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Preparation of Substained-Release Microspheres of Phenylpropanolamine HCl and Their Release Characteristics

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Abstract□Sustained release microspheres containing phenylpropanolamine HCl (PPA) were prepared with acrylic polymer (Eudragit RL/RS) sand hydroxypropylmethylcellulose phthalate (HPMCP) using a emulsion-solvent evaporation method. Magnesium stearate was used a smoothing agent for preparation of microspheres. The microspheres obtained were very spherical and free-flowing particles. Scanning electron microscopy showed that microspheres have a smooth surface and a sponge-like internal structure.

The dissolution rate of PPA from the microspheres was dependent on the pH of dissolution media. PPA showed faster release in pH 1.2 solution than in pH 7.4 solution due to the solubility of PPA. Therefore we prepared new microspheres containing 5% (w/v) HPMCP in order to control the release of PPA. The release rate of PPA from these new microspheres was similar in pH 1.2 and pH 7.4 solution.

Keywords□Phenylpropanolamine HCl, sustained-release, microencapsulation, solvent evaporation method, Eudragit RL/RS, HPMCP, dissolution.

The main purpose of administering drug in controlled drug delivery system is to promote the therapeutic benefits while simultaneously minimizing undesirable side effects[1]. With controlled drug delivery systems, both unnecessarily high toxic concentrations and subtherapeutic levels can be avoided.

In the present study, we prepared sustained release PPA microspheres by using emulsion-solvent evaporation method. This method comprises dispersing drugs in the film forming wall material solution and then dispersed with mechanical stirrer into an immiscible vehicle to form an emulsion. As the solvent is evaporated, the droplets become more and more concentrated and nucleation takes place. Drug-loaded microspheres are thus produced[2-5].

Eudragit RL/RS as a matrix material is copolymer synthesized from acrylic acid esters with a low content of quaternary ammonium groups[6]. Microspheres with Eudragit RL/RS are one of the possible candidates for preparing controlled or sustained-release drug formulation[7]. PPA as a core drug is an indirectly acting sympathomimetic agent and used as treating a nasal decongestant and endogeneous obesity[8].

The aim of this study was to elucidate the possibility of manufacturing sustained-release microspheres in liquid media and to test their release characteristics. We also investigated the effect of other factors on the formation and properties of these microspheres.

EXPERIMENTAL METHODS

Materials and apparatus

Phenylpropanolamine HCl (PPA) was supplied by Whan In Pharm. Co. Eudragit RL/RS (Röhm Pharma Co.) and hydroxypropylmethylcellulose phthalate (Shin-Etsu) were used as a matrix materials. Magnesium stearate was used as a smoothing agents. Acetone (Duksan Chem) and light mineral oil (Witco Sonneborn Div., Holland) were used as first and second dispersion medium, respectively. n-Hexane was used as a washing solvent. All other chemicals used were of reagent grade and used without further purification. Six-baffled cylinderical vessel (inside diameter and height are 7.5 cm and 16 cm, respectively) and mechanical stirrer with screw-type six blades (5 cm diameter) were used.

Preparation of phenylpropanolamine HCl microspheres

Three grams of dried powder (Eudragit RL/RS and HPMCP) were added to 30 m*l* of acetone in a glass vessel and dissolved completely. PPA and magnesium stearate were added, and the mixture was stirred in a water bath at 10°C over 20 min. The above solution was poured into 150 m*l* of light mineral oil with 1.5 m*l* of Span 80 and maintained at 30°C with

Table I. Operation conditions of the microcapsulation

1. Setting conditions
   1) The size of vessel
      6-baffled cylinderical form; 7.5 cm in diameter, 16 cm long and 400 m*l* in volume
   2) Agitator
      6-blade screw type impeller, 6 cm in diameter
   3) The volume of suspending liquid
      150 m*l* of mineral oil
   4) The weight of solid
      6 g (phenylpropanolamine HCl, Eudragit and HPMCP)
   5) Agitation speed
      600 rpm for 4 hrs
2. Variable conditions
   1) The proportion of Eudright RL and Eudragit RS
      1:0, 1:1, 1:3, 0:1
   2) The amounts of Magnesium stearate
      0, 5, 10 w/w %

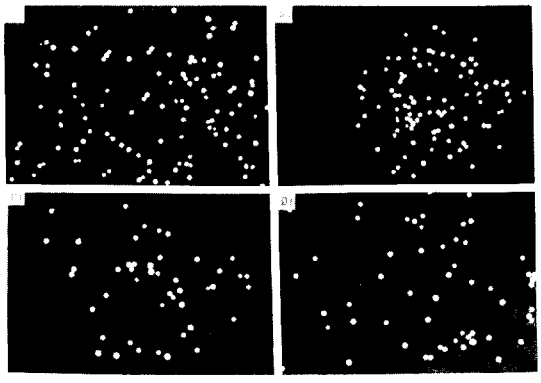

Fig. 1. Photographs of PPA microspheres prepared with Eudragit RL and RS.
A) Eudragit RL:PPA (1:1)
B) Eudragit RS:PPA (1:1)
C) Eudragit RS:PPA (1:1) with 5% Mg.stearate
D) Eudragit RS:PPA (1:1) with 10% Mg.stearate
PPA: phenylpropanolamine

stirring at 600 rpm for 4 hrs. During this time, acetone used as a solvent of polymer was removed completely by evaporation. The microspheres were sepa-rated by filtration, washed three times with 50 m*l* of n-hexane and allowed to dry in a desiccator overnight.

Dissolution studies

The rotating paddle method as described by the USP XXI was used to determine the release of drug[9]. 500 m*l* of dissolution medium (pH 1.2 hydrochloric acid solution or pH 7.4 phosphate buffer solution) was introduced into a beaker and stirred at 100 rpm.

An accurately weighed amount (500 mg) of PPA microspheres was gently spread over the surface of the dissolution medium at 37°C. At appropirate intervals, 5 m*l* samples were withdrawn using a pipette. The solution was filtered through a membrane filter (pore size: 0.45 μm) and filtrate taken for analysis.

An equivalent volume (5 m*l*) of fresh dissolution medium was added to keep the volume of dissolution medium in the beaker constant (500 m*l*). The released PPA concentration was determined spectrophotometrically by measuring the absorbance at 257 nm. The release results were plotted as percentage of PPA extracted into the dissolution medium from the microspheres versus time.

Physical measurement

Sieve analysis: Particle size distribution was evaluated by a sieve analysis using 16-, 18-, 20-, 25 mesh screen and pan. The charge weight on the 7.5 cm diameter screen was 10g.

Microscopic studies: The surface and cross-sectional characteristics of microspheres were studied by scanning electron microscopy. The surface and size of microspheres were observed on enlarged photography.

RESULTS AND DISCUSSION

Operating conditions

In preliminary experiment, the various operating conditions were selected (Table I). Formation of microspheres took place in the specially designed cylinderical vessel which have smooth surfaces and free from sharp corners so that no pockets would be available in which the solid could be accumulate. It is important to select the shape of blade and agitator speed properly to prepare microspheres with narrow size distribution. Particle size and size distribution can be controlled according to the agitation speed. In this experiment, agitation was carried out at 600 rpm for 4 hrs. Generally, as the stirring speed is more rapid, the viscosity of a polymer is high and the amount of surfactants is much more, the size of microspheres obtained become smaller.

The concentration of coating material in solvent, which may vary according to the combination of the coating material and the solvent, may be optionally selected so that the viscosity of the solution may be within such a range as to permit emulsifying thereof

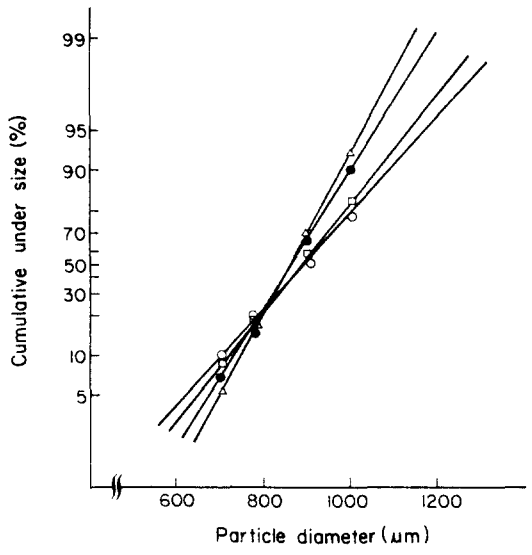

Fig. 2. Particle size distribution of microspheres.
●, Eudragit (RL:RS = 3:1):PPA = 1:1;
○, Eudragit (RL:RS = 1:0):PPA = 1:1;
△, Eudragit (RL:RS = 1:1):PPA = 1:1;
□, Eudragit (RL:RS = 0:1):PPA = 3:1.

in fine droplets in a vehicle. Contents of soild are generally acceptable from about 2.5 to 25 w/v percents. The first dispersion which we made has 10 w/v percents. If the concentration of the first solution is too high, aggregated or large microspheres are produced.

Fig. 1 illustrates the physical appearances of the resultant PPA microspheres which were made by this process. They were very spherical and free-flowing particles. Size distributions of these microspheres were represented in Fig 2. There were no great variances in size distribution among microspheres which have different ratios of coating material, Eudragit. Mean diameter of these microspheres is 0.883 mm.

Dissolution studies

The release of microspheres showed biphasic process. The first phase was due to burst out effect and the second phase was due to the diffusion through the pores in the microspheres.

The release profiles of PPA from microspheres with varying ratio of Eudragit RL and Eudragit RS were shown in Fig 3. Since Eudragit RL is more freely permeable than Eudragit RS, the microspheres with the higher percentage of Eudragit RL showed faster release profile in pH 7.4 medium.

In this experiment, Magnesium stearate was used as an additive. The addition of a small quantity of

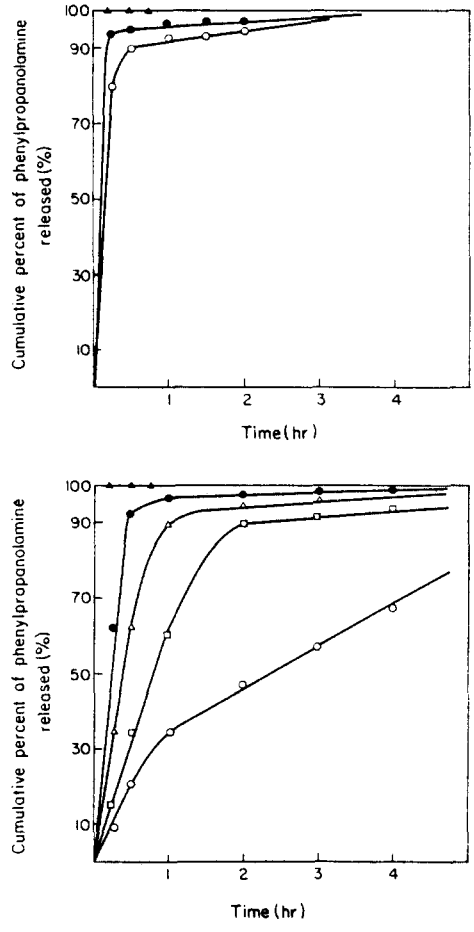

Fig. 3. Cumulative percent of PPA released from microspheres prepared with Eudragit RL and RS in pH 1.2 and in pH 7.4 medium.
A) In pH 1.2
▲, PPA;
●, Eudragit RL:PPA = 1:1;
○, Eudragit RS:PPA = 1:1.
B) In pH 7.4
▲, PPA;
●, Eudragit (RL:RS = 1:0):PPA = 1:1;
△, Eudragit (RL:RS = 1:1):PPA = 1:1;
□, Eudragit (RL:RS = 1:3):PPA = 1:1;
○, Eudragit (RL:RS = 1:3):PPA = 1:1.

magnesium stearate reduced the stickiness of these microspheres and made the surface of the matrix smooth. Because of hydrophobicity of magnesium stearate, it retarded the permeability of matrix and showed slower release with increasing amount of magnesium stearate (Fig. 4).

According to the above release profiles, microsphere which we had prepared in various ratios had

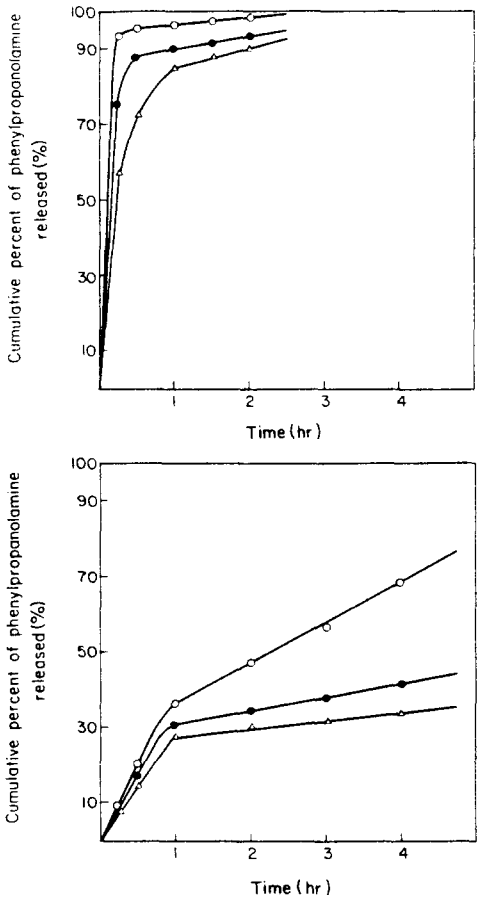

Fig. 4. Effect of Mg. stearate on the release of PPA from Eudragit RS-PPA (1:1) microspheres in pH 1.2 and pH 7.4 medium.

A) In pH 1.2

○, Eudragit RS-PPA microspheres without Mg. stearate; ●, Eudragit RS-PPA microspheres with 5% Mg. stearate; △, Eudragit RS=PPA microspheres with 10% Mg. stearate.

B) In pH 7.4

○, Eudragit RS-PPA microspheres without Mg. stearate; ●, Eudragit RS-PPA microspheres with 5%, Mg. steastar; △, Eudragit RS-PPA microspheres with 10% Mg. stearate.

faster release patterns in pH 1.2 than pH 7.4 solution (Fig. 3). Eudragit RL/RS substances are insoluble in water and digestive juices, but they are capable of swelling and are permeable, which means that active ingredients are released by diffusion and their permeability is independent of pH. Since Eudragit-PPA microspheres produced by solvent evaporation method have homogeneous matrix and some pores,

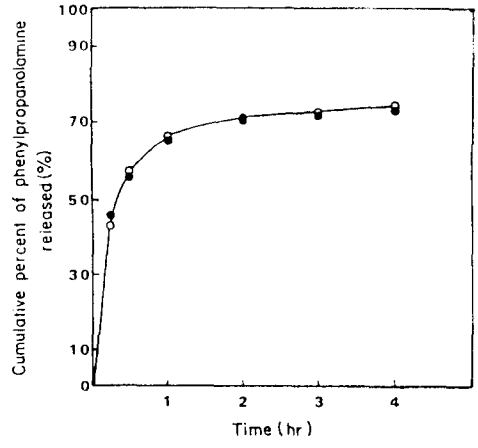

Fig. 5. Cumulative percent of PPA released from Eudragit-HPMCP microspheres in pH 1.2 and pH 7.4 medium.

○, pH 1.2; ●, pH 7.4.

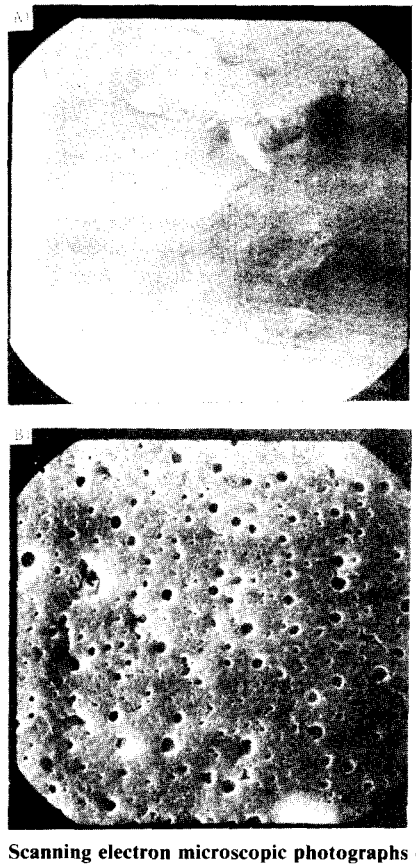

Fig. 6. Scanning electron microscopic photographs of Eudragit RS-PPA (1:1) microspheres before and after release test.

A) before, B) after

the release of drug from microspheres depends on the diffusion from the pores in the microspheres. Therefore, faster release profiles in pH 1.2 solution were due to the solubility and diffusivity of PPA itself.

In order to control the release of PPA in simulated gastric juice, we prepared new microspheres containing 5% (w/w) HPMCP and Eudragit RS. HPMCP is one of the most popular enteric coating materials. It dissolves at a lower pH (at 5 to 5.5) than CAP or acrylic copolymers, and these solubility characteristics may result in higher bioavailability of some specific drugs[10]. The release patterns of PPA from new microspheres were similar in pH 1.2 and pH 7.4 solution (Fig. 5).

In pH 1.2 solution, release of PPA from new microspheres was very retarded in comparison with Eudragit RS-microspheres. On the contrary, the release of PPA in pH 7.4 solution was a little faster than that from Eudragit RS-microspheres. Since HPMCP in the matrix was dissolved fast in pH 7.4 solution, there are many pores in the matrix. Therefore, the release of PPA from the microspheres was faster than that from the microspheres without HPMCP. The photographs of microspheres before and after release studies were shown in Fig 6. Generally microspheres had a smooth surface before release test, but many pores were created on the surface of microspheres after refease test.

ACKNOWLEDGEMENT

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