] Type TG-2S, Erweka-Apparatebau GMBH, Frankfurt (Main), West Germany.
[6] Pfizer hardness tester.

Table IV—Percent Cumulative Release of Tripelennamine Hydrochloride from Fused Cores Containing Various Amounts of I (mol. wt. 10,000) [a]

I, %	Dissolution Time, hr										
	0.5	1	2	3	4	5	6	7	8	9	10
0	16.2	21.4	30.4	34.9	40.1	44.1	50.8	51.2	62.4	59.4	60.7
5	16.6	23.1	33.2	41.3	48.5	55.8	62.9	74.4	82.1	81.7	82.8
10	17.7	24.6	34.7	47.2	53.0	64.6	71.6	78.0	88.9	89.2	90.8
20	20.9	29.5	42.8	57.4	63.2	78.1	85.0	88.4	94.0	93.7	96.4

[a] Values reported are the average of duplicate samples, three cores each.

Modified intestinal fluid[7] also was used for the cores containing the higher molecular weight I. Furthermore, to determine the effect of I when present in the dissolution medium on drug release from polymer-free cores, dissolution of these cores in intestinal fluid containing 0.005, 0.05, 0.5, 1.0, and 2.0% I (mol. wt. 40,000) was investigated. The 0.005% represents the I concentration in the dissolution medium if all polymer in the cores dissolves. Samples were withdrawn from the vessel after 0.5, 1, 4, 8, and 10 hr.

Disintegration Time—The USP apparatus and procedure with disks were used to determine tablet disintegration time in simulated intestinal fluid at 37° (4). The reported value is an average of six tablets.

Tripelennamine Hydrochloride Assay—Aliquots (0.5 or 1.0 ml) of the dissolution medium were acidified with 10% HCl (0.1 or 0.2 ml), diluted to 10 ml with methanol, and assayed for tripelennamine hydrochloride content by measuring absorbance[8] at 240 nm against a methanol blank containing the same volumes of dissolution medium and acid as the sample. The drug concentration in the sample was calculated from a standard Beer's law plot. The cumulative drug released was computed from the sample assay using the Wurster and Taylor equation (5).

RESULTS AND DISCUSSION

Table II shows the values for the hardness and weight of the cores prepared by double compression. The values obtained for the fused formulations are similar to those obtained with the dry-blended batches.

Figure 1 shows the release of tripelennamine from the cores prepared by double compression. These dissolution profiles clearly indicate that the incorporation of I in the core had no significant effect on drug release. The lack of cohesiveness in these cores is evident from the relatively short disintegration time of the polymer-free cores (Table III) when compared with the time (about 5 hr) for the fused cores.

The failure of I to improve the release profile from a wax matrix, when the cores are prepared by the slugging method, probably can be attributed to the absence of channels in the dry-blended cores and the extensive diffusive blending of the water-soluble I throughout the tablet matrix. The fusion process apparently is necessary to prevent core disintegration and subsequent rapid drug release. In other words, fusion is essential for channel formation within the core. The apparent lack of cohesiveness in such cores is also evident from the fact that a 90% plateau was approached within 5 hr. The high initial release within the first 30 min (Fig. 1) was due to the drug on the surface being released more rapidly than the drug in the matrix, as well as to rapid penetration of the medium in the cores.

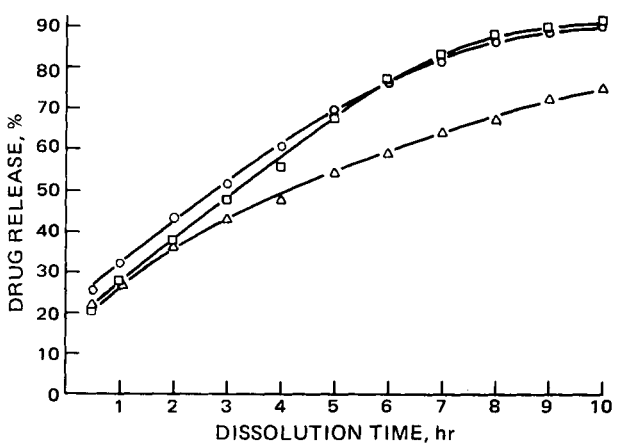

Figure 3—*Effect of I (mol. wt. 40,000) on tripelennamine hydrochloride release in simulated intestinal fluid USP from fused cores. Key (polymer concentration): △, 5%; □, 10%; and ○, 20%.*

[7] Simulated intestinal fluid USP without pancreatin.
[8] Gilford model 240 spectrophotometer.

The effect of I content in the fused cores on dissolution rate is illustrated in Fig. 2. The polymer appears to influence significantly drug release when incorporated in the wax matrix by the fusion method. The dissolution rate increased significantly with an increase in I concentration, suggesting a concomitant increase in porosity within the matrix. Between 0.5 and 8 hr, the drug appeared to be released by a zero-order process; *i.e.*, the correlation coefficient was higher by linear regression analysis for the zero-order process.

The amount of tripelennamine released is listed in Table IV. The increase in total drug release at the end of each run with an increase in I content (61% for 0% and 96% for 20% polymer) shows that the amount of drug effectively coated with wax decreased as the amount of I in the core increased. The amount of stearyl alcohol in the formulation was reduced to accommodate polymer addition. Furthermore, channel formation increased with an increase in polymer.

The effect of I (mol. wt. 40,000) on drug release from fused cores is shown in Fig. 3. As with the lower molecular weight I, an increase in drug release was observed with an increase in polymer content. However, in contrast to I (mol. wt. 10,000), there was no significant difference ($p > 0.001$) between the release profiles of 10 and 20% polymer cores. Furthermore, the plateau was approached only after a 9-hr interval, and it was not as well defined as in the case of I (mol. wt. 10,000).

More drug was released at the end of 10 hr when the lower rather than the higher molecular weight I at the same concentration was used. As the molecular weight of the polymer increases, the channeling effect in the granules that are effectively coated with wax probably decreases, thus making it more difficult for the medium to leach drug out. Furthermore, the difference observed with the lower and higher molecular weights may relate to a difference in their aqueous solubility.

The dissolution profiles of the fused cores containing I in intestinal fluid are shown in Fig. 4. These profiles are similar to those in Fig. 3; there was a noticeable increase as the polymer level was increased from 0 to 5% and from 5 to 10% but no significant difference between 10 and 20% levels. However, the presence of pancreatin in the dissolution medium caused about a 5% decrease in drug release at the end of 10 hr.

These results indicate that I acts as a channeling agent within the wax matrix. If complexation between tripelennamine and I is the mechanism underlying the increase in the drug dissolution rate from cores containing

Table V—Percent Decrease in Dissolution of Tripelennamine Hydrochloride from Polymer-Free Cores in Modified Intestinal Fluid Containing Various Amounts of I (mol. wt. 40,000) [a]

I, %	Dissolution Time, hr				
	0.5	1	4	8	10
0.005	—	—	—	—	0.4
0.05	1.9	—	—	—	2.7
0.5	3.8	—	—	1.1	4.9
1.0	3.8	0.4	0.4	4.4	5.4
2.0	6.0	3.9	3.9	8.8	8.0

[a] Using dissolution in intestinal fluid (simulated intestinal fluid USP without pancreatin) as control.

Table VI—Slope and Correlation Coefficient of the Zero-Order Component of the Release Profile of Fused Cores Containing Various Amounts of I (mol. wt. 10,000)

I, %	Slope, %/hr	Correlation Coefficient
0	5.56	0.988
5	8.42	0.998
10	9.23	0.996
20	9.85	0.982

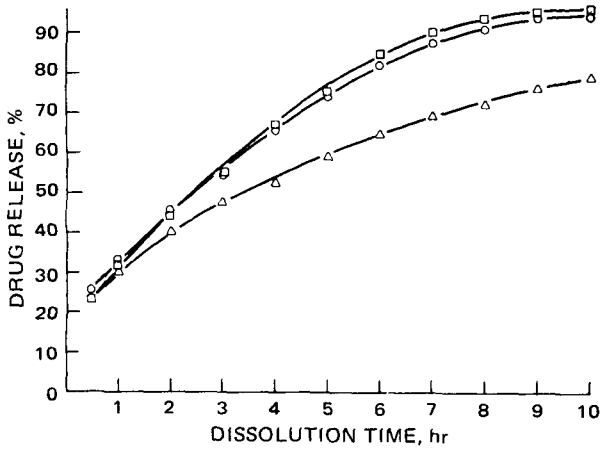

Figure 4—*Effect of I (mol. wt. 40,000) on tripelennamine hydrochloride release in modified intestinal fluid from fused cores. Key (polymer concentration):* △, *5%;* □, *10%; and* ○, *20%.*

the polymer, then the same effect should be expected when I is included in the medium. This was not the case, because there was a decrease in the drug release rate (Table V). The decrease in dissolution became more pronounced as the polymer concentration in the medium was increased. The apparent decrease was probably due to the increasing viscosity of the medium as the polymer concentration increased.

This conclusion was further substantiated by an IR study. Tripelennamine and low and high molecular weight I were dissolved in ethanol, the solvent was evaporated on a boiling water bath, and the mixture was dried under vacuum. The high frequency region of the IR spectrum[9] of the drug–polymer system was simply the summation of the spectra of the two components; there was no evidence of complexation between the two compounds. This result was not unexpected, because the tripelennamine molecule cannot hydrogen bond with the carbonyl group of I. Such bonding is possible with, for example, tolbutamide (6).

The optimum situation for the tripelennamine core would be the release of its entire content in 10 hr. Therefore, an average of 6.67 mg (66.7 mg/200-mg core) of drug should be released each hour. Table VI shows the slope and correlation coefficient for the zero-order component of the release profile of cores having various levels of I (mol. wt. 10,000) and prepared by fusion. At the 10–20% I level, the drug was released in a fashion approaching the optimum situation, at least in the 0.5–8-hr interval, with a total release of 89% for the 10% level and 94% for the 20% level over 10 hr.

Table III shows the effect of the method of preparation, concentration, and type of I on the core disintegration time. There was a rank correlation between the disintegration time and polymer concentration for both types. It appears that I acts as a disintegrant through channel formation. The data also clearly indicate the lack of cohesiveness in the cores prepared by double compression in comparison with the fused cores. While in the dissolution apparatus, the fused polymer-free and 5% I cores remained intact with a smooth surface at the end of 10 hr. On the other hand, cores containing higher concentrations of I appeared to have fissures as dissolution proceeded. The occurrence of the latter phenomenon was probably due to the I reducing the interparticle bonding of the drug–wax granules during compression.

The higher release of drug initially (0.5–8 hr) suggests that it may be possible to incorporate 100 mg of tripelennamine hydrochloride into a sustained-release matrix and to design the formulation in such a manner that 30–40% of the drug would be released in the first 2 hr in the stomach, with the remaining 60–70% released over the following 8 hr in the intestinal tract.

While it might be possible to design a sustained-release form as described, a certain percentage of the drug, about 10%, probably will always be coated very effectively with a wax film that is impermeable to GI fluids. Consequently, total drug release may be difficult to achieve.

[9] Perkin-Elmer model 567 grating IR spectrophotometer.

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Analysis of Betamethasone and Its Organic Esters in Pharmaceutical Products

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Received March 28, 1977, from the **Food and Drug Administration, Dallas District, Dallas, TX 75204,* and the ‡*Department of Chemistry, Southern Methodist University, Dallas, TX 75275.* Accepted for publication July 1, 1977.

Abstract □ A rapid, quantitative analysis for betamethasone and its organic esters at room temperature is described. The method is similar to the official blue tetrazolium reaction for corticosteroids, except that methylene chloride is used as the solvent. The reaction is complete in 27–69 min, and the formazans produced are stable for at least 90 min after the addition of tetramethylammonium hydroxide. The results of the analysis of 13 different pharmaceutical formulations by the proposed method are reported. The degradation of betamethasone and its esters caused by strong bases is a pseudo-first-order reaction in methylene chloride. The average half-life of the corticosteroids studied is 56 min under the basic conditions described.

Keyphrases □ Betamethasone and various esters—spectrophotometric analyses in pharmaceutical products □ Spectrophotometry—analyses, betamethasone and various esters in pharmaceutical products □ Glucocorticoids—betamethasone and various esters, spectrophotometric analyses in pharmaceutical products

Betamethasone and its esters are synthetic corticosteroids which are included in several types of pharmaceutical preparations. Chafetz *et al.* (1) reported a colorimetric procedure for betamethasone benzoate in topical gel preparations that utilized preliminary oxidation of the 17-keto function, followed by reaction with phenylhy-