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Optimization of Solvent Chasing in API Manufacturing Process: Constant Volume Distillation

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Abstract:

Solvent exchange by distillation is a common unit operation in active pharmaceutical ingredient (API) manufacturing processes. Either a stepwise solvent displacement mode or a constant volume solvent displacement mode can be used to carry out the solvent exchange. The constant volume mode can be more efficient as the chasing solvent acts as an effective displacer by keeping concentrations of the solvent being displaced at higher levels. As demonstrated during a production application at Abbott Laboratories, the constant volume solvent displacement mode resulted in a 30% reduction in the quantity of displacing solvent, 2-propanol (IPA), when compared with the equivalent process using a stepwise solvent displacement mode. As a consequence, 30% reduction in the waste solvent generation was realized. This mode of operation dose not adversely impact product quality nor process yield.

1. Introduction

Solvent exchange by distillation is a common unit operation in active pharmaceutical ingredient (API) manufacturing processes. For example, solvent exchanges are used in preparing a nonisolated intermediate for the next reaction step in preparation of solutions for crystallization. In addition to heat sensitivity, API compounds also exhibit different solubility in different solvents, leading to different process constraints for the chasing distillation.

In the traditional, stepwise solvent exchange process, the initial solvent mixture is reduced in volume by distillation to a low level. The initial low distilled level is mainly determined by the solubility of the chemical compound in the initial solvent. It is normally desired not to have solids precipitated/crystallized out at this point in order to prevent trapped solvent in the solids. Once the desired low level is achieved, the chasing solvent is then charged into the batch and distillation is repeated to further reduce the quantity of residual initial solvent. This cycle of exchange may be repeated several times to achieve very low levels of the initial solvent.

In the constant volume solvent exchange mode, the initial solvent mixture is distilled to a low level as in the stepwise distillation. Once the low level is obtained, a constant volume is maintained during distillation by a continuous, simultaneous charge of the displacing solvent. Thus, the displacing solvent is not used as a dilutor, as in the stepwise exchange. Rather, it is used as a true displacer for removing the initial solvent. As a result, the solvent exchange is carried out with less chasing solvent, with the attendant decrease in solvent waste.

From the process point of view, the constant volume solvent exchange mode of operation is desired in the crystallization process as it prevents the excessive buildup of solids on a reactor wall. Due to the heat sensitivity of some products, it is often desired to maintain the temperature as low as possible during distillation. In this mode of operation, the vacuum level in the reactor is much easier to maintain due to the small addition of solvent. Therefore, one would not expect to observe large temperature swings that usually occurs in the stepwise distillation mode.

Although the concept and theory of constant volume solvent exchange distillation are cited in the literature,[1,2] limited practical implementation has been reported. This article documents the solvent savings obtained within an actual manufacturing process at Abbott Laboratories when the solvent exchange distillation was switched from a stepwise to a constant volume chasing mode.

The two modes of solvent displacing distillation were demonstrated in the API manufacturing process of Erythromycin A Oxime. The process is summarized below:

Erythromycin A reacts with aqueous hydroxylamine in 2-propanol (IPA) and acetic acid to form Erythromycin A Oxime.[3] The Oxime formation reaction is halted upon addition/extraction of the product into isopropyl acetate (IPAc). To crystallize the Erythromycin A Oxime from 2-propanol (IPA), the solvent mixture of IPA/H_2O/IPAc must be converted to a solvent mixture consisting essentially of IPA.

This contribution focuses on this solvent exchange step and details model development and production results from implementation of the models. A 30% reduction of fresh IPA usage was realized when the distillation exchange mode was switched from stepwise to constant volume, with the added consequence of a 30% reduction in waste solvent generated from this process.

2. Model Description. Solvent exchange distillation utilizes the simplest form of batch distillation, which involves a heated vessel (also called a hot pot), a condenser, and a receiver. The feed is charged into the hot pot and is brought to a boil by vacuum and/or heating. The vapors are condensed as distillate that is collected in a receiver. This solvent exchange process is

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(1) Gentilcore, M. Reduce Solvent Usage In Batch Distillation. *Chem. Eng. Progress* **2002**, (January), 56–59.

(2) Elgue, S.; Prat, L.; Cabassud, M.; Cezerac, J. Optimisation of Solvent Replacement Procedures According to Economic and Environmental Criteria. *Chem. Eng. J.* **2006**, *117*, 169–177.

(3) Chang, S. Process For Preparing Erythromycin A Oxime. U.S. Patent 5,808,017, 1998.

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Table 1. **Summary of simulation results for stepwise chasing distillation**

in the crystallizer	distill - 1		distill - 2		distill - 3		dilution - 3	
	initial (A)[a]	final (B)[a]	initial (C)[a]	final	initial	final	initial	final (D)[a]
[IPAc], kg/kg	51.40%	15.54%	6.250%	1.95%	0.90%	0.36%	0.36%	0.22%
[IPA], kg/kg	38.6%	70.2%	88.010%	93.4%	97.0%	98.2%	98.2%	98.9%
[H2O], kg/kg	10.0%	14.3%	5.740%	4.7%	2.1%	1.5%	1.5%	0.9%
total solvent, kg	5313	1105	2745	1245	2775	1385	1385	2265

[a] Corresponding points in Figure 2.

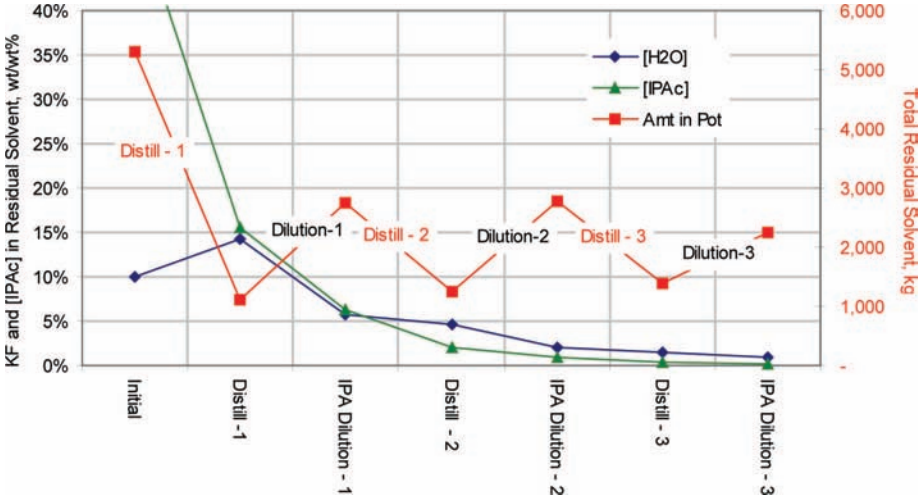

Figure 1. **Concentration and weight profiles in the hot pot during stepwise chasing distillation.**

also called a batch or differential distillation. The distillation rate is controlled by both vacuum and heating, and is governed thermodynamically by the vapor–liquid equilibrium (VLE) curve of the solvents involved.

The mathematical model for the distillation follows the Rayleigh equation, which is as follows:

$$\ln \frac{M_i}{M_f} = \int_{x_f}^{x_i} \frac{dx}{y - x} \qquad (1)$$

where M represents the moles of liquid in the pot, x the mole fraction of the more volatile component in this liquid, and y the mole fraction of the same component in the vapor. M_i and x_i represent the initial state and M_f and x_f represent the final state. The relationship between x and y is governed by the liquid–vapor equilibrium (VLE) curve for the solvents involved.[4] In this particular study, the NRTL-RK method was used for predicting the VLE for the mixture of IPAc/IPA/H_2O. Aspen Plus Version 2004.1 simulation software from AspenTech was used in the calculations for both stepwise and constant volume chasing distillations below.

Stepwise Chasing Distillation. The stepwise chasing distillation can be modeled using initial solvent ratios and typical volumes from manufacturing experience. After completion of Erythromycin A Oxime formation step, the reaction is halted effectively by the addition of IPAc, resulting in two separate liquid layers. The organic layer is separated from the aqueous layer via phase separation. Using a stepwise displacing distillation process, the organic layer is then distilled from 5310 kg to about 1110 kg in a hot pot (Distill - 1) at the pressure of 100 mmHg. During this first distillation, the IPAc content is reduced by about 94% and the water content is reduced by about 70%.

At the end of the first distillation step, IPA (1640 kg) is charged into the hot pot (Dilution - 1) and the contents reconcentrated to about 1245 kg to remove additional IPA, IPAc and water (Distill - 2). About 86% of the remaining IPAc and 63% of remaining water are removed at this step.

At the end of the second distillation step (Distill-2), additional IPA (1530 kg) is charged to the hot pot (Dilution-2), and the contents are reconcentrated by distillation to the 1385 kg level. This further reduces the remaining IPAc by 80% and water by 65% in Distill - 3.

At this point, IPA (880 kg) is added to dilute the solution in preparation for crystallization (Dilution - 3) and a sample is analyzed for water content by Karl Fischer (KF) moisture determination measurement. The target residual water level after dilution is not more than 0.9% w/w. The Erythromycin A Oxime is crystallized from the solution upon cooling. Table 1 summarizes the sequence results from Distill - 1 to Dilution - 3.

The stepwise solvent chasing distillation process consists of two unit operations: batch distillation (Distill-1, Distill-2, and Distill-3) and dilution with fresh solvent (Dilution-1, Dilution-2, and Dilution-3). The amount of IPA charged in Dilution-1 and Dilution-2 is 3170 kg. Figure 1 shows the concentration and total solvent weight profiles in the hot pot during the stepwise chasing distillation mode.

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(4) Perry, R. H., Green, D. W., Maloney, J. O., Eds. *Batch Distillation*, *Perry's Chemical Engineers Handbook*, 6th ed.; McGraw-Hill: New York, 1984; pp 13-82–13-90.

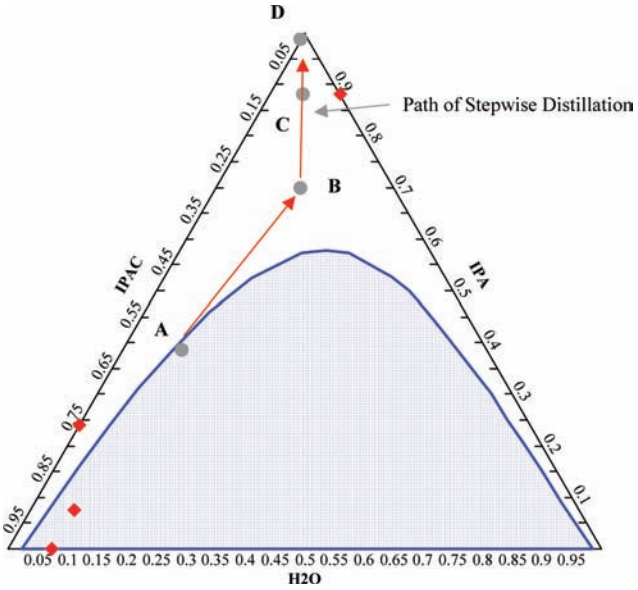

Figure 2. **Stepwise solvent chasing distillation for IPA/IPAc/H_2O system.**

Table 2. **Summary of constant volume distillation (CVD)**

	distill - 1			dilution - 3	
in the crystallizer	initial (A)[a]	final (B)[a]	CVD chasing	initial	final (C)[a]
[IPAc] kg/kg	51.40%	15.54%		0.18%	0.10%
[IPA], kg/kg	38.6%	70.2%		98.3%	99.6%
[H_2O], kg/kg	10.0%	14.3%		1.5%	0.83%
total residual solvent, kg	5313	1105	1105	1105	1985

[a] Corresponding to points in Figure 4.

Figure 2 illustrates the distillation and dilution progress plotted upon the ternary phase diagram for IPA/IPAc/water at 100 mmHg pressure based upon the NRTL-RK model for both liquid−vapor and liquid−liquid equilibrium.[5] The resulting phase diagram predicts four azeotropic compositions as noted in the red dots. The arrows indicate the direction of chasing steps.

The Distill-1 started with the organic layer saturated with water at Point A, (i.e., the phase separation between organic and aqueous layers) and the Distill-1 was halted once the contents are reduced by 80% (Point B). Next, IPA is charged, resulting in a dilution of the solution to Point C. This dilution shifts the solvent mixture across the azeotrope, which then enables the distillation to proceed along the other side of the IPA/water azeotrope.

Note that the ratio of residual [IPAc]/[H_2O] was initially greater than 1 (i.e., residual [IPAc] was higher than that of [H_2O]). However, once past the azeotrope line, the ratio is less than 1. In other words, the residual concentration of water is always higher than that of isopropyl acetate (IPAc). Therefore, the residual water content can be used as a single indicator for both residual IPAc and water.

It is the dilution step (i.e., from point B to point C) that results in the inefficiency of this type of chasing distillation. A large amount of IPA solvent is used as a dilutor to move the mixture across the azeotrope from Point B to Point C. During this dilution step, neither IPAc nor H_2O has been removed from the system.

Constant Volume Solvent Chasing Distillation. The constant volume solvent chasing distillation was modeled. In this mode, Distill-1 is unchanged, but Dilution-1, Distill-2, Dilution-2, and Distill-3 steps are combined into a single step (Table 1).

At the end of the Distill-1 step, rather than charging a large volume of IPA at once, the IPA is charged continuously at the same rate as the distillation rate (i.e., the liquid level in the hot pot is maintained at a near-constant, low level). For the simulation calculation, the constant volume solvent exchange chasing distillation mode is digitized as follows: charge 55 kg of IPA, distill off 55 kg of mixture, charge again 55 kg of IPA, and then distill off 55 kg of mixture repeatedly. This loop continues until the residual H_2O in the hot pot reaches not more than 1.5%. The pressure condition for this distillation mode is kept the same as for the stepwise mode, i.e., 100 mmHg.

Table 2 summarizes the simulation results, with similar IPA (98.3%) and final residual water content values (1.5%) as for the stepwise chasing mode [see Table 1 showing IPA (98.2%) and H_2O (1.5%) at the end of Distill - 3]. During dilution - 3 step, 880 kg of fresh IPA is added to reach the target volume for crystallization and the target KF moisture value as with the stepwise distillation.

Figure 3 summarizes both concentration and weight profiles in the hot pot. Figure 4 indicates the distillation pathway for the constant volume chasing mode plotted on a ternary phase diagram for IPA/IPAc/water at 100 mm pressure.

From the phase diagram (Figure 4), it indicates that there is a savings in IPA usage because there is no IPA used in a dilution step as in the stepwise mode (red arrow in Figure 2, the mixture composition from point B jumps to point C). Instead, IPA charging is used as a true displacer to remove both residual IPAc and H_2O in the system.

From a liquid vapor equilibrium point of view, the higher the concentrations of H_2O and IPAc in the liquid phase, the higher the corresponding species partial pressure in the vapor phase. Since the residual solvents are removed from the vapor phase, the removal efficiency is higher due to their high vapor phase pressures. If IPA is added in a large amount to the crystallizer in the liquid phase at one time, it dilutes the residual concentrations of both H_2O and IPAc in the liquid phase, which results in smaller partial pressures of H_2O and IPAc in the vapor phase (due to their vapor liquid equilibriums). It is this dilution that causes the inefficient usage of the displacement solvent, IPA, in this case.

The reduction in use of IPA comes from a more efficient use of the displacing solvent. Figure 5 compares the two modes of distillation: stepwise and constant volume. The constant volume mode is noticeably more solvent efficient: 1600 kg of IPA is charged to achieve 0.4% residual IPAc in the hot pot. Distilling further in the constant volume mode with an additional 590 kg of charged IPA, the residual IPAc and water reduce to 0.2% and 1.5%, respectively. The stepwise mode reduces IPAc to 2.0% using 1600 kg of IPA. Using the stepwise chasing

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(5) *Aspen Plus Version 2004.1*; Aspen Technology, Inc.: Cambridge, MA, U.S.A., 2004.

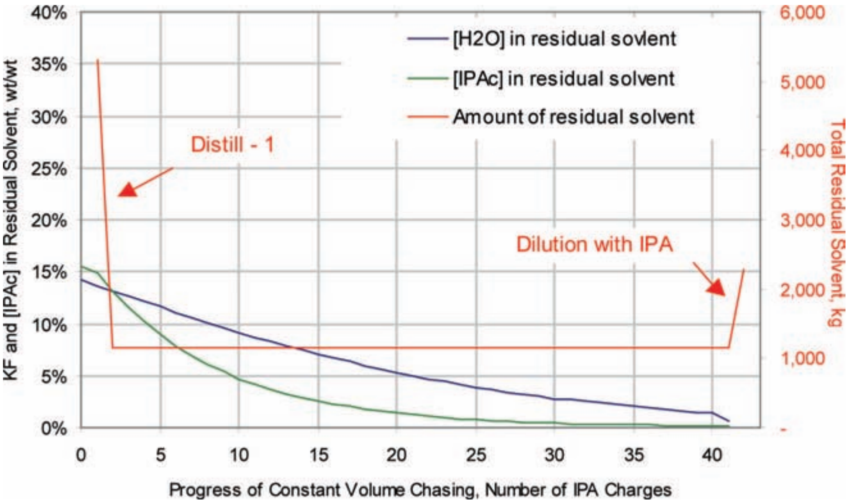

Figure 3. **Concentration and weight profiles in the hot pot during constant volume chasing.**

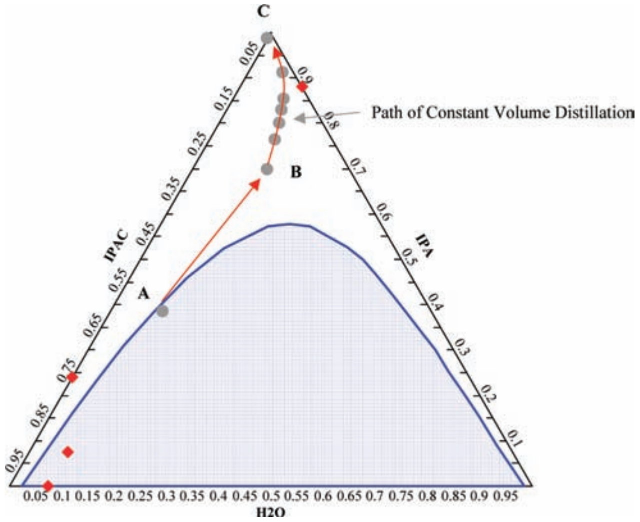

Figure 4. **Constant volume solvent chasing distillation for IPA/IPAc/H_2O system.**

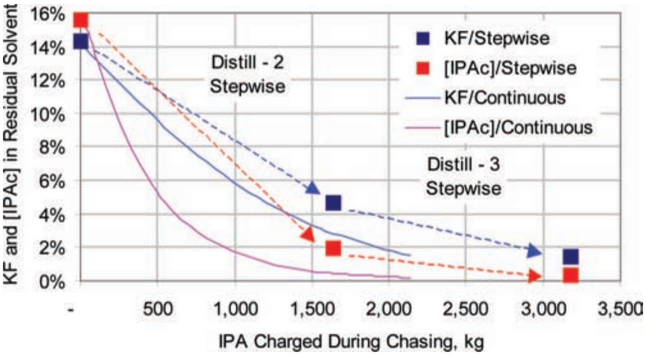

Figure 5. **Comparison of distillation profiles for stepwise and constant volume of chasing distillation.**

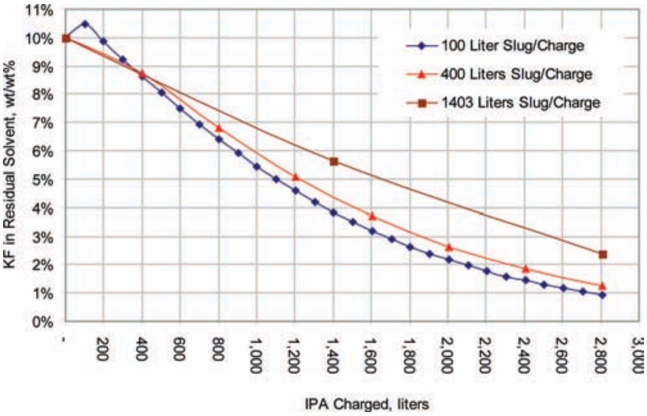

Figure 6. **Effect of step size upon residual water level in residual solvent.**

Table 3. **Comparison of two distillation modes**

	stepwise mode		const. vol. mode	
in the crystallizer	initial	final	initial	final
total residual solvent, kg	5313	1385	5313	1105
[IPAc] kg/kg	51.4%	0.4%	51.4%	0.2%
[IPA], kg/kg	38.6%	98.2%	38.6%	98.3%
[H_2O], kg/kg	10.0%	1.5%	10.0%	1.5%
total amt of IPA charged, kg	3170		2190	

Table 4. **Summary of process conditions**

ID		process conditions			
mode of operations	batch #	IPA charged, kg	IP result, KF (%)	centrifuging time (h)	drying time (h)
constant volume chasing	CVD-1	2995	0.6	12	12
	CVD-2	2910	0.4	12	15
	CVD-3	3000	0.9	10	17
stepwise chasing	average	4495	0.6	13	13

mode, a total of 3180 kg of IPA must be charged to reach the 0.4% residual IPAc and 1.5% residual water.

Table 3 compares the two chasing modes of distillation for the same end point (at the end of distillation, but before the dilution by IPA addition). The results indicate that a savings of 980 kg of fresh IPA solvent per batch, which is about a 31% solvent usage reduction per batch.

3. Plant Trial Results. Based upon the model prediction, which was verified at laboratory scale, three demonstration runs were carried out in actual production scale. The goal was to maintain an IPA solvent charging rate equal to the solvent distillation rate. The trial runs were carried out manually. Due to the marker resolution inside the crystallizer, it was decided that 100 L step size would be used. Figure 6 shows the simulation results that summarize the effect of step size upon the water removal efficiency: the smaller the step size, the lower the residual water in the crystallizer. If the process is automated, the step size can easily be further decreased. Therefore, the water

Table 5. **Summary of purity and batch yield results**

mode of operations	batch # unit	relative change in total product related impurities, %, impurities from CVD/impurities from stepwise	relative change in product purity, wt/wt, purity from CVD/purity from stepwise	relative change in yield, %, yield from CVD/yield from stepwise
constant volume chasing	CVD-1	80.0	101.6	97.9
	CVD-2	98.5	100.7	100.5
	CVD-3	86.2	101.0	99.5
stepwise chasing	relative average	100.0	100.0	100.0

removal efficiency will be further increased, and the amount of IPA charged can be reduced.

During the trials, the total amount of IPA solvent charged was precalculated using the NRTL-RK VLE model in the Aspen Plus software version 2004.1. At the end of the chasing distillation, an in-process sample was taken for residual water measurement per current manufacturing procedure. Once the in-process sample passed, the process moves forward to the next step of centrifugation and drying.

As expected the temperature profile in the crystallizer during the trial was different from the one using stepwise chasing distillation. Unlike the large temperature swings for the stepwise distillation, the temperature was gradually decreased about 5 °C from 40 to 35 °C at 100 mmHg. The high amplitude of the temperature swing during the stepwise distillation is mainly due to the charging of displacement solvent, IPA, during which time the vacuum in the crystallizer was broken. In the constant volume distillation mode, the vacuum level in the crystallizer was maintained.

In theory, since less amount of chasing solvent was used for the constant volume distillation, one would expect that the distillation time should be shortened accordingly. However, during the trial runs, the cycle time was similar to that for stepwise distillation. This could be due to the manual operation during the constant volume distillation, or it may be a result from the poor heat transfer during distillation.

Unlike the stepwise distillation, the liquid level in the crystallizer was maintained at a low volume in the constant volume distillation. Therefore, the heat transfer area between the liquid and the internal surface of the crystallizer is smaller as compared with that for stepwise distillation. As a result, the amount of heat transferred into the crystallizer is less for the constant volume distillation mode than that for the stepwise distillation mode.

Table 4 summarizes the process conditions for three constant volume distillation runs. The results indicate that the water content after dilution is below the specification of 0.9%. The average volume of IPA used in stepwise chasing is included in Table 4. The savings of 1500 kg of IPA solvent was realized when the distillation mode is constant volume instead of stepwise displacing distillation.

The potential for a crystal property change was a concern in evaluating the new mode of chasing distillation. The laboratory-scale runs indicate no difference in the crystal habits from these two modes of operation. During the trial runs, the cycle times of both the centrifugation and drying did not change.

Table 5 summarizes the isolated Erythromycin A Oxime yield and quality results. The yields from the three constant volume distillation trial runs fall within the production range of stepwise distillation runs. All lots passed quality testing requirements. Changing the distillation conditions does not adversely impact product quality or yield.

5. Conclusions

The constant volume solvent displacing distillation mode is a solvent-efficient process in comparison to the stepwise displacing distillation mode as was demonstrated in the manufacturing scale of Erythromycin A. Oxime crystallization process. This efficiency is due to the lack of chasing solvent (i.e., IPA in this case) used in the dilution step of the constant volume distillation compared to a similar step in the stepwise distillation. Instead, the displacing solvent is used as a true displacer to remove both residual IPAc and H_2O in the system.

The theoretical model for these two solvent distillation modes has been developed and successfully tested in manufacturing. Testing demonstrates that the constant volume solvent displacing distillation mode resulted in a savings of more than 30% in displacing solvent in the Erythromycin A. Oxime production. As a consequence, 30% reduction in the waste solvent generation was realized.

Acknowledgment

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