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PREPARATION AND EVALUATION OF A LONG ACTING LIQUID ANTITUSSIVE PRODUCT

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ABSTRACT

Microparticles containing a dextromethorphan-resin complex were prepared by a modified emulsion solvent evaporation method. The particles were evaluated for size distribution and dissolution rate. Selected microparticles were suspended in various liquid media and stored at room temperature. Dissolution of suspended microparticles was studied after storage up to 40 days. The particles were found to be stable and did not release drug in a suspending media containing 30% propylene glycol, 35% syrup and 35% of 1% methylcellulose 1500 cps solution.

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INTRODUCTION

Synthetic ion-exchange resins are finding wide use in pharmaceutical dosage forms. The adsorption of bad tasting drugs onto ion-exchange resins to achieve taste coverage has been reported (1,2). The main use of ion-exchange resins as drug carriers is for obtaining a prolonged release effect. Several products have been developed and some are marketed. Generally, the drug bases are absorbed onto cation exchange resins of a strongly acidic type with an approximate pKa of 2. They are completely dissociated at all acidities encountered in the gastrointestinal tract and the release of drug is governed by the total concentration of ions in the gastrointestinal secretion. Smith et al (3) reported sulfonic acid-type resins gave a more prolonged release of methapyrilene than the carboxylic acid type in dilute hydrochloric acid. More recently Raghunathan et al (4) successfully pretreated resinate particles with polyethylene glycol 4000 to prevent rupture of the coating due to swelling of the resinate. The resulting microcapsules of amine drug showed prolonged continuous release of the drug under conditions encountered in the gastrointestinal tract.

Dextromethorphan hydrobromide, a widely accepted, nonnarcotic antitussive agent, is a common ingredient in many cough and cold preparations. The drug is usually given three to four times a day. Repeat administration of the drug to children several times a day is inconvenient. Dextromethorphan in a

prolonged release liquid dosage form would be suitable for children and patients who cannot swallow tablets. The objective of this investigation was to prepare and study a prolonged release liquid suspension of dextromethorphan microparticles.

EXPERIMENTAL

Preparation of Resinate and Microparticles

The resin (Aldrich Chemical Co.) was added to a solution of dextromethorphan (DMP) hydrobromide (Hoffman-LaRoche Inc.) in deionized water. This was stirred for several hours, filtered and the resinate washed and dried. The resinate particles were ground and sieved through a 230 mesh screen.

The particles were coated with a polymer using a modified emulsion-solvent evaporation method. The microparticles were sized through standard sieves nos. 60, 80, 120, 170 and 230. The fraction of microparticles remaining on each sieve was collected for dissolution studies.

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 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.

TABLE 1

Composition of Suspending Vehicles

Vehicle #	Syrup U.S.P. ml	1% Methylcellulose 1500 CPS ml	Propylene Glycol ml
1	100	-	-
2	50	50	-
3	45	45	10
4	35	35	30

DMP Microparticle Suspension

Four different liquid suspending media were used as shown in Table 1. Each vehicle contains 0.2% of Arlacel 85 as an antifoaming agent. Suspensions were prepared in such a way that each 5 ml of suspension contains 150 mg of microparticles. All suspensions were stored at room temperature.

Dissolution Studies

Dissolution tests were carried out using a USP dissolution assembly. Each dissolution beaker contained 800 ml of either simulated gastric fluid (pH 1.3) or simulated intestinal fluid (pH 7.3). Both are without enzyme. Polysorbate 80 (0.02%) was added to the dissolution medium 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. One-hundred fifty mg of microparticles or 5 ml of DMP microparticle suspension were used in each test. 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

Microparticles were examined by scanning electron microscope, and it is evident from the electron micrograph (Fig. 1) that the particles are spherical with smooth surfaces. They were also free flowing particles with a small range of size distribution (Fig. 2). Most of microparticles have an average diameter of about 151 um, therefore, this particle size was used for suspension. Dissolution profiles of different particle size of microparticles in Figure 3 indicate that smaller particles release drug faster than larger size due to more surface area. The drug content was 23.92, 22.93 and 19.53% for microcapsule with average size of 151, 107 and 75 um respectively.

Several suspending media were used in an attempt to formulate a stable and palatable suspension of selected microparticles. Syrup USP alone is not a good vehicle for the particles since they formed aggregates after one day. These

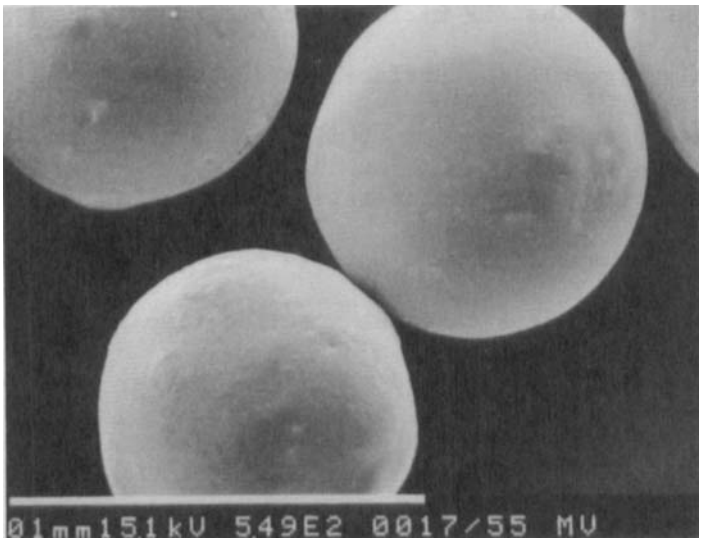

FIGURE 1

Electron micrograph of microparticles

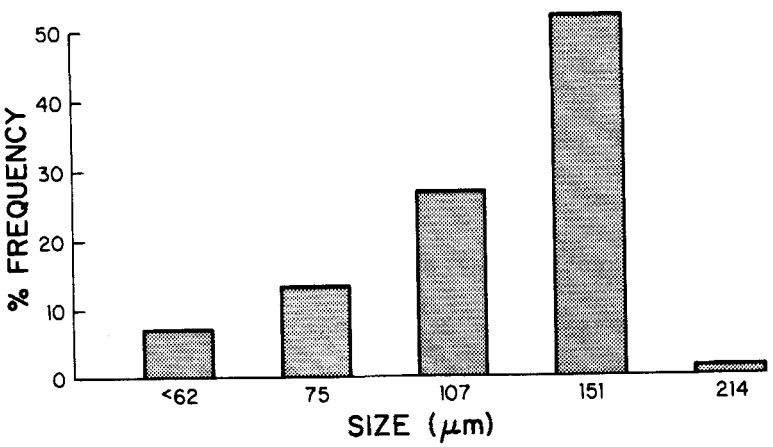

FIGURE 2

Microparticle size distribution

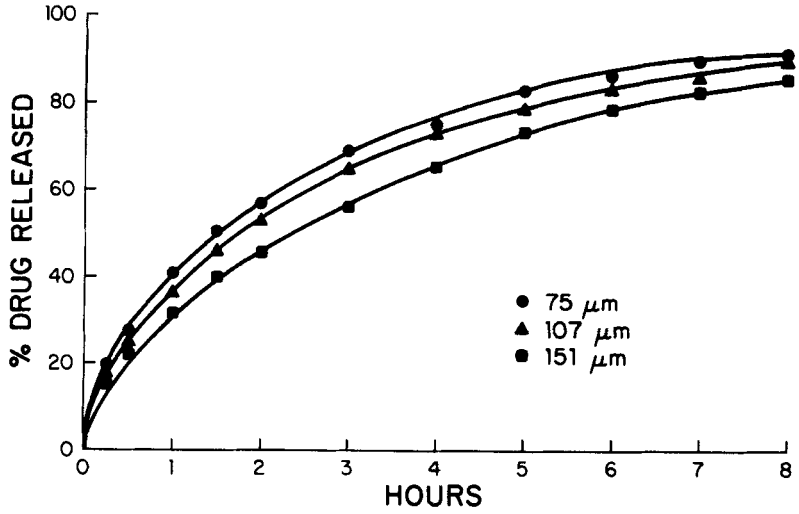

FIGURE 3

Effect of microparticle size on dissolution profile

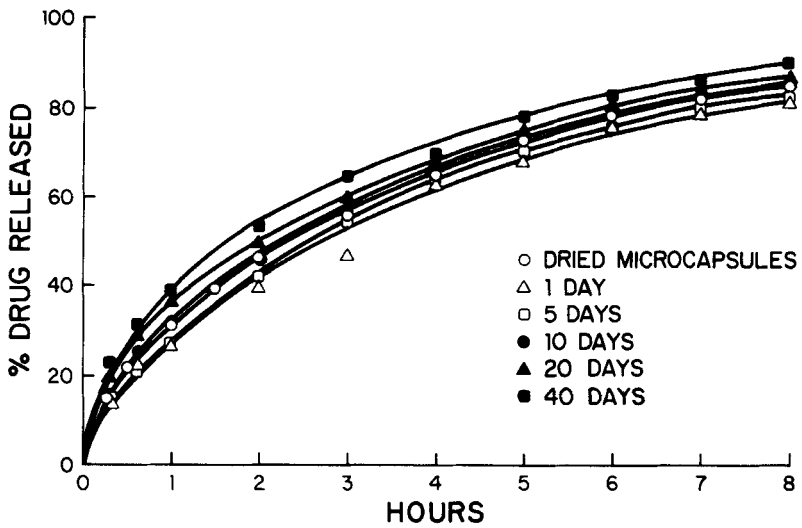

FIGURE 4

Dissolution profile of suspended microparticles in vehicle No. 3 after various storage times

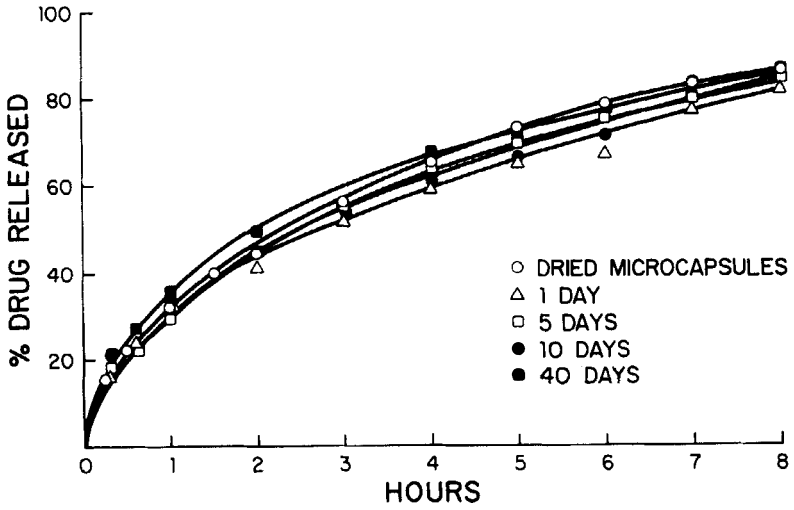

FIGURE 5

Dissolution profile of suspended microparticles in vehicle No. 4 after various storage times

aggregates floated on the surface of the syrup and were difficult to redisperse. Replacement of 50% of syrup with 1% methyl cellulose 1500 cps did not help to keep the microparticles well dispersed after storage for few days. Therefore, the dissolution of these two suspensions was not carried out. Suspending media #3 and 4 were found to be good suspending vehicles. All microparticles were well dispersed in these two media for more than 5 months. Figures 4 and 5 show the release of the drug from suspended microparticles after storage at room temperature up to 40 days. There was a slight increase in dissolution rate of

suspended microparticles in vehicle #3 after storage for 20 and 40 days. As the concentration of propylene glycol was increased to 30% (vehicle #4), there was no significant change in release rate of suspended microparticles after storage for 40 days (Fig. 5). Since the liquid vehicles contained no ions the drug remained bound to the ion exchange resin and no drug was released in the suspensions.

This method of preparation and suspension of microparticles in liquids is a satisfactory method for preparation of a long acting liquid antitussive. The process is efficient, reproducible and not time consuming.

ACKNOWLEDGEMENTS

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