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Short communication

Electrospray technique for cocrystallization of phytomolecules

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ABSTRACT

Poor aqueous solubility of most of the phytomolecules has restricted their vital biological use. Cocrystal approach can be one of the remedies for the problem. The present work was carried out with an objective to screen the potential of electrospray technique towards cocrystallization of quercetin (QUE). QUE was cocrystallized with caffeine (CAF) and nicotinamide (NIC) as coformers. Saturated methanolic solutions of QUE with either of the coformers (CAF and NIC) in 1:1 ratio were electrosprayed at 40 °C. The technique was successfully used for cocrystallization of QUE with CAF and NIC separately as revealed by Powder X-ray Diffraction, Differential scanning calorimetry and Fourier transform infrared spectroscopy studies. Additionally, the results of saturation solubility study suggested 14 and 11 folds increase in solubility of QUE upon its cocrystallization with CAF and NIC respectively. Herein we propose a new technique for cocrystallization and in turn resolving solubility issues of phytomolecules which can be an alternative to the existing cocrystallisation techniques.

1. Introduction

Several biological activities including anticancer, antimicrobial, antiviral and antioxidant have been reported for most of the phytomolecules such as curcumin, plumbagin, galangin, and quercetin. However, formulation development of many phytomolecules has remained a challenge for researchers owing to the drawback of poor aqueous solubility. It is put onto the record that the fundamental properties of crystalline materials are dependent on the molecular arrangement within the solid, and these properties are greatly influenced upon alteration in the arrangement of molecules (Seddon and Zaworotko, 1999; Gandhi et al., 2016). Thus in order to obtain desired properties of crystals, crystal engineering has remained one of the focus areas of formulation scientists. Cocrystallization of active pharmaceutical ingredient is widely used amongst the several approaches of engineering crystals to address problems such as poor aqueous solubility and stability associated with APIs. According to USFDA guidelines, pharmaceutical co-crystals are crystalline materials consisting of an active pharmaceutical ingredient (API) and a co-former present in the same crystal lattice (FDA, 2011).

The methods proposed for cocrystal synthesis includes solution crystallisation (Friščić, 2012), Liquid assisted grinding (Trask et al., 2005), use of ultrasound (Aher et al., 2012), spray drying (Patil et al., 2014) and twin screw extrusion (Kelly et al., 2012). These methods have drawbacks like the conventional solution crystallization method has been found unsuitable for non-congruent cocrystal pairs, liquid assisted grinding lacks scalability and has issues related to solvent selection and stoichiometric diversity. Solvent free cocrystallization of APIs using twin screw extrusion is unsuitable for thermolabile drugs. Thus researchers are searching new methods for cocrystallization of APIs to mitigate the drawbacks of existing ones. Recently, we have proposed use of electrospray technology for cocrystallization of caffeine and maleic acid which is known to be one of the most difficult pairs for cocrystallization (Patil et al., 2016). However, applicability of this technique for other molecules including phytomolecules is questionable. Thus in the present work we have tried to apply electrospray technique for cocrystallization of quercetin, a well known phytomolecule.

Electrospray technique uses an electric charge for dispersing the liquid into droplets by overcoming the surface tension of the solvents. The process involves formation of Taylor cone at the tip of needle having positive charge through which a mist of ultrafine charged solution droplets is emitted and travel towards collector plate having negative charge. It is well known that the Taylor cone exhibits high energy vibrations which propagate into jet forming

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mist of droplets (Rulison and Flagan, 1993). Additionally this single step technique can be used in a continuous manner (Wang et al., 2012). The technique is currently being used for the preparation of nanofibres. The high energy vibrations of Taylor cone and rapid solvent evaporation during electrospray were thought to be beneficial in cocrystal synthesis as these factors will increase the rate of crystal nucleation and growth tremendously. Thus objective of the present work was to analyze suitability of electrospray technique for synthesis of cocrystals. Quercetin, 3,3′,4′,5,7-pentahydroxyflavone (QUE) a flavonoid of plant kingdom was taken as a model molecule. QUE has many beneficial pharmacological effects however its *in vivo* performance is questionable due to poor aqueous solubility leading to unfavorable pharmacokinetics (Karadag et al., 2014; Fang et al., 2011). In the present work cocrystallization of QUE with caffeine and nicotinamide coformers has been attempted using electrospray technique.

2. Materials and methods

2.1. Materials

Quercetin (QUE), Caffeine (CAF) and nicotinamide (NIC) were purchased from Sigma Aldrich, Bengaluru, India. The analytical-grade solvents used for the studies were obtained from the commercial sources.

2.2. Methods

2.2.1. Electrospray process

Saturated methanolic solutions of QUE with either of the coformers (CAF and NIC) were prepared separately in 1:1 ratio. The prepared solutions of QUE/CAF and QUE/NIC were electrosprayed using E-spin nano (PECO-Chennai, India) equipment. The parameters used for the whole process include syringe (10 mL), Flow rate-2 mL/hr, temperature-40 ± 1 °C, Voltage-15 kV with a distance between needle tip and collector being 25 cm. The cocrystals recovered upon electrospraying of solutions are abbreviated as QUECAF and QUENIC.

2.3. Characterization

2.3.1. Powder X-ray Diffraction (PXRD)

Powder X-ray diffraction (PXRD) patterns for QUE, CAF, NIC, QUECAF and QUENIC were recorded using X-ray diffractometer (PW 1729; Philips, Almelo, Netherlands) having Cu Kα radiation of 1.542 Å and operating at a voltage of 40 kV. Samples were scanned from 3° to 30° at 2θ.

2.3.2. Differential Scanning Calorimetry (DSC)

DSC thermograms of QUE, CAF, NIC, QUECAF and QUENIC were recorded using DSC 821^e (Mettler-Toledo, Greifensee, Switzerland). Samples (5–10 mg) were heated in hermetically sealed aluminium pan with a heating rate of 10 °C/min over a range of 25–350 °C under a nitrogen atmosphere (flow rate 50 ml/min).

2.3.3. Fourier transform infrared spectroscopy (FTIR)

KBR discs were prepared containing about 2–3 mg of QUE, CAF, NIC, QUECAF and QUENIC separately. IR spectra were recorded from 4000 to 400 cm^{-1} with a Fourier transform infrared spectrometer (FTIR-8400; Shimadzu Corporation, Kyoto, Japan) equipped with a diffuse reflectance accessory (DRS-8000; Shimadzu Corporation, Japan).

2.3.4. Saturation solubility

Saturation studies were carried out for QUE, QUECAF and QUENIC. The crystals in amounts that exceeded its solubility were separately transferred to screw capped vials containing 5 mL 1:1v/v ethanol/water mixture separately. Magnetic stirrer was used to stir the contents of vials at room temperature for 24 h. Preliminary experiments suggested this duration to be sufficient to reach equilibrium, after which no improvement in solubility was observed. After 24 h, samples were filtered through a Whatman paper (0.45-μm) diluted with distilled water and analyzed for QUE content at 360 nm using a spectrophotometer (Shimazdu-1601, UV–vis spectrophotometer, Shimadzu Corp, Kyoto, Japan).

3. Results

In the preliminary studies, electrospraying of methanolic solutions containing QUE/CAF and QUE/NIC (1:1 ratio) was attempted at different voltages below 15 kV. However as stated previously the surface tension forces of solvent must be overcome by the electrical forces to initiate the electrospray process. The voltages below 15 kV were insufficient to initiate electrospray involving formation of mist of droplets through Taylor cone. Thus the present work has been performed at 15 kV. Further the distance between the needle tip and plate collector was kept 25 cm so as achieve complete evaporation of methanol till the API molecules reach the collector plate. Since, the objective of the present work was to screen suitability of electrospray technique towards cocrystal synthesis, the electrospraying was carried out at a voltage of 15 kV with a needle aperture of 23G (0.6 mm) keeping needle tip and collector 25 cm apart.

3.1. Powder X-ray Diffraction

PXRD pattern of QUE showed characteristic peak of 2θ at 10°, 10.7°, 13.5°, 16.5°, 17.8°, 21.7°, 24.4°, 25.1°, 26° and 27.7° (Fig. 1). PXRD pattern of CAF showed characteristic peaks at 12° and 12.2° 2θ whereas NIC showed peaks at 11.16°, 14.6°, 18.8°, 22°, 25.69°, and 27.18° 2θ. PXRD pattern of QUECAF showed distinct peaks at 9.5°, 11.25°,12.39°, 12.93°, 14.56°, 16.29°, 21.19°, 23.18°, 26.18° and 26.85° 2θ which were in accordance with the literature (Smith et al., 2011) whereas QUENIC showed peaks at 6.65°, 7.43°, 11.13°, 11.81°, 12.58°, 14.86°, 16.14°, 19°, 24.61° and 25.39° 2θ revealing their purity and existence in crystalline form (Leyssens et al., 2012; Patil et al., 2015). Additionally, the distinct peaks

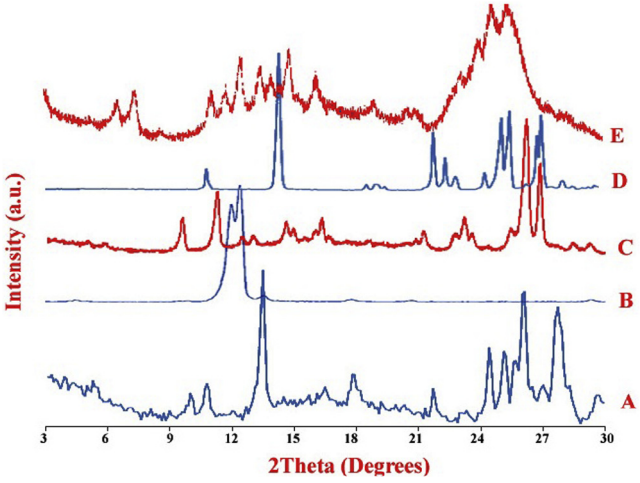

Fig. 1. PXRD patterns of (A) QUE, (B) CAF, (C) QUECAF, (D) NIC and (E) QUENIC.