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The Proparation and Long-term Storage Stability of Carbomer Loaded Polydatin Nanocrystals Hydrogels

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Abstract: This work aims to develop carbomer (934, 0.25%) loaded polydatin nanocrystals hydrogel (Pol-NaH) as a novel dermal formulation..Polydatin nanocrystals were prepared by high pressure homogenization technique, applying 1500 bar up to 15 cycles. The long-term storage stability of Pol-NaH was studied after stored at room temperature for 180 days. The physicochemical characteristics of Pol-NaH were conducted and used to evaluate the stability. The results showed that the particle size (PS), polydispersity index (PDI) and zeta potential (ZP) were 188.3±3.7 nm, 0.193±0.041 and −12.67±0.91 mV, respectively. After six months of storage, the Pol-NaH showed no significant changes in PS and PDI except a miner change in ZP. These results demonstrate that Pol-NaH could be a promising formulation for enhanced pharmacological activity of polydatin and were stable at at room temperature.

Keywords nanocrystals; hydrogels; polydatin; stability; long-term storage

INTRODUCTION

Polydatin or piceid (Pol, Figure1), resveratrol-3-O-β-glucopyranoside, is a precursor of resveratrol isolated from *Polygonum cuspidatum* Sieb. et Zucc. (Chinese name: Huzhang), and is commonly used as a quality control marker. Pol has obtained permission for clinical trials from the China Food and Drug Administration. Pol, the most abundant form of resveratrol in nature, glycosylation of resveratrol protects it from enzymic oxidation [Regev-Shoshani *et al.*, 2003]. The content of Pol was found higher than that of resveratrol in grape seed, red wine and red sorghum grains [Brohan *et al.*, 2011]. Pol has been reported to exhibit promising pharmacological activities including anticarcinogenic [Zhang *et al.*, 2014], antiplatelet aggregation [Orsini *et al.*, 1997], anti-inflammatory [Lou *et al.*, 2015], antihemorrhagic shock [Wang *et al.*, 2013], protect against carbon tetrachloride-induced liver Injury [Zang *et al.*, 2012], ameliorates oxidative stress-related inflammatory responses resulting in renal injury [Chen *et al.*, 2013], anti-aging [Wen *et al.*, 2014], ameliorates insulin resistance and hepatic steatosis [Zhang *et al.*, 2015], and anti- oxidation activity [Su *et al.*, 2013]. Recently, it is found that Pol promotes Nrf2-ARE anti-oxidative pathway through activating Sirt1 to resist AGEs-induced up-regulation of fibronetin and transforming growth factor-β1 in rat glomerular messangial cells [Huang *et al.*, 2015]. However, Pol is hardly water-soluble and its absorption is very poor after administration.

Nanocrystal is a carrier-free nanoparticle system containing only pure drug crystal and minimum surfactant and/or polymer for stabilization [Gao *et al.*, 2013]. Reduction of particle size by nanocrystal technology to the nano-scale usually leads to a significant increase in drug solubility and dissolution rate with a obvious improvement in drug bioavailability. Liversidge reported that [Liversidge *et al.*, 1995], in the same dosage, danazol NS with the average particle size of 169 nm could obtain the C_{max} as high as 3.01 mg/ml and the bioavailability of 82 % in beagle dogs, while the commercially available danazol suspension with the average particle size of 10 mm could only obtain the C_{max} of 0.20 mg/ml and the bioavailability of 5 %. It could be found that NS significantly enhanced the oral absorption of danazol, a poorly water-soluble drug. The principle of nanocrystals is that they improve the transport of drugs across a barrier/membrane. Surprisingly pharmaceutical attention focussed only on oral and i.v. administration. Other interesting areas such as dermal and ocular administration were completely neglected. This changed in 2005 with the filing of the first patent application for dermal delivery of cosmetic and pharmaceutical actives [Petersen, 2007]. It could be shown that the bioactivity in the skin of the original, poorly soluble plant molecule rutin is 500 times higher when compared to its water-soluble derivative rutin-glycoside. The first dermal products were placed on the market as cosmetic products by Juvena Switzerland in March 2007 (product line JUVEDICAL, product “DNA skin optimizer fluid” and “eye optimizer cream”). Incorporation of

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nanocrystals into dermal products is very simple. A concentrated nanosuspension is added to the water phase of creams or lotions. By now relatively little is published about dermal nanocrystals [Kobierski *et al.*, 2009]. A few techniques have been used to prepare drug loaded nanocrystal, including nanoprecipitation, pearl-milling, high speed homogenization, sonication, and high-pressure homogenization (HPH) [Keck *et al.*, 2006]. Among these techniques, HPH with a high productivity and a lower level contamination which is favorable for implementation of industrial products has shown great superiority over other methods. This work aims to develop carbomer (934, 0.25%) loaded polydatin nanocrystals hydrogel (Pol-NaH) as a novel dermal formulation. Polydatin nanocrystals were prepared by high pressure homogenization technique, applying 1500 bar up to 15 cycles.

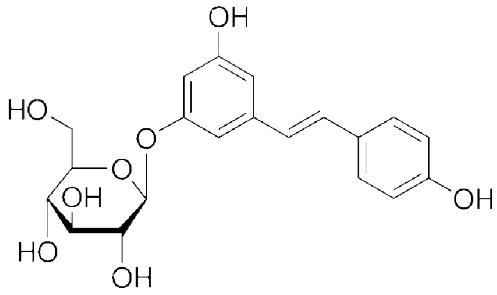

Figure 1 Chemical structure of polydatin

MATERIALS AND METHODS

Preparation of the Pol-NaH

HPH technique was applied to prepare Pol-Nanocrystal. Briefly, poloxmer188 (Pluronic® F68, BASF, Germany) 0.8 % and HPMC (hydroxypropylmethylcellulose, E15 LV, Dow Chemicals, UK） 0.45 % were dissolved in distilled water. The Pol powder 0.05 % was dispersed in the aqueous surfactant solution using high speed homogenization (IKA® T18 basic ULTRA-TURRAX® Germany) for 10 min at 5000 rpm. Then the pre-mix was passed through a Lab HPH (APV-2000, Germany), 5 cycles were performed at 500 bar, and 15 cycles at 1500 bar. Then, the Pol-NaH was prepared by added the Pol-Nanocrystal suspensions to the 0.25% carbomer 934 gel.

Characterization of the Pol-NaH

The particle size (PS), polydispersity index (PDI), and Zeta potential (ZP) measurements were performed on a Nano-ZS90 (Malvern Instruments Ltd., Malvern, UK) thermostated at 25 ^{0}C. The sample was diluted 50 times with bi-distilled water before the measurements. All values were measured at an analysis angle of 90 ^{0}C in a 10-mm diameter cell. Each value reported is the average of three measurements.

Statistical analysis

Results were expressed as mean ± standard deviation (SD). Student's t-test was used to compare the mean differences between samples using the statistical software SPSS version 16.0 (SPSS, Chicago). In all cases $P < 0.05$ was considered statistically significant.

RESULTS

The physicochemical characteristics of Pol-NaH

The characteristics of Pol-NaH are shown in table 1. After six months of storage at room temperature, the mean PS and PDI of Pol-NaH display no significant differences except a little decrease in ZP, as compared with the fresh preparation.

Table 1 Characteristics of Pol-NaH (mean±SD, n = 3)

Time/month	PS	PDI	ZP
0	188.3±3.7	0.193±0.041	−12.67±0.91
3	190.1±4.4	0.199±0.038	−11.83±0.86
6	191.7±3.9	0.198±0.046	−10.78±0.98

CONCLUSION AND DISCUSSION

These results demonstrate that Pol-NaH were stable at at room temperature and could be a promising formulation for enhanced pharmacological activity of polydatin. The nanoparticle size, polydispersity index and zeta potential have been used to evaluate the stability of nanocrystals suspensions [Zhang *et al.*, 2007; Kakran *et al.*, 2012]. In this study, Pol-NaH had good stability at room temperature. After six months of storage at room temperature, the suspension did not have agglomeration. Although a decrease in the zeta potential was observed, the zeta potential of the nanoparticles in the suspension was still over −10 mV.

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