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EFFECT OF PROCESS VARIABLES ON DRUG RELEASE FROM MICROPARTICLES CONTAINING A DRUG-RESIN COMPLEX

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ABSTRACT

Microparticles consisting of dextromethorphan-resin complex (resinate) coated with a cellulose derivative were prepared by a modified emulsion-solvent evaporation method. Adjustment of the release rate was achieved by varying resinate (core) to polymer (coat) ratio or by using additives. Higher ratios of resinate to polymer gave faster release of the drug. Polyethylene glycol (PEG) 4000 also increased the release rate. Increasing core to coat ratio also increased average particle size. Placing the

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emulsifying agent in different phases of the emulsion in the fabrication process also affected the particle size distribution. The microparticles showed good sustained release of the drug.

INTRODUCTION

Controlled release drug delivery systems offer both convenience and therapeutic benefits. New approaches have been used in recent years in the preparation of controlled release oral dosage forms. The use of ion exchange resins in the formulation of certain controlled release systems has been successful. Smith et al (1) investigated the use of various carboxylic acid and sulfonic acid cation exchange resins for the preparation of a sustained release liquid preparation containing the antihistamine methapyrilene. The sulfonic acid type resin showed much greater prolonged release of drug than the carboxylic acid type in dilute hydrochloric acid. Sulfonic acid cation exchange resins with pKa value of 2 are normally highly dissociated at all pH's encounted in the gastrointestinal tract.

A number of patents and reports involving coating of drug-loaded resins have been reported. Koff (2) described the use of castor wax to improve the palatability of cation-exchange-resins loaded with amprotropine. Clarke (3) applied cellulose acetate phthalate as an enteric coating on drug-loaded cation-exchange resin beads using a coating pan. Raghunathan et al (4) reported that direct application of ethylcellulose-vegetable oil

coating by an air suspension technique on amine drugs bound to sulfonic acid cation exchange resin was unsuccessful. The coating tended to rupture in the diluted hydrochloric acid medium due to the swelling of the resinate. Pretreatment of the resinate particles with polyethylene glycol 4000 overcame the problem.

A coated resinate may be suspended in a suitable liquid for a liquid dosage form or enclosed in a gelatin capsule to give as a solid dosage form. Upon ingestion, ions from the gastrointestinal tract diffuse through the outer coating and displace drug from the ion-exchange resin. The concentration of ions in gastrointestinal secretion remains relatively constant, therefore, a relatively constant rate of drug release can be obtained.

The objective of this study was to utilize cation exchange resins as adsorbants for dextromethorphan and to coat the drug resinate with a cellulose derivative. Dissolution testing was then used to determined if there was prolonged release of drug from the resinate. The effect of additives on the size and on the characteristics of the microparticles was investigated.

METHOD OF PREPARATION AND TESTING OF MICROPARTICLES

The resinate was prepared by dissolved DMP in deionized water, adding the resin and stirring for several hours. The resinate was separated by filtration, dried and screened. The resinate was obtained in the form of a fine, free flowing powder.

The resinate was coated using cellulose acetate butyrate (CAB) as the coating material by a modified emulsion-solvent evaporation method (5).

Variations in the fabrication process

1. The polymer to resinate ratios were varied as follows: 3:3, 2:3, 1:3 and 3:1.5, 3:3 and 3:4.
2. The concentrations of the PEG were 5, 10 and 20% of total weight of CAB used.
3. The emulsifying agent Arlacel 85 was placed in different phases of the emulsion.

Assay for DMP content

About 20 mg of microparticles was weighed accurately and transferred into a 125 ml separatory funnel. Twenty-five ml of ethyl acetate was added to dissolve the CAB coating polymer, then 100 ml of 0.3 N HCl was added to extract DMP from the resinate. The DMP in the aqueous phase was determined spectrophotometrically at 277 nm. All the assays were carried out in triplicate.

Dissolution Studies

Dissolution tests were carried out using a USP dissolution assembly. Each dissolution beaker contained 800 ml of simulated intestinal fluid without enzyme at pH 7.3. Polysorbate 80 (0.02%) was added to the dissolution fluid to overcome the nonwetting characteristic of the DMP microparticles and to make the solution more closely resemble the surface tension of gastrointestinal fluid. The solution was kept at 37°C and stirred at

100 ± 1 rpm. Accurately weighed 150 mg quantities of microparticles were used. Samples of dissolution medium were taken at specific time intervals and spectrophotometrically assayed at 277 nm. After the assay, the samples were immediately returned to the dissolution beakers.

RESULTS AND DISCUSSION

Figure 1 shows the influence of varying the core (resinate) to coat ratio on the size distribution of the microparticles. The larger the core to coat ratio the greater the size of microparticles. This was due to the fact that the higher ratios produced a more viscous internal phase which was more difficult to disperse in the external phase during emulsification resulting in larger microparticles. The stirring speed and solvent volume were kept constant. The drug content of the microparticles was 11.48, 17.52 and 21.30% for formulations with core:coat ratios of 1:3, 2:3, and 3:3 respectively.

Figure 2 shows the dissolution profile of microparticles with varying core to coat ratios compared to dissolution of resinate. A sustained release is evident. Coated resinate released the drug more slowly than the uncoated resinate. Varying the quantity of resinate and CAB resulted in different release characteristics. The quantity of CAB polymer was kept constant as the ratio of core to coat was increased from 1:3 to 2:3 to 3:3. The time for 50% of drug to be released from the

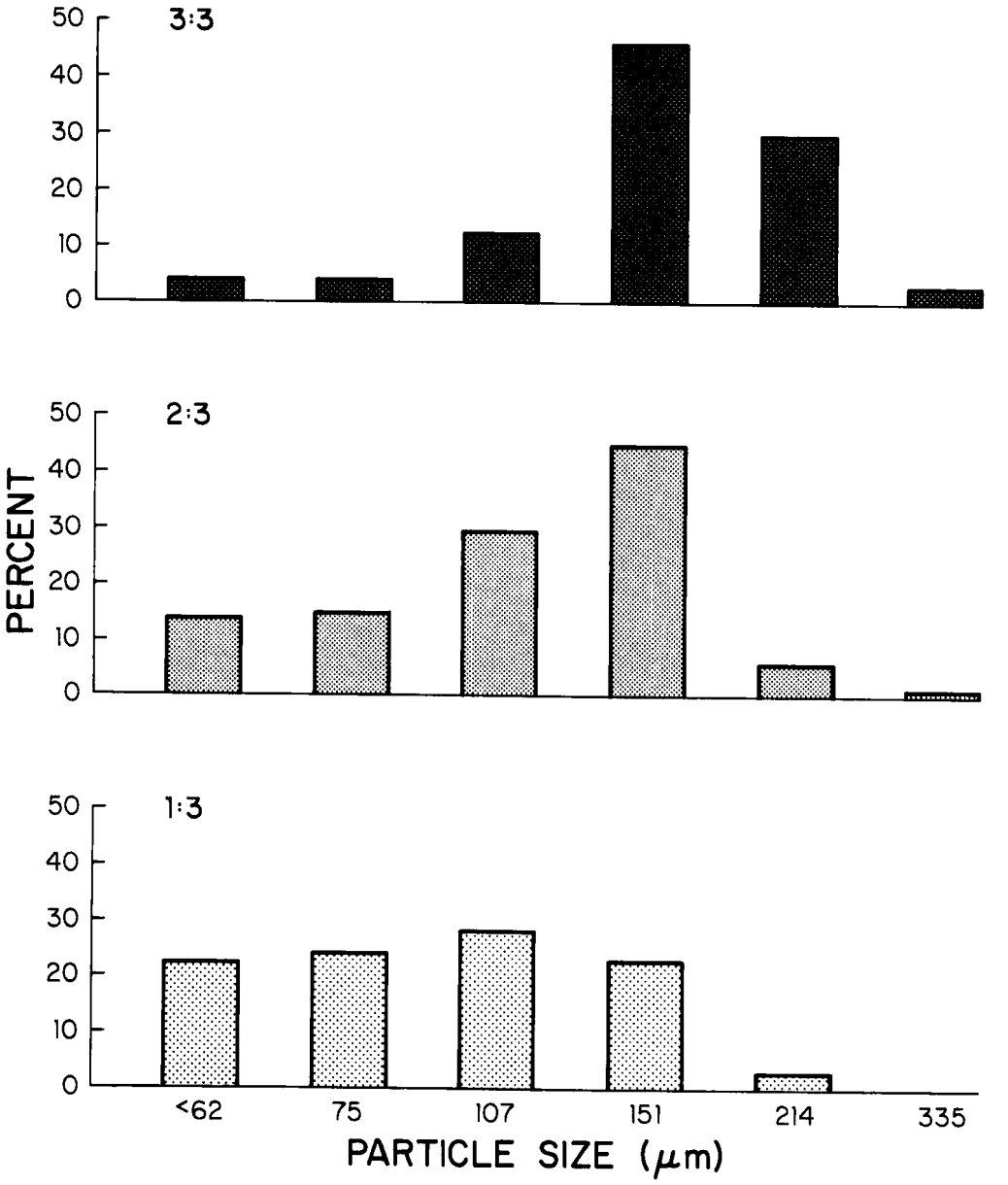

FIGURE 1

Particle size distribution in weight percent of microparticles as a function of resinate to polymer ratio for ratios of 1:3, 2:3 and 3:3

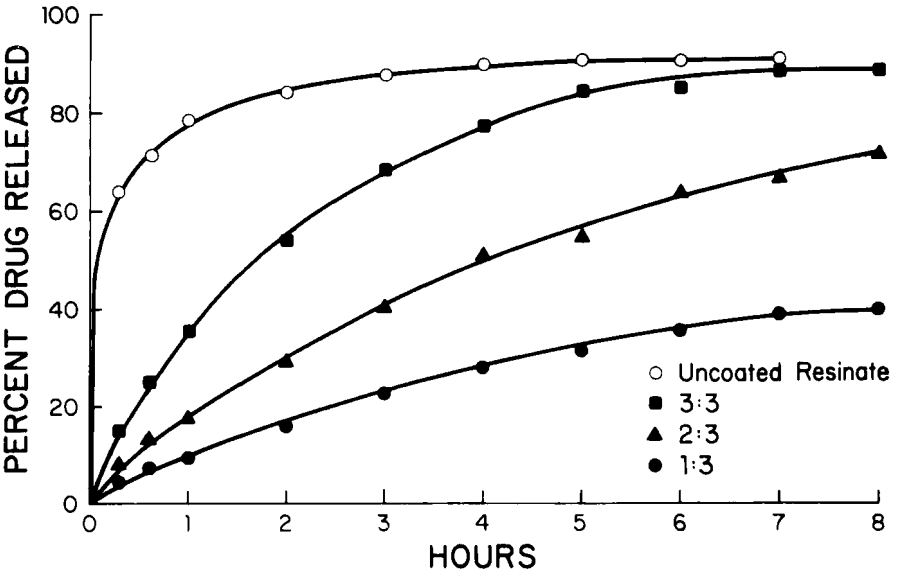

FIGURE 2

Effect of resinate to polymer ratio on dissolution characteristics of microparticles for ratios of 1:3, 2:3 and 3:3

microparticles with average size of 151 um decreased from more than 8 hours to about 2 hours. This was due to the thinner coating of polymer for the high ratio of core to coat. Similar release characteristics were obtained when the quantity of core was kept constant and the quantity of CAB coating polymer varied (Fig. 3). As the amount of polymer decreased, the release rate of the drug increased.

PEG 4000 was used as channeling agent to improve drug release. As it dissolves out of the microparticles, it leaves

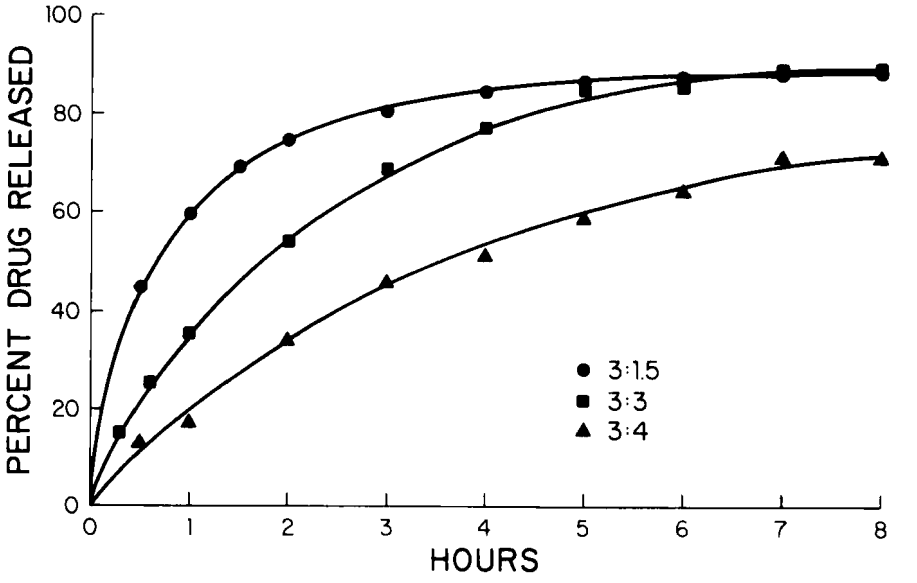

FIGURE 3

Effect of resinate to polymer ratio on dissolution characteristics of microparticles for ratios of 3:1.5, 3:3 and 3:4

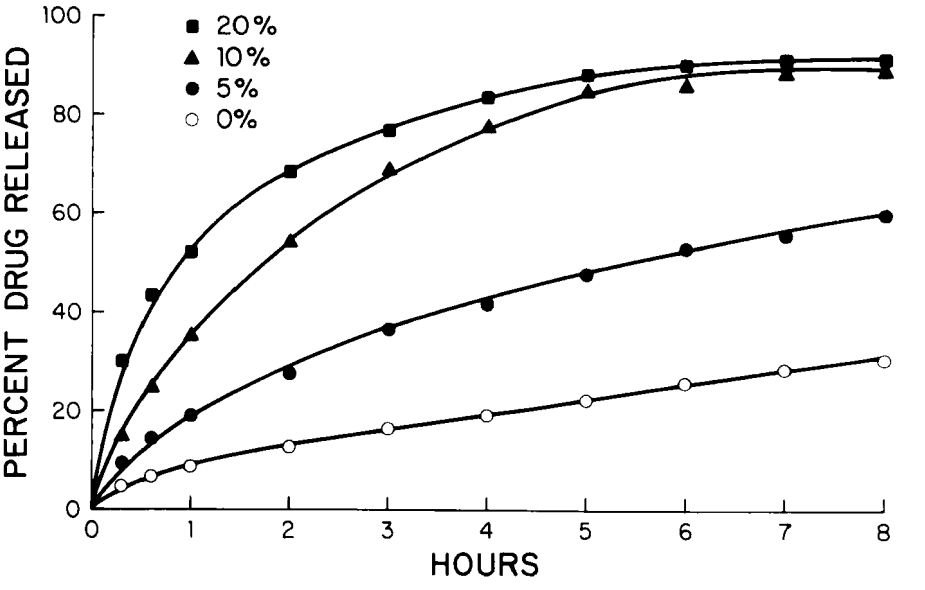

FIGURE 4

Effect of PEG 4000 concentration on dissolution characteristics of microparticles

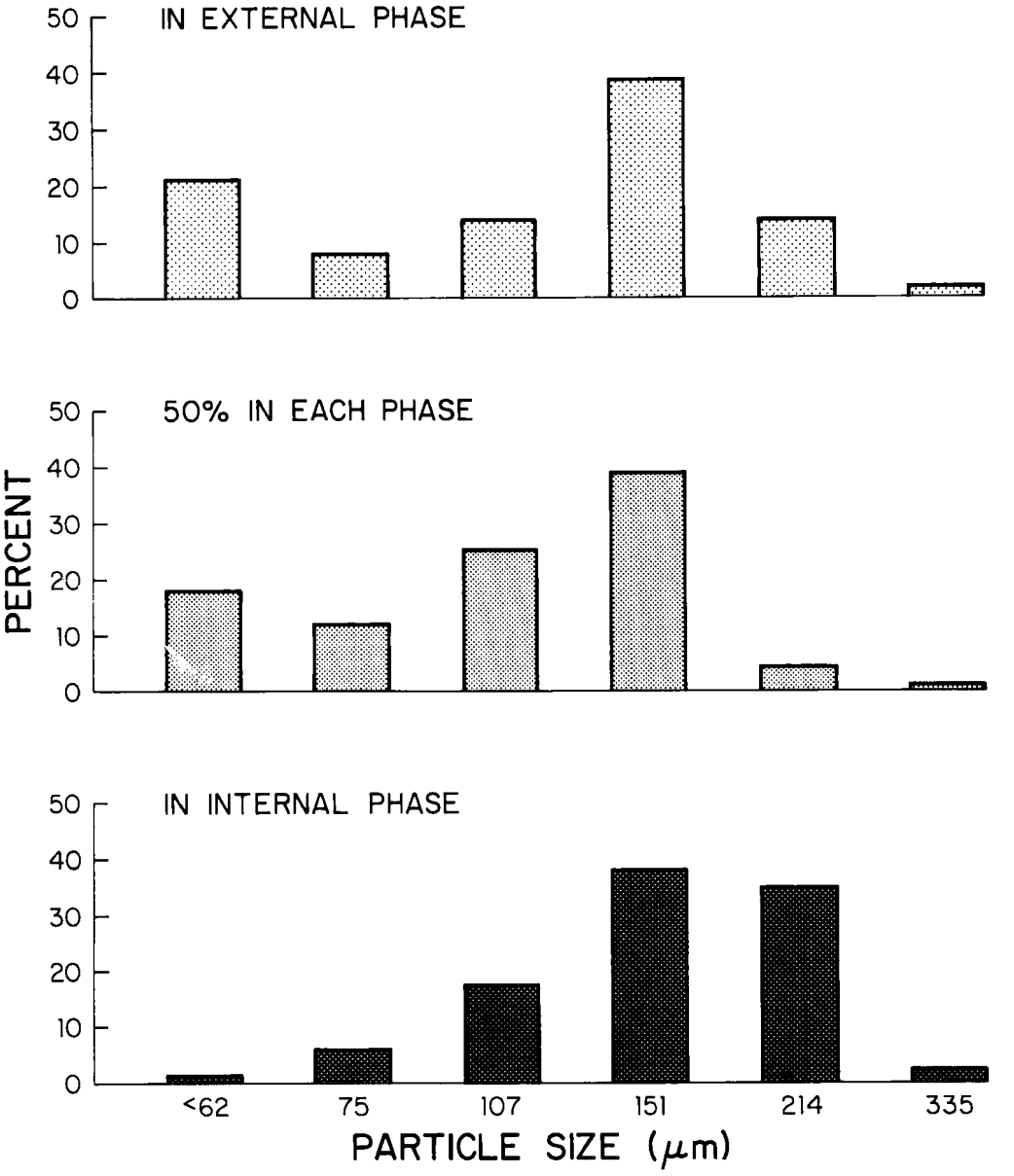

FIGURE 5

Effect of placing the emulsifying agent in different phases of the emulsion on the microparticle size distribution in weight percent

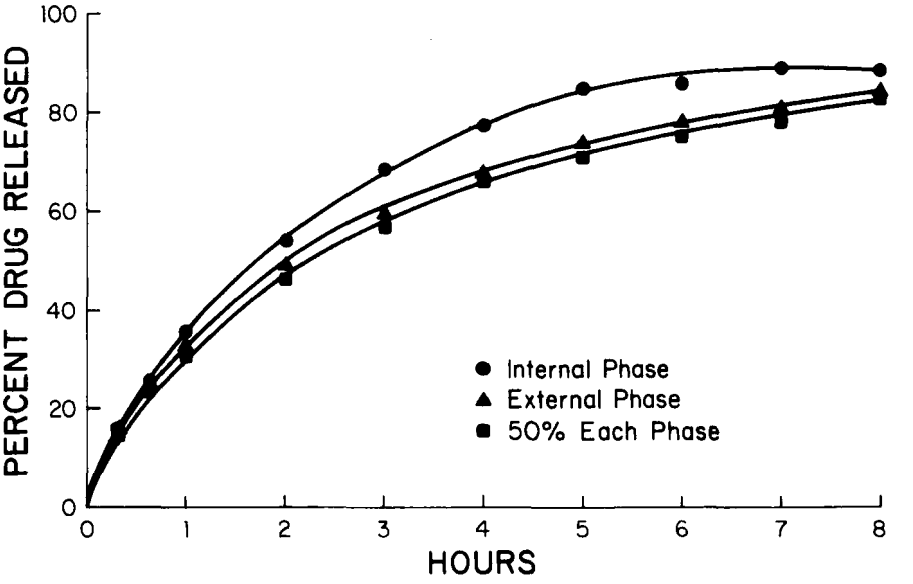

FIGURE 6

Effect of placing the emulsifying agent in different phases of the emulsion on the dissolution characteristics of the microparticles

channels creating more surface area from which drug is released. Figure 4 demonstrates the increase in release rate as the % of PEG 4000 is increased. The time for 50% drug release was 5.5, 1.8 and 1 hour for microparticles containing 5, 10 and 20% respectively of PEG 4000.

In preparing microparticles by emulsion-solvent evaporation the emulsifier can be placed in either the internal or the external phases of the emulsion. If it is placed in the polymer solution which is the internal phase, the emulsifier will act as

a plasticizer for the polymer and the emulsifying property may be decreased. Figure 5 shows the size distribution resulting when the emulsifying agent, Arlacel 85, was placed in different phases. When it was placed in internal phase the particle size was larger than when it was placed in external phase only. When 50% of the emulsifier was placed in each phase, the particle size distribution fell between the other two sizes. Although the same size of microparticles were used, the dissolution studies show faster drug release from those prepared with the emulsifier in the internal phase (Fig. 6).

CONCLUSIONS

A method was found which was suitable for coating a drug-resin complex. The release rate of drug could be changed by varying the core to coat ratio or by increasing the concentration of PEG 4000. It was also possible to modify the dissolution profile as desired by using mixtures of coated and uncoated resinate. The particle size distribution of microparticles was smaller when the emulsifier was placed in the external phase of the emulsion.

ACKNOWLEDGEMENT

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REFERENCES

1. H.A. Smith, R.V. Evanson and G.J. Sperandio, J. Amer. Pharm. Assoc. Sci. Ed. 49, 94 (1960).

2. A. Koff, US Patent, (1964), 3,138,525.

3. C.A. Clarke, British Patent, (1971) 1,218,102.

4. Y. Raghunathan, L. Amsel, O. Hinsvark and W. Bryant, J. Pharm. Sci. 70, 379 (1981).

5. Y. Pongpaibul, J.C. Price and C.W. Whitworth, Drug Dev. and Ind. Pharm. 10, 1597 (1984).