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MICROENCAPSULATION BY EMULSION NON-SOLVENT ADDITION METHOD

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ABSTRACT

Cellulose acetate butyrate microcapsules containing propranolol were prepared by emulsion non-solvent addition method. The effects on drug release of different polyethylene glycols (PEG), various concentrations of PEG 4000, and particle size of the drug to be encapsulated were investigated. In vitro dissolution of microcapsules in simulated intestinal fluid and buffers at different pH was also studied. PEGs were found to increase drug release for this system. The pH dissolution profiles of the microcapsules indicated that dissolution was slightly pH dependent during the first 8 hours of dissolution.

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INTRODUCTION

Microencapsulation is a useful method for the preparation of dosage forms which control the release rate of the drug. Many microencapsulation processes have been reviewed (1), however, not much has been published on coacervation by non-solvent addition. This method was granted a patent in 1976 (2). The process involves dispersing or dissolving a core substance (drug) in a film-forming polymer solution, dispersing this mixture in a vehicle which is poorly miscible with the solvent of the polymer solution and which does not dissolve the polymer or core substance. Then, a non-solvent for polymer and core substance which is miscible with the polymer solvent and poorly miscible with the encapsulating vehicle is added to the system thereby precipitating the polymer film around the core material and forming isolatable microcapsules.

Microcapsules of ethylcellulose containing sulfamethizole and 5-fluorouracil prepared by means of coacervation-phase separation by addition of non-solvent was reported (3). The resulting microspheres of both drugs gave a longer release half-life. Feinstein et al (4) prepared dexamethasone microcapsules for aerosol formulation by using ethycellulose in toluene and precipitating the polymer with petroleum ether. The microcapsules obtained exhibited timed release which appeared to be pH independent.

PEGs were used in this investigation to modify drug release from cellulose acetate butyrate (CAB) microcapsules. These are

hydrophilic polymers existing in a wide range of molecular weights. Solid PEGs are not significantly absorbed from the gastrointestinal tract while the liquids are absorbed and a large proportion is excreted unchanged in the urine (5). PEGs are tasteless, stable and non-toxic. PEG 6000 has been used as a carrier for solid dispersions of poorly water soluble liquids to increase the solubility of liquid drugs (6). Solid solutions of water insoluble drugs such as digitoxin, griseofulvin, hydrocortisone acetate, methyltestosterone and prednisolone acetate made from PEG 6000 have also been reported (7). Such solid solutions had greatly improved dissolution rates.

Reports on the influence of the particle size of the drug to be coated on the particle size of microcapsules and release rate are very limited. El-Egakey et al (8) used different sizes of ascorbic acid powders in preparing microcapsules and found that the finer particles of the drug resulted in smaller average microcapsule size. In contrast, Jalsenjak et al (9) reported that the particle size of isoniazid used in preparation of microcapsules had no significant influence on the mean particle size of microcapsules obtained.

This study involves the preparation of microcapsules by emulsion non-solvent addition method using CAB as the coating material and propranolol hydrochloride as a model drug. Various types and concentrations of PEG for modifying drug release were investigated to determine the most suitable one for the system.

The effect of different particle sizes of the drug to be encapsulated and pH of dissolution medium on dissolution profile of microcapsules were also studied.

EXPERIMENTAL

Preparation of Microcapsules

Microcapsules were initially prepared with three different water insoluble polymers, CAB, cellulose propionate (CP) and Eudragit RS by emulsion non-solvent addition. A comparison of the release rates of propranolol from microcapsules with an average size of 213.5 um revealed that only the cellulose polymers gave a good prolongation of drug release. Microcapsules prepared with CAB had a slower release rate than CP microcapsules. The size distribution of CAB microcapsules is slightly narrower than CP microcapsules. Therefore, CAB was chosen for further investigation.

Weighed amounts of PEG[1] were dissolved in 10 ml of warm acetone and 30 ml of 10% CAB[2] solution in acetone was added. Propranolol hydrochloride[3] was added with stirring. This mixture was then dispersed by stirring at 580 rpm in 200 ml of light mineral oil containing 0.5% of magnesium stearate and one drop of Simethicone[4] as encapsulating medium. After the polymer solution was well dispersed in mineral oil, either hexane or isopropranol was added dropwise to precipitate CAB around the drug particles. After the microcapsules were formed, the liquid paraffin was

decanted off and the microcapsules were washed with three 50 ml portions of heptane and dried under reduced pressure at room temperature.

Variables Studied

Various types and concentrations of PEG were included in the formulations to act as channelling agents to increase drug release where desirable. PEG 400, 1000, 4000 and a mixture of PEG 400, 40% and PEG 6000, 60% were tested in various concentrations. In each formulation, the drug-polymer ratio was kept constant at 2:3.

Another variable investigated was the effect of particle size of encapsulated drug on microcapsule characteristics and release profiles. Three different particle sizes of propranolol were used including a fine powder (44 um) medium size crystals (75 um) and course crystals (213.5 um). In the particle size study the drug to polymer ratio was 3:3 and PEG 4000 was present in the amount of 15% of the CAB coating material.

Particle Size Analysis

The particle size distribution of the dried microcapsules was determined by sieving with Nos. 12, 14, 16, 20, 30, 40 and 60 mesh sieves. The fractions collected on each screen were retained for dissolution studies.

Assay of Propranolol

At least duplicates of accurately weighed amounts of around 20 mg of microcapsules of each batch were placed in 250 ml

separatory funnels. Twenty-five milliliters of ethyl acetate was added to dissolve the CAB coating material. Then 200 ml of 0.1 N hydrochloric acid was added to dissolve the drug. The amount of propranolol in the aqueous phase was determined spectrophotometrically[5] at 289 nm.

In Vitro Dissolution

The USP dissolution apparatus[6] was used at a stirring speed of 100 ± 1 rpm. Simulated intestinal fluid pH 7.3 without enzyme and containing 0.02% Tween 80 was used as dissolution media. One hundred milligrams of microcapsules mean particle size of 1300 um were placed in 1000 ml of dissolution fluid maintained at 37 ± 0.1°C. Samples were taken at appropriate intervals. The concentration of propranolol in the samples was determined by measuring the UV absorption at 289 nm and the sample was immediately poured back into the dissolution beaker. All dissolution studies were run at least in duplicate for each batch.

The dissolution rate of the propranolol microcapsules was determined as a function of pH. Dissolution media were 0.1 N HCl (pH 1.4) citrate buffer (pH 4.5), phosphate buffer (pH 6.5) and simulated intestinal fluid (pH 7.3). All dissolution media contained 0.02% Tween 80. The method used was as previously described, samples were taken at 3, 6, 9 and 12 hour intervals and assayed.

RESULTS AND DISCUSSION

Microcapsules were prepared by adding isopropyl alcohol which is a non-solvent for the polymer, miscible with the polymer solvent (acetone) and poorly miscible with the encapsulating vehicle (mineral oil) similar to the method reported by Norishita et al (2). The resulting microcapsules are too light in weight, however, when the non solvent hexane which is miscible with both encapsulating vehicle and polymer solvent was used, dense microcapsules were obtained which were more suitable for this study, therefore hexane was selected as the non-solvent for making the microcapsules.

Effects of Various Types of PEG

The different types of PEG did not significantly affect particle size distribution when the concentration of PEG and drug to polymer ratio were held constant at 10% and 2:3 respectively. The dissolution profiles of propranolol from microcapsules prepared with different types of PEG are shown in Figure 1. Microcapsules studied had an average microcapsule size of 1300 um. The dissolution rate of microcapsules containing PEG's is markedly higher than that without PEG. This was expected since PEG's are water soluble polymers.

Effect of Different Concentrations of PEG

As the concentration of PEG 4000 in the formulation was increased from 10% to 20% of the CAB dry weight, there was no effect on particle size distribution. However, when a 30%

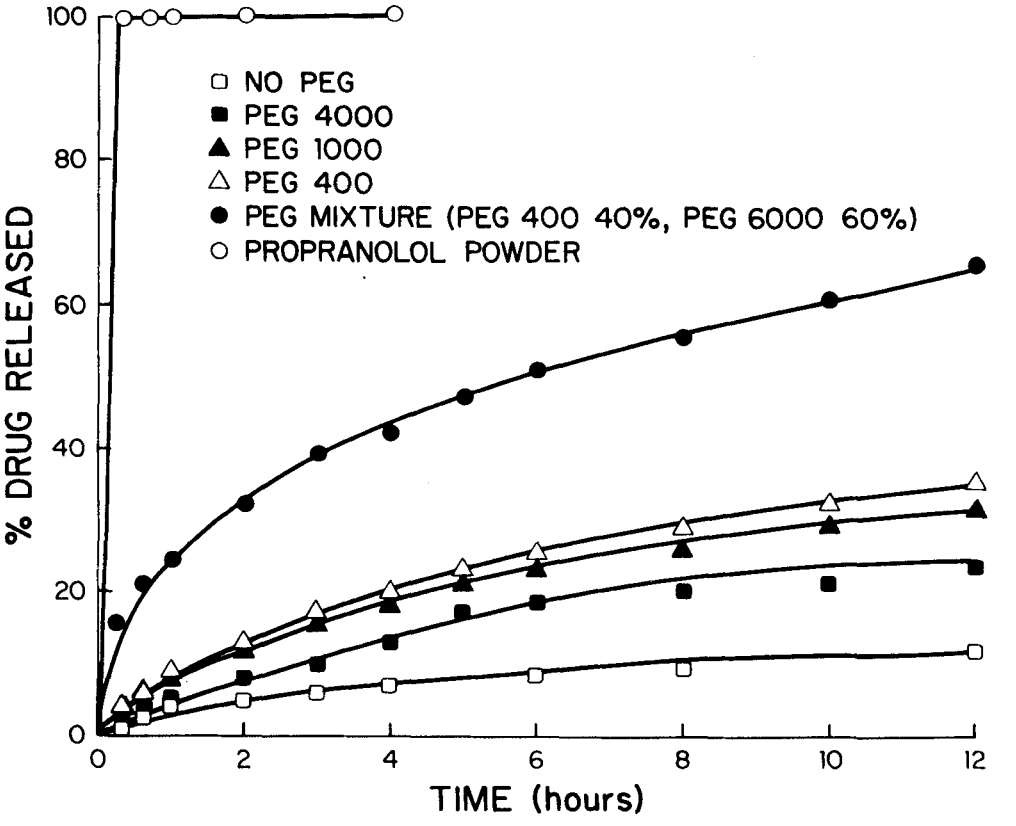

FIGURE 1

Effect of different types of PEG on dissolution profiles of propranolol microcapsules

concentration of PEG 4000 was used a wider distribution range and its average microcapsule size shifted toward the smaller size (Fig. 2). Except for one formulation containing the highest percent of PEG all microcapsules prepared by this method were almost monosized at 1300 um. The dissolution rate of propranolol also increased as the concentration of PEG 4000 increased (Fig.

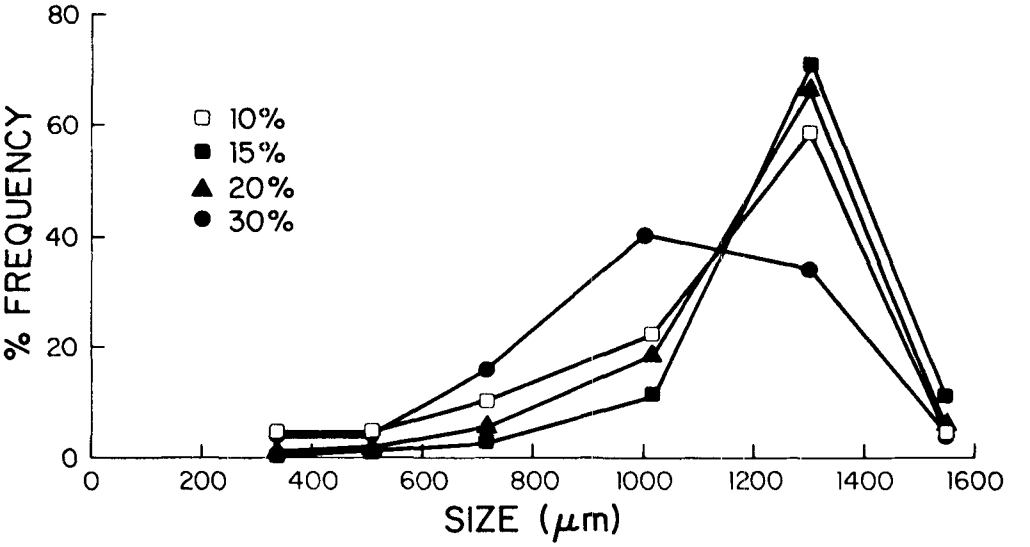

FIGURE 2

Effect of different concentrations of PEG 4000 on particle size distribution of microcapsules

3). As the concentration of PEG 4000 was increased from 15% to 30%, t_{50} decreased from 11.9 to 2.9 hours but, at concentrations of PEG 4000 less than 15%, t_{50} was more than 24 hours. This was due to the water soluble property of PEG which formed channels on dissolution and allowed the release of drug from the microcapsules.

Effect of Drug Particle Size

The particle size of propranolol used in the preparation of microcapsule were 44, 75 and 213.5 um. There is no significant influence of drug particle size on microcapsule size distribution and mean particle size of microcapsules obtained. This is in

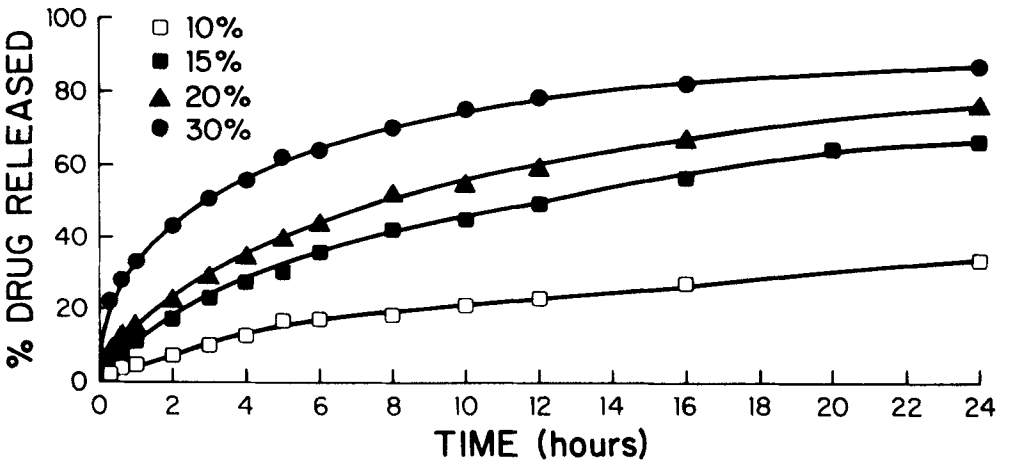

FIGURE 3

Effect of different concentrations of PEG 4000 on dissolution profiles of microcapsules

agreement with the results reported by Jalsenjak (9). The decrease in the dissolution rate of the drug from the microcapsules as the drug particle size in microcapsules increased (Fig. 4) was due to the decrease in surface area of drug in contact with dissolution media. Another factor which might also contribute to the fast dissolution of microcapsules containing fine powder drug is the thinner coating film compared to microcapsules containing drug crystals prepared with the same drug to polymer ratio of 3:3. Generally, small particles required more coating than large particles to achieve a given film thickness (10). It was reported that approximately 17.5 times as much coating was required to produce a film thickness of

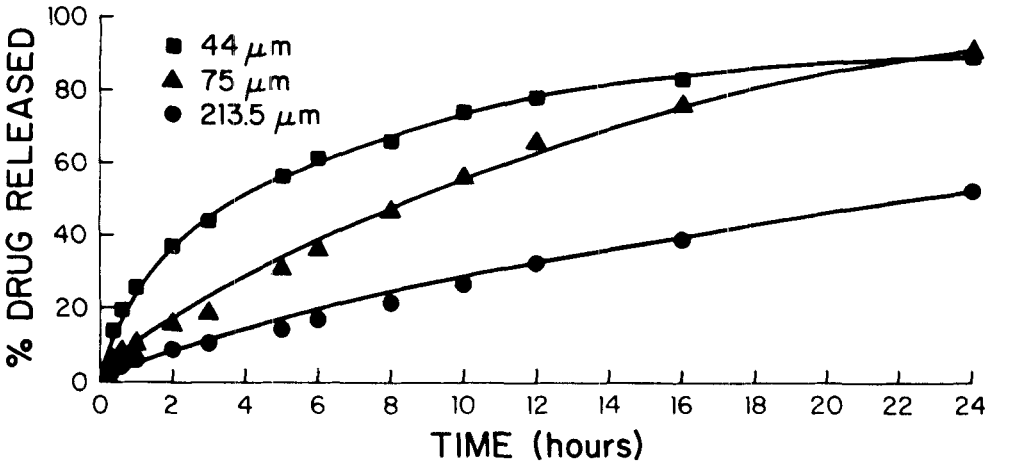

FIGURE 4

Particle size effect on dissolution profiles of microcapsules

0.1 mm when the particle diameter decreased from 1 mm to 0.074 mm (11).

A scanning electron micrograph of microcapsules obtained from fine powder drug (44 um) and crystal (213.5 um) are shown in Figures 5 and 6. The fine powder gave smooth spherical microcapsules whereas those made with drug crystals were irregularly shaped.

Effect of pH on dissolution rate

The previous results were all obtained using simulated intestinal fluid without enzyme (pH 7.3) and containing 0.02% of Tween 80 as dissolution medium. However, if the microcapsules are taken orally the pH of the gastric fluid will be lower than

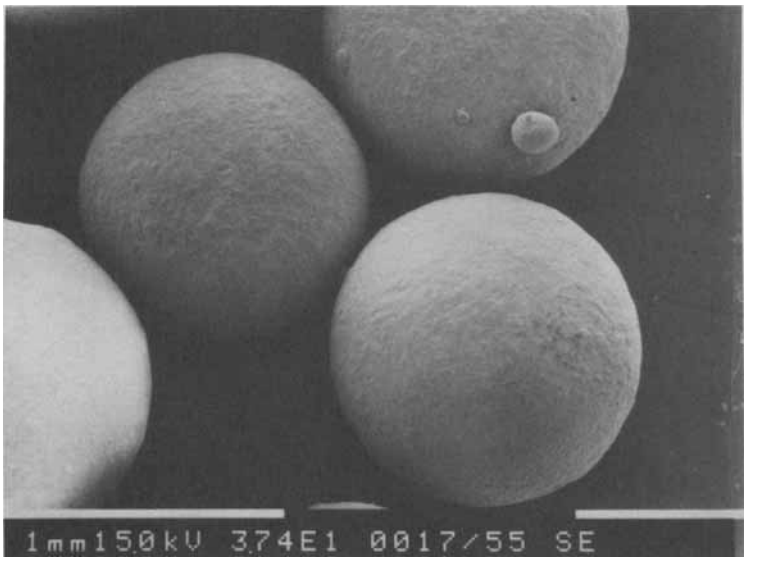

FIGURE 5

Electron micrograph of propranolol microcapsules containing 42.83% of fine powdered drug

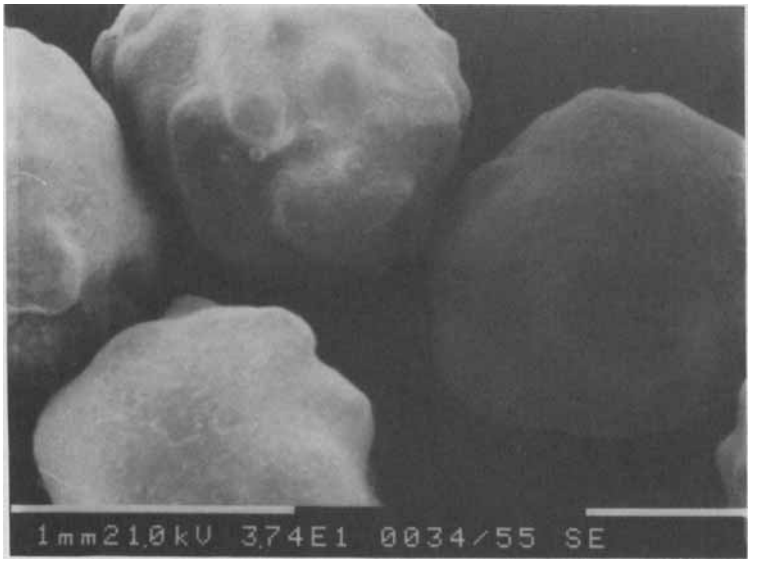

FIGURE 6

Electron micrograph of propranolol microcapsules containing 44.88% of drug crystals

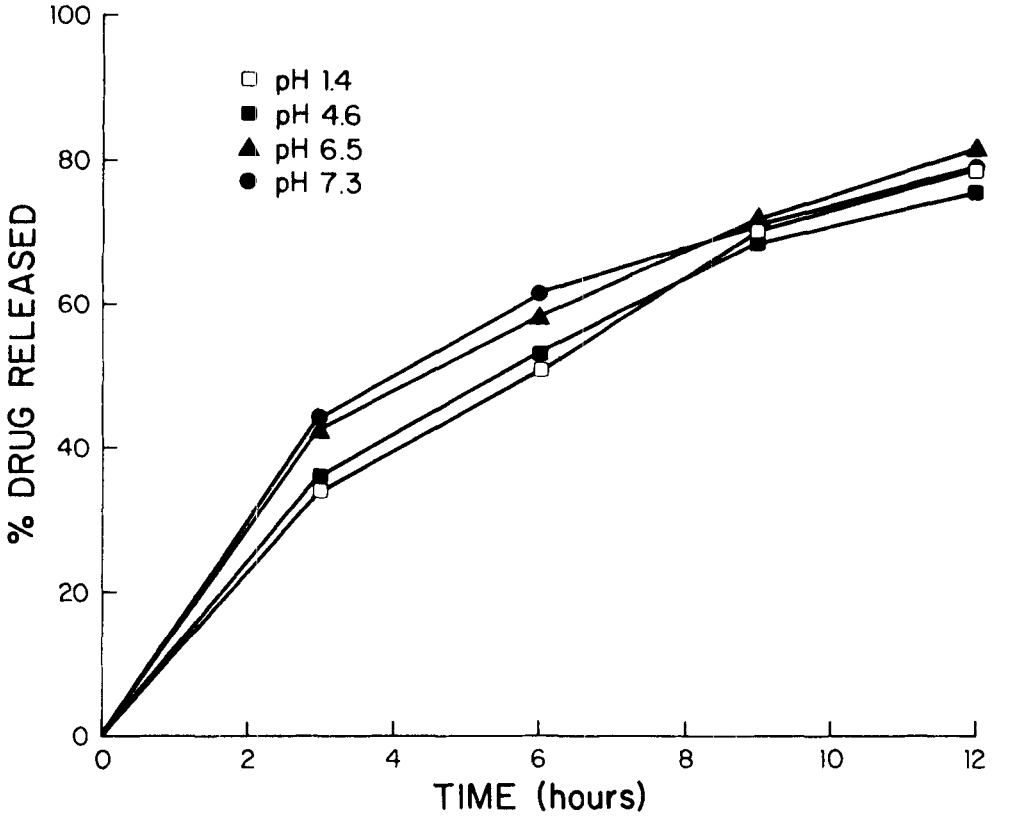

FIGURE 7

Dissolution profiles of propranolol microcapsules at different pH's

this. Therefore, dissolution was also studied at different pH's. The effect of the pH between 1.4 and 4.6 and between 6.5 and 7.3 were small and insignificant (Fig. 7). When the pH was increased from 1.4 to 7.3 a faster release was evident and t_{50} decreased from 5.9 hours to 4.0 hours respectively. The difference in the release rate was not significant after 9 hours of dissolution, where 70% of the drug had been released.

TABLE I

Microencapsulation Parameters

Formulation No.	Drug:Polymer Ratio	Type of PEG	Concentration of PEG (%)	Drug Loading % ± S.D.	t_{50} (Hours)
1	2:3	1000	10	33.40±0.08	>24.0
2	2:3	4000	10	34.03±0.10	>24.0
3	2:3	PEG Mixture	10	34.02±0.34	4.0
4	2:3	400	10	34.00±0.34	>24.0
5	2:3	4000	0	34.71±0.21	>24.0
6	2:3	4000	10	34.03±0.15	>24.0
7	2:3	4000	15	33.56±0.28	11.9
8	2:3	4000	20	32.29±0.27	7.9
9	2:3	4000	30	29.80±0.12	2.9
10	3[a]:3	4000	15	42.83±0.30	3.8
11	3[b]:3	4000	15	44.88±1.26	22.7
12	3[c]:3	4000	15	44.57±0.44	8.6

a: fine powder propranolol, 44 um
b: propranolol crystals, 213 5 um
c: propranolol crystals, 75 um

Table 1 shows microencapsulation parameters of at least two batches of each formulation. PEG types did not effect the drug loading but, when the concentration of PEG 4000 was varied from 0 to 30%, the drug loading decreased from 34.71 to 29.80%. The particle size of the drug to be encapsulated also effected the drug loading, larger particle size gave more fluctuation in drug loading.

It is logical to assume that one could obtain desired release characteristic of microcapsules through the control of

the drug particle size, using different types and/or concentrations of channelling agent (PEG). The process utilized is efficient, gives reproducible results and is not time consuming.

FOOTNOTES

1. Ruger Chemical Co. Inc., Irvington, NJ
2. Scientific Polymer Products, Ontario, NY
3. Knoll Fine Chemicals, New York, NY
4. Union Corbide Corp., Atlanta, GA
5. Spectronic 2000, Bausch and Lomb, Inc., Rochester, NY
6. Easy Lift Model, Hanson Research Corp., Northridge, CA

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