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Preparation and in vitro dissolution characteristics of propranolol microcapsules

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Summary

Propranolol hydrochloride was encapsulated with cellulose acetate butyrate by an emulsion non-solvent addition method to develop a controlled released dosage form. This process was efficient, reproducible and not time consuming. Different release characteristics were obtained by changing the drug-to-polymer ratio and varying the particle size of microcapsules. High drug-to-polymer ratio resulted in increased viscosity of the internal phase and increased microcapsule size and drug release rate. In vitro release into a simulated gastric fluid and simulated intestinal fluid showed slight pH-dependence.

Introduction

Controlled release drugs used for hypertension, angina pectoris and cardiac arrythmia have been developed and marketed both in oral and transdermal dosage forms. Advantages and disadvantages of the systemic absorption of drugs by transdermal methods and also controlled delivery using many sub-unit doses in oral dosage forms have been reviewed (Beckett, 1982).

Propranolol hydrochloride is a β-adrenergic blocking agent used in the treatment of hypertension (Oh et al., 1985), angina pectoris (Charlap et al., 1985) and cardiac arrhythmias (Morganroth et al., 1985). It is rapidly metabolized in man with a plasma elimination half-life of 2–4 h (Shand et al., 1970) or 4–6 h (Borgstrom et al., 1981). Because of its relatively short plasma half-life the drug is normally prescribed 2–4 times daily. Treatment for both hypertension and angina is long-term, therefore an effective controlled release dosage form of propranolol to be taken once or twice a day would be beneficial to the patient.

Several studies have been reported on pharmacokinetics of long-acting propranolol (McAinsh et al., 1978; Parker et al., 1982; Bottini et al., 1983; Lopez et al., 1984). Unfortunately, little information is available about the preparation of the dosage form. Long-acting propranolol prepared by pan coating propranolol-HCl microspheres containing about 60% drug and 40% microcrystalline cellulose, with a film of ethylcellulose and hydroxypropyl methylcellulose have been reported (McAinsh et al., 1979).

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Controlled release oral dosage forms can be fabricated as single-unit or multiple-unit doses. Single-unit preparations tend to follow food and are assumed to have a normal transit time through the small intestine of between 3 and 8 h. As the sub-unit of the multiple-unit formulations are distributed freely throughout the gastrointestinal tract, their transport may be less affected by transit time of the food (Benet, 1973). Studies of intestinal transit time of sub-unit doses were performed in ileostomy subjects. It was concluded that the gastrointestinal transit time of the subunits depended largely on their density rather than on their diameter, as the density increased from 1.0 to 1.6. This significantly increased the average transit time from 7 to 25 h (Bechgaard et al., 1978).

This work was undertaken to try to prepare propranolol microcapsules by an emulsion, non-solvent addition method. Other objectives were to study the effect of drug-to-polymer ratio on in vitro dissolution rate and on the density of the microcapsules. The dissolution profile of microcapsules at different pH's was determined.

Materials and Methods

Propranolol hydrochloride (Knoll Fine Chemicals) was milled for 16 h and sieved through a U.S. standard sieve of 270 mesh. Cellulose acetate butyrate (CAB) containing 17% butyrate, 29.5% acetyl and 1.5% hydroxyl (Scientific Polymer Products), polyethylene glycol (PEG) 4000 (Ruger Chemical Co.), simethicone (Union Carbide Co.), magnesium stearate, light mineral oil and all solvents were used as received.

Microencapsulation method

Microcapsules were prepared by emulsion, non-solvent addition, acetone was used as the polymer solvent, light mineral oil as the encapsulating vehicle and hexane as the non-solvent.

PEG 4000, 0.45 g, which was used as a plasticizer, was dissolved in 10 ml of warm acetone and 30 ml of 10% CAB in acetone was added. Various amounts of propranolol, either 1, 2, 3 or 4 g were added while the mixture was stirring. The mixture was then dispersed with stirring at 580 rpm into 200 ml of light mineral oil containing 0.5% magnesium stearate as a protective colloid and one drop of simethicone as an antifoaming agent. After the mixture was well dispersed, hexane was added dropwise to precipitate CAB-PEG, forming a matrix containing drug particles. After the microcapsules were formed, the liquid paraffin was decanted off and the microcapsules were washed with 50 ml of heptane 3 times and dried under reduced pressure at room temperature.

The microcapsules were sized through standard sieves, nos. 12, 14, 16, 20, 30, 40 and 60 mesh. The fraction of microcapsules remaining on each sieve was collected for further study.

Assay of propranolol

At least duplicates of accurately weighed amounts of around 20 mg of microcapsules were placed in 250 ml separatory funnels and 25 ml ethyl acetate added to dissolve the CAB coating material. Then 200 ml of 0.1 N HCl was added to dissolve the drug and the amount of propranolol in the aqueous phase was determined spectrophotometrically at 289 nm. The ingredients composing the microcapsule wall showed no absorbance at this wavelength.

In vitro dissolution

USP dissolution apparatus (Easy Lift, Hanson Research) was used for all the dissolution rate studies. Simulated intestinal fluid, pH 7.3, and simulated gastric fluid, pH 1.3 without enzyme but containing 0.02% polysorbate 80 were used as the dissolution media. Unless otherwise specified 100 mg of propranolol microcapsules of 14–16 mesh, average particle size of 1300 μm were transferred directly into 1000 ml of dissolution fluid maintained at 37°C and stirred with a paddle at a speed of 100 ± 1 rpm. Samples were taken at appropriate intervals and the amount of propranolol determined by measuring the UV absorbance at 289 nm. The sample was immediately returned to the dissolution tank. All dissolution studies were run at least in duplicates. Generally the results showed good reproducibility.

In the studies of the dissolution rates of propranolol microcapsules in different buffers of pH

1.4–7.3, sodium citrate buffer pH 1.4 and 4.6 and phosphate buffer pH 6.5 and 7.3 containing polysorbate 80, 0.02% were used as dissolution media. Microcapsule samples obtained from drug : polymer, 3 : 3 and 4 : 3 ratios having average particle size of 1300 μm were placed in the basket and rotated at a rate of 25 ± 1 rpm in 250 ml of dissolution media maintained at 37°C. This procedure was followed to approximate in vivo conditions. The dissolution media were changed at appropriate intervals to vary pH and to maintain sink conditions.

Density determinations

Densities of microcapsules were determined by the displacement method using a pycnometer and heptane which is a non-solvent for CAB. Each determination was carried out in at least triplicate.

Results and Discussion

A scanning electron micrograph of propranolol microcapsules is shown in Fig. 1. Propranolol crystals larger than 53 μm produced irregularly shaped microcapsules with rough surfaces. Smaller sized crystals produced spherical microcapsules with smooth surfaces, as seen in Fig. 1, therefore the propranolol was milled to reduce particle size before making microcapsules. Microcapsules prepared with different ratios of drug-to-polymer resulted in products with various particle size distribution (Fig. 2). As the drug-to-polymer ratio was increased from 1 : 3 to 4 : 3, the particle size distribution was shifted to the larger side. This was due to the increase in viscosity of the internal phase leading to more difficulty in dispersing into the external phase resulting in larger microcapsules.

In vitro dissolution of drug from microcapsules with different drug-to-polymer ratios in simulated intestinal fluid of pH 7.3 is shown in Fig. 3. As expected, drug-to-polymer ratio decrease resulted in greater dalays in the release rate due to the thicker coating membrane. This is in agreement with findings by several researchers (Jalsenjak et al., 1976; Mortada, 1982). The release of the drug from microcapsules of constant drug : polymer ratio of 3 : 3 is also illustrated in Fig. 4. The drug content of microcapsules size 1545 μm, 1300 μm and 1015 μm are 42.10, 42.02 and 42.05%, respectively. Since the drug content in all sizes is almost the same, it can be assumed that the rapid drug release of the smaller microcapsules is due to the greater surface area subjected to dissolution. Because of the narrow particle size distribution of microcapsules obtained, this study was carried out by using only three different particle sizes but from two different drug-to-polymer ratios of 3 : 3 and 4 : 3. A similar trend of increased release rate with decreased particle size was observed with microcapsules made from drug-to-polymer ratio of 4 : 3 (Fig. 4).

The time required for 50% of drug to be released from the microcapsules has been suggested as the most reasonable parameter to explain the

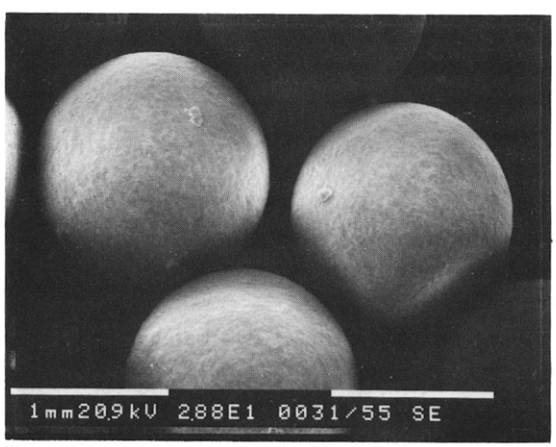


Fig. 1. Scanning electron micrograph of propranolol microcapsules.

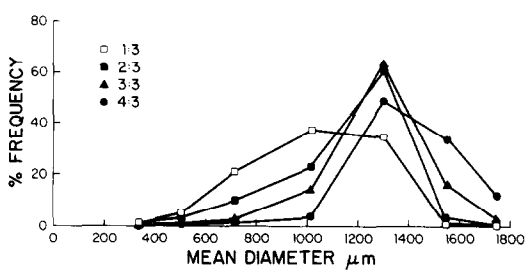


Fig. 2. Particle size distribution by weight percent of microcapsules prepared with different ratios of drug-to-polymer, 1 : 3, 2 : 3, 3 : 3 and 4 : 3.

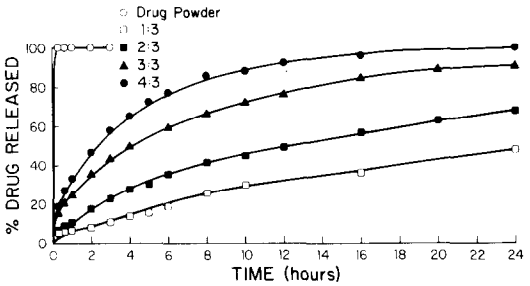


Fig. 3. Dissolution profiles of propranolol microcapsules (average size 1300 μm) prepared with different ratios of drug-to-polymer in simulated intestinal fluid of pH 7.3 compared to drug powder.

coating effect on the dissolution behavior of coated solid dosage forms (Wagner, 1971). Fig. 5 shows the time required for 50% of propranolol (t_{50}) to be released as a function of the mean diameter of the microcapsules. A good linear relationship was observed in both formulations prepared with drug : polymer ratios of 3 : 3 and 4 : 3.

The fraction of the drug released was plotted against time (Fig. 6) to test the adaptability of the release data to Baker and Lonsdale model (Baker et al., 1974). It was found that propranolol release process for the microcapsules obeyed the Baker and Lonsdale model well at a low drug : polymer ratio and deviated slightly at higher drug : polymer ratio after the drug had been released up to 85%. This indicated that the microcapsules exhibited a matrix type drug release.

Fig. 7 shows the release profile in simulated gastric fluid and simulated intestinal fluid. The

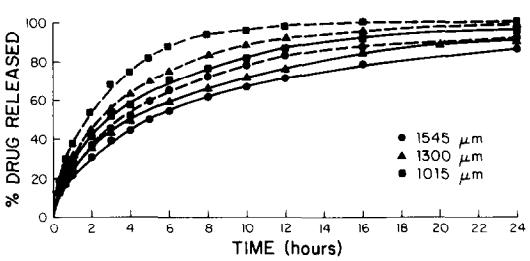


Fig. 4. Dissolution profiles of three different sizes of propranolol microcapsules in simulated intestinal fluid of pH 7.3. The drug-to-polymer ratios were 3:3 (solid Line) and 4:3 (broken Line).

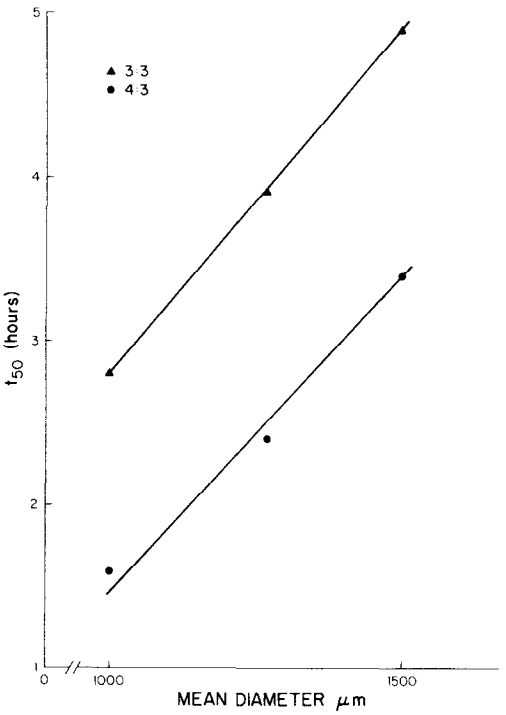


Fig. 5. Time required for 50% of propranolol to be released (t_{50}) from microcapsules as a function of mean diameter of the microcapsules.

drug was released faster in simulated intestinal fluid than in simulated gastric fluid due to greater solubility of cellulose acetate butyrate at higher pH. It is seen that the higher the drug-to-polymer ratio the greater the dissolution rate due to thinner coatings on the drug particles.

Since this product is intended for oral use, the release patterns were also studied throughout the pH range 1.4–7.3 which approximately corresponds to the conditions met in vivo. The release profile of microcapsules into changing pH of the dissolution medium is depicted in Fig. 8. Microcapsules prepared with drug : polymer ratios of 4 : 3 show 100% release after 24 hours and t_{50} of 2.8 h.

In these studies at least two batches of microcapsules of each formulation were prepared. Excellent reproducibility of the process with regard to drug loading, t_{50} and density of microcapsules was obtained (Table 1). Since propranolol hydrochloride is insoluble in the polymer solution, some

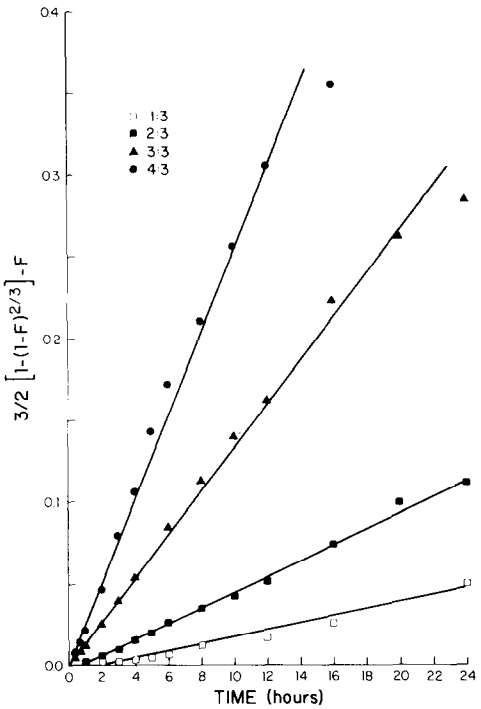
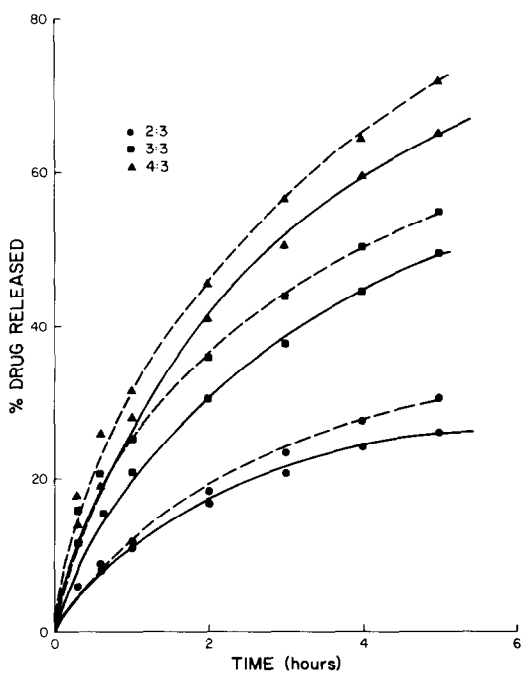


Fig. 6. Fraction of drug released from microcapsules plotted against time for formulation containing different ratios of drug-to-polymer of 1 : 3, 2 : 3, 3 : 3 and 4 : 3.



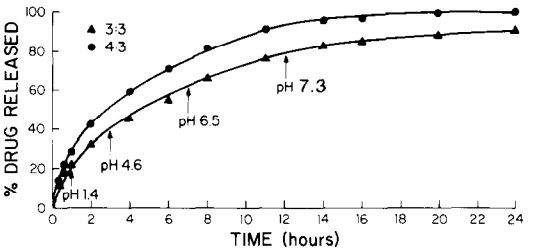


Fig. 8. Drug release profiles of propranolol microcapsules containing drug-to-polymer ratios of 3 : 3 and 4 : 3 into dissolution media with changing pH.

drug was lost when this mixture was poured into the mineral oil phase and subsequently emulsified. This resulted in the actual drug content of the microcapsules being less than theoretical values calculated from the drug : polymer ratios. The density of the microcapsules increased as the drug-to-polymer ratio decreased but there was no specific relationship. Another advantage of this process besides excellent reproducibility is that it is not time-consuming. Each batch can be prepared in less than 2 h.

TABLE 1

REPRODUCIBILITY OF PROCESS WITH REFERENCE TO DRUG LOADING, DENSITY AND t_{50}

Batch no.	Drug: polymer ratio	% Drug loading ± S.D.	Density ± S.D.	t_{50} (h)
1	1 : 3	20.37 ± 0.18	1.26 ± 0.08	> 24
2		20.52 ± 0.22	1.29 ± 0.02	> 24
3	2 : 3	33.17 ± 0.03	1.31 ± 0.05	12.0
4		33.71 ± 0.09	1.30 ± 0.05	10.6
5		32.66 ± 0.20	1.20 ± 0.03	12.3
6	3 : 3	41.95 ± 0.07	1.20 ± 0.05	4.2
7		41.88 ± 0.25	1.25 ± 0.03	4.6
8		42.22 ± 0.11	1.25 ± 0.06	3.4
9	4 : 3	48.13 ± 0.02	1.11 ± 0.03	2.4
10		48.77 ± 0.02	1.13 ± 0.05	2.2
11		48.45 ± 0.04	1.13 ± 0.06	2.3

←

Fig. 7. Dissolution profile of propranolol microcapsules containing drug-to-polymer ratios of 2 : 3, 3 : 3 and 4 : 3 in simulated intestinal fluid (broken lines) and simulated gastric fluid (solid lines).

Based on the results reported here, propranolol can be encapsulated in CAB and the desired release characteristics of this dosage form can be obtained by controlling drug-to-polymer ratio and by changing the particle size of microcapsules.

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