DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(1), 111-118 (1994)

CONTROLLED DRUG DELIVERY OF pH DEPENDENT SOLUBLE DRUG-PINDOLOL

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ABSTRACT

Pindolol, a pH dependent soluble beta adrenoceptor blocker has been formulated into a controlled drug delivery system. Drug pellets were prepared by extrusion - spheronization technique. These were coated with different retardant polymers, namely ethylcellulose and Eudragit RS 100. The effect of different variables such as coating level and pH of dissolution medium have been studied. Drug release from pellets were found to be influenced by the pH of the dissolution medium. A flux release of the drug in the acidic buffer was observed from pellets coated with these polymers. To avoid this flux, a top coat using different pH sensitive polymers, namely Hydroxypropylmethyl cellulose phthalate (HPMCP 55) and Eudragit S 100 was successfully attempted and the drug release from the pellets was modified.

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INTRODUCTION

There are various problems associated with the formulation of pH dependent soluble drugs because of their inherent property which affect the release from the pellets[1]. Pindolol[2,3] a beta adrenoceptor blocking drug, exhibits a very high solubility in the gastric pH but the absorption would be minimal because of drug ionization. It is imperative that a controlled release formulation should have a uniform release pattern at the different sites of the gastrointestinal tract over the period of dosing[4]. The present study reveals the systematic development of modified multi unit dosage forms of Pindolol and the optimization of the in vitro drug release to the therapeutic need.

MATERIALS

Pindolol (Sandoz Ltd., India), Polyvinylpyrrolidone-Kollidon K 30 (BASF, India), Eudragit RS 100 and Eudragit S 100 (Rohm Pharma, Germany) Ethylcellulose - 14 cps (BDH, India), Hydroxypropylmethyl cellulose phthalate 55 NF (Shin-Estu Chemicals Japan), Avicel PH 101 (FMC Corpn., Philadelphia), Diethyl phthalate (Loba chemie India), Triacetin (Aldrich-chemie, Steinheim).

All ingredients were used as supplied and reagents were of analytical grade.

METHODS

Development of Drug Cores by Extrusion-Spheronization :

Pindolol and Avicel PH 101 (10:90) were dry blended and granulated using 2% w/v solution of PVP (K-30) and then extruded & spheronized (Q-230 Fuji Paudal spheronizer). The processing conditions were as follows:

Extrusion speed - 23 rpm, Screen size - 0.8 to 1.2 mm,
Spheronizer speed - 950 rpm, Spheronization time - 5 min,
Temperature and duration of drying - 50°C for 4 hours.

Polymer Coating of Drug Cores :

The drug cores were coated with polymer at various levels by pan coating technique. The compositions of the polymer solutions are described below.

Retardant Polymer Solutions			
Ethylcellulose	- 3.5 g	Eudragit RS 100	- 5g
Diethyl phthalate	- 0.35g	Diethyl phthalate	- 0.5g
Solvent system	- 100 ml	Solvent system	- 100 ml
pH Sensitive Polymer Solutions			
HPMCP 55	- 5g	Eudragit S 100	- 5g
Triacetin	- 0.5g	Diethyl phthalate	- 0.5g
Solvent system	- 100 ml	Solvent system	- 100 ml

The Solvent system in all the cases were same and consisted of isopropyl alcohol : dichloromethane (1:1).

Drug Release Studies from Pellets:

The in vitro drug release studies were carried out using USP XXII dissolution apparatus, type I, at 37± 0.5°C and speed of 100 rpm in buffers of pH 1.2, pH 4.5 and pH 7.2 using pellets equivalent to 15 mg pindolol with withdrawal of samples at definite intervals of time. The drug content was determined spectrophotometrically at 264 nm.

RESULTS AND DISCUSSION

Drug Release Pattern of Pellets:

Figures 1 & 2 reveal the dissolution profiles of spheronized pellets with and without retardant polymer coating in pH 7.2. The plain spheronized pellets showed a sustained drug release in pH 7.2, probably because of insoluble matrix formation by the diluent Avicel PH 101 and the drug release from this matrix could be described using the pore controlled release mechanism[5]. In the case of pellets coated with retardant polymers (ethycellulose (0.5%) and Eudragit RS 100 (1.5%)), the release was found to be controlled for 12 hours in pH 7.2. However, it was evident that by buffer change method (Fig. 3 & 4) at polymer levels where successful drug retardation could be

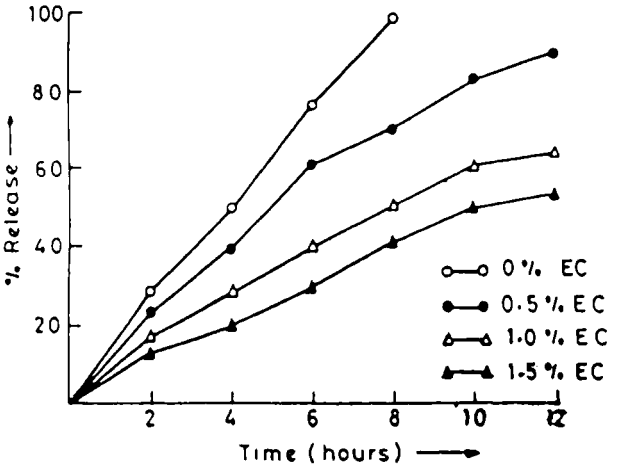

Figure 1: Effect of ethylcellulose coating on Pindolol release from spheronized pellets in pH 7.2.

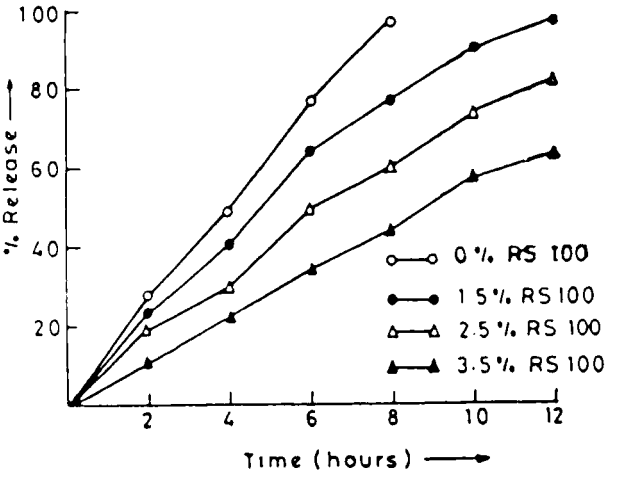

Figure 2: Effect of Eudragit RS 100 coating on Pindolol release from spheronized pellets in pH 7.2.

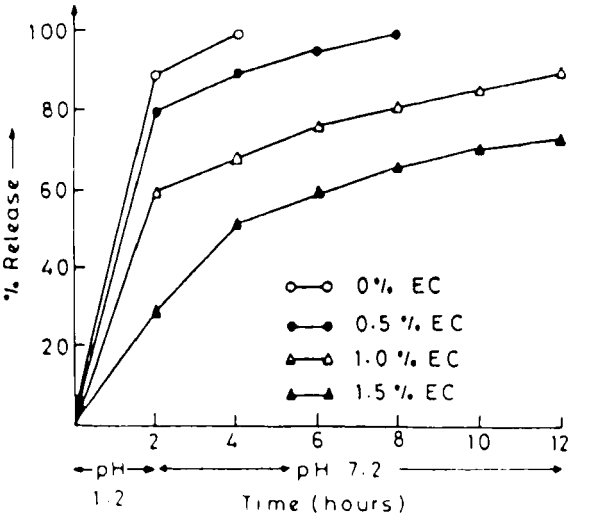

Figure 3: Pindolol release from spheronized, ethyl-cellulose coated pellets subjected to buffer change.

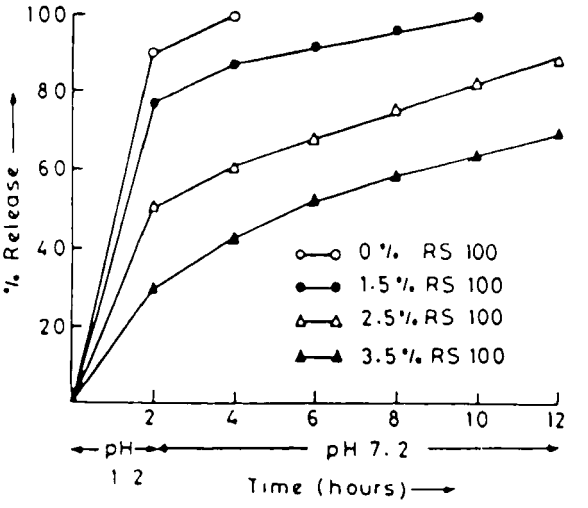

Figure 4: Pindolol release from spheronized, Eudragit RS 100 coated pellets subjected to buffer change.

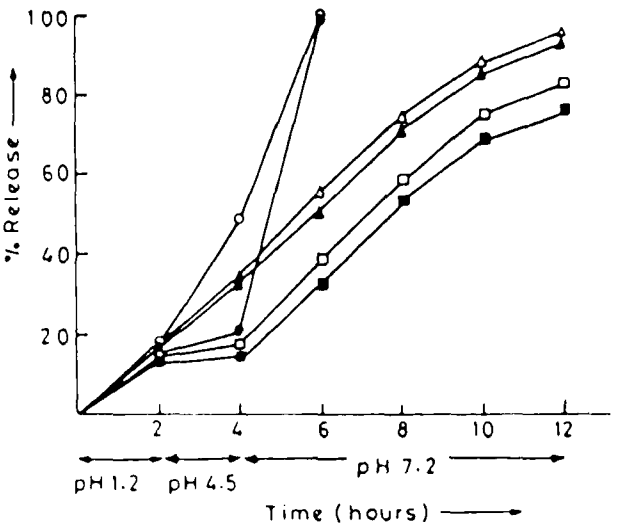

Figure 5: Pindolol release from modified (top coated) spheronized pellets by buffer change method.

obtained in pH 7.2, a burst release of the drug was observed in pH 1.2. The burst release of the drug in the acidic pH could be attributed to the physical property and the intrinsic dissolution of the drug in the acidic pH[6,7]. The solubility and the diffusivity of the drug in the permeating fluid probably determine the release rate of the drug through the retarding polymeric membrane[8].

Release Pattern of Pellets Top Coated by pH Sensitive Polymers:

Since plain spheronized pellets showed a retarded drug dissolution in pH 7.2 (Fig. 1 & 2), it was attempted to control the drug flux in the acidic pH by a coat of HPMCP 55/ Eudragit S 100 on the plain pellets (Fig. 5). It was observed that although the drug flux in the acid medium was controlled, a burst release in pH 7.2 was observed after the dissolution of these polymers. This could be attributed to the entrapment of

drug solution within the polymer membrane and dissolution of these polymers in pH 7.2 would result in burst release of the drug. As is evident from the release profiles, a topcoat of pH sensitive polymers namely HPMCP 55 or Eudragit S 100 over the retardant polymer coat successfully controlled the drug release in pH 1.2 and pH 4.5; further control of the drug release was brought by ethylcellulose (0.5%) or Eudragit RS 100 (1.5%) on the spheronized pellets.

The results obtained with the top coat of HPMCP 55 were found to be superior over that of Eudragit S 100. Eudragit S 100 has a threshold pH above 6.8 and hence this polymer coat would maintain its integrity in pH 4.5[9]. However, owing to the inherent decrease in drug solubility at pH 4.5 compared to pH 1.2, the diffusion of the drug through Eudragit S 100 film would decrease, whereas, with HPMCP 55 (threshold pH 5.4), the the drug release was uniform in pH 1.2 and pH 4.5; this could be possibly because of a softening and swelling of the HPMCP 55 film in pH 4.5, resulting in the formation of media filled pores facilitating the drug diffusion. In accordance with similar studies, the thickness of the coating of pH sensitive polymer was found to play an important role in the drug release in the acidic pH.[10]

CONCLUSIONS

Pindolol pellets produced by extrusion - spheronization behaved as an inert matrix system when subjected to dissolution in pH 7.2. Coating of Pindolol pellets using retardant polymers namely ethylcellulose and Eudragit RS 100 could control the drug release in pH 7.2, but did not control in pH 1.2. Top coating of these pellets with further coat of HPMCP 55 or Eudragit S 100 resulted in control of drug flux in pH 1.2. The results with HPMCP-55 were found to be better than Eudragit S 100 when used as pH sensitive polymer to control Pindolol release in acidic conditions.

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