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Preparation and characterization of sustained-release rotigotine film-forming gel

Xiang Li[a], Renyu Zhang[a], Rongcai Liang[a,b], Wei Liu[a], Chenhui Wang[a], Zhengxing Su[a], Fengying Sun[a,**], Youxin Li[a,b,*]

[a] School of Life Science, Jilin University, 2699 Qianjin Street, Changchun, China
[b] School of Pharmacy, Yantai University, No. 30 Qingquan Road, Yantai, China

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ABSTRACT

Objective: The aim of this study was to develop a film-forming gel formulation of rotigotine with hydroxypropyl cellulose (HPC) and Carbomer 934. To optimize this formulation, we applied the Response Surface Analysis technique and evaluated the gel's pharmacokinetic properties.
Methods: The factors chosen for factorial design were the concentration of rotigotine, the proportion of HPC and Carbomer 934, and the concentration of ST-Elastomer 10. Each factor was varied over three levels: low, medium and high. The gel formulation was evaluated and optimized according to its accumulated permeation rate (Flux) through Franz-type diffusion. A pharmacokinetic study of rotigotine gel was performed with rabbits.
Results: The Flux of the optimized formulation reached the maximum (199.17 $\mu g/cm^2$), which was 3% rotigotine and 7% ST-Elastomer 10 with optimal composition of HPC: Carbomer 934 (5:1). The bioavailability of the optimized formulation compared with intravenous administration was approximately 20%.
Conclusion: A film-forming gel of rotigotine was successfully developed using the response surface analysis technique. The results of this study may be helpful in finding an optimum formulation for transdermal delivery of a drug. The product may improve patients' compliance and provide better efficacy.

1. Introduction

Rotigotine is a potent and selective D-2 dopaminergic receptor agonist with very low oral bioavailability. Due to its phenolic moiety, the hepatic first-pass effect of rotigotine is extensive (Swart and De Zeeuw, 1992). Moreover, non-physiological pulsatile stimulation of dopamine receptors causes motor complications, which are a common source of disability for patients with Parkinson's disease (Olanow et al., 2006). Due to these reasons, a more effective delivery route that causes the drug to avoid the hepatic first-pass effect and that allows it to continuously stimulate dopamine receptors is required.

Topical drug delivery of rotigotine in various formulations had seldom been described until Neupro was developed by Schwarz Pharma, which was a rotigotine transdermal patch (Mucke, 2003). In 2008, Neupro was recalled by Schwarz Pharma because the formation of rotigotine crystals was observed in some patches. Nugroho et al. (2004) reported transdermal iontophoresis of rotigotine, but pharmacokinetic studies were not performed, so the effect of transdermal iontophoresis of rotigotine was not clear.

Recently, researchers have demonstrated that bioadhesive films formed by polymer materials possess good qualities for skin application and that they may provide a promising method for use as a transdermal drug delivery system (TDDS) (Guo et al., 2011; Krishnaiah et al., 2002; Nesseem et al., 2011). Gelnique® (Watson, USA), approved by FDA in 2009, was a kind of rapid drying gel. Nesseem et al. (2011) developed transdermal films (TFs) with Eudragit L30D-55 copolymer, polyethylene glycol (PEG) and propylene glycol as permeation enhancers. Guo et al. (2011) developed hybrid gels with modified poly(vinyl alcohol) (PVA) gel, gamma-(glycidyloxypropyl) trimethoxysilane (GPTMS) as an inorganic-modifying agent, poly(*N*-vinyl pyrrolidone) (PVP) as a tackifier and glycerol (GLY) as a plasticizer. In this study, HPC was chosen as film former because it has been used as film coating of tablets since 1977. Recently, HPC has been used as film former in mucoadhesive films (Rajput et al., 2011) and tear film (Wander and Koffler, 2009). Rajput et al. reported that Glipizide/hydroxypropyl cellulose/PEG 400 (2.5:1:0.5) (GF5) was the optimal composition for a novel mucoadhesive stomach formulation (Rajput et al., 2011). Wander and Koffler (2009) proved that hydroxypropyl cellulose ophthalmic insert was a relatively safe, tolerable, and effective therapy for dry eye, either alone or in conjunction with other

* Corresponding author at: School of Life Science, Jilin University, 2699 Qianjin Street, Changchun, China. Tel.: +86 431 85155320; fax: +86 431 85155320.
** Corresponding author. Tel.: +86 431 85155320; fax: +86 431 85155320.
E-mail addresses: sunfengying@jlu.edu.cn (F. Sun), liyouxin@jlu.edu.cn (Y. Li).

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therapies. In our study, the combination of HPC and Carbomer 934 could form very thin and transparent films, which could provide a promising formulation for TDDS.

It is crucial for pharmaceutical scientists to design drug delivery systems with a minimum number of tests. Utilizing factorial experiments, which can give a combination of variables that result in near-maximum output, are more efficient in multi-factor designs compared with one-factor-at-a-time experimentation (Rhee et al., 2008). In this study, we utilized HPC as a film-forming formulation and Carbomer 934 as a gelling agent. Using the response surface analysis technique, we evaluated the effects of three factors – the amount of rotigotine, the amount of ST-Elastomer 10, and the proportion of HPC relative to Carbomer 934 – on the drug permeation rate. The optimized formulation was also evaluated *in vivo* in rabbits.

2. Materials and method

2.1. Materials

The following materials were used as received without further purification. Rotigotine was kindly donated by Luye Pharma. HPC and Carbomer 934 were purchased from Shanghai Yunhong Pharmaceutical Excipients & Technology Co., China. ST-Elastomer 10 was kindly donated by Dow Corning Corporation, USA. All other chemicals used in the experiments were of analytical grade. New Zealand rabbits and Nude Mice were provided by the Experimental Animal Center of Jilin University, China.

2.2. Hydrogel preparation

Different proportions of HPC and Carbomer 934 (total amount of 25 g) were mixed by screening through an 80 mesh screen and then sprinkled into purified water to be swollen. The gel was well-swollen after 12 h, and the pH was adjusted to 7.0 with trolamine. Rotigotine was dissolved in ethanol and added dropwise into the gel to be completely mixed. ST-Elastomer 10 was added into the gel as prescribed and adjusted to a total weight of 100 g with purified water. Experimental conditions for the factorial design are shown in Table 1.

2.3. Measurement of film thickness

Film thickness was measured by using a 0.02 mm vernier caliper. A 4 cm × 4 cm sample of the film was measured in ten different positions. The determination was performed in triplicate and the average value was used (Xiao et al., 2012).

2.4. Experimental design

It is possible to model curvature with response surface methodologies, such as Box–Behnken and Central Composite Design (CCD). Because Box–Behnken requires fewer runs than CCD in cases of three or four variables, we chose it in our study. In this study, a 17-run, 3-factor, 3-level Box–Behnken statistical screening design was used to statistically optimize the formulation factors and evaluate the main effects, interaction effects, and quadratic effects on skin permeation rates. Statistical analysis was performed using Expert-Design software (Version 7.1, Stat-EASE INC., Minneapolis, MN, USA) and the optimized formulation was selected for the pharmacokinetic studies in rabbits. The selected dependent and independent variables are shown in Table 2. Each experiment was repeated six times, and the mean value and standard deviation are presented.

Table 1
Variables and their levels in the Box–Behnken design.

Factors	Levels		
	Low (−1)	Medium (0)	High (+1)
Independent variables			
Rotigotine	0.5%	1.5%	3%
HPC:Carbomer 934	3:1	5:1	7:1
ST-Elastomer 10	2%	7%	10%
Dependent variables			
Y = accumulated release rate (μg/cm^2)			

Total amount of HPC and Carbomer 934 was 25 g.

Table 2
Matrix of a 3^{3}factorial design for formulation of rotigotine gel and permeation parameters of rotigotine through nude mice skins.

Trial No.	Levels			Dependent variables (μg/cm^2)
	*X*1	*X*2	*X*3	Y
1	0	1	1	180.23
2	0	0	0	167.89
3	0	0	0	178.92
4	1	−1	0	106.14
5	0	0	0	169.38
6	−1	0	1	130.15
7	0	1	−1	199.17
8	−1	1	0	178.28
9	1	0	−1	139.27
10	0	0	0	186.37
11	0	−1	−1	107.13
12	1	0	1	145.68
13	0	−1	1	113.29
14	−1	0	−1	123.43
15	0	0	0	176.9
16	1	1	0	176.9
17	−1	−1	0	120.78

2.5. Checkpoint analysis and optimization of model validation

Statistical validation of the polynomial equations generated by Design Expert was established using an ANOVA. The optimum formulation was based on the maximum cumulative release rate.

2.6. Skin permeation of rotigotine through excised nude mice skin

All experiments were performed according to the Guidelines for Animal Experiments, Jilin University. The skin of nude mice is more similar to human skin compared with the skin of normal mice, and thus, nude mice were used in this study (Behl et al., 1980; Lia and Chang, 2001; Wang et al., 2009). Nude mice, weighing 18–22 g, were killed by cervical dislocation and the skin from their abdomen was obtained. After removing the adhering fat and other visceral tissue, the skin was stored at −20 °C and used within 14 days. Franz-type diffusion cells were used for *in vitro* release studies of rotigotine from the skin of nude mice. The receptor compartment of the Franz diffusion cell was 5.0 ml, and the effective diffusion area was 0.636 cm^2. 10 mM isotonic phosphate buffer saline (PBS, pH 7.4) was used as the receptor medium, which was maintained at 32 ± 0.1 °C and stirred at a constant rate of 200 rpm during the experiment. At predetermined time intervals, 5.0 ml of the receptor medium was withdrawn and replaced with an equal volume of freshly prepared medium. Each prescription was repeated for six times. The amount of rotigotine that permeated through the skin into the receptor medium was determined using a validated HPLC method, as described in Section 2.9.1.