Molecular Scale Drug Entrapment as a Precise Method of Controlled Drug Release II: Facilitated Drug Entrapment to Polymeric Colloidal Dispersions

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Abstract □ Further studies have been carried out to investigate drug–polymer flocculation as a means of molecular scale drug entrapment. It has been shown that a suitable organic acid greatly increases the degree of interaction between the drug and the polymer and provides a mechanism controlling both interaction and subsequent drug-release properties. Results of tests indicate that the products prepared by the facilitated entrapment method possess excellent sustained-action characteristics. In addition, the drug entrapped as the carboxylate salt or in conjunction with the appropriate dicarboxylic acid, while demonstrating substantially complete drug-dissolution release in intestinal fluid, could be maintained in the entrapped form in aqueous suspensions during storage periods in excess of 1 month. X-ray diffraction analysis confirmed the molecular scale level of entrapment of the drug in the polymer flocculated systems.

Keyphrases □ Drug entrapment, molecular scale—controlled-release method □ Polymer–drug interaction—drug salt form effect □ Particle-size effect—drug release from polymer–drug flocculates □ X-ray diffraction—polymer–drug flocculates

Although control of the intensity and duration of drug action has been of interest to the medical and pharmaceutical profession for many years, it is only recently that controlled-action pharmaceuticals have been exploited commercially to any extent.

The advantages resulting from prolongation of drug action have been summarized by Wilson (1). Perhaps the most important is the maintenance of therapeutic effect for extended periods of time, particularly when continuous action at a therapeutic level is essential for efficient therapy. Another factor of importance is the convenience offered to the patient by this type of preparation. It has also been reported that the number of occasions when patients forget their medicine is significantly reduced when sustained-action preparations are used (2).

Optimization of drug action, including improved drug safety, may often be approached by controlling the rate of drug delivery to the absorption pool from the dosage form. A very rapid rate of drug delivery from the dosage form undoubtedly often does not represent the optimum delivery system.

It is somewhat surprising, in view of the many advantages offered by sustained-action or controlled-release dosage forms, that greater use has not been made of this approach in designing drug delivery systems. Although some drugs are inadequately absorbed along the gastrointestinal tract or have an insufficient margin of safety between therapeutic and toxic doses for sustained-action formulation to be feasible, other reasons are apparent for the still limited application of this frequently advantageous approach to the pharmacodynamic improvement of drug action. These reasons include, but are not limited to, the fact that most approaches to sustained-release formulation have involved empirical coating methods applied to nonuniform particulate drug-containing systems, which are coated at several thicknesses or with several compositions to provide a range of release characteristics. The manufacturing sequence of such products is subject to considerable variation, and control is difficult. Such processes are often costly and the resultant products are expensive; development and manufacture of such dosage forms are also complex, at least somewhat imprecise, and time consuming. Molecular scale quantitative approaches to the physicochemical binding of drugs by polymers, by ion exchange, or by complexation mechanisms offer a number of advantages over conventional coating techniques. Optimization of drug action to provide precisely controlled drug release rates will only become possible when accurate methods of drug entrapment and release, based on physicochemical phenomena, are developed.

The present paper reports studies performed during the development of a new method for the formulation of sustained- or controlled-action pharmaceuticals. The technique described involves application of stoichiometric entrapment of drugs by polymer flocculation, the products being suitable for administration in either solid or liquid dosage forms.

Earlier work by Goodman *et al.* (3) indicated that the molecular scale interaction between drugs and polymers could facilitate the quantitative development of reproducible sustained-action pharmaceuticals. The method developed by the present authors is similar to that previously described (3). However, it has been found that the properties of drug–polymer flocculates, in which the drug contains an amino functional group, can be markedly improved if a suitable organic acid is included in the formulation. The presence of such a carboxylic acid anion has been shown to increase the amount of drug which may be bound by the polymer and to provide improved control of drug release from the polymer flocculate. The inclusion of the carboxylic acid in the drug–polymer flocculate has also made possible the development of liquid and other dosage forms.

The described method of molecular scale drug entrapment by these studies is extremely simple (3) and offers many advantages over the conventional lengthy and intricate methods used in the preparation of sustained-action pharmaceuticals. The present paper describes a method of facilitated drug entrapment in which a solution of the drug and an appropriate carboxylic acid is added slowly to a suitable polymer emulsion. The resultant flocculate is washed and dried.

Table I—Effect of Carboxylic Acid Anion upon the Entrapment of Chlorpheniramine by the Acrylic Copolymer Emulsion

Chlorpheniramine Salt	Initial Concn. of Drug Soln., % w/v	% Drug Bound	% Drug in Dry Flocculant
Hydrochloride	2	54	3.3
Maleate[a]	2	91	3.7
Oxalate	2	80	3.7
Malonate	2	90	3.9
Succinate	2	98	4.5
Succinate	5	93	10.0
Succinate	10	86	17.5
Adipate	5	96	10.4

[a] Obtained from Smith Kline & French Laboratories, Philadelphia, Pa.; all other salts synthesized.

Products so obtained may be readily milled to a fine powder, tableted, encapsulated, or suspended to provide controlled-release systems.

EXPERIMENTAL

Effect of Drug Salt Form upon Binding—To determine the effect of the drug anion moiety on the polymer–drug interaction, solutions of various salts of chlorpheniramine were employed to produce polymer flocculation. In this study, 100 ml. of each drug solution was used to coagulate 100 ml. of an acrylic copolymer emulsion.[1] Each flocculated system was mixed for 30 min. and then filtered under reduced pressure, the filtrate being collected and assayed for drug content. The drug salts used were either obtained commercially or synthesized. Those that were synthesized were recrystallized one to three times from an isopropanol–ether solvent mixture and vacuum dried at 40°; the purity was checked by melting point and IR analyses. Results of the flocculation studies are shown in Table I.

Effect of Particle Size on *In Vitro* Drug Release—The dissolution release of chlorpheniramine from a chlorpheniramine maleate–acrylic copolymer entrapment product in both simulated gastric juice (without enzyme) and simulated intestinal juice (without enzyme) was determined as a function of particle size (Table II). One-half-gram samples of each polymer–drug particle-size fraction were placed in 50 ml. of gastric or intestinal fluid, rotated at 37° according to the method of Goodman *et al.* (3), and assayed at the times specified.

Release of Drug from Aqueous Solutions of Polymer–Drug Flocculates—In the initial study, 5-g. quantities of chlorpheniramine maleate–acrylic copolymer product containing 3.7% drug, as a 60-mesh undersize powder, were suspended in 100 ml. of selected vehicles in 4-oz. reagent bottles, which were shaken daily throughout the test period. The amount of drug released at room temperature into the various vehicles was determined over a period of 30 days (Table III).

A more detailed study was also performed to investigate the effect of drug concentration upon release rate. In this experiment, 5-g. quantities of polymer–drug material were placed in 60-ml. volumes of vehicle, and the resultant suspensions were rotated continuously at 37° for the time specified (Tables IV and V).

X-Ray Diffraction Studies of Drug–Polymer Flocculates—X-ray diffraction patterns of a commercially available sustained-action pharmaceutical,[2] which makes use of polymeric materials as matrices, were studied as well as drug-entrapped products made by the method described herein. All patterns were obtained with copper K-α radiation generated to 40,000 v., using a General Electric XRD-5 source and the General Electric powder diffraction camera, 143.2-mm. diameter. One-half-millimeter glass capillary tubes were used to rotate the sample in the beam. Results are shown in Fig. 1.

Table II—Release of Chlorpheniramine Maleate from a Polymer–Drug Entrapment Product[a] in Gastric and Intestinal Media as a Function of Particle Size and Time

Particle Size (Sieve Fraction)	% Drug Released in 24 hr. Gastric Juice	% Drug Released in 24 hr. Intestinal Juice	96 hr. Gastric Juice
30 mesh oversize	62	92	67
30/40 mesh	65	92	70
40/60 mesh	67	91	72
60/120 mesh	69	93	76
120/170 mesh	71	91	75
170/230 mesh	75	93	80
230 undersize	77	91	80

[a] In all cases the concentration of the drug in the polymer–drug flocculate was 4%.

Table III—Release of Chlorpheniramine Maleate from a Polymer–Drug Entrapment Product in Various Vehicles

	pH of Suspension	—% Drug Released, days— 2	7–8	14–15	30
Phosphate buffer pH 4.5	4.3	2.4	2.5	2.3	3.6
Phosphate buffer pH 6.0	5.6	0	3.8	4.2	3.6
Phosphate buffer pH 8.0	6.1	32.3	42.4	45.3	60.0
Orange syrup USP	2.4	1.6	2.0	2.4	2.7
1% Citric acid solution	2.3	11.7	23.1	27.0	35.4
Distilled water	3.3	6.4	7.1	7.5	9.6
Distilled water (stirred)[a]	3.3	4.6	6.1	6.8	7.0
Standard solution (200 mg. drug, no polymer)	4.5	100	100	100	100

[a] Stirred by a magnetic stirrer at about 30 r.p.m.

DISCUSSION

Studies with selected drug salts indicated that the addition of a stoichiometric quantity of an appropriate organic acid to the drug hydrochloride salt solutions, or the use of a drug carboxylate as the flocculant solution, greatly increased the amount of drug that could be bound by the polymer. The data shown in Table I clearly indicate the utility of the organic acid anion, since 80–90% of the drug was bound in the presence of such an anion-entrapment facilitator whereas only half the amount of drug could be bound when no facilitator was present, *i.e.*, the hydrochloride drug salt. Entrapment was facilitated equally well regardless of whether the drug carboxylate salt was prepared and entrapped or a stoichiometric quantity of the carboxylic acid was added to the drug hydrochloride salt solution. It is also significant that a 2% solution of the hydrochloride salt could only be entrapped to the extent of 54% efficiency while a 5% solution of the adipate was 96% entrapped and a 10% solution of the succinate was entrapped with 86% efficiency.

The results in Table II show several desirable features of the entrapment system from the point of view of a potential controlled-release product. Even though there is apparently a strong interaction between the drug and polymer, over 90% of the drug is available in simulated intestinal juice. Further, even though particle size has some effect upon the release in gastric juice, this dependency is not great. The release in intestinal juice appears to be substantially independent of particle size. Also, the facts that about one-third of the available drug is not released in gastric juice, even after as long as 24 hr., and as little as 5 or 10% is released in selected buffers, even on stirring for 30 days (Table III), indicate the potential of these products for controlled-release or sustained-action liquid dosage forms.

Table III describes the dissolution release of the drug from a finer than 60-mesh 3.7% chlorpheniramine maleate–polymer entrapment product. The drug, in the products made by this technique, is evenly distributed throughout the polymer matrix; the drug remains associated to the polymer without alteration

[1] Acrysol ASE-75; a 100% linear, anionically charged acrylic acid copolymer with a molecular weight in excess of 300,000; supplied in emulsion form, containing 40% solids, Rohm & Haas Co., Philadelphia, Pa.

[2] Desoxyn Gradumet, 15-mg. tablet, methamphetamine hydrochloride, Abbott Labs., North Chicago, Ill.

Table IV—Release of Chlorpheniramine from Drug–Polymer Flocculates as a Function of Carboxylic Acid Anion Type and Drug Concentration

Facilitator	% Drug Concn.	Suspension Medium[a]	% Drug Release, hr. 24	48	120	Final Suspension, pH
Succinate	4.3	1	57	62	69	1.4
Succinate	4.3	2	3	3	3	4.1
Succinate	4.3	3	99	97	—	7.1
Succinate	10.3	1	86	84	84	1.4
Succinate	10.3	2	12	12	12	4.5
Succinate	10.3	3	91	97	—	7.4
Succinate	18.9	1	81	83	85	1.4
Succinate	18.9	2	18	19	21	4.9
Succinate	18.0	3	89	94	—	8.0
Oxalate	4.0	1	50	56	56	1.4
Oxalate	4.0	2	6	6	6	3.8
Oxalate	4.0	3	86	92	—	7.0
Malonate	4.1	1	62	67	68	1.4
Malonate	4.1	2	5	5	5	3.6
Malonate	4.1	3	88	98	—	7.0
Maleate	3.9	1	55	58	67	1.4
Maleate	3.9	2	5	6	6	3.9
Maleate	3.9	3	91	100	—	7.0
Adipate	9.9	1	82	81	85	1.4
Adipate	9.9	2	10	10	10	4.4
Adipate	9.9	3	92	95	—	7.7

[a] Suspension medium: 1, simulated gastric fluid USP without enzyme; 2, phosphate USP buffer, pH 4.5; and 3, simulated intestinal fluid USP without enzyme.

after high-speed milling in a comminutor and is contained in the various particle-size fractions in the same concentration. While substantial drug release was indicated in gastric fluid and nearly complete release in intestinal fluid (Table II), minimal drug dissolution occurs at pH values of 4.5–6, and drug dissolution in vehicles which correspond to this pH was minimal (less than 3% in orange syrup in 30 days).

Results shown in Table IV further indicate that the products obtained by this flocculation technique have potential for use as controlled release-suspensions, since the amount of drug released from suspensions in vehicles at pH values between about 4 and 6 is very low.

Continuous stirring of a distilled water suspension over a 30-day period produced no substantial alteration in the release pattern as compared with a similar suspension that was only shaken daily (Table III). Likewise, samples stored at an elevated temperature demonstrated no significant difference in release rate. The results recorded in Table V show that particle size has a negligible effect upon the amount of drug release from suspensions buffered at pH 4.5; this property of the product is, of course, most advantageous for sustained-action liquid suspensions.

Figure 1 presents photographs of the X-ray diffraction patterns of a molecular scale entrapment product, a physical mixture of the drug plus polymer employed in the entrapment system, and a commercially available polymer–drug matrix system.[2]

Photo A of Fig. 1 is a photograph of the X-ray diffraction pattern of a commercial methamphetamine hydrochloride–polymer matrix system (15 mg./tablet, tablet weight 115 mg.). The diffraction lines show crystalline methamphetamine hydrochloride to be present. All the lines listed in Pattern Number 5-0246 for methamphetamine hydrochloride, American Society for Testing Materials, are found in Fig. 1A. Thus, in this product the drug is not dispersed within the

Table V—Release of Chlorpheniramine from a Chlorpheniramine Maleate–Polymer Entrapment Product (3.7% Drug) in pH 4.5 Buffer as a Function of Particle Size

Particles Size (Sieve Fraction)	% Drug Release, hr. 24	48	120
30/40 mesh	4.7	4.8	5.1
80/120 mesh	5.4	5.4	5.5
170/230 mesh	5.3	5.4	5.5

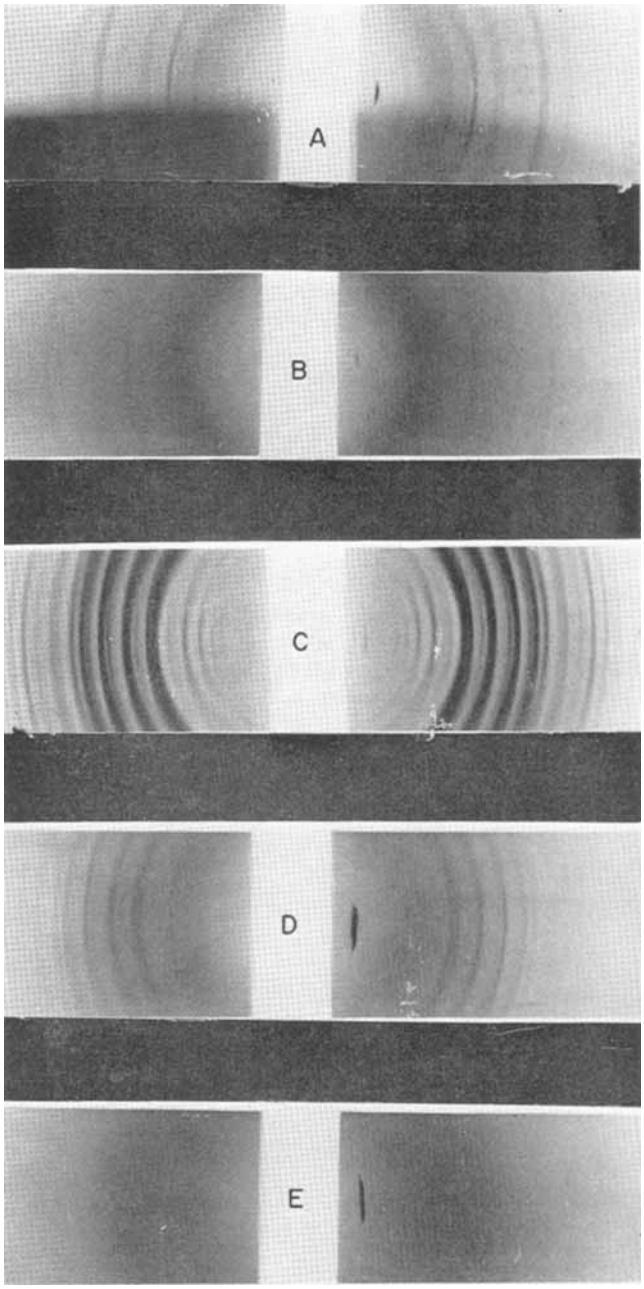

Figure 1—*X-ray diffraction patterns: A, commercial methamphetamine–polymer matrix product; B, commercial product following drug extraction; C, chlorpheniramine acid succinate; D, chlorpheniramine acid succinate, 25% as a flocculated polymer, 75% as a physical mixture; and E, chlorpheniramine acid succinate–polymer entrapment product containing 25% drug.*

product at the molecular level but merely consists of a physical compressed mixture of crystalline drug and polymer.

After leaching the commercial product with 0.1 *N* hydrochloric acid for 2 days, the X-ray diffraction pattern (Fig. 1B) shows that nearly all of the crystalline drug has been removed. The faint lines remaining may be due to talc, coloring agent, or other components of the tablet. The polymer itself shows no crystalline X-ray pattern. It is, however, responsible for the heavy, undefined, scattered radiation apparent in Fig. 1B.

Figure 1C shows the X-ray diffraction pattern of crystalline chlorpheniramine acid succinate. Figure 1D reproduces the diffraction pattern of a mechanical mixture of chlorpheniramine acid succinate (25%) and the acrylic copolymer as mechanically separated from the polymer emulsion, clearly showing the presence of crystalline drug. However, Photo E of Fig. 1, a picture of the X-ray diffraction pattern of a chlorpheniramine acid succinate–

acrylic copolymer entrapment product containing 25% drug, is quite different. The diffraction pattern indicates that crystalline drug is absent. The absence of crystalline drug in this sample demonstrates that the drug in the entrapment product is uniformly dispersed at a molecular level.

The mechanism by which the carboxylic acid anion facilitator increases the amount of drug bound by the polymer is of considerable theoretical interest and is the subject of a further study. Several modes of action appear possible. The formation of complex ions between the polymer carboxyl group, drug, and acid anions has been suggested, the resultant electrostatic forces binding the drug to the polymer. Presumably, inclusion-type complex formation may also be involved to some extent.

SUMMARY

A new method for the preparation of sustained-action pharmaceuticals by stoichiometric entrapment of drugs in polymer flocculates is described.

The advantages of the use of a suitable entrapment facilitator, an organic acid, to enhance the binding of drugs by polymers is demonstrated.

In vitro tests indicate that the products obtained by this technique could be used in either solid or liquid dosage forms.

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Molecular Scale Drug Entrapment as a Precise Method of Controlled Drug Release III: *In Vitro* and *In Vivo* Studies of Drug Release

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Abstract □ Controlled-release drug-entrapped systems of phenylephrine and phenylpropanolamine have been prepared by the facilitated molecular scale drug-entrapment method previously described. Variables influencing the entrapment process, such as flocculation pH and rate of agitation, have been investigated. These variables are readily controllable. The influence of various polymers and carboxylic acid anions on the entrapment and release of the drugs was examined. Tests applied to the products so obtained indicate that they are well suited for pharmaceutical use. An *in vivo* study verified the sustained-release properties of a molecular scale entrapped phenylpropanolamine.

Keyphrases □ Drug entrapment, molecular scale—release-rate control □ Flocculation pH effect—drug binding, release □ Stirring rate effect—drug binding □ Release rates, *in vivo*, *in vitro*—polymer-bound drug

Parts I and II of this series described the development of a method of molecular scale drug entrapment for the physicochemical preparation of controlled-release pharmaceuticals; the advantages offered by this new technique were also discussed (1, 2). Part I described the flocculation of polymeric colloidal dispersions as a mechanism of precise drug entrapment. It was demonstrated that the resultant drug–polymer flocculates, when administered as a fine powder, exhibited very satisfactory sustained-action characteristics. However, less success was obtained when weakly basic drugs such as phenylephrine were used as flocculants.

Table I—Efficiency of Various Carboxylic Acid Anions in Binding Phenylephrine to Acrylic Copolymer Emulsion 1

Facilitator	pKa	Drug Bound by Polymer, %[a]
(Hydrochloride)		25
Adipate, H	4.43	28
Citrate, H	4.74	32
Malonate, H	2.85	32
Citrate, HH	3.06	33
Glutarate, H	4.34	35
Glutarate	5.12	36
Tartrate, H	3.01	41
Tartrate	4.54	44
Fumarate	4.47	46
Succinate, H	4.19	49
Succinate	5.57	49
Maleate, H	2.20	49
Ascorbate, H	4.17	50
Adipate	5.27	53
Citrate	5.40	58
Ascorbate	11.57	60
Maleate	6.26	60

[a] Percentage of drug entrapped from solution.

In Part II the study of drug entrapment by polymer flocculation was considerably extended. It was shown that the presence of a carboxylic acid anion greatly facilitated drug entrapment, increasing the binding of the drugs by the polymer, which substantially increased the efficiency of the drug-entrapment process and provided added control over drug release.