PHARMACEUTICALS PRODUCT-ONLY DESIGN

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Abstract

The Resource Consumption and Recovery Act (RCRA), 1976, encourages waste minimization via practices like source reduction and solvent recycle. Waste streams treated with the orthodox *end-of-pipe* treatment options like thermal incineration, chemical oxidation etc. has to be reported as *RCRA hazardous*. To avoid strict environmental regulations imposed on all such effluent streams, this paper explores alternatives to avoid wastes altogether. The main idea is to explore future pharmaceutical manufacturing practices delivering a principal high value added product alongside *complimentary products* each for direct sale to a market customer. This conjecture gives rise to a novel paradigm of *product-only manufacturing* processes. In this pollution-free view, all effluent streams are specified such that they lead to a set of ancillary products. No waste streams are allowed. We propose a novel synthesis methodology for the design of product-only manufacturing recipes. Our methodology synthesizes optimal product-only operating procedures by purification and mixing for an entire manufacturing site. It will allow corporate managers to optimally convert their wastes into marketable products.

Keywords

Product-Only Design, Combinatorial Process Synthesis, Separation-Mixing Networks.

Introduction

In traditional pharmaceutical manufacturing stringent product purity requirements often generate huge amount of waste loads per unit mass of final product, c.f. Fig. 1(a). These wastes generally stem from the extensive use of solvents for extracting the bulk drug product from the mother liquor after bio-reactions or organic synthesis steps. The extensive use of solvents cannot be avoided because the long and complex organic synthesis routes for large drug molecules require sophisticated chemical reaction and separation pathways. Moreover, approved manufacturing practices (FDA) cannot be altered without expensive re-approval procedures. These solvent-rich effluents cannot be recycled back into the process due to strict concerns of cross-contamination.

In conventional plants solvent-rich waste streams are incinerated either onsite or in an offsite facility, if solvent-recovery is not economically viable. However, end-of-pipe treatment practices lead to high environmental impact and increased operational costs.

A viable alternative to waste treatment is converting effluents into marketable products. In pharmaceutical manufacturing this approach is often quite attractive, since the by-product streams are rich in expensive solvents. The products-only plant aims at delivering a principal high value added product (drug) alongside complimentary products lower in the quality spectrum such as paint-additive, line-flush, wash solvents etc. Products-Only design practices involve suitable by-product conditioning via advanced separations, mixing or further reactions steps as depicted in Fig. 1(b). Avoidance of wastes and conditioning of all effluents for the use as ancillary products can be accomplished by: (i) different reaction routes, (ii) improved recoveries, and (iii) blending/conditioning of effluents.

In this paper we will develop an automatic computer-aided methodology to perform optimal conversion/conditioning of all process streams into the changing product portfolio. The exploration of different reaction pathways, making necessary new FDA approval of the original manufacturing recipe, is beyond the scope of this paper. Hence this work will focus on purification and blending of existing original recipes. Our methodology will propose physical separation methods like distillation, decantation, etc. whenever possible for the recovery of high-value raw materials trapped within spent solvents, wash solutions, or other by-products. Rigorous mathematical programming will reveal the optimal waste blending opportunities as well as all simple solvent separation steps.

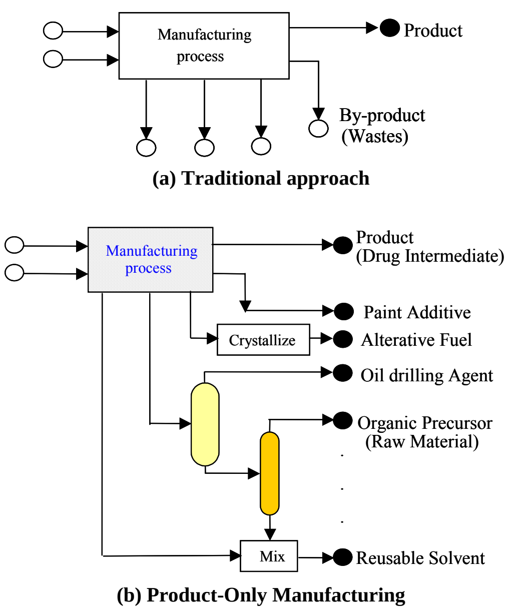

Fig. 1. Future pharmaceutical manufacturing-Product-Only Plant: All effluents are products.

Outline. In this paper we will introduce a novel product-only design methodology. Section 2 will present rigorous mathematical programming formulation for finding optimal product-only design of batch manufacturing processes. The case study of section 3 will demonstrate our product-only design concept. The article will close with conclusions and significance.

2. Product-Only Design Methodology

Background. Avoiding wastes has been a target of research for some time. Linninger et al (1995) introduced the concept of Zero-Avoidable Pollution (ZAP) for batch processes. Process-synthesis algorithms to maximize benefits have been discussed in the literature (e.g. Narayan et al, 1996; Ismail et al, 1999). Chakraborty and Linninger (2002, 2003) introduced a novel *combinatorial process synthesis* methodology to synthesize optimal recovery and treatment policies for entire manufacturing sites. In this paper we will extend combinatorial process synthesis to create product-only processes. Our novel methodology consists of two steps: (i) Synthesis of product-only recipes, (ii) Superstructure optimization.

2.1. Synthesis of Product-Only Recipes.

The first step of our methodology synthesizes the recipe for product-only design by conceiving a *superstructure*. The objective is to create a (nearly) complete network of separation and mixing tasks to convert effluents into products. Figure 2 shows a schematic superstructure. The main inputs are the waste/byproduct stream-table and the portfolio of marketable solvent uses (product targets). How to construct product-only superstructure systematically is described next.

Synthesis of Separation Tasks. Pre-conditioning of wastes by simple physical separation techniques like ideal distillation, decantation, etc. are identified prior to mixing. In order to obtain the residual node information, the selected separation tasks are simulated using short-cut methods (e.g. Underwoods method for distillation).

The feasibility of each of the separation tasks is identified rigorously by using the MIDI algorithm of Zhang and Linninger (2004). This paper does not consider non-ideal separation tasks like azeotropic distillations, since they require complex column sequencing in dedicated facilities, which are often impractical to implement at multi-purpose pharmaceutical manufacturing sites.

Separation Scenarios. Each combination of feasible separation tasks comprises a separation scenario, τ. For S possible separation tasks, the total number of separation scenarios embedded in our superstructure is 2^S.

Mixing/Blending. In addition to easy separations simple blending of effluents may achieve the desired target product compositions. Unavoidable wastes and residual nodes emanating from the separation steps are matched into appropriate disposal nodes (e.g. offsite incineration, waste water treatment). It should be noted that each separation scenario, τ_i, produces a discrete set of residuals, $M_i = \{M_1, M_2 \ldots\}$. Each residual offers new mixing opportunities (c.f. Fig. 2).

Pruning of Search Space. For each separation scenario, the problem of matching M solvent rich streams into P marketable products lead to a search space of $P\times(M\text{-}1)^M$ paths. Assessment of an entire production plant consisting of 2^S separation scenarios may lead to a combinatorial explosion. Therefore, we keep our problem size tractable by eliminating infeasible separation steps, S_i, in a preprocessing step and unrealistic blending operations. Figure 3 illustrates the logic for search-space pruning using the following heuristics:

Rule 1: Test feasibility of separation and include only feasible separation tasks, S_i,

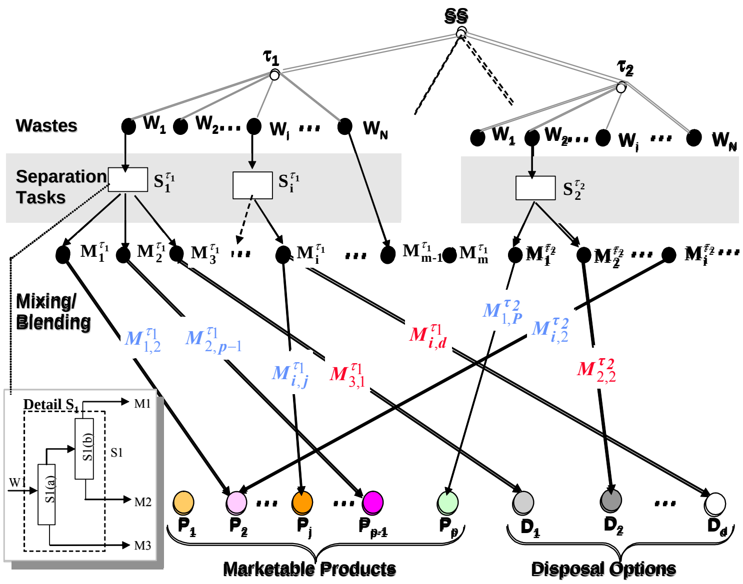

Figure 2: Superstructure Generation for Product –Only Design

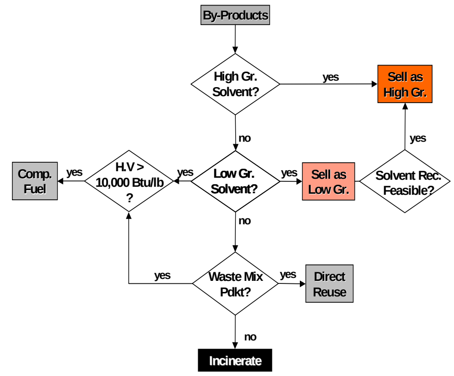

Figure 3: Simplified Decision Tree

Rule 2: If waste i is rich in product j then do not separate, sell directly.

Rule 3: Connect high-purity material nodes after separation directly to terminal product node. Do not mix product after separation (Douglas, 1985).

Optimal Policy. The execution of the short-cut separation step in all possible separation scenario, τ, leads to all intermediate material nodes, M. The permutation of all mixing options of these intermediate nodes forms the superstructure, SS. The objective of the optimal product-only recipe is to identify which separation and blending option should be picked from the superstructure, so as to maximize a suitable performance function (e.g. maximize profit, minimize effluent or a trade-off between both).

2.2. Optimal for Product-Only Manufacturing Process

In superstructure optimization we find the optimal sequence of separation and mixing steps to maximize product-benefits, while only allowing unavoidable wastes. In the mathematical programming formulation of (1) – (4), the objective (1) maximizes the total benefit and minimizes the total amount of materials sent for disposal. The objective also penalizes cost associated with difficult separation and disposal options. Continuous variables $M_{i,j}$ denote the amount of stream i going to product j. All terminal node obtained by separation/waste-blending must satisfy the product-purity constraints of inequality (2). Inequality (3) enforces environmental regulations, d_k, on disposal options (e.g. organic thresholds in waste waters, maximum VOC threshold in off gases). Equation (4) guarantees that only one separation scenario, τ, is chosen from within the superstructure with the help of binary decision variables, X_τ.

$$\underset{M_{i,j},M_{i,k},X_\tau}{\textbf{Max}} \quad \text{Profit} = \sum_{\forall\tau}\sum_{\forall i}\Big(\sum_{\forall j}\text{Price}_j \times M^{\tau}_{i,j} - \sum_{\forall k}\text{Cost}_p \times M^{\tau}_{i,k}\Big)X_\tau - \sum_{\forall\tau}\sum_{\forall i}\text{CostS}^{\tau}_i \qquad (1)$$

$$\textbf{s.t.} \quad \frac{\sum_{\forall i\in \text{wastes}} M^{\tau}_{i,j} \times x_{j,i}}{\sum_{\forall i\in \text{wastes}} M^{\tau}_{i,j}} \geq x_j \;;\; \forall j\in\text{Products};\ \forall\tau\in SS \qquad (2)$$

$$\frac{\sum_{\forall i\in \text{wastes}} M_{i,k} \times x_{k,i}}{\sum_{\forall i\in \text{wastes}} M_{i,k}} \leq d_k \;;\; \forall k\in\text{Disposal};\ \forall\tau\in SS \qquad (3)$$

$$\sum_{\forall\tau\in SS} X_\tau = 1 \qquad (4)$$

The MINLP formulations of (1) - (4) is cast into an MILP by replacing the bi-linear products in objective (1) with artificial variables and using logical *"if – then-else"* constraints (Floudas, 1995).

3. Case-Study:

In this case study we want to demonstrate the product-only manufacturing approach for 5 wastes from a hypothetical manufacturing site. Table 1 lists the composition and amount of the waste loads.

Table 1: Waste Tank Composition at Site A

Solvents	Waste Tank Compositions				
	W_1	W_2	W_3	W_4	W_5
Alcohol-A	0.4	0.7	-	0.1	-
Aromatic-B	-	-	0.6	0.9	0.7
Ketone-C	-	-	0.4	-	-
Water	0.6	0.3	-	-	0.3
Total (Tons)	**20**	**60**	**40**	**70**	**25**

The waste streams from this site are typical solvents used in extraction and wash operations and are very similar to real industrial sites, but camouflaged to avoid proprietary concerns. Table 2 lists 6 possible products, $P_1 – P_6$, and 3 disposal options, $D_1 – D_3$, for unavoidable wastes.

Table 2: Marketable Product Portfolio

Label	Product/Disposal	Quality (wt %)	Price (c/kg)
P_1	Low-Grade A	Alcohol-A (> 60%)	1
P_2	High-Grade A	Alcohol-A (> 90%)	31
P_3	Low Grade-B	Aromatic-B (> 80%)	16
P_4	High-Grade B	Aromatic-B (> 90%)	20
P_5	Low Grade C	Ketone-C (> 80%)	6
P_6	High Grade C	Ketone-C (> 95%)	14
D_1	High Btu Disposal	Btu/lb > 5000	-16
D_2	Disposal Low-Btu	Btu/lb < 5000	-45
D_3	Wastewater Tr.	Organics < 20 wt%	-30

Superstructure Generation. For this site, two separation tasks were possible: (i) S_1: distillative recovery of aromatic B and Ketone-C from waste, W_3, (ii) S_2: phase separation by decantation to recover aromatic B from water in W_5. Therefore, the superstructure resulting for this case comprised of $2^2 = 4$ distinct separation scenarios, $\tau_1 – t_4$. ($\tau_1 = \{S_1\}$, $\tau_2 = \{S_2\}$, $\tau_3 = \{S_1, S_2\}$, $\tau_4 = \{\ \}$) and approximately 1.87 million mixing pathways.

The MILP formulation of (1) – (4) revealed that the separation scenario τ_1 renders the most economic mixing/blending policy. This scenario offers a benefit of $24,910 by recovering high-grade aromatics and ketone prior to mixing. All five waste streams could be converted to marketable secondary utilization including line-flush agents, paint-additives, wash-solvents etc. The resulting optimal separation/blending policy is depicted in Figure 4.

Table 3 compares the alternative product-only policies with classical end-of-pipe treatment. Separation policies τ_2 and τ_3 offer lower benefit due to additional waste water streams produced from the decantation operations. The waste water treatment cost annihilates any additional benefits associated with higher-solvent recovery. Scenario $\tau_{4,}$ without purification is less attractive and yields to waste disposal (35% W_3)$_.$ End-of-pipe treatment of the above wastes would have produced 215 tons of waste with a treatment cost of $34,000.

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Table 3: Cost Comparison of different Policies

Scenario	Benefit ($)
τ_1 (Separate W_3 and Mix)	24,910
τ_2 (Separate W_5 and Mix)	19,325
τ_3 (Separate W_3 & W_5 and Mix)	22,967
τ_4 (Mixing without Separation)	17,910
End-of-pipe Treatment	34,400 (cost)

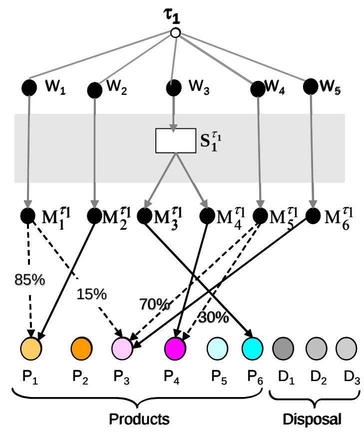

Fig. 4. Optimal Separation/Mixing policies

Conclusions/Significance

This paper proposes a new approach titled product only manufacturing practice. In contrast to many continuous processes, waste avoidance by different solvents or no solvents at all is often impractical for drug manufacturing. The alternative approach aims at getting rid of wastes by directing them to ancillary secondary uses. This article presents the first attempt to implement product-only manufacturing processes by deploying ideal separation tasks and blending operations. Future extensions may solve for optimal effluent-product matchings for an entire region or world-wide corporate operations under uncertain market demands.

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