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Ionic Liquid-salt Aqueous Two-phase System, a Novel System for the Extraction of Abused Drugs

She Hong LI, Chi Yang HE, Hu Wei LIU, Ke An LI, Feng LIU*

The Key Laboratory of Bioorganic Chemistry and Molecular Engineering, Ministry of Education, College of Chemistry, Peking University, Beijing 100871

Abstract: A 1-butyl-3-methylimidazolium chloride-salt aqueous two-phase system was studied on extraction of abused drugs. The effects of sorts of salts, temperature, concentration of salt and drugs on system were investigated systematically. A satisfactory extraction efficiency of 93% was obtained for papaverine while that of morphine was 65%. The extraction mechanism was primarily discussed.

Keywords: Aqueous two-phase system, ionic liquids, 1-butyl-3-methylimidazolium chloride, extraction, abused drugs.

Extraction of drugs from complex sample is a crucial step for determination of drugs. However, most of existing extraction methods use poisonous volatile solvents[1]. The traditional aqueous two-phase system (ATPS) might be an alternative, but most of phase-forming polymers have high viscidity and form an opaque solution. Recently, ionic liquids (ILs) are gaining attention for their potential use as green solvents and possible replacements for common volatile organic solvents[2,3]. In this work, the ATPS consisting of 1-butyl-3-methylimidazolium chloride ([C_4mim]Cl,) and K_2HPO_4 with unique property of nonvolatility and lower viscidity was employed to replace traditional ATPS for extraction of abused drugs for the first time.

Experimental

Aqueous two-phase system is made up of [C_4mim]Cl and salt. In a 5 mL centrifugal tube, 1.0 mL stock solution of [C_4mim]Cl (20%, w/V), a suitable amount of drug and salt were added. Then, the contents was diluted to the mark with water and mixed thoroughly. The systems were equilibrated at room temperature and separated into two clear phases by centrifugation at 1600 rpm for 5 min. The concentration of drugs in upper phase was determined by UV spectrophotometer or HPLC.

Results and Discussion

ATPS can be formed by adding KOH, NaOH, K_2CO_3, K_2HPO_4, Na_2HPO_4 or K_3PO_4 to aqueous solution of [C_4mim]Cl over a large composition range. Among these salts,

* E-mail:liufeng@pku.edu.cn

KOH, K_2CO_3 and K_2HPO_4 were chosed to determine phase diagrams by cloud point method[4] at 22 ℃ (**Figure 1**) to seek for the most effective phase-separated salt. Here, K_2HPO_4 is the optimum phase-separated salt since it has, compared with other salts, a higher ability for phase separation and can offer a relatively appropriate pH condition for determining abused drugs.

The effect of salt concentration on extraction efficiency (*E*) was studied in the system containing 3% [C_4mim]Cl, 30 μg papaverine and various amount of K_2HPO_4. Within the range 37-47% of K_2HPO_4, ATPSs were formed with extraction efficiencies of 84-98% for papaverine. The maximum *E*, which was about 96%, could be obtained when 39-41% salt was used. Moreover, temperature has little influence on extraction efficiencies of papaverine. Within 15-65 ℃, the extraction efficiencies of papaverine were almost 90-95%.

To evaluate selectivity of this method, the extraction efficiencies of papaverine and morphine with a series of drug concentration were determined under the best extraction condition of 3% [C_4mim]Cl and 40 % K_2HPO_4. The results in **Table 1** showed that with increase of the concentration of papaverine or morphine, little variance in extraction efficiency was observed. The average extraction efficiency of papaverine was 93% while that of morphine was 65%. This phenomenon could be interpreted as follow. Similar to traditional APTS[5], the hydrophobic interaction between drugs and the upper phase might be the main drive for their extraction. As shown in **Figure 2**, papaverine is more hydrophobic than morphine, therefore the former is prone to transfer to the IL-enriched upper phase, while the latter has stronger hydrogen bond interaction with K_2HPO_4 phase. As a result, papaverine has a higher extraction efficiency than morphine.

Figure 1 The phase diagrams of [C_4mim]Cl-salts-water systems.

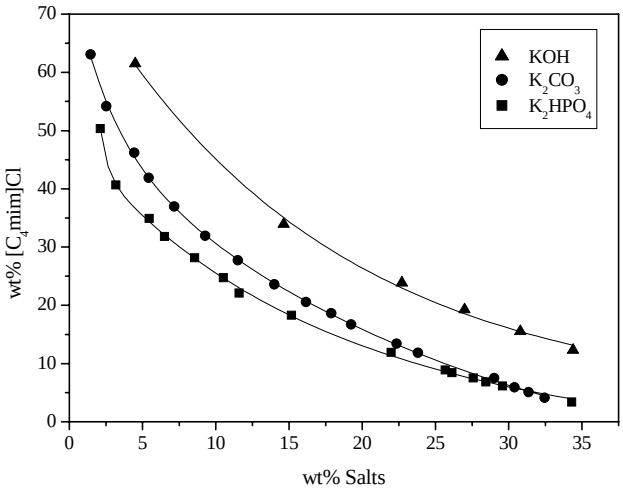
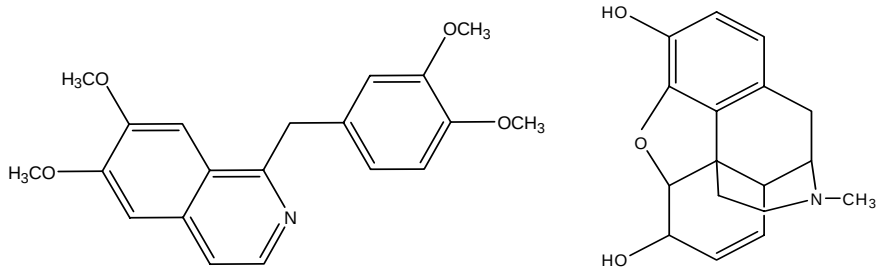


Table 1 Effect of abused drugs concentration on extraction efficiency

Drug (μg/mL)	1.0	2.0	4.0	8.0	10.0	20.0	$\overline{E}$ (%)	RSD(n=6)
$E_{papaverine}$(%)	93	93	92	90	96	95	93	2.1
$E_{morphine}$(%)	65	63	64	66	67	66	65	1.5

Figure 2 The structures of abused drugs



Papaverine Morphine

In conclusion, [C_4mim]Cl solution can form ATPS in the participation of salts. [C_4mim]Cl-K_2HPO_4 ATPS is a useful extraction media for abused drugs. This extraction system has high efficiency and obvious selectivity. It is promising that ionic liquid-salt ATPS should provide a new sample pretreatment procedure followed by HPLC, CE or FIA to determine the abused drugs from biological samples.

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