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Maltodextrin fast dissolving films for quercetin nanocrystal delivery. A feasibility study

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ABSTRACT

The objective of this study was to evaluate the feasibility to prepare fast dissolving films as quercetin nanocrystal delivery systems, using maltodextrins as film forming material and glycerin as plasticizer, with the goal of enhancing quercetin oral bioavailability. Quercetin nanosuspensions were prepared using a high-pressure homogenizer, and then directly used to prepare the films by a casting method. Spectroscopic and calorimetric analysis evidenced that reduction of quercetin size at nanoscale and incorporation in maltodextrin films do not affect the solid state of the active ingredient. The loading of quercetin nanocrystals into the film determined a slight variation of film elasticity and ductility. Indeed, the elastic modulus of the loaded films resulted about a half of the placebo ones, while the elongation at break increased four folds. Free and film loaded quercetin nanocrystals showed a comparable dissolution rate, much higher than that of bulk quercetin.

1. Introduction

Quercetin (3,3,4,5,7-pentahydroxyflavone, QUE), one of the most common dietary polyphenols widely found in the plant kingdom including vegetables, fruits, medicine herbs and red wine, has been intensively investigated for its anti-inflammatory, antioxidant, antiviral, anticarcinogenic and cardioprotective properties (Nijveldt et al., 2001), without any evidence of toxicity, carcinogenicity or genotoxicity related to consumption (Harwood et al., 2007; Okamoto, 2005; Utesch et al., 2008). In the western world, the average daily intake of QUE has been estimated to be between 20 mg and 40 mg, but more research is necessary to establish the dosage required to achieve health effects while avoiding toxicity (Kelly, 2011). Moreover, biomedical applications of this natural compound are severally hampered by its low oral bioavailability due to poor water solubility and rapid metabolism (Cai, Fang, Dou, Yu, & Zhai, 2013).

To overcome these issues, several formulation approaches have been developed, involving the use of drug delivery systems such as cyclodextrin inclusion complexes, liposomes, micelles, and nanoparticles, which provide higher water solubility and bioavailability (Chessa et al., 2011; Fatma et al., 2014; Ribeiro et al., 2009; Zheng & Chow, 2009). Moreover, it has been reported that systems based on solid dispersions of quercetin in polymer matrices, are a promising approach for developing quercetin formulations with enhanced oral bioavailability. Polymer matrices include polyethylene glycol (Li, Zhang, Deng, & Liang, 2004), polyvinylpirrolidone (De Mello Costa et al., 2010) and, recently, cellulose derivative (Li et al., 2013).

Among the several strategies widely described in the literature, drug nanocrystal technologies are considered one of the most valuable approaches to formulation of poorly soluble drugs (Kocbek, Baumgartner, & Kristl, 2006; Müller, Gohla, & Keck, 2011). These technologies produce dispersions of drug nanocrystals in a liquid medium (typically water), which has to be eliminated by means of specialized techniques (spray drying or freeze drying) to obtain the final solid dosage form, namely tablets, capsules, granules and pellets. The main challenge in developing solid nanoparticle formulations is the redispersibility of dried drug nanoparticles that must have the ability to return to their original size (Lai et al., 2011; Van Eerdenbrugh et al., 2008). Interestingly, drug nanocrystals have been recently proposed in combination with the novel fast dissolving film technology (Shen et al., 2013). In this case, the nanosuspension was mixed with an aqueous solution containing fast dissolving film components and the final blend was casted and dried, thus obtaining a nanocrystal-loaded film, which was cut to

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the desired size. However, also in this case one of the main issues associated with the production of these dosage forms is nanocrystal aggregation and growth. Indeed, fast dissolving films can be made of polysaccharide polymers plasticized by low molecular weight excipients, such as glycerin, polyethylene glycol or propylene glycol, which could cause a physical instability of the drug nanocrystals.

The first polysaccharide employed to produce fast dissolving films was pullulan, a glucan consisting of maltotriose units obtained by the fungus *Aureobasidium pullulans* (Leathers, 2003). Pullulan can be considered the most suitable excipient for the design of these dosage forms since it presents favorable rheological and mechanical properties and processability. Nevertheless, its use is limited by the low availability and high costs. Thus, other edible hydrocolloids such as modified starches and cellulose ethers have been proposed as substitutes (Pinna & Pinna, 2009; Zerbe & Guo, 1998). The possibility of using maltodextrin (MDX) as film forming material and glycerin as plasticizer has been also demonstrated (Cilurzo et al., 2010; Selmin, Franceschini, Cupone, Minghetti, & Cilurzo, 2015).

MDX are water-soluble biopolymers obtained from the partial hydrolysis of food grade starch. They contain linear amylase, branched amylopectin and a relatively small amount of dextrose and maltose. D-Glucose units are primarily linked by α-(1,4) bonds, but there are also branched segments linked by α-(1,6) bonds. MDXs, which can differ in average molecular size, are commonly classified by their dextrose equivalent (DE) values, defined as the percentage of reducing sugars calculated as glucose on a dry substance basis. Several physical and functional characteristics are influenced by the DE such as solubility, freezing temperature and viscosity (Garnero, Chattah, & Longhi, 2013).

The purpose of this study was to evaluate the feasibility of preparation of orodispersible fast dissolving films containing QUE nanocrystals, using maltodextrins as film forming material and glycerin as plasticizer (Cilurzo et al., 2010; Cilurzo, Cupone, Minghetti, Selmin, & Montanari, 2008), with the purpose of enhancing QUE oral bioavailability bioavailability. Indeed, these films, when placed onto or under the tongue disintegrate in a short time favoring the local drug absorption, avoiding first-pass hepatic metabolism. Moreover, they are useful for patients who have difficulty in swallowing (Shen et al., 2013).

In this work, QUE nanosuspensions were prepared using a high pressure homogenizer (Lai et al., 2014), and then directly used for drying by lyophilisation or preparing the fast dissolving films. The solid state of bulk QUE, QUE nanocrystals and QUE films were investigated by means of FTIR, DSC and XRPD analyses. Moreover, QUE nanocrystals were characterized by photon correlation spectroscopy for mean size and size distribution and by transmission electron microscopy for morphological studies. The dissolution profile of QUE nanocrystal-loaded films was compared to that of freeze dried QUE nanocrystals and bulk QUE. Furthermore, the effect of nanocrystals on fast dissolving film tensile properties was investigated.

2. Materials and methods

2.1. Materials

Maltodextrin having a D.E. equal to 6 and molecular mass 2720 g/mol (Glucidex® IT6, MDX6) was obtained by Roquette, (France). Glycerin (GLY) and sorbitan monooleate (Span® 80, S80) were purchased from Carlo Erba Reagenti (Italy) and Croda (Italy), respectively. Polysorbate 80 (Tween® 80, T80) was purchased from Galeno (Italy) and QUE was purchased from Sigma-Aldrich (Italy). All solvents were of analytical grade, unless otherwise specified.

2.2. QUE nanosuspension preparation

QUE nanosuspensions were prepared by high pressure homogenization. 5% (w/w) QUE coarse powder was dispersed in water with 1% (w/w) Tween 80 and disintegrated into microsuspensions by a high shear homogenizer (Ultra-Turrax® T25, IKA, Germany) at 12.000 rpm for 5 min. Obtained microsuspensions were homogenized at high pressure using a high pressure homogenizer (EmulsiFlex-C5, Avestin Inc., Ottawa, Canada). At first, 5 cycles at 500 bar were conducted as pre-milling step, and then 20 cycles at 1000 bar were run to obtain the nanosuspension. The obtained nanosuspensions were freeze dried or directly used to obtain fast dissolving films containing QUE nanocrystals.

2.3. Fast dissolving film preparation

Films were prepared modifying the solvent casting technique previously described (Cilurzo et al., 2008). Briefly, drug loaded films were obtained by gradually adding MDX6 to a QUE nanosuspension under magnetic stirring until the film forming material was completely dissolved. Afterwards, GLY and S80 were added. The component amounts were set in order to have a MDX6/GLY/S80 ratio of 76/21/3 w/w (film thickness was set to achieve a final weight of about 100 mg/6 cm^2) and a final drug content of 10 mg/6 cm^2. To better investigate the QUE solid state, a placebo formulation with the same composition, including the Tween 80 used for the production of the nanosuspension but without quercetin was also prepared as control.

After a rest period of 16 h, slurries were cast over a silicone release liner by a laboratory-coating unit Mathis LTE-S(M) (Switzerland). Operative conditions: coating rate: 1 m/min; drying temperature: 50 °C; drying time: 20 min; air circulation speed: 1200 rpm. Films were cut into suitable shape and size as required for testing, packed immediately after the preparation in individual airtight aluminum seal packs and stored at 25 °C until use. Placebo films were also prepared following the same procedure.

2.4. Analytical characterization

Infrared absorption spectra were recorded on a Perkin Elmer (MA, USA) FTIR Spectrometer "Spectrum One" in the middle infrared region (4000 and 450 cm^{-1}). The solid samples, mixed in a mortar with KBr (1:100), were pressed in a hydraulic press (9 tons) to small tablets and analyzed by transmittance technique with 8 signal-averaged scans collected at a spectral resolution of 4 cm^{-1}.

The XRPD analyses were carried out by using a Rigaku Miniflex diffractometer. The setting parameters were Ni-filtered Cu*K*α radiation detector (λ = 1.5405 Å), voltage of 30 kV, current of 15 mA, scan angular speed 2°/min and scan step time 2.00 s in the 2θ range from 3° to 60°. The XRPD patterns of QUE raw material, freeze dried QUE nanocrystal, QUE nanocrystal-loaded films and placebo films were recorded. The films were cut in disks of a diameter comparable with that of the aluminum sample plate and then analyzed in the conditions above described.

The DSC curves of the different samples were recorded on a Perkin Elmer DSC 6 differential scanning calorimeter calibrated with indium. The thermal behavior was studied by heating 2.5 mg samples in aluminum crimped pans under nitrogen gas flow. The samples were heated from 25 °C to 100 °C at 10 °C/min to eliminate moisture, quickly cooled at 25 °C and then heated from 25 °C to 350 °C at 10 °C/min; reported thermograms refer to the second heating scan.