Addressing the Acetonitrile Supply by Implementing Recovery and Reuse Strategies

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Abstract

With the increased use of high-grade acetonitrile (ACN) for peptides and oligonucleotides synthesis and purification, the demand for ACN is expected to sky-rocket and double by 2036 (233 kMTA). This demand will likely exceed production capacity, resulting in a sharp increase in the ACN price, as well as a supply shortage putting many drug manufacturing supply chains at risk.

It is therefore essential to consider either alternative solvents in synthesis and/or to implement **recovery and re-use** strategies. However, these strategies face three real challenges: **Feasibility**, **Cost**, and **Regulatory Approval**.

In the past 2 years, SK pharmteco has been evaluating a technology that can provide high-quality ACN at a lower cost than traditional processes recovering ACN streams from the synthesis of oligonucleotides. Coupled with a preliminary evaporation step, the continuous melt crystallization process provides an equivalent or better-quality solvent than fresh ACN. The work performed is presented below.

Key Benefits and Applications:

- Insurance of supply
- Higher grade ACN for synthesis
- High yield
- Cost control
- Reduced waste - Green Chemistry
- Lower energy demand
- Robust process

Objective

The work was initiated to evaluate the feasibility of recovering and recycling ACN from non aqueous streams and multiple sources as an effort to reduce our waste and procurement cost.

Project is in collaboration with **IONIS Pharmaceuticals**, a manufacturer of oligonucleotides.

- The synthesis process requires between 800 and 1,600 L of ACN per kg of oligonucleotide produced
- The ACN needs to be “dry”
- A fraction of the synthesis stream is collected for recovery and reuse (56%)
- The stream contains Toluene, Pyridine, and organic waste (dark compounds)

Note: SK pharmteco also consumes ACN for the plant (synthesis) and the labs (QC/R&D)

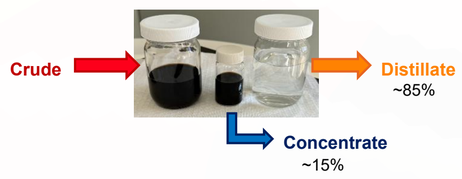
Multiple techniques exist to recover ACN:

- Fractionation distillations in series
- Membrane technologies: nanofiltration, pervaporation, reverse osmosis
- Melt crystallization

The work demonstrates the process feasibility and the resulting ACN quality.

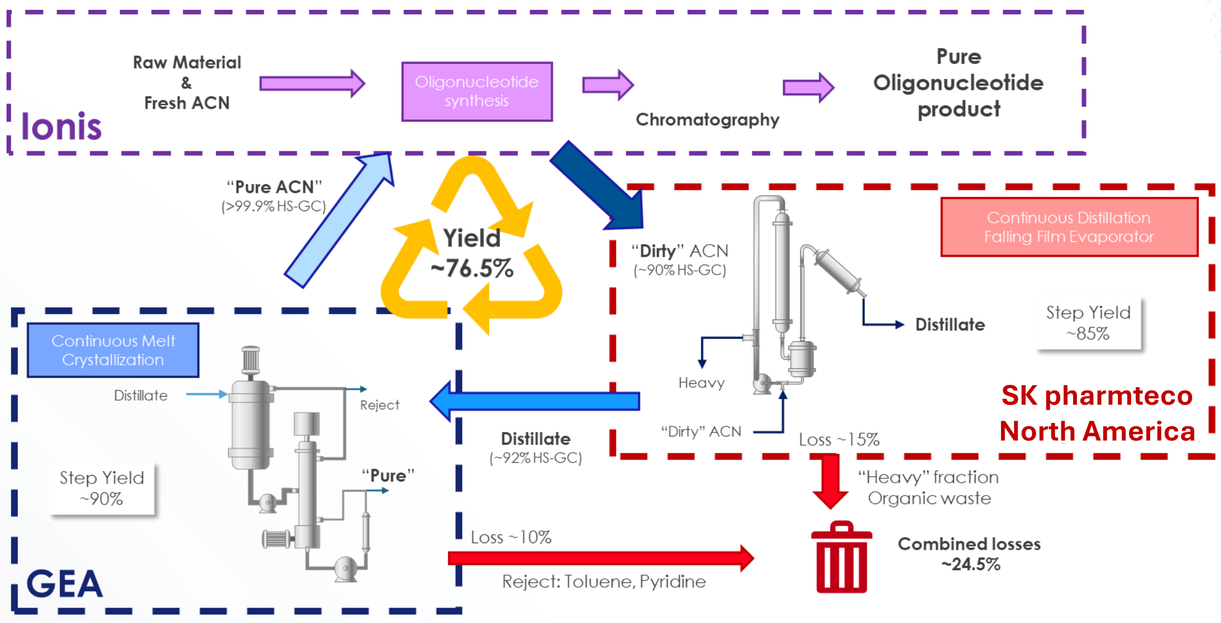
The Process

The oligonucleotide synthetic process requires large volumes of ACN. The “dirty” ACN is recovered and then processed through a falling film evaporator to remove the “heavy” impurities.



The distillate, a “clean” mixture of ACN, toluene and pyridine (~85% yield) is then processed through the “melt” crystallization step to recover clean, high purity ACN.

Description	Appearance	ACN Purity	Major impurity		Water (KF)
		Area%	Toluene	Pyridine	Wt%
Crude Waste Stream, Drum 4	Clear brown liquid	89.22	4.58	5.72	0.2820
Distillate Drum 4	Clear colorless liquid	92.39	5.38	2.20	0.6033
Product at -48.04 ºC	Clear colorless liquid	100.0	ND	ND	0.00
Product at -50.33 ºC	Clear colorless liquid	100.0	0.00	0.00	0.40
Product at -52.11ºC	Clear colorless liquid	100.0	0.00	0.00	0.46



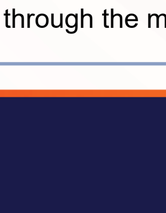
The work was demonstrated on the pilot (0.15) melt crystallizer at GEA in the Netherlands on ~400 L of distilled ACN. The recovered pure ACN is currently being used at Ionis to close the recycle and re-use loop. The melt crystallization performed between -48 and -50 ºC to crystallize ACN away from the “impurities” (toluene and pyridine) results in ACN of high purity. The yield for the crystallization is about 90%. Higher yield can be obtained with lower temperature (-52 ºC). The water content in the crude is the only concern at this stage. The water eutectic is estimated around 2% and needs to be controlled in the input stream. An overall yield of 76.5% is achieved in the process (FFE + XST).

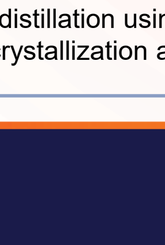
Easy Scale-up and Large Capacity Available

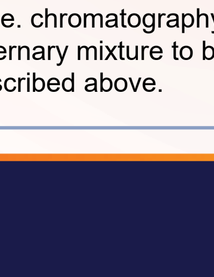
SK pharmteco’s manufacturing plant in Rancho Cordova, California, operates several falling film evaporator units associated with the continuous chromatography equipment (SMB). These FFE units can be operated as stand-alone and process significant volumes at a low cost.

Falling Film Evaporators Existing Capacity				
8 x 200	2,405	MTA	3,072	m^3/A
6 x 800	16,838	MTA	21,504	m^3/A
5 x 1,000	45,101	MTA	57,000	m^3/A

320 days of operations


1.6 and 4 m^2
100 to 400 l/h


2 x 14.2 m^2
500 to 2,800 l/h


2 x 65 m^2
2,000 to 5,000 l/h

Melt Crystallization Units		Pilot	DC 1.5	DC 4	DC 4
Product Rate	m^3/d	**0.15**	**1.5**	**1.5**	**5**
	kg ACN /d	118	1,178	1,178	3,925
Capacity	MTA ACN	38	377	377	1,260
Column Diameter	cm	6.0	20	20	33
Crystallizer	Size	Small	Small	Large	Large
Process Equipment	kWh/h	1.8	9	11	20
Refrigeration Compressor	kWh/h	1.5	7	9	19
Cooling Water for Compressor	m3/h	0.25	1	2	3
Total Cooling Load Crystallization	kWh/h	1.5	7	9	19
	at ºC	-64	-64	-60	-64

The melt crystallization is used at very large scale in the chemical and food industry. The proposed size to address the pharmaceutical demand is small (DC 1.5) compared to existing operating units.

The energy demand is low since the enthalpy of crystallization is a third of the enthalpy of evaporation of ACN. Also, the crystallizer volume and the separator column are quite small limiting energy losses.

Scale-up of the unit operation is straightforward as it is a continuous process.

Conclusion

SK pharmteco in collaboration with **Ionis Pharmaceutical** and **GEA**, has demonstrated the **Recovery and Re-use process** for **ACN** from a non-aqueous stream from the oligonucleotide synthesis. The process allows for the reduction of procured fresh acetonitrile by ~75% as well as a reduction in waste stream. This process provides a significant reduction in carbon footprint as well as an increase in public safety by eliminating trucks on the road.

Based on the estimated throughput, investment and operating cost, a significant saving is expected allowing for 5 to 10 years amortization period. Since higher ACN price is expected due to the projected demand increase, this period is likely to be significantly shorter.

The ACN produced is of high purity. Crystallization of fresh ACS technical grade can result in high grade ACN at reduced cost. This high quality ACN can be used for HPLC and LC-MS analytical work as well as in R&D for process development and at the plant for synthesis.

Next Steps

Processing ACN from aqueous waste streams (i.e. chromatography purification steps) will be evaluated next. The first step (FFE) needs to be modified to eliminate the water from the “crude” feed. A fractionation distillation using a ternary mixture to break the azeotrope can be used to remove all the water (and the heavy impurities). The “clean” distillate will then be processed through the melt crystallization as described above.