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Research Article

Simultaneous production planning and scheduling in a production line of I.V. (intravenous) fluids and irrigation solutions

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Abstract

Background and Objectives:
In this work, simultaneous production planning and scheduling in a real-world application, a production line of intravenous fluids and irrigation solutions at Darou Pakhsh Pharmaceutical Manufacturing Company is addressed.

Methods: A novel mixed-integer linear programming model is formulated for multi-period simultaneous production planning and scheduling. Since the problem is NP-hard in the strong sense, a memetic algorithm is proposed that reduces the computational effort of the problem. The chromosome representation is based on a permutation matrix, and a new algorithm is developed to construct a complete schedule from the permutation matrix through the planning horizon.

Results: 40 problems were investigated, containing 36 randomly generated instances and four real problems according to the data within the last two years. The generated instances were divided into small-sized, medium-sized, and large-sized instances. Among the 36 instances, 22 instances were optimally solved by both the exact method and the proposed memetic algorithm. The average gap for small-sized, medium-sized, and large-sized instances are respectively 0.00%, -1.15%, and -51.38%, indicating as the size of instances grows, the gap becomes considerable. The exact method could not reach an optimal solution for four real instances. The running time for real instances is expanded to 8 hours. The results revealed that the proposed memetic algorithm significantly outperformed the exact method in obtaining better solutions for real instances.

Conclusions: The computational results showed that the proposed memetic algorithm obtained optimal solutions on all the instances solved optimally by the exact method. It outperformed the exact method in other problems. This outperformance becomes more evident as the size of instances grows.

Keywords: Simultaneous production Planning and Scheduling, production line of I.V. fluids and irrigation solutions, Mixed-integer linear programming, Memetic algorithm, Darou Pakhsh Pharmaceutical Manufacturing Company

Background and objectives

In a supply chain, a manufacturer is linked to its suppliers and its distributors/customers. Thus, the supply chain includes functions of procurement of raw materials, the transformation of raw material into finished products, and distribution of finished products to customers[1].

There are three levels of planning in supply chains: Strategic (long-term) planning, Medium-term (tactical) planning, and short-term (operational) planning. By implementing a networked and integrated supply chain management system, companies will be able to match supply to demand, reduce inventory levels, improve delivery service, speed product time to market, and use assets more effectively[2].

The manufacturer is an important part of supply chain flow because it is connected to the supplier(s). On the other hand, it is linked with distributors or customers. In a supply chain, Production planning and scheduling are medium-term and short-term planning, respectively. An integrated approach in production planning and scheduling typically optimizes several consecutive stages in a supply chain.

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The traditional production planning and scheduling were carried out hierarchically. To be more specific, the company initially develops an aggregate production plan according to customer orders, demand forecasts, and historical data. Then, the aggregate production plan is broken down into a detailed master production schedule (MPS) to specify production quantities and inventory levels during a whole range of months or other time span within the planning horizon. Finally, according to the master schedule, scheduling is carried out, and the operation sequence and machine assignment for each time period are determined.

The hierarchical strategy can lead to a solution determined at the planning level that is not necessarily feasible at the scheduling level. These infeasibilities may result because the machine idle times and changeovers are not considered at the planning level. Therefore, it is necessary to develop methods to integrate planning and scheduling effectively[3].

Pharmaceutical supply chain management was neglected by companies in the past. Nowadays, competitive advantage has changed traditional ways of business, and pharmaceutical supply chain management has become more complex because it helps to provide life-saving treatments and requires the participation and cooperation of different participants such as pharmaceutical manufacturers, wholesalers, distributors, and customers[4].

Some significant challenges in the pharmaceutical chain supply include lack of coordination between manufacturers and distributors and between distributors and customers, lack of demand information at different chain levels, drug shortages, transportation management, and warehouse management. Drug shortages are the most important challenge, which has caused plenty of difficulties for hospitals and clinicians even in developed countries[5].

An integrated approach in production planning and scheduling in pharmaceutical industries increases productivity, improves delivery service and leads to better performance of several consecutive stages in the pharmaceutical supply chain.

Integration of production planning and scheduling

Production planning and scheduling are two important tasks in a production unit. They play an important role in the profitability of production, timely delivery, and optimal resource use. Production planning and scheduling are NP-hard, so their integration is strongly NP-hard.

Production planning and scheduling involve resource allocation and are closely integrated. The optimality of the scheduling is dependent on the production planning results. Traditionally, production planning and scheduling were carried out in two separate phases, where the scheduling was implemented discretely after production planning. The traditional approach was suitable for non-competitive production, but today the production environment is very different from the traditional condition due to tight delivery deadlines, high-quality standards, and high diversity of the products as well.

Related Works

Integration of production planning and scheduling aims for effective planning of many components and execution of those plans. These components include raw materials, machinery, operations, inventories, and demands. The idea of integration in preliminary studies was organized in a hierarchical framework[6, 7].

The integration was followed or developed by other researchers during the next years, including different strategies and methods[8-10].

A comprehensive review on integration of production planning and scheduling is done by Maravelias and Sung[11]. According to research of Maravelias and Sung[11], solution strategies proposed in the literature to solve integrated problems are classified into three categories: monolithic approach, hierarchical approach, and iterative approach. In the monolithic approach, which is also called simultaneous production planning and scheduling, production planning and scheduling are solved simultaneously. This approach is typically based on mathematical models, which are hard to solve because of high complexity. In hierarchical and iterative strategies, the problem is decomposed into a higher-level problem used to determine production targets, and one or more lower-level problems with detailed scheduling. The solution of the planning problem is used as an input for the scheduling problem. If the flow of information is only from the higher-level problem to the lower-level problem(s), the strategy is hierarchical. If there is a feedback loop from the scheduling lower-level problems to the higher-level problem, then the strategy is iterative.

Maravelias and Sung[11] also categorized modeling approaches proposed in the literature into four modeling approaches. The first approach is the detailed planning and scheduling modeling, in which constraints on resources and costs are added to the model, and a detailed scheduling model is achieved. Each scheduling horizon is equal to a planning period. Then, all planning periods are connected together, and an integrated model is obtained. The second approach is a relaxed and aggregated formulation derived from the removal of some constraints from the original model or the aggregation of some decisions in the formulation of the original model. The third approach is the application of offline surrogate models. This approach aims to create constraints in which feasible region is defined as a function of production target at each time period. The fourth approach, called the rolling horizon approach, is hybrid modeling in which detailed scheduling models are used for a few upcoming periods. A relaxation or aggregation models are applied for late periods.

In the past one and a half-decade, the problem of integrated production planning and scheduling has been extensively investigated by researchers, especially in the past few years. Erdirik-Dogan and Grossmann[3] addressed simultaneous planning and scheduling of multi-product continuous production with a single machine. They presented a mixed-integer linear programming model considering multiple periods. They implemented a bi-level decomposition scheme as the solution method because the model becomes computationally expensive to solve large-size problems. Erdirik-Dogan and Grossmann[12] extended their work to the case of parallel machines. Both of their works followed a recursive manner between a planning problem and some scheduling sub-problems.

Xue et al.[13] considered aggregate production planning problem with sequence-dependent family setup times. They proposed a model that integrates aggregate production planning and family disaggregation planning and scheduling problems with sequence-dependent setup times and costs. They converted their proposed non-linear model into a linear model.

Kis and Kovács[14] addressed integrated production planning and scheduling in a parallel machine environment. They formulated a mathematical model for the problem and also proposed a decomposition method based on a hierarchical approach by using cutting planes.

Zhong et al.[15] integrated planning and scheduling in RFID-enabled real-time ubiquitous manufacturing environment (Radio frequency identification). They proposed discrete mathematical models for production planning and scheduling levels. They implemented an iterative procedure and proposed a heuristic framework for the problem.

Yan et al.[16] investigated multi-period integrated production planning and scheduling problem for a batch job-shop environment with setup times. They presented a non-linear mixed-integer programming model and applied two hybrid genetic algorithms to optimize plan and schedule alternately.

An and Yan[17] focused on simultaneous production planning and scheduling for synchronous assembly lines. They constructed a mixed-integer programming model by concurrently considering production planning and detailed scheduling constraints and developed a Lagrangian relaxation method for the proposed model.

Kim and Lee[18] suggested an iterative procedure for synchronized production planning and scheduling in semiconductor fabrication. Their proposed method consisted of an optimization model and a simulation model, which created the production plan and the schedule.

Ramezanian et al.[19] addressed simultaneous lot-sizing and scheduling in the flexible flow shop environment. They provided a mixed-integer programming model for the problem and applied a rolling horizon heuristic and particle swarm optimization algorithm to solve the problem.

Cho and Jeong[20] applied a two-level hierarchical method for production planning, and scheduling of reentrant hybrid flow shop problems to improve productivity and customer satisfaction. They considered an upper-level planning problem and a lower-level scheduling problem and applied their proposed method to TFT-LCD (Thin Film Transistor-Liquid Crystal Display) production.

Torkaman et al.[21] formulated a mixed-integer programming model for multi-product multi-period capacitated production planning problem with sequence-dependent setups. They considered the flow of products from manufacturers to customers in a closed-loop supply chain and remanufacturing of each product. They proposed four heuristic methods based on the rolling horizon approach and a simulated annealing for solving the model.

Aguirre and Papageorgiou[22] considered integrating production planning, scheduling and maintenance in a parallel machines environment assuming limited resources, flexible recovery operations, resource availability, product lifetime, and sequence-dependent setup times. They presented a novel MILP based on the travelling salesman problem and precedence-based constraints.

Hassanzadeh and Zegordi[23] investigated simultaneous production planning and scheduling in a hybrid flow shop environment considering daily work shifts. They presented a mixed-integer linear programming model

Han et al.[24] provided a fuzzy bi-level decision model for the integrated production planning and scheduling with some uncertainties. The processing time and the changeover time of jobs, and the startup time of machines were supposed to be fuzzy. They developed a hybrid fuzzy method consisting of a particle swarm optimization algorithm for the planning level and a heuristic algorithm for the scheduling level.

Most of studies on integrated production planning and scheduling consider simple and classic scheduling problems such as a single machine, parallel machines, flow-shop, or job-shop problem. There are few researches considering complex real-world problems with particular assumptions. Even most of researchers have not considered usual assumptions in most of the industries. For example, in most industries, the available working time within a period is not continuous, although it can be continued only for a daily shift or a workweek. Nevertheless, most of researchers consider a planning period to be continuous. Another neglected assumption is the availability of raw materials. Material requirement planning (MRP) is an important subject in production planning, but the inventory of raw materials and consuming them during the manufacturing is neglected in integration models of production planning and scheduling. Nowadays, companies generally try to optimize a productivity-based performance measure, but most research on integrated production planning and scheduling tends to optimize a traditional scheduling performance measure or a combination of some of them.

In addition to these common assumptions, each industry has its unique assumptions and constraints, such as the relationship between demands and production rates, setup times or changeover times, production costs, holding costs, and lost sales/backorder costs. For the problem of this study, a productivity-based performance measure (profit) is optimized.

For the pharmaceutical industry, instead of integrated planning and scheduling, most of the research is conducted either on production planning or scheduling[25-27]. Other researchers investigate the integration of some other parts of the pharmaceutical supply chain[28-33].

Problem Description:

The problem is then to determine the jobs to be processed in each period and each workweek, the sequencing and scheduling of these jobs, and the inventory levels for each job. The objective is to maximize the total profit, in terms of sales revenues, lost sales costs, and inventory costs. Other operating costs are supposed to be fixed in each period and are not considered in the objective function.

Growth of product market and the significance of products

Most of the capacity of the production line is devoted to manufacturing I.V (Intravenous) fluids. One of the most common forms of treatment offered at hospitals is intravenous therapy. I.V. fluids are a complete mix of essential nutrients intended to replenish fluid losses, treat electrolyte imbalances, and maintain fluid balance in intravenous therapy in patients. They also provide required nutrients to patients suffering from diabetes, cancer, and other diseases. I.V. fluids may contain water with electrolytes, sugar, or medications added in concentrations per the patient's need. The global I.V. fluids market size was valued at US$ 8.4 million in 2019 and is expected to witness a compound annual growth rate of 6.1% for upcoming years. Prevalence of diseases, such as gastrointestinal disorders, neurological diseases, cancer, and diabetes, due to unhealthy eating habits is the key factor for the growth of the I.V. fluids market. Developing countries are increasing their investment in the healthcare and hospitality sector which is expected to drive the demand for I.V. fluids.

In hospitals and clinics, wound irrigations solutions are used to remove surface pathogens and cellular debris in wound exudates. Compared to bathing or swabbing, wound irrigation is considered the most effective wound cleaning method, especially in hospitals' burn and surgical wards. The incidence of accidents and injuries during sports, commutes, and adventures has increased drastically in the last decade. Road accidents and violence are major causes of trauma, which requires medical attention. Traumatic injuries and burns are also major causes of acute wounds, which require advanced therapies in hospitals. If not treated properly, these acute wounds increase the burden of chronic wounds and the overall health care burden. The global wound irrigation solutions market is anticipated to be driven by an increase in the geriatric population rise burden of chronic diseases and the introduction of technologically advanced wound care products. Chronic diseases that affect skin integrity, such as peripheral vascular diseases (arterial insufficiency and venous hypertension) and diabetes, have become increasingly common among the geriatric population. This causes more need for Hospital endocrinology services. Frequent consequences include skin breakdown with the formation of ulcers and chronic wounds. Non-communicable diseases also need surgical interventions, which consequently drives the global wound irrigation solution market. Normal sterile saline is the most appropriate and preferred cleansing solution because it is a non-toxic, isotonic solution that does not damage healing tissues.

Additionally, the global COVID-19 pandemic has sharply focused the world's attention on critical care as a specialty. As a novel disease, fluid management principles in critical care provide the foundation for fluid therapy in COVID-19. While issues such as staffing, resources, and ventilation strategies are undoubtedly important when considering a holistic approach to treating COVID-19, fluid management remains a cornerstone of intensive care. World Health Organization guidelines recommend that patients with COVID-19 in respiratory failure be treated cautiously with I.V. fluids, especially in settings with limited availability of mechanical ventilation. COVID-19 can affect the global economy of I.V. fluids in three main ways: by directly affecting production and demand, by creating supply chain and market disruption, and by its financial impact on firms and financial markets.

Better management of the supply chain leads to greater efficiency, fewer losses, higher profits, and higher levels of services. The better supply chain management and the smooth flow of information between different actors can increase the availability of I.V. fluids and irrigation solutions for end-users, including hospitals, ambulatory surgical centers, clinics, and long-term care centers. Hospitals are estimated to report the highest market share contributing to over a third of the total end-user market value.

Integrated Production Planning and scheduling is one of the logical steps in managing the supply chain. Production planning occurs at an aggregate level; creating a production plan involves grouping products into product families. These groupings are based on products' similarities in design, manufacturing process, and resource usage. Scheduling involves making decisions regarding allocating available capacity or resources (equipment, labor, and space) to jobs, activities, tasks, or customers over time.

Assumptions

Problem assumptions are as follow:

Technological assumptions:

- The model parameters, such as due dates, prices, lost sales costs, processing times, and inventory costs per period, are assumed to be deterministic.
- There is unlimited buffer capacity between two successive processing stages.
- Transfer times are assumed to be neglected.
- Machines are available at all times, with no breakdowns or scheduled/unscheduled maintenance.
- All jobs are available at zero time. Job processing cannot be interrupted (no preemption is allowed), and jobs have no associated priority values.
- Machines in parallel are identical in capability and processing rate.

Timing relations and assignments:

- The production planning horizon is divided into several planning periods. Each planning period is considered as a scheduling horizon. For the problem, the duration of planning horizon is considered three months, and the duration of a planning period is one month. Each period consists of several work weeks. For the problem, like the real situation, it is assumed that the beginning or ending time of a planning period is not necessarily coincident with the beginning or ending time of a workweek. Therefore, a workweek beginning at a planning period might end at the next planning period.
- Every batch must be processed on a processing unit without interruption until it is processed completely.
- Each operation must be done within a workweek. It can't be interrupted at the end of a workweek and resumed in the next workweek.
- Changeover times between the operations are sequence-independent. The changeover time is the time taken to modify a line or a machine to run a new batch of the same product or a different product. Many pieces of equipment have long set-up times in the pharmaceutical industry because equipment must be torn down, cleaned up, and set back up to GMP criteria. For the production line of I.V. fluids and irrigation solutions, these preparations begin as soon as the machine is available without the need for the presence of the batch that has to be processed. Thus, changeover times are supposed to be anticipatory.

Inventory/Lost sale related assumptions:

- Due to the importance of the product, orders are lost if they don't meet due dates. In this case, lost sale cost is imposed on the manufacturer, and the shortage is not compensable in future periods
- Raw materials, including the active pharmaceutical ingredient (API), are needed to manufacture batches of products. The raw materials are divided into raw materials with long consumption dates, and raw materials on the verge of expiration. The raw material on the verge of expiration is referred to the material that is to be expired at the end of the planning horizon. Therefore, this type of raw material must be discarded if not used during the planning horizon.

Selection of products to manufacture:

The drug distribution company's orders are generally announced for a three-month period to the production company, where the requirement of each product is specified at the end of each monthly period. Due to the possibility that the stated demand (by the drug distribution company) does not cover the total production capacity of the production line, to avoid or decrease unused capacity and machines idle times, the manufacturing company will produce more than that ordered and will deliver additional batches of products during the monthly periods (in some cases with offering discounts), or due to prior experience, high-demand products in the upcoming three-months periods. Therefore, the product quantities ordered by the distribution company are usually a subset of the overall aggregate production program for future periods (3 periods). The aggregate production program is considered as the model input.

The demand and batch size of each product are specified, so it is easy to compute the demands of products according to their batch sizes. One batch of each product is considered a task allocated to a machine at each stage of production.

Objective function:

In this problem, the objective function is to maximize profit, which is equal to the sales value of products minus the raw material cost and the raw material on the verge of expiration (with the larger coefficient), inventory cost, and lost sales cost. To optimize the objective function, products are selected that have higher margins, and these products are produced as much as possible based on model constraints. This reduces the production of products with lower margins or causes not to produce those products. This leads to reducing the variation of products manufactured during a time period. Therefore, based on the solution of the model, it is likely that some products ordered by the drug distribution company are not produced at all, and some other products will be produced more than demand, which is not acceptable because it should be given priority in production planning for the stated demand by the distribution company. To prioritize the orders declared by the distribution company and increase the diversity of produced products, a lost sale cost is imposed on each unsatisfied batch ordered by the distribution company. Suppose it is impossible for the manufacturer to provide all the demand reported by the distribution company. In that case, the manufacturer is capable to quickly inform the distribution company to provide unsatisfied demand through another producer.

Raw materials:

Under a pull supply chain, actual customer demand drives the process, while long-term projections of customer demand drive push strategies. The manufacturers purchase raw materials based on demand forecasting, but they eventually produce the products based on the market demand. Therefore, there is a possibility of non-use of received raw materials in several successive periods. These raw materials are sometimes expired because of the lack of consumption. To avoid expired raw materials or reduce them, the raw material on the verge of expiration is considered to be isolated from the raw material with a longer consumption date in the planning model. It should also be considered in the constraints of the model that the consumption of raw material on the verge of expiration is given priority to the raw material with a longer consumption date.

Methods

Problem formulation:

The simultaneous production planning and scheduling problem is formulated as a mixed-integer linear programming model. First, the indices, parameters, and decision variables are introduced. Then, the objective function and constraints of the mathematical model are demonstrated.

Symbols

Symbols are categorized into indices, parameters, and decision variables, which are introduced as follows:

Indices

i,j	Jobs
t	time periods
w	Workweeks
l	manufacturing stages
r	raw materials
p_k	product k

Parameters

PT_{il}	Processing time of batch i at stage l
CHG_{il}	Changeover time of batch i at stage l
Lag_{il}	The minimum lag time between start times of processing batch i at stage l and its previous
SP_btc_i	Sale price of batch i
Due_btc_{it}	Binary variable to denote if due date of job i is at the end of time period t
$DMN_{p_k,t}$	Demand of product p_k at the end of time period t
$Max\_sale_{p_k,t}$	Maximum amount of product p_k that can be sold at the end of time period t
$Dsc\_rate_{p_k}$	Discount rate for additional sales of product p_k
BGN_wk_{tw}	Beginning time of work week w in time period t
END_wk_{tw}	Ending time of work week w in time period t
MAX_flw_i	Maximum allowable flow time for batch i
HLD_cost_i	Holding cost of batch i
LST_cost_i	Lost sale cost of batch i
PUR_r	Purchase cost of every unit of raw material r
EXP_coef_{rt}	Cost coefficient of raw material r on the verge of expiration at the beginning of time period t
INV_{i0}	Inventory level of batch i at the beginning of planning horizon (beginning of first time period)
$R\_LNG\_Inv_{r0}$	Inventory level of raw material r (with long consumption date) at the beginning of planning horizon (beginning of first time period)
$R\_EXP\_INV_{r0}$	Inventory level of raw material r on the verge of expiration at the beginning of planning horizon (beginning of first time period)
$RCV_{r,t}$	Amount of received raw material r at the end of time period t
RQU_{ri}	Requirement of raw material r to manufacture batch i
w_t	The workweeks which overlap time period t
A	a large number

Decision variables

X_{ilw}	Binary variable to denote if batch i is processed at stage l in workweek w
W_{ijlw}	Binary variable to denote if batch j is processed after batch i (not necessarily immediately) on at stage l in workweek w
ST_{ilw}	Start time of processing batch i at stage l in workweek w
FN_{ilw}	Finish time of processing batch i at stage l in workweek w
$INV\_prdc_{p_k,t}$	Inventory level of product $\mathrm{p_k}$ at the end of time period t
$LOS\_prdc_{p_k,t}$	Amount of lost sales of product $\mathrm{p_k}$ at the end of time period t
INV_lng_{rt}	Inventory level of raw material r with long expiration date at the beginning of time period t
INV_exp_{rt}	Inventory level of raw material r on the verge of expiration at the beginning of time period t

PLN_btc_i	Binary variable to denote if processing of batch i is manufactured in the planning horizon
$STRT\_btc_{it}$	Binary variable to denote if processing of batch i is started in time period t
CMP_btc_{it}	Binary variable to denote if processing of batch i is completed in time period t
SAL_btc_{it}	Binary variable to denote if batch i is sold at the end of time period t

Simultaneous production planning and scheduling model

The simultaneous production planning and scheduling problem is formulated as a novel mixed-integer linear programming model. The proposed mixed-integer linear programming model is as follow:

$$\begin{aligned} Max\ Z = {} & \textstyle\sum_i SP\_btc_i * PLN\_btc_i - \sum_k \sum_t \left(Dsc\_rate_{p_k} \times ADD\_prdc_{p_k,t}\right) - \sum_k \sum_t (HLD\_cost_i \times INV_{it}) - \\ & \textstyle\sum_k \sum_t (LST\_cost_i \times LOS_{it}) - \sum_t \sum_r (EXP\_coef_{rt} * INV\_exp_{rt}) - \\ & \textstyle\sum_r \sum_i (PLN\_btc_i \times RQU_{ri} \times PUR_r) \end{aligned} \tag{1}$$

$$\textstyle\sum_t CMP\_btc_{it} = PLN\_btc_i \qquad \forall\, i \tag{2}$$

$$\textstyle\sum_t STRT\_btc_{it} = PLN\_btc_i \qquad \forall\, i \tag{3}$$

$$CMP\_btc_{it} \leq \textstyle\sum_{w \in \{w_t\}} X_{iSw} \qquad \forall\, i, t \tag{4}$$

$$STRT\_btc_{it} \leq \textstyle\sum_{w \in \{w_t\}} X_{i1w} \qquad \forall\, i, t \tag{5}$$

$$STRT\_btc_{it} + CMP\_btc_{i,u} \leq 1 \qquad \forall\, i, t > u \tag{6}$$

$$X_{ilw} = X_{iSw} \qquad \forall\ i, l \in [1, S-1], w \tag{7}$$

$$ST_{ilw} \geq BGN\_wk_w + CHG_{il} - M * (1 - X_{ilw}) \qquad \forall\, i, l, w \tag{8}$$

$$FN_{ilw} \leq END\_wk_w + M * (1 - X_{ilw}) \qquad \forall\, i, l, w \tag{9}$$

$$ST_{ilw} = FN_{ilw} - (PT_{il} * X_{ilw}) \qquad \forall\, i, l, w \tag{10}$$

$$ST_{i1w} \geq END\_per_{t-1} - M * (2 - STRT\_btc_{it} - X_{i1w}) \qquad \forall\, i, t \in [2, T], w \in \{w_t\} \tag{11}$$

$$ST_{i1w} < END\_per_t + M * (2 - STRT\_btc_{it} - X_{i1w}) \qquad \forall\, i, t \in [2, T], w \in \{w_t\} \tag{12}$$

$$FN_{iSw} > END\_per_{t-1} - M * (2 - CMP\_btc_{it} - X_{iSw}) \qquad \forall\, i, t \in [2, T], w \in \{w_t\} \tag{13}$$

$$FN_{iSw} \leq END\_per_t + M * (2 - CMP\_btc_{it} - X_{iSw}) \qquad \forall\, i, t \in [2, T], w \in \{w_t\} \tag{14}$$

$$FN_{jlw} - FN_{ilw} + \mathrm{A}\left(1 - W_{ijlw}\right) \geq PT_{jl} + CHG_{jl} \qquad \forall\, i, j (i \neq j), l, w \tag{15}$$

$$\textstyle\sum_w FN_{iSw} - \sum_w ST_{i1w} \leq MAX\_flw_i \qquad \forall\, i \tag{16}$$

$$FN_{i1w} \geq PT_{i1} + CHG_{i1} - \mathrm{A}(1 - X_{i1w}) \qquad \forall\, i, m \in [1, m_1], w \tag{17}$$

$$ST_{ilw} - ST_{i,l-1,w} + \mathrm{A}\left(2 - X_{ilw} - X_{i,l-1,w}\right) \geq Lag_{il} \qquad \forall\, i, l > 1, w \tag{18}$$

$$2\left(W_{ijlw} + W_{jilw}\right) - \left(X_{ilw} + X_{jlw}\right) \leq 0 \qquad \forall\, i, j (i \neq j), l, w \tag{19}$$

$$W_{ijlw} + W_{jilw} + \mathrm{A}\left(2 - X_{ilw} - X_{jlw}\right) \geq 1 \qquad \forall\, i, j (i \neq j), l, w \tag{20}$$

$$\textstyle\sum_t SAL\_btc_{it} \leq \sum_{y \leq t} CMP\_btc_{iy} \qquad \forall\, i, t \tag{21}$$

$$INV\_prdc_{p_k,t} = INV\_prdc_{p_k,t-1} + \textstyle\sum_{i \in p_k} CMP\_btc_{it} - \sum_{i \in p_k} SAL\_btc_{it} \qquad \forall\, p_k, t \tag{22}$$

$$\textstyle\sum_{i \in p_k} SAL\_btc_{it} \leq Max\_sale_{p_k,t} \qquad \forall\, p_k, t \tag{23}$$

$$LOS\_prdc_{p_k,t} = DMN_{p_k,t} - \textstyle\sum_{i \in p_k} SAL\_btc_{it} + ADD\_prdc_{p_k,t} \qquad \forall\, p_k, t \tag{24}$$

$$INV\_lng_{rt} + INV\_exp_{rt} = INV\_lng_{r,t-1} + INV\_exp_{r,t-1} + RCV_{r,t-1} - \textstyle\sum_i (RQU_{ri} \times STRT\_btc_{it}) \qquad \forall\, r, t \tag{25}$$

$$INV\_exp_{rt} \geq INV\_exp_{r,t-1} - \textstyle\sum_i (RQU_{ri} \times STRT\_btc_{it}) \qquad \forall\, r, t \tag{26}$$

$$PLN\_btc_i, STRT\_btc_{it}, CMP\_btc_{it},\ X_{ilw},\ W_{ijlw} \in \{0,1\} \qquad \forall\, i,j(i \neq j),k,l,t,w \tag{27}$$

$$ST_{ilw}, FN_{ilw}, INV\_prdc_{p_k,t}, LOS\_prdc_{p_k,t}, ADD\_prdc_{p_k,t}, INV\_lng_{rt}, INV\_exp_{rt} \geq 0 \qquad \forall\, i,k,r,l,t,w \tag{28}$$

The objective (1) is to maximize profit. The profit equals sum of sales revenues minus inventory costs, lost sale costs, material purchasing costs, and expired raw material costs (with coefficients). Labor costs and overhead costs are considered fixed for every planning period and are not considered in the objective function. Constraints (2) ensure that if a batch is manufactured during the planning horizon, its manufacturing is completed in only one planning period. Constraints (3) ensure that if a batch is manufactured during the planning horizon, its manufacturing starts in only one planning period. Constraints (4) state that if a batch is processed at the last stage in one of the workweeks, its manufacturing can be completed in a time period that overlaps that workweek. It is likely to exist more than one time period which overlaps the workweek, but manufacturing of the batch must be completed in only one time period, so “less than or equal to” is used. Constraints (5) state that if a batch is processed at the first stage in one of the workweeks, its manufacturing can start in a time periodthat overlaps that workweek. Constraints (6) state that if manufactured a batch is completed in one of planning periods, its manufacturing can’t be started in one of the following periods. Constraints (7) indicate that if a batch is processed at the last stage in one of the workweeks; it is processed at all previous stages in that workweek. Constraints (8) enforce the start time of processing a batch at a stage in a workweek not to be less than the beginning of that workweek. Constraints (9) enforce the finish time of processing a batch in a stage in a workweek not to be greater than the ending time of that workweek. Constraints (10) define the relationship between start and finish processing times at each stage. Constraints (11) enforce the start time of processing a batch in the first stage not to be less than the ending time of the previous time period its manufacturing is started, and constraints (12) enforce the start time as mentioned above to be less than the ending time of the time period covering the start point of manufacturing the batch. Constraints (13) enforce start time of processing a batch in the last stage to be greater than the ending time of the previous time period its manufacturing is completed, and constraints (14) enforce the finish time as mentioned above not to be greater than the ending time of the time period covering the completion point of manufacturing the batch. Constraints (15) define the relationship between finish processing times of two batches that are processed at a stage. Constraints (16) enforce the flow time of a batch not to be greater than its maximum allowable flow time. Constraints (17) state that the departure time of a batch in the first stage is greater than its processing time, plus its change over time in that stage. Constraints (18) define the relationship between start times of a batch between two consecutive stages in a workweek of a planning period. Constraints (19-20) link assignment variables with sequencing variables for batches that are processed at a processing stage in a workweek. Constraints (19) state that if at most one of two batches is processed at a specified stage, then the sequencing variables of these batches equal to zero. Constraints (20) state that for any pair of batches processed at the same stage in a workweek, one of the batches is processed after another (not necessarily immediately). Thus, one of the two sequencing variables regarding those jobs equals one. Constraints (21) indicate that a batch can be sold at the end of a time period if it is manufactured during that time period or previous time periods. Constraints (22) link inventory levels, amount of production, and sales for each product. Constraints (23) indicate that amount of sales of a product can’t be greater than its maximum saleable at the end of a time period. Constraints (24) link the amount of sales, lost sales, and additional sales for each product. According to the objective function, values of the variables of lost sales and additional sales must be as less as possible. Constraints (25) relate the inventory levels of raw materials with long consumption date and raw materials on the verge of expiration at the end of a time period to their inventory levels at the end of the previous time period. Because of the objective function, the raw materials on the verge of expiration at the end of the previous time are considered raw material with long consumption dates at the end of the current time period. Constraints (26) prevent Constraints (25) from taking this consideration into account in the model. Constraints (27) imply the binary property of some of the decision variables. Constraints (28) imply the non-negativity of the corresponding variables.

Solution methodology:

Solution representation

It is simple to represent a schedule in a permutation flow shop environment. It can be easily encoded by a vector that represents the sequence of jobs at processing stages. Nevertheless, the problem is not only a classic flow shop scheduling but planning and scheduling in a production line of intravenous fluids and irrigation solutions during a planning horizon. There are some time periods and several workweeks. Therefore, there is a sequence for each workweek. Several vectors are required to represent these sequences. Unlike scheduling within a finite continuous time, scheduling a set of jobs is more complex during certain time periods and workweeks. To overcome these obstacles, a matrix (multi-permutation) of batches is used. Each permutation of the matrix includes the batches related to a specific period and represents their processing order to be manufactured during the corresponding time period. Each row of the matrix is related to a specific time period.

Procedure for constructing a complete schedule

T : number of periods
i_t : corresponding batch to the position i in permutation of period t
n_t: quantity of batches to be manufactured in period t
W : number of workweeks
w_k: workweek k
S : number of stages
$bgn(w)$: beginning time of workweek w
$end(w)$: ending time of workweek w
$bgn\ (t)$: beginning time of time period t
$end(t)$: ending time of time period t
$f_{i_t,l}$: finish time of processing batch $\mathrm{i_t}$ in stage l

At first, assume t and b_t equal to zero.
The procedure for constructing a complete schedule of a batch multi-permutation is essentially a method based on the steps as follows:

***Step* 1.** Set $t = t + 1$. Update inventories of raw materials with long consumption dates and raw materials on the verge of expiration. If $t \leq T$, go to step 2. Otherwise, go to step 9.

Step 2. If $bgn\ (t) \geq end(w)$ go to step 3. Otherwise, go to step 4.

Step 3. Set $w = w + 1$. If $bgn\ (w) < end(t)$ go to step 4. Otherwise, go to step 1.

Step 4. Set $i_t = i_t + 1$. If $i_t \leq n_t$ and there are adequate raw materials for manufacturing batch i_t, set $l = 1$ and go to step 6. Otherwise, go to step 1.

Step 5. Set $l = l + 1$. If $l \leq S$ go to step 6. Otherwise, update inventory of raw materials. Subtract required raw materials for manufacturing $\mathrm{i_t}$ from the inventory of raw materials by prioritizing the use of raw materials on the verge of expiration. Then, go to step 4.

Step 6. Calculate $ef_{b_t,l}$. If $ef_{b_t,l} \leq end(w)$, go to step 7. Otherwise, go to step 3.

Step 7. Consider processing time and change over time of batch b_t in stage l and calculate $f_{b_t,l}$ (finish time of processing batch b_t in stage l). Go to step 8. Otherwise, go to step 4.

Step 8. If $f_{b_t,l} \leq end(w)$ and $f_{b_t,l} \leq end(t)$, assign batch b_t to machine in stage l and update the available time of the machine. If $f_{b_t,m,l} > end(t)$ go to step 1. Otherwise $(if\ f_{b_t,l} \leq end(t)$ and $f_{b_t,l} > end(w))$, delete batch i_t from previous stages (stage 1 up to stage l-1) on the schedule, edit the available time(s) of scheduled machine(s) for processing batch i_t from the first stage up to stage l-1, and go to step 3.

Step 9. Exit.

Memetic algorithm:

The solution method used in this work is a memetic algorithm. The memetic algorithm is one of the most popular metaheuristics obtained by combining a genetic algorithm with a local search method. As biologists see genes as a unit of transmission of physiological properties such as eye color, hair color, and … from parents to children, psychologists have also called for the transmission of behavioral traits such as irritability and ambition from parents to people. For each individual of the population, a local search is carried out in the solution space.

The local search applied in the memetic algorithm can eliminate the weakness of evolutionary methods such as genetic algorithm by diversifying the search process. The memetic algorithm first encodes a set of initial solutions. The algorithm then calculates the fitness value of each for every solution based on a fitness function and generates new solutions using operators such as crossover and mutation. At the end of each generation, a local search is carried out on a set of solutions of that generation to diversify the search process to enhance the quality of local optimal solutions.

Then, a subset of solutions of the current generation (current solutions, parents and new answers, children) are transferred to the next generation according to the concept of the struggle for survival. The process of producing new generations continues until the stopping criterion is reached.

Chromosome representation

Each chromosome is indicated by a matrix. Each row of the matrix is related to one period of the planning horizon and represents the sequence of batches whose due dates are at the end of the period. Thus, the number of rows of each matrix is equal to the number of periods within the planning horizon. The number of columns of the matrix is equal to the maximum number of batches belonging to a period. Since the numbers of batches related to different periods are not necessarily equal, the lengths of strings for different rows can be different. In a matrix, the number of entries in a row is equal to other rows. So, the length of a row (number of columns) is considered equal to the maximum number of batches belonging to a period. For the rows having fewer batches, the rest of the row entries are represented by “0” at the end of the row. Fig 1 shows the structure of a chromosome consisting of a sequence matrix $[X]_{4\times10}$. The number of batches to be manufactured in periods 1, 2, 3, and 4 are respectively 9, 7, 9, and 10. Therefore, the last entry in the first and third row and the three last entries in the second row are represented by “0” which means there is no corresponding batch to manufacture.

4	7	2	5	1	8	9	6	3	0
13	15	12	14	16	10	11	0	0	0
17	19	24	21	22	20	25	18	23	0
34	26	29	35	32	33	30	27	31	28

Figure 1. A randomly generated initial solution

Initial population

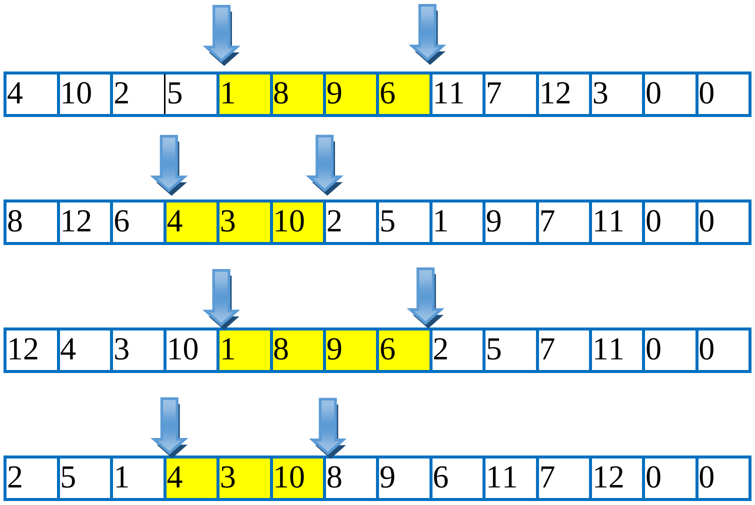
First, the initial population is generated, in which individuals are created randomly. This means the sequence of batches in each row of a matrix is created randomly.

Parent Selection Mechanism

Selection of parents per generation is made using tournament selection. A certain number of chromosomes are selected, and among them, the chromosome with the best fitness function is chosen as the parent. This practice is repeated until all the parents who need to be chosen are picked for mating. The probability of crossover is considered equal to one, and by applying crossover between two parents, two children are created. Thus, parents must be selected as the number of children that are to be created. An individual can be chosen more than once as a parent at each generation.

Crossover

For the effective discovery of the search space, the crossover operator is used. Given that each of the numbers in a row of each matrix is unique, it is best to use one of the classical operators Partially Mapped Crossover (PMX), Cycle Crossover (CX), Order Crossover (OX), or Linear Order Crossover (LOX). Due to the better ability of the LOX operator to solve the scheduling problems, the operator is used as a crossover operator. The LOX operator is illustrated in Fig 2.


4 10 2 5 1 8 9 6 11 7 12 3 0 0

8 12 6 4 3 10 2 5 1 9 7 11 0 0

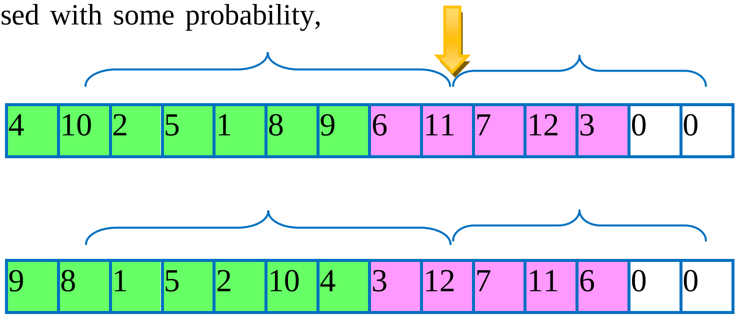
12 4 3 10 1 8 9 6 2 5 7 11 0 0

2 5 1 4 3 10 8 9 6 11 7 12 0 0

Figure 2. LOX operator

Mutation

To preserve diversification in the search process, the mutation is performed. In a memetic algorithm, the mutation is performed after crossover, usually with a small probability. In this work, applying mutation is different from its typical usage in a memetic algorithm. If there is no better solution after a certain number of successive generations, the mutation is performed on the current population. Therefore, the mutation is not used with some probability, but the condition must be met. The mutation is carried out so that one point in a vector is selected, and the sequences of two parts on both sides of the point are arranged inversely. The selected point can't be situated at the position before the first entry of the sequence or after an entry with zero value. If the selected point is after the last non-zero value of the sequence, then the whole sequence is reversed. The mutation operator is illustrated in Fig 3.


4 10 2 5 1 8 9 6 11 7 12 3 0 0

9 8 1 5 2 10 4 3 12 7 11 6 0 0

Figure 3. Mutation operator

Fitness function

The fitness function in the proposed method is the objective function of the problem, maximizing profit. For each permutation matrix, the batches are scheduled according to the procedure previously described, and the batches which can be manufactured are specified. The fitness function is then evaluated for each matrix.

Local search

At the end of each generation, the local search is applied to the permutation vectors of the best solutions among the current population. A certain number of neighborhoods are created by insertion move, and the best solution is selected, if it is better than the current solution. This kind of move has been proven very effective for scheduling problems. The move can't be applied to entries represented by "0". If none of the generated solutions is better than the current solution, the same number of neighborhoods are generated by insertion move for three successive entries. Three successive entries are selected and relocated into another randomly selected position. The order of the three entries is maintained.

Stopping criterion

The search process terminates when a predefined number of generations are reached, or the best solution found so far has not changed during a predefined number of consecutive generations.

The flow diagram of the proposed memetic algorithm is shown in Fig 4.

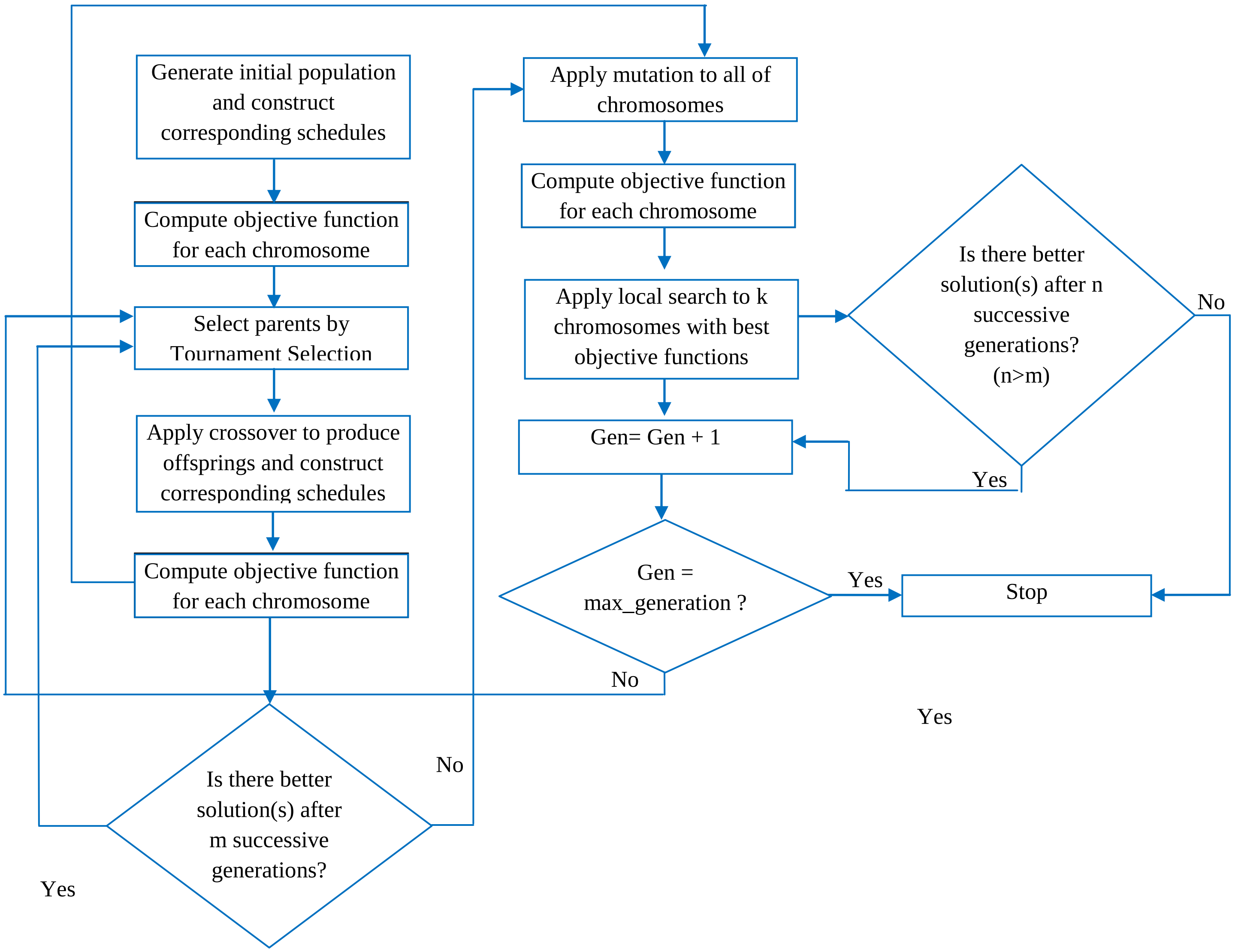


Figure 4. Flow diagram of the proposed memetic algorithm

Results

Case study

The problem investigated in this paper is based on a production line of intravenous fluids and irrigation solutions at Darou Pakhsh Pharmaceutical Manufacturing Company. It's a batch production system, and each batch of product is transferred to the next stage after a certain time elapsed since the start of processing the batch at the current stage. The batch size for each product is different and is determined according to the limitations of the production capacity of machinery and the volume of intermediate tanks for different products. Manufacturing various types of intravenous fluids and irrigation solutions, as shown in Fig 5, consists of six stages.

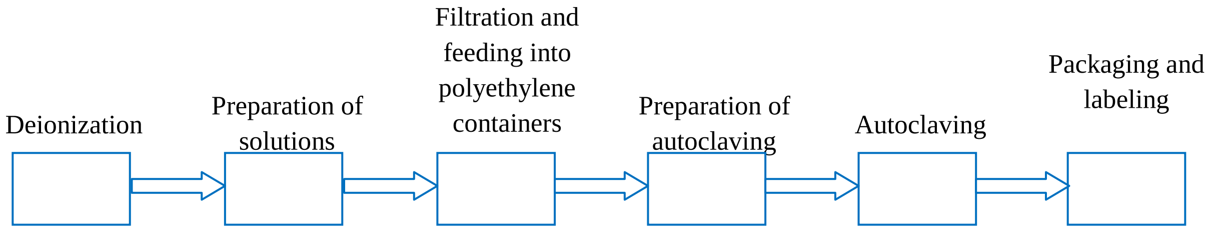


Fig 5ure. Processes of manufacturing intravenous fluids and irrigation solutions

At the first stage, as it is known by its name, deionized water is made. Before the second and third stages, the construction of the solution and filtration, and the feeding of polyethylene, the equipments should be washed. The duration of the washing is only dependent on the type of product and is not dependent on the previous product. In the second stage, the deionized water is mixed with active pharmaceutical ingredients, usually dextrose, sodium chloride, or a mixture of calcium chloride, potassium chloride, and sodium chloride. In this stage, the solution is prepared. The process of the third stage is multi-stepped. In the third stage, the solution passes through a filter. This process is called filtration. Moreover, in this stage the containers are formed, filled and sealed in an automated system to reduce the risk of microbial contamination and foreign particulates. The process begins with the extrusion of polyethylene or polypropylene granules in the form of a hot hollow pipe of molten plastic called a parison. The parison is closed between the mould, and the container gets formed either by blowing sterile compressed air or by vacuum. The container assumes the shape of the cavity in the mould. The container produced is open from the top and its top part, the plastic is still hot and in molten state until the subsequent steps of filling and container sealing. The subsequent step is the filling of the formed container from the top, which is still open. Filling nozzles are specially designed and constructed to facilitate automatic cleaning and automatic sterilization. The next step of the third stage is sealing the top of the container, which is still open and in a hot molten state. The top gets pressed between head moulds and as a consequence, the top part of the container gets formed, sealed and at the same time, gets cooled. The result is a hermetically sealed container. The final steps are deflashing to remove the flash or scrap, trimming the containers and delivering the containers outside the machine.

Then, the containers and the autoclave are prepared before the autoclaving process starts. The containers need to be checked before placed into the autoclave, and the autoclave has to become cooled. In the next stage, the containers are transmitted to the autoclave machine. Autoclaving is a sterilization method that uses high-pressure steam. The autoclaving process works by the concept that the boiling point of water (or steam) increases when it is under pressure. Items to be autoclaved are subjected to gradual temperature increases under high pressure until 121 °C is reached and then steamed for around 15–20 minutes. Autoclaving can inactivate fungi, bacteria, spores, viruses and other microorganisms. The I.V. fluids and irrigation solutions are resistant to heat. After autoclaving, the products become cold, and then they are labeled and packaged.

Although there are parallel machines in some stages, the environment is considered a flow shop. This is because at any time, it is only possible to process one batch in a stage on parallel machines, and the processing time of every batch at each stage is measured, taking into account all the parallel machines to process the batch. Therefore, the set of parallel machines in each stage is considered a processing unit, and the hybrid flow shop turns into a flow shop environment.

There are seven types of I.V. fluids and irrigation solutions to be manufactured in this production line; see Table 1. Each kind of intravenous fluid or irrigation solution is packaged in 500 ml and 1000 ml containers; hence, there are 14 final products.

Table 1. List of intravenous fluids and irrigation solutions

Product no	Product name
1	Sodium Chloride 0.9% Intravenous Infusion (Normal Saline or NS)
2	Sodium Chloride 0.9% cleansing
3	Sodium Chloride 0.45% Intravenous Infusion (Half-Normal Saline or HNS)
4	Dextrose 5% Intravenous Infusion (D5)
5	Dextrose 5% in 0.9% Sodium Chloride (D5NS)
6	3.3% Dextrose / 0.3% saline (2/3 + 1/3)
7	Ringer's solution (containing sodium chloride, potassium chloride, and calcium chloride)

The products are manufactured in batches. With pharmaceutical manufacturing, a batch refers to a specific quantity of a drug or other material intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture. Notably, a batch refers to the quantity of material and does not specify the mode of manufacture. With the production of a batch, Good Manufacturing Practice (GMP) requires that a detailed record be kept of every stage of the manufacturing, testing, and release process.

Computational experiments

In this section, the computational performance of the proposed memetic algorithm is compared to the results achieved by running the integrated model. The MILP model was run in GAMS1. GAMS aids to simplify modeling, solving, and analyzing mathematical programming problems specifically designed to solve linear, nonlinear, and mixed-integer optimization models. The proposed memetic algorithm was coded in Matlab. The experiments were run on a personal computer with AMD Rizen 7 1700 and 16 GB RAM.

The proposed memetic algorithm is evaluated by real-world data from Darou Pakhsh Pharmaceutical Manufacturing Company. Specifically, data from 2019 and 2020 are picked up because they reflect the actual and recent planning and scheduling to achieve productivity, and four instances are created. The instances created by the data are large, so the optimality can't be obtained by the simultaneous model. Thus, 30 instances of small and medium-size are generated to test the capability of the proposed method to reach the optimality obtained by the exact method. All the parameters are the same as the real problems except several batches, inventory of raw materials, and the duration of periods and workweeks. Processing times and changeover

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[1] General Algebraic Modeling System

times of products in each stage are shown in Table 2. The processing times of all products with the same container volume are equal, and so are the changeover times.

Table 2. Processing times and changeover times of products

Container	Stage 1		Stage 2		Stage 3		Stage 4		Stage 5		Stage 6	
	Chng times	Prcs time (h)	Chng times	Prcs time (h)	Chng times	Prcs time (h)	Chng times	Prcs time (h)	Chng times	Prcs time (h)	Chng times	Prcs time (h)
500 ml	2.6	22.3	3.1	18.4	2.4	19.2	1.2	19.3	0.8	21.5	0.9	16.0
1000 ml	2.6	22.3	3.1	18.4	2.4	19.0	1.2	18.7	0.8	21.5	0.9	15.3

At any time, it is only possible to process one batch in a stage. There is overlap between processing a batch at two consecutive stages, and it is not necessary to finish processing a batch at a stage before transmitting it to the next stage. There is a minimum lag time between the start times of processing a batch in two consecutive stages, as indicated in Table 3.

Table 3. Minimum Lag times between processing start times in consecutive stages

Minimum Lag time (h)	Stage 1-Stage 2	Stage 2-Stage 3	Stage 3-Stage 4	Stage 4-Stage 5	Stage 5-Stage 6
500 ml	4.3	4.1	2.8	3.3	3.7
1000 ml	4.3	4.1	2.6	3.3	3.5

After a specified amount of time since the beginning of a batch process at a stage, processing the batch in the next stage can get started in the next stage.

Table 4 indicates the comparison results for small and medium-size instances. A set of instances, ranging from 6 batches to 40 batches, are selected. The instances from 6 to 15 batches are considered small size instances. The instances from 15 to 30 batches are considered medium-size instances, and the rest of instances from 40 to 80 batches are considered large ones. The running time for each instance is limited to 2 hours. Instances with a run time of less than 7200 seconds for the exact method are the ones that were solved optimally.

Table 4. Numerical results for small, medium, and large-sized instances

Instance	No. of batches	No. of periods	No. of workweeks	Duration of each workweek (h)	MILP model		Proposed memetic algorithm		
					Objective Function	Run time (s)	Objective Function	Run time (s)	Gap (%)
1	6	1	1	45	153	0.03	153	34.87	0.00
2	6	1	1	55	516	0.09	516	52.31	0.00
3	6	1	2	40	378	0.24	378	28.66	0.00
4	8	1	1	60	787	4.18	787	67.49	0.00
5	8	1	2	40	127	0.37	127	37.09	0.00
6	8	1	2	45	464	2.31	464	50.61	0.00
7	10	1	2	45	415	26.92	415	62.13	0.00

Instance	No. of batches	No. of periods	No. of workweeks	Duration of each workweek (h)	MILP model		Proposed memetic algorithm		
					Objective Function	Run time (s)	Objective Function	Run time (s)	Gap (%)
8	10	1	3	40	509	18.15	509	84.29	0.00
9	10	2	3	45	891	48.10	891	125.37	0.00
10	12	1	3	45	732	135.22	732	109.45	0.00
11	12	1	2	50	754	259.63	754	162.86	0.00
12	12	1	2	55	966	464.96	966	244.19	0.00
13	15	1	2	50	577	389.60	577	271.38	0.00
14	15	1	3	50	1645	627.43	1645	417.22	0.00
15	15	2	3	45	1016	239.49	1016	348.61	0.00
16	20	1	3	55	1588	2184.07	1588	625.80	0.00
17	20	2	3	50	1120	1006.45	1120	480.78	0.00
18	20	2	4	50	1336	2491.84	1336	704.57	0.00
19	25	2	3	50	679	1681.56	679	531.30	0.00
20	25	2	4	50	1167	2670.38	1167	865.10	0.00
21	25	2	5	50	1882	2745.90	1882	1038.32	0.00
22	30	2	4	60	2012	7200	2193	1496.74	(9.00)
23	30	2	5	50	1577	7200	1653	1216.08	(4.82)
24	30	2	6	45	859	3659.75	859	1061.55	0.00
25	40	2	5	60	2669	7200	3334	2076.46	(24.92)
26	40	2	6	55	2547	7200	3084	1781.02	(21.08)
27	40	3	7	50	2510	7200	2726	1663.60	(8.61)
28	50	2	6	60	3135	7200	4297	3086.48	(37.07)
29	50	3	8	50	2074	7200	2560	2683.95	(23.43)
30	50	3	9	50	2616	7200	3398	2877.41	(29.89)
31	60	3	7	60	3107	7200	5133	3889.95	(65.21)
32	60	3	7	55	2286	7200	3241	3619.27	(41.78)
33	60	4	10	50	2914	7200	3988	3475.44	(36.86)
34	80	3	10	60	3365	7200	8224	6339.21	(144.40)
35	80	4	11	55	3009	7200	6270	5612.58	(108.37)
36	80	4	13	50	3225	7200	5642	5946.16	(74.95)
								average	(17.27)

According to the results depicted in Table 4, the proposed memetic algorithm obtained optimal solutions in all the instances, which were optimally solved by the integrated model of production planning and scheduling. The computational time of running memetic algorithm was longer than the exact method for small-size instances, but as the size of instances grows (the remaining small-size instances and all of the medium-size instances), the proposed memetic algorithm takes much less time than the exact method. The proposed memetic algorithm obtained better solutions for instances in which the exact method couldn't reach an optimal solution in the specified time. The average gap for all the instances, as shown in Table 4, is -17.27%. The average gap for small-sized, medium-sized and large-sized instances are respectively 0.00%, -1.15% and -51.38%. As the size of instances increases, the gap becomes considerable. Comparing large-size instances indicates that there are extremely larger amounts of gaps for more complex ones, implying the superiority of the proposed method.

The other four instances were obtained directly from the pharmaceutical company. Each of these instances has a three-month duration of the production planning horizon, containing three monthly periods. The duration of the workweek is 120 hours if there is not a holiday within the workweek. If there is(are) holiday(s) at the beginning of the workweek or the end of it, the workweek duration decreases. If there is a holiday in the middle of the workweek, the workweek is broken into two shorter workweeks placed before and after the holiday. There is no time overlap between the production planning horizons of different instances. The exact method could not reach an optimal solution for large-sized instances, so it is not capable of obtaining optimal solutions for the practical instances. The running time for practical instances is expanded to 8 hours for the real instances, which is permissible time for integrated production planning and scheduling in real cases.

Table 5 indicates the results of the exact method and the proposed memetic algorithm for real instances. Due to the stochastic nature of the memetic algorithm, the obtained results of a unique instance are unlikely to be same. Hence, to improve solution quality, the proposed memetic algorithm is performed ten times for each instance, and the average and the best solution are obtained over ten runs. The reported run time for each instance in Table 5 is the average CPU time over ten runs.

Table 5. Numerical results for real instances

Instance	No. of batches	MILP model		Proposed memetic algorithm			Gap (%)
		Objective Function	Run time (s)	Objective Function		Run time (s)	
				Mean	Best		
1	163	3691	28800	9235.2	8818	19394	(138.91)
2	194	2875	28800	11094.6	10542	18648	(266.68)
3	202	2437	28800	12766.1	11935	24875	(389.74)
4	188	3060	28800	11853.9	11076	26372	(261.93)
						average	(264.31)

Since the optimal solutions are not known, the objective function obtained by the exact method and mean and best objective functions calculated by the proposed method are reported in the next columns. The results shown in Table 5 revealed that the proposed memetic algorithm significantly outperformed the exact method in obtaining better solutions. The results of Table 5 obtained by the proposed method were compared with the plans created by the planning section of the company. They indicated an average improvement of 14.2% in the objective functions of four instances.

Conclusions

In this study, simultaneous production planning and scheduling in a production line of intravenous fluids and irrigation solutions at Darou Pakhsh Pharmaceutical Manufacturing Company is investigated. This is the first study that considers the existence of the planning horizon, planning periods, workweeks, holding cost, lost sales cost, inventory, and cost of raw materials conjointly in simultaneous production planning and scheduling. The problem was first formulated as a mixed-integer linear programming model. The objective is to maximize the profit that is a productivity-based performance measure. The problem and the formulation differ considerably from the ones being addressed in the literature. Since the problem is NP-hard in the strong sense, a memetic algorithm is proposed reducing the computational effort of the problem. The chromosome representation is based on a permutation matrix, and a new algorithm is developed to construct a complete schedule from the permutation matrix through the planning horizon. Two kinds of instances are implemented to compare the exact method and the proposed memetic algorithm. The computational results for generated instances and real instances showed that the proposed memetic algorithm obtained optimal solutions on all the instances solved optimally by the mathematical model. It outperformed the exact method in other instances. Therefore, the performance of the proposed memetic algorithm is satisfactory in profit maximization for the simultaneous production planning and scheduling in a hybrid flow shop organization.

In future studies, we can suggest simultaneous production planning and scheduling for other real-world applications, in which the integration of production planning and scheduling is necessary. Furthermore, adding other considerations like overtime cost, backorder cost, maintenance, and limited availability of machines. Another direction of further research is to develop more effective approaches and methods for the proposed simultaneous model, such as Lagrangian relaxation, etc. Also, using the multi-objective optimization approach can be suggested for further research.

Conflict of interests

None.

Authors' contributions

The authors are the same

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