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A New Purification Process for Pharmaceutical and Chemical Industries

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Abstract:

A novel separation and purification process suitable for pharmaceutical and chemical industries has been developed. The process is based on the difference in adsorption and solubility of organic compounds. The process was carried out under mechanical stirring, and individual components were isolated in short time with excellent purity. The process can be suitably adopted for the purification of organic compounds in large scale.

The separation and purification of organic compounds are very important to chemical and pharmaceutical industries. It is a challenging task to separate a required product from a mixture of components during industrial production. Even though different distillation[1] and recrystallization[2] techniques are widely employed in industries, the application of the above methods are limited and time-consuming, leading to cost escalation. The column chromatographic method,[3−5] used in some industries, is a process that is too complicated, particularly for large-scale production (Table 1).

To overcome the above barriers, herein we bring a preliminary communication of our new invention for the separation of organic compounds, which can be applied in kilogram reactors to purify drugs and chemicals. The process is very simple and does not require any special kind of glassware. The process is carried out under mechanical stirring in a round-bottom flask.

Thus, the crude reaction mixture to be purified was dissolved in a minimum amount of a suitable solvent, selected preferably from low-boiling solvents such as hexane, dichloromethane, chloroform, ethanol, etc. To this solution 3−4-fold (if the spots are close as in aniline and 4-nitroaniline 5−6-fold) of a selected adsorbent was added and mixed well. Then the solvent was removed completely under vacuum. To the above solvent-free slurry, a selected solvent or mixture of solvent was added and stirred mechanically; the solution was decanted, and the solvent was evaporated. When the quantity of solvent and length of stirring time were increased, comparatively more quantity of a particular compound was isolated. When the polarity of the solvent was slowly increased, successive components were isolated.

The success of the process is evident by the fact that it is able to separate a mixture of very close-moving (chromatographically) aniline and 4-nitroaniline. Aniline and 4-nitroaniline are moving in 5% ethyl acetate:petroleum ether, and the R_f difference between aniline and 4-nitroaniline is just 0.09. A variety of organic compounds that were mixed and isolated successfully are summarized in Table 2.

To demonstrate suitability the method for separation of the required component from a chemical reaction mixture, the technique was applied to Biginelli condensation, and pure 6-methyl-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-carboxylic acid ethyl ester was isolated from a mixture of benzaldehyde, ethyl acetoacetate, and 6-methyl-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-carboxylic acid ethyl ester. This reaction was carried out in 1-mole scale, and by employing our technique the quantitative separation of 6-methyl-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-carboxylic acid ethyl ester was achieved with very high purity (99%).

Explanation of the Process with an Example. *p*-Methyl acetophenone (500 g) and resorcinol (500 g) were dissolved in 2 L of ethanol. To this solution 3 kg of neutral alumina activity I−II was added and mixed well; the solvent was removed completely under vacuum. To the above solvent-free slurry was added 2% ethyl acetate:petroleum ether 40−60 °C (7 L); the solution was stirred for 20 min and decanted, and the solvent was evaporated. The residue weighed 120 g of *p*-methyl acetophenone. Thus, five elutions (each elution was carried out with 7 L of solvent and 20 min stirring) in 2% ethyl acetate:petroleum ether at 40−60 °C separated 455 g of *p*-methyl acetophenone with 100% purity (based on gas chromatography). Then the polarity of solvent was increased to 5% ethyl acetate:petroleum ether 40−60 °C. In 5% ethyl acetate:petroleum ether 40−60 °C (7 L) mixture were isolated *p*-methyl acetophenone and resorcinol. The elution in 5% ethyl acetate:petroleum ether 40−60 °C was continued until the isolated resorcinol was single on TLC. Then 7 L of ethyl acetate was added and stirred for 20 min and then decanted; the solvent was evaporated. The elution in ethyl acetate was repeated for three times to complete the isolation of resorcinol. Thus 400 g of pure (100%, based on gas chromatography) resorcinol was isolated. The mixture of *p*-methyl acetophenone and resorcinol isolated in 5% ethyl acetate:petroleum ether 40−60 °C were combined, solvent was removed, and the process was repeated. Thus, each component was isolated in almost pure state in a short time.

The results of our study indicate the following salient features: (1) Direct separation based on solubility differences gave a mixture of two products, whereas adsorption on silica gel followed by elution with same solvent gave separation

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Table 1. **Comparison between chromatographic method and our new method**

s. no.		purification based on column chromatographic method	purification based on our new method
1	ratio of adsorbent (employed in the purification process) to compound	25−50:1[6]	4−6:1
2	quantity of solvent required	large excess of solvent is required for continuous elution	minimal solvent consumption; 2−3 times the slurry weight is sufficient
3	time (for 1-kg batch)	several hours	10 h
4	apparatus	very large size colum is required	does not require special equipment; performed in reactor vessel.

Table 2. **Separation of some mixed compounds based on our new technique**

				yield[a] %		purity[b]	
s. no.	cmpd 1	cmpd 2	adsorbent	cmpd 1	cmpd 2	cmpd 1	cmpd 2
1	benzophenone	dimedone	silica gel 60−120 mesh	98	97	100	98
2	aniline	4-nitroaniline	neutral alumina activity I−II	98	98	99	98
3	*p*-chlorobenzaldehyde	acetoacetanilide	neutral alumina activity I−II	99	97	100	99
4	*p*-methylacetophenone	resorcinol	neutral alumina activity I−II	97	96	100	100[c]

[a] After purification. [b] Based on gas chromatography. [c] Carried out in 40-g as well as in 1-kg scale.

of the chemical mixture. Example: dimedone and benzophenone.

(2) The nature of the adsorbent plays a vital role in the above separation process.[7] Low-grade adsorbent is preferable when the compounds are not close moving on TLC. When ethyl acetoacetate, benzaldehyde, and 6-methyl-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-carboxylic acid ethyl ester were adsorbed on silica gel, the isolation of product was very easy compared to the adsorption on neutral alumina activity I−II.

(3) High-grade adsorbent is preferable when the compounds are close moving on TLC. For example, aniline and 4-nitroaniline adsorption on silica gel gave a mixture of two compounds, whereas adsorption on neutral alumina activity I−II resulted in the separation of individual compounds.

(4) The eluent for the separation of a particular compound from a mixture was chosen on the basis of a trial and error method. The prepared slurry was collected in different vials, solvent systems of increasing polarity were added, and the eluates were analyzed by TLC to scout for the best solvent system. It is recommended to use a solvent of slightly reduced polarity and then choose one from TLC analysis to perform large-scale elution.

We strongly believe that further intensive research in this technique will enhance its application to the separation of all kinds of organic compounds of industrial importance.

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