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COMMUNICATION

The Effects of Plasticizers on the Release of Metoprolol Tartrate from Granules Coated with a Polymethacrylate Film

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ABSTRACT

For coating metoprolol tartrate granules, coating dispersions of Eudragit RS 30 D containing 6%, 12%, or 18% (based on polymer weight) of one of the following plasticizers were used: polyethylene glycol 400 (PEG400), propylene glycol (PG), tributyl citrate (TBC), and triethyl citrate (TEC). The release of metoprolol tartrate from these coated granules was determined at pH 1.2 and 7.4. Slower release resulted from the use of each plasticizer, being slower with increasing concentration of the plasticizer. Release was faster with the more water soluble PEG400 and PG than with TBC and TEC. pH-dependent release was observed with PEG400, PG, and TBC, while TEC gave pH-independent release of drug.

INTRODUCTION

Plasticizers are used in polymeric coating dispersions to optimize the mechanical and other properties of the film. Such properties include permeability, solubility, and adhesiveness and mechanical properties such as flexibility and brittleness (1,2). For the plasticizer to be effective, it must be compatible with the other ingredients in the dispersion and must also be permanent, both initially and during storage (1–3).

Three types of plasticizers are commonly used: (*a*) polyols (e.g., glycerin, propylene glycol [PG], and polyethylene glycols [PEGs]); (*b*) fixed oils (e.g., castor oil and oleic acid); and (*c*) organic esters like triacetin, tributyl citrate (TBC), and triethyl citrate (TEC).

Some plasticizers are completely miscible with water (e.g., glycerin, PEG400); these will be compatible with aqueous systems. Others are not miscible with water (e.g., castor oil).

Plasticizers may be classified as internal or external. The internal plasticizers modify the chemical nature of the basic polymer, thereby altering the physical properties. The external plasticizers change the mechanical and adhesive properties of the film.

Plasticizers are known to affect, among other properties, film permeability (4–7), elasticity and tensile

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strength (8), adhesion of the film (8), viscosity of the solution (9), and the glass transition temperature of the polymer (10). Several researchers have studied the effects of plasticizers when used with various grades of Eudragits (3,5,11–16). Dyer and coworkers evaluated, in part, the effect of plasticizers on drug release from film-coated pellets (16).

The aim of the current work was to determine and compare the effects of 6%, 12%, and 18% (based on polymer weight) of four plasticizers (PEG400, PG, TBC, and TEC) on the release of metoprolol tartrate from granules coated with a Eudragit RS 30 film. The dissolution of the coated granules was compared at pH 1.2 and 7.4.

Metoprolol tartrate is a white crystalline compound that is freely soluble in water (17). Eudragit RS 30 D is an aqueous dispersion of ammonio methacrylate copolymer and has a polymer content of 30%. The polymer is insoluble in aqueous media in the physiological pH range (18,19).

EXPERIMENTAL

Materials

Povidone (PVP K-30) was received from BASF (Mount Olive, NJ); metoprolol tartrate was supplied by Cipla Pharmaceuticals (India). Spray-dried lactose monohydrate was supplied by Foremost (WI). Eudragit RS 30 D was obtained from Rohm Tech, Incorporated (Malden, MA); FD&C blue 2 was from Lake; talc was supplied by Whittaker Clark and Daniels (South Plainfield, NJ). Tributyl citrate, triethyl citrate, polyethylene glycol 400, propylene glycol, and simethicone were obtained from Sigma Chemical Company (St. Louis, MO).

Equipment

The equipment used were the Robot Coupe RSI 10V mixer/granulator (Jackson, MS), Key Industries Rotary Granulator (Stokes 43A), Colton model 2433-E tray dryer, Aeromatic fluid bed coater/dryer (Aeromatic AG), Van Kel dissolution apparatus, and an ultraviolet/visible (UV/Vis) spectrophotometer (Beckman DU 640).

Method

Preparation of Metoprolol Tartrate Granules

The 18–25 mesh granules were made from 5% metoprolol tartrate, 7.5% povidone, and 88.5% lactose. The weighed materials were charged into the 3-L bowl of the Robot Coupe mixer/granulator. The powders were premixed for 45 sec at 1500 rpm, forward, and granulated with approximately 300 ml of purified water. The wet granulation was dried at room temperature for 24 hr to a loss on drying (LOD) of less than 1%. The dried granules were then passed through 18- and 25-mesh screens, and the granules between 18 and 25 mesh in size were used.

Preparation of Coating Dispersion

The aqueous coating dispersion was prepared with 166 g Eudragit RS 30 D in a stainless steel beaker. The required amount of plasticizer to give 6%, 12%, or 18% of the polymer weight was added, and the mixture was stirred for 10 min. The talc, pigment, and simethicone were added, and the dispersion was stirred for 5 min.

Coating of Granules

The granules were coated in the fluid bed coater/dryer at an application rate of 5 g/min using the following coating conditions: inlet temperature 40°C, atomizing pressure 1.0 bar, outlet temperature 25°C, load (uncoated granules) 100 g, particle size range 18–25 mesh, spray rate 5 g/min, coating time 60 min, and drying time 2 min.

After spraying the coating dispersion, the coated granules were dried for an additional 2 min in the fluid bed coater/dryer.

Dissolution Testing

The coated granules, 800 mg, were tested in 1000 ml 0.1 N hydrochloric acid or pH 7.4 phosphate buffer using USP apparatus 1 at 100 rpm and at 37°C ± 0.5°C. Five ml of fluid were collected at each test interval and replaced with 5 ml of fresh medium. The samples were analyzed by UV spectroscopy at 271 nm.

RESULTS AND DISCUSSION

The uncoated granules and the granules coated with Eudragit RS 30 D film without plasticizer released the metoprolol tartrate within 5 min. Slower dissolution resulted when each plasticizer was added, with the release becoming slower with increasing plasticizer concentration.

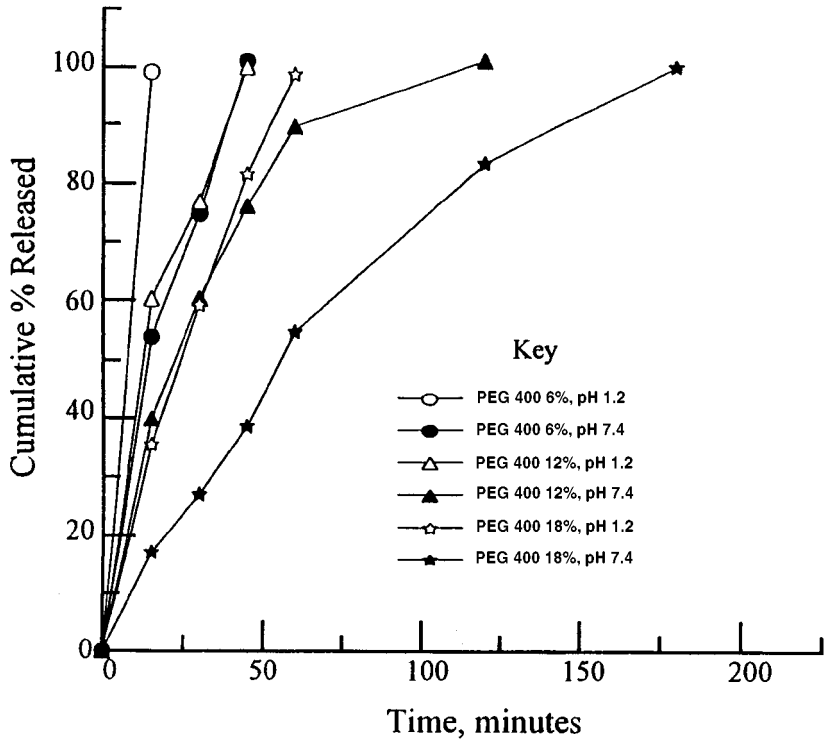

Figure 1. The release of metoprolol tartrate at pH 1.2 and 7.4 from granules coated with Eudragit RS 30 D film containing 6%, 12%, or 18% PEG400 as plasticizer.

Without coating, the very soluble metoprolol tartrate was released very quickly from the porous granules. With no plasticizer, the Eudragit RS 30 D film was brittle, and the dissolution medium would penetrate easily, giving fast dissolution results. The mechanical properties of the film improved with the addition of a plasticizer, and as more plasticizer was added, the film formed a better barrier and prevented the rapid penetration of the dissolution medium. That resulted in a slower dissolution rate as the concentration of each plasticizer increased, as seen in Figs. 1–4.

The PEG 400 and PG are readily water soluble and are therefore incompatible with the insoluble Eudragit RS 30 D polymer system. As a result, the mechanical properties of the film were not as good as the films formed from dispersions containing TBC and TEC, which are less water soluble and are more compatible with the polymer system. As seen in Figs. 1–6, the release of metoprolol tartrate from the granules coated with dispersions containing TBC and TEC was slower than was observed with granules coated with dispersions containing the less compatible, but more water soluble, PEG400 and PG. The more water-soluble plasticizers PG and PEG 400 would create channels, allowing more rapid penetration of the dissolution medium. This observation underscores the need for a careful selection of the plasticizer in a coating system to ensure compatibility with the polymer system and to obtain the desired release profile.

With PEG400, PG, and TBC, the dissolution was pH dependent at all the concentrations of plasticizer studied, being slower at pH 7.4 than at pH 1.2 (Figs. 1–4). With TEC, the dissolution was not pH dependent at any of the concentrations studied.

Eudragit RS 30 D is an ammonio methacrylate copolymer consisting of polymerized copolymers of acrylic acid and methacrylic acid esters with quaternary ammonium groups. Metoprolol tartrate is soluble in the concentration of the plasticizer and the pH range studied. The pH dependence, therefore, is attributed to the polymer. This polymer is insoluble in aqueous media at the physiological pH range at which it is expected to be pH independent. However, it becomes permeable to drugs as it hydrates and swells due to the presence of the quaternary ammonium groups. In pH 7.4 buffer, these quaternary

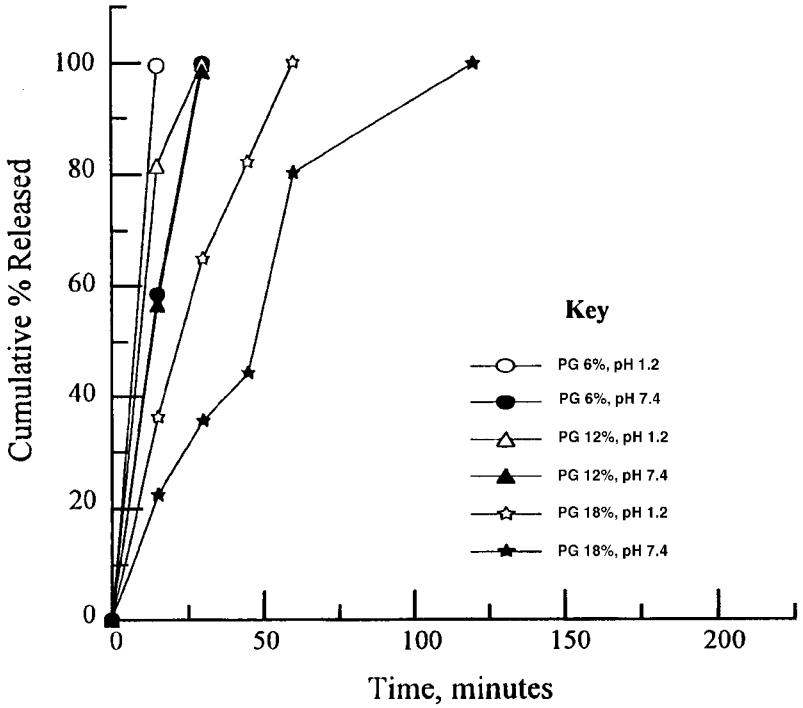

Figure 2. The release of metoprolol tartrate at pH 1.2 and 7.4 from granules coated with Eudragit RS 30 D film containing 6%, 12%, or 18% propylene glycol as plasticizer.

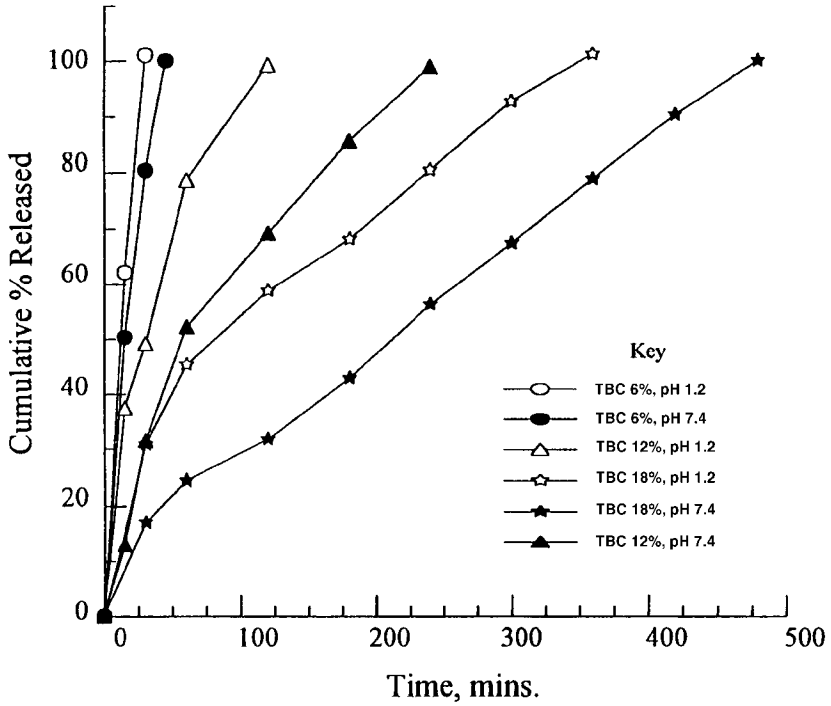

Figure 3. The release of metoprolol tartrate at pH 1.2 and 7.4 from granules coated with Eudragit RS 30 D film containing 6%, 12%, or 18% tributyl citrate as plasticizer.

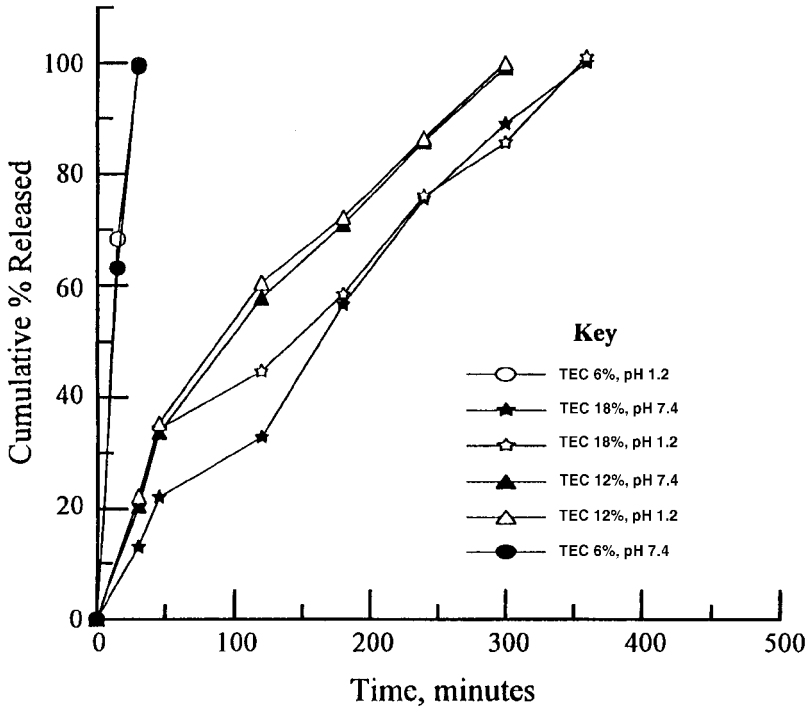

Figure 4. The release of metoprolol tartrate at pH 1.2 and 7.4 from granules coated with Eudragit RS 30 D film containing 6%, 12%, or 18% triethyl citrate as plasticizer.

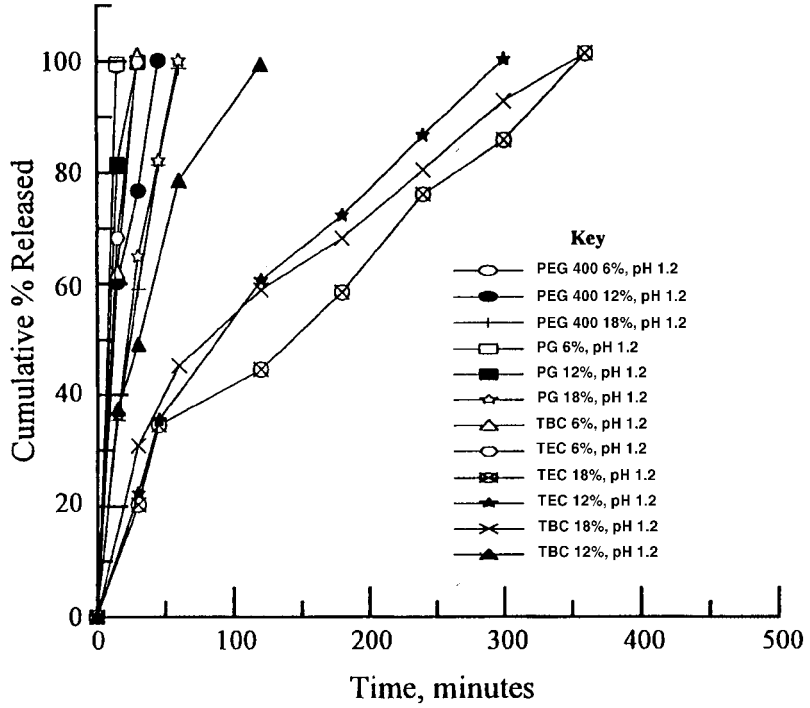

Figure 5. The release of metoprolol tartrate at pH 1.2 from granules coated with Eudragit RS 30 D film containing 6%, 12%, or 18% PEG400, propylene glycol, tributyl citrate, or triethyl citrate as plasticizer.

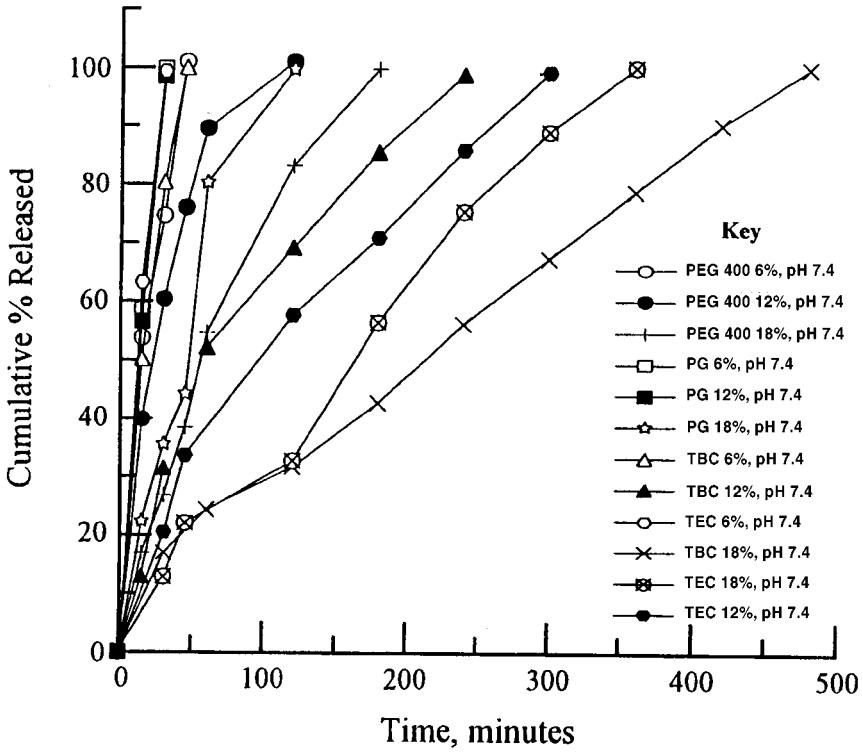

Figure 6. The release of metoprolol tartrate at pH 7.4 from granules coated with Eudragit RS 30 D film containing 6%, 12%, or 18% PEG400, propylene glycol, tributyl citrate, or triethyl citrate as plasticizer.

groups would exchange anions with the buffer species, affecting the rate and extent of hydration and the dissolution rate.

CONCLUSION

The type and concentration of plasticizer affected the release of metoprolol tartrate from the granules. In each case, the addition of the plasticizer resulted in slower dissolution and release of the metoprolol tartrate. The dissolution became slower with increasing concentration of plasticizer and the resulting improvement of the film. The slower release was more significant with TBC and TEC, which are more compatible with the polymer system, than with the more water soluble and less compatible PEG400 and PG. pH-dependent drug release was observed with PEG400, PG, and TBC, but not with TEC.

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