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A Model for Mother Liquor Recycle in Batch Processing

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Abstract:

A simple model for the continuous recycle of mother liquors from a crystallization or precipitation is discussed. It is shown that the impurity profile of the mother liquors, at moderate recycle levels, quickly reaches a steady state according to $(1 - x^{n+1})/(1 - x)$, where n is the number of times the process is operated and x is the fraction of mother liquors recycled. Practical applications of the procedure are discussed, and it is shown that a relatively small amount of laboratory work would be required to test a real system under the continuous recycle conditions. An example of the successful application of the procedure to a multitonne per annum manufacturing operation is described.

Introduction

Maximizing chemical yield and process efficiency while minimizing losses of product to liquors is an important goal for economic and environmental reasons. However, when a product precipitates from a reaction mixture, or in a crystallization, there are generally losses of product to the liquors.

Either this loss may be accepted as part of the economics of the process or steps may be taken to recover part of the product contained within the prime mother liquors.

Often one accesses the desired component by some "second crop" recovery procedure. This may be done by concentration of the mother liquors, by addition of another solvent to facilitate crystallization, or by exploiting some chemical functionality of the product (i.e., extraction into water via salt formation).

As the mother liquors from the initial crystallization will generally contain higher levels of impurities, one frequently finds that the second crop is of lower quality and further processing may be required.

An alternative to "second crop" recovery is recycle of mother liquors into a subsequent batch; the product contained within the mother liquors, after crystallization, is by definition at its limit of solubility, and reuse of the liquors in a subsequent crystallization should, other things being equal, give extra yield in subsequent batches equivalent to the mass of product in the reused mother liquors.[1] There can be a reluctance to do this since it is recognized that impurities may build up, giving a lower quality product.

In the following, a strategy for recovering part of the desired product from the mother liquors without lowering product quality will be described.[2]

Discussion

Model System. Consider a process where starting material A is transformed to product B. The process is conducted in a solvent, and B crystallizes from the solvent during processing. The process may involve a chemical change followed by precipitation, or it may simply be a crystallization.

The chemist tries to arrange things so that, when B crytallizes from the mother liquors, the impurities I remain in the mother liquors. The factors which govern this are undoubtedly complex,[3,4] but it is enough for this discussion to say that the concentration of impurities does not exceed their limit of solubility.

If one were to recycle all the mother liquors from batch to batch, the following situation would develop:

1st pass

$$A \rightarrow B + I_1$$

2nd pass

$$A + I_1 \rightarrow B + I_1 + I_2$$

3rd pass

$$A + I_1 + I_2 \rightarrow B + I_1 + I_2 + I_3$$

Clearly, the impurity profile would build up linearly with recycle. Using this strategy one would quickly exceed the solubility of the impurities in the mother liquors and hence deposit increasing quantities of impurities with the desired product.

Assume now that some fraction x of the mother liquors is recycled and the required batch volume is made up with fresh solvent; this volume is held constant despite the additional mass intake of material.

1st pass

$$A \rightarrow B + I_1$$

2nd pass

$$A + xI_1 \rightarrow B + I_2 + xI_1$$

3rd pass

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(1) It is assumed that sufficient solvent is available to completely dissolve the increased batch in the crystallization process. This would often, but not necessarily, be the case. Note that this condition does not apply where product has been precipitated as a result of chemical change, since it may be that the starting materials are freely soluble in the solvent and it is the product which has significantly lower solubility.

(2) Recycle of mother liquors and associated buildup of impurity profile has been commented on, see: Lee, S.; Robinson, G. *Process Development: Fine Chemicals from Grams to Kilograms*; Oxford University Press: Oxford, 1995; p 14.

(3) Nyvlt, J. *The Kinetics of Industrial Crystallisation*; Elsevier: Amsterdam, 1985.

(4) Garside, J.; *et al. Advances in Industrial Crystallisation*; Butterworth-Heinemann: Boston, 1991.

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$$A + xI_2 + x^2I_1 \rightarrow B + I_3 + xI_2 + x^2I_1$$

For simplicity it is assumed that the impurities generated at each pass are the same ($I_1 = I_2 = I_3$ etc.). After n cycles the impurity profile would be

$$I_{total} = I + xI + ... + x^nI = I\sum_0^n x^n \quad (1)$$

Clearly it is the behaviour of the geometric progression that is of interest. The expression may be rewritten and solved in the usual way to give eq 2, where $I_n = I_{total}/I$. Equation 2 expresses the normalized impurity profile as a function of the fraction of liquors reused (x) and the number of times the process is operated (n):

$$I_n = \sum_0^n x^n = \frac{1 - x^{n+1}}{1 - x} \quad (2)$$

From a chemical perspective $x = 0$ represents no liquors recycled and $x = 1$ represents all the liquors recycled. The latter case has been discussed earlier and would quickly lead to quality problems.

It is useful to realize that the impurities will tend to a limit when $1 > x > 0$ as $n \rightarrow \infty$ and eq 2 simplifies to eq 3:

$$I_\infty = \frac{1}{1 - x} \quad (3)$$

Thus one may calculate the impurity profile after an infinite number of recycles as a function of the fraction of mother liquors reused (Figure 1). Notice that a significant proportion of the mother liquors may be recycled with a relatively modest increase in liquor impurity profile. For example, up to 50% of the liquors could be recycled and, by application of eq 3, the impurity profile of the liquors would only double. Assuming that the process will tolerate this impurity level, the benefit is clear since B is at its limit of solubility, and a yield increase equivalent to the mass of B contained in the recycled liquors would be expected.

To illustrate this, assume an 80% yield from a crystallization; the mother liquors contain 18% product and 2% other impurities. By recycling 50% ($x = {}^1/_2$) of the mother liquors into subsequent crystallizations one would expect an immediate yield increase to 89% (i.e., 80% + ${}^1/_2 \times$ 18%). From eq 3 the impurities in the liquors would build up to 4% (i.e., 2% $\times$ 1/(1 − ${}^1/_2$)). If these impurities are of similar solubility or are more soluble than the product, they would not be expected to crystallize with the product.

Practical Considerations. In order to test the above model on a batch or semibatch process one would run a laboratory investigation. Obviously it would take a long time to build the impurity level to I_∞, so the number of experiments required to test the suitability of a process is important for practical reasons.

It is found that at recycle levels of interest, 70% or below, the number of experiments necessary to generate >99% of the theoretical maximum impurities is quite small. From eqs 2 and 3,

$$\frac{I_n}{I_\infty} = \frac{1 - x^{n+1}}{1 - x}\frac{1 - x}{1}$$

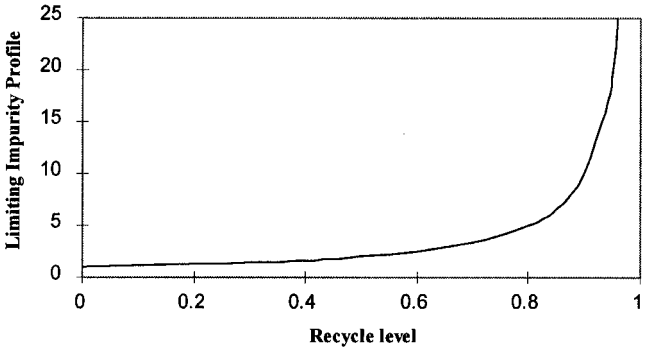

Figure 1. **Plot of eq 3.**

Table 1

x	n	no. of recycles[a]
0.2	1.86	2
0.3	2.82	3
0.4	4.03	5
0.5	5.64	6
0.6	8.02	9
0.7	11.91	12
0.8	19.64	20

[a] Generates an impurity profile >99% of the theoretical maximum.

Table 2

batch no.	n	impurity profile[a]
1	0	I_0
2	1	$I_1* + {}^1/_2I_0$
3	2	$I_2 + {}^1/_2I_1* + {}^1/_4I_0$
4	3	$I_3 + {}^1/_2I_2 + {}^1/_4I_1* + {}^1/_8I_0$
5	4	$I_4 + {}^1/_2I_3 + {}^1/_4I_2 + {}^1/_8I_1* + {}^1/_{16}I_0$

[a] An asterisk denotes the batch with a process deviation.

which for these purposes should be 99% (i.e., $1 - x^{n+1} = 0.99$) and may be rearranged to give eq 4:

$$n = \left(\frac{\ln 0.01}{\ln x}\right) - 1 \quad (4)$$

The utility of eq 4 may be seen in Table 1, which shows that only a modest amount of laboratory work would be required to test a real process. For example, assume a simple crystallization process. At a 50% recycle level, one would need to recycle the liquors from the first crystallization into six subsequent crystallizations. Thus seven experiments would be required in total.

In the real world processes may be subject to uncontrolled deviations. Sometimes this has no effect on the impurity profile or product quality, while at other times a lower quality product is obtained. Clearly, unless the impurities generated from the process deviation are all precipitated with the errant batch, the impurity profile of the liquors will increase.

To see how this situation would affect the profile of the liquors, assume that the recycle level is 50% and that the second batch has a higher than expected impurity level (Table 2). In the second batch the full impact of the higher impurity level is realized. Subsequently the contribution to the profile of the liquors diminishes. Obviously the lower the recycle level x, the smaller the impact on the subsequent batches.

Limits of Applicability. Crystallization may well be suitable, but a distinction must be drawn between crystallizations which use only one solvent and those which use a mixture of solvents but do not involve addition of any solvent to drive the crystallization.

In the case where a solvent is added to drive the crystallization process, the solubility properties of the mother liquors at the end of the crystallization will be markedly different from those required to initially dissolve the batch. One could anticipate that recycle of these mother liquors in subsequent batches might result in failure to achieve complete solution in subsequent batches unless trivially small amounts of mother liquors are recycled.

In the model system described, it was assumed that the change in impurity profile does not affect the solubility of the desired component B. This may not always be the case, and impurities may act as a cosolvent. For instance, one could imagine a process where an alcohol crystallizes from a nonpolar solvent such as hexane, and in the process there is a hexane-soluble alcoholic impurity. Recycle of the mother liquors then increases the polarity of the mother liquors and hence tends to increase the solubility of the desired component.

Conversely one could envisage situations where the change in impurity profile would be expected to have a negligible effect on the solubility or quality of the product. This situation may occur when the impurities are much more soluble than the product. For example, consider the formation of an amine via a Ritter reaction where the major impurities are unreacted alcohol and alkene (by elimination of water from the starting alcohol). The amine may be isolated by addition of hydrogen chloride, whereupon the amine hydrochloride may be collected by filtration.

Here the mother liquors would contain the amine hydrochloride (at the limit of solubility) along with alcohol and alkene which are assumed to be freely soluble in the solvent. One could expect that a significant fraction of these mother liquors may be recycled from batch to batch without appearance of the impurities in the product. One could equally argue that such changes in the composition of the liquors might affect the crystal form of the product thus modifying the efficiency of washing sequences and in this way have a deleterious effect on quality.

Changes in the composition of solvent through recycle may make certain processes unsuitable. Consider the case of charcoalation of an amine hydrochloride in aqueous solution. The charcoal may be removed by filtration and the amine precipitated by the addition of caustic. Since the amine would have finite solubility in the aqueous phase, one might anticipate additional recoveries by recycle of part of the aqueous mother liquors. However, the buildup of salt in the aqueous phase might well be expected to cause solubility problems with the amine hydrochloride due to the common ion effect.

Other problems may be observed once a process is subjected to mother liquor recycle. For instance, the change in impurity profile may affect the characteristics of phase separation during a washing sequence, either by slowing the separation process, by formation of a large amount of interfacial sludge, or by formation of an emulsion.

In the model no account is taken of the possibility of additional impurities occurring as a function of recycle. One could imagine oligomeric species forming through the repeated stress of recycle and hence causing quality issues. Practical considerations such as these must be determined for each process individually, but if a process is stable at 60% recycle for 20 cycles before quality deviations are noted, one may simply arrange to discard the liquors before the 20th cycle and then start afresh.

It is clear from the above that the suitability of a given system to protracted mother liquor recycle needs be evaluated on a case by case basis.

Experimental Section

The above strategy has been tested on a ChiRex pharmaceutical product, which provides material to the US Pharmacopoeia specification on a multitonne per annum basis. A laboratory study indicated that the final recrystallization was stable at the ~40% recycle level for seven cycles (see Table 1), and plant trials were begun to assess the strategy.

Initially a one-batch trial was run where 60% of the liquors was recycled. The impurity profile would be expected to increase to 1.6 times the ordinary level. This level of impurity profile, from eq 3, would be expected from continuously recycling mother liquors at the 38% level. In this way the basic idea could be initially tested, committing only one batch to quarantine and accelerated stability testing.

Subsequently a number of trials were begun to assess the continuous recycle of mother liquors. During the initial trials no deterioration of product quality was observed. Subsequently 53 batches were processed at the 38% recycle level without interruption. Since by eq 4 it is expected that the impurity profile would be >99% of the theoretical maximum after only 5 recycles, the data at hand implies that the process is stable at this recycle level. Trials were then carried out at an increased recycle level of 61%. After 9 recycles (which according to the model would bring the impurity profile to >99% of the theoretical maximum) no deterioration of quality was observed. The process has been operated at the 61% recycle level for over 50 batches continuously, with the consequent yield benefit.

Conclusion

A model for the recycle of a significant fraction of mother liquors has been described. It is expected that the additional yield of product will be in proportion to the amount of liquors recycled. The impurities present in the liquors build up quickly, at moderate recycle levels, to a steady state and thus allow for practical laboratory investigation of the strategy.

Some limits of applicability of the method are discussed in order to guide experimental efforts.

This type of continuous batchwise recycle is an alternative to second crop recovery and may improve yield and minimize effluent with minimal additional processing.

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