Molecular-Scale Drug Entrapment as a Precise Method of Controlled Drug Release I: Entrapment of Cationic Drugs by Polymeric Flocculation

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Abstract □ A system of molecular-scale drug entrapment has been developed which provides a physicochemical and highly reproducible method of effecting drug entrapment and subsequent controlled drug release from polymeric matrices. The flocculation of highly concentrated colloidal polymeric dispersions (latices), in the presence of the drug in solution which is to be occluded, provides the entrapment mechanism. A solid-state, highly reproducible molecular entrapment combination of methapyrilene hydrochloride and an acrylic copolymer was prepared and evaluated for sustained-action characteristics. A significant increased duration of action and a reduction of the acute toxicity of methapyrilene in the entrapped form were established by *in vivo* effectiveness studies. The broad application of the entrapment process to acid salts of 11 widely used cationic nitrogen-containing drugs was demonstrated.

Keyphrases □ Polymeric flocculation—cationic drug entrapment □ Flocculation, polymeric—drug-concentration effect □ Drug release, controlled—polymeric matrices □ Release rates—drugs in polymeric matrices □ Dialysis—methyapyrilene–polymer, binding determination

Potentiation and alteration of drug action have been of interest to the medical and pharmaceutical professions for many years. In the last 15 years, prolongation of the therapeutic effects of orally administered medicinals has become of prime interest and concern to the industrial pharmacist.

The methods employed for the production of sustained-action dosage forms can be broadly classified into two categories: phsyicochemical and mechanical. These can be further subdivided into various groups such as gastroresistant coatings, chemical complexes, drug embedments, and ion-exchange techniques.

The majority of the methods employed are based on some type of gross embedment or coating of the medicament to yield the desired effects. The procedures are usually time consuming and laborious, involve mechanical techniques which are difficult to control, and in many cases result in products with excessive variability. Much of this variability can probably be traced to the product design and methods of production.

If optimization of drug action through controlled drug delivery rates from solid oral dosage forms is to become a reality, precise physicochemical methods of controlling drug release must replace earlier empirical and mechanical controlled-release methods.

This investigation was motivated by the need for a simple and highly reproducible procedure for drug entrapment and the development of controlled-release dosage forms employing this principle. The purpose of this study was to investigate the applicability of a molecular entrapment phenomenon as a unique approach to sustained-action dosage forms. The major objectives were:

1. The investigation of the properties of various polymeric materials as they would apply to a sustained-release mechanism based on molecular scale, solid-state entrapment of drugs.
2. The utilization and investigation of a process exhibiting broad application to the molecular entrapment of drugs.
3. The *in vitro* and *in vivo* evaluations of the sustained-action characteristics and activity of a polymer–drug entrapment system.

EXPERIMENTAL

Materials and Equipment—A linear, anionically charged, acrylic copolymer[1] composed of acrylic and methacrylic acids and esters and having a molecular weight exceeding 300,000 was supplied in an emulsion (latex) form, containing 40 ± 0.5% solids. Also used were other polymeric materials evaluated as possible entrapment media.[2,3,4]

The drugs studied were NF or USP grade; where appropriate, the purity was checked by melting point and chloride determinations.

Particle-size reduction and classification of all polymer and polymer–drug systems were accomplished using a comminuting machine (Fitzpatrick model M) and a series of standard sieves. All pH determinations were made on a pH meter (Beckman model N) equipped with a glass electrode (Beckman type E-2). A constant-temperature bath equipped with a mechanism for the rotation of sample bottles, similar to that reported by Souder and Ellenbogen (1), was employed for *in vitro* release-rate studies.

Initial Polymer Screening—Based on a polymer literature screening of toxicity and physical properties, the following polymers were chosen for initial study and aqueous solubility characterization: (*a*) acrylic copolymer emulsion,[1] (*b*) carbohydrate polymers,[2] (*c*) polyethylene glycol,[3] and (*d*) a sodium polyacrylate solution.[4]

Samples evaluated for solubility characteristics were comminuted, and the fraction passing a 60-mesh screen was employed. The two acrylic acid derivatives (the acrylic copolymer emulsion and the sodium polyacrylate solution) were first extracted from their aqueous media to provide the solid polymeric materials for solubility study.

Approximate rates of solubility of the polymeric materials in artificial gastrointestinal fluids were determined employing the rotating-bottle method (1, 2). Seven 1.0-g. samples of each polymer were sprinkled onto the surface of separate 60-ml. portions of artificial gastric fluid USP (without pepsin) in 3-oz. amber glass powder jars. The jars were sealed with a water-resistant electrical tape[5] and were rotated at 41 r.p.m. in a constant-temperature bath at 37 ± 2°. At specified time intervals, a sample bottle was removed and its contents vacuum filtered through a fine sintered-glass filter. The sample was then carefully transferred to a watch glass and dried at 50°. The remaining sample bottles were adjusted in pH as outlined in Table I. The data in Table I illustrate the approximate pH levels for the designated sample time intervals employed and the changes in the test fluids that were made to establish these levels.

[1] Acrysol ASE-75, Rohm & Haas Co., Philadelphia, Pa.
[2] Cerons are water-soluble anionic, cationic, or nonionic etherified carbohydrate polymers available in powder form, Hercules Chemical Co., Wilmington, Del.
[3] Polyglycols, E-4000, 6000, 9000, and 20,000; polyethylene glycol, the Dow Chemical Co., Midland, Mich.
[4] Acrysol G.S. is a sodium polyacrylate polymer supplied as a 12–13% w/v solution, Rohm & Haas Co., Philadelphia, Pa.
[5] Scotch Brand Electrical Tape No. 33, Minnesota Mining and Manufacturing Co., St. Paul, MN 55106

Table I—pH Gradient for Approximate Rate of Solubility Test

Time, hr.	Amount of Fluid Removed, ml.[a]	pH of Test Fluid
1	0.0	1.4
2	20.0	2.1
3	15.0	2.6
4	20.0	5.5
5	30.0	6.9
6	50.0	7.4
8	—	7.4

[a] The clear supernatant fluid removed was replaced by an equal quantity of artificial intestinal fluid USP (prewarmed to 37°).

The dried polymeric material was weighed, and the percentage of polymer dissolved at each time interval was calculated. The acrylic copolymer emulsion showed the most promising rate of solution, and this material was studied by further evaluative methods.

Drug Assay Procedures—Methapyrilene hydrochloride[6] was used because it represents a widely employed compound having characteristics suitable for development as a sustained-action dosage form. The drug is quick acting, having a fairly short duration of action, with single doses exhibiting a therapeutic effect for about 3.5 hr. (3, 4).

A pH-induced differential spectrophotometric method was developed which permitted the analysis of methapyrilene hydrochloride without interference from the polymer (5).

A base-line UV spectrophotometric analysis method, outlined by Reilly and Sawyer (6), was successfully adopted for the quantitative determination of phenylephrine hydrochloride in the presence of the polymeric material. The spectra were all analyzed at pH 12.9 to eliminate any shifts of the absorption maxima of this compound (5). This pH value was found to concur with that reported by Riegelman *et al.* (7).

Entrapment Procedure—Various methods of producing the polymer–drug entrapment systems were attempted. The addition of the acrylic copolymer emulsion to concentrated aqueous solutions of methapyrilene hydrochloride resulted in the flocculation and precipitation of the polymer affording the greatest possibility of drug entrapment since the drug molecules themselves were causing the flocculation. Other methods attempted included the addition of the drug solution to the polymeric system and the acidification of an alkaline aqueous solution of the drug and the polymer.

The following formula and procedure were the basic entrapment method used:

Formula I

Methapyrilene hydrochloride	20.0 g.
Distilled water	100.0 ml.
Acrylic copolymer emulsion	125.0 ml.

The acrylic copolymer emulsion was slowly added to a constantly mixing solution of the methapyrilene in distilled water, resulting in an immediate flocculation and precipitation of the added polymeric material. When the addition of the emulsion was complete, the slurry was allowed to mix for another 5 min. The mixture was then vacuum filtered through a coarse sintered-glass filter, applying vacuum from a water aspirator for about 10 min. The collected material was dried for 4 hr. at 50°. The dried material (a granular white solid) was then comminuted in a comminuting machine, employing a 40-mesh screen and the hammer edge of the blades in the forward position. The comminuted material was then screened through a 60-mesh sieve.

Reproducibility of the entrapment procedure was evaluated by preparing replicate batches and determining the percentage of drug entrapped in each batch.

The effect of drug (solution) concentration on the entrapment product was investigated by utilizing various drug concentrations in aqueous solution and holding constant the amount of polymer emulsion employed.

[6] Methapyrilene hydrochloride (Histadyl HCl), Eli Lilly and Co., Indianapolis, Ind.

Table II—pH Gradient for the *In Vitro* Release-Rate Test

Cumulative Time, hr.	pH of Test Fluid
0.5	1.3
1.5	1.3
2.5	2.3
4.5	6.7
6.5	7.3
8	7.3

Dialysis Studies—A dialysis study was conducted to determine whether methapyrilene hydrochloride was chemically bound to the polymeric material (in solution) in such a manner as to reduce the availability and the therapeutic activity of the drug. A dialysis method similar to that described in the literature (8, 9) was used. Dialysis sacs prepared from a semipermeable cellulosic membrane[7] were used for investigation of free methapyrilene hydrochloride, free acrylic copolymer, and acrylic copolymer–methapyrilene hydrochloride entrapment products. The dialysis samples were rotated for preselected time periods of 48, 72, or 107 hr. at 37°. The dialysis fluid employed was artificial intestinal fluid USP (without pancreatin) adjusted to pH 7.4. This medium caused dissolution of the polymer as well as the drug. The fluids inside the sacs, as well as the surrounding media, were assayed for drug content.

***In Vitro* Release-Rate Procedure**—A rotating-bottle method (1, 2) was used for the evaluation of the powdered and compressed sustained-action dosage forms. The comminuted polymer–drug samples were weighed into six individual dosage units, each to contain 100 mg. of methapyrilene hydrochloride. The samples were carefully transferred to 3-oz. amber glass powder jars and filled with 60 ml. of artificial gastric fluid. Table II illustrates the pH levels for the designated sample time intervals employed. These pH values agree well with those found by Borgstrom (10) in numerous *in vivo* tests. The test fluids were treated with artificial intestinal fluid and 1.0 *N* sodium hydroxide solution in such a manner as to yield the noted pH levels for the designated time intervals.

Suitable aliquots of the filtered test medium were taken (at the specified time periods) and differentially analyzed for methapyrilene hydrochloride.

***In Vivo* Evaluation**—Various methods have been proposed to evaluate the activity and the duration of action of antihistaminic compounds (3, 4, 11, 12). A guinea pig histamine aerosol procedure (4, 12, 13) was employed in this study. Duration of action of an orally administered dose of an acrylic copolymer–methapyrilene hydrochloride entrapment product was compared with that of the free drug.

It has been reported (4, 12) that 1–3 mg./kg. of methapyrilene hydrochloride administered to guinea pigs has shown protective action against histamine vapor for about 3.5 hr. In this study, a dosage level of 2.5 mg./kg. of body weight was employed. The powdered forms of the product were washed through a catheter tube directly into the stomach of the animal. The product and control drug were code labeled so that the investigator performing the actual experiments did not know which system was being given to the individual guinea pigs, thereby reducing prejudiced judgments. A total of 20 experimental runs was made, with 10 test animals receiving the free drug and 10 a polymer–drug entrapment product.

Toxicity Reduction—A reduction in the acute toxicity of a drug should occur with its formulation into a sustained-action dosage product. A preliminary investigation established a dose of 200 mg./kg. as the approximate LD_{83} in rats for orally administered methapyrilene hydrochloride. Six rats were orally dosed with 200 mg./kg. of the free methapyrilene hydrochloride, and another six were given 200 mg./kg. of the drug in a polymer–drug entrapment product. The time of death after oral administration was noted, and a 24-hr. survival time was considered the "cutoff" point for the test procedure.

Flocculation Phenomenon—It was felt that the precipitation of the polymer emulsion in the presence of methapyrilene hydrochloride was due to a flocculation phenomenon. Riddle (14) has stated: "The presence of salts in polymer dispersions usually has

[7] NoJax Casing, Size 30, Visking Co., Chicago, Ill.

the same effect as in other colloidal systems, *i.e.*, the particle size is increased and some of the polymer may coagulate."

It was also hypothesized that as the pH of the acrylic copolymer emulsion (an anionically charged copolymer) was increased, the polymeric compound would become more hydrophilic, resulting in increased solvation and increased stability to electrolytes. Conversely, as the pH decreases, the colloidal system becomes more hydrophobic and more prone to flocculation due to the presence of electrolytic agents.

To test this hypothesis, the acrylic copolymer emulsion was adjusted to pH values of 3.3 and 6.0, maintaining a 20% polymer solids content in both systems. Five-milliliter samples of the system being evaluated were placed in 15.24-cm. (6-in.) (20-ml. capacity) test tubes, and 5 ml. of varying concentrations of sodium chloride or methapyrilene hydrochloride solutions was added. The contents were mixed by inverting the test tubes three or four times. The flocculation value was taken as the minimum concentration of an electrolyte that caused complete flocculation within 2 hr. Complete flocculation was observed as a separation of a voluminous solid phase and a clear aqueous layer.

Flocculation Phenomenon in the Presence of Drugs—Flocculation values for acid salts of 11 widely used cationic nitrogen-containing drug compounds were determined in the copolymer emulsion system. The compounds studied varied in salt form, molecular weight, solubility characteristics, and therapeutic use. Included in this group of drugs were primary, secondary, and tertiary amines and a quaternary ammonium compound.

Preparation of Tablet Samples—Tablets were prepared from acrylic copolymer–methapyrilene hydrochloride entrapment products containing 13.3 and 33.4% active ingredient. In all cases, the tablets contained 100 mg. of drug, and they were compressed (on a Carver laboratory press) directly from the finer than 60-mesh material (hydraulic pressure setting of 8000 lb./in.^{2}). Two sets of tablets were prepared from each of the two employed polymer–drug systems, one set containing 10% starch as a disintegrant while the other contained no disintegrating agent. The tablets containing 13.3% active ingredient were prepared with a 1.27-cm. (0.5-in.) s.c. punch and die set, and those containing 33.4% drug were prepared with a 0.95-cm. (0.375-in.) s.c. punch and die set. Tablet hardness was determined using a hardness tester (Monsanto), and their *in vitro* release rates were determined using the rotating-bottle method.

RESULTS AND DISCUSSION

Polymer Solubility—The powdered polyethylene glycols and the carbohydrate polymers were eliminated from the study since all samples dissolved (all commercial types and molecular weights evaluated) within 1 hr. in artificial gastric fluid.

The polymeric material of the acrylic copolymer emulsion was found to exhibit solubility characteristics desirable for use as a sustained-action matrix. The polymer showed limited solubility in the pH region of 1.4–5.5 (7–11% of the polymer dissolved over a period of 5 hr.). The solubility rate greatly increased as the pH was raised from 5.5 to 6.9 and finally to 7.4. The sodium polyacrylate exhibited similar solubility characteristics in the low pH range but dissolved almost immediately when the pH of the test fluid was raised to 5.5.

The results indicate that the sodium polyacrylate might be suitable as an enterosoluble agent and that the acrylic copolymer has solubility properties more appropriate for a sustained-action preparation. The high molecular weight (over 300,000), available toxicity data (15), and linear nature of this acrylic copolymer (16), coupled with its solubility characteristics, justified further investigation as to its applicability to drug entrapment and sustained-release preparation.

Reproducibility of the Entrapment Procedure—The data in Table III show the assayed amounts of drug found in each of six identically prepared entrapment products. Two analyses were performed on each batch, with the averages being used to calculate the standard deviation of the batches prepared.

Based on the statistical analysis of the experimental data, one can expect that approximately 90% (employing 5 degrees of freedom) of the sample values will fall within ± 5.12 of the sample mean (*i.e.*, 132.87 ± 5.12). The coefficient of variability falls within the 5% limits that are established for most pharmaceutical preparations.

Table III—Reproducibility of the Entrapment Process

Batch No.	mg. of Methapyrilene HCl/g. of Collected Solid	Average of Two Assays
1	135.28 134.59	134.94
2	133.05 139.11	136.08
3	133.94 133.87	133.91
4	130.99 129.77	130.38
5	132.95 131.69	132.32
6	127.22 131.98	129.60

Effect of Drug Concentration on Entrapment Results—Figure 1 depicts the results obtained when various concentrations of methapyrilene hydrochloride solutions were employed with a constant amount of acrylic copolymer emulsion. The same formula (except for the drug concentration) and technique were employed as outlined for the drug entrapment procedure. It appears that a linear relationship exists between the initial drug concentration (in the range of 0.13–2.01 molal) and the amount of drug entrapped in the solid product. The equation for the line covering this portion of the graph was estimated employing the method of least squares.

The equation established was:

$$X_m = 14.22\,(M) + 4.19 \qquad \text{(Eq. 1)}$$

where M represents the molality of the methapyrilene hydrochloride solution and X_m is the amount (g.) of methapyrilene hydrochloride found in 100 g. of the resultant mixture. The sample correlation coefficient (r) found for the points used to calculate the equation was 0.995, indicating that the observed points are all very close to the calculated regression line. It is, therefore, possible to predict accurately the amount of methapyrilene hydrochloride to be found in an entrapment product. This relationship also allows for the reproducible production of products that might exhibit different and desirable effects, which are controllable by the drug–polymer ratio of the system.

No definite explanation can be presented for the break in the curve (Fig. 1) as the molality of the methapyrilene hydrochloride solution exceeds 2.01. The aqueous solubility limit of methapyrilene hydrochloride is being approached at the 3.0 molal concentration level. However, the range of 0.13–2.01 molal solutions presents a very broad and useful area for the production of acrylic copolymer–methapyrilene hydrochloride entrapment compositions.

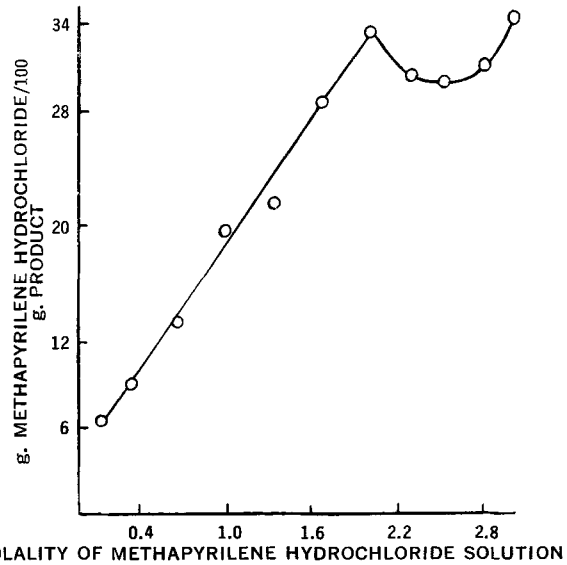

Figure 1—*Effect of drug concentration on the acrylic copolymer–methapyrilene hydrochloride entrapment ratio.*

Table IV—Dialysis of Acrylic Copolymer–Methapyrilene Hydrochloride Entrapment Compositions

Sample No.	Hours Dialyzed	Molarity[a] of System	Molarity Outside the Sac	Molarity Outside / Molarity of System
1[b]	48	7.36	7.24	0.98
2	48	7.68	7.12	0.93
3	48	7.77	7.08	0.91
4[b]	72	7.05	6.97	0.98
5	72	7.39	6.97	0.94
6[b]	107	6.92	6.50	0.94
7	107	7.43	6.50	0.87
8	107	7.42	7.12	0.96
9	107	7.00	6.30	0.90

[a] Molarity of the system was based on the total drug concentration found inside and outside of the dialysis sacs. All molarity concentrations presented are times 10^3. [b] Represents free drug samples, while all others are polymer–drug entrapment compositions.

Drug Availability from Polymer–Drug Solutions—Preliminary dialysis studies showed that the dialysis membrane employed acted as an impermeable barrier towards the polymer molecules (acrylic copolymer) while allowing free passage of the methapyrilene hydrochloride. The pH of the test fluid (range 1.4–7.4) had no apparent effect on the dialysis of the drug across the membrane or upon the impermeability of the membrane towards the polymer molecules. Table IV presents the dialysis data for the drug and polymer–drug entrapment systems.

If complete equilibration occurred, the value obtained by dividing the molarity outside the dialysis sac by the total calculated molarity of the system would be equal to 1; but as can be noted in Table IV, even in the cases of the free drug samples the values attained were not exactly 1. These slight differences of the drug systems from unity may be attributed to errors involved in the dialytic and analytical procedures or to a low order of drug binding to the membrane.

No major differences were noted at the three time intervals employed. It appears that approximately 5–10% of the drug in the polymer–drug product is not passing freely through the membrane and, in some manner, is being bound or retarded by the polymeric system. It was concluded that the major portion (90% or more) of the methapyrilene hydrochloride present in the polymer–drug entrapment products is readily available for passage through a semipermeable membrane. It was felt that this would also be true in a biological system where the membrane of the gastrointestinal tract would act as the semipermeable barrier, excluding the high molecular weight polymer and permitting passage (absorption) of the unbound drug molecules.

***In Vitro* Release-Rate Studies**—Data given in Table V show the release-rate patterns of six individually prepared batches of the acrylic copolymer–methapyrilene hydrochloride entrapment product. In all cases, the samples had been screened through a 60-mesh screen and were weighed to contain 100 mg. of drug (all mixtures contained approximately 13.3% active ingredient) (Table III).

Standard deviations of the release rates for the individual sample periods are shown at the bottom of Table V. Figure 2 represents a graphical presentation of the mean cumulative percent release values plotted against time.

Table V—Release Rates of Acrylic Copolymer–Methapyrilene Hydrochloride Entrapment Compositions

Batch No.	Cumulative Percent Release 0.5 hr.	1.5 hr.	2.5 hr.	4.5 hr.	6.5 hr.	8 hr.
1	54.8	63.2	77.2	87.5	95.9	95.9
2	49.5	71.5	78.3	84.4	101.6	101.6
3	42.3	63.2	70.2	85.2	105.1	—
4	38.1	57.3	66.5	72.9	95.0	95.0
5	45.3	63.2	72.8	76.8	98.7	100.0
6	40.9	57.3	65.4	72.1	98.4	99.3
Mean	45.7	62.6	71.7	79.8	99.1	98.4
SD	6.2	5.2	5.4	6.7	3.7	2.8

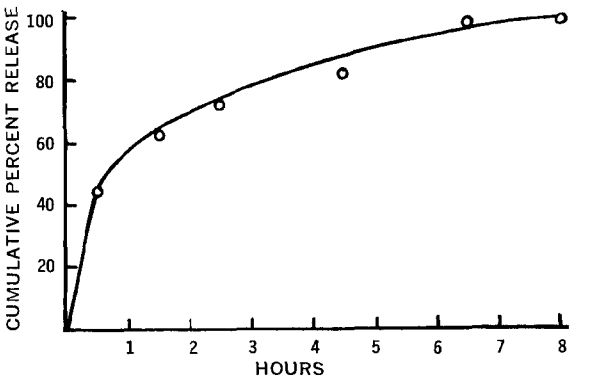

Figure 2—In vitro *release-rate pattern of the acrylic copolymer–methapyrilene hydrochloride entrapment product.*

Several investigators (1, 17–19) have attempted to correlate *in vitro* release-rate patterns with *in vivo* results. Urinary excretion rate data of various sustained-action dosage forms of dextroamphetamine sulfate, phenylpropanolamine hydrochloride, and trimeprazine maleate have been compared with *in vitro* release-rate results obtained with the rotating-bottle method.

The reported *in vitro* release values shown in Table VI were for those products exhibiting suitable sustained-action properties (usually 10–12 hr.) when evaluated *in vivo* by urinary excretion studies. The experimental data (entrapment composition) depicted in Table VI were found to lie within or very close to the values reported for the satisfactory sustained-action products. The entrapment product exhibited *in vitro* sustained-action characteristics in the fine subdivided state without further formulation into granules, pellets, and compression-coated, sugar- or film-coated, or layer tablets.

The results shown in Table VII illustrate the effect of the polymer–drug ratio (percent drug present in the entrapment product) on the release-rate pattern. The polymer–drug ratio may be another means of controlling and changing release-rate patterns.

The 13.3% level of entrapment was used for *in vivo* evaluation because it presented what was believed to be the best *in vitro* characteristics for methapyrilene hydrochloride. The more rapid release patterns may be useful for drugs with a more limited solubility characteristic or when this fine material is formulated into some compacted dosage form.

***In Vitro* Release Rates from Tablet Preparations**—The results in Table VIII show the effect of tableting on the release-rate patterns. The tablets containing 13.3% drug with 10% starch as a disintegrant completely broke apart in about 10 min. The resultant material exhibited almost the identical release-rate pattern as the original 60-mesh screened powder employed for the production of these tablets. This formulation and tableting approach could be used advantageously when the original powdered material exhibits suitable release characteristics.

The tablets (13.3% drug) compressed without any disintegrating agent failed to break apart in the 8-hr. period investigated. In the first 0.5–1.5 hr. of immersion in artificial gastric fluid, the tablets were swollen to about twice their original size. During the initial test period (0–1.5 hr.), 45.6% of the entrapped drug was being released, presumably by a leaching action of the test fluids. This

Table VI—Comparison of Reported Release Values with Experimental Results

Time, hr.	Cumulative Percent Release—Reported Values	Experimental Values
0.5	32–43	45.7
1.5	—	62.6
2	39–69	68.5[a]
2.5	—	71.4
4.5	60–90	79.8
6.5	—	99.1
7	86–98	97.0[a]

[a] These values were graphically determined from Fig. 2.

Table VII—Effect of the Polymer–Drug Ratio on the Release-Rate Pattern

Time, hr.	Percent Drug			
	13.3	19.7	28.5	33.4
	Cumulative Percent Release			
0.5	45.7	60.4	60.4	74.3
1.5	62.6	73.2	71.8	81.3
2.5	71.7	82.8	77.1	83.2
4.5	79.8	87.3	82.3	88.7
6.5	99.1	93.1	92.0	91.7
8	98.4	94.7	94.3	92.6

leaching effect was felt to be the predominant mechanism of release until about the 3rd or 4th hr. when the tablets began to diminish in size due to the slow dissolution of the polymeric material (as the pH of the test fluid increased). The portion of the drug content more tightly entrapped in the polymeric network was then being slowly released as the polymer dissolved.

The tablets containing 33.4% drug prepared with and without the addition of starch had the same general appearance during release-rate evaluation as those containing 13.3% drug without any added disintegrating agent (*i.e.*, initial swelling and then slow dissolution with increasing pH of the test fluids). The total release (in 8 hr.) from these tablets was less than that found for the tablets containing 13.3% drug. This reduction in total release of the two-tablet systems containing 33% drug is undoubtedly due to the increased hardness of these tablets (Table VIII).

The tablets containing 13.3% active ingredient (no starch) and the ones containing 33.4% drug with 10% starch demonstrated very uniform hourly rates of drug release for the test period from 2.5 to 8 hr. (Table IX).

***In Vivo* Studies**—Results shown in Table X were obtained after oral administration of free methapyrilene hydrochloride samples and a polymer–drug entrapment product to guinea pigs, with the animals then being subjected to the histamine aerosol chamber. The 95% confidence interval for the *difference* between the means (pure drug and entrapped drug) was found to be 4.9 ± 1.2 hr., indicating an increased duration of activity of the drug when it is administered in the polymer–drug entrapment system. It was concluded that the drug was slowly being released from the entrapment product in concentrations adequate to maintain a pharmacologic effect over this extended period of time.

Toxicity Reduction—An oral dose of 200 mg./kg. of free methapyrilene hydrochloride was found to kill five out of six rats within 30 min. after administration of the drug. The rats died in an acute convulsive state. One of the six rats survived the preselected 24-hr. cutoff point.

The same dose of methapyrilene hydrochloride administered in a polymer–drug entrapment product had no lethal effect on six rats when observed over a 24-hr. period. The results of this acute toxicity study present further supportive data for the *in vitro* and guinea pig investigations, showing that the polymer–drug entrapment product is preventing the immediate release of all the drug and is protracting its availability over an extended period of time.

Mechanism of Entrapment—Table XI summarizes the results obtained when testing the hypothesis that the acrylic copolymer emulsion system would be more stable to electrolytes as the pH of the system was increased. The results indicate that the original hypothesis was correct and that the presence of methapyrilene hydrochloride was causing flocculation of the polymeric system as exemplified in the drug entrapment procedure.

During the entrapment procedure as the added polymeric system was being flocculated, the drug molecules were entrapped (enclosed) in the formed aggregates, thus retarding their release in subsequent test procedures.

The cause of flocculation can be traced to the added electrolyte (drug molecules), which decreased the thickness of the diffuse ionic layer (of the polymeric material) and thus facilitated the flocculation of the polymeric material. Whether the approaching particles agglomerate or not is determined by the balance of the attractive van der Waals-London forces and the repulsive coulombic forces (20).

Further evidence that the drug was not chemically interacting with the polymer in some salt or direct ionic bond formation was the fact that a chloride analysis showed that approximately 50% of the entrapped drug was still in the chloride salt form. Jirgensons (20) reports that instances in which discharging and resultant flocculation can be explained as an ionic interaction between the ions of the particles and those of the added electrolyte are very rare.

Baron (21) has defined a type of entrapment product, known as inclusion compounds, which does not arise from the linkage of two reactants by means of covalent or coordinate bonds but from the ability of one compound to enclose another spatially. "The enclosed compound (guest) is in a situation whereby it cannot readily

Table IX—Uniformity of Release from Selected Polymer–Drug Tablets

Time Intervals, hr.	Percent Hourly Release	
	13.3% Drug Tablet (No Starch, Hardness 5.0 kg.)	33.4% Drug Tablet (10% Starch, Hardness 9.0 kg.)
2.5–4.5	4.3	4.2
4.5–6.5	4.4	4.2
6.5–8	6.5	4.7

Table X—Measurable Protection Times Afforded to the Guinea Pigs by Free Methapyrilene Hydrochloride and a Polymer–Drug Entrapment Product

Free Methapyrilene HCl		Entrapped Methapyrilene HCl	
Animal No.	Hours Protected	Animal No.	Hours Protected
1	2	10	10
2	6	11	10
3	Sick	12	10
4	2	13	Sick
5	3	8	11
6	1	9	4
7	6	4	9
8	8	5	10
9	6	6	9
5	2	8	10
6	2	9	4
	x_1 = 3.8 hr.		x_2 = 8.7 hr.

Table VIII—Effect of Tableting on the *In Vitro* Release-Rate Pattern

Time, hr.	Cumulative Percent Release					
	13.3% Drug (Fine Powder)	13.3% Drug Tablet (10% Starch)	13.3% Drug Tablet (No Starch)	33.4% Drug (Fine Powder)	33.4% Drug Tablet (10% Starch)	33.4% Drug Tablet (No Starch)
0.5	45.7	45.5	17.2	74.3	16.1	25.3
1.5	62.6	64.9	45.6	81.3	30.0	38.1
2.5	71.7	73.8	59.9	83.2	40.0	51.0
4.5	79.8	81.8	68.1	88.7	48.3	53.8
6.5	99.1	97.0	76.9	91.7	56.7	63.8
8	98.4	100.0	86.7	92.6	63.7	64.4
		Tablet Hardness, 5.0 kg. Tablet Weight, 946–758 mg.			Tablet Hardness, 9.0 kg. Tablet Weight, 299–306 mg.	

Table XI—Flocculation Values of Sodium Chloride and Methapyrilene Hydrochloride for an Acrylic Copolymer Emulsion System

	Flocculation Value[a] pH 3.3	pH 6.0
Sodium chloride	250	1000–1250
Methapyrilene hydrochloride	10	35

[a] Flocculation value is the concentration of the drug in mmoles/l. in the final system required to cause complete flocculation within 2 hr.

leave its position, although it is not actually bonded to the including compound" (21).

The polymer–drug entrapment products formed in this study do not directly fall into this class but may be considered as a type of inclusion system where the host molecules are being held together in a flocculated (aggregated) state entrapping the guest (drug) molecules.

Application of the Process to Entrapment of Other Drugs—Table XII depicts the results obtained employing the flocculation procedure for 11 other cationic drugs. The drugs studied readily caused flocculation of the polymeric material, and the majority of these had flocculation values of about 10–20. The method of drug entrapment described in this study appears applicable to many cationic drugs, without changing the procedure. Possible modifications that could be made in the entrapment process are: (*a*) the use of anionic medicinal agents for the flocculation of cationic polymeric systems; (*b*) the application of nonaqueous solvent systems to cause flocculation; and (*c*) the use of physiologically inert electrolytes to aid in the flocculation and entrapment technique.

Figure 3 illustrates the effect of the phenylephrine concentration employed in the entrapment procedure on the amount of drug found entrapped in the collected solid mixture. The percent of drug concentration of the entrapment product was found to increase sharply as the molality of the solution employed increased from 0.98 to 1.72. Further increases in molality produced only comparatively slight changes in the polymer–drug ratio until the sudden upswing occurring at the molalities of 3.50 and 3.68, similar to the upswing noted with methapyrilene hydrochloride (Fig. 1). The study of acrylic copolymer–phenylephrine hydrochloride entrapment products further exemplifies the applicability of the developed entrapment procedure to other drugs.

SUMMARY AND CONCLUSIONS

The phenomenon of the flocculation of polymeric systems has been evaluated for the molecular entrapment of drugs as a physicochemical approach to the development of oral controlled- or sustained-action dosage forms.

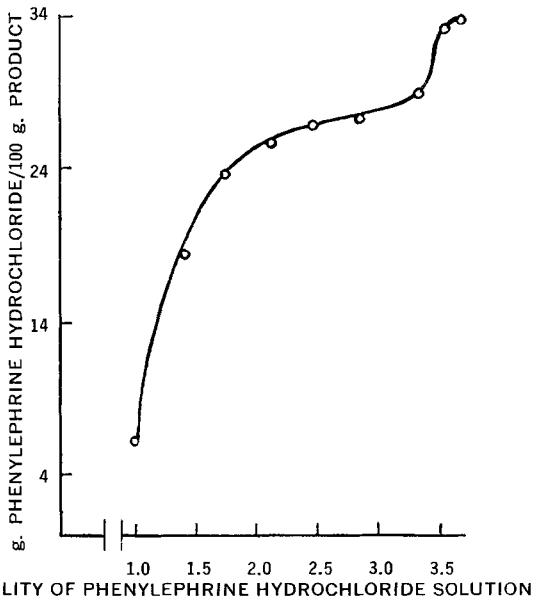

Figure 3—*Effect of drug concentration on the acrylic copolymer–phenylephrine hydrochloride entrapment ratio.*

A solid reproducible molecular entrapment composition of methapyrilene hydrochloride and an acrylic copolymer was prepared and evaluated for sustained-action properties.

In vitro results obtained using the rotating-bottle method indicated satisfactory sustained-release properties of the drug from the entrapment product. The results of *in vivo* studies in guinea pigs were found to correlate with the *in vitro* data. An increase in the continuous duration of action of 4.9 ± 1.2 hr. was shown for the polymer–drug product when compared with a mean duration for the free drug.

A reduction of the acute toxicity of methapyrilene hydrochloride in the entrapped form was established by an *in vivo* investigation in rats.

The polymer–drug entrapment product was found to exhibit characteristic protracted-release patterns in the tableted as well as the fine-powder state.

The broad application of the entrapment process to the acid salts of numerous cationic nitrogen-containing medicinal agents was demonstrated.

Table XII—Flocculation of an Acrylic Copolymer Emulsion System by Acid Salts of Various Cationic Nitrogen-Containing Medicinals

Compound	Molecular Weight	Type of Amine	Category	Flocculation[a] Value
d-Amphetamine sulfate	368.5	Primary	Central stimulant	10
Chlorpromazine hydrochloride	355.3	Tertiary	Tranquilizer	10
Atropine sulfate	694.9	Tertiary	Parasympatholytic	10
Homatropine methylbromide	370.3	Quaternary ammonium	Parasympatholytic	20
Ephedrine hydrochloride	201.7	Secondary	Sympathomimetic	20–25
Phenylephrine hydrochloride	203.7	Secondary	Sympathomimetic	40–50
Morphine sulfate	758.9	Tertiary	Narcotic analgesic	10–15
Dihydrocodeinone bitartrate	494.5	Tertiary	Antitussive	20
Methapyrilene hydrochloride	297.9	Tertiary	Antihistaminic	10
Pyrilamine maleate	401.5	Tertiary	Antihistaminic	10
Chlorpheniramine maleate	390.9	Tertiary	Antihistaminic	10

[a] The flocculation value is the concentration of the drug in mmoles/l. in the final system required to cause complete flocculation within 2 hr.

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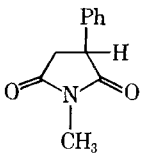
Synthesis and Anticonvulsant Properties of Some Derivatives of *N*-Methyl-2-phenylsuccinimide II

H. C. CLEMSON*, E. O. MAGARIAN†, and J. F. REINHARD*

Abstract □ Several substituted *N*-methyl-2-phenylsuccinimides have been prepared and evaluated for protective activity against convulsions induced by electroshock and pentylenetetrazole.

Keyphrases □ *N*-Methyl-2-phenylsuccinimide derivatives—synthesis □ Anticonvulsant activity—*N*-methyl-2-phenylsuccinimide derivatives □ IR spectrophotometry—structure □ NMR spectroscopy—structure

Phensuximide,[1] *N*-methyl-2-phenylsuccinimide (I), is a well-known anticonvulsant agent which has been employed in the treatment of petit mal epilepsy. The first paper of this series described the synthesis and biological evaluation of several *tert*-aminoalkyl derivatives of Structure I as potential anticonvulsants (1). As part of a continuing study, several additional derivatives of I have been prepared and screened for anticonvulsant properties.

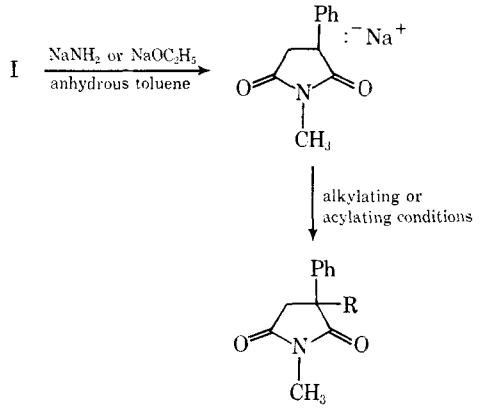


I

[1] Marketed as Milontin by Parke, Davis and Co., Detroit, MI 48232

DISCUSSION

Until recently, the methods used in the preparation of succinimide anticonvulsants have involved the cyclization of appropriate succinonitrile and succinic acid derivatives (2–6). However, the feasibility of direct substitution on the succinimide ring has been demonstrated as a useful synthetic tool (1, 7, 8).



IIa; R = $-CH_2Ph$
IIb; R = $-COCH_3$
IIc; R = $-COPh$

Scheme I