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Formulation and process optimization of multiparticulate pulsatile system delivered by osmotic pressure-activated rupturable membrane

Sheng-Feng Hung [a,1], Chien-Ming Hsieh [c,1], Ying-Chen Chen [a], Cheng-Mao Lin [a], Hsiu-O Ho [a,*], Ming-Thau Sheu [a,b,*]

[a] School of Pharmacy, College of Pharmacy, Taipei Medical University, Taipei, Taiwan
[b] Clinical Research Center and Traditional Herbal Medicine Research Center, Taipei Medical University Hospital, Taipei, Taiwan
[c] Department of Cosmetic Science, Providence University, Taichung City, Taiwan

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ABSTRACT

In this study, a multiparticulate pulsatile drug delivery system activated by a rupturable controlled-release membrane (Eudragit® RS) *via* osmotic pressure (with NaCl as the osmogent) was developed and characterized for omeprazole, omeprazole sodium, and propranolol HCl which have different water solubilities. Multiparticulates in pellet form for incorporation with or without the osmogent were manufactured by three methods and then used to coat a polymeric membrane. Results demonstrated that drug/osmogent-containing pellets manufactured by the extrusion/spheronization method with incorporation of the osmogent were optimal. The lag time (t_L) to initiate pulsatile release is regulated by $t_L = l^2/(6 \times D)$, which is dependent on the coating levels (l^2) and plasticizer content (D). The pulsatile release pattern was found to be dependent on the osmotic pressure (osmogent), drug solubility, and mechanical properties of the polymeric membrane (elasticity and toughness). Omeprazole with lower water solubility could not generate sufficient osmotic pressure to create a crack in the membrane to activate pulsatile release, whereas the two other model drugs with higher solubilities could. But adsorption of omeprazole sodium on Eudragit® RS *via* charge–charge interactions led the its incomplete release. Finally, with 4% osmogent of NaCl added, a lag time in a range from 0 to 12 h proportionally regulated by varying both the membrane thickness and plasticizer level initiated the complete pulsatile release of propranolol HCl. In conclusion, a multiparticulate pulsatile drug delivery system activated by a rupturable controlled-release membrane *via* osmotic pressure was successfully developed, and clinical applications of chronotherapy with drugs like propranolol HCl are expected.

1. Introduction

The chronopharmacokinetics and chronotherapy of drugs have been comprehensively explored as clinical therapies to enhance drug efficacy and minimize undesired side effects and potential tolerance to drugs (Lemmer, 1996; Smolensky and Peppas, 2007; Ohdo, 2010; Youan, 2010). To emulate innate circadian rhythms, an equitable and generally recognized rationale is to release drugs in a pulsatile fashion at programmed times and/or at specific sites following oral administration instead of continuous delivery (Kikuchi and Okano, 2002; Lemmer, 2005; Roy and Shahiwala, 2009; Mandal et al., 2010; Lin et al., 2012). Most current pulsatile delivery systems are characteristically time-controlled in that the commencement of drug release is activated by in-built mechanisms regardless of the differing conditions they may encounter in the gastrointestinal (GI) environment. Presently, a time-controlled pulsatile drug delivery system is mainly achieved by applying a functional polymeric coating to a drug-containing core. The core may either be a single- or multiple-unit dosage form, the latter facilitating amended reproducibility in GI transit and less absorption variability (Bianchiniet al., 1992, 1993). In view of that, coating membranes with rupturable, erodible, permeable, or semipermeable characteristics applied onto cores can offer pulsatile release (Bussemer et al., 2001; Maroni et al., 2005, 2010). Regarding this respect, various coating techniques including spray-coating, dry-coating (double compression), dipping, and powder-layering have been employed. However, the spray-coating process, whereby a solid substrate is provided with a thin layer of

* Corresponding authors. Tel.: +886 2 23771942; fax: +886 2 23771942.
E-mail addresses: hsiuoho@tmu.edu.tw (H.-O. Ho), mingsheu@tmu.edu.tw (M.-T. Sheu).
[1] These authors contributed equally to this work.

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polymeric material deposited from a nebulized suspension or solution of the polymer itself, is by far the most commonly utilized owing to its advantages in terms of (i) time, costs, and scalability of the process; (ii) homogeneity of the thickness, structure, and surface of the coat; (iii) fine modulation of the coating level; and (iv) versatility with respect to the type and dimensions of the starting cores. Therefore, its applications in this particular field have been reviewed (Maroni et al., 2013).

Rupturable coatings are insoluble and yet temperately permeable polymeric films that go through timed disruption following introduction to an aqueous medium, thereby allowing the drug to be released after a programmed lag phase. Rupture occurs due to a hydrostatic pressure that builds up inside the core mainly as a result of the swelling of hydrophilic polymers or of an osmotic water influx. Ethylcellulose (EC) has most frequently been employed as a rupturable film and also in combination with swellable polymers, *i.e.*, low-substituted hydroxypropylcellulose (L-HPC), (Uedaet al., 1994a, b, c; Bussemer et al., 2003a, b; Mohamad and Dashevsky, 2006, 2007; Liu et al., 2009), low- and high-viscosity grades of hydroxypropyl methylcellulose (HPMC) (Feng et al., 2008; Yadav et al., 2011), polyvinyl alcohol (PVA) (Morita et al., 2000), or a superdisintegrant, such as croscarmellose sodium (Ac-Di-Sol®) (Ueda et al., 1994a, b, c; Bussemer et al., 2003a, b; Mohamad and Dashevsky, 2006, 2007; Liu et al., 2009) or crospovidone (Hartman Kok et al., 2001), as a rupturing force. Apart from EC, cellulose acetate with the aid of generating CO_2 gas (Schultz and Kleinebudde, 1997) and mixtures of Eudragit® RS and Eudragit® RL with a swelling layer composed of low-viscosity HPMC (Zhang et al., 2003), were explored for manufacturing pulsatile delivery systems empowered with rupturable coatings.

Pulsatile delivery based on a rupturing mechanism with the aid of osmotic pressure was invented by Baker (1976). Accordingly, the lag time for rupture is optimally regulated by varying the film materials and/or film thickness. Razaghi et al. further examined the influential interaction of combining polyethylene oxide (PEO) as a swellable polymer in osmotically rupturable tablets on the time of rupture and subsequent drug release profiles (Razaghi and Schwartz, 2002). A novel pulsatile release system based on a bilayer-coated tablet containing an osmotically active agent was reported by Zhang et al. (2003) with HPMC being applied as the swelling layer and a mixture of Eudragit® RS and RL as the semipermeable outer coating. The osmotic rupture mechanism was found to play an important role in controlling the lag time for drug release and profile of compression-coated tablets prepared with micronized EC as the outer layer (Lin et al., 2002, 2008; Lin and Kawashima, 2012).

In our previous study, we reported on drug release in a pulsed fashion following a programmable lag time was produced simply by varying the coating level of Eudragit® RS (plasticized with 20% triethylcitrate (TEC)) on drug-containing pellets (Kao et al., 1997). The hypothesis of osmotic pressure caused by diltiazem salt across the semipermeable coating of Eudragit® RS being the responsible mechanism for rupturing was confirmed and further established as an *in vitro–in vivo* correlation of the pulsatile pattern in another study (Lin et al., 2008). In this study, a multiparticulate pulsatile drug delivery system activated by membrane rupture *via* osmotic pressure was developed and characterized for three model drugs with different solubilities.

2. Experimental procedures

2.1. Materials

Omeprazole (very slightly soluble, water solubility: 0.331 mg/ml), omeprazole sodium (OS; freely soluble, water solubility: 641.5 mg/ml), and propranolol HCl (soluble, water solubility: 34.9 mg/ml) were purchased from Ipca (Mumbai, Indian). EC (10 cps) was purchased from Aqualon (Wilmington, DE, USA). Eudragit® RL 30D and RS 30D were supplied by Evonik Rohm (Essen, Germany). HPMC of various grades (60SH-50, 60SH-4000, and Pharmacoat606) was obtained from Shin-Etsu (Tokyo, Japan). HPMC E10M and K100M were from Colorcon (London, UK). Microcrystalline cellulose (MCC PH101) was obtained from Wei Ming Pharmaceutical (Taipei, Taiwan). TEC was from Merck (Hunterdon, Germany), and Tween 80 (Polysorbate 80) was from Riedel-de Haën (Seelze, Germany). All materials were used as received, and all other chemicals were of reagent grade.

2.2. Methods

2.2.1. Preparation and characterization of free films

The plasticizer (TEC) was first thoroughly mixed in an aqueous solution. Then Eudragit® RS was added as an aqueous dispersion solution at a final polymer level of 15% (w/w) and blended for 30 min for plasticizing. Dried free films were prepared by pouring the resultant mixture onto the parafilm-sealed bottom of a polyacrylic column, dried at 40 °C for 12 h, and further cured at 50 °C for 12 h. Wet films were prepared by soaking the dried free films in 500 ml of simulated gastric fluid (SGF, 0.1 M HCl solution) or simulated intestinal fluid (SIF, phosphate buffer, pH 6.8) at 37 °C for 4 h, to simulate *in vivo* conditions. The mechanical strengths of the free films (10 × 3 mm with a thickness of 0.20–0.40 mm) were measured (Dynamic Mechanical Analyzer, DMA7e, PerkinElmer, Waltham, MA, USA) by monitoring the time-modulus curve conducted at ambient temperature. The initial applied force was 5 mN, with an extension rate of 100 mN/min. The stress-strain curves for polymeric free films were obtained and the strain (%, ε) and stress (MPa, σ) at the rupture point were respectively recorded. The slope at the origin of the stress-strain curve gives Young's modulus (MPa/%, E), and the total area under the stress-strain curve up to rupture is termed the modulus of toughness (MJ/m^3, T) (n = at least 4).

Table 1
Formulations of drug layering on a nonpareil (C1) and osmotic core (C2).

	C1	C2
Core (g, %)		
Cellet® (500~700 μm)	500	
Osmotic core (0.85~1.18 mm) (MCC:lactose NaCl = 150:250:100)		500
Drug layering (g, %)		
Omeprazole	50	
HPMC 6 cps (on pellet and drug)	33 (4.4%)	
TEC (on HPMC)	3 (9.1%)	
Talc (on HPMC)	3 (9.1%)	
Total solid content in coating solution	10.0%	

HPMC, hydroxypropyl methylcellulose; TEC, triethylcitrate.

Table 2
Coating conditions of the Glatt GPCG-1 fluid bed coater.

Polymer (plasticizer)	RS/TEC15	RS/TEC20	S9L1/TEC15	Drug layering
Inlet temperature (°C)	52.4	49.0	54.1	40.9
Outlet temperature (°C)	36.0	35.4	35.9	33.3
Product temperature (°C)	36.2	36.0	36.2	34.5
Spray pressure (psi)	25	25	25	25
Rotor (rpm)	180	180	180	180
Nozzle orifice (mm)	1	1	1	1
Flow rate (g/min)	6.3	7.0	5.0	5.6
Coating efficiency (%)	95.2	94.4	96.6	91.5

RS/TEC15 (g): RS 30D/TEC/talc = 667/30/40.
RS/TEC20 (g): RS 30D/TEC/talc = 667/40/40.
S9L1/TEC15 (g): RS 30D/RL 30D/TEC/talc = 600/67/30/40.

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