European Journal of Pharmaceutics and Biopharmaceutics 91 (2015) 59–65

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Note

Dual-directional regulation of drug permeating amount by combining the technique of ion-pair complexation with chemical enhancers for the synchronous permeation of indapamide and bisoprolol in their compound patch through rabbit skin

Wenting Song [a], Dongmei Cun [a], Peng Quan [a], Nannan Liu [a], Yang Chen [a], Hongxia Cui [a], Rongwu Xiang [b,*], Liang Fang [a,*]

[a] Department of Pharmaceutical Science, School of Pharmacy, Shenyang Pharmaceutical University, Shenyang, China
[b] School of Medical Instrument, Shenyang Pharmaceutical University, Shenyang, China

ARTICLE INFO

Article history:
Received 11 November 2014
Accepted in revised form 27 January 2015
Available online 4 February 2015

Keywords:
Indapamide
Bisoprolol
Dual-directional regulation
Synchronous permeation
Ion-pair
Enhancer combination
Compound transdermal patch

ABSTRACT

To achieve the synchronous skin permeation of indapamide (IND) and bisoprolol (BSP) in their compound patch, the techniques of ion-pair complexation and chemical enhancers were combined to dual-directionally regulate drug permeating amounts. Ion-pair complexes of BSP and various organic acids were formed by the technique of ion-pair complexation. Among the complexes formed, bisoprolol tartrate (BSP.T) down-regulated the permeating amount of BSP to the same extent as that of IND. Then, to simultaneously up-regulate the amounts of the two drugs, an enhancer combination of 15.8% Span80 (SP), 6.0% Azone (AZ) and 2.2% N-methyl pyrrolidone (NMP) was obtained by central composite design and exhibited an outstanding and simultaneous enhancement on IND and BSP with enhancing ratio (*ER*) of 4.52 and 3.49, respectively. The effect of the dual-directional regulation was evaluated by *in vitro* permeation experiments and *in vivo* pharmacokinetic studies. For IND and BSP, their observed permeation profiles were comparable and their MAT (mean absorption time) showed no significant difference, which both demonstrated these two drugs achieved the synchronous skin permeation in their compound patch by the dual-directional regulation strategy of combining the technique of ion-pair complexation with chemical enhancers.

1. Introduction

Indapamide (IND) and bisoprolol (BSP) have been widely used as a thiazide-type diuretic and a selective type β_1 adrenergic receptor blocker, respectively. Their combination is designated as acceptable which can add considerable antihypertensive efficacies without the increase of side effects [1]. As listed in Table 1, for IND and BSP both the daily dose and bioavailability of their respective oral preparations are quite close. It indicated that in order to exert expected therapeutic effects, their required amounts entering into body in 24 h were comparable. Accordingly, their skin permeating amounts from their compound patch were also expected to be comparable, and it would be better to achieve synchronous skin permeation. However, as shown in Fig. 1, the accumulated permeating amount of BSP was about 16 times that of IND. The two drugs with such remarkable disparity in their permeating amounts cannot achieve synchronous permeation. Therefore, an effective regulating method was in great demand.

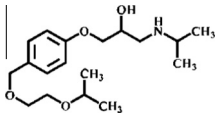
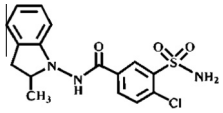
The change in drug loading is a commonly-used way to regulate drug permeation in compound transdermal delivery [2]. Unfortunately, since the physicochemical properties of IND and BSP (Table 1) were quite different, the change in their loadings failed to regulate their permeating amounts to reach a comparable level. Similarly, the change in adhesives and enhancers in patches can also hardly succeed. It was because that any change regulating the permeating amount of one drug may have an uncontrollable impact on the other drug in compound patch. Until now there has no suitable method that can regulate the permeating amounts of two drugs with quite different physicochemical properties and

* Corresponding authors. School of Medical Instrument, Shenyang Pharmaceutical University, 103 Wenhua Road, Shenyang, Liaoning 110016, China. Tel./fax: +86 24 23986529 (R. Xiang). Department of Pharmaceutical Science, School of Pharmacy, Shenyang Pharmaceutical University, 103 Wenhua Road, Shenyang, Liaoning 110016, China. Tel./fax: +86 24 23986330 (L. Fang).

E-mail addresses: xrwlove@163.com (R. Xiang), fangliang2003@yahoo.com (L. Fang).

http://dx.doi.org/10.1016/j.ejpb.2015.01.025
0939-6411/

Table 1
Chemical structure and physicochemical properties of bisoprolol (BSP) and indapamide (IND) and the pharmacokinetic parameters of their respective oral preparations.

Drug	Chemical structure	MW[a]	Melting point	Solubility[b]	Oral dose/day (mg)	Bioavailability (%)
BSP		325	Liquid (25 °C) [3]	22.61 mg/ml	2.5–5[c]	>80[a]
IND		366	160–162 °C[a]	85 μg/ml	2.5[d]	100[d]

[a] Data were obtained from the Drug Bank database.
[b] Solubility in phosphate-buffered solution (pH 7.4) ($n = 4$).
[c] Data from clinical trials of BSP in hypertension.
[d] Data from clinical trials of IND in hypertension.

finally achieve the synchronous permeation in their compound patch.

Therefore, in this work an interesting dual-directional regulation strategy was initiated combining the technique of ion-pair complexation with chemical enhancers for the synchronous skin permeation of drugs.

2. Materials and methods

2.1. Chemicals and animals

Bisoprolol fumarate and indapamide were from Yuancheng Ltd. (Zhuhai, China) and Kangya Pharmaceutical Co., Ltd. (Ningxia, China), respectively. DURO-TAK® 87-2287 was obtained from Henkel Corp. (New Jersey, USA). Cellophane® membrane was supplied by ShangYu Cellophane Co., Ltd. (Zhejiang, China). All other chemicals were of the highest reagent grade available.

Rabbits (male, 1.5 ± 0.2 kg) were used as animal models and supplied by the Experimental Animal Center of Shenyang Pharmaceutical University (Shenyang, China). The experiments were conducted in accordance with the Institutional Animal Care and Use Committee, Shenyang Pharmaceutical University.

2.2. Preparation

2.2.1. Preparation of BSP and its complexes

BSP and its ion-pair complexes were prepared and characterized as described previously [3].

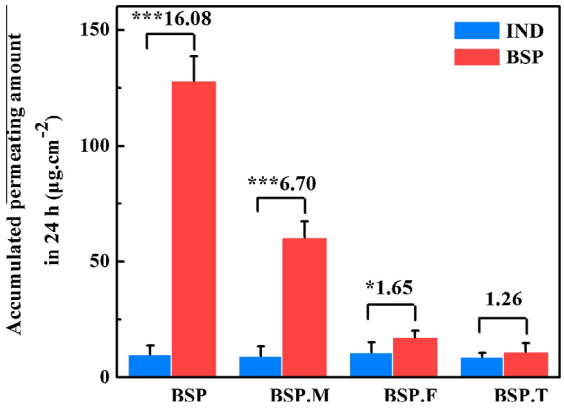


Fig. 1. Effect of BSP ion-pair complexes on the accumulated skin permeating amounts of IND and BSP in 24 hours (h) from patches. Their respective $R_{BSP/IND}$ was shown above the columns. $^{*}p < 0.05$, $^{***}p < 0.001$. ($n = 4$) (mean ± S.D.). (For the interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.2.2. Preparation of compound patches

The compound patches containing equal molar IND, BSP (or its ion-pair complexes) or enhancers were prepared as described previously [3].

2.3. In vitro studies

2.3.1. Determination of drug solubility in receptor fluid

Excess drug was added to the receptor fluid (pH 7.4 phosphate-buffered solution), vortexed to dissolve the drug and then equilibrated at 32 ± 0.5 °C for 48 h. The supernatant solution was filtrated, then diluted and analyzed by HPLC.

2.3.2. Drug permeation experiments

Excised rabbit skin was used to investigate the permeating amounts of IND and BSP and obtained as illustrated previously [3]. Side-by-side diffusion cells (effective diffusion area = 0.95 cm^2) were employed at a water bath of 32 °C [3]. The dermal side of skin faced the receiver cell filling with 3 ml receptor fluid, in which the sink condition for IND and BSP was guaranteed. The receptor fluid was stirred at 600 rpm with a star head magnetic bead. The patch was pressed on the skin with the adhesive side facing stratum corneum. Then 2.0 ml of receptor fluid was withdrawn at predetermined times 2, 4, 6, 8, 10, 12 and 24 h for analysis and replaced with the same volume of fresh receptor fluid to maintain sink conditions.

The accumulated skin permeating amounts of IND and BSP per unit area in 24 h were represented by $Q_{IND,24h}$ and $Q_{BSP,24h}$, respectively. The regulation effects of ion-pair complexes and chemical enhancers were expressed by $R_{BSP/IND}$ and ER_{BSP} (or ER_{IND}), respectively, which were calculated using following equations.

$$\text{Ion-pair complexes} \quad R_{BSP/IND} = Q_{BSP,24h}/Q_{IND,24h} \tag{1}$$

$$\text{Chemical enhancers} \quad ER_{BSP} = Q_{BSP,24h}\ (\text{enhancer})/Q_{BSP,24h}\ (\text{control}) \tag{2}$$

$$ER_{IND} = Q_{IND,24h}\ (\text{enhancer})/Q_{IND,24h}\ (\text{control}) \tag{3}$$

2.3.3. Drug release experiments

The release behavior of IND, BSP or its complexes from compound patches was also investigated by the diffusion cell mentioned above. The patch was attached to a kind of semipermeable membrane called Cellophane®, which substituted the skin. The other experiment procedure was the same as that in permeation experiment.