

# Effect of Low Molecular Weight Chitosans on Drug Permeation through Mouse Skin: 1. Transdermal Delivery of Baicalin

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**ABSTRACT:** The aim of this work was to evaluate the low molecular weight chitosans (LMWCs) as enhancers of transdermal administration of baicalin, an useful drug for the treatment of atopic dermatitis, viral hepatitis, and HIV infection. Permeation experiments were performed *in vitro* through mouse skin by using Franz cells. Improved baicalin skin penetration was obtained with the addition of LMWCs or D-glucosamine ( $\beta$ -D-GlcNH<sub>2</sub>) to the donor solutions. Chitosan molecular weight, degree of deacetylation, pH of donor baicalin solutions, and enhancer concentration all affected LMWC enhancement effects. Significant enhancement was observed at pH 7.0 or 7.5 for CS80-1000, and the enhancement factor (EF) in the co-delivery method was calculated as 11.7 or 15.9, respectively. Simultaneously,  $\beta$ -D-GlcNH<sub>2</sub> showed greatest enhancement at pH 7.0 with an EF of 11. Moreover, there was an optimal concentration range (0.5–1% by weight for CS80-1000 and 1.0–1.5% for  $\beta$ -D-GlcNH<sub>2</sub>) to enhance baicalin transdermal delivery. It was concluded that the effective fractions for the enhancement of LMWCs were  $\beta$ -D-GlcNH<sub>2</sub> oligomers, and the repeated number of  $\beta$ -D-GlcNH<sub>2</sub> was suggested to be in the range 2–6. Enhancement mechanism of LMWCs was also discussed and suggested to be relative to the interactions of LMWC with both baicalin and the lipid of stratum corneum.

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**Keywords:** transdermal drug delivery; permeation enhancers; low molecular weight chitosan; baicalin; permeability

## INTRODUCTION

The transdermal route is an attractive alternative to deliver therapeutic drugs that are subject to extensive first-pass metabolism into the systemic circulation.<sup>1</sup> However, the remarkable barrier properties of the skin membrane, especially the outermost stratum corneum layer, cause a poor skin permeability of compounds that are hydrophilic, very lipophilic, of high molecular weight, or charged.<sup>2,3</sup> Several strategies have been explored, such as the use of chemical enhancers and of physical techniques. The use of chemical penetration enhancers would be a convenient method. But the problem with most known dermal penetration enhancers is that they are often toxic, irritating, or allergenic.<sup>4</sup>

Chitosan is attracting increasing attention in drug delivery systems due to its excellent biocompatibility, biodegradability, and nontoxicity.<sup>5,6</sup> High molecular weight chitosans (HMWCs, unmodified form or chemically/physically modified form) have been found to be good carriers for enhancing skin penetration of effective substances, such as buprenorphine<sup>7</sup> and propranolol hydrochloride.<sup>8</sup> However, the high molecular weight and low solubility in water or organic vehicles prohibit it from interacting with the underneath layer from the skin surface and thus significantly limit its enhancement effect.<sup>9</sup> Fortunately, these drawbacks can be partially circumvented by using low molecular weight chitosan (LMWC), which is water soluble in a wide pH range. Moreover, LMWCs showed superior biological activities compared to HMWCs, including biodegradability, biocompatibility, antioxidant, and antibacterial activity.<sup>10–13</sup> But to date there are few reports on the drug skin permeation effects of LMWCs.

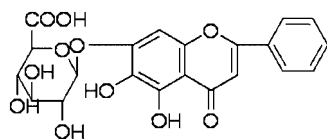
Flavonoid glucuronide structure represents a kind of significant effective ingredients in Chineseherbal

Additional Supporting Information may be found in the online version of this article.

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**Figure 1.** Structure scheme of baicalin.

medicine.<sup>14,15</sup> Baicalin (Fig. 1) is a flavonoid glucuronide that is isolated from the Chinese traditional medicinal plant *Scutellaria baicalensis* Georgi (Labiateae). It has antioxidant, antiinflammatory, anti-HIV, and antiangiogenesis activities, induces apoptosis, inhibits formation of colon aberrant crypts, inhibits cancer cell proliferation, protects bone marrow, promotes hemopoiesis, and protects the intestines from adverse drug effects.<sup>16–18</sup> Baicalin has been used clinically against atopic dermatitis, viral Hepatitis, and HIV infection, by oral or intravenous formulations.<sup>19,20</sup>

However, following intravenous administration of baicalin has a short biological half life of 0.16 h<sup>21,22</sup> for its relative high molecular weight (MW = 447) and typical physical property (dissociation constant  $pK_a$  of 2.9, water solubility of 0.091 g/L at 20°C and partition coefficient  $P_{1-octanol-water}$  of 1.29).<sup>23</sup> Furthermore, significant hepatic first-pass metabolism has been observed, and the bioavailability is only 54% after oral administration.<sup>24</sup> These undesirable side effects could be offset by using the transdermal route.<sup>25,26</sup> However, the skin barrier needs to be overcome.

In this article, we investigated the transdermal delivery of baicalin in aqueous solution. LMWCs with different molecular weights were applied to enhance the baicalin transdermal delivery. The effects of pH and LMWC concentration on this enhancement were studied. Finally the enhancement mechanism of LMWCs was discussed in detail.

## MATERIALS AND METHODS

### Materials

LMWCs with molecular weights of 1 kDa (CS80-1000), 2 kDa (CS80-2000), 4 kDa (CS80-4000), or 5 kDa (CS80-5000) were supplied by Southern Yangtze University (Wuxi, China). The degree of deacetylation was about 80%.<sup>27</sup> *N*-acetylglucosamine ( $\beta$ -D-GlcNAc, >99%) and D-glucosamine hydrochloride ( $\beta$ -D-GlcNH<sub>2</sub>·HCl, >98%) were obtained from Acros Organics (New Jersey, USA). Baicalin contrast product (No. 110715–200212, >99%) was purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Baicalin (97% for injection) was obtained from SiChuan ShiFang RuiBang Natural-Chemical Co. Ltd (SiChuan Province, China). Glycerol was

purchased in officinal grade from Xiangxi Chemical Industry (Hubei Province, P.R. China). All other chemicals were of reagent or HPLC grade.

### Preparation of LMWCS with Different Degree of Deacetylation

CS80-1000 (1.016 g) was dissolved in 100 mL of 60% (v/v) methanol aqueous solution. Acetyl anhydride (6, 12, or 18 mL) was added to the mixture and allowed to react at room temperature for 16 h. Then the solution was poured into 200 mL ethanol. The precipitate was separated, washed with ethanol and ethyl ether, and dried *in vacuo*. The degree of deacetylation of products was measured as reported by Gupta and Jabrail.<sup>27</sup>

### Preparation of Pretreated LMWC Solutions

LMWC was dissolved in acetic acid solution (pH 3.0) and the concentration was controlled as 0.5% (by weight). pH value was adjusted exactly with triethanolamine to 6.0, 6.5, 7.0, 7.5, or 8.0. The controls were prepared using the same procedure, except for 0.5% (w/w) acetic acid solution (pH 3.0) that did not contain LMWC.

### Preparation of Baicalin Solutions

Baicalin was dissolved in a solution of glycerol, triethanolamine and deionized water at a ratio of 5:3:25 (v/v) and kept in the dark before use.

### Preparation of Baicalin-LMWC Solutions

Baicalin was dissolved in a solution of glycerol, triethanolamine, and deionized water at a ratio of 5:3:25 (v/v). This solution was added to 0.5% (by weight) acetic acid solution (pH 3.0), with or without LMWC, until the final baicalin concentration reached 100 mg mL<sup>-1</sup>. Finally the pH value was adjusted exactly with triethanolamine or acetic acid to 6.0, 6.5, 7.0, 7.5, or 8.0. The controls were prepared using the same procedure, except for 0.5% (w/w) acetic acid solution (pH 3.0), which did not contain LMWC.

### *In Vitro* Transdermal Delivery Experiments

Kunming mice weighing 25–30 g (supplied and approved by Tianjin Municipal Institute for Drug control) were killed by cervical dislocation and the hair of the abdominal region was carefully shaved. Then a portion (about 1.5 × 1.5 cm<sup>2</sup>) of the full thickness of the skin was carefully excised, washed with saline and used afresh. The integrity of the skin was checked upon mounting on the diffusion cells with the aid of a small flashlight. All procedures were approved by Ethics Committee of Tianjin Changzheng Hospital.

*In vitro* skin penetration studies were performed using Franz vertical diffusion cells. The receptor medium consisted of PEG 400 and 0.9% saline at a

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