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Solubility of luteolin in several imidazole-based ionic liquids and extraction from peanut shells using selected ionic liquid as solvent

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ABSTRACT

Several hydrophilic and hydrophobic 1-alkyl-3-methylimidazole ionic liquids (ILs) were screened for their dissolution ability of luteolin to determine the IL suitable for extraction of luteolin from peanut shells. The experimental data indicated that hydrophilic 1-butyl-3-methyl-imidazolium nitrate ($[C_4mim]NO_3$) shows considerably higher dissolution ability of luteolin than commonly used organic solvents and other ILs investigated, which can be used as an efficient substitute of organic solvent for extraction of luteolin. The extraction of luteolin from peanut shells was performed using $[C_4mim]NO_3$ aqueous solution as solvent, and extraction conditions were analyzed and optimized by response surface methodology (RSM) with central composite design (CCD). Extraction temperature has significant effect on the yield of luteolin, followed by $[C_4mim]NO_3$ concentration. Under the optimal conditions namely liquid–solid ratio of 7.6 mL g^{-1}, temperature of 100 °C and $[C_4mim]NO_3$ aqueous solution of 49%, determined by RSM, the yield of luteolin was 79.8 ± 1.48%, which was close to the 78.4% predicted by RSM.

1. Introduction

Luteolin is an important natural flavonoid widely distributed in plant materials [1], which bioactivities were reported including antioxidant [2], anti-inflammatory [3], vasodilation [4], and cancer prevention [5]. The recent studies have also suggested that luteolin could enter the cellular nuclei and suppress the oxidative damage of DNA [6], reduce IL-6 production in microglia by inhibiting JNK phosphorylation and activation of AP-1 [7] and reverse xylazine/ketamine-induced anesthesia [8].

Luteolin can be obtained via organic solvent extraction directly from natural herbs, such as *Reseda luteola* and *Angelica keiskei* [9,10]. However, most of herbs used in traditional medicine are more or less expensive. Peanut shells are abundant and inexpensive by-products of peanut industry. Every year, the yield of peanut shells reaches as high as 5 million tons in China alone, and most of the peanut shells are either sludged for forage and fuel or abandoned, resulting in an enormous waste of natural resources [11]. Investigations have demonstrated that peanut shells are rich in flavonoid and polyphenol components, such as luteolin, eriodictyol and 5,7-dihydroxychromone, and in which luteolin is the major compound [12,13]. Luteolin occurs in plants as the glycosylated form in most cases, but in peanut shells it is in the form of aglycone. Several studies have reported the solvent extraction of luteolin from peanut shells [14–16]. However, with increasing safety considerations for operating personnel and consumers, extraction by organic solvents is a challenge due to the volatility, flammable and toxicity of the solvents. Therefore, the desire to reduce the use of organic solvents in the extraction processes for bioactive substances has led to the development of alternative solvents, such as ionic liquids (ILs). In the past decade, ILs have gained great interests as separation media due to their unique physical and chemical properties of low vapor pressure, high thermal and chemical stability, etc [17,18]. Some of recent studies have revealed the ability of ILs to extract natural organic compounds since Huddleston et al. reported the first successful extraction of substituted-benzene derivatives using ILs $[Bmim]PF_6$ initially [19–24]. In the present work, we investigate the solubility of pure luteolin in several imidazole-based ILs, and report the successful extraction of luteolin from peanut shells using 1-butyl-3-methylimidazolium nitrate, as well as the optimization of extraction conditions by response surface methodology (RSM).

2. Materials and methods

2.1. Materials

Luteolin (mass fraction > 98%) was purchased from Shaanxi Sunrun Bio-technology Co., Ltd., (Xi'an, China), and it was recrystallized twice in ethanol, dried in a vacuum oven at $T = 378.5$ K for 24 h, and then stored in a desiccators before use. The purity of

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Table 1
ILs used in this work.

Ionic liquids	Abbreviation	Water content (%)
1-Butyl-3-methylimidazolium nitrate	$[C_4mim]NO_3$	<0.1
1-Butyl-3-methylimidazolium tetrafluoroborate	$[C_4mim]BF_4$	<0.1
1-Butyl-3-methylimidazolium hexafluorophosphate	$[C_4mim]PF_6$	<0.05
1-Butyl-3-methylimidazolium bis((trifluoromethyl)sulfonyl)imide	$[C_4mim]NTF_2$	<0.05
1-Hexyl-3-methylimidazolium nitrate	$[C_6mim]NO_3$	<0.1
1-Hexyl-3-methylimidazolium tetrafluoroborate	$[C_6mim]BF_4$	<0.05
1-Hexyl-3-methylimidazolium hexafluorophosphate	$[C_6mim]PF_6$	<0.1

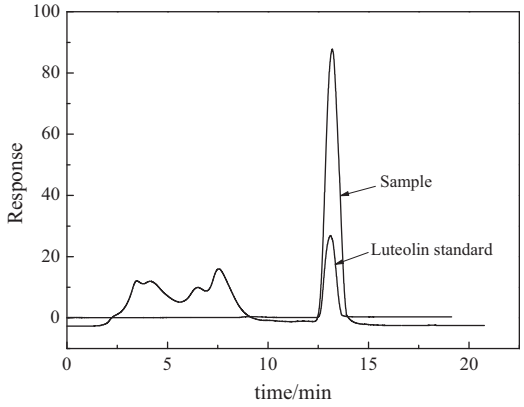

Fig. 1. Chromatograms of sample and luteolin standard.

Table 2
Levels of independent variables for CCD.

	Liquid–Solid ratio X_1 (mL g^{-1})	Extraction temperature X_2 (°C)	IL concentration X_3 (%)
Min	5	30	30
Max	10	80	80

Table 3
Coded variables and actual variables for CCD.

Coded variables x_i (i = 1,2,3)	Actual variables		
	X_1 (mL g^{-1})	X_2 (°C)	X_3 (%)
−1.68	3.3	12.0	12.0
−1.00	5.0	30.0	30.0
0.00	7.5	55.0	55.0
1.00	10.0	80.0	80.0
1.68	11.7	97.0	97.0

the luteolin crystal was more than 99.5% mass fractions, determined on Agilent 1100 HPLC system (Agilent, USA). Eriodictyol (mass fraction ⩾ 97%) and 5,7-dihydroxychromone (mass fraction ⩾ 98%) were purchased from Shanghai PureOne Biotechnology (Shanghai, China). All of the ILs (purity > 99%, Table 1), were purchased from Lanzhou Greenchem ILS, LICP, CAS (Lanzhou, China). These ILs were distilled in a rotary evaporator for 4 h and dried at 398.5 K under vacuum for 24 h to remove any residual volatile compounds and water prior to use. The HPLC purity of the ILs employed in the experiment were higher than 99.5%, and the water content was determined to be less than 0.1% based on a Karl-Fischer titration using a Metrohm 798 MPT Titrino

Table 4
Central composite design arrangement and results.

Runs	Factors						Response
	Coded variables			Actual variables			Y (%)
	x_1	x_2	x_3	X_1 (mL g^{-1})	X_2 (°C)	X_3 (%)	
1	0	1.68	0	7.5	97.0	55.0	77.2
2	0	0	1.68	7.5	55.0	97.0	5.7
3	0	0	0	7.5	55.0	55.0	31.4
4	0	0	−1.68	7.5	55.0	13.0	5.5
5	1	1	−1	10.0	80.0	30.0	49.8
6	−1	1	−1	5.0	80.0	30.0	44.9
7	0	0	0	7.5	55.0	55.0	35.7
8	1	−1	1	10.0	30.0	80.0	4.5
9	0	0	0	7.5	55.0	55.0	32.2
10	−1.68	0	0	3.3	55.0	55.0	28.7
11	1.68	0	0	11.7	55.0	55.0	35.0
12	0	0	0	7.5	55.0	55.0	30.7
13	0	−1.68	0	7.5	13.0	55.0	5.0
14	1	1	1	10.0	80.0	80.0	40.1
15	0	0	0	7.5	55.0	55.0	34.1
16	−1	−1	1	5.0	30.0	80.0	6.1
17	1	−1	−1	10.0	30.0	30.0	13.3
18	0	0	0	7.5	55.0	55.0	29.6
19	−1	1	1	5.0	80.0	80.0	47.1
20	−1	−1	−1	5.0	30.0	30.0	13.8

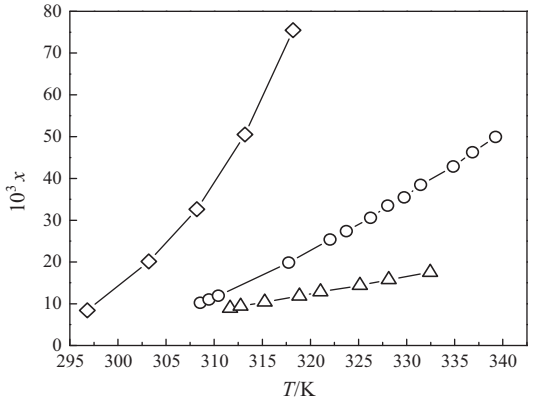

Fig. 2. Solubility of luteolin in hydrophilic ILs $[C_4mim]NO_3$ (◇), $[C_6mim]BF_4$ (○) and $[C_4mim]BF_4$ (△).

(Metrohm Co., Switzerland). Mature peanuts were purchased from a market in Nanning of China. The peanuts were washed and hand-shelled. All peanut shells were air dried, pulverized in a knife mill (Model FW-100, Taisite Instrument Ltd., Tianjin, China) and passed through a 40-mesh sieve respectively. The content of luteolin, eriodictyol and 5,7-dihydroxychromone in peanut shells were determined as 0.803%, 0.313% and 0.201% by HPLC analysis, respectively.

2.2. Chromatographic conditions

The HPLC analysis of luteolin was performed on a Waters symmetry C_{18} column (250 mm × 4.6 mm, 5.0 μm). The mobile phase consisted of methanol and 0.1% phosphoric acid aqueous solution in a 55:45 volume ratio and employed in the separation at a flow rate of 1.0 mL min^{-1} with the detector wavelength at 275 nm. The chromatograms of sample and luteolin standard are shown in Fig. 1. The HPLC analysis of eriodictyol and 5,7-dihydroxychromone was carried out on a Waters symmetry C_{18} column using the method proposed by Zhang et al. [25] with no modification.

2.3. Extraction of luteolin from peanut shells using IL

Two grams of dried samples powder were put into a 20 mL glass vessel with heating jacket and a magnetic stirrer, followed by