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Assessing the Benefits of Direct Isolation Processes

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Abstract:

Direct isolation processes are often used in pilot-plant and manufacturing operations. The primary benefit of a direct isolation process over a process using a conventional extractive workup and crystallization is the decreased cost of goods (COG) due to decreased processing time. Direct isolation processes may be beneficial even when the yield is 5−15% below the yield from a conventional extractive workup and crystallization. The costs of scaling up both direct isolation and extraction processes can be calculated by a mathematical model, and the proportional costs of raw materials, labor, and waste disposal can be assessed. Although direct isolation processes are generally more economical than extraction processes, the direct isolation option is not suitable for all strategies. A perspective is offered on when to develop a direct isolation process over an extractive workup and crystallization process.

Introduction

Direct isolation processes are designed to crystallize or precipitate the product directly from the reaction mixture, without first resorting to an extractive workup. Extractive workups may include evaporative removal of the reaction solvent (usually a water-miscible solvent), dissolution into a water-immiscible organic solvent, extracting with water or aqueous solutions to remove impurities, and concentration. As discussed by Chen and Singh in their guidelines for the "bottom-up" approach to process development through direct isolation,[1] these additional steps require additional amounts of labor and solvents. By avoiding the extra steps of an extractive workup, direct isolation processes can decrease the product cost of goods (COG).

The direct isolation approach has been applied to many types of molecules[1] (Scheme 1). Solubility limitations may limit the ability to extract compounds into a range of useful organic solvents, and compounds such as the tetrapeptide **1**[2] and the multiply charged antibiotic **2**[3] may be conveniently prepared by direct isolation. Compounds with high water solubility, such as captopril, **3**, have also been economically isolated from water using the direct isolation approach.[4,5]

There are advantages and disadvantages to the three choices for workup and isolation, i.e., direct isolation, extraction and isolation, or telescoping. The advantages to the direct isolation approach can include the following: (1) increased productivity due to reduced cycle time on scale, thus decreasing the COG; (2) decreased number of solvents and reagents that need to be ordered and qualified before use; (3) decreased amounts of wastes (salty waste and condensed solvents from concentration); and (4) fewer opportunities for product contamination and physical loss due to simplified operations. While lengthier, an extractive workup provides additional opportunities to remove impurities that might impede a direct isolation, making a reliable crystallization easier to develop (vide infra). Repeated extractions may lead to more complete product recovery, key for high-value-added products. By telescoping, one avoids the inevitable losses due to handling and unrecovered product in the mother liquor. Telescoping is an excellent way to increase productivity, provided that the impurities present do not prove troublesome in subsequent steps.

Often the disadvantages found in a workup and isolation protocol dictate the development of a process. In a direct isolation process more impurities are present, particularly ionic impurities that might not partition into an organic solvent with the product. Such impurities may affect isolated product purity, color, crystal morphology, and ruggedness of both the step under development and downstream steps. On scale, processes with extractions often include extended concentrations with heat, which can lead to formation of impurities,[6] decreased product yields, and safety risks.[7] A processing option may also affect crystal morphology and have undesirable affects on isolation and drying. To gain the advantages of direct isolation processes, scientists may need to search for optimal isolation conditions that provide the suitable balance of high yield with minimal levels of impurities. Thus, the most useful isolation approach must be selected by experimentation, based on processing goals.

On scale the direct isolation approach can dramatically reduce processing times and materials costs. Eckert has noted

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(1) Chen, C.-K.; Singh, A. K. *Org. Process Res. Dev.* **2001**, *5*, 508.

(2) Frazén, H. M.; Bessidskaia, G.; Abedi, V.; Nilsson, A.; Nilsson, M.; Olsson, L. *Org. Process Res. Dev.* **2002**, *6*, 788.

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(4) Anderson, N. G.; Bennett, B. J.; Feldman, A. F.; Lust, D. A.; Polomski, R. E. (E. R. Squibb & Sons). U.S. Patent 5,026,873, 1991.

(5) Anderson, N. G. *Practical Process Research & Development*; Academic Press: San Diego, 2000; p 234.

(6) For a quantified example, see: Daugs, E. D. *Org. Process Res. Dev.* **2000**, *4*, 301.

(7) A reviewer pointed out that by heating a sensitive substrate during concentration there is a potential risk of initiating runaway reactions.

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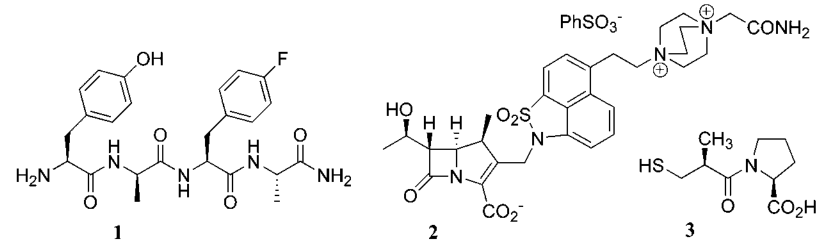
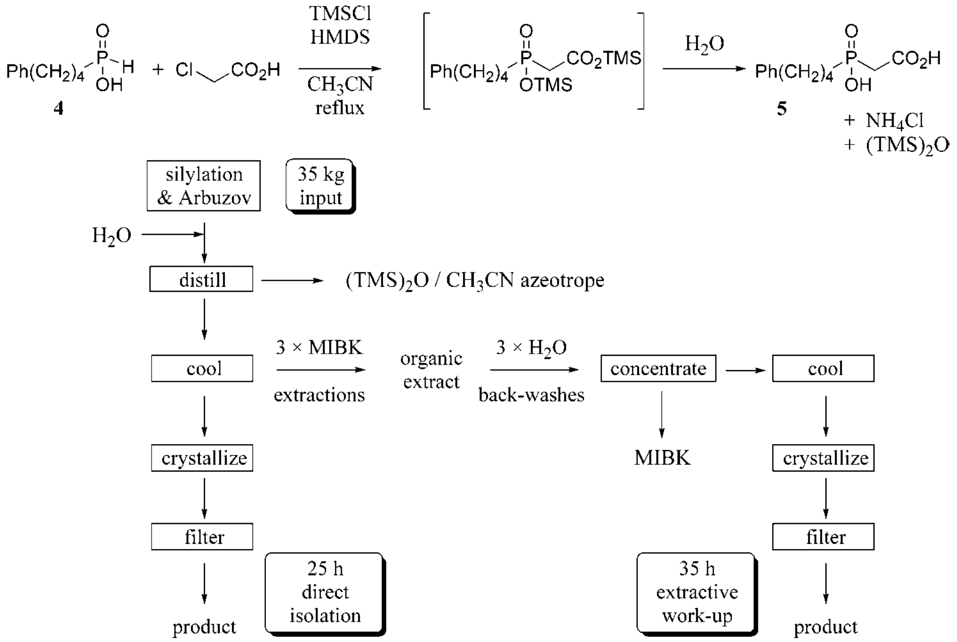
Scheme 1. **Some compounds prepared by direct isolation**



Scheme 2. **Operations and processing times for direct isolation and extraction processes**



that "In a typical chemical operation, 60−80% of both capital expenditures and operating costs go to separations."[8] Considering the increasing focus on improving productivity in the pharmaceutical industry[9] and the opportunities to increase productivity through direct isolation processes, it is timely to assess the benefits and drawbacks of the direct isolation option.

Results and Discussion

To compare the benefits of direct isolation and extractive workups, data from the modified Arbuzov process[10] (Scheme 2) were considered. The direct isolation process was developed first, and **5** was crystallized from the reaction mixture following an aqueous quench and distillative removal of the solvent and the byproduct hexamethyldisiloxane. The aqueous mother liquor dissolved the second primary byproduct, NH_4Cl, and washing the wet cake of **5** with H_2O displaced some oily impurities. Vacuum drying returned **5** in 85% average yield and 97−98% average purity. Because the isolation procedure on scale was not rugged enough to effectively purge other impurities in isolated **5** that hindered conversion to the next intermediate, production batches of **5** were frequently upgraded by recrystallization from methyl isobutyl ketone (MIBK). Thus, overall the process was unreliable, sometimes necessitating two isolations and two drying steps, which increased process and analytical efforts.[11] Supplies of **5** were urgently needed for the manufacture of the drug substance. Rather than invest additional time and effort to fine-tune the direct isolation process, we decided to combine an extractive workup and MIBK crystallization with the silylation−modified Arbuzov process. In this variant, after the solvent and hexamethyldisiloxane were distilled off, the cooled pot mixture was extracted with three portions of MIBK, and the combined extracts were back-washed with three portions of H_2O. The organic phase was azeotropically dried during concentration and cooled to initiate crystallization of the product. The slurry was cooled, and the product was washed with MIBK.[12] The extractive process gave **5** in slightly lower yield (82% average), but at an average purity of 99.9%. Batches of **5** from the extractive

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(8) Zurer, P. *Chem. Eng. News* **2000**, *78*(1), 26.

(9) Mullin, R. *Chem. Eng. News* **2003**, *81*(22), 16.

(10) Anderson, N. G.; Ciaramella, B. M.; Feldman, A. F.; Lust, D. A.; Moniot, J. L.; Moran, L.; Polomski, R. E.; Wang, S. S. Y. *Org. Process Res. Dev.* **1997**, *1*, 211.

(11) The tandem direct isolation−MIBK recrystallization was probably less productive than the extractive workup, as the need to dry each batch twice may have created a bottleneck with the dryer. In the implementation of Process E (ref 10) minimal volumes of MIBK were used for extraction, thus minimizing the amount of time needed to reduce the rich organic phase to the crystallization volume. The unreliability of the process (Process C in ref 10) primarily led to its redevelopment. A tandem direct isolation−recrystallization or direct isolation−reslurry process may be productive alternatives to direct isolation or extraction and isolation options; when considering the tandem process options, the impact of additional isolation and drying steps must be considered.

workup and MIBK crystallization were reliably processed to the next intermediate.

With inputs of 35 kg of **4**, about 35 h was required for the extractive process from the time of charging **4** to the reactor to transferring **5** to the dryer. When **5** was isolated directly from the concentrate after removal of the hexamethyldisiloxane–acetonitrile azeotrope, about 25 h was required.[13] Thus, on the 35 kg scale, the extractive workup required 10 h more, or an additional 40% of the processing time for the direct isolation process. For the purposes of this discussion, drying times for isolated **5** are presumed to be the same for each processing option, and the drying operation is presumed not to be a bottleneck. The processing times for these two processes are the bases for developing the discussion following.

Equations for Calculations

$$N_eO_e = N_dO_d \tag{1}$$

$$N_d = N_e + 1 \tag{2}$$

$$O = Y \times Q \tag{3}$$

$$N_e = \frac{Y_d/Y_e}{1 - Y_d/Y_e} \tag{4}$$

$$\$ = N \times (R + P + D) \tag{5}$$

$$R = M \times B \tag{6}$$

$$P = L \times T \times \mathrm{TF} \tag{7}$$

$$\mathrm{TF} = \frac{\text{(vol./SA) of batch}}{\text{(vol./SA) of std. batch}} = \frac{\text{radius of batch}}{\text{radius of std. batch}} = \frac{(\text{batch vol.})^{1/3}}{(\text{std. batch vol.})^{1/3}} \tag{8}$$

$$\text{batch volume} = (\text{standard volume/kg}) \times B \tag{9}$$

$$\mathrm{TF} = \frac{(\text{batch size})^{1/3}}{(\text{std. batch size})^{1/3}} \tag{10}$$

$$\mathrm{TF} = (B/B_{\mathrm{std}})^{1/3} \tag{11}$$

$$P = L \times T \times (B/B_{\mathrm{std}})^{1/3} \tag{12}$$

$$D = \mathrm{DC} \times W \times B \tag{13}$$

$$\$ = N[\mathrm{MB} + \mathrm{LT}(B/B_{\mathrm{std}})^{1/3} + \mathrm{DC}(W \times B)] \tag{14}$$

$$B = \left[\frac{L[N_e(T_d - T_e) + T_d]}{(B_{\mathrm{std}})^{1/3}(N_e[(M_e - M_d) + \mathrm{DC}(W_e - W_d)] - \mathrm{DC}W_d - M_d)}\right]^{3/2} \tag{15}$$

Abbreviations Used in Equations and Discussion

N = number of batches
O = output/batch
Y = process yield, based on theoretical output
d = direct isolation process
e = extraction process
Q = theoretical output, kg
\$ = campaign cost
R = raw materials cost/batch
P = plant (labor) cost/batch
D = disposal cost/batch
M = raw material cost/kg of starting material
B = batch size, kg of starting material
L = labor cost/hour
T = number of processing hours/standard batch
TF = scale-up factor
B_{std} = batch size of standard batch, kg
DC = disposal cost/L of waste
W = waste, L/kg of starting material
SA = surface area

Calculating the Break-Even Batches

The benefits of a direct isolation process over an extraction process are easy to assess if the yields and qualities of the two processes are equal: the direct isolation process is more productive. For instance, in 120 h (three 8-h shifts per day for 5 days) 4.8 batches could be produced from an input of 35 kg of **4** by the direct isolation process, versus 3.4 batches for the extraction process.[14,15] Unnecessarily using the extraction process may lead to a considerable opportunity cost, the opportunity to make additional material or expand processing knowledge.

However, even if yields are less with the direct isolation process than with the extraction process, in campaigns of multiple batches the direct isolation process may be favored if the goal is to minimize processing and run additional batches in an equipment train. This will be true provided that materials from each process meet identical specifications. The number of batches to generate identical amounts of product by the direct isolation and extraction processes can be calculated by considering the outputs per batch and defining the number of direct isolation batches to be one more than the number of extraction batches (eq 4, by substituting eqs 2 and 3 into eq 1 and solving). The corresponding number of batches from the direct isolation and extraction processes, the break-even batches, can be used to determine the number of batches in campaigns and labor costs.

As shown in Figure 1, fewer batches (extraction or direct isolation processes) are needed to prepare the same amount

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(12) The processing alternatives described herein (Processes C and E in ref 10) can be considered one-pot processes, which are often thought to be the simplest and most desired processes. Productivity considerations often dictate how a process is conducted on scale. In the manufacturing of **5** two process trains were used, one for the silylation and modified Arbuzov reaction, and one for the quench, extraction, and workup. By splitting the processing into two equipment trains in this fashion, two batches can be run simultaneously, thus increasing productivity when equipment is available.

(13) The operating time of 25 h is estimated from the processing times of the process using the extractive workup, since the direct isolation process was never run on a 35-kg scale in the same pilot-plant facility.

(14) This calculation ignores the time spent in cleaning equipment, which can be significant. The amount of time allocated to cleaning and equipment preparation can vary greatly, depending on the requirements of the cleaning procedure and the operators. Often, people view cleaning as an opportunity to “take it easy” before focusing on the next batch, and the total time to clean an equipment train three times might be the same as that for four cleanings. For high productivity in a manufacturing setting, attention must be paid to minimize the time spent on cleaning, while ensuring that the vessels are suitably clean.

(15) For the modified Arbuzov processes outlined in Scheme 2, the vessel used for extractions and crystallizations was subjected to minimal cleaning between batches. Silylation of **4** and chloroacetic acid was sensitive to the presence of water; cleaning and vessel preparation were simplified by never allowing water to contact the equipment train used for silylation and heating.

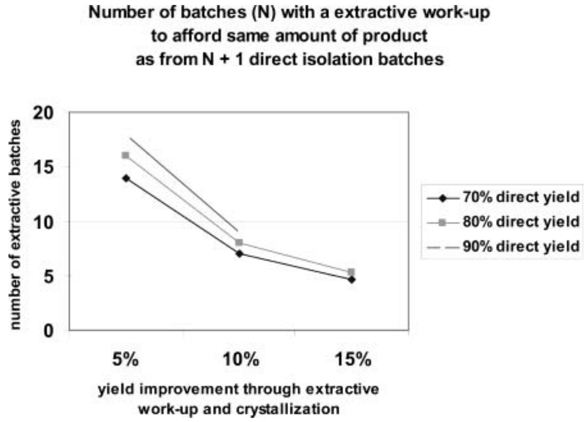

Figure 1. **Effect of yield improvement on the number of break-even batches.**

Table 1. **Comparison of processing times for direct isolation and extraction and isolation processes**

processing option	direct isolation	extraction and isolation
yield	70%	80%
output/batch	31.7 kg	36.2 kg
hours/batch	25	35
number of batches/campaign (break-even batches)	8	7
total output/campaign	253.4 kg	253.4 kg
total campaign time[a]	200 h	245 h
additional processing time relative to direct isolation option	–	45 h (22%)

[a] Neglecting time for cleaning equipment.

of product as the yield of the extraction process increases relative to that of the direct isolation process. For example, if the direct isolation yield were 70% and the extraction yield were 75% (a 5% yield improvement relative to the theoretical yield of the process), then 15 direct isolation batches would provide the same output as 14 extraction processes. If the direct isolation yield were 70% and the extraction yield were 80%, then the break-even batches would be eight direct isolation batches and seven extraction processes. Under the latter conditions, eight direct isolation batches and seven extraction batches with processing times as described in Scheme 2, the extraction campaign requires an additional 45 h, or 22% of the direct isolation campaign (Table 1).

Calculating Scale-Up Campaign Costs and Batch Sizes

As processes are scaled up the COG decreases, due to the decreased proportional labor cost (vide infra). The differing costs of raw materials and waste disposal may also be considered in choosing between campaigns using direct isolation or extraction options. Due to the increased space–time productivity of large-scale batches, the size of the break-even batches will also increase. This section assesses the impact of these factors.

The campaign cost can be calculated as the product of the number of batches times the sum of the raw materials cost, the plant cost, and the disposal cost per batch[16] (eq 5).

The raw materials cost per kg of starting material often decreases with scale-up, as suppliers discount the cost of large-volume purchases. A useful rule of thumb is that bulk prices in the United States will be 20–25% of the lowest U.S. catalog prices; this estimate hinges on availability, purity requirements, negotiations, and other factors. For the purpose of this COG it is assumed that the bulk chemical costs per kilogram of starting materials are the same for 35- and 350-kg batches. The raw materials cost per kg of **4** equals the product of cost per kg of starting material times the batch size, i.e., the input of starting material (eq 6). From Table 2 it can be seen that the raw materials cost of the direct isolation process is \$336/kg, while the raw materials cost of the extraction process is \$356/kg. This increased cost is due to the use of 14 L of MIBK/kg of **4** for the extractions and washing the product on the filter. Thus, for the example in Scheme 2, instituting an extractive workup increases the raw materials cost by only \$20/kg of starting material, less than 6% of the total raw materials cost.

The plant (labor) cost is the product of the hourly plant rate times the number of hours per standard batch times a scale-up factor (TF), as shown in eq 7. Heat-transfer rates control/limit the scale-up of most semi-batch processes, and in Scheme 2 heat-transfer rates are involved in 60% of the overall process time. Other operations similarly require more time on scale, such as equipment preparation, separation time for biphasic mixtures during extractions, gravity transfers of liquids, filtrations, and more. TF can be estimated by considering the increased time needed to transfer heat on scale, considering the ratios of volume-to-surface area for vessels as spherical reactors[17] (eq 8). The reaction volume can be expressed as the product of a standard volume per kg of starting material times the batch size (eq 9). TF can be simplified to eq 10, then expressed as the cube root of the ratio of the batch size divided by the standard batch size (B_{std}, 35 kg for Scheme 2), as shown in eq 11. Substituting eq 11 into eq 7, the expression for labor cost is shown in eq 12.

The general sense of the scale-up factor TF can be confirmed as follows. A 10-fold scale-up is known to at least double the processing time. Substituting 10 into eq 10 for B/B_{std}, TF would be 2.15.[18]

The disposal cost per batch is the product of the disposal cost per liter of waste times the volume of waste per kilogram

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(16) Overhead costs are ignored to simplify the discussion, making this discussion appropriate for a contract manufacturing organization (CMO). Overhead costs could be included as a separate category in eq 5, or as part of the plant costs in eq 7.

(17) Equation 8 incorporates the standard equations for a sphere, $V = 4/3\pi r^3$ and $SA = 4\pi r^2$.

(18) Using data from Pfaudler Inc. (www.pfaudler.com), the ratio of volume/heat transfer area for the 300 gal RA-48 series reactor may be calculated as 5.66/1, while that for the 3000 gal RA-96 series reactor is 12.7/1. Thus, as the volume increased 10-fold, the volume/heat transfer area ratio increased by a factor of 2.25, very close to the calculated value of TF = 2.15. These general-purpose vessels are squat cylinders with domed ends, and the heat transfer area includes part of the bottom head of the reactors. Thus, the approach of modeling spherical reactors for general-purpose reactors is reasonable. Similar values result when reactor vessels are considered as cylinders with identical geometries, i.e., with the height/radius ratio (h/r) held constant. In this case $V/SA = \pi r^2 h/2\pi rh$, or $r/2$. Expressing the radius as a function of the volume, $r = [V/\pi\ (\mathrm{constant})]^{1/3}$. Under these conditions a 10× increase in scale also generates $TF = (10)^{1/3} = 2.15$.

Table 2. **Raw materials costs for direct isolation and extraction options**

raw material	input of **4** (kg)	catalog price/kg ($)	estimated bulk price/kg[a] ($)	estimated cost/batch ($)	estimated cost/kg of **4** ($)
4	35.0	−	300[b]	10,500	300
chloroacetic acid	21.7	29	$6	127	4
TMSCl	26.4	65	13	345	10
HMDS	39.4	88	18	695	20
CH_3CN[c]	27.5	17	3	96	3
total cost for direct isolation process				**11,764**	**336**
MIBK	392	9	2	713	20
total cost for extraction process				**12,477**	**356**

[a] Estimated at 20% of best catalog price. [b] Starting material **4** contributes 85−90% to the cost of the raw materials for the calculations summarized in Table 2. To minimize the cost of **5** one would focus on minimizing the purchase cost of **4**. [c] For either process only 1.0 L of solvent (acetonitrile)/kg of **4** is charged, making the contribution of reaction solvent less than 1% of the raw material cost of either process option.

Table 3. **Comparing COG for direct isolation and extraction and isolation processes**

	direct isolation	extraction and isolation	direct isolation	extraction and isolation
input of **4**	35 kg	35 kg	350 kg	350 kg
output of **5**	38.5 kg	37.1 kg	385 kg	371 kg
yield of **5**	85%	82%	85%	82%
raw materials cost/kg of **4**	$336	$356	$336	$356
raw materials cost	$11,760	$12,480	$117,600	$124,800
(portion of COG estimate)	(47%)	(39%)	(78%)	(69%)
h/batch	25	35	53.9	75.4
labor cost/h	$500	$500	$500	$500
labor cost/batch	$12,500	$17,500	$26,900	$37,700
(portion of COG estimate)	(50%)	(55%)	(18%)	(21%)
waste disposal cost/drum	$500	$500	$500	$500
waste/batch, L	267	690	2670	6900
waste disposal cost	$641	$1660	$6410	$16,600
(portion of COG estimate)	(3%)	(5%)	(4%)	(9%)
total cost/batch	$24,900	$31,600	$151,000	$179,000
cost/kg of **5**	$648	$853	$393	$483
increased cost/kg of **5** produced for extraction and isolation vs direct isolation	−	+32%	−	+23%

of starting material time the batch size (eq 13). Substituting eqs 6, 12, and 13 into eq 5, the campaign cost is shown in eq 14.

When eq 14 is used to compare the cost of direct isolation and extraction for one batch using the process in Scheme 2, it can be seen that labor contributes 50−55% to the COG estimate on a 35-kg basis, but on a 350-kg basis the labor cost drops to 18−21% (Table 3). This economy on scale is due to increased space−time productivity on scale. For the larger batches waste disposal constitutes 4−9% of the COG, indicating that minimizing solvent usage through direct isolations will have a proportionally bigger effect on a larger scale as labor costs decrease. On the 35-kg scale the COG for product is increased by 32% on going to an extractive workup, and the COG using an extractive workup rises by 23% on the 350-kg scale. With increasing batch size (but *not* increasing number of batches in a campaign), both the labor portion of the COG and hence the COG estimate per kilogram of product will continue to fall.[19,20]

Even when labor and raw materials costs are reduced, direct isolation processes may be less costly than extraction and isolation processes. For instance, labor and raw materials costs charged by contract manufacturing organizations in Asia are generally considered to be 10−25% of current rates in the United States. If these rates relative to U.S. rates were reduced by the same percentages, clearly the direct isolation option would be preferred as shown in Table 3. If these rates were 10 or 25% of the U.S. rates and the rates were not identical, the direct isolation process to make **5** would still be preferred economically (see Table 4).

For equal cost of campaigns from direct isolation and extractive workup, batch sizes will increase as the number of break-even batches in a campaign increases. This can be calculated by setting the two right-hand sides of eq 14 equal

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(19) The calculations in the Tables were performed using spreadsheets, which is very convenient for evaluating “what if” scenarios. The author is not aware of any commercially available spreadsheet program to calculate COGs for multistep chemical processes.

(20) Suitable safety analyses must be completed to ensure safety and successful runs on a larger scale.

Table 4. **Impact of reduced raw materials and labor costs on choosing between direct isolation and extraction and isolation processes**

input of **4**	35 kg	350 kg	35 kg	350 kg
raw materials and waste cost[a]	10%	10%	25%	25%
labor cost[a]	25%	25%	10%	10%
increased cost of **5** by extraction and isolation process	+37%	+28%	+26%	+20%

[a] As fraction of values shown in Table 3.

Table 5. **Effect of batch sizes on campaign costs, based on Equation 15[a]**

entry	B_e (kg)	B_d (kg)	N_e	N_d	extraction campaign cost ($)	direct isolation campaign cost ($)
1	207	207	5	6	577,000	577,000
2	842	842	6	7	2,340,000	2,340,000
3	15,800	15,800	7	8	45,600,000	45,600,000
4	100	100	5	6	326,000	319,000
5	100	100	6	7	391,000	372,000
6	100	100	7	8	456,000	425,000
7	300	300	5	6	784,000	791,000
8	300	214	5	7	784,000	692,000

[a] Parameters: $M_d = \$336/\text{kg}$; $M_e = \$356/\text{kg}$; $L = \$500/\text{h}$; $T_d = 25$ h; $T_e = 35$ h; DC = \$2.40/L; $W_d = 7.6$ L/kg; $W_e = 19.7$ L/kg.

to each other and using equal batch sizes for each processing option. After substituting eq 2 and solving the equation for B, the relationship is shown in eq 15. Table 5 shows that as the number of break-even batches increases (as the yield difference between direct isolation and extraction processes becomes less) the size of the break-even batch must also increase for equal campaign costs (entries 1−3). When the batch size is less than the break-even batch size, the direct isolation campaign is less costly (entries 4−6). When the batch size is greater than the break-even batch size, the cost of the direct isolation campaign may be slightly greater than that of the extraction campaign (entry 7); if this is calculated to occur, it may be more profitable to conduct a direct isolation campaign using more runs of smaller batches to make the same amount of material (entry 8).[21]

Conclusions and Perspective

Direct isolation processes can save considerable time over a routine extraction and crystallization process: in the current example an additional 40% operating time was necessary to change from a direct isolation process to an extraction and crystallization process. By minimizing processing time through direct isolations, increased productivity may result, provided that batches from both options meet the same specifications. The financial impact of an extraction and crystallization process may have to be assessed through a cost estimate for the final product, considering the savings per kilogram of intermediate and the amount of intermediates made relative to the amount of final product made. Since time may be needed to develop a rugged direct isolation, it may not be cost-effective to develop a direct isolation to prepare only a few small batches.

Provided that the product quality is acceptable, a direct isolation process is preferred if that yield is equal to or greater than the yield of the extraction and isolation process. Even if a lower yield is reached through a direct isolation, running direct isolation batches may complete a pilot-plant campaign faster than processing one fewer batch from an extraction and isolation process. This may be determined by calculating the number of break-even batches. As the difference between yields of the direct isolation and extraction and isolation processes decreases, the sizes of the break-even batches will increase.

By an analysis of the COG estimate, the biggest impact on increased COG through extractive workups is due to increased labor cost. For the example discussed, using an extractive workup increased the raw materials cost (for solvents) by only ∼6%, and the waste disposal costs rose from 3 to 5% on a small scale. On a small scale the labor costs contribute more to the COG, and as the batch size increases, the proportional contribution of labor costs to the overall COG decreases, due to economy of scale.

To summarize, from a productivity standpoint a direct isolation process is preferred over an extraction and isolation process, provided that batches from each process meet identical specifications. Even when the direct isolation process provides a lower yield of product than the extraction and isolation process, the former may be preferred. The cost of each option can be assessed through a COG analysis, using the equations shown above. Employing direct isolation processes can significantly increase the productivity of materials made through production campaigns.

Acknowledgment

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Note Added after ASAP Publication: There was an error in equation 15 in the version published on the Web 2/6/2004. The final Web version published 2/6/2004 and the print version are correct.

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(21) In this case the campaign savings from running an additional batch with direct isolation processing should be considerably greater than the additional analytical costs.