International Journal of Biological Macromolecules 64 (2014) 144–149

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

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

Investigation of antihypertensive activity of carbopol valsartan transdermal gel containing 1,8-cineole

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ARTICLE INFO

Article history:
Received 21 October 2013
Received in revised form
11 November 2013
Accepted 22 November 2013
Available online 1 December 2013

Keywords:
Antihypertensive activity
Transdermal gel
Valsartan

ABSTRACT

The purpose of this work was to develop a transdermal gel formulation for enhanced delivery of valsartan for the management of hypertension. Transdermal gels bearing valsartan, carbopol and 1,8-cineole (penetration enhancer) were prepared and characterized for various parameters including in vitro skin permeation studies, pH, spreadability, viscosity, skin irritation potential and in vivo antihypertensive activity. Optimized valsartan gel formulation (VTGF9) showed highest transdermal flux (143.51 μg/cm^2/h), with an enhancement ratio of 4.53 when compared to control gel formulation (VTGF8). Incorporation of 1,8-cineole and ethanol in gel formulation enhance the permeation of valsartan significantly. Skin irritation and histopathological study revealed that the VTGF9 was safe, less irritant and well tolerable formulation for transdermal delivery. In vivo antihypertensive activity revealed that optimized VTGF9 was successful in reverting the rat BP to normal values in experimental hypertensive rats. Finally, it could be concluded that VTGF9 accentuates the flux of valsartan and is an efficient transdermal therapeutic system for delivery of valsartan.

1. Introduction

Transdermal route has been utilized since ancient times to transport a range of therapeutically active molecules into the systemic circulation via skin. Transdermal systems are particularly useful when drug therapy is required for chronic ailments or for a long period of time as compliance as high for last of administration. Therefore the formulation of a transdermal system for hypertension is a rational prospect [1]. Drug delivery through percutaneous route promises many advantages over conventional modes of drug administration as it avoids hepatic first pass metabolism and improves patient compliance, decrease in frequency of administration and reduction in gastrointestinal side effects [2] but human skin is designed in such a way that it keeps our inside in and outside out [3]. The principal barrier to the topical drug delivery is the stratum corneum (SC) which is the outermost layer of the skin. Many approaches have been employed to mitigate SC permeability, and most commonly used approach is the use of sorption promoters also called penetration enhancers [4]. Terpenes are very safe and effective class of penetration enhancers obtained from natural sources and USFDA classifies them as GRAS (generally regarded as safe). Terpenes (constituents of volatile oils) exhibit excellent permeation enhancing effects to facilitate transdermal drug delivery. They can enhance the permeation of both lipophilic drugs (such as testosterone) and hydrophilic drugs (such as propranolol) [5]. They cause no skin toxicity or if any, only mild irritation [6,7]. Even terpenes which are considered to be skin irritant did not cause lasting erythema at all [8].

Valsartan (Fig. 1) has been previously identified as a promising candidate for transdermal drug delivery [9–14]. Valsartan having low oral bioavailability of about 23% [15]. It has low molecular weight (435.5 Da) and melting point (116–117 °C) with a log partition coefficient (4.5), p*K*a (4.73) and mean biological half-life (7.5 h), there are no reports of skin irritation attributed to valsartan. [9,11]. Due to its low bioavailability after oral administration, and the adverse effects related to oral administration, the development of transdermal therapeutic system for valsartan has rational significance.

Previously [9] we have reported that 1% (w/w) 1,8-cineole (Fig. 2) was found to be the most effective enhancer than other investigated terpenes (D-limonene, L-menthol, linalool and forskolin) for diffusion of valsartan through rat skin.

Hence, the present work was carried out to develop a carbopol loaded transdermal gel of valsartan using 1,8-cineole as penetration enhancer for the efficacious transdermal delivery of drug and to elucidate the skin irritation potential and antihypertensive activity of developed valsartan transdermal gel formulation (VTGF).

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http://dx.doi.org/10.1016/j.ijbiomac.2013.11.018

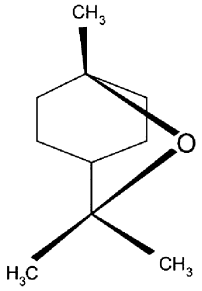

Fig. 2. The chemical structure of 1,8-cineole.

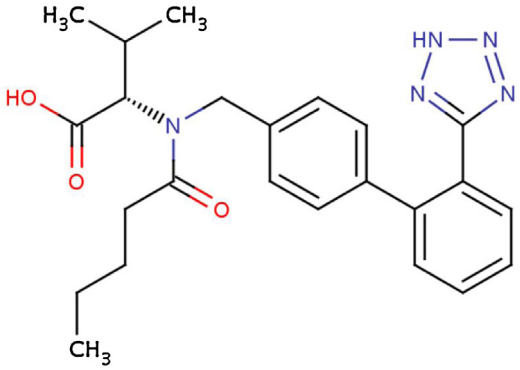

Fig. 1. The chemical structure of valsartan.

2. Materials and methods

2.1. Materials

Valsartan was received as a gratis sample from Ranbaxy Research Laboratories Ltd, Gurgaon, India. 1,8-cineole was purchased from Sigma–Aldrich, USA. Carbopol® 940, polyethylene glycol-400 (PEG) and triethanolamine (TEA) were purchased from S.D. Fine Chemicals, India. Methyl prednisolone acetate (MPA) injection (Depo-Medrol™) was purchased from Pfizer manufacturing Belgium, Nevada. Absolute ethanol was purchased from Merck, Germany. Water for HPLC was purchased from Thomas Baker (Chemicals) Ltd., Mumbai. Double distilled water was used for all experiments.

2.2. Animals

Twenty four albino Wistar rats (6–8 weeks/120–125 g) were supplied by Central Animal House of Hamdard University and inhabited under standard laboratory conditions in 12 h light/dark cycle at 25 ± 2 °C. Animals were nourished with pellet diet (Lipton, India) and water ad libitum. The animals were received after the study was duly approved by the University Animal Ethics Committee, and CPSCEA (Committee for the purpose of control and supervision on experiments on animals), Government of India.

2.3. Preparation of VTGF

For the preparation of transdermal gel several polymers were employed such as chitosan, hydroxypropyl methycellulose, carbopol, sodium carboxymethyl cellulose, carboxymethyl cellulose, etc. with different grades. The carbopol on the basis of its good consistency was used. Many placebo gels were prepared with this polymer at different concentration. Carbopol polymers are GRAS polymers and as such are extensively used in pharmaceutical industry [16,17]. Thus, carbopol 940 in the concentration range of 0.5–1% (w/w) was selected for gel preparation.

VTGF were prepared by dispersing 0.5 to 1% (w/w) carbopol 940 in distilled water. The polymer dispersion was kept in dark for 24 h to allow for the complete swelling of the polymer. Then 2.95% (w/w) of valsartan was dissolved in the specified quantity of ethanol (15% (w/w)). The 1% (w/w) 1,8-cineole (permeation enhancer) was added to the above alcoholic solution of drug. This alcoholic solution of drug was added slowly in the aqueous dispersion of polymer. Then other ingredients like PEG and triethanolamine were added to get homogeneous dispersion of gel [18]. The composition of different developed formulation are given in Table 1.

2.3.1. Preparation of rat skin

Wistar rat was sacrificed with prolonged ether anesthesia, the abdominal skin of each rat was excised. Hairs on the skin of animal were removed with electrical clipper; subcutaneous tissues were surgically removed, and dermis side was wiped with isopropyl alcohol to remove residual adhering fat. The skin was washed with isotonic phosphate buffer (IPB), wrapped in aluminum foil and stored in a deep freezer at −20 °C until further use (used within two weeks of preparation). On the day of experiment, skin was brought to room temperature and skin samples were mounted over the diffusion cells in such a way that SC side faced the donor compartment whereas the dermis faced the receiver compartment [19,20].

2.3.2. In vitro skin permeation studies

In vitro permeation studies were carried out through rat skin using an automated diffusion transdermal diffusion cell sampling system (SFDC 6, LOGAN Instruments, NJ, USA). The system consisted of three side-by-side cells with area of diffusion 0.636 cm^2 and 4 mL of receptor cell volume. The water was warmed with the inbuilt heater thermostated set at 37 ± 1 °C throughout the experiments to provide a skin surface temperature of approximately 32 ± 1 °C [21,22]. A Teflon coated mini magnetic stirrer was kept in the receiver compartment for agitating the contained vehicle (ethanol: IPB (pH 7.4) (40:60) at 600 rpm. The receptor compartment was filled with vehicle, containing 0.003% (w/v) sodium azide as a preservative. Receptor fluid was sonicated to remove dissolved gases before placing in the receptor compartment. Hydrated skin samples were mounted into the diffusion cells facing SC toward

Table 1
Composition of transdermal gel formulations (% w/w).

Constituents	Formulations code								
	VTGF1	VTGF2	VTGF3	VTGF4	VTGF5	VTGF6	VTGF7	VTGF8	VTGF9
Valsartan	2.95	2.95	2.95	2.95	2.95	2.95	2.95	2.95	2.95
Carbopol 940	0.5	0.5	0.5	0.75	0.75	0.75	1.0	1.0	1.0
Ethanol	5	5	5	10	10	10	15	15	15
PEG	0	5	5	0	10	10	0	15	15
1,8-Cineole	0	0	1	0	0	1	0	0	1
TEA	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Water for HPLC	91.05	86.05	85.05	85.8	75.8	74.8	80.55	65.55	64.55