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# Development of Timely Controlled-Release Systems for Chronotherapy of Propranolol with Minimization of the pH Effect in the Simulated Gastrointestinal Medium

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## ABSTRACT

A timely controlled release dosage form with minimization of transit time and pH effects of gastrointestinal tract for chronotherapy of propranolol was developed. Ethylcellulose (EC) and Eudragit RS selected as the controlling membrane for drug-layering non-pareil seeds (NP) or extrusion-spheronized pellets incorporated with matrix materials or osmogents were characterized in the simulated gastric fluid (SGF) and pH change medium. Results demonstrated that when propranolol was layered on NP, Eudragit RS plasticized with 30% triethylcitrate (TEC) coated at 15% level could adjust a lag time close to the reference but with a slower release rate after then, while EC plasticized with HPMC could not delay drug release at a lag time close to the reference. Furthermore, EC incorporated with lactose coated on the extrusion-spheronized pellets could adjust the lag time, but a release rate correspondingly decreased with increasing lag time. Nevertheless, coating Eudragit RS on matrix pellets as controlling membrane at different levels could adjust a desired lag time with a pulsatile release pattern. However, the lag time adjusted was only within a 5 h range. Finally, coating Eudragit RS at different level on matrix pellets containing various ratio of osmogent, NaCl or lactose, could effectively adjust a desired lag time as long as 15 h with a pulsatile release pattern to accomplish the timely controlled release with minimization of the pH effects of gastrointestinal tract that could meet the clinical need for chronotherapy of propranolol.

Key words: timely controlled release, lag time, ethylcellulose, Eudragit RS, osmogents

## INTRODUCTION

Recently the concept of the chronopharmacokinetics and chronotherapy of drugs has been extensively utilized in clinical therapy for improving drug efficacy and minimizing side effects and drug tolerance[1-3]. To avoid developing tolerance and to follow the innate circadian rhythm, a reasonable and generally acceptable rationale is to have a delivery system capable of delivering drugs in a pulsatile fashion or timely controlled release instead of a continuous manner at predetermined time points and/or sites following oral administration[4-7]. For this purpose, many systems including the time clock system have been developed using various technique and functional polymers or additives[8-11]. Press coating technique disclosed by Ishino *et al.* is one of such novel system that not only acts as a rate controlling system but also delivers the drug in the gastrointestinal (GI) tract in a time-controlled fashion as required[12].

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Oral pulsatile drug delivery systems applied to these drugs often have a high first-pass effect or special chronopharmacological needs have been reviewed by Bussemer *et al.*[13] and by Maroni *et al.*[14]. Pulsatile drug delivery systems can be classified into site-specific system, in which the drug is released at the desired site within the intestinal tract (e.g., the colon), or time-controlled devices, in which the drug is released often after a well-defined time period. Site-specific controlled release is usually controlled by environmental factors, like the pH or enzymes present in the intestinal tract, whereas the drug release from time-controlled systems is controlled primarily by the delivery systems that provided with rupturable membrane layers, swellable/erodible membrane layers, increasingly permeable membrane layers, or release-controlling plugs.

The incidence of many cardiovascular diseases varies predictably in time over 24 h, i.e., in a circadian rhythm fashion[15]. A rapid increase in both acute myocardial infarction and systolic blood pressure has been reported in the well-controlled studies on actual patients. In such cases,

administration of a different kind of unit dosage form delivers the drug in higher concentrations during the time of the greatest need, typically during the early morning hours, and in lesser concentrations when the need is less, such as during late evening and early sleep hours. A pulsatile release system was disclosed by U.S. application Ser. No. 09/778,645, which includes a combination of two or three pellet populations, each with a well-defined release profile and a plasma profile was obtained which varies in a circadian rhythm fashion following administration[16]. Recently, several reviews have been published to report drug delivery technologies for chronotherapeutic applications[17-22].

Propranolol is a β-adrenergic blocking agent and as such is a competitive inhibitor of the effects of catecholamines at beta-adrenergic receptor sites. The principal effect of propranolol is to reduce the cardiac activity by diminishing or preventing beta-adrenergic stimulation. Therefore, a delivery system for circadian rhythm release of cardiovascular drug propranolol in a timed and sustained release pattern was designed and commercially available to provide a plasma concentration-time profile, which varies according to physiological need during the day, i.e., mimicking the circadian rhythm and severity/manifestation of a cardiovascular disease[23]. This timed and sustained release multi-particulate dosage form, Innopran XL, comprised a propranolol core with a first membrane of sustained release polymer and a second membrane of mixture of water insoluble polymer and enteric polymer (2nd or outer membrane), wherein the water insoluble polymer and the enteric polymer may be present at a weight ratio from 10:1 to 1:2. Since the lag time period for the initiation of drug release was regulated by the enteric (HPMCP, hydroxypropylmethyl cellulose phthalate) polymer mixing with a sustained release polymer (EC, ethylcellulose), the variations in the transit time of stomach and the pH value in the intestinal tract will influence both lag time period and subsequent sustained release rate. It was thought that development of a timed and sustained release membrane system with minimization of pH effects in the GI tract would be beneficial in the design of a delivery system for circadian rhythm release of drug propranolol. In this study, two water-insoluble and pH-independent rate-controlling polymeric membranes of EC and Eudragit RS were compared for timed controlled release characteristics and pellet formulations were optimized for pH-independency of pulsatile or sustained release pattern.

## MATERIALS AND METHODS

### I. *Materials*

Propranolol HCl (IPCA Laboratories Limited, India) was used as the model drug in this study. EC was supplied as aqueous dispersion (Surelease, Colorcon, UK) and powder form (100 cps, Hercules, USA). Eudragit RS (Rohm Pharma GMBH, Germany), supplied as either 30% aqueous dispersion (designated as Eudragit RS 30D) or powder form (designated as Eudragit RS 100), was used as the rate-controlling polymer. Triethyl citrate (TEC, Tokyo Chemical Industry Corp., Japan) and Hydroxypropyl methylcellulose (HPMC, Pharmacoat 606, Shin-Etsu, Japan) were selected as a pore former and plasticizer. MCC (microscrystalline cellulose, PH 101) was used with the aid of spheronization and supplied by Wei-Ming Pharmaceutical Manufacturing Ltd. Co. (Taipei, Taiwan). Talc (Matsumura Industrial Co., Ltd., Japan) was used as an anti-adhering agent. Non-pareil seeds (NPs, mean size of 0.71 - 0.85 mm) were purchased from Pack-System Corporation (Taiwan). De-ionized distilled water (DDW) and 95% alcohol (Tobacco and Liquor Corp., Taiwan) were used as the solvent for preparing the coating solution. Innopran XL (batch number: 1AB0025) was a product of GlaxoSmithKline LLC.

### II. *Experimental Methods*

#### (I) *Preparation of Drug-Containing Pellets*

Drug-containing pellets were prepared by either drug solution layering onto NPs or extrusion-spheronization method. For drug solution layering method, 1 kg of NPs were charged into the chamber of a fluidized-bed granulator and coater (Glatt Air Technologies, model GPCG-1, Germany) and fluidized by opening the inlet air flap. When the outlet air temperature reached the desired level, 10% propranolol in alcohol was tangentially sprayed onto the fluidized NPs from an atomized nozzle (1 mm, dia.) attached to a peristaltic pump. During processing, the spraying rate and inlet air temperature were adjusted to maintain the outlet air temperature at a desired range. When the spraying was finished, pellets were dried at 50°C for another 5 min in the chamber. The detailed processing conditions were listed in Table 1 and the formulation was listed in Table 2. For extrusion-spheronization method, a total of 500 g mixture containing propranolol HCl powder, MCC, and lactose (according to formulations listed in Table 3-5) was mixed for 3 min in a planetary mixer. The aqueous dispersion solution containing EC (Surelease) or Eudragit RS was then gradually added in a period of 1 min and the blending was continued for another 30 min. The wet mass was immediately extruded in an extruder (Chuan Yung Industrial Co., Taiwan) of cylinder type with a 0.8 mm orifice screen. The resultant extrudes were spheronized at a speed of 800 rpm for 5 min on the crosshatched plate of 9 inches (dia,) in a spheronizer (Shang-Yuh Machine Co., Ltd., Taiwan). After spheronization, pellets were cured in a hot-air oven at 40°C for 10 h.

#### (II) *Controlling-Release Film Coating of Drug-Containing Pellets*

Four hundred grams of propranolol-containing pellets were placed into the chamber of a fluidized-bed granulator and coater (Model GPCG-1, Glatt Air Techniques, Germany), rotated at 200 rpm and fluidized by opening the inlet air flap. A film dispersion was prepared by mixing Surelease® latex or Eudragit RS 30D with plasticizer and talc (according to

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**Table 1.** The coating conditions for propranolol hydrochloride and various polymers in fluidized-bed processor

| Apparatus conditions | Drug coating | Polymer coating | | | | | |
|---|---|---|---|---|---|---|---|
| | | HPMC | EC-HPMC | EC-Lactose | Surelease | Eudragit RS 30D | Eudragit RS 100 |
| Inlet temp. (°C) | 55 | 40 | 44-47 | 45-47 | 55 | 42-46 | 40-42 |
| Outlet temp. (°C) | 37-39 | 35-37 | 33-37 | 34-38 | 30-33 | 27-35 | 27-31 |
| Spray rate (mL/min) | 5-10 | 3-5 | 5-7 | 5-7 | 5-8 | 4-10 | 4-5 |
| Spray pressure (psi) | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Flap (%) | 25 | 30 | 20-35 | 20-35 | 30 | 30-35 | 35 |
| Nozzle orifice (mm) | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |

**Table 2.** The formulation compositions for drug-layering NP coating with Eudragit RS 100 or ethylcellulose (EC) dissolved in alcohol solution plasticized by triethyl citrate (TEC) or hydroxypropylmethyl cellulose (HPMC), respectively

| Formulations | 2A | 2B | 2C |
|---|---|---|---|
| **Core (g, Non-pareil)** | | | |
| Non-pareil seed (NP) | | 500 | |
| Propranolol HCl | | 200 | |
| **Coating** | | | |
| EC:HPMC (% of NP) | | 0:25 (5)[#] | 2.2:1 (10, 15); 1.8:1 (15, 20) |
| Eudragit RS100 (g, % of NP) | 30(6); 45(9); 60(12); 75(15) | 30(6); 45(9); 60(12); 75(15) | -- |
| TEC (g, % of polymer)[$] | 6(20); 9(20); 12(20); 15(20) | 9(30); 13.5(30); 18(30); 22.5(30) | -- |
| Talc (g, % of polymer) | 9(30); 13.5(30); 18(30); 22.5(30) | 9(30); 13.5(30); 18(30); 22.5(30) | -- |
| **Parameters** | | | |
| Initial release rate (%/h) | 88.04 ± 0.70 (6%)* | 57.84 ± 1.68 (6%) | 22.82 ± 1.34 (10%) |
| | 65.83 ± 2.44 (9%) | 27.40 ± 1.01 (9%) | 10.95 ± 0.07 (15%) |
| | 32.06 ± 1.10 (12%) | 13.70 ± 0.16 (12%) | 13.08 ± 0.31 (15%) |
| | 15.89 ± 1.95 (15%) | 6.88 ± 0.11 (15%) | 10.76 ± 0.34 (20%) |
| Lag time (h) | 0.05 ± 0.01 (6%) | 0.51 ± 0.02 (6%) | 0.43 ± 0.05 (10%) |
| | 0.47 ± 0.05 (9%) | 0.95 ± 0.08 (9%) | 0.54 ± 0.11 (15%) |
| | 0.93 ± 0.10 (12%) | 1.69 ± 0.09 (12%) | 0.76 ± 0.49 (15%) |
| | 1.27 ± 0.19 (15%) | 2.30 ± 0.30 (15%) | 0.97 ± 0.10 (20%) |

[#]The added amount of HPMC in drug-layered solution that used to layer drug on the nonpareil seeds.
[$]The added amount of TEC in the coating solution.
*Number in parenthesis indicates the coating % of membrane.

formulations listed in Table 2-5) in an amount of 10 - 40% (w/w) polymer, and then the final solid content was adjusted to 12.5% (w/w) by dilution with DDW. When the outlet temperature reached a desired level, the dispersion of the film polymer was tangentially-sprayed onto the fluidized pellets from an atomizing nozzle (1 mm) attached to a peristaltic pump. During processing, the spraying rate and inlet air temperature were adjusted to maintain the outlet air temperature at 27-30°C. The spraying continued until the designated amount of film polymer was applied according to formulations listed. Finally, the film-coated pellets were cured in a hot-air oven for another 10 h at 40°C.

(III) *Dissolution Studies*

The USP dissolution apparatus 2 (Model DT-610, Jasco Spectroscopic, Japan) was used to measure the release of propranolol from the coated pellets at an agitation speed of 100 rpm. The temperature of the dissolution medium was maintained at 37 ± 0.5°C. The drug release was compared in the simulated gastric fluid (SGF) without enzyme (pH 1.2) and the pH change medium (2 h in SGF, 1 h in pH 4.5 phosphate buffer (PBS), and then the rest time period in pH 6.8 PBS). Aliquots of 5 mL of sample were withdrawn for the assay at predetermined time intervals and replaced with

the same volume of fresh medium. Propranolol content was determined on a UV/VIS spectrophotometer (Model V550, Jasco Spectroscopic, Japan) at 263 nm after appropriate dilution with the dissolution medium. Each dissolution data point was the mean of at least 3 individual trials. The assay method was validated before implementation. The precision (CV%) and accuracy (RE%) were 0.02 to 2.80% and -1.40 to 0.27% for intra-day runs and were 0.01 to 1.40% and -0.33 to 1.96% for inter-day runs, respectively, in a concentration range of 0.5 to 100 μg/mL.

**Table 3.** The formulation compositions for pellets prepared by extrusion-spheronization method with MCC and lactose using EC and lactose at two ratios of 3 : 1 and 2 : 1 applied as alcohol solution as the controlling membrane with a separating layer of HPMC

| Formulations | 3A | 3B |
|---|---|---|
| **Core (g, Extrusion and Spheronization)** | | |
| Propranolol HCl | 400 | 400 |
| Lactose monohydrate | 400 | 400 |
| MCC PH 101 | 200 | 200 |
| PVP K30 | 10 | 10 |
| **Coating** | | |
| Pharmacoat 606 (g, % of NP) | 25 (5) | 25 (5) |
| EC:Lactose (% of NP) | 3:1 (10; 15; 20) | 2:1 (10; 15; 20) |
| Talc (g, % of polymer) | 10 | 10 |
| **Parameters** | | |
| | 5.87 ± 0.90 (10%)* | 8.22 ± 0.25 (10%) |
| Initial release rate (%/h) | 4.60 ± 0.90 (15%) | 4.77 ± 0.13 (15%) |
| | 2.39 ± 0.08 (20%) | 3.3 ± 0.11 (20%) |
| | 0.45 ± 0.20 (10%) | 0.22 ± 0.11 (10%) |
| Lag time (h) | 0.92 ± 0.08 (15%) | 0.82 ± 0.10 (15%) |
| | 1.58 ± 0.11 (20%) | 0.99 ± 0.07 (20%) |

*Number in parenthesis indicates the coating % of membrane.

(IV) *Characterizations of Pulsatile Pattern*

The lag time and initial release rate were characterized from the drug release profiles measured in the SGF and in the pH change medium to evaluate the pulsatile pattern for various membrane compositions. The initial release rate was calculated from the line slope of the first three points in the drug release profile of plotting cumulative amount *vs.* time. The lag time was estimated by extrapolating the linear portion of cumulative *vs.* time plot to the time-axis. Mean and standard variation (SD) were reported for at least triplicate. Statistical analysis of one-way analysis of variance (ANOVA) was used to determine the statistical significance on the initial release rate and the lag time, (PASW Statistics ver. 18.0) with $p < 0.05$ being considered to be statistically significant.

## RESULTS

The pH-dependency of propranolol release from Innopran XL was first examined and demonstrated in Figure 1. A lag time of 3-5 h and then a sustained release of propranolol

**Table 4.** The formulation compositions for matrix pellets prepared by extrusion-spheronization method with matrix materials of EC in either aqueous dispersion (Surelease, 10 and 20%) or alcoholic solution (20 and 50%) using Eudragit RS 30D plasticized with 20% TEC as the controlling membrane without a separating layer of HPMC

| Formulations | 4A | 4B | 4C | 4D |
|---|---|---|---|---|
| **Core (g, Extrusion and Spheronization)** | | | | |
| Propranolol HCl | | 400 | | |
| MCC PH 101 | | 250 | | |
| Surelease® (% of powder) | 10 | 20 | -- | -- |
| EC (acetone, % of powder) | -- | -- | 20 | 50 |
| **Coating** | | | | |
| Eudragit RS 30D (% of pellets) | | 20; 30; 40 | | |
| TEC (% of polymer) | | 20 | | |
| Talc (% of polymer) | | 40 | | |
| **Parameters** | | | | |
| | 44.19 ± 0.10 (20%)* | 47.19 ± 1.07 (20%) | 44.79 ± 1.11 (20%) | 50.94 ± 1.72 (20%) |
| Initial release rate (%/h) | 39.60 ± 2.01 (30%) | 36.50 ± 2.56 (30%) | 23.50 ± 1.16 (30%) | 39.35 ± 1.37 (30%) |
| | 24.40 ± 2.00 (40%) | 16.07 ± 0.42 (40%) | 15.90 ± 1.06 (40%) | 19.93 ± 1.61 (40%) |
| | 1.22 ± 0.03 (20%) | 1.23 ± 0.03 (20%) | 0.82 ± 0.03 (20%) | 1.17 ± 0.08 (20%) |
| Lag time (h) | 1.98 ± 0.03 (30%) | 2.04 ± 0.03 (30%) | 1.92 ± 0.06 (30%) | 1.86 ± 0.03 (30%) |
| | 2.89 ± 0.06 (40%) | 2.74 ± 0.16 (40%) | 4.41 ± 0.41 (40%) | 3.34 ± 0.10 (40%) |

*Number in parenthesis indicates the coating % of membrane.

**Table 5.** The formulation compositions for matrix pellets prepared by extrusion-spheronization method with the addition of either NaCl as osmogent and solubility modifier or Lactose as osmogent using Eudragit RS (plasticized with 30% TEC) as the controlling membrane

| Formulations | 5A | 5B | 5C | 5D | 5E | 5F |
|---|---|---|---|---|---|---|
| **Core (g, Extrusion and Spheronization)** | | | | | | |
| Propranolol (%) | 49 (5 : 1)[$] | 42 (2.5 : 1) | 29.4 (1 : 1) | 49 (5 : 1) | 49 (5 : 1) | 58.8 |
| NaCl (%) | 9.8 | 16.8 | 29.4 | 9.8 | 9.8 | -- |
| MCC (%) | 41.2 | 41.2 | 41.2 | 28.8 | 20.6 | 41.2 |
| Lactose (%) | -- | -- | -- | 12.4 | 20.6 | -- |
| **Coating (%)** | | | | | | |
| Eudragit RS30D (% of pellets) | 20; 30; 40 | | | | | |
| TEC (% of polymer) | 20 | | | | | |
| Talc (% of polymer) | 20 | | | | | |
| **Parameters** | | | | | | |
| Initial release rate (%/h) | 8.68 ± 1.18 (20%)* | 14.32 ± 1.12 (20%) | 22.89 ± 0.74 (20%) | 16.32 ± 0.48 (20%) | 20.85 ± 0.96 (20%) | 78.66 ± 1.25 (20%) |
| | 5.95 ± 0.14 (30%) | 8.53 ± 0.47 (30%) | 20.29 ± 1.72 (30%) | 12.56 ± 0.33 (30%) | 11.33 ± 0.54 (30%) | 34.54 ± 0.87 (30%) |
| | 6.69 ± 0.29 (40%) | 5.92 ± 0.46 (40%) | 9.79 ± 0.25 (40%) | 10.25 ± 1.19 (40%) | 15.43 ± 0.56 (40%) | 40.31 ± 1.69 (40%) |
| Lag time (h) | 3.62 ± 0.21 (20%) | 2.34 ± 0.30 (20%) | 1.94 ± 0.16 (20%) | 4.44 ± 0.07 (20%) | 4.84 ± 0.28 (20%) | 0.35 ± 0.05 (20%) |
| | 9.00 ± 0.45 (30%) | 4.83 ± 0.46 (30%) | 3.57 ± 0.22 (30%) | 8.25 ± 0.18 (30%) | 6.92 ± 0.47 (30%) | 1.36 ± 0.11 (30%) |
| | 15.15 ± 0.18 (40%) | 7.51 ± 0.82 (40%) | 6.08 ± 0.29 (40%) | 9.86 ± 0.04 (40%) | 9.91 ± 0.04 (40%) | 1.59 ± 0.07( 40%) |

[$]Number in parenthesis indicates the ratio of propranolol to NaCl.
[*]Number in parenthesis indicates the coating % of membrane.

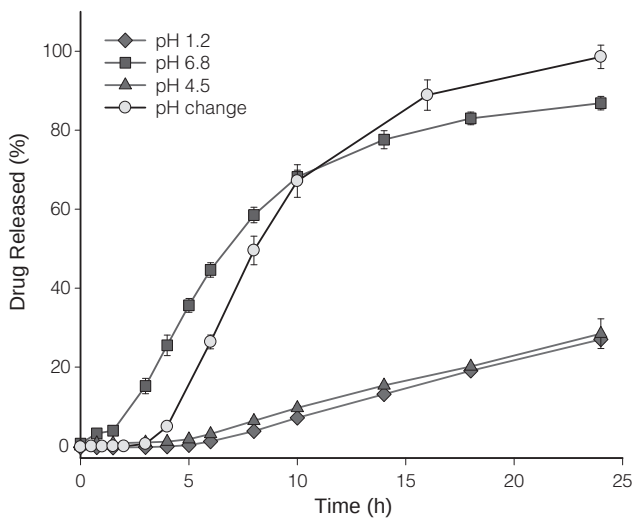


**Figure 1.** The release profiles of propranolol from Innopran XL in various media, (◆) simulated gastric fluid (SGF, pH 1.2); (▲) pH 4.5 phosphate buffer solution (PBS); (■) pH 6.8 PBS; (●) the pH change medium.

at a slower rate were observed in both SGF and pH 4.5 PBS. However, a shorter lag time (~2 h) was noted when dissolution was conducted in pH 6.8 PBS and then propranolol was released within a period of 24 h in a sustained manner. Similarly, the same period of lag time as that in SGF or pH 4.5 PBS was observed in the pH change medium (3.47 ± 0.11 h) and then propranolol was completely released within 24 h following the similar profile as that in pH 6.8 PBS (initial release rate, 10.49 ± 0.74%/ h).

Two water insoluble and pH-independent controlling membrane materials of Eudragit RS 100 and EC dissolved in organic solution plasticized with triethyl citrate (TEC) and HPMC, respectively, at two levels were initially examined for their controllability of the release patterns. Propranolol HCl was solution-layered on NPs and then coated with these two rate-controlling membrane materials using fluidized-bed coating system by following the procedure described in Experimental section. The drug release profiles were evaluated in SGF and pH change medium to examine the dependency of the drug release and the lag time on the pH value of the medium and results were illustrated in Figure 2. It demonstrated that the release profile in both media were similar with an $f_2$ value at least greater than 70 for all coating formulations examined (data not shown). However, the increase in the amount of plasticizer TEC added with Eudragit RS 100 in alcoholic solution from 20 to 30% led to a longer lag time and then a slower release rate for Eudragit RS plasticized with 30% TEC and coated at the same percentage as the controlling membrane (Figure 2A vs. 2B). On the other hand, no lag time was seen for those controlling membranes composed of EC and HPMC at two different ratios, even at increasing coating level. The integrity of EC membrane also seemed to be enhanced with increasing the proportion of HPMC added (1.8 : 1 vs. 2.2 : 1 as shown by Figure 2C).

Extrusion-spheronization method was applied to incorporate propranolol HCl with commonly used excipients such as MCC and lactose for preparing pellets. The controlling membrane composed of EC and lactose (also used as a pore

former) at two ratios (EC : lac) of 3 : 1 and 2 : 1 was then applied as alcohol solution on the pellets with a separating layer of HPMC to minimize the migration of water soluble drug into the controlling membrane during its coating. The release profiles were conducted in SGF and the pH change medium to assess the dependency of the drug release and the lag time on the pH value of the medium and results were shown in Figure 3. The independence on the pH change of medium was demonstrated by that the release profiles conducted at the pH 1.2 solution and the pH change medium were similar for the controlling membranes composed of EC and lactose at two ratios (Figure 3A: EC : lac = 3 : 1 and Figure 3B: EC : lac = 2 : 1) with three coating levels of 10, 15, and 20%. The lag time increased with increasing the EC : lac ratio (3 : 1 vs. 2 : 1) and also with increasing the thickness of the controlling membrane (10% < 15% < 20%). However, the release rate correspondingly decreases either with increasing the EC : lac ratio (3 : 1 vs. 2 : 1) at the same coating thickness or with increasing the thickness of the controlling membrane at the same EC : lac ratio.

Extrusion-spheronization method was also applied to

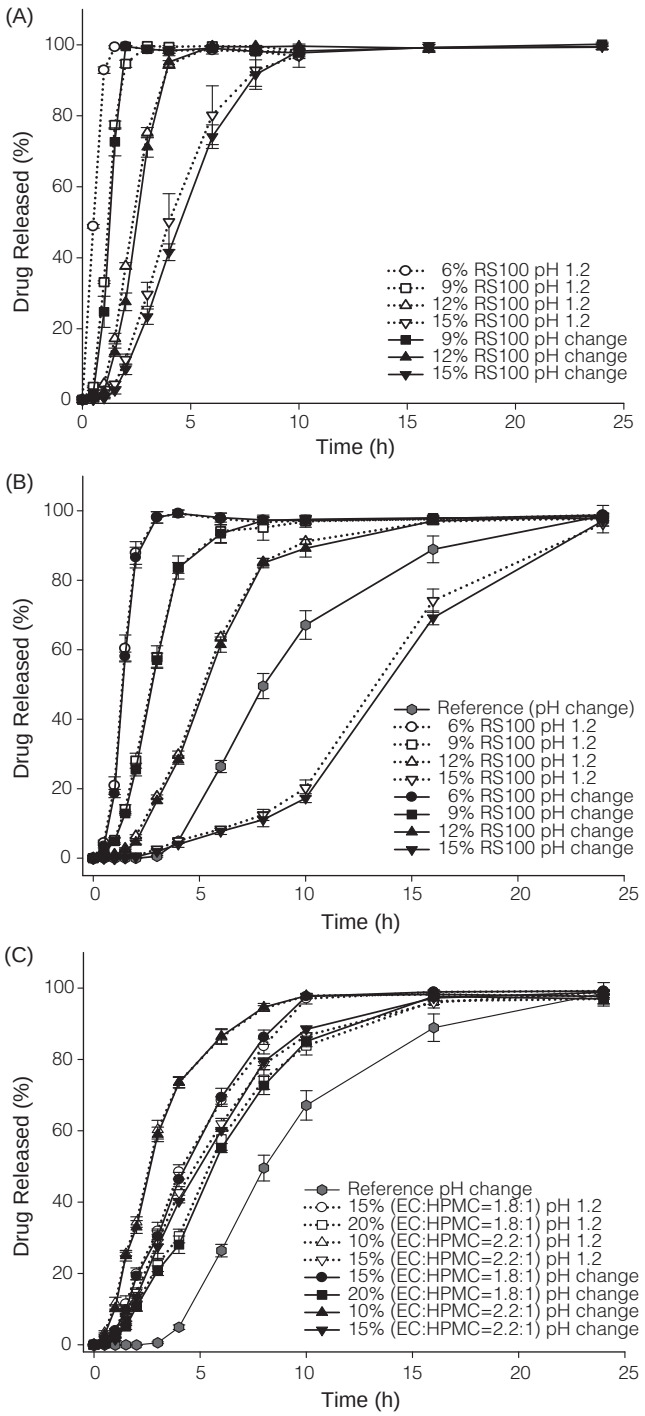


**Figure 2.** The release profiles of propranolol from drug solution layering NPs coated with the rate-controlling membrane composed of either Eudragit RS 100 plasticized with TEC at two levels (**A**: 20% and **B**: 30%) applied as alcohol solution at various coating levels (○●: 6%; □■: 9%; △▲: 12%; ▽▼: 15%) or ethylcellulose (EC) and Pharmacoat 606 (HPMC) in a ratio of 1.8 : 1 (○●: 15%; □■: 20%) and 2.2 : 1 (△▲: 10%; ▽▼: 15%) applied as alcohol solution at two different levels (**C**).

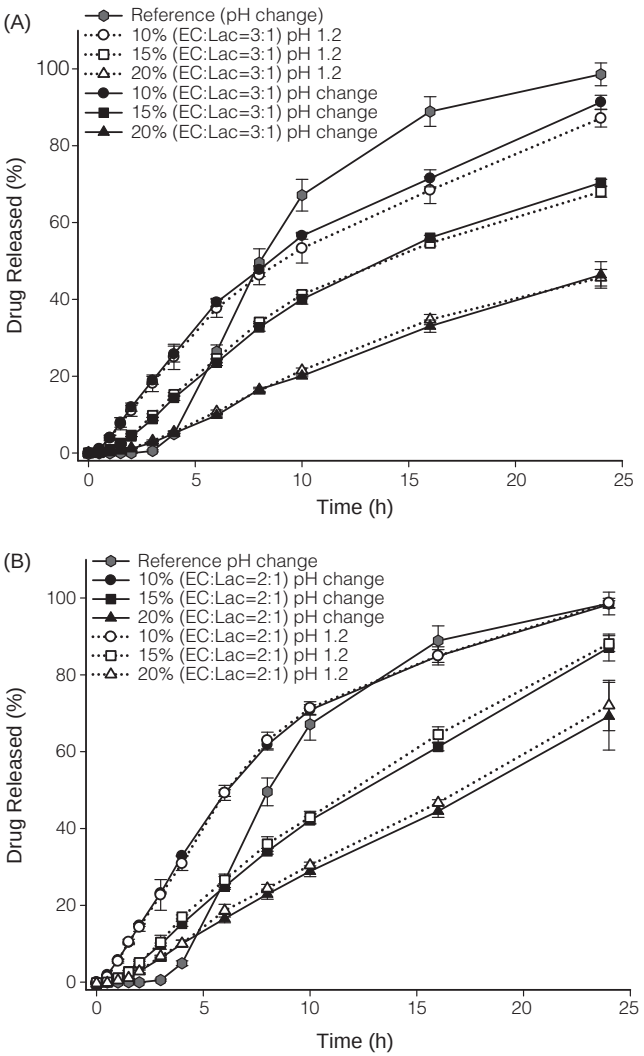


**Figure 3.** The release profiles of propranolol from extrusion-spheronization pellets coated with the HPMC separating layer and the rate-controlling membrane composed of ethylcellulose:lactose (**A**: EC : Lac = 3 : 1; **B**: EC : Lac = 2 : 1) applied as alcohol solution at various coating levels (○●: 10%; □■: 15%; △▲: 20%).

incorporate propranolol HCl and MCC with matrix materials of EC in either aqueous dispersion (Surelease, 10 and 20%) or alcoholic solution (20 and 50%) for preparing pellets to minimize the migration of water soluble drug into the controlling membrane during membrane coating. The controlling membrane composed of Eudragit RS 30D plasticized with 20% TEC was then applied on the pellets at different ratio without a separating layer of HPMC. The release profiles were then examined in the pH 1.2 solutions and the pH change medium for comparison and results were listed in Figure 4. It demonstrates that the lag time and the release rate after the lag time for all release profiles were independent of the pH change of the medium, and the lag time was delayed and the release rate was slightly slowed down with increasing the coating level of the controlling membrane of Eudragit RS.

The influence of the addition of either NaCl as osmogent and solubility modifier or lactose as osmogent in the matrix of pellets with using Eudragit RS (plasticized with 30% TEC) as the controlling membrane on the lag time and resulting release rate was compared at two dissolution media of the SGF and the pH change medium. Results were revealed in Figure 5 and demonstrated that the drug release of all profiles was independent of the pH change of the medium. The increase in the amount of NaCl only, but not lactose, and the increase in the coating level of the controlling membrane were found to disproportionally extend the lag time to as long as 15 h and to result in a similar pulsatile release pattern as compared to those pellets without adding either NaCl or lactose in the formulation (Figure 5F).

## DISCUSSION

As demonstrated in Figure 1, the pH-dependency of propranolol release from Innopran XL was obvious. This is because that Innopran XL comprised a propranolol core with a first membrane of a sustained release polymer and a second membrane of a mixture of water insoluble polymer and an enteric polymer (2$^{nd}$ or outer membrane). Since its outer layer of coating membrane was composed of EC and HPMCP and the inner layer was composed of the former

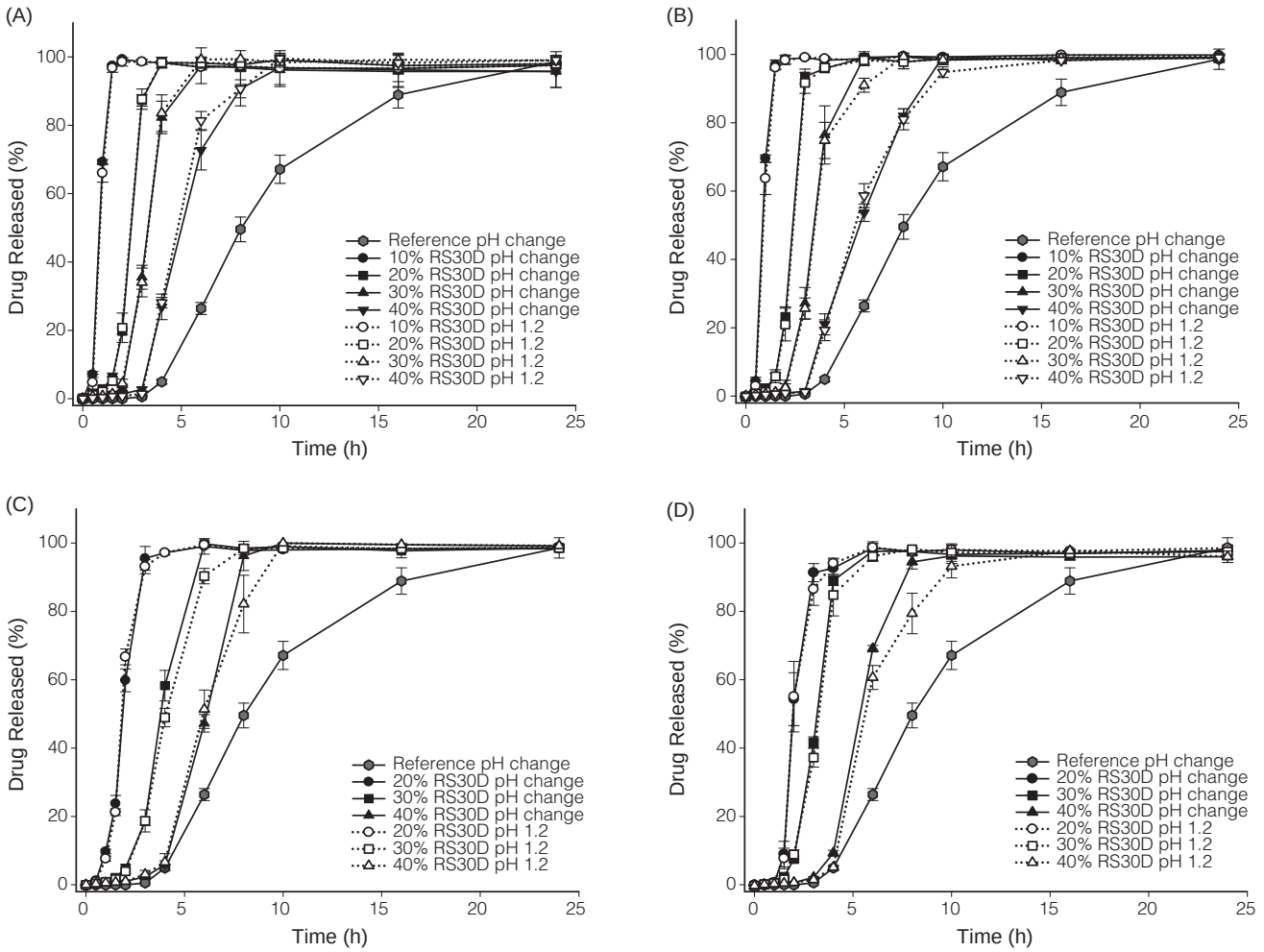


**Figure 4.** The release profiles of propranolol from extrusion-spheronization matrix pellets using **A**: Surelease 10%, **B**: Surelease 20%, **C**: EC 20%, and **D**: EC 50% as binder and then coated with the rate-controlling membrane composed of Eudragit RS 30D at various coating levels (○●: 10%; □■: 20%; △▲: 30%; ▽▼: 40%).

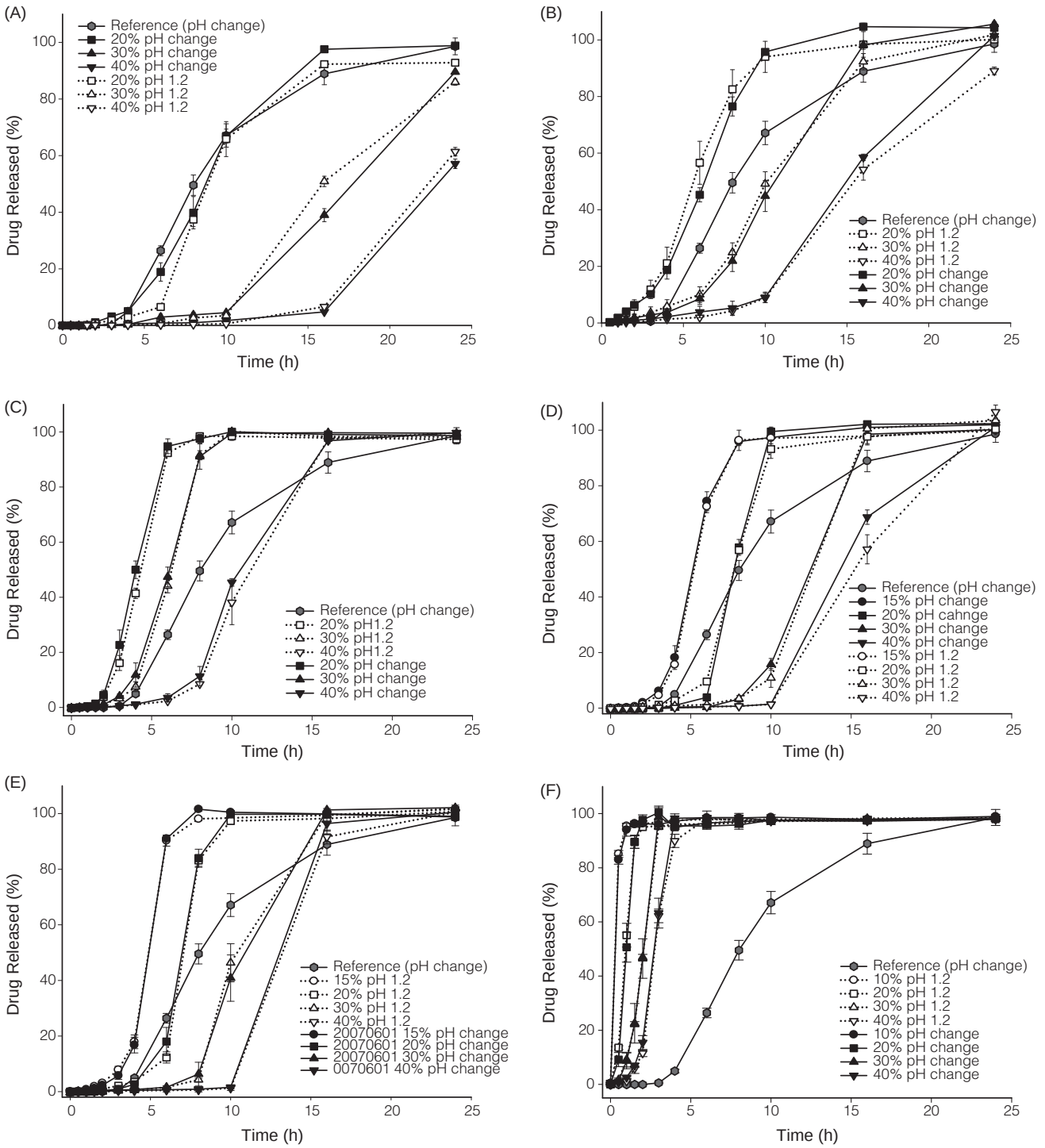


**Figure 5.** The release profiles of propranolol from extrusion-spheronization matrix pellets containing NaCl (**A**: 1/5; **B**: 1/2.5; **C**: 1/1; **F**: 0/0) and lactose (**D**: 3/7; **E**: 5/5; **F**: 0/0) coated with the rate-controlling membrane composed of Eudragit RS30D at various coating levels (○●: 10 or 15%; □■: 20%; △▲: 30%;▽▼: 40%).

only, the insolubility of both EC and HPMCP in those media with lower pH value (SGF, pH 4.5 PBS, and first 2 h in SGF of pH change medium) was expectable to make a longer period of lag time that was necessary for medium to wet both membranes to initiate the release of propranolol from Innopran XL. However, a shorter period of lag time should be expected when dissolution was conducted in pH 6.8 PBS, the pH value of which could make the outer membrane layer more hydrophilic as a result of neutralization of HPMCP leading to shorten the lag time. After a lag time for wetting to initiate the drug release in pH 1.2 and 4.5 PBS, both inner and outer layers of membrane remained

integrity as the rate-controlling membrane led to a sustained release of propranolol from Innopran XL at a slower rate, while it was the inner layer solely composed of EC as the rate-controlling membrane in pH 6.8 PBS and the pH change medium (the pH value was adjusted to 6.8 after 3 h) since HPMCP in the outer layer of membrane should be soluble to make rate-controlling ability residing on the inner layer of membrane that was solely composed of water-insoluble EC. It was concluded that the lag time to initiate a pulsatile release of propranolol from Innopran XL should be expected to depend on the transit time of dosage form in the GI tract, and variations in pH value of the GI tract might complicate the lag time and subsequent sustained release manner. It was also rational to examine the pH dependency of the release profile by comparing the drug release in the SGF and the pH change medium.

Two water insoluble and pH-independent controlling membrane materials of Eudragit RS100 and EC dissolved in organic solution plasticized with TEC or HPMC, respectively, at two levels were firstly coated on NPs solution-layered with Propranolol HCl using fluidized-bed coating system for their controllability of the release patterns. As expected, the release profiles controlled by two water insoluble and pH-independent membrane materials were independent of the change of pH value in the media. However, it was due to the integrity of controlling membrane of Eudragit RS enhanced by the increase in the amount of plasticizer (TEC) added with Eudragit RS 100 in alcoholic solution from 20 to 30% leading to a longer lag time and then a slower release rate for Eudragit RS plasticized with 30% TEC and coated at the same percentage as the controlling membrane (Figure 2A vs. 2B). Nevertheless, no lag time was shown for those controlling membranes composed of EC and HPMC at two different ratios, even with increasing coating level. Since the lag time observed for the release from a water-soluble membrane was closely related to the time necessary for media solution to wet membrane, the addition of water soluble polymeric material of HPMC seems to be able to increase the hydrophilicity of hydrophobic EC membrane at these two ratios, leading to the increase of wettability of EC membrane with shortening the lag time. Furthermore, the hydrophilicity of EC membrane also seems to be enhanced with increasing the proportion of HPMC added (1.8 : 1 vs. 2.2 : 1 as shown in Figure 2C) resulting in a faster release rate using EC : HPMC at the 1.8 : 1 ratio as the controlling membrane. However, the increase in the hydrophilicity for the controlling membrane composed of EC and HPMC at a 1.8 : 1 ratio caused the retardation in the release rate not greater with increasing its thickness than that at a higher ratio of 2.2 : 1. It was thus concluded that Eudragit RS membrane plasticized with 30% TEC coated at an amount of 15% was able to adjust a lag time close to that for reference product but with a slower release rate after then, while EC membrane plasticized with HPMC was not able to delay the release of drug at a lag time closely similar to the reference product.

Matrix pellets incorporated with propranolol HCl and commonly used excipients such as MCC and lactose were prepared by extrusion-spheronization method. The controlling membrane composed of EC and lactose (also used as a pore former) at two ratios (EC : lac) of 3 : 1 and 2 : 1 was then applied as alcohol solution on the pellets with a separating layer of HPMC to minimize the migration of water soluble drug into the controlling membrane during its coating. The independency on the pH change of medium was confirmed by that the release profiles conducted at the pH 1.2 solution and the pH change medium are similar for the controlling membranes composed of EC and lactose at two ratios (Figure 3A: EC : lac = 3 : 1 and Figure 3B: EC : lac = 2 : 1) with three coating levels of 10, 15, and 20%. The lag time was observed to increase with increasing the EC : lac ratio (3 : 1 vs. 2 : 1) and with increasing the thickness of the controlling membrane (10% < 15% < 20%). However, the release rate correspondingly decreases either with increasing the EC : lac ratio (3 : 1 vs. 2 : 1) at the same coating thickness or with increasing the thickness of the controlling membrane at the same EC : lac ratio. Since lactose was water soluble, it was recognized as a pore former and a hydrophilic additive when added with water insoluble material of EC as the controlling membrane. Therefore, the increase in the amount of lactose incorporated into the EC controlling membrane was expected to increase its porosity that would enhance the release rate and also to increase its wettability that would shorten the lag time. It was concluded that the controlling membrane of EC incorporated with lactose coated on the pellets manufactured by extrusion-spheronization method is able to adjust the lag time pattern by coating at different level, but resulting in a release rate correspondingly decreasing with increasing lag time, of which the lag time was shorter and the release rate was slower than that for the reference product.

Pellets containing propranolol HCl and MCC with matrix materials of EC in either aqueous dispersion (Surelease, 10 and 20%) or alcoholic solution (20 and 50%) were also prepared by extrusion-spheronization method. The controlling membrane composed of Eudragit RS 30D plasticized with 20% TEC was then applied on the pellets at different ratio without a separating layer of HPMC. Their release profiles in Figure 4 demonstrated that the lag time and the release rate after the lag time for all release profiles were independent of the pH change of the medium, and the lag time was delayed and the release rate was slightly slowed down with increasing coating level of the controlling membrane of Eudragit RS. The release patterns for those pellets using two different forms of EC as the matrix material with the same controlling membrane of Eudragit RS were similar demonstrating that the release of propranolol was mainly controlled by the diffusion across its controlling membrane of Eudragit RS. However, with increasing the content of matrix material in the pellets for both forms of EC, only the lag time slight increased but the release rate similarly remianed at the same coating level of the controlling membrane. Furthermore, all those release profiles showed a shorter lag time and the release after the lag time in a more pulsatile pattern than that for the reference product. It was concluded that using Eudragit RS as the controlling

membrane at different coating level is able to adjust a lag time of desire with a pulsatile release pattern to accomplish the timely controlled release independent of the pH change. However, the lag time could be adjusted only within a range of 5 h, that would be not so practical to meet the requirements for longer lag time in clinics.

The addition of either NaCl as osmogent and solubility modifier or lactose as osmogent in the matrix of pellets with using Eudragit RS (plasticized with 30% TEC) as the controlling membrane was examined for their influence on the lag time and resulting release rate at two dissolution media of the pH 1.2 solution and the pH change medium. Results shown in Figure 5 demonstrated that the drug release of all profiles was independent of the pH change of the medium. The increase in the amount of both additives (the ratio of drug to additive decreases), either NaCl or lactose, and the increase in the coating level of the controlling membrane were found to disproportionally extend the lag time to as long as 15 h, but to result in a similar pulsatile release pattern as compared to those pellets without adding either NaCl or lactose in the formulation (Figure 5F). The extension of the lag time with increasing the coating level was rationally attributed to the increase in the thickness ($h$) of the controlling membrane that would regulate the lag time ($t_L$) as theoretically predicted ($t_L=h^2/6D$)[11]. On the other hand, the decrease of the lag time with increasing extent of NaCl or lactose (decreasing ratio of drug to additives) was assumed to be a result of increasing osmotic effect with increasing the amount of NaCl or lactose, of which the influx of water from the medium into pellets was promoted leading to the shortening of the lag time. There exists the osmotic effect for the controlling membrane of Eudragit RS simply because it was water insoluble polymeric material as to possess the semi-permeable character.

Furthermore, as shown in Figure 5A, 5B and 5C, the increased extent of the release rate was observed for those pellets containing NaCl with increasing added NaCl amount at the same coating level of the controlling membrane, while it was observed that the decrease of release rate with increasing coating level of the controlling membrane at the same level of NaCl amount. The former phenomenon was explainable similarly by the osmotic effect of NaCl (being as an osmogent) promoting the drug release rate for the same coating level of the controlling membrane. According to theoretical equation describing diffusion through membrane at sink condition : $dQ/dt = (DK/h)*C_s$, it might also be partially attributed that the solubility for HCl salt of propranolol ($C_s$) decreased with increasing the NaCl amount (not for lactose) in the matrix pellets as a result of common ion effect. The latter phenomenon is simply due to the release rate is a reciprocal function to the thickness ($h$) of the controlling membrane at the same level of NaCl according to the above equation. Nevertheless, simply being as an osmogent, the decreased extent of the release rate from those pellets containing increasing amount of lactose added would not be as significant as that for those pellets containing increasing NaCl amount at the same coating level (Figure 5D and 5E). It was concluded that using Eudragit RS as the controlling membrane at different coating level and the addition of osmogent in the pellet formulation are able to effectively adjust a lag time of desire for as long as 15 h with a pulsatile release pattern to accomplish the timely controlled release membrane system with the minimization of the pH effects of GI tract that could meet the practical need in clinics.

## CONCLUSIONS

In conclusion, matrix pellets that incorporated propranolol with osmogents, NaCl or lactose with a timely controlled release independent of the pH change that could meet the practical need in clinics for chronotherapy of propranolol was developed. A timely and sustained release of the in vitro dissolution profile in the pH change medium was demonstrated to be similar to that for Innopran XL but with less dependency on the pH chang that might be encountered during *in vivo* transits in the GI tract. However, independency of *in vivo* release profile on the pH change in the GI tract will be confirmed in the future.

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