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Integrated shelf-life rules for multi-level pharmaceutical tablets manufacturing processes

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ABSTRACT

This paper discusses the multi-level capacitated lot-sizing problem with linked lot sizes and back-orders (MLCLSP-L-B) considering deterministic product shelf-life applied to pharmaceutical tablets manufacturing processes. This paper's motivation, essential concepts, and conclusions for the pharmaceutical industry were already presented and discussed in the International Workshop on Lot-Sizing (IWLS), see Simonis and Nickel (2023a. *International Workshop on Lot-Sizing-IWLS'2023*, Vol. 13, 30–33). Material's shelf-life depends on the remaining shelf-life of issued ingredients in tablets manufacturing processes. This particular shelf-life behaviour is named integrated shelf-life rules. The MLCLSP-L-B is extended by integrated shelf-life rules (MLCLSP-L-B-SL). Moreover, an exact mathematical problem formulation is provided. First In-First Out (FIFO) and First Expire-First Out (FEFO) heuristics are developed for the MLCLSP-L-B. The MLCLSP-L-B-SL, FIFO, and FEFO heuristics are evaluated based on anonymised real-world data of five multi-level tablets manufacturing problem instances. Additionally, proposed solutions regarding manufacturing costs and shelf-life conflicts are compared. Finally, planning rules and managerial insights are derived for tablets manufacturing processes.

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1. Introduction

Effective containment of the globally raising prevalence of chronic symptoms and incidence of novel viral diseases requires products to remain stable in medicinal effects across varying treatment periods. Thus, governmental regularities worldwide have defined that all prescription tablets have a shelf-life label to indicate when they expire. Those regulatory authorities require comprehensive, stable medicine for market approval. Moreover, Colberg et al. (2017) highlighted that tablets shortage situations caused by shelf-life issues led to significant destruction costs and caused a considerable image loss through publicity in the last decades. Hence, pharmaceutical tablets manufacturers spend much effort steering manufacturing processes to avoid competitive disadvantage by delivering medicine with sufficient long shelf-life, see Kopp (2006).

Vickery and Markland (1986) studied large-scale pharmaceutical tablets manufacturing systems. During the authors' studies, it turned out that serial production processes are often implemented to manufacture pharmaceutical tablets in practice. Moreover, Savage, Roberts, and Wang (2006) grouped a tablets manufacturing process into three stages: The production of active pharmaceutical ingredients (API), the bulk, and the packaging stage. The stages consist of multiple machines which can produce several products but only one product at the same time. Figure 1 visualises an example of such a manufacturing process: The API stage consists of reactors, which consume raw materials from tanks and produce two kinds of active ingredients through chemical reactions. Then, mixers produce two sorts of tablets by granulating, mixing, pressing, and enamelling those ingredients. The tablets can either be stored in silos or processed into finished goods in the packaging stage. The packaging stage consists of packaging lines, which put tablets and recipes either into plastic bottles or in blisters and folding boxes of different sizes. The finished goods can be stored in stock or transported directly to distribution centres. Ingredients significantly impact finished good shelf-life stability in multi-level manufacturing processes. Waterman (2009) and Bajaj, Singla, and Sakhuja (2012) studied the shelf-life and stability of pharmaceutical products. API products are essential in analysing finished products' stability and shelf-life. This phenomenon is not limited to the pharmaceutical sector. Young and O'Sullivan (2011)

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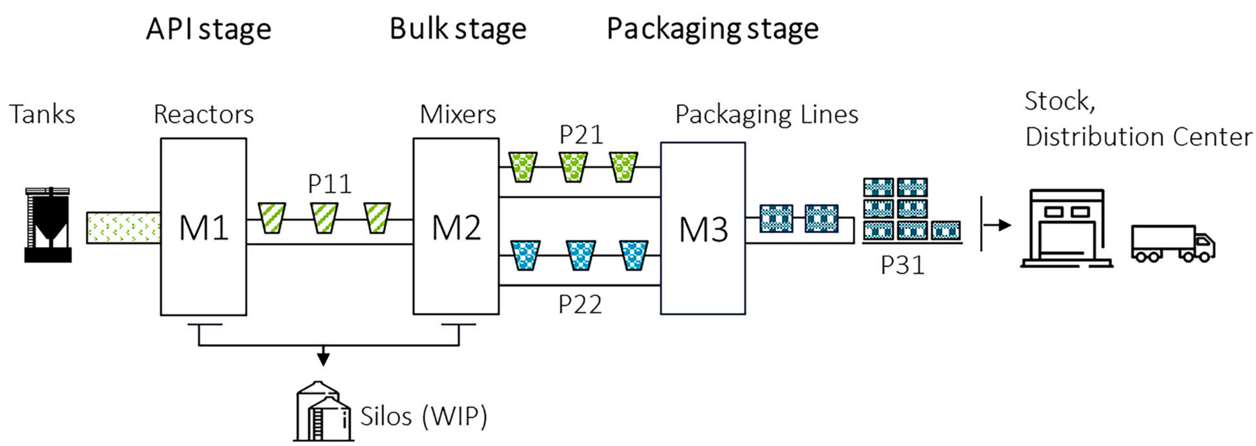

Figure 1. Example of a large-scale tablets manufacturing system with implemented serial production processes.

discussed the influence of ingredients on shelf life for perishable products in the food and beverage industry. The authors described how the industry uses ingredients to extend end products' shelf-life. Among these research, Simonis and Nickel (2023a) presented a concept to represent these shelf-life interdependencies within the MLCLSP-L-B. The authors modelled these shelf-life dependencies by *integrated shelf-life rules* for tablets manufacturing processes. If dependencies play no role, the rule is named *isolated shelf-life rule*. The terms were established across their practical studies with industrial partners to classify model approaches that consider or ignore ingredients' remaining shelf-life in the product's shelf-life determination.

The following demonstrates the behaviour of integrated and isolated shelf-life rules. Figure 2 illustrates the remaining shelf-life calculation for an exemplary finished good $P31$ based on predefined shelf-life rule configurations: Whenever the API material $P11$ is produced, it has a constant shelf-life of 40 periods. No product interdependencies have to be considered. Thus, the shelf-life behaviour is called isolated shelf-life rule. The material is stored for 10 periods. Hence, the remaining shelf-life is 30 periods. In the following, the expression lay time is used to quantify the inventory age of a material (amount of periods a particular lot is stored in a warehouse or silo). In this example, the lay time of material $P11$ equals 10 periods. This lot is consumed by bulk products $P21$ and $P22$. An integrated shelf-life rule models this product dependency. The rule applies a formula on the remaining shelf-life of $P11$. The shelf-life equals 25 and 28, and the remaining shelf-life reduces to 20 and 8 periods due to lay time for $P21$ and $P22$, respectively. With an analogue calculation logic, finished good $P11$ has a remaining shelf-life of 9 periods. If the associated customer tolerance value is lower than 9 periods, then no *shelf-life conflicts* exist. Generally speaking, determining a material's production lot remaining shelf-life relies on five steps. These five steps are executed recursively from raw materials to finished goods, and they are defined as follows:

(1) Collect all consumed units within a production run of a material.
(2) Determine the inventory age of the lot by the inventory lay time.
(3) Calculate the remaining shelf-life for all issued ingredients and calculate the shelf-life by applying the integrated shelf-life rule formula.

Products	Lay Time	Integrated Shelf-Life Rule	Shelf-Life	Remaining Shelf-Life (RSL)
$P11$	10	Constantly 40	40	$40 - 10 = 30$
$P21$	5	$10 + 0.5 \cdot \mathrm{RSL}(P11)$	$10 + 0.5 \cdot 30 = 25$	$25 - 5 = 20$
$P22$	20	$10 + 0.6 \cdot \mathrm{RSL}(P11)$	$10 + 0.6 \cdot 30 = 28$	$28 - 20 = 8$
$P31$	4	$5 + \min(\mathrm{RSL}(P21), \mathrm{RSL}(P22))$	$5 + \min(20, 8) = 13$	$13 - 4 = 9$

Figure 2. Example of remaining shelf-life determination for one lot of $P31$.

(4) Determine the remaining shelf-life of the considered material by subtracting from the shelf-life (Step 3) the lay time (Step 2).
(5) Identify (potential) shelf-life conflicts by comparing the remaining shelf-life with a customer tolerance value. Resolve them by backordering affected demand (delayed demand is acceptable instead of delivering expired medicine).

Alshemari et al. (2020) studied strategies to reduce waste within the pharmaceutical supply chain. Pharmaceutical tablet manufacturers' lot-sizing decisions significantly support lowering medicine waste by steering the shelf-life efficiently. Planning teams often focus on one year to derive midterm tactical production plans. They identify production, stock, and backorder quantities for each material, machine, and period in the planning horizon, such that inventory, backorder, and setup costs are kept at a minimum, demands are fulfilled on time, capacities are not exceeded, and shelf-life issues are avoided. Nonetheless, the practice shows that shelf-life conflicts occur occasionally due to a lack of modelling integrated shelf-life rules in MRP procedures in planning systems. On the one hand, SAP (2021) documented that classic MRP and MRP2 procedures are restricted to planning procedures using the more straightforward isolated shelf-life rules, ignoring shelf-life interdependencies. On the other hand, Buschkühl et al. (2010) outlined that MRP and MRP2 calculations overemphasise batch sizes and almost entirely ignore capacity restrictions of production resources on a medium-term planning horizon. The financial risk regarding shelf-life conflicts gets amplified. If expired production lots occur, the released production plan loses feasibility in execution, expired lots must be destroyed, and significant destruction costs must be considered. Thus, planning teams search for solution approaches that elaborate production plans containing no shelf-life conflicts so that proposed lot sizes can have cost-efficiency and even feasibility in tablets manufacturing.

Multi-level capacitated lot-sizing problems with linked lot sizes and backorders are MIPs (Mixed-Integer Programs), which are well established in the literature and already used in a wide range of applications in process industries, see Buschkühl et al. (2010). The MLCLSP-L-B is a multi-machine, multi-item, multi-period, and time-discrete model that balances production quantities, inventories, backorders, and setup operations for each product and period of the planning horizon, such that setup, inventory, and backorder costs are kept at a minimum, deterministic demands are fulfilled, and resource capacities are not exceeded. Among this research, new solution approaches consider inventories affected by shelf-life, and novel formulations were established to incorporate shelf-life restrictions into such MIPs. This paper contributes to the existing literature in three aspects. First, it established a novel exact model formulation of integrated shelf-life rules for the MLCLSP-L-B. Second, the paper provides a quantitative discussion on the performance of standard inventory policies, isolated and integrated shelf-life rules for real-world tablets manufacturing problem instances. Third, it grants practitioners unfettered access to problem instances and imparts valuable managerial insights to decision-makers regarding lot size optimisation with shelf-life constraints in the pharmaceutical tablet manufacturing industry.

The remaining paper is organised as follows: The following section summarises and reviews the related literature to the MLCLSP-L-B and applications with deterministic product shelf-life. Section 3 introduces a MIP formulation for the MLCLSP-L-B. Section 4 provides a detailed description of mathematical modelling methods to develop the MLCLSP-L-B-SL. Section 5 outlines developed FIFO and FEFO heuristics. Insights of numerical experiments with anonymised real-world data of tablets manufacturing processes across all developed solution approaches are presented in Section 6. Finally, Section 7 summarises remarkable insights and future research opportunities.

2. Literature review

This section presents a literature review with a focus on the MLCLSP-L-B. A brief summary is shown in Table 1. The MLCLSP was first introduced by Billington, McClain, and Thomas (1983). Besides the studies of the MLSLCP, Florian, Lenstra, and Rinnooy Kan (1980) proved that the capacitated lot-sizing problem (CLSP) is NP-hard. Trigeiro, Thomas, and McClain (1989) showed that even the search for feasible solutions for the multi-item CLSP with positive setup times is NP-complete. Hence, the MLCLSP and all extensions of the MLCLSP are also NP-hard.

The literature provides much work for the MLCLSP with setup carry-overs. Based on the work of Haase and Drexl (1994), which focused on setup carry-overs in a single-stage model and established the synonym term linked lot size for setup carry-over, Suerie and Stadtler (2003) and Stadtler (2003) introduced the MLCLSP with linked lot sizes (MLCLSP-L). The authors applied a time-oriented decomposition heuristic in combination with Cut-and-Branch (C&B) and Branch-and-Cut (B&C) algorithms to solve small and medium-sized simulated test instances. Tempelmeier and Buschkühl (2009) solved the MLCLSP-L with a slightly modified Lagrangean heuristic of Tempelmeier

Table 1. Relevant literature summary on capacitated lot-sizing problems.

Reference	Level	Linked lot size	Backordering	Shelf-life rule	Industry
Smith-Daniels and Ritzman (1988)	Multi		✓		Food
Hung and Chien (2000)	Multi		✓		
Suerie and Stadtler (2003)	Multi	✓			
Stadtler (2003)	Multi	✓			
Lütke Entrup et al. (2005)	Multi			Isolated	Food
Marinelli, Nenni, and Sforza (2007)	Single			Isolated	Food
Tempelmeier and Buschkühl (2009)	Multi	✓			
Akartunalí and Miller (2009)	Multi	✓			
Helber and Sahling (2010)	Multi				
Wu et al. (2013)	Multi	✓	✓		
Chen (2015)	Multi	✓			
Tempelmeier and Copil (2016)	Single			Isolated	
Sahling and Hahn (2019)	Multi			Isolated	Bio-pharma
Slama et al. (2020)	Multi		✓		
Taghizadeh et al. (2020)	Single			Isolated	
Soler, Santos, and Akartunalı (2021)	Single			Isolated	Food
Chen et al. (2021)	Single	✓		Isolated	
Simonis and Nickel (2023b)	Single	✓	✓		Pharma
This paper	Multi	✓	✓	Integrated	Pharma

and Derstroff (1996). The Lagrangean heuristic applies iteratively Lagrangean relaxations on constraints of the MLCLSP-L and solves resulting subproblems by a dynamic programming (DP) algorithm. Lagrangian multipliers are updated accordingly in each iteration. Helber and Sahling (2010) developed a fix-and-optimise (F&O) approach for the MLCLSP and combined the F&O procedure with several decomposition methods based on product, machine, and process characteristics. The F&O approach outperforms the solution approaches of Stadtler (2003) and Tempelmeier and Buschkühl (2009) regarding lower calculation time and manufacturing costs. Chen (2015) combines variable neighborhood search (VNS) methodology and F&O approaches to solve the MLCLSP and the MLCLSP-L. The author worked out that the VNS approach was able to find solutions that have lower costs compared to most test instances of the solution approach presented in Helber and Sahling (2010).

By reason of the importance of backordering in practice, the literature provides much work for the MLCLSP with backorder quantities. Smith-Daniels and Ritzman (1988) extended the MIP formulation of single-level to multi-level capacitated lot-sizing problems, including backorder quantities (MLCLSP-B). A heuristic that covered setup times was developed but excluded setup costs from the objective. Hung and Chien (2000) used the MLCLSP-B with setup times and costs and solved problem instances with the metaheuristics tabu search (TS), simulated annealing (SA), and genetic algorithm (GA). Akartunalí and Miller (2009) solved the MLCLSP-B with overtimes by a heuristic framework, which contains valid inequalities (VI) and a relax-and-fix (R&F) procedure. The solution approach outperforms the introduced heuristic of Stadtler (2003). Wu et al. (2013) introduced a complete MIP formulation of the MLCLSP with linked lot sizes and backorders (MLCLSP-L-B). The authors solved randomly generated large-size problem instances with capacity overtimes by a progressive time-oriented decomposition heuristic and a linear program (LP) embedded in a LP-fix (LP&F) procedure. Slama et al. (2020) developed for the MLCLSP-B with product defects and overtime a novel MIP formulation. The authors provided sensitivity studies on disassembly capacity, setup time, and procurement cost. Simonis and Nickel (2023b) provided numerical experiments for tablets packaging processes that are modelled by CLSPs with linked lot sizes and backorders (CLSP-L-B). The authors developed a generalised uncertainty framework that embeds a VNS algorithm in a F&O procedure to deal with probabilistic demands.

Shelf-life quantifies the duration until perishable products can not be used to satisfy internal and external demand anymore. Thus, shelf-life is closely related to perishability. All following studies deal with perishable products. However, they differ in the shelf-life model representation and the managerial consequences if a product is spoiled. Nahmias (1982) separated models into two shelf-life classes, namely deterministic and probabilistic shelf-life. Despite the importance of shelf-life in process industries, the literature does not provide much work for the MLCLSP-L-B with deterministic shelf-life. Lütke Entrup et al. (2005) developed a MIP based on the MLCLSP with overtimes and shelf-life fulfilling special requirements of the food industry. Shelf-life was treated as part of the objective to model a customer benefit for a longer material's shelf-life. Marinelli, Nenni, and Sforza (2007) modelled a yogurt production process as a CLSP with parallel machines and applied a two-stage optimisation decomposition approach. Shelf-life was not incorporated in the model objective or constraints. Instead, the authors modelled shelf-life critical parts of the manufacturing process as make-to-order production. Tempelmeier and Copil (2016) introduced a MIP formulation for CLSPs with parallel machines and shelf-life. Shelf-life is controlled by constraints satisfying that the amount of periods between the production and consumption of a material does not exceed a specific limit. Sahling and Hahn (2019) applied the MLCLSP on biopharmaceutical manufacturing processes with batch production and shelf-life constraints. Shelf-life was modelled in a way such that it depends not on ingredients remaining shelf-life. Furthermore, the authors developed a F&O heuristic to find high-quality solutions in a reasonable time. Taghizadeh et al. (2020) applied the CLSP on a manufacturing process with reworking and perishable materials on parallel machines. Fixed time constraints were used to integrate shelf-life into the model. The authors solved the exact problem formulation on small problem instances. A metaheuristic algorithm was developed, and performance was evaluated on large problem instances. Soler, Santos, and Akartunalı (2021) solved the CLSP with sequence-dependent setup structures on multiple production lines with scarce resources, temporary workstations, and perishable products. An exact MIP formulation was provided and solved with branch-and-bound (B&B) algorithm and R&F procedure. Fixed time constraints integrated shelf-life into the MIP. Chen et al. (2021) introduced shelf-life constraints for the CLSP with linked lot sizes (CLSP-L). Shelf-life was modelled by a newly introduced decision variable representing the lay time for inventories. The authors tested a model formulation with and without the disposal of expired materials on simulated problem instances.

3. Problem definition

This section provides the MIP formulation of the MLCLSP-L-B for serial production processes. The model determines lot sizes so that setup, inventory, and backorder costs are kept at a minimum while demands are satisfied. Let $M, P, T \in \mathbb{N}$ be the number of machines, materials, and planning periods, respectively. Each material is allocated to exactly one machine, but one machine can produce several materials. Thus, a particular machine index is not required for production-related decision variables and model parameters. Each finished good is requested by period-specific deterministic demands.

Moreover, a material can be stocked or backordered. For both cases, holding and backorder costs must be considered per unit at the end of each period. Each machine has a period-specific capacity. The production of materials requires variable production and fixed setup times. A setup operation is associated with product-specific setup costs. This paper assumes lead times to equal 0 periods, setups to be sequence-independent, and validity of linked lot sizes. If a material is produced, then several ingredients are issued. The set of issued ingredients can intersect with other sets of issued materials. Tables 2 and 3 summarise model decision variables and parameters of the MLCLSP-L-B. The correspondent MIP is based on an extension of Quadt and Kuhn (2008) and Helber and Sahling (2010). It is formulated as follows:

Table 2. Decision variables of the MLCLSP-L-B.

$x^{su}_{p,t}$	Equals 1, if $p \in \mathcal{P}$ is prepared for setup in $t \in \mathcal{T}$, otherwise 0
$x^{l}_{p,t}$	Equals 1, if the production of $p \in \mathcal{P}$ is continued from t to $t+1$ on period domain $\mathcal{T}_0$, otherwise 0
$x^{p}_{p,t}$	Production quantity of product $p \in \mathcal{P}$ in period $t \in \mathcal{T}$
$x^{inv}_{p,t}$	Inventory quantity of a product $p \in \mathcal{P}$ in period $t \in \mathcal{T}_0$
$x^{bo}_{p,t}$	Backorder quantity of a product $p \in \mathcal{P}$ in period $t \in \mathcal{T}_0$

Table 3. Model sets and parameters of the MLCLSP-L-B.

$\mathcal{M}$	Set of machines $\{1,\ldots,M\}$
$\mathcal{P}$	Set of products $\{1,\ldots,P\}$
$\mathcal{T}$	Set of periods $\{1,\ldots,T\}$
$\mathcal{T}_0$	Set of periods including initial period $\{0,\ldots,T\}$
$\mathcal{P}^{suc}_p$	Set of successors of a product $p \in \mathcal{P}$
$\mathcal{P}_m$	Set of products that can be produced on machine $m \in \mathcal{M}$
$\mathcal{P}^{Int}$	Set of intermediate products $\{p \in \mathcal{P} \mid \mathcal{P}^{suc}_p \neq \emptyset\}$
$b_{m,t}$	Capacity of machine $m \in \mathcal{M}$ in period $t \in \mathcal{T}$
$d_{p,t}$	Demand of product $p \in \mathcal{P}$ in period $t \in \mathcal{T}$
c^{su}_p	Setup cost for a product $p \in \mathcal{P}$
c^{inv}_p	Inventory holding cost for a product $p \in \mathcal{P}$
c^{bo}_p	Backorder cost for a product $p \in \mathcal{P}$
t^{su}_p	Setup time for a product $p \in \mathcal{P}$
t^{p}_p	Production time for a unit of product $p \in \mathcal{P}$
$r_{p,q}$	Number of units of product $p \in \mathcal{P}$ required to produce one unit of successor product $q \in \mathcal{P}^{suc}_p$
$\bar{x}^{l}_p$	Initial setup state for $p \in \mathcal{P}$, such that $\sum_{p\in\mathcal{P}_m} \bar{x}^{l}_p \leq 1$ for all $m \in \mathcal{M}$
$M_{m,p,t}$	Large number, e.g. $M_{m,p,t} = \min\{\sum_{\tau\in\mathcal{T},\tau\geq t} d_{p,\tau}, b_{m,t}/t^{p}_p\}$ for $m \in \mathcal{M}, p \in \mathcal{P}_m$ and $t \in \mathcal{T}$ whereby $d_{p,\tau}$ represents primary demand in case of finished goods and is replaced by secondary demand for intermediates

$$\min Z = \min \left\{ \sum_{p\in\mathcal{P}} \sum_{t\in\mathcal{T}} c^{su}_p x^{su}_{p,t} + c^{bo}_p x^{bo}_{p,t} + c^{inv}_p x^{inv}_{p,t} \right\}, \tag{1}$$

$$\text{s.t. } x^{inv}_{p,t-1} + x^{bo}_{p,t} + x^{p}_{p,t} = x^{inv}_{p,t} + x^{bo}_{p,t-1} + d_{p,t} + \sum_{p'\in\mathcal{P}^{suc}_p} r_{p,p'} x^{p}_{p',t}, \tag{2}$$

$$\sum_{p'\in\mathcal{P}_m} t^{su}_{p'} x^{su}_{p',t} + t^{p}_{p'} x^{p}_{p',t} \leq b_{m,t}, \tag{3}$$

$$x^{p}_{q,t} \leq M_{m,q,t} \left(x^{su}_{q,t} + x^{l}_{q,t-1} \right), \tag{4}$$

$$\sum_{s \in \mathcal{P}_m} x^l_{s,t} \leq 1, \quad (5)$$

$$x^l_{q,t} - x^{su}_{q,t} - x^l_{q,t-1} \leq 0, \quad (6)$$

$$x^l_{q,t} + x^l_{q,t-1} - x^{su}_{q,t} + x^{su}_{r,t} \leq 2, \quad (7)$$

$$x^{bo}_{p'',t} = 0, \quad (8)$$

$$x^{inv}_{p,0} = 0,\ x^l_{p,0} = \bar{x}^l_p,\ x^{bo}_{p,0} = 0,\ x^{bo}_{p,T} = 0, \quad (9)$$

$$x^{su}_{p,t} \in \{0,1\},\ x^l_{p,t} \in \{0,1\},\ x^{bo}_{p,t} \geq 0,\ x^p_{p,t} \geq 0,$$
$$x^{inv}_{p,t} \geq 0,\ \forall m \in \mathcal{M},\ p \in \mathcal{P},\ q, r \in \mathcal{P}_m,$$
$$q \neq r,\ p'' \in \mathcal{P}^{Int},\ t \in \mathcal{T}.$$

(1) aims to minimise the sum of setup, inventory, and backorder costs for all materials over the planning horizon. The material balance equation is covered by (2), capacity constraints are included by (3), (4) binds a positive production quantity to a setup in the same or a linked lot size in the previous period, (5) satisfies that at most one linked lot size per period occurs, (6) guarantees that a linked lot size is only allowed when a setup in the same period or a linked lot size in the previous period take place and (7) synchronises production runs that continue over more than two periods on a machine $m \in \mathcal{M}$. If $x^l_{q,t} = x^l_{q,t-1} = 1$, then either $x^{su}_{r,t-1} = 0$ for all $q, r \in \mathcal{P}_m$, $q \neq r$ or for some $r \neq q$, $x^{su}_{r,t-1} = 1$ and $x^{su}_{q,t-1} = 1$. That is, either product q is produced exclusively in period $t-1$ or product q is produced at the beginning of $t-1$, some other products were produced next and the facility was reset to produce product q at the end of period $t-1$. (8) restricts the backorders to final products. This prohibits final products from being processed further if intermediate product shortages occur. Moreover, (9) sets the initial inventory and setup state, and the initial and final backorder quantities, respectively.

4. Problem extension by integrated shelf-life rules

Integrated shelf-life rules consider that a material's shelf-life depends on the remaining shelf-life of ingredients. The extended model formulation has the following assumptions:

- Lay time and shelf-life are always multiples of the model time bucket dimension. This is a manageable factor since the period buckets can be chosen on any reasonable dimensional level.
- Shelf-life conflicts are not accepted by released production lots in tablets manufacturing processes. Thus, the MIP formulation is assumed to be infeasible if products exceed their shelf-life limits (customer tolerance values).
- Parameters of the shelf-life rules (shelf-life surplus and formula weights) are time-independent within the planning horizon.
- Expired products can not be processed further or sold to customers. It is cheaper to backlog demand instead of destroying products.
- Destruction costs are not included in the model objective of the MLCLSP-L-B-SL. They are determined in post-processing calculations after the optimisation procedure. This is manageable due to backlogging decisions that are represented by backorder costs in the objective function.
- Tablets manufacturing processes rely on affine-linear and minimum shelf-life rules. No other rules are mathematically formulated.
- Chemical processes and material characteristics that influence the shelf-life of a stocked product are approximated by a material-dependent constant value (sl_p).

Table 4. Additional model sets and parameters of the MLCLSP-L-B-SL.

$\mathcal{P}^{pre}_p$	Set of predecessors of a product $p \in \mathcal{P}$
sl_p	Fix shelf-life surplus for a product $p \in \mathcal{P}$
t^{arsl}_p	Internal or external required minimum remaining shelf-life for a $p \in \mathcal{P}$
$w_{p,q}$	Remaining shelf-life dependency weight of a ingredient $q \in \mathcal{P}^{pre}_p$ issued by a product $p \in \mathcal{P}$
$M^{sl}_{p,t}$	Large number, e.g. $M^{sl}_{p,t}$ equals total expected demands after period $t \in \mathcal{T}$
M^{arsl+}	Large number, e.g. T

This section provides the MIP formulation of the MLCLSP-L-B with integrated shelf-life rules (MLCLSP-L-B-SL), which turned out to be a generalised formulation of isolated shelf-life rules. First, the MLCLSP-L-B is extended by the material's inventory consumption. Second, the inventory lay time is introduced into the MIP formulation. Third, two classes for integrated shelf-life rules are described, and an extension of the MIP formulation is provided for each class. Fourth, the remaining shelf-life calculation is incorporated. Finally, a brief discussion on shef-life conflicts and cost impacts is outlined. Newly introduced model parameters and decision variables for the MLCLSP-L-B-SL are summarised in Tables 4 and 5, respectively.

4.1. Link inventory quantities with demand satisfaction

Chen et al. (2021) introduced a novel mathematical formulation to model lay time and shelf-life in single-level

Table 5. Additional decision variables of the MLCLSP-L-B-SL.

$x^{inv}_{p,t,s}$	Inventory quantity of a product $p \in \mathcal{P}$ in period $t \in \mathcal{T}$ used to fulfill primary or secondary demand in period $s \in \mathcal{T}$
$x^{inv+}_{p,t,s}$	Equals 1 if $x^{inv}_{p,t,s} > 0$, else 0
$x^{rsl}_{p,t,s}$	Remaining shelf-life of a stored lot of a product $p \in \mathcal{P}$ in period $t \in \mathcal{T}$ consumed in $s \in \mathcal{T}$
$x^{arsl}_{p,q,t}$	Actual remaining shelf-life of a product $q \in \mathcal{P}^{pre}_p$ issued by $p \in \mathcal{P}$ in period $t \in \mathcal{T}$
$x^{arsl+}_{p,q,t}$	Equals 0 if $w_{p,q}x^{arsl}_{p,q,t}$ of a issuer $p \in \mathcal{P}$ in period $t \in \mathcal{T}$ is minimal for all products $q \in \mathcal{P}^{pre}_p$, otherwise 1 such that $\sum_{q\in\mathcal{P}^{pre}_p} x^{arsl+}_{p,q,t} = 1$ for all $p \in \mathcal{P}$ and $t \in \mathcal{T}$
$x^{slrule}_{p,t}$	Outcome of integrated shelf-life rule of a product $p \in \mathcal{P}$ in period $t \in \mathcal{T}$

problems. The authors analysed two model formulations. The first approach uses the disaggregated inventory variables to track the inventory flow. The second approach uses the disaggregated quantity to decompose the relationship between demand, inventory, and production in the material balance equation. The second approach finds feasible solutions faster than the first but takes more computational time to reach high-quality solutions on considered research data. Thus, the first model approach with disaggregated inventory quantities seems promising for tablets manufacturing processes since the company's business set the duration to find high-quality lot sizes to 5 days.

Chen et al. (2021) disaggregated the decision variable $x^{inv}_{p,t}$ by a adding a third index $s \in \mathcal{T}$. Let $x^{inv}_{p,t,s}$ be the inventory quantity taken from period t to satisfy a primary or secondary demands $d_{p,s} + \sum_{q\in\mathcal{P}^{suc}_p} r_{p,q}x^{p}_{q,s}$ in a period $s > t$ for a material $p \in \mathcal{P}$. Figure 3 illustrates the expected behaviour of inventory consumptions by a matrix representation. The following observations are visible: The material balance equation (2) satisfies that no inventory from future periods can be used to fulfil earlier demands so that identity $x^{inv}_{p,t,s} = 0$ has to be satisfied for all $s \leq t$ (all values on the diagonal of the matrix and below equal 0). Column sums have to be lower than primary and secondary demand. Moreover, the inventory consumptions represent the net consumptions (e.g. $x^{inv}_{p,2,3}$ has to consider previous consumption $x^{inv}_{p,1,2}$ to determine net consumption). Finally, the total sum of inventories for a product $p \in \mathcal{P}$ equals the incremental sums $(t - s)x^{inv}_{p,t,s}$ due to telescope sums (e.g. $\sum_{t\in\mathcal{T}} x^{inv}_p = 540 = \sum_{s\in\mathcal{T},s>t}(s-t)x^{inv}_{p,t,s}$) Thus, objective (1) can be replaced by

$$\min Z^{SL} = \min \left\{ \sum_{p\in\mathcal{P}}\sum_{t\in\mathcal{T}} c^{su}_p x^{su}_{p,t} + c^{bo}_p x^{bo}_{p,t} + c^{inv}_p \sum_{s\in\mathcal{T},s>t} (s-t)x^{inv}_{p,t,s} \right\}. \quad (10)$$

Moreover, the following constraints have to be fulfilled

$$\sum_{t'\in\mathcal{T}} x^{inv}_{p,t,t'} \geq x^{inv}_{p,t} - x^{inv}_{p,t-1} + \sum_{t'\in\mathcal{T},t'<t} x^{inv}_{p,t',t}, \quad (11)$$

$$\sum_{t\in\mathcal{T}} x^{inv}_{p,t,s} \leq d_{p,s} + \sum_{q\in\mathcal{P}^{suc}_p} r_{p,q}x^{p}_{q,s}, \quad (12)$$

$$x^{inv}_{p,t,s} = 0 \quad \forall s \leq t,$$

$$x^{inv}_{p,t,s} \geq 0 \quad \forall s > t,$$

$$\forall p \in \mathcal{P},\ s,t \in \mathcal{T}.$$

(11) satisfies, that $x^{inv}_{p,t,t'}$ sums over index t' to the increments $x^{inv}_{p,t} - x^{inv}_{p,t-1}$ by taking previous storage's $\sum_{t'\in\mathcal{T},t'<t} x^{inv}_{p,t',t}$ into account. Together with objective (10), the sum even matches the positive value of $x^{inv}_{p,t} - x^{inv}_{p,t-1}$ corrected by previous storage. (12) guarantee, that the sum of $x^{inv}_{p,t,s}$ over index t never exceeds

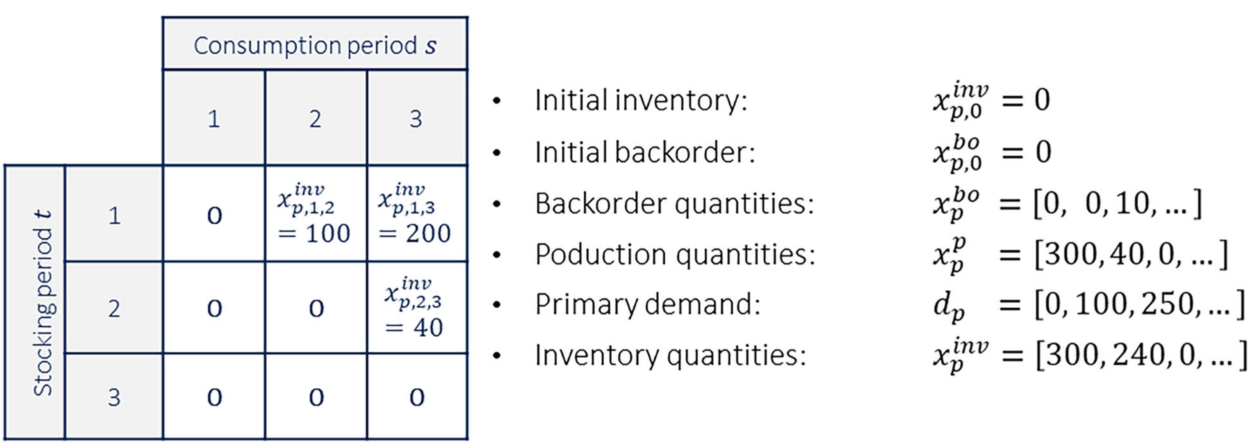

Figure 3. Illustration of inventory consumption for a finished good $p \in \mathcal{P}$.

primary and secondary demands in consumption period $s \in \mathcal{T}$.

4.2. Determine inventory lay time

Let $x^{inv+}_{p,t,s} \in \{0,1\}$ be a binary variable that represents the usage of storage in $t \in \mathcal{T}$ for consumption in $s \in \mathcal{T}$. It equals 1 if $x^{inv}_{p,t,s} > 0$, otherwise 0. Then, the lay time equals $(s-t)x^{inv+}_{p,t,s}$ for all $p \in \mathcal{P}$, see Figure 4. (13) and (14) introduce the lay time to the MIP by a big-M formulation:

$$x^{inv}_{p,t,s} \leq M^{sl}_{p,t} x^{inv+}_{p,t,s}, \tag{13}$$

$$x^{inv}_{p,t,s} \geq x^{inv+}_{p,t,s}, \tag{14}$$

$$x^{inv+}_{p,t,s} = 0 \quad \forall s \leq t,$$

$$x^{inv+}_{p,t,s} \in \{0,1\},$$

$$\forall p \in \mathcal{P},\ s,t \in \mathcal{T}.$$

4.3. Incorporate integrated shelf-life rules

Let $sl_p \geq 0$ be a shelf-life surplus of a material $p \in \mathcal{P}$. This surplus represents a baseline of shelf-life coming from chemical stabilisers or special product characteristics. Furthermore, let $x^{arsl}_{p,q,t} \geq 0$ the actual remaining shelf life of a product $q \in \mathcal{P}^{pre}_p$ issued by $p \in \mathcal{P}$ in period $t \in \mathcal{T}$. Then, two integrated shelf-life rules are used in tablets manufacturing to make the remaining shelf-life of material $p \in \mathcal{P}$ dependent on the actual remaining shelf-life of all ingredients:

(1) *Affine-linear shelf-life rules* add to product-specific shelf-life surplus the weighted sum of actual remaining shelf-life across all predecessors

$$sl_p + \sum_{q \in \mathcal{P}^{pre}_p} w_{p,q} x^{arsl}_{p,q,t}.$$

This rule is usually applied for miscible liquids and active pharmaceutical ingredients because the remaining shelf-life depends mainly on the used ratios of ingredients for production $r_{k,p,q}$ with $k \in \mathcal{M}_q$.

(2) *Minimum shelf-life rules* add to product-specific shelf-life surplus the minimum actual remaining shelf-life over all predecessors

$$sl_p + \min_{q \in \mathcal{P}^{pre}_p} \{w_{p,q} x^{arsl}_{p,q,t}\}.$$

This rule is usually applied for composed solids and finished goods, because the product characteristic depends on each composed ingredient. Hence, the expiration date equals the lowest remaining shelf-life of all used ingredients.

Per design, the integrated rules simplify to isolated rules if raw materials are considered. Let denote with $x^{slrule}_{p,t}$ the outcome of the shelf-life rule. If $r \in \mathcal{P} \setminus \bigcup_{q \in \mathcal{P}} \mathcal{P}^{pre}_q$ (or alternatively $\mathcal{P}^{pre}_r = \emptyset$), then affine-linear and minimum shelf-life rules simplify to $x^{slrule}_{r,t} = sl_r$ for all $t \in \mathcal{T}$. Constraints (15) till (18) incorporate the two rules:

$$x^{slrule}_{p,t} = sl_p + \sum_{r \in \mathcal{P}^{pre}_p} w_{p,r} x^{arsl}_{p,r,t}, \tag{15}$$

$$x^{slrule}_{p,t} \leq sl_p + w_{p,q} x^{arsl}_{p,q,t}, \tag{16}$$

$$x^{slrule}_{p,t} \geq sl_p + w_{p,q} x^{arsl}_{p,q,t} - M^{arsl+}\left(1 - x^{arsl+}_{p,q,t}\right), \tag{17}$$

$$\sum_{r \in \mathcal{P}^{pre}_p} x^{arsl+}_{p,r,t} = 1 \tag{18}$$

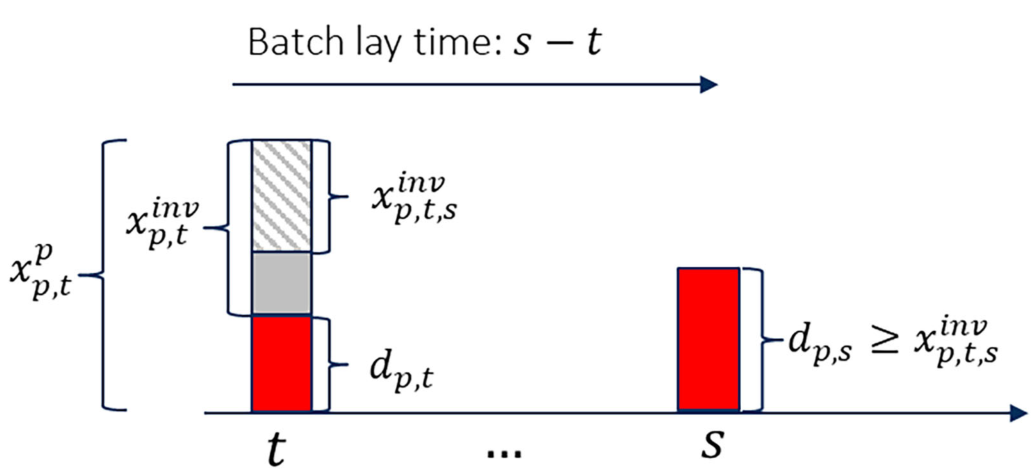

Figure 4. Illustration of lay times for a fixed material $p \in \mathcal{P}$.

$\forall p \in \mathcal{P},\ q \in \mathcal{P}_p^{pre},\ t \in \mathcal{T}.$

Inequality (15) models the affine-linear rule. It ensures that $x_{p,t}^{slrule}$ equals the weighted average of the actual remaining shelf-life of all consumed ingredients plus the shelf-life surplus. A big-M formulation models the minimum rule. Constraints (16) till (18) represent the minimum rules. The constraints force $x_{p,r,t}^{arsl+} = 1$ for exactly one $r \in \mathcal{P}_p^{pre}$ that minimises $w_{p,r}x_{p,r,t}^{arsl}$. Hence, upper and lower boundaries provided by (16) and (17) imply that $x_{p,t}^{slrule} = sl_p + w_{p,r}x_{p,r,t}^{arsl}$. Remarkably, isolated shelf-life rules can be modelled by setting $w_{p,q} = 0$ for all $p \in \mathcal{P}$ and $q \in \mathcal{P}_p^{pre}$ (all shelf-life dependencies of ingredients are removed from the MIP).

Consider the illustrative example presented in Figure 2. The intermediates $P11$, $P21$, and $P22$ where processed to a pharmaceutical tablet $P31$. Figure 5 visualises the recursive behaviour of constraints (15) till (18). Since $P11$ has no shelf-life dependencies, the intermediate is modelled by an isolated shelf-life rule. Thus, equality (15) simplifies to $x_{P11,t}^{slrule} = sl_{P11} = 40$ for all $t \in \mathcal{T}$. The shelf-life of intermediates $P21$ and $P22$ is influenced by affine-linear rules considering the actual remaining shelf-life of $P11$. Thus, equality (15) simplifies to $x_{P21,t}^{slrule} = sl_{P21} + w_{P21,P11}x_{P21,P11,t}^{arsl} = 10 + 0.5x_{P21,P11,t}^{arsl}$ and $x_{P22,t}^{slrule} = sl_{P22} + w_{P22,P11}x_{P22,P11,t}^{arsl} = 10 + 0.6x_{P22,P11,t}^{arsl}$ for products $P21$ and $P22$, respectively. These intermediates, again, influence the shelf-life of the finished good $P31$ by a minimum rule. Equations (16) till (18), together with $sl_{31} = 5$ and $w_{P31,P21} = w_{P31,P22} = 1$, simplify to

$$x_{P31,t}^{slrule} \le 5 + x_{P31,P21,t}^{arsl},$$
$$x_{P31,t}^{slrule} \le 5 + x_{P31,P22,t}^{arsl},$$
$$x_{P31,t}^{slrule} \ge 5 + x_{P31,P21,t}^{arsl} - M^{arsl+}(1 - x_{P31,P21,t}^{arsl+}),$$
$$x_{P31,t}^{slrule} \ge 5 + x_{P31,P22,t}^{arsl} - M^{arsl+}(1 - x_{P31,P22,t}^{arsl+}),$$
$$x_{P31,P21,t}^{arsl+} + x_{P31,P22,t}^{arsl+} = 1,$$
$$\forall\, t \in \mathcal{T}.$$

These equations force $x_{P31,P21,t}^{arsl+} = 1$ if and only if $x_{P31,P21,t}^{arsl+} \le x_{P31,P22,t}^{arsl+}$, otherwise the decision variable equals zero. Thus, the equations (16) till (18) can be rewritten as $x_{P31,t}^{slrule} = 5 + \min\{-x_{P31,P21,t}^{arsl}, -x_{P31,P22,t}^{arsl}\}$ for all periods $t \in \mathcal{T}$. Since $x_{P31,P21,t}^{arsl}$ and $x_{P31,P21,t}^{arsl}$ depend on their shelf-life rules, $x_{P31,t}^{slrule}$ depends on the actual remaining shelf-life of $P11$.

4.4. Calculate remaining shelf-life

Next, the remaining shelf-life is modelled. $x_{p,t}^{slrule}$ meets the rule outcome. Thus, remaining shelf-life equals $x_{p,t,s}^{rsl} = x_{p,t}^{slrule} - (s-t)x_{p,t,s}^{inv+}$ for all $s, t \in \mathcal{T}$ whereby $s > t$. Otherwise, equality $x_{p,t,s}^{inv+} = 0$ implies that $x_{p,t,s}^{rsl}$ equals $x_{p,t}^{slrule}$. However, if a product $p \in \mathcal{P}$ satisfies a requested demand in period t, several stored production lots in period $s = 1, \ldots, t-1$ could be used. In such a case, the lowest remaining shelf-life across all stored lots has to be taken, see Figure 6. Thus, inqeuality $x_{p,q,t}^{arsl} \le x_{p,s,t}^{rsl}$ has to be satisfied for all $q \in \mathcal{P}_p^{pre}$ and $s < t$. Furthermore, tolerance values ($t_p^{arsl} \ge 0$) of customers for remaining shelf-life are represented by inequality $x_{p,q,t}^{arsl} \ge t_p^{arsl}$. Hence, the following inequalities implement integrated shelf-life rules, lots aggregation, and internal and customer requirements on remaining shelf-life:

$$x_{p,t,s}^{rsl} = x_{p,t}^{slrule} - (s-t)x_{p,t,s}^{inv+}, \tag{19}$$
$$x_{p,q,s}^{arsl} \le x_{q,t,s}^{rsl}, \tag{20}$$
$$x_{p,q,s}^{arsl} \ge t_p^{arsl}, \tag{21}$$
$$x_{p,t,s}^{rsl} \ge 0, \quad x_{p,t}^{slrule} \ge 0,$$
$$\forall p \in \mathcal{P},\ q \in \mathcal{P}_p^{pre},\ t, s \in \mathcal{T}.$$

(19) defines the remaining shelf-life by the increment of the integrated shelf-life rule and lay time, (20) satisfies that stocked lots are aggregated by lowest

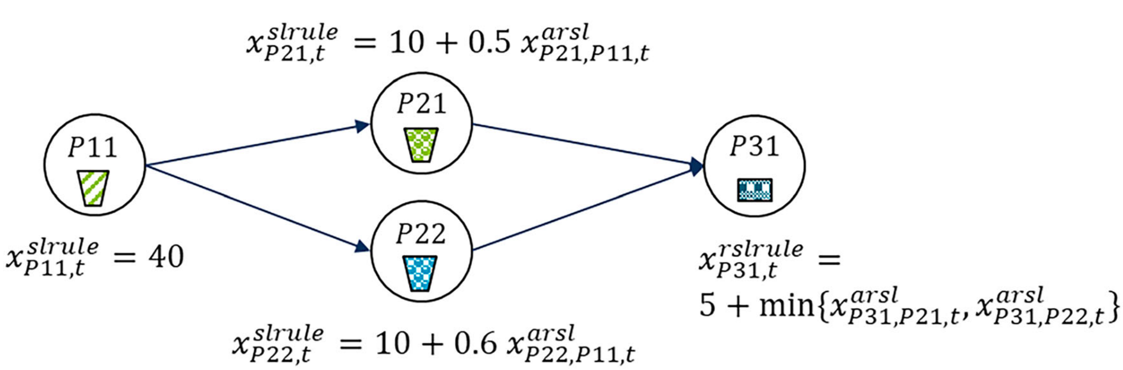

Figure 5. Integrated shelf-life rules applied on illustrative example.

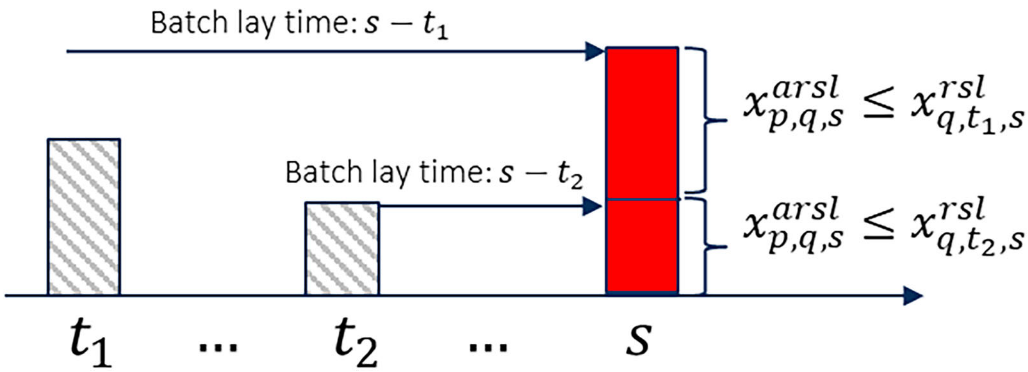

Figure 6. Illustration of multi-lot consumption of a material $q \in \mathcal{P}^{pre}_p$ issued by $p \in \mathcal{P}$.

remaining shelf-life, and (21) represents internal or customer requirements on remaining shelf-life. In summary, the multi-level capacitated lot-sizing problem with linked lot sizes, backorders, and integrated shelf-life rules (MLCLSP-L-B-SL) is defined by the MLCLSP-L-B, whereby (1) is replaced with (10), constraints (11) until (21) are added, whereby either (15) or (16) till (18) is set per material.

4.5. Identify shelf-life conflicts

Process industries like tablets manufacturing identify shelf-life conflicts on the production lot level. A shelf-life conflict is an event that is associated with a stocked unit $x^{inv}_{p,t,s} > 0$, of a material $p \in \mathcal{P}$ stored in $t \in \mathcal{T}$ and consumed in $s \in \mathcal{T}$, and remaining shelf-life $x^{rsl}_{p,t,s} < t^{arsl}_p$. Thus, shelf-life conflicts are determined by counting the elements of the set $\{(p,t,s) | x^{inv}_{p,t,s} > 0, x^{rsl}_{p,t,s} < t^{arsl}_p, p \in \mathcal{P}, t, s \in \mathcal{T}\}$. If a produced lot of material $p \in \mathcal{P}$ has a shelf-life conflict, then the lot cannot be used to satisfy primary or secondary demand. A released production plan with a shelf-life conflict is not feasible. Even worse, expired production lots have to be destroyed. Thus, additional destruction costs $c^{destr}_p > 0$ have to be taken into account. Destruction costs depend on the amount of shelf-life conflicts, particularly the size of expired units $x^{inv}_{p,t,s}$. Thus, production planners measure shelf-life conflicts on the material level by counting affected production lots. If a shelf-life conflict is present, then costs are evaluated by the term $c^{destr}_p x^{inv}_{p,t,s}$. Remarkably, this paper provides no MIP formulation with destruction costs due to the obligation to backorder demand. Hence, the MLCLSP-L-B-SL backorders demand if production fails the remaining shelf-life targets instead of wasting these affected lots.

5. Standard inventory control policies

Sazvar et al. (2016) and Khan, Faisal, and Al Aboud (2018) outlined that FIFO and FEFO inventory policies became a global standard for inventory management in the pharmaceutical sector. By 2022, World Health Organization (2022) recommended on empirical studies that pharmaceutical companies should use FEFO instead of FIFO heuristics to organise their inventories. The company considered in the next section's case study follows this recommendation. Its planning procedures already use FEFO instead of FIFO heuristics for several product groups to assign stored production lots to primary and secondary demand. Thus, this section provides summaries of developed FIFO and FEFO heuristics applicable to solutions of the MLCLSP-L-B so that the MLCLSP-L-B-SL can be benchmarked against the industrial implemented standard.

Let the positive value function be denoted by $(x)^+ = \max\{x, 0\}$ for a real number $x \in \mathbb{R}$. FIFO prefers to use the latest stocked production lot if a material is requested. At the same time, FEFO prioritises the lot with the lowest remaining shelf-life and prefers to consume lots with the lowest remaining shelf-life first. Thus, FIFO and FEFO inventory policies are equivalent if only isolated shelf-life rules (no product dependencies in shelf-life determination) are present in a manufacturing process because the lowest remaining shelf-life equals the first stocked lot. However, tablets manufacturing relies on integrated shelf-life rules. Hence, FIFO and FEFO policies will return different outcomes. Algorithm 1 describes the FIFO policy. Based on any feasible solution of the MLCLSP-L-B and selected product $\hat{p} \in \mathcal{P}$ the algorithm iterates through any stocking period $t \in \mathcal{T}$ and consumption period $s \in \mathcal{T}$ and determines the available inventory $\Delta_{t,s}$ to assign for consumption by

$$\Delta_{t,s} = x^{bo}_t - x^{bo}_{t-1} + x^p_t - d^{int}_t - \sum_{\tau \in \mathcal{T}, \tau > t, \tau \neq s} x^{inv}_{t,\tau} + \sum_{\tau \in \mathcal{T}, \tau < t} x^{inv}_{\tau\, t}. \quad (22)$$

(22) uses the material balance equation (2) to determine increments $x^{inv}_{\hat{p},t} - x^{inv}_{\hat{p},t-1}$. It is remarkable, that $\Delta_{t,s}$

Algorithm 1 Pseudo code of FIFO heuristic for a fixed $\hat{p} \in \mathcal{P}$

Require: Production quantities $x^{p}_{\hat{p},t} = x^{p}_{t}$, inventories $x^{inv}_{\hat{p},t} = x^{inv}_{t}$, backorders $x^{bo}_{\hat{p},t} = x^{bo}_{t}$, primary and secondary demands $d^{int}_{\hat{p},t} = d^{int}_{t}$
Ensure:
  Inventories: $x^{inv}_{t,s} \in x^{inv}, x^{inv} \leftarrow [0, \dots, 0] \in \mathbb{R}^{T\times T}_{+}$
  Determine feasible set of consumption periods $\mathcal{T}^{feas}_{t} \subset \mathcal{T}$ for a all stocking periods $t \in \mathcal{T}$
  for $t \in \{\hat{t} \in \mathcal{T} | x^{inv}_{\hat{t}} > 0\}$ **do**
    for $s \in \{\hat{s} \in \mathcal{T} | \hat{s} \in \mathcal{T}^{feas}_{t}, \hat{s} > t, d^{int}_{\hat{s}} - x^{bo}_{\hat{s}} + x^{bo}_{\hat{s}-1} > 0\}$ **do**
      Set $\Delta_{t,s} \leftarrow x^{bo}_{t} - x^{bo}_{t-1} + x^{p}_{t} - d^{int}_{t} - \sum_{\tau\in\mathcal{T},\tau>t,\tau\neq s} x^{inv}_{t,\tau} + \sum_{\tau\in\mathcal{T},\tau<t} x^{inv}_{\tau\, t}$
      if $\Delta_{t,s} \leq 0$ **then**
        Continue
      end if
      Update $x^{inv}_{t,s} \leftarrow (\min(\Delta_{t,s}, d^{int}_{s} - x^{bo}_{s} + x^{bo}_{s-1} - \sum_{\tau\in\mathcal{T},\tau<s} x^{inv}_{\tau\, s}))^{+}$
    end for
  end for
  return x^{inv}

has to be reduced by already assigned stock reservations in period t of future demands $\sum_{\tau\in\mathcal{T},\tau>t,\tau\neq s} x^{inv}_{t,\tau}$ and increased by already assigned stock reservations for demands in period t in all earlier periods $\sum_{\tau\in\mathcal{T},\tau<t} x^{inv}_{\tau\, t}$. If a stock (including reservations) increases ($\Delta_{t,s} > 0$), then it is distributed across all future consumption periods $s > t$ by calculating

$$\left(\min\left(\Delta_{t,s}, d^{int}_{s} - x^{bo}_{s} + x^{bo}_{s-1} - \sum_{\tau\in\mathcal{T},\tau<s} x^{inv}_{\tau\, s}\right), 0\right)^{+}. \tag{23}$$

(23) expresses the maximal share of $\Delta_{t,s}$ which is available to satisfy demand inclusive corrected by backordering $d^{int}_{s} - x^{bo}_{s} + x^{bo}_{s-1}$ in period s reduced by previously assigned inventory shares $\sum_{\tau\in\mathcal{T},\tau<s} x^{inv}_{\tau\, s}$t. Thus, (23) equals the share of inventory which is stocked in t and consumed in s ($x^{inv}_{t,s}$).

Algorithm 2 describes the FEFO policy. While the FIFO policy moves for each stocking period t through all consumption periods $s > t$, the FEFO policy moves for each consumption period s through all stocking periods t (reordered ascending regarding remaining shelf-life). Thus, the FEFO policy requires the remaining shelf life and a feasible solution for the MLCLSP-L-B. For a fixed consumption periods $s \in \mathcal{T}$ the algorithm checks if demand is positive ($d^{int}_{s} > 0$), then it reorders the set of periods $\mathcal{T}$ by ascending order of $(x^{rsl}_{t,s})_{t\in\mathcal{T}}$. Reordered periods are stored in $\mathcal{T}^{prio}$ so that the first value in $\mathcal{T}^{prio}$ equals the period $t \in \mathcal{T}$ in which $x^{rsl}_{t,s}$ is lowest for a fixed $s \in \mathcal{T}$. Then, the algorithm iterates through all $t \in \mathcal{T}^{prio}$ and calculates for all $s > t$ possible inventory reservation $\Delta_{t,s}$ by (22). If a stock reservation is possible ($\Delta_{t,s} > 0$), then $\Delta_{t,s}$ is distributed across all future stocking periods $t < s$. If remaining shelf-life of production lot $x^{inv}_{t,s}$ has lower remaining shelf-life than a current produced lot ($x^{rsl}_{t,s} < x^{slrule}_{s}$), then (23) is assigned to $x^{inv}_{t,s}$. Otherwise, the expression

$$\left(\min\left(\Delta_{t}, d^{int}_{s} - x^{bo}_{s} + x^{bo}_{s-1} - x^{p}_{s} - \sum_{\tau\in\mathcal{T},\tau<t} x^{inv}_{\tau\, s}\right)\right)^{+} \tag{24}$$

is used. If the remaining shelf-life of $x^{inv}_{t,s}$ is larger than a current produced one ($x^{rsl}_{t,s} \geq x^{slrule}_{s}$), then (24) reduces demand d^{int}_{s} by production quantity x^{p}_{s}. Both heuristics apply to feasible solutions of the MLCLSP-L-B.

6. Numerical experiments with real-world data

This section discusses the insights of numerical experiments based on real-world data of five tablets manufacturing problem instances. Details and characteristics of used problem instances are summarised in Appendix 1. Further information about proposed solutions and quality development over the optimisation procedure can be found in Appendix 3. First, the experimental design is introduced. Second, details on the chosen solver and model parametrisation are summarised. Third, a detailed discussion of five problem instances is provided.

The experimental design covers five problem instances and follows the four model approaches presented in Figure 7. It illustrates four evaluation procedures to determine shelf-life conflicts, affected inventory units, and costs of expired production lots based on the MLCLSP-L-B, MLCLSP-L-B-SL, and the heuristics of the previous section. These four solution approaches are described below:

- Figure 7(a) visualises the FIFO heuristics application to derive the remaining shelf-life in three steps:

Algorithm 2 Pseudo code of FEFO heuristic for fixed $\hat{p} \in \mathcal{P}$

Require: Production quantities $x^{p}_{\hat{p},t} = x^{p}_{t}$, inventories $x^{inv}_{\hat{p},t} = x^{inv}_{t}$, backorders $x^{bo}_{\hat{p},t} = x^{bo}_{t}$, primary and secondary demands $d^{int}_{\hat{p},t} = d^{int}_{t}$, minimum remaining shelf-life $x^{slrule}_{\hat{p},t} = x^{slrule}_{t}$, remaining-shelf-life $x^{rsl}_{\hat{p},t,s} = x^{rsl}_{t,s}$
Ensure:
Inventories: $x^{inv}_{t,s} \in x^{inv}, x^{inv} \leftarrow [0,\dots,0] \in \mathbb{R}_{+}^{T\times T}$
Determine feasible set of stocking periods $\mathcal{T}^{feas}_{s} \subset \mathcal{T}$ for a all consumption periods $s \in \mathcal{T}$
for $s \in \{\hat{s} \in \mathcal{T} | d^{int}_{\hat{s}} - x^{bo}_{\hat{s}} + x^{bo}_{\hat{s}-1} > 0\}$ **do**
  Reorder periods in $\mathcal{T}^{prio}$ by prioritisation of ascending $(x^{rsl}_{t,s})_{t\in\mathcal{T}}$
  for $t \in \{\hat{t} \in \mathcal{T}^{prio} | \hat{t} \in \mathcal{T}^{feas}_{s}, s > \hat{t}, x^{inv}_{\hat{t}} > 0\}$ **do**
    $\Delta_{t,s} \leftarrow x^{bo}_{t} - x^{bo}_{t-1} + x^{p}_{t} - d^{int}_{t} - \sum_{\tau\in\mathcal{T},\tau>t,\tau\neq s} x^{inv}_{t,\tau} + \sum_{\tau\in\mathcal{T},\tau<t} x^{inv}_{\tau\, t}$
    if $\Delta_{t,s} \leq 0$ **then**
      Continue
    end if
    if $x^{rsl}_{t,s} < x^{slrule}_{s}$ **then**
      Set $x^{inv}_{t,s} \leftarrow (\min(\Delta_{t,s}, d^{int}_{s} - x^{bo}_{s} + x^{bo}_{s-1} - \sum_{\tau\in\mathcal{T},\tau<s} x^{inv}_{\tau,s}))^{+}$
    else
      Set $x^{inv}_{t,s} \leftarrow (\min(\Delta_{t,s}, d^{int}_{s} - x^{bo}_{s} + x^{bo}_{s-1} - x^{p}_{s} - \sum_{\tau\in\mathcal{T},\tau<s} x^{inv}_{\tau,s}))^{+}$
    end if
  end for
end for
return x^{inv}

(1) (1)The MLCLSP-L-B is applied to each problem set, ignoring shelf-life rules. The model derives production lots $x^{p}_{p,t}$, inventories $x^{inv}_{p,t}$, and backorder quantities $x^{bo}_{p,t}$ for all $p \in \mathcal{P}$ and $t \in \mathcal{T}$.
(2) (2)Algorithm 2 is applied on $x^{inv}_{p,t}$ using the definition of integrated shelf-life rules. The FIFO heuristic determines inventory consumptions $x^{inv}_{p,t,s}$ and remaining shelf-life $x^{rsl}_{p,t,s}$ for all $p \in \mathcal{P}$ and $t, s \in \mathcal{T}$.
(3) (3)Shelf-life conflicts are counted and evaluated regarding costs.

- Figure 7(b) shows the recommended FEFO heuristics application to derive the remaining shelf-life in three steps:
  (1) (1)The MLCLSP-L-B is applied in the same way as described in step 1 of the FIFO approach.
  (2) (2)Algorithm 2 is applied on $x^{inv}_{p,t}$ using the definition of integrated shelf-life rules. The FEFO heuristic determines inventory consumptions $x^{inv}_{p,t,s}$ and remaining shelf-life $x^{rsl}_{p,t,s}$ for all $p \in \mathcal{P}$ and $t, s \in \mathcal{T}$.
  (3) (3)Shelf-life conflicts are counted and evaluated regarding costs.
- Figure 7(c) summarises the isolated shelf-life rules application with the MLCLSP-L-B-SL formulation. Isolated shelf-life rules are configured by setting $w_{p,q} = 0$ for all $p \in \mathcal{P}$ and $q \in \mathcal{P}^{pre}_{p}$. The model parameter sl_{p} is set to the expected value of the integrated shelf-life rule outcome. The approach relies on two steps:
  (1) (1)The MLCLSP-L-B-SL is applied to each problem set with the isolated shelf-life rules. The model derives production lots $x^{p}_{p,t}$, inventory consumptions $x^{inv}_{p,t,s}$, and backorder quantities $x^{bo}_{p,t}$ for all $p \in \mathcal{P}$ and $t, s \in \mathcal{T}$. The remaining shelf-life $x^{rsl}_{p,t,s}$ is determined using the definition of integrated shelf-life rules.
  (2) (2)Shelf-life conflicts are counted and evaluated regarding costs.
- Figure 7(d) describes the integrated shelf-life rules application with the MLCLSP-L-B-SL formulation in two steps.
  (1) (1)The MLCLSP-L-B-SL is applied to each problem set with the integrated shelf-life rules. The model derives production lots $x^{p}_{p,t}$, inventory consumptions $x^{inv}_{p,t,s}$, backorder quantities $x^{bo}_{p,t}$, and remaining shelf-life $x^{rsl}_{p,t,s}$ for all $p \in \mathcal{P}$ and $t, s \in \mathcal{T}$.
  (2) (2)Shelf-life conflicts are counted and evaluated regarding costs.

This paper focuses mainly on the MIP formulation of integrated shelf-life rules, the impact on solution characteristics, and the vast complexity that standard optimisation procedures have to deal with. Research issues like particular heuristics that improve the solution quality compared to the standard optimisation procedures or the application on further benchmark sets are listed in Section 7. The presented model approaches cover 20 MIPs in total. All MIPs are solved by Gurobi's standard

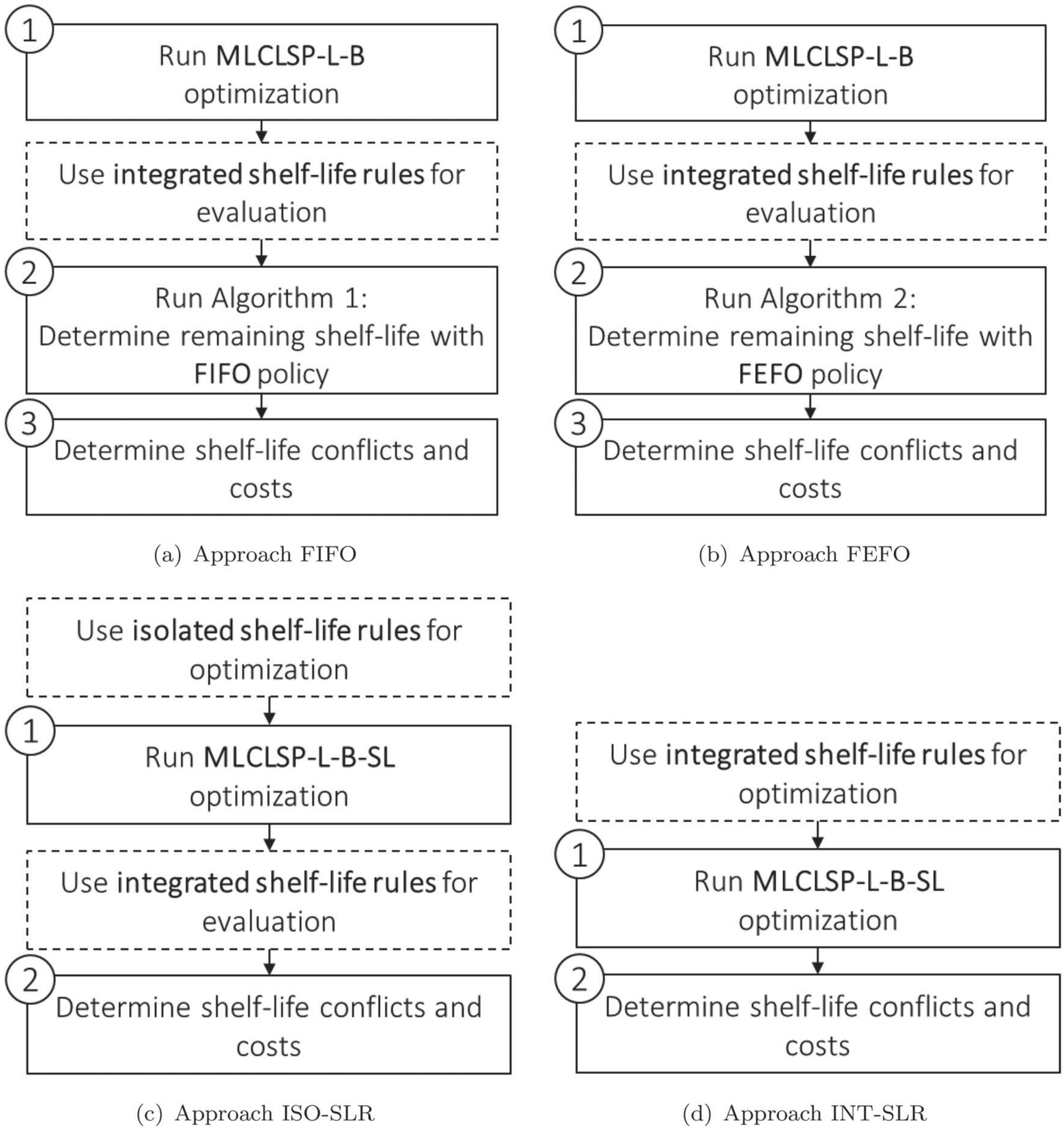

Figure 7. Four different models to derive lot sizes.

solver (version 9.3), which combines B&B, VI, B&C, and C&B heuristics. Moreover, the MIP gap stays with Gurobi's standard value of $1e{-}4$. The maximal calculation time (CT) is set to 5 days per problem instance so that the timely manners of the monthly lot-sizing planning cycles in the tablets manufacturing processes are satisfied. All five problem instances set customer shelf-life tolerance time $t_p^{arsl} = 0$ (all production lots are accepted from internal or external customers with a non-negative remaining shelf-life).

Table 6 summarises the results of KPIs for all five problem instances. Remarkably, the presented destruction costs are not part of the MLCLSP-L-B and MLCLSP-L-B-SL objectives. A what-if scenario evaluates destruction costs to show the monetary risk of model simplifications regarding shelf-life: If a solution approach recommends lot sizes that lead to shelf-life conflicts and the lot sizes are released, then the expected destruction costs associated with the expired products are calculated. Optimal solutions are found for SET1 and SET2 only. Feasible solutions are found for SET3, SET4, and SET5 so that they come 5.00%, 5.55%, and 5.70% on average close to the linear boundary (LB). High optimality gaps are reasoned by the high model complexity through shelf-life integration

Table 6. Summary KPIs for solutions of five problem instances with $CT = 5$ days.

		Model KPIs						
		OT (h)	Obj.	State	LB (%)	Shelf-life	Expired stock (abs. / %)	Exp. destruction costs
SET1	FIFO	0.01	52,174	Opt.	0.00	7	2751/7.5	5502
	FEFO					7	2751/7.5	5502
	ISO-SLR	0.01	52,647	Opt.	0.00	0	0 / 0.0	0
	INT-SLR	0.01	52,647	Opt.	0.00	0	0 / 0.0	0
SET2	FIFO	21.84	33,067	Opt.	0.00	9	193,984/6.3	5819
	FEFO					9	145,662/4.7	4369
	ISO-SLR	3.52	35,791	Opt.	0.00	3	34,574/1.2	1037
	INT-SLR	4.16	35,791	Opt.	0.00	0	0/0.0	0
SET3	FIFO	120.00	38,491	Feas.	3.56	8	1692/1.7	8061
	FEFO					8	1692/1.7	8061
	ISO-SLR	120.00	39,983	Feas.	5.04	2	400/0.4	2000
	INT-SLR	120.00	40,011	Feas.	7.75	0	0/0.0	0
SET4	FIFO	120.00	270,641	Feas.	4.34	15	48,668/6.9	36,501
	FEFO					14	47,606/6.7	35,705
	ISO-SLR	120.00	288,689	Feas.	6.99	4	19,100/2.3	14,325
	INT-SLR	120.00	288,141	Feas.	6.54	0	0/0.0	0
SET5	FIFO	120.00	242,830	Feas.	4.89	21	355,816/5.7	32,332
	FEFO					20	285,177/4.6	25,268
	ISO-SLR	120.00	266,448	Feas.	6.90	15	422,713/6.9	42,271
	INT-SLR	120.00	26,2944	Feas.	6.12	0	0/0.0	0

(a detailed analysis is provided in Appendix 2). However, it is astonishing that Gurobi's standard optimisation procedures can deal with such complex models and find high-quality solutions within the predefined optimisation time. Feasible solutions of FIFO and FEFO are on average 1.79% and 2.80% closer to the LB than ISO-SL and INT-SLR, respectively. Only INT-SLR was able to resolve all shelf-life conflicts across all problem instances. Using FIFO and FEFO, over 1% of inventories are expired across all problem instances. ISO-SLR can keep expired units below 1% of total stocked quantities on SET1 and SET3. ISO-SLR leads to the same result as INT-SLR on SET1. All other instances include at least 2 shelf-life conflicts (4.8 on average). FIFO performs worst across all problem instances with at least 7 shelf-life conflicts. FEFO dominates FIFO regarding shelf-life conflicts on SET4 and SET5 and weakly dominates FIFO on SET1, SET2, and SET3. FIFO leads to the same result as FEFO on SET1. Remarkably, problem complexity and available capacity are critical drivers for the amount of shelf-life conflicts and performance of INT-SLR. SET1 is a simple 2-level problem with no multi-users and an average utilisation of 68.96%. FIFO and FEFO lead to the same results, such as INT-SLR and ISO-SLR. Moreover, SET3 has a slightly higher average utilisation of 72.86% but 1 multi-user. FIFO and FEFO perform equally, and ISO-SLR contains 2 shelf-life conflicts for the multi-user product $P015$. SET2 has a significantly higher utilisation of 81.11%. Thus, FIFO and FEFO differ in expired stock size, and ISO-SLR includes 3 shelf-life conflicts. 89.12% and 76.22% average utilisation and 7 and 12 multi-users are determined for SET04 and SET05, respectively. FEFO dominates FIFO, and INT-SRL dominates FIFO, FEFO, and ISO-SLR regarding shelf-life conflicts and destruction costs. INT-SLR performs best regarding total costs (objective and destruction costs). It improves the total cost structure by 6.37%, 5.38%, 12.54%, 6.02%, and 8.00% on average for SET1 till SET5, respectively.

Next, a detailed analysis of the cost structures is provided. The decomposition of the cost structure into setup, inventory, backorder, and destruction costs of FIFO, FEFO, and ISO-SLR compared to INT-SLR helps to understand the behaviour of the model INT-SLR. Figure 8 shows relative cost structure improvements and deterioration. INT-SLR can archive at least 4.64%, 1.96%, and 0.00%, and at most, 16.35%, 16.35%, and 17.41% cost improvements across all problem instances compared to FIFO, FEFO, and ISO-SLR, respectively. On the other hand, high-qualitative solutions of FIFO and FEFO significantly reduce backorder costs across all problem instances (excluding SET3) and setup costs for all problem instances (excluding SET2). Also, ISO-SLR slightly improves setup structures compared to INT-SLR. Nevertheless, destruction costs exhaust archived cost improvements of FIFO, FEFO, and ISO-SLR. Thus, solutions of INT-SLR tend to have the following advantages compared to FIFO, FEFO, and ISO-SLR to avoid shelf-life conflicts:

(1) More setup operations are prepared: Inventory lay time is pushed to an acceptable minimum to resolve shelf-life bottlenecks. This strategy is helpful if free capacity is available.
(2) More backordering occurs: Shelf-life conflicts are prevented by directly backordering primary or secondary demand. This strategy is helpful to ensure

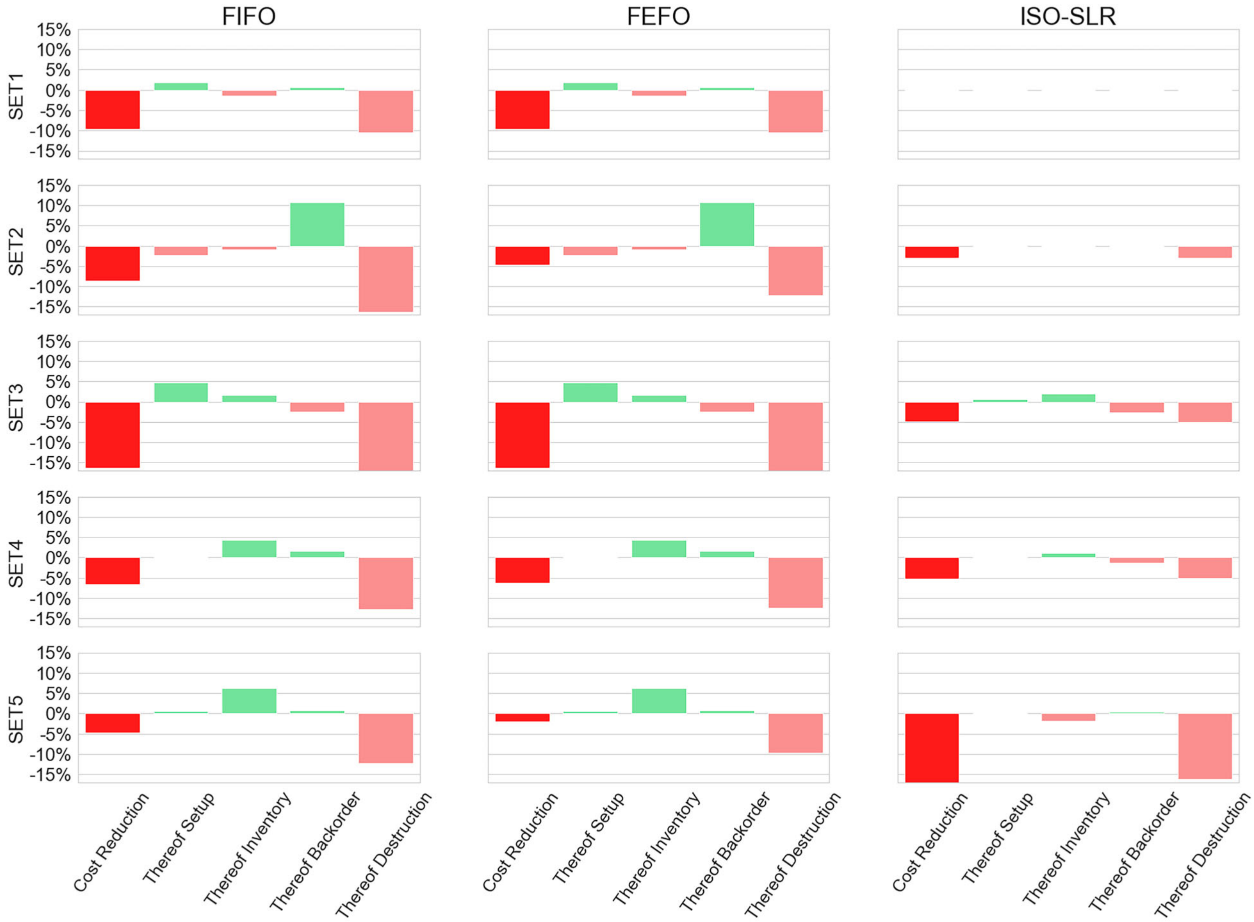

Figure 8. Cost-reduction potential decomposition compared to INT-SLR.

production plan feasibility if shelf-life conflicts are not resolvable.

The following detailed analysis focuses on problem instance SET03 in which integrated shelf-life rules perform best compared to the other approaches. Figure 9 visualises boxplots of lay times and the remaining shelf-life of all stocked materials. Different colors represent model approaches, and red crosses mark average values. In particular, Figure 9(a) shows boxplots of all materials with positive lay times per lot ($(s-t)x^{inv+}_{p,t,s}$). All models have a lay time of 1 for each stocked unit of materials $P009$ and $P010$. However, FIFO and FEFO lead to significantly more average lay times for materials $P008$, $P010$, $P015$, and $P038$. Moreover, INT-SLR has significantly longer average lay times than ISO-SLR for materials $P014$, $P015$, and $P038$. To understand how longer lay times in INT-SLR (especially for the multi-user material $P015$) might help to resolve shelf-life conflicts, Figure 9(b) presents boxplots of all stocked materials of their remaining shelf-life per produced lot ($x^{rsl}_{p,t,s}$). If the remaining shelf-life becomes negative, then a shelf-life conflict is counted. Both shelf-life conflicts are documented in Table 6 for SET3 and model ISO-SLR for material $P015$, the only multi-usage material. Hence, INT-SLR is the only model that efficiently steers the ingredient's consumption of material $P015$. It balances the remaining shelf-life of $P038$ and $P039$ such that it has the highest remaining shelf-life of $P015$. Remarkably, $P015$ has a higher average lay time in INT-SLR than in ISO-SLR. Nonetheless, INT-SLR resolves all shelf-life conflicts for the bottleneck material $P015$, while ISO-SLR cannot resolve two conflicts. Thus, higher inventory costs of INT-SLR compared to FIFO, FEFO, and ISO-SLR are justified by using pre-production for materials with uncritical shelf-life requirements to achieve more flexibility for materials heavily impacted by shelf-life.

7. Conclusions

The previous section observed that MLCLSP-L-B can be successfully extended by integrated shelf-life rules leading toward the MLCLSP-L-B-SL. Five real-world problem instances of tablets manufacturing processes confirm that FIFO and FEFO inventory policy rules and even isolated shelf-life rules can not adequately resolve shelf-life

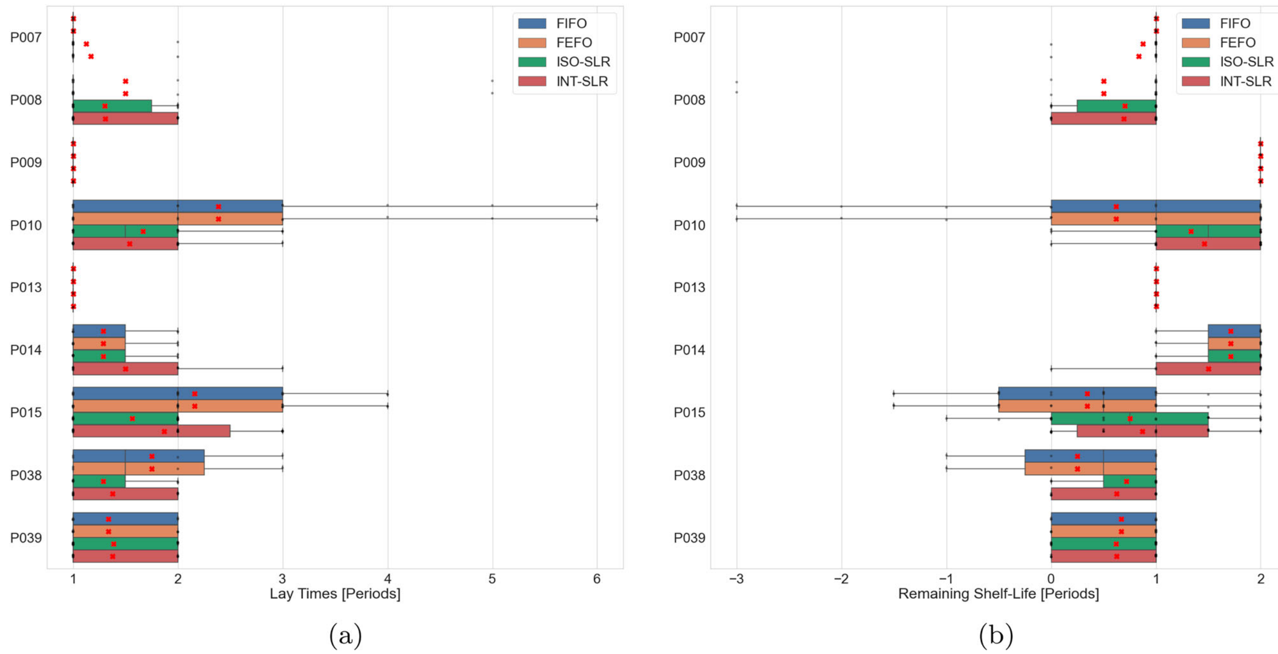

Figure 9. Detailed analysis of SET3 inventory consumption behaviour. (a) Positive lay times of material lots and (b) remaining shelf-life of material lots.

conflicts in tablets manufacturing processes. This critical lack is amplified whenever the complexity of production structures increases, or resource capacity utilisation becomes high. Integrated shelf-life rule formulations incorporated in the MIP formulation were able to avoid shelf-life conflicts in proposed production plans. Furthermore, models with integrated shelf-life rules reduce costs (including destruction costs) by 7.66% and expired inventory volumes by 4.27% on average across all considered problem instances and used benchmark models. Suppose integrated shelf-life rules are incorporated into the optimisation model. In that case, lot-sizing models can efficiently steer lay times and remaining shelf-life in multi-level production systems by preparing more setup operations, targeted pre-production, and backordering strategies driven by shelf-life bottlenecks. Nowadays, industry partners are the widely spread FEFO heuristics on created production schedules. Hence, the proposed MIP approach with integrated shelf-life rules effectively improves the company's manufacturing processes by reducing destruction costs.

The primary insights of this paper are promising. Nonetheless, several open research issues remain to be audited. First, the paper deals with problem instances from tablets manufacturing processes. Other shelf-life-impacted industries, like chemistry and the food industry, might profit from applications of the MLCLSP-L-B-SL to resolve shelf-life conflicts as well. Researchers could apply numerical experiments with problem instances from these industry sectors to provide the foundation for further discussions of integrated shelf-life rule applicability. Second, pharmaceutical companies request a model which resolves all shelf-life conflicts. However, other industry sectors might have weaker regulations, so customers accept expired units at a discount. For such cases, the MLCLSP-L-B-SL might be extended by contract penalties mapped on exceeded customer shelf-life target values. Furthermore, researchers could improve the quality of the solution of the optimisation procedure by developing novel VI or special-purpose heuristics. Third, the remaining shelf-life might not be deterministic for some tablets manufacturing process steps due to temperature, humidity, chemical reactions, or supplier quality problems. Thus, formulating the MLCLSP-L-B-SL with probabilistic integrated shelf-life rules seems a valuable direction for industrial applications.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data that support the findings of this study are openly available in Simonis (2023) at https://data.mendeley.com/datasets/wt4s58xwj3/4.

References

Akartunalí, Kerem, and Andrew J. Miller. 2009. "A Heuristic Approach for Big Bucket Multi-level Production Planning Problems." *European Journal of Operational Research* 193 (2): 396–411. https://doi.org/10.1016/j.ejor.2007.11.033.

Alshemari, Abdullah, Liz Breen, Gemma Quinn, and Uthayasankar Sivarajah. 2020. "Can We Create a Circular Pharmaceutical Supply Chain (CPSC) to Reduce Medicines Waste?" *Pharmacy* 8 (4): 221. https://doi.org/10.3390/pharmacy8040221.

Bajaj, Sanjay, Dinesh Singla, and Neha Sakhuja. 2012. "Stability Testing of Pharmaceutical Products." *Journal of Applied Pharmaceutical Science* 2 (3): 129–138.

Billington, Peter J., John O. McClain, and L. Joseph Thomas. 1983. "Mathematical Programming Approaches to Capacity-Constrained MRP Systems: Review, Formulation and Problem Reduction." *Management Science* 29 (10): 1126–1141. https://doi.org/10.1287/mnsc.29.10.1126.

Buschkühl, Lisbeth, Florian Sahling, Stefan Helber, and Horst Tempelmeier. 2010. "Dynamic Capacitated Lot-Sizing Problems: A Classification and Review of Solution Approaches." *Or Spectrum*32 (2): 231–261. https://doi.org/10.1007/s00291-008-0150-7.

Chen, Haoxun. 2015. "Fix-and-Optimize and Variable Neighborhood Search Approaches for Multi-level Capacitated Lot Sizing Problems." *Omega* 56:25–36. https://doi.org/10.1016/j.omega.2015.03.002.

Chen, Shuo, Regina Berretta, Alexandre Mendes, and Alistair Clark. 2021. "Integrating Shelf Life Constraints in Capacitated Lot Sizing and Scheduling for Perishable Products." In *Data and Decision Sciences in Action 2*, 33–46. Springer.

Colberg, Lene, Lone Schmidt-Petersen, Merete Kock Hansen, Birgitte Smolsky Larsen, and Sigrid Otnes. 2017. "Incorrect Storage of Medicines and Potential for Cost Savings." *European Journal of Hospital Pharmacy* 24 (3): 167–169. https://doi.org/10.1136/ejhpharm-2015-000744.

Florian, Michael, Jan Karel Lenstra, and A. H. G. Rinnooy Kan. 1980. "Deterministic Production Planning: Algorithms and Complexity." *Management Science* 26 (7): 669–679. https://doi.org/10.1287/mnsc.26.7.669.

Haase, Knut, and Andreas Drexl. 1994. "Capacitated Lot-Sizing with Linked Production Quantities of Adjacent Periods." In *Operations Research'93*, 212–215. Springer.

Helber, Stefan, and Florian Sahling. 2010. "A Fix-and-Optimize Approach for the Multi-level Capacitated Lot Sizing Problem." *International Journal of Production Economics* 123 (2): 247–256. https://doi.org/10.1016/j.ijpe.2009.08.022.

Hung, Yi-Feng, and Kuo-Liang Chien. 2000. "A Multi-class Multi-level Capacitated Lot Sizing Model." *Journal of the Operational Research Society* 51 (11): 1309–1318. https://doi.org/10.1057/palgrave.jors.2601026.

Khan, Ahmad Khalid, Syed Mohammad Faisal, and Omar Abdullah Al Aboud. 2018. "An Analysis of Optimal Inventory Accounting Models–Pros and Cons." *European Journal of Accounting, Auditing and Finance Research* 6 (3): 65–77.

Kopp, Sabine. 2006. "Stability Testing of Pharmaceutical Products in a Global Environment." *RAJ Pharma* 5:291–294.

Lütke Entrup, Matthias, H.-O. Günther, Paul Van Beek, Martin Grunow, and Thorben Seiler. 2005. "Mixed-Integer Linear Programming Approaches to Shelf-Life-Integrated Planning and Scheduling in Yoghurt Production." *International Journal of Production Research* 43 (23): 5071–5100. https://doi.org/10.1080/00207540500161068.

Marinelli, Fabrizio, Maria Elena Nenni, and Antonio Sforza. 2007. "Capacitated Lot Sizing and Scheduling with Parallel Machines and Shared Buffers: A Case Study in a Packaging Company." *Annals of Operations Research* 150 (1): 177–192. https://doi.org/10.1007/s10479-006-0157-x.

Nahmias, Steven. 1982. "Perishable Inventory Theory: A Review." *Operations Research* 30 (4): 680–708. https://doi.org/10.1287/opre.30.4.680.

Quadt, Daniel, and Heinrich Kuhn. 2008. "Capacitated Lot-Sizing with Extensions: A Review." *4OR* 6 (1): 61–83. https://doi.org/10.1007/s10288-007-0057-1.

Sahling, Florian, and Gerd J. Hahn. 2019. "Dynamic Lot Sizing in Biopharmaceutical Manufacturing." *International Journal of Production Economics* 207:96–106. https://doi.org/10.1016/j.ijpe.2018.11.006.

SAP. 2021. "Include Batch Expiration in Material Requirement Planning." Accessed April 7, 2024. https://community.sap.com/t5/enterprise-resource-planning-blogs-by-members/include-batch-expiration-in-material-requirement-planning/ba-p/13493856.

Savage, Christopher J., Kevin J. Roberts, and Xue Z. Wang. 2006. "A Holistic Analysis of Pharmaceutical Manufacturing and Distribution: Are Conventional Supply Chain Techniques Appropriate?" *Pharmaceutical Engineering* 26 (4): 1–8.

Sazvar, Z., S. M. J. Mirzapour Al-e Hashem, K. Govindan, and B. Bahli. 2016. "A Novel Mathematical Model for a Multi-period, Multi-product Optimal Ordering Problem Considering Expiry Dates in a FEFO System." *Transportation Research Part E: Logistics and Transportation Review* 93:232–261. https://doi.org/10.1016/j.tre.2016.04.011.

Simonis, Michael. 2023. "Tablets Manufacturing Processes: Single-Machine Multi-item Capacitated Lot-Sizing with Linked Lot Sizes and Backlogging." Mendeley Data, Vol. 4. https://doi.org/10.17632/wt4s58xwj3.4.

Simonis, Michael, and Stefan Nickel. 2023a. "Integrated Shelf-Life Rules for Multi-level Tablets Manufacturing Processes." In *International Workshop on Lot-Sizing-IWLS'2023*, Vol. 13, 30–33. https://gwr3n.github.io/books/IWLS2023_BoA.pdf#page = 39.

Simonis, Michael, and Stefan Nickel. 2023b. "A Simulation–Optimization Approach for a Cyclic Production Scheme in a Tablets Packaging Process." *Computers & Industrial Engineering* 181 (C): 109304. https://doi.org/10.1016/j.cie.2023.109304.

Slama, Ilhem, Oussama Ben-Ammar, Alexandre Dolgui, and Faouzi Masmoudi. 2020. "New Mixed Integer Approach to Solve a Multi-level Capacitated Disassembly Lot-Sizing Problem with Defective Items and Backlogging." *Journal of Manufacturing Systems* 56:50–57. https://doi.org/10.1016/j.jmsy.2020.05.002.

Smith-Daniels, V. L., and Larry P. Ritzman. 1988. "A Model for Lot Sizing and Sequencing in Process Industries." *The International Journal of Production Research* 26 (4): 647–674. https://doi.org/10.1080/00207548808947890.

Soler, Willy A. O., Maristela O. Santos, and Kerem Akartunalı. 2021. "MIP Approaches for a Lot Sizing and Scheduling Problem on Multiple Production Lines with Scarce Resources, Temporary Workstations, and Perishable Products." *Journal of the Operational Research Society* 72 (8): 1691–1706. https://doi.org/10.1080/01605682.2019.1640588.

Stadtler, Hartmut. 2003. "Multilevel Lot Sizing with Setup Times and Multiple Constrained Resources: Internally Rolling Schedules with Lot-Sizing Windows." *Operations Research* 51 (3): 487–502. https://doi.org/10.1287/opre.51.3.487.14949.

Suerie, Christopher, and Hartmut Stadtler. 2003. "The Capacitated Lot-Sizing Problem with Linked Lot Sizes." *Management Science* 49 (8): 1039–1054. https://doi.org/10.1287/mnsc.49.8.1039.16406.

Taghizadeh, Elham, Setareh Torabzadeh, Abdollah Mohammadi, and Farshid Evazabadian. 2020. "A Bi-Objective Lot Sizing and Scheduling Problem Dealing with Reworking Perishable Items in a Parallel Machine System." In *Proceedings of the 2nd African International Conference on Industrial Engineering and Operations Management*. IEOM Society International.

Tempelmeier, Horst, and Lisbeth Buschkühl. 2009. "A Heuristic for the Dynamic Multi-level Capacitated Lotsizing Problem with Linked Lotsizes for General Product Structures." *Or Spectrum* 31 (2): 385–404. https://doi.org/10.1007/s00291-008-0130-y.

Tempelmeier, Horst, and Karina Copil. 2016. "Capacitated Lot Sizing with Parallel Machines, Sequence-Dependent Setups, and a Common Setup Operator." *OR Spectrum* 38 (4): 819–847. https://doi.org/10.1007/s00291-015-0410-2.

Tempelmeier, Horst, and Matthias Derstroff. 1996. "A Lagrangean-based Heuristic for Dynamic Multilevel Multi-item Constrained Lotsizing with Setup Times." *Management Science* 42 (5): 738–757. https://doi.org/10.1287/mnsc.42.5.738.

Trigeiro, William W., L. Joseph Thomas, and John O. McClain. 1989. "Capacitated Lot Sizing with Setup Times." *Management Science* 35 (3): 353–366. https://doi.org/10.1287/mnsc.35.3.353.

Vickery, Shawnee K., and Robert E. Markland. 1986. "Multi-stage Lot Sizing in a Serial Production System." *International Journal of Production Research* 24 (3): 517–534. https://doi.org/10.1080/00207548608919747.

Waterman, Kenneth C. 2009. "Understanding and Predicting Pharmaceutical Product Shelf-Life." In *Handbook of Stability Testing in Pharmaceutical Development: Regulations, Methodologies, and Best Practices*, 115–135. Springer.

World Health Organization. 2022. "Standard Operating Procedures for Supply Chain Management of Health Products for Neglected Tropical Diseases Amenable to Preventive Chemotherapy. Accessed January 1, 2023. https://www.who.int/publications/i/item/9789240049581.

Wu, Tao, Kerem Akartunalı, Jie Song, and Leyuan Shi. 2013. "Mixed Integer Programming in Production Planning with Backlogging and Setup Carryover: Modeling and Algorithms." *Discrete Event Dynamic Systems* 23 (2): 211–239. https://doi.org/10.1007/s10626-012-0141-3.

Young, N. W. G., and G. R. O'Sullivan. 2011. "The Influence of Ingredients on Product Stability and Shelf Life." In *Food and Beverage Stability and Shelf Life*, 132–183. Elsevier.

Appendices

Appendix 1. Tables manufacturing datasets

The case study covers five problem instances, see Simonis (2023). A period equals one week. The planning horizon covers the year 2018 and $T = 50$. Each problem instance has a unique set of finished goods (tablets) assigned. The assigned finished goods have different backorder and inventory costs, run rates, and setup times (measured in hours). The labour costs are the key cost driver for setup operations in the tablets packaging stage. Thus, the setup costs are approximated by the standard labour cost rate of 56.50 per hour multiplied by the setup time. Each problem instance has an assigned weekly shift model (no weekend work), which maps available capacity in hours to each planning period. An overview of problem instance characteristics is summarised in Table A1. The number of production levels, machines, and materials are summarised. Multi-usages counts the materials which consume several ingredients ($|\ \mathcal{P}_p^{pre}\ | > 1$ for $p \in \mathcal{P}$). Furthermore, the problem instances cover the following manufacturing stages: SET1 and SET2 cover a 2-level packaging stage in which a primary packaging step packs tablets into blisters and a secondary packaging step packs blisters into folding boxes. SET3

Table A1. Data characteristics of five problem instances.

Problem instance	Level	Machines	*Materials*	*Multi − usages*
SET1	2	2	6	0
SET2	2	2	6	0
SET3	2	2	15	1
SET4	2	2	20	7
SET5	3	5	22	12

and SET4 represent a 2-level bulking process, which prepares and mixes granulates and fills them into plastic bottles. SET5 consists of a 3-level API and bulking process, which processes active pharmaceutical ingredients into granulates.

Appendix 2. Complexity analysis

In the following, the number of decision variables and constraints are theoretically and numerically summarised for the MIP formulations MLCLSP-L-B and MLCLSP-L-B-SL.

Table 2 shows that $5PT+3P$ decision variables are used in the MLCLSP-L-B. Let $n^{int} = |\mathcal{P}^{Int}|$. Equations (8) and (9) assign values to $n^{int}T$ and $4P$ decision variables, respectively. Thus, the MLCLSP-L-B has to determine

$$dv = 5PT - Tn^{int} - P \tag{A1}$$

values for decision variables in the optimisation procedure. Moreover, the number of constraints in this MIP formulation can be determined by counting the constraints (2) till (9). Let $n^{alloc} = \sum_{p\in\mathcal{P}} |\mathcal{M}_p| - 1$. Then, the amount of constraints equals

$$con = 2MT + 3PT + T(n^{int} + n^{alloc}). \tag{A2}$$

Consider the MLCLSP-L-B-SL and let $n^{pre} = \sum_{p\in\mathcal{P}} |\mathcal{P}_p^{pre}|$. The amount of decision variables used in Table 5 equals $3PT^2 + PT + 2T\alpha^{pre}$. The decision variables $x_{p,t,s}^{inv}$ and $x_{p,t,s}^{inv+}$ are set to 0 if the stocking period is smaller or equal the consumption period ($s \le t$). The number of zeros equals the number of indices below and on the diagonal of the consumption matrix shown in Figure 3 for one decision variable with fixed index $p \in \mathcal{P}$. If T is even, the number equals $T/2(T+1)$, otherwise (T is odd) $\lceil T/2\rceil T$. Both cases can be combined by the term $\Delta = \lceil T/2\rceil T + T/2(1-(T-2\lfloor T/2\rfloor))$. The MIP formulation uses the MLCLSP-L-B as a foundation. With (A1) it follows, that the MLCLSP-L-B-SL has to determine

$$dv^{SL} = DV + 3PT^2 + PT + 2Tn^{pre} - 2P\Delta \tag{A3}$$

values for decision variables in the optimisation procedure. Let $n^{al} \ge 0$ be the amount of configured affine-linear and $n^{min} \ge 0$ the amount of minimum shelf-life rules. Then, the number of constraints in this MIP formulation is determined by counting the constraints presented in Section 4 and adding (A2). It equals

$$con^{SL} = con + PT + 4PT^2 + 2P\Delta + n^{pre}T(T+1) + PTn^{al} + (T(T+1)n^{pre} + PT)n^{min}. \tag{A4}$$

Finally, equations (A1), (A2), (A3), and (A4) can be used to determine the number of decision variables and constraints for all considered problem sets. Table A2 summarises the numbers accordingly. The model complexity continuously increases from SET1 to SET5 for both model approaches. However, integrating the integrated shelf-life rules into the MLCLSP-L-B has a price in terms of complexity. The number of decision variables and constraints increase through shelf-life extensions by the factors 23.42 and 42.62 on average, respectively. This tremendous increase in model complexity relies mainly on the quadratic terms T^2 in (A3) and (A4).

Appendix 3. Details for the numerical experiments with real-world data

Table A3 summarises the average utilisation, total setup operations, total inventory quantity, total backorder quantity, and average lay time of five problem instances discussed in Section 6.

Furthermore, Section 6 observed that MIP gaps above 5% occur in the solutions of the MLCLSP-L-B and MLCLSP-L-B-SL regarding problem instances SET3, SET4, and SET5. The following discusses the development of the objective and the lower boundary across the CT of 5 days. Figure A1 visualises the development of the objective value (thick line) and the LB (dashed line) determined by the solver algorithm. The MLCLSP-L-B, ISO-SLR, and INT-SLR are represented by the colours blue, red, and green, respectively. The best (or even optimal) solution's cost that was determined within $CT = 5$ days is flagged with a diamond marker. Moreover, Table A4 lists the quality improvements for the intervals 1, 24, 48, 72, 96, and 120 h the MIP gap of the best-found solution from the visualisation. The following observations can be made per problem set:

SET1 The solver found for all approaches the optimal solution within 56.43 s. Fastest, the optimal solution was found for the MLCLSP-L-B (26.74 s with objective 52,174), followed by INT-SLR (35.12 s with objective 52,647). Gurobi requires the most time (56.43 s with objective 52,647) to derive an optimal solution for the ISO-SLR. The slowest development of the LB is realised for ISO-SLR. It increases very slowly after 20 s. The LB of INT-SLR increases much faster. The quality development of the LB of the MLCLSP-L-B is slightly faster than that of INT-SLR in the first 10 s of the optimisation time.

SET2 The solver found for all approaches the optimal solution within 21.84 h. Fastest, the optimal solution was found for the INT-SLR (3.52 h with objective 35,791), followed by ISO-SLR (4.16 h with objective 35,791). Gurobi requires the most time to find the optimal solution for the MLCLSP-L-B (21.84 h with objective 33,067). The LB of the INT-SLR is slightly higher than that of the ISO-SLR LB. The slowest development of the LB is realised for the

Table A2. Number of decision variables (DV) and constraints (CON) for all considered problem instances.

Problem instance	n^{int}	n^{alloc}	n^{pre}	n^{al}	n^{min}	MLCLSP-L-B DV	MLCLSP-L-B CON	MLCLSP-L-B-SL DV	MLCLSP-L-B-SL CON
SET1	3	12	3	3	3	1344	1850	32,244	109,250
SET2	3	12	3	3	3	1344	1850	32,244	109,250
SET3	8	98	8	15	0	3335	7750	80,635	226,900
SET4	11	182	16	19	1	4430	12,850	108,030	364,450
SET5	16	86	27	22	0	4678	8900	119,578	376,950

Table A3. Detail information for solutions of five problem instances with $CT = 5$ days.

		Further model information				
		Util. (%)	Setups	Inventories	Backorders	Lay time
SET1	FIFO	68.86	166	36,906	96,666	1.83
	FEFO					1.83
	ISO-SLR	69.06	172	24,835	99,767	1.41
	INT-SLR	69.06	172	24,835	99,767	1.41
SET2	FIFO	81.20	166	3,102,255	406,538	1.91
	FEFO					1.97
	ISO-SLR	81.03	161	2,875,761	564,054	1.45
	INT-SLR	81.03	161	2,875,761	564,054	1.55
SET3	FIFO	72.73	255	101,010	40,540	1.49
	FEFO					1.41
	ISO-SLR	72.97	266	112,249	35,910	1.29
	INT-SLR	73.00	268	100,291	28,655	1.34
SET4	FIFO	89.09	641	708,360	38,407	1.19
	FEFO					1.20
	ISO-SLR	89.17	643	686,784	44,576	1.11
	INT-SLR	89.15	643	839,318	49,520	1.13
SET5	FIFO	76.14	660	6,203,555	217,016	1.79
	FEFO					1.79
	ISO-SLR	76.30	668	6,129,082	229,706	1.66
	INT-SLR	76.29	670	6,666,712	288,465	1.68

Table A4. Quality increase per problem instance by means of the MIP gap [%].

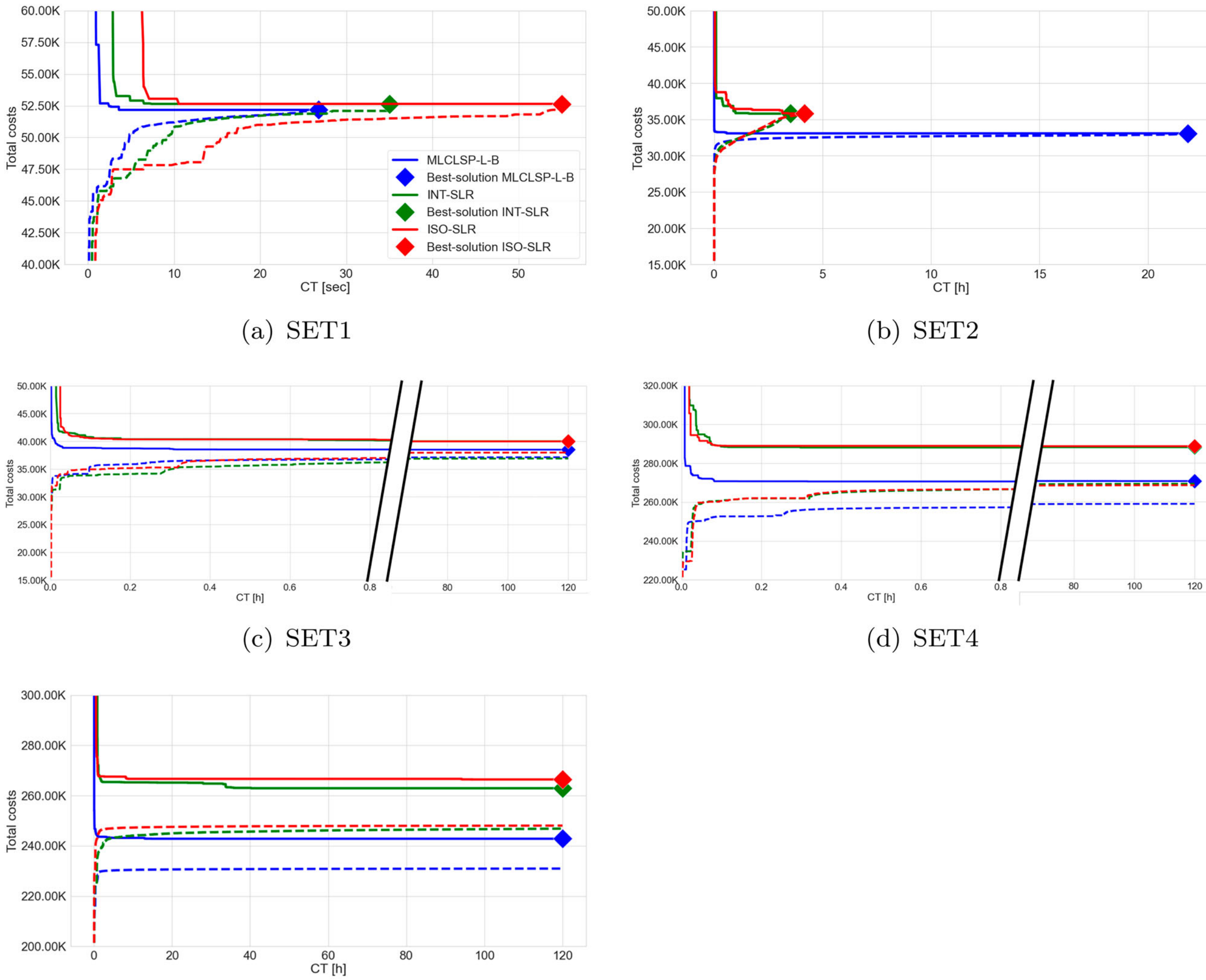
Problem	Model	1h	24h	48h	72h	96h	120h
SET1	MLCLSP-L-B	0.00	–	–	–	–	–
	ISO-SLR	0.00	–	–	–	–	–
	INT-SLR	0.00	–	–	–	–	–
SET2	MLCLSP-L-B	2.84	0.00	–	–	–	–
	ISO-SLR	11.98	0.00	–	–	–	–
	INT-SLR	10.19	0.00	–	–	–	–
SET3	MLCLSP-L-B	4.58	3.79	3.69	3.63	3.59	3.56
	ISO-SLR	7.14	5.30	5.18	5.12	5.07	5.04
	INT-SLR	9.61	8.14	8.00	7.87	7.80	7.75
SET4	MLCLSP-L-B	4.89	4.53	4.45	4.40	4.36	4.34
	ISO-SLR	7.68	7.19	7.10	7.05	7.02	6.99
	INT-SLR	7.39	6.80	6.68	6.62	6.58	6.54
SET5	MLCLSP-L-B	6.25	5.02	4.96	4.93	4.91	4.89
	ISO-SLR	9.14	7.14	7.06	7.02	6.93	6.90
	INT-SLR	13.26	7.55	6.50	6.33	6.22	6.12

MLCLSP-L-B. It almost stagnates after 2 h with minimal improvements along the remaining optimisation time.

SET3 The solver needed more time to find an optimal solution within 5 days. Instead, the solver terminates with objective values of 38,491, 39,983, and 40,011 for the MLCLSP-L-B, ISO-SLR, and INT-SLR, respectively. The LB improvement is similar but very slow for all MIP formulations after 1 day. By Table A4, the boundary decreases on average by 0.058%, 0.065%, and 0.096% per day for the MLCLSP-L-B, ISO-SLR, and INT-SLR, respectively.

SET4 The solver could not find an optimal solution within 5 days. The best-found solution within 5 days has an objective value of 270,641, 288,689, and 288,141 for the MLCLSP-L-B, ISO-SLR, and INT-SLR, respectively. While the LB of the MLCLSP-L-B is significantly lower than that of the ISO-SLR and INT-SLR, the LB development of the last two approaches is very similar. The LB improvement is prolonged for all MIP formulations after 2 days. By Table A4, the boundary decreases on average by 0.037%, 0.037%, and 0.047% per day for the MLCLSP-L-B, ISO-SLR, and INT-SLR, respectively.

SET5 The solver could not find an optimal solution within 5 days. The best-found solution within 5 days has an objective value of 242,830, 266,448, and 262,944 for the MLCLSP-L-B, ISO-SLR, and INT-SLR, respectively. The slowest development of the LB is realised for the MLCLSP-L-B and ISO-SLR. Already, after 5 h, no significant improvement was archived. The INT-SLR has a major improvement until 40 h. Afterwards, the LB and objective developed very slowly. The LB improvement stagnates for all MIP formulations after 2 days. By Table A4, the boundary decreases on average by 0.023%, 0.053%, and 0.127% per day for the MLCLSP-L-B, ISO-SLR, and INT-SLR, respectively.



(a) SET1 (b) SET2 (c) SET3 (d) SET4 (e) SET5

Figure A1. MIP development of MLCLSP-L-B, ISO-SLR, and INT-SLR across considered problem instances.