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DEVELOPMENT OF AN EMULSION-SOLVENT EVAPORATION TECHNIQUE FOR MICROENCAPSULATION OF DRUG-RESIN COMPLEXES

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ABSTRACT

Chlorpheniramine maleate was complexed with a carboxylic acid cation-exchange resin and the complexes were microencapsulated with polymethyl methacrylate using an emulsion-solvent evaporation technique. Microcapsules of larger mean diameters resulted from polymer solutions of increased viscosities. Addition of 3% finely divided solids to the encapsulation vehicle resulted in smaller microcapsules, whereas a 6% concentration had the opposite effect, an increased capsule mean diameter. Emulsion stabilizers, such as magnesium stearate, up to a 1%

concentration reduced microcapsule size by as much as 50%. The process efficiency ranged from 73% to 99%, depending on the formulation and manufacturing conditions used. The rate of drug release from the microcapsules was directly related to the amount of polymer deposited and inversely proportional to the capsule size.

INTRODUCTION

Chlorpheniramine is commonly used as an antihistaminic for allergic rhinitis, especially in conjuction with pseudoephedrine. The dosage interval for chlorpheniramine ranges from 4 to 6 hours (1), even though the elimination half-life has been reported as high as 20 hours (2). A dosage form which releases chlorpheniramine slowly over a 12 hour period would have substantial advantages over conventional, immediate release preparations.

Microencapsulation of pharmaceuticals with diffusion retarding polymers with the aim of sustaining the release of the drug in order to prolong the plasma drug concentration with in the therapeutic range is routinely done. The emulsion-solvent evaporation technique for microencapsulation has attracted a growing interest, possibly due to the simplicity of the procedure (3-5). A recent report descibes the effects of solvent:polymer ratio, polymer:drug ratio, and evaporation temperature on the rate of drug release from microspheres (6).

Most reports on microencapsulation using this technique are primarily concerned with the rate of drug release from the microcapsules, and do not offer much information on particle size control through additives. To incorporate microencapsulated drug particles in a final dosage form which can be marketed, microcapsule size distribution control is of critical importance.

This report describes the encapsulation of chlorpheniramine-resin complex particles with polymethyl methacrylate (PMMA) employing an emulsion-solvent evaporation technique, and investigates the use of finely divided solids and other protective additives to control the microcapsule size distribution. The influence on the rate of drug release is also determined.

EXPERIMENTAL

Materials

Carboxylic acid cation-exchange resin (Amberlite CG-50^{R}) and chlorpheniramine (Aldrich), polymethyl methacrylate (Scientific Polymer), acetone, hexane, and liquid paraffin (J.T. Baker), magnesium stearate and carbon black (Fisher), and Veegum^{R} and bentonite (Ruger) were used as supplied.

Methods

Resin particles were suspended in deionized water for one hour, after which chlorpheniramine maleate was added and the slurry was stirred for 24 hours to allow adsorption of the drug

onto the resin. The complexes were washed with deionized water and dried at 50°C.

The dried complexes were suspended in an acetone solution of PMMA and the dispersion was emulsified in liquid paraffin containing the various additives. After emulsification, agitation was continued for 12 hours to allow complete evaporation of the polymer solvent. The microcapsules were collected, washed with hexane and dried.

Drug release studies were performed by use of a modified USP paddle method with simulated intestinal fluid (pH 7.5) without enzymes, but containing 0.02% polyoxyethylene sorbitan monooleate. A spectrophotometric assay at 260 nm was employed.

RESULTS AND DISCUSSION

Drug-Resin Complex Formation

During drug-resin complex formation, equilibrium distribution of chlorpheniramine between the "free" form and the resin bound form was reached within three hours (see Figure 1).

The amount of chlorpheniramine (in moles) adsorbed per gram of resin increased as a function of increased initial drug concentration or increased equilibrium drug concentration, as shown in Figure 2.

As drug concentration increased it produced an increased counter-ion concentration through exchange, which, in conjunction

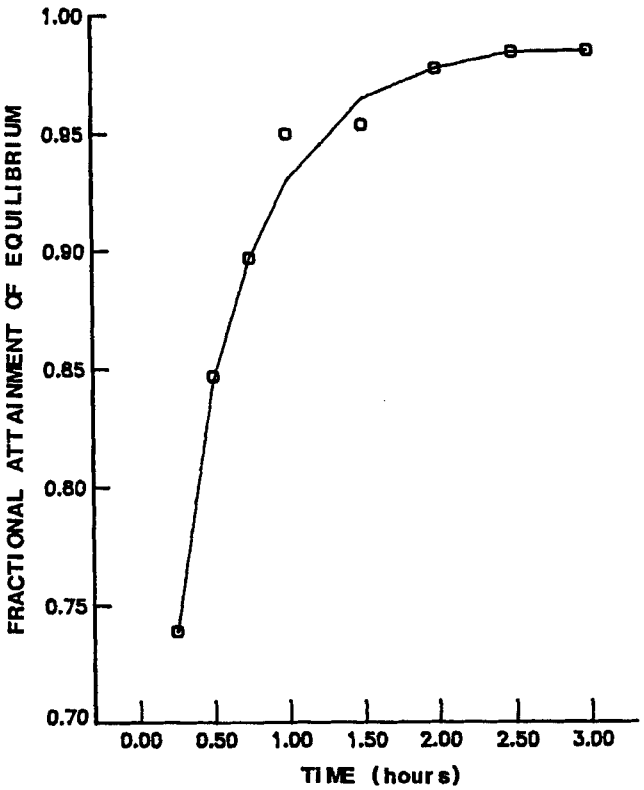

FIGURE 1
Adsorption of Chlorpheniramine onto Carboxylic Acid Cation-Exchange Resin.

with the shrinking number of binding sites, increased the competition between the ionized drug and the hydrogen ion for the remaining binding sites, leading to a reduced adsorption efficiency at higher drug concentrations.

Effect of Polymer Solution Concentration on Microcapsule Size

Microcapsules containing chlorpheniramine complexes prepared with a 10% PMMA solution had a 156 μm geometric mean diameter,

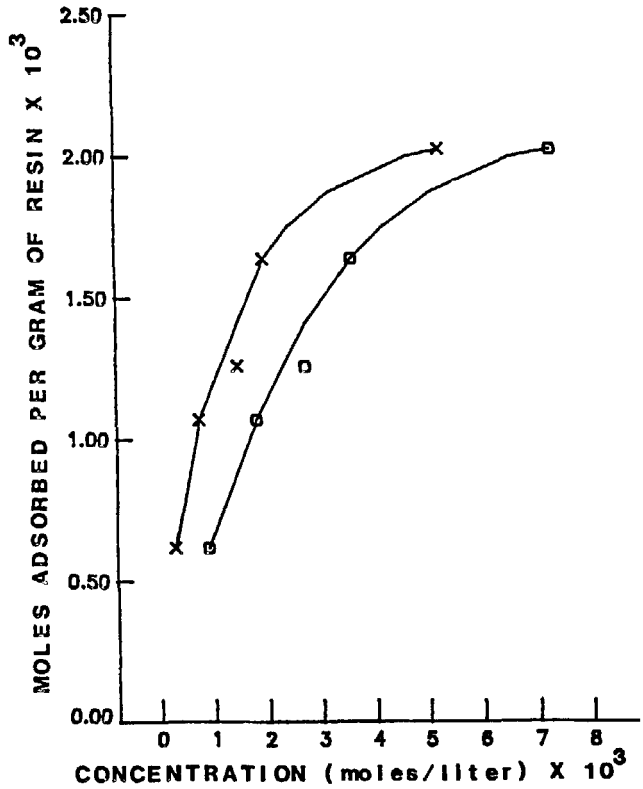

FIGURE 2
Effect of Initial or Equilibrium Concentration of Drug Solution on the Amount of Drug Adsorbed per Gram of Cation-Exchange Resin. KEY: (O) initial concentration and (X) equilibrium concentration.

whereas those prepared under the same conditions with a 20% PMMA solution had a geometric mean diameter of 398 μm, a size increase of more than twofold (see Table 1).

Polymer solutions with higher percentages of PMMA were more viscous. Since the rate of agitation was maintained constant, emulsification of complex dispersions of higher viscosities

TABLE 1

The Effect of Polymer Concentration on the Particle Size Distribution of PMMA Microcapsules Containing Chlorpheniramine-Resin Complexes.

SIEVE SIZE MICRONS	POLYMER CONCENTRATION 10%	15%	20%
	% RETAINED ON SIEVE		
>600	0.00	0.00	10.10
600/425	0.00	2.10	24.30
425/300	1.90	13.70	21.50
300/212	25.60	36.00	15.10
212/150	51.40	34.40	3.50
150/106	20.90	13.10	1.90
GMD	156.20	185.70	398.11
GSD	1.30	1.4	1.75

GMD: Geometric Mean Diameter
GSD: Geometric Standard Deviation

resulted in larger droplets, which hardened in to microcapsules of larger sizes.

Effect of Emulsion Stabilizers or Protective Agents on Microcapsule Size

With the emulsion-solvent evaporation method of preparation, the microglobules that are formed are liable to coalesce and aggregate which may result in clusters of microcapsules. To

reduce this aggregation, various stabilizers were compared including finely divided solids, silicone oils, glyceryl monostearate, strearyl alcohol, and magnesium stearate.

Addition of 3% bentonite, Veegum^R, or carbon black to the external phase reduced the microcapsule mean diameter from 398 um to 298 μm, 244 μm, and 201 μm, respectively. Increasing the concentration of these powders in the continuous phase to 6%, resulted in a size differential ranging from a negligible reduction for bentonite (370 μm) to a significant increase for carbon black (562 μm) (see Table 2).

The finely divided solids added to the continuous phase were wetted to some degree by both acetone and liquid paraffin, and some partitioned to the interface. The particulate film surrounding the droplets made coalescence more difficult, perhaps by preventing close contact between the droplets. In concentrations above 3%, some of the powder was incorporated into the interior of the microcapsule, counter-acting the size reduction effects of the additive. This was evident from a total recovered weight of microcapsules larger than the expected yield.

Microencapsulation with the aid of 10% silicone fluid 50 cP yielded microcapsules of slightly smaller size (370 μm) than those prepared with no additives (398 μm); silicone fluid 60,000 cP, at 5% and 10% concentrations, reduced the microcapsule mean diameter from 398 μm to 258 um and 266 um, respectively (see Table 3).

TABLE 2

Effect of Finely Divided Powders on Particle Size Distribution of PMMA Microcpasules Containing Chlorpheniramine-Resin Complexes

FINELY DIVIDED POWDER	CONCENTRATION[a]	GEOMETRIC MEAN DIAMETER[b]	GEOMETRIC STANDARDd DEVIATION
BETONITE	3	298.5	1.59
	6	370.0	1.61
VEEGUM	3	244.8	1.40
	6	425.2	1.70
CARBON BLACK	3	201.8	1.40
	6	562.3	5.46

[a] in % W/V; [b] in microns

TABLE 3

Effect of Silicone Fluid, Glyceryl Monostearate, and Stearyl Alcohol on the Particle Size Distribution of PMMA Microcapsules Containing Chlorpheniramine-Resin Complexes

ADDITIVE	CONCENTRATION[a]	GEOMETRIC MEAN DIAMETER[b]	GEOMETRIC STANDARD DEVIATION
Silicone Fluid[c]	5	258.5	1.33
Silicone Fluid[c]	10	266.1	1.33
Silicone Fluid[d]	10	370.5	1.30
Glyceryl Monostearate	1	325.5	1.26
Stearyl Alcohol	1	354.8	1.19

[a] in %W/V; [b] in microns; [c] 60,000 cP; [d] 50 cP

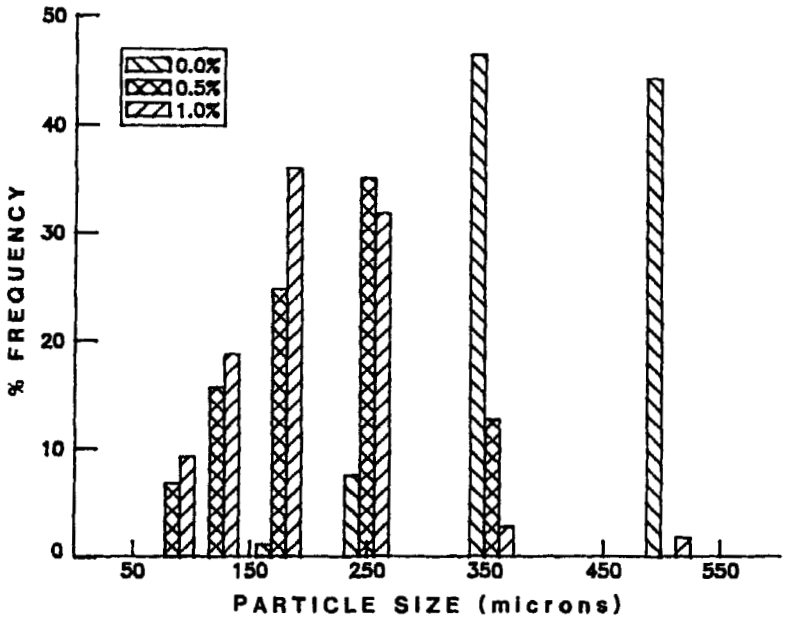

FIGURE 3
Effect of Magnesium Stearate Concentration on the Particle Size Distribution of PMMA Microcapsules Containing Chlorpheniramine-Resin Complexes.

Polydimethylsiloxane fluids have very limited solubilities in both acetone and mineral oil, and probably tend to collect at the interface as a separate phase between the acetone and the oil. However, the 50 cP fluid has insufficient viscosity to be an effective stabilizer.

Glyceryl monostearate and stearyl alcohol reduced the mean size of coated complexes to a lesser degree than higher viscosity silicone fluids, to 325 μm and 354 μm, respectively (see Table 3).

TABLE 4

Process Efficiency as Indicated by a Ratio of PMMA Microcapsules Larger than 90 Microns versus Total Input as a Function of Preparation Variables

P:C[a]	ADDITIVE	CONCENTRATION %W/V	EFFICIENCY %
1:1	magnesium stearate	0.5	85.80
1.5:1	magnesium stearate	0.5	84.20
2:1	magnesium stearate	0.5	99.93
1.5:1	magnesium stearate	0.0	93.62
1.5:1	magnesium stearate	1.0	72.85
1.5:1	silicone fluid[b]	5.0	97.91
1.5:1	silicone fluid[b]	10.0	93.18
1.5:1	silicone fluid[c]	10.0	93.38
1.5:1	stearyl alcohol	1.0	97.99
1.5:1	glyceryl monostearate	1.0	95.36

[a] Polymer:Complex ratio; [b] 60,000 cP; [c] 50 cP.

Glyceryl monostearate, stearyl alcohol, and magnesium stearate dissolve in mineral oil at elevated temperatures, but form colloidal gel structures upon cooling to room temperature. Because of their polar-nonpolar nature they tend to collect at interfaces and act as emulsion stabilizers. All three increase the viscosity of mineral oil upon cooling, but magnesium stearate is more effective.

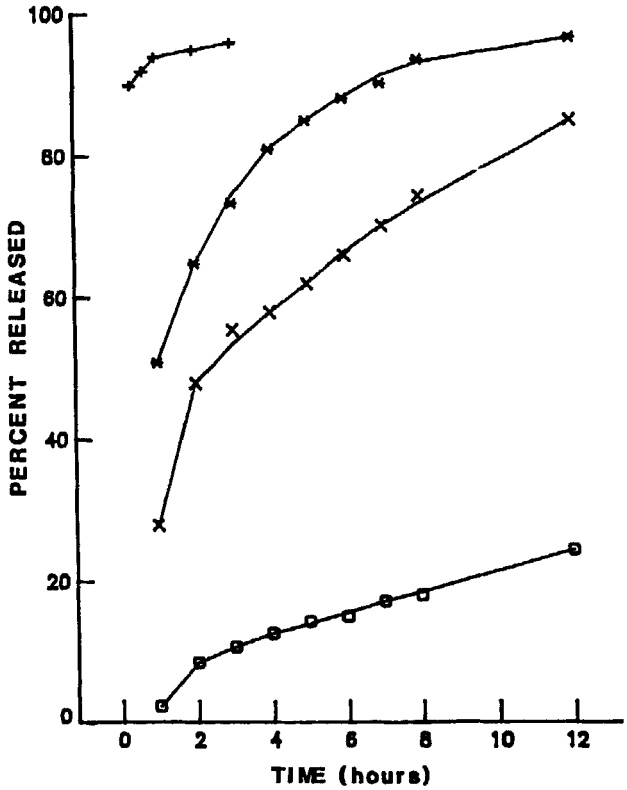

FIGURE 4
Effect of Polymer:Complex Ratio on the Release of Chlorpheniramine from PMMA Microcapsules (362 um). KEY: (+) uncoated; (✱) 1:1; (✕) 1.5:1; and (○) 2:1.

Figure 3 shows the microcapsule particle size distribution obtained with 0%, 0.5%, and 1% magnesium stearate as emulsion stabilizer. Geometric mean particle size shifted from 398 μm with no additive to 205 μm with 0.5% and 177 μm with 1% magnesium stearate.

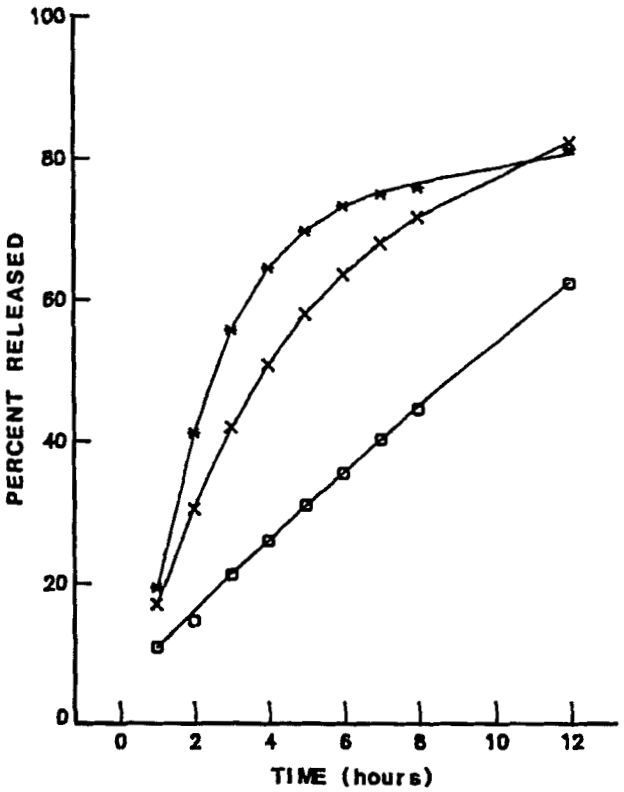

FIGURE 5
Effect of Particle Size on the Release of Chlorpheniramine from PMMA Microcapsules. KEY: (✱) 181 μm; (✕) 362 μm; (○) 512 μm.

The efficiency with which the emulsion-solvent evaporation technique encapsulated the complexes ranged from 73% to 99%, depending on the formulation selected (see Table 4).

Since the efficiency of the encapsulation process was calculated from the weight ratio of microcapsules larger than 90 μm versus total material used, the figure is an indirect measure of polymer loss. The emulsion stabilizers, in addition to

reducing microcapsule size, also influenced the deposition of polymer around the complexes; hence a varied process efficiency.

Dissolution

The uncoated complexes released chlorpheniramine rapidly, with equilibrium being attained within two hours. The rate of chlorpheniramine release from microcapsules varied considerably as a function of polymer to complex ratio. The time required for 50% of the drug content to be released ($T_{50\%}$) decreased from more than 12 hours for a 2:1 coating ratio to 1.1 hours for a 1:1 coating ratio, whereas microcapsules prepared at a 1.5:1 coating ratio released 50% of their drug content in 3.8 hours (see Figure 4).

An increase in formulation polymer to complex ratio caused an increase in the coating thickness of the microcapsule, as observed microscopically. By increasing the pathlength through which the drug molecule has to diffuse, the time required to traverse the membrane increased; hence slower release from microcapsules prepared at higher polymer to complex ratios.

The rate of chlorpheniramine release from microcapsules prepared at a 1.5:1 coating level was inversely proportional to the capsule size (181 μm to 512 μm), with the $T_{50\%}$ ranging from 2.8 hours to 4.0 hours (see Figure 5). This would be expected from the decreased relative surface area exposed to the dissolution environment.

SUMMARY

1. Microcapsules prepared from solutions containing higher percentages of PMMA were of larger diameter.
2. Bentonite, Veegum^{R}, and carbon black reduced microcapsule diameter at 3% concentration, but increased the microcapsule size when used at the 6% level.
3. Silicone fluid 60,000 cP was more effective in reducing microcapsule size than was silicone fluid 50 cP.
4. Glyceryl monostearate and stearyl alcohol were moderately effective in reducing microcapsule size, whereas magnesium stearate caused the greatest decrease in size.
5. Higher formulation coating ratios resulted in slower release of chlorpheniramine from microcapsules.
6. Larger microcapsules released chlorpheniramine at a slower rate than did smaller microcapsules.

REFERENCES

1. Respiratory drugs, in "Facts and Comparisons", J.R. Boyed eds, J.B. Lippicott Company, St. Louis, Missouri (1982), p188.
2. W.A. Ritschel,in "Pharmacokinetic Parameters of Important Drugs", Handbook of Basic Pharmacokinetics, Drug Intelligence Publications Inc., Hamilton, Illinois,1986, p500.

3. R.K. Chang, in "Dual Polymer Microsphere Systems to Control Drug Release", Ph.D. Dissertation, University of Georgia, Athens, Georgia, 1984.

4. C.L. Wen, in "Formulation of a Sustained Release Dosage Form of Acetaminophen", M.S. Thesis, University of Georgia, Athens, Georgia, 1982.

5. A.J. Shukla, in "Cellulose Esters as Microencapsulation Polymers for Oral Controlled Release Theophyllin and Synthesis of a Polyamino acid for Possible Parenteral Controlled Release", Ph.D. Dissertation, University of Georgia, Athens, Georgia, 1985.

6. Y. Pongpaibul, J.C. Price, and C.W. Whitworth, Drug Dev. Ind. Pharm.,10, 1597 (1985).