Bio-based building blocks, case study of a large-scale manufacturing process

NICOLAS-JULIEN HILBOLD, FREDERIC SCHAB
*Corresponding author
1. Marketing Manager, Novasep, 82 Boulevard de la Moselle, Site Eiffel BP 50, 54340 POMPEY, France
2. R&D Project Manager, Novasep, 5 rue du Pilon, Saint-Maurice de Beynost, 01708 MIRIBEL, France

ABSTRACT

Bio-based chemicals are gaining interest as alternatives or additional sources of chemicals. Among them, organic acids are promising as building blocks and chemical platforms. To integrate the chemical industry supply chain, bio-based products must become commodity products and meet current specifications applied to petro-based chemicals in terms of quality and purity. This article will illustrate several purification challenges that manufacturers encounter by describing an industrial manufacturing process for citric acid production from fermentation to purification.

Each step will be reviewed and explained with special emphasis on the continuous chromatography step based on acid retardation since it is the core operation unit of the described purification process.

KEYWORDS
Bio-based chemical, organic acid, manufacturing, citric acid, building block, continuous chromatography.

INTRODUCTION

Worldwide, over 400 billion dollars are generated every year from biomass including chemicals, pharmaceuticals, fuels, detergents, grease, and paint (1). Arguments in favor of a switch from petrochemical feed stocks to alternative ones such as bio-based chemicals are now well-known. First of all, the volatility of oil and gas prices remains high; while access to these resources implies a certain risk, and the impact of the greenhouse effect is still a reality. Secondly, bio-based chemicals production has a better carbon footprint and can rely on local feed stocks. Lastly, the hardening of environmental policy discourages activities that produce greenhouse effect gas. However, bio-based chemicals are not intended to replace petrochemicals, but represent alternative chemical sources and bedrocks for new products. More and more bio-based chemicals will be integrated into the traditional value-added chemical production routes. Among them, bio-based building blocks are gaining momentum because of their potential as “synthon” for the synthesis of further required chemicals and their rapid integration into the chemicals supply chain. Most of the bio-based chemicals identified as potential building blocks are sugars, sugar-derivatives, and lignin-derivatives. Among them, organic acids are particularly promising, as shown in the Table 1. Most of these organic acids are already used as fine chemicals or ingredients for pharmaceutical and food industries. To ensure a reliable and sustainable supply chain for large industrial applications, it is necessary to turn these bio-based chemicals into commodity products. Commodity chemicals production implies developing large-scale manufacturing processes for production of constant quality and purity while ensuring a very low price of the final product (usually less than 2 USD per kilogram).

Bio-based chemicals are produced from the fermentation or direct transformation (enzymatic or synthetic catalysis) of natural feed stocks (upstream processing), followed by several operation units which aim to isolate and purify the target molecules (downstream processing). While great importance is usually given to the upstream aspect, downstream processing has attracted less attention, yet warrants the compliance

<table>
<thead>
<tr>
<th>Organic Acid</th>
<th>Carbon number</th>
<th>Current use</th>
<th>Current and potential uses as building block</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-hydroxypropionic acid</td>
<td>3</td>
<td>No real current use (some application in biopolymers)</td>
<td>1.3-propanediol, Acrylates derivatives, malonic acid and acrylamide production</td>
</tr>
<tr>
<td>Acrylic acid</td>
<td>3</td>
<td>Polyacrylic polymers and copolymers</td>
<td>Supplementation and substitution to oil-based acrylic acid</td>
</tr>
<tr>
<td>Succinic acid</td>
<td>4</td>
<td>Acidulant, formulation ingredient, polyester precursor</td>
<td>Direct integration in maleic anhydride-based process (THF, 1,4-BDO, GBL production), pyromellitide production, polymerization</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>4</td>
<td>Sweeteners production</td>
<td>Amino-analogs, poly-aspartic polymer</td>
</tr>
<tr>
<td>Isocnic acid</td>
<td>5</td>
<td>Copolymer</td>
<td>Similar to succinic acid</td>
</tr>
<tr>
<td>Levulinic acid</td>
<td>5</td>
<td>Precursor for pharmaceuticals, plasticizers and other additives</td>
<td>Acrylic acids and Acrylate polymers, diphenoic acids, lactone-derivatives</td>
</tr>
<tr>
<td>Citric acid</td>
<td>6</td>
<td>Acidulant, antioxidant, detergent</td>
<td>Methacrylic acid, 1,5-pentanediol, pyromellitides, poly-esters</td>
</tr>
<tr>
<td>Glucaric acid</td>
<td>6</td>
<td>Flavoring and leavening agent, precursor for other additives</td>
<td>Lactones, polyesters, polyamides</td>
</tr>
</tbody>
</table>

Table 1. Some examples of high-potential organic acids as building blocks (3-5).
between chemical industry requirements and final product specifications. A very productive upstream process may require a complex purification process that may not be interesting from an economic point of view. purification alone requires a specific expertise, as upstream processing does; and only an approach integrating upstream and downstream processing can generate a viable and sustainable bio-based chemicals production. Today, one of the most produced bio-based organic acids is citric acid (see Figure 1) with an estimated production of 1.4 million tons in 2004 (2) and reaching about 1.8 million tons in 2013. citric acid prices vary from 0.7 to 2.0 USD per kilogram. Typically, purification represents 50% of the citric acid production cost. At Novasep, process design teams have developed an industrial purification process implemented in the most modern production plants and already totaling about 20% of the worldwide citric acid purified per annum (i.e. >300,000 tons). As a potential building block and a long-established commodity, this article illustrates the manufacturing process of an organic acid.

CITRIC ACID CASE STUDY

Upstream processing
Historically, lemon juice was the main source of citric acid, based on the precipitation of calcium citrate with a lime treatment. Bio-production of citric acid began in 1919 with the development of the first commercial fermentation process using Aspergillus Niger. Synthetich routes have also been developed, but in spite of optimization efforts, the profitability has always been an obstacle due to the high price of the starting materials. In the 1960s and 70s, due to cheap petrol prices, several strains of yeast were used for the industrial production of citric acid based on these hydrocarbon sources. Fungal fermentation with A. Niger is, nowadays, the gold standard for citric acid production. The production of other organic acids may be performed through aerobic or anaerobic fermentation, depending on the biological process and its productivity. citric acid production and accumulation mechanisms by the micro-organism are not yet fully understood; however, it is known that citrate is an important intermediate in the Krebs Cycle, occurring in all organisms under aerobic conditions. Other organic acids, such as succinate, malate, and fumarate are also part of this metabolic pathway. About 80% of the citric acid world production is performed by submerged fermentation (6) (i.e. performed in liquid). Submerged fermentation can be carried out in batch, fed-batch or continuous mode, but this choice depends strongly on the productivity target. Most critical parameters for citric acid accumulation are the deficiency of specific nutrients (nitrogen, phosphate); the fungi’s morphological stage; the aeration level; and, most importantly, the pH of the broth and the abundance of nutrients such as sugars which represent the main source of carbon. Increasing the biomass requires that the spores first be grown at a pH greater than 5 to favor germination and reach the optimal biomass (fungi) level necessary to maximize productivity. Other parameters quoted above are adjusted in order to promote fungal growth. In a second step, the production and accumulation of citric acid requires a decrease of the pH below 2 (7). Above this level, the production of citric acid by A. Niger is inhibited; any pH increase results in a dramatic drop in yield and in promoting the production of unwanted organic acids such as gluconic and oxalic acids. Citric acid is a tri-carboxylic acid (pKa = 3.1 – 4.8 – 6.4) as illustrated by Figure 1. As a result, at pH < 2, citric acid is mainly non-dissociated in the broth and behaves as a neutral molecule which will be the driver for the purification process design. After fermentation, the citric acid is obtained in the broth, still mixed with impurities such as raw materials, proteins, enzymes, side-reaction products, etc. The purification process will transform the broth into a standardized chemical product.

Downstream processing
Downstream processing is the guarantee for a high recovery yield at an adapted purity level which is required to produce standardized commodity chemicals. The industrial purification strategy has to be adapted to maximize recovery and purity while containing the costs. In the case of citric acid production, the fermentation generates an acid broth (pH<2) and typically presents a citric acid purity of 85 – 94%. It contains impurities of different natures (see Table 2), the most important being the residual sugars.

The “Gypsum Process” was the traditional purification solution, characterized by an alternating treatment of the crude by lime and sulfuric acid. This process requires a high amount of chemicals (approximately 1 ton of H2SO4 and 1 ton of CaCO3 per ton of citric acid) and generates Gypsum (1.3 tons of CaSO4 per ton of citric acid) to be treated as an additional waste. This process demands manpower due to intensive cleaning of the multiple filtration skids; the highly fouling compounds that are generated must be removed.

The process developed by Novasep, shown in Figure 2, allows the removal of residual sugar using acid retardation continuous chromatography as a key technology. Acid retardation is based on affinity capture phenomenon between the acid and the resin. The resin typically used is an Applexion® XA3114/45, which is an acrylic- and divinylbenzene-based matrix, functionalized with a tertiary amino group and used under SO42- form. Due to the low pH of the broth, the citric acid is mainly neutral and interacts with the sulfate ions of the resin (3 hydrogen bonds can be formed through the 3 carboxylic groups of citric acid). The acid is “retarded” and later eluted. Sugars present a lower affinity with the resin and are less retained compared to citric acid. The reason is...
likely conformational: the structure of sugar is more constrained with no easy rotation of the carbon-carbon bonds bearing the hydroxyl groups which would have favored interactions with sulfate ions. Conversely, citric acid carbon bonds can rotate freely to maximize these hydrogen interactions. The combination of continuous chromatography with acid retardation moderates any chemical consumption which reduces operational expenditures (OPEX). However, acid retardation chromatography is not immediately applicable after fermentation: cross-flow filtration and ion exchange steps are first required to prepare the broth and avoid damaging the resin.

Cross-flow filtration is a membrane separation process (Figure 3) which consists in applying pressure on a fluid which is in contact with a ceramic or organic membrane. The cut-off is chosen to enable the desired molecules to go through the pores. Citric acid is recovered in the permeate while larger compounds, such as organic and cell debris or solid salts, are kept in the retentate. For citric acid, Kerasep® Diamond ceramic membranes are usually used to perform the filtration because of their cleanability and durability. Geometry is selected according to the viscosity of the broth. This step removes more than 99.5% of the solids in suspension to avoid clogging of the chromatography resin and to ensure a low and stable pressure drop along the purification line. This operation typically presents a yield of around 99%. All ionic species present in the broth are removed by the combination of a strong cationic exchanger in hydrogen form followed by a weak anionic exchanger in hydroxyl form.

Ion exchange allows the separation of ions and neutral molecules based on their charge. Due to its three carboxylic groups, citric acid may chelate cations and this interaction may compete with the acid retardation phenomenon. This step is then necessary to enhance the efficiency of the next step based on citric acid retardation by interacting with the resin’s sulfate ions rather than ions remaining in the feed. This ion exchange step is also typically used to demineralize the permeate coming from the filtration step. In addition, the capture of chloride ions is very important to achieve since they are not compatible with stainless steel (due to corrosion, especially at low pH) which remains the main material for large-scale equipment. By conception, the final pH at the outlet of the anionic exchanger is close to the broth’s initial pH before ion exchange (cross-neutralization of H⁺ and OH⁻). As a result, no citric acid is lost in the next steps due to citrate formation. In total, the ion exchange step removes more than 90% of the ashes, which is economically optimal in state-of-the-art citric acid production processes.

The evaporation step allows the demineralized solution to be concentrated from 20% to more than 55% (in weight on dry substance) before injection into the chromatography column. The chromatography step is designed according to the volume to be treated; the lower the volume to be injected, the smaller the column has to be. Therefore, reducing the volume to be treated has a direct impact on capital investment and OPEX of the chromatography step. Depending on the product type, plate or falling film evaporators can be used to perform this operation. This operation typically leads to a 99.9% yield.

Continuous chromatography is far more productive and requires less eluent than a batch chromatography process. In the case of citric acid, it has been combined with acid retardation chromatography whose principles have been explained previously. Solids have been eliminated thanks to cross-flow filtration (no risk of clogging) and the acid retardation phenomenon is preserved by reducing the ionic load through the ion exchange operation. Citric acid elution is performed thanks to a water-based eluent containing highly diluted sulfuric acid. As a result, chemical consumption is maintained at a very low level. Continuous chromatography is particularly well adapted for the large-scale production of commodity chemicals. The process used is Applexion™ Sequential Simulated Moving Bed (SSMB – Figure 4) chromatography which is derived directly from the Simulated Moving Bed (SMB) process. The system is composed of typically 4 to 6 columns connected as a loop. The sequential switching of inlet and outlet valves first enables the chromatographic profile to be displaced across the columns and second, to collect extract (most retained fraction) and raffinate (less retained fraction) by pushing them respectively with eluent and feed. This process design optimizes resin use and offers a compromise between a higher CAPEX and smaller OPEX. The SSMB process is, nowadays, commonly used for the industrial purification of citric acid, polyols, glucose-fructose separation, etc. With this technology, more than 97% of the residual sugars are removed for a citric acid yield higher than 97%. Residual coloring species and ashes are then removed through carbon treatment. This step also contributes to a higher quality of the final citric acid crystals.

An intermediary evaporation/concentration step is performed...
in order to further crystallization. The **crystallization step** conditions have been designed to favor germination of citric acid crystals while not precipitating the other organic acids which are present in the broth at very low concentrations. Crystallization has been designed not only as a final shaping step, but also as a true step in the purification process. The product obtained is 99.5% pure and presents a sugar and ash content below 0.1% in weight on dry substance.

**Economic evaluation**

Environmental and economic matters are also integrated into the process development approach. Very little waste is generated and most of it is valorized. Compounds, such as mother liquor, are recycled and exhausted to increase the final yield, reaching more than 92% on the whole process. Economic aspects are, of course, critical for commodity chemicals production and an optimized purification process has a direct positive impact on profitability as well as on market price. Table 3 presents an economic analysis showing that a smart purification process design can decrease operational expenses by 20%. This example illustrates that it is possible to design processes that reconcile a limited environmental footprint and a positive economic impact without compromising quality and profitability.

**NEW ORGANIC ACIDS, NEW CHALLENGES**

As bio-based chemicals are gaining interest, new production process are being experimented at the demonstration stage and implemented at industrial scale. The starting point is usually a new process based on metabolism (fermentation) or catalysis (chemical or enzymatic) engineering. The composition of the broth greatly depends on the type of transformation. For example, the conjugated base of lactic acid (lactate) is produced by neutral fermentation, while gluconic acid is obtained through the oxidation of glucose. The broth complexity will have a huge impact on the purification process and associated technologies. For the purification of citric acid, chromatography based on acid retardation is the core operation unit; while, in the case of converting a lactate into lactic acid, the focus shifts to the ion exchange step.

Technologies have to be chosen carefully depending on the target product, broth composition, target capacity and local constraints (manpower and utilities costs). These last two parameters play a major role in selecting the adapted technologies (see Figure 5). The development of upstream and downstream processing in an integrated approach is, then, mandatory to offer sustainable bio-based chemicals manufacturing.

**CONCLUSION**

Bio-based chemicals are good alternatives as drop-in products for the chemical industry. In particular, organic acids as building blocks are gaining momentum to build new synthetic routes or to integrate existing ones. Whether it is by fermentation or direct transformation of biomass, the upstream processing development is the first step required to produce bio-based chemicals. A coming challenge is the integration of industrial waste as a regular carbon source for bio-transformation. Identified feed stocks are typically waste from the food or agro-industries, such as beef or cane molasses, wood or brewery waste, soybean oil, etc. Such low-grade sugar sources are, by definition, highly variable depending on their origin (variety and cultivation); previous industrial processing; and storage conditions. In this case, processes will have to be robust and designed in a way to withstand variations.

Some processes are already using such resources, but advances are still required to produce standardized and high-quality bio-based chemicals. The development of an optimized purification strategy will then be the only assurance to meet the chemical industry standards. The citric acid example particularly illustrates several challenges specific to fermentation-based manufacturing processes. Having been produced for decades at the multi-ton scale as a bio-based chemical, there is a lot to be learned from the citric acid experience.

**REFERENCES**