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Systemic Delivery of Calcium Channel Blockers for Hypertension through Transdermal Delivery - A Review

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Abstract. Hypertension is a significant public health challenge, responsible for a substantial proportion of deaths and disability globally. Calcium Channel Blockers (CCBs) are an essential class for the treatment of hypertension. However, most of CCBs must be taken more than once daily due to their low oral bioavailability and limited half-life leading to non-compliance in patients. The development of delivery methods for CCBs is an ongoing effort to overcome the issues related to their delivery via their traditional forms. The administration of the drug through the skin for systemic delivery has been recognised as one of the potential routes in hypertension treatment, especially when drugs suffer from low bioavailability, undesirable side effects and short biological half-life following oral administration. The main limitation of transdermal drug delivery is the resistance barrier of skin layers to penetrant molecules. Remarkable research efforts have been made worldwide to minimise the skin barrier and to create transdermal systems of several CCBs via employing skin-enhancing potential. The persistent progress in this field is promising for development the transdermal dosage forms advance technology in the long term and being commercialised sooner rather than later. This review explores the investigations on the viability and applicability of systemic delivery of numerous CCBs through the skin.

Introduction

The most prevalent heart disease in the world is high blood pressure, also known as hypertension. Hypertension is the condition whereby systemic arterial pressure is increased beyond normal levels over long periods [1]. According to worldwide studies on disease burden 5.2 million deaths were attributed to heart disease in economically developed countries. In developing countries, this figure is almost doubled at 9.1 million deaths [2]. Treatment of chronic high blood pressure occurs over a long period, often burdening the patient with repeated administration of drugs in conventional form. As a result, treatment compliance among patients is often low [3].

Transdermal drug delivery offers several advantages over traditional routes of drug administration: (1) by-passing the first-pass effect (2) lowering dosage size and frequency (3) extended drug therapeutic range (4) prolonged drug half-life (5) smaller variability in patients and across patients [4]. In transdermal delivery research, researchers are faced with the hurdle of crossing the skin barrier while avoiding trauma or irritation at the delivery site. The stratum corneum specifically is the skin layer that presents the biggest hurdle against delivery of the drugs transdermally [5].

Extensive studies have been done to overcome the barrier property of the stratum corneum for effective transdermal drug delivery. Transdermal patches currently in use in clinical settings were developed as first-generation methods, and the properties of the drug limited them. The properties of the drug that limits the permeation were low molecular weight, lipophilicity, and effective at low dose. Third-generation transdermal delivery advances focused on high permeability through the stratum corneum while preserving the deeper tissue layers from damage [6, 7]. Microneedles, thermal ablation, microdermabrasion, electroporation and cavitational ultrasound were developed to achieve these objectives.

Therapeutics against hypertension can be categorized via their mode of actions; some common agents include thiazide diuretics, β-blockers, the ACE inhibitors, calcium channel blockers (CCBs) and angiotensin II receptor antagonists [8].

Calcium channel blockers (CCBs), can be divided into two classes: dihydropyridines (DHP) and non-dihydropyridines (non-DHP). DHP class CCBs are clinically classified based on the difference in the formula and the length of their action to 1st, 2nd, 3rd, and 4th generations while non-DHP classified to benzothiazepines (Diltiazem) and phenylalkylamines (Verapamil) [9, 10]. Most of these drugs have negative physicochemical traits that pose a challenge to their delivery, including low bioavailability in the body, short half-life, poor absorbance across the skin, and adverse reactions as well as the majority of these drugs are susceptible to first-pass metabolism [11]. Transdermal delivery systems have become a viable method for CCB drugs due to their ability to avoid the pitfalls associated with delivery via conventional means. Our manuscript describes recent advances in CCB transdermal delivery research.

Dihydropyridines

Nifedipine. Nifedipine is a first-generation of DHD calcium channel blocker that is prescribed extensively in patients with hypertension and angina [12, 13]. The molecular weight of nifedipine is 346.33, with a log P of 2.49, biological half-life of 2 h and 50 - 70% bioavailability [14]. Oral administration of nifedipine encounters pre-systemic metabolism phase in the GI tract that limits its bioavailability and absorption [15]. Nifedipine is a suitable drug for the development of transdermal delivery routes due to its low molecular weight, the small daily dose (10-60 mg). Development of an effective transdermal system will increase patient compliance [16].

Proniosomes are non-ionic surfactant vesicles in a microscopic lamellar structure formed by the admixture of non-ionic surfactants, with or without cholesterol which are subsequently hydrated in aqueous media to form niosomes [17]. Yasam et al. (2016) developed nifedipine loaded niosomes for the transdermal treatment of hypertension. The biodistribution analysis of nifedipine showed that the developed niosomal formulation maintained sustained-release concentration in the cardiovascular tissue [16].

Felodipine. Commonly prescribed second-generation of dihydropyridine CCB agent against hypertension and angina is Felodipine. It is commercialised as a tablet (2.5-10 mg) for oral administration, and it has a bioavailability of 15-20% after going through pre-systemic metabolism [18]. Felodipine log P is 4.36, and the molecular weight is 384.26 Da. Its terminal elimination half-life ranges from 7 to 21 h [14].

Yusuf et al. (2014), used a rotary evaporation sonication method to formulate transfersomal formulations of felodipine for enhancement of its transdermal delivery. Also, they investigated the parameters for optimisation of variable membrane compositions containing soya and egg lecithin and edge activator. The bioavailability of felodipine from the transdermal formulation was found to be 358.42% compared to oral administration. Confocal laser scanning microscopy provided further evidence of the fast penetration of drug to across dermal layers [18].

Nisoldipine. Nisoldipine is a second-generation of dihydropyridine CCB. It is used alone or in combination with other drugs to manage hypertension and angina pectoris [19]. Nisoldipine is classified under BCS, as a class II drug; hence, nisoldipine has poor solubility but high permeability [20].

El Maghraby et al. (2015) in their study reported the preparation of proniosomes for nisoldipine transdermal delivery. The proniosomes were either plain, contained lecithin, or permeation enhancers. The authors found that proniosomes increased nisoldipine transdermal flux up to 12 fold compared to an aqueous drug solution at maximal saturation (from 0.46 to 12.18 $\mu g/cm^2/h$). The addition of lecithin to the formulation further improved transdermal flux values to 28.51$\mu g/cm^2/h$ [21].

Amlodipine. Amlodipine belongs to the third-generation of dihydropyridine categories of CCBs, and the antihypertensive action of amlodipine is attributed to its ability to relax the vascular smooth muscle [22].

Recently, Kapoor and colleagues investigated the effect of nanostructured lipid carriers (NLCs) for transdermal transport of amlodipine. The optimised amlodipine NLCs displayed enhanced transdermal flux (58.33 μg/cm^2/h), low particle size (123.8 nm), and higher entrapment efficiency (88.11%). Experiments using Wistar rats showed increased bioavailability of the drug. At the same time, rhodamine red (RR)-loaded NLCs facilitated increased dye penetration into the deeper layers of the skin, as shown by CLSM [23].

Cilnidipine. Cilnidipine is a fourth-generation of DHD calcium channel blocker used in the management of hypertension; it emerged as a good candidate for combination therapy [24]. Cilnidipine is a BCS Class II drug; it is highly lipid-soluble with a log P of 4.7, poorly soluble in aqueous, and has a low dissolution rate [25].

Khatoon et al. (2019) attempted to formulate cilnidipine loaded transfersomes for transdermal application. As per the published report, the final formulation showed small vesicle size (206.24 ± 5.94 nm) with a useful polydispersity index (0.302 ± 0.034), sufficient drug entrapment (96.45 ± 1.92%) and a good transdermal flux (27.72 ± 3.55 μg/cm^2/h) [26].

Phenylalkylamines and Benzothiazepines.

Transdermal researches of verapamil and diltiazem illustrated in Table 1.

Table 1. Transdermal researches of verapamil and diltiazem

Name of drug	Chemical profile	Transdermal outcome	Reference
Phenylalkylamines (Verapamil HCl)	Log P (5.23) MW (491.07 Da) Low bioavailability around 20-30%	Elastic liposomes for the delivery showed that elastic vesicles led to an enhanced transdermal flux (50.2 ± 4.52 μg/cm^2/h) of verapamil HCl as compared to liposomes (11.6 ± 2.12μg/cm^2/h).	[27]
Benzothiazepines (Diltiazem)	Log P (3.09) MW (414.53 Da) Low bioavailability (40%)	Diltiazem matrix films via the solvent casting method increased the transdermal of diltiazem to the highest levels of transdermal flux (89.7l μg/cm^2/h).	[28]

Summary

Transdermal drug delivery systems may present a solution for effective CCB delivery, due to their ability to by-pass the pre-systemic metabolism, prolong drug action, and reduce non-compliance in patients. This review presents briefly transdermal delivery systems developed for CCBs to overcome the problems associated with conventional delivery formats. However, much work still needs to be carried out on transdermal delivery systems for CCBs to achieve effective therapeutic dosages for clinical use.

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