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A set of efficient heuristics and meta-heuristics to solve a multi-objective pharmaceutical supply chain network

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ABSTRACT

In this paper, we propose a new multi-objective optimization approach for the pharmaceutical supply chain network (PSCN) design problem to minimize the total cost and the delivery time of pharmaceutical products to the hospital and pharmacy, while maximizing the reliability of the transportation system. A new mixed-integer non-linear programming model was developed for the production-allocation-distribution-inventory-ordering-routing problem. Three new heuristics (H-1), (H-2), and (H-3) have been proposed and to validate the model, two new meta-heuristic algorithms, namely, an Improved Social Engineering Optimization (ISEO) and Hybrid Firefly and Simulated Annealing Algorithm (HFFA-SA) have been developed. The proposed mathematical model has been evaluated through extensive simulation experiments by analyzing different criteria. The results show that the proposed model along with the solution method provides a reliable and powerful instrument to solve the PSCN design problem.

1. Introduction

The supply chain is a complex system of linked segments like multiple suppliers, manufacturer, and retailer that can involve other chains. This makes supply chains more vulnerable to encounter several disturbances that may affect negatively the performance of the companies in the whole chain (Rivera, Afsar, & Prins, 2015; Bekdaş, 2015; Naderi, Govindan, & Soleimani, 2019). Furthermore, today's supply chain is progressively complicated, and the competitive advantage of companies not only depend on producing products with lower costs, higher quality, and higher service level but also on their ability to survive unexpected disruptions, *i.e.* they should be resilient (Chung, 2013; Lücker and Seifert, 2017; Genovese, Acquaye, Figueroa, & Koh, 2017; Nematollahi, Hosseini-Motlagh, Ignatius, Goh, & Nia, 2018; Aguayo, Sarin, & Cundiff, 2019).

In recent years, research in pharmaceutical supply chains has gained considerable momentum with the rise of several deadly diseases/viruses such as COVID-19, Ebola, SARS, and Bird Flu (Shirazi, Kia, & Ghasemi, 2020). The pharmaceutical supply chain has features that distinguish it from other supply chains (Ghasemi & Khalili-Damghani, 2020). Medicine is considered a strategic commodity. A commodity that is linked to the health of the people and society and the smallest disruption to its supply chain can cause severe crisis (Ghasemi, Khalili-Damghani, Hafezalkotob, & Raissi, 2019). Therefore, supplying and distributing medicines in the right amount, at a reasonable time and in the right place are among the most significant considerations when managing this chain. In this scenario vehicle's reliability for the transportation of pharmaceutical products becomes very important. Pharmaceutical items are hence vital for the successful functioning of any health care system (e.g. hospitals), are of high priority and any risk can affect the entire pharmaceutical supply chain instantaneously (Xian, Qiu, & Zhang, 2013; Yeganeh & Zegordi, 2019). This problem can not only waste resources but can also jeopardize patients' lives due to lack of access to pharmaceutical products (Genovese et al., 2017; Sabouhi, Pishvaee, & Jabalameli, 2018; Hooker, 2019; De Carvalho Bento, Bitar, da Cruz Neto, Soubeyran, & de Oliveira Souza, 2020).

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Table 1
The summary of the literature review.

Reference	Number of periods		Type of the objectives					Solution methods			Type of the model
	Single period	Multi-period	Cost	Delivery time	Reliability	Profit	Unmet demand	Exact	Meta-heuristic	Heuristic	MILP/ MINLP/ILP and …
Sousa et al. (2005)	*	–	–	–	–	*	–	–	*	–	MILP
Susarla and Karimi (2012)	*	–	*	–	–	–	–	–	–	–	MILP
Firoozi et al. (2014)	*	–	*	–	–	–	–	–	Memetic	–	MINLP
Mousazadeh et al. (2015)	*	–	*	–	–	–	*	*	–	–	MILP
Hansen and Grunow (2015)	*	–	–	*	*			*	–	–	MILP
Haji Abbas and Hosseininezhad (2016)	*	–	*	–	–	–	–	*	–	–	MINLP
Zahiri et al. (2017)	–	*	*	–	–	–	–	–	DVG, NSGA-II, MOICA	–	MILP
Zandieh et al. (2018)	*	–	*	–	–	–	*	–	NSGA-II	–	MILP
Bijaghini and SeyedHosseini (2018)	*	–	–	*	–	–	–	*	–	–	MILP
Dai et al. (2018)	*	–	*	–	–	–	–	–	HHS, HGA	–	MINLP
Gharaei and Jolai (2018)	*	–	*	–	–	–	–	–	EA	–	MILP
Zahiri, Torabi, et al. (2018)	*	–	*	–	–	–	*	–	NSGA-II, MOICA	–	MILP
Zahiri, Jula et al. (2018)	*	–	*	–	–	–	*	*	–	–	MILP
Zhu and Ursavas (2018)	*	–	*	–	–	–	–	*	–	–	MILP
Savadkoohi et al. (2018)	–	*	*	–	–	–	–	*	–	–	MILP
Singh and Goh (2019)	*	–	*	–	–	–	–	*	–	–	MILP
Tirkolaee, Mardani et al. (2020)	–	*	*	–	*	–	–	*	–	–	MILP
Tirkolaee, Goli et al. (2020)	*	–	*	–	*	–	–	–	MOSA, NSGA-II	–	MILP
Zandkarimkhani et al. (2020)	*	–	*	–	*	–	–	*	–	–	MILP
Akbarpour et al., 2020))	–	*	*	–	–	–	*	*	–	–	MILP
Franco and Alfonso-Lizarazo (2020)	–	*	*	–	–	–	–	*	–	–	MILP
Our study	–	*	*	*	*	–	–	Epsilon-constraint	ISEO, HFFA-SA	H-1, H-2, H-3	MINLP

The World Health Organization (WHO) describes a medicine or pharmaceutical preparation as: "any substance or mixture of substances manufactured, sold, suggested for sale or represented for use in the diagnosis, treatment, mitigation or prevention of disease, abnormal physical state or the symptoms thereof in man or animal; [and utilize in] restoring, correcting or modifying organic functions in man or animal" (Kickbusch, 2003). Access to medicine is also one of the important human rights that must be the central objective of any healthcare systems (Recioui, 2012; Escudero, Garín, Pizarro, & Unzueta, 2018; Moons, Waeyenbergh, & Pintelon, 2019).

Several researchers have proposed various models and heuristics to solve the pharmaceutical supply chain problems. Sousa, Shah, and Papageorgiou (2005) designed an allocation-distribution problem in the supply chain network for pharmaceuticals by considering the maximizing of profit in the network. Accordingly, they formulated a mixed-integer linear programming (MILP) model and used metaheuristic algorithms to solve the model. Susarla and Karimi (2012) suggested integrated planning in multi-site and multi-echelon pharmaceutical supply chain networks by considering procurement, production, and distribution problems. Whereas Firoozi et al. (2014) extended an integrated network design for storage, inventory, facility location, and distribution problem of perishable products by considering medical and pharmaceutical items. They formulated a MINLP mathematical model and developed a memetic algorithm to solve the problem. Mousazadeh, Torabi, and Zahiri (2015) proposed a bi-objective MILP for a PSCN problem by considering two objective functions; minimizing the total cost and minimizing the unmet demand. Hansen and Grunow (2015) designed a MILP mathematical model in the pharmaceutical supply chain network. Haji Abbas and Hosseininezhad (2016) developed a multi-period location-allocation problem in the pharmaceutical supply chain. They considered two objective functions; the minimization of total cost and maximization of customer satisfaction. Zahiri, Zhuang, and Mohammadi (2017) proposed a new resilient-sustainable model for pharmaceutical network design. They proposed a novel hybrid meta-heuristic algorithm to solve the model. Zandieh, Janatyan, Alem-Tabriz, and Rabieh (2018) designed a multi-objective distribution network in the pharmaceutical supply chain network. Consequently, the NSGA-II algorithm with the Pareto-optimal front for the model has been used to solve the model. Bijaghini and SeyedHosseini (2018) developed a novel bi-level production-routing-inventory model for a medicine supply chain network and used the Benders Decomposition algorithm to solve the model. Dai, Aqlan, Zheng, and Gao (2018) extended a location and inventory supply chain network model by utilizing two heuristic approaches for perishable products. Whereas, Gharaei and Jolai (2018) proposed a multi-agent method to integrate the production-scheduling-distribution problem in a supply chain network. They also formulated a Mixed Integer Programming (MIP) problem and applied a hybrid multi-objective evolutionary algorithm to attain Pareto solutions. Recently, Zahiri, Torabi, Mohammadi, and Aghabegloo (2018) extended a multi-stage stochastic programming method for blood supply chain planning. They proposed a new hybrid multi-objective self-adaptive differential evolution algorithm to solve the problem. In another study, Zahiri, Jula, and Tavakkoli-Moghaddam (2018) developed a novel analytical model for bi-objective pharmaceutical supply chain network design including minimizing the total cost and maximum unmet demand. Zhu and Ursavas (2018) proposed a location and routing problem with time windows and direct delivery in the pharmaceutical industry. Savadkoohi, Mousazadeh, and Torabi (2018) designed a three-echelon pharmaceutical distribution network via a novel location-inventory model considering the perishability feature of pharmaceutical items. The goal

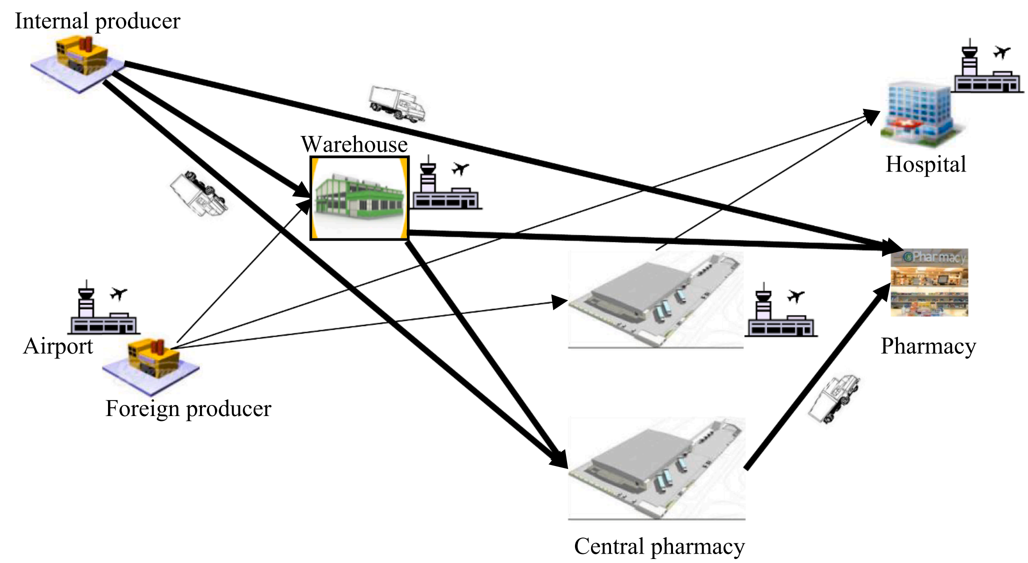

Fig. 1. The general scheme of PSCN.

of the model is to minimize the total cost of the network. More recently, Singh and Goh (2019) proposed a multi-objective mixed integer linear programming in a pharmaceutical supply chain. Whereas Tirkolaee, Mardani, Dashtian, Soltani, and Weber (2020) presented a novel hybrid method utilizing fuzzy decision making and multi-objective programming for sustainable-reliable supplied selection in a two-level supply chain network. The goals were minimization of the total cost, maximization of the weighted value and reliability. To deal with multi-objectiveness, they used the weighted goal programming method. In another study, Tirkolaee, Goli, Faridnia, Soltani, and Weber (2020) developed a new bi-objective MILP model for the reliable pollution-routing problem with Cross-Dock Selection utilizing Pareto-based algorithms. The first objective was to minimize total cost and the second was to maximize supply reliability. The multi-objective simulated-annealing (MOSA) algorithm and NSGA-II are used to find Pareto solutions. Zandkarimkhani, Mina, Biuki, and Govindan (2020) used a chance-constrained fuzzy goal programming method for perishable PSCN design. Also, a bi-objective MILP model was designed, where the objectives of the model are to minimize the total cost and demand amount. Akbarpour, Torabi, and Ghavamifar (2020) designed a bi-objective integrated pharmaceutical relief chain network under drug's perishability. A cooperative coverage mechanism for moving mobile pharmacies at post-disaster was used. Franco and Alfonso-Lizarazo (2020) developed a simulation-optimization method according to the stochastic counterpart in PSCN. Two MILP models are formulated based on this method. In this regard, the classification of the PSCN studies is given in Table 1.

Recent general discussion (see Shah, 2004; Rossetti, Handfield, & Dooley, 2011; Uthayakumar & Priyan, 2013; Narayana, Pati, & Vrat, 2014; Meiler, Tonke, Grunow, & Günther, 2015; Settanni, Harrington, & Srai, 2017; Sbai & Berrado, 2018) on PSCNs show that supply chain network research remains far from sufficient to address the needs and challenges of the pharmaceutical industry. Moreover, in the statement above, none of the above-mentioned papers considers reliability and multi-modal transportation contained in the production-allocation-distribution-inventory-ordering-routing problem of PSCNs. More importantly, a PSCN design including the integration of allocation, production, distribution, routing, inventory, and ordering problems has not been addressed properly. Furthermore, an objective function is defined to minimize the total cost, two other objective functions are stated to minimize the delivery time of pharmaceutical products and to maximize the reliability of transportation systems and routes between the network. To address the research gaps, this paper presents a PSCN by considering multi-modal transportation, multi-products, multi-period, the reliability of the transportation system and routes between network, and delivery on time of pharmaceutical products. A three objective MINLP model for PSCN is formulated.

Accordingly, two novel Improved Social Engineering Optimization (ISEO) and Hybrid Firefly and Simulated Annealing (HFFA-SA) algorithms are extended to efficiently solve the proposed large-sized problems. This has not been attempted in the existing studies so far. Then, three heuristics (H-1), (H-2), (H-3) approaches, and the ISEO, HFFA-SA algorithms were used to solve the proposed problem is developed. The main contributions of this work to the knowledge domain is shown by the following aspects:

- Designing a novel multi-period, multi-echelon, and multi-product PSCN with multi-modal transportation considering reliability,
- Formulating a new multi-objective MINLP model in the PSCN,
- Considering the reliability of the proposed network,
- Developing three fast heuristic approaches (H-1), (H-2), and (H-3) based on linear relaxation for the first time in this paper,
- Developing two novel ISEO and HFFA-SA algorithms to find Pareto solutions in the PSCN problem,
- Demonstrating the effectiveness and efficiency of developed approaches through different criteria and analyses,
- Validation of the performance of the developed model by some sensitivity analyses.

The paper is organized as follows. Section 2 describes the problem as well as the mathematical formulation. Section 3 explains the solution methodology. The computational results, making a balance among total cost, delivery time, and reliability, and numerical examples are demonstrated in Section 4. Finally, Section 5 concludes the paper with an implication to future studies as well as discusses the managerial implication of the outcomes.

2. Problem description

This section describes the proposed model. A four-level, multi-product, and multi-period PSCN including internal and foreign producer, warehouse, and customer zones (central pharmacy, hospital and local pharmacy) based on Fig. 1 are designed. Furthermore, production centres are divided into two categories: internal and foreign producers. The foreign producer is considered due to the pharmaceutical product shortages by the internal producer. Pharmaceutical products are transmitted from the internal and foreign producers to the warehouses and customers and from warehouses to customers based on specified demands and orders using different vehicles. Then, pharmaceutical products are delivered from internal and foreign producers to the warehouses and customers and from warehouses to customers on defined routes and at different periods. These pharmaceutical products are delivered through air or land transportation means. Re-order of pharmaceutical products in the customer demands from warehouses, and warehouse and customer demand from internal and foreign producers are allowed. However, customers are prioritized based on pharmaceutical products' re-order costs. Further, the transportation cost is considered variable and multi-modal transportation systems as aerial and terrestrial are recognized. On the other hand, to save on the delivery cost, the delivery of pharmaceutical products is considered batch delivery. In this regard, travel times from internal and foreign producers to warehouses and customers, and from warehouses to customers on the different routes are assumed. At the customers level (central pharmacy, hospital and local pharmacy), the preparation and packing costs are considered. After that, the maximum amount of required pharmaceutical products is considered in the internal and foreign producers, warehouses, and customers.

2.1. Assumptions

Assumptions for modelling the problem are as follow:

- Each vehicle can traverse a maximum of one route per period.
- Each customer can receive more than one vehicle of pharmaceutical products at any time. This means that the transportation system for each customer can be divided into two or more vehicles for each customer.
- Customer's demand for pharmaceutical products from warehouses and warehouse's demand from internal and foreign producers are allocated during the planning horizon.
- Only vehicles allocated to the customer, warehouse, and internal and foreign producers at that time can deliver pharmaceutical products to customers and warehouses at each time period are dedicated.
- Each customer and warehouse have various capacities with the corresponding cost. If it is open can employ only one capacity level.
- There is no route between internal and foreign producers and customers.
- Pharmaceutical products are transferred through the air transportation system if there is an airport at those levels of the network, otherwise, it will be transmitted through the land transportation system. Moreover, product delivery from foreign producers will only be possible through the air transportation system.
- If each unit faces the late delivery of pharmaceutical products in each period must pay the penalty cost.

2.2. Notations

Indices

m	Index for the internal and foreign producer ($m_1 \cup m_2 = M$)	v	Index for vehicle type (airplane and truck) ($v_1 \cup v_2 = V$)
t	Index for time period	c	Index for customers (central pharmacy, hospital and local pharmacy)
w	Index for warehouse	r	Index for routes (r_{mw}, r_{wc}, r_{mc})
p'	Index for pharmaceutical product		

Parameters

$\alpha^t_{wp'}$	Inventory holding cost at the warehouse w for the product p' at the period t
$\alpha^t_{mp'}$	Inventory holding cost at internal/foreign producer m for the product p' at the period t
$\alpha^t_{cp'}$	Inventory holding cost at the central pharmacy c for the product p' at the period t
δ^t_m	Fixed cost for an internal and foreign producer m
δ^t_w	Fixed cost for warehouse w
$\beta^t_{wmp'}$	Order cost by the warehouse w to the internal/foreign producer m for the product p' at the period t
$\beta^t_{cmp'}$	Order cost by the central pharmacy c to the internal/foreign producer m for the product p' at the period t
$\beta^t_{cwp'}$	Order cost by the central pharmacy c to the warehouse w for the product p' at the period t
$P^t_{p'}$	Penalty cost for the wasted product p' at the period t
$C^t_{p'}$	Penalty cost for the late delivery product p' at the period t
$\psi^t_{p'm}$	Production cost to produce the product p' at the internal/foreign producer m at the period t
$\phi^{t\,r_{mw}}_{p'mwv}$	Transportation cost for the product p' from internal/foreign producer m to the warehouse w using truck/airplane v on the route at the period t
$\phi^{t\,r_{mc}}_{p'mcv}$	Transportation cost for the product p' from internal/foreign producer m to the customer using truck/ airplane v on the route r_{mc} at the period t
$\phi^{t\,r_{wc}}_{p'wcv}$	Transportation cost for the product p' from warehouse w to the customer c using truck/airplane on the route r_{wc} at the period t
$L^t_{p'}$	Tariff cost of product p' in the airport at the period t
$B^t_{p'm}$	Back-order cost for the product p' at internal/foreign producer m at the period t
$D^t_{wmp'}$	Delivery cost by the warehouse w to the internal/foreign producer m for the product p' at the period t
$D^t_{cmp'}$	Delivery cost by the customer c to internal/foreign producer m for the product p' at the period t
$D^t_{cwp'}$	Delivery cost by the customer to the warehouse w for the product p' at the period t
E^t_c	Establishing and packing cost of the customer at the period t
$K^t_{p'w}$	Keeping the cost of product p' in the warehouse w at the period t
$\theta^t_{p'wm}$	Purchase cost of the product p' by warehouse w from the internal/foreign producer m at the period t
$\theta^t_{p'cm}$	Purchase cost of the product p' by the customer from the internal/ foreign producer m at the period t
$\theta^t_{p'cw}$	Purchase cost of the product p' by the customer c from the warehouse w at the period t
$\mu_{mwr_{mw}}$	Travel time from internal/foreign producer m to the warehouse w on route r_{mw}
$\mu_{mcr_{mc}}$	Travel time from internal/foreign producer m to the customer on the route r_{mc}
$\mu_{wcr_{wc}}$	Travel time from warehouse w to the customer c on the route r_{wc}
D	Fixed-rate of demand for the order of product p'
d_{mw}	Distance from internal/foreign producer m to warehouse w
d_{mc}	Distance from internal/foreign producer m to customer c
d_{wc}	Distance from the warehouse w to the customer c
$I_{p'}$	Intact rate of product p'
R	Reliability rate of vehicles per kilometer
ω_w	Capacity of warehouse w
ω_c	Capacity of customer c
ω_v	Capacity of truck /airplane v
$\partial^t_{p'wm}$	Product p' demand required by warehouse w from the internal/foreign producer m at the period t
$\partial^t_{p'cm}$	Product p' demand required by customer c from the internal/foreign producer m at the period t
$\partial^t_{p'cw}$	Product p' demand required by customer c from the warehouse w at the period t
$Init^t_{wp'}$	Initial inventory of product p' in the warehouse w
$Init^t_{cp'}$	Initial inventory of product p' in the customer c
D_{max}	Maximum desired number of customer
M_{max}	Maximum desired number of internal/foreign producer
W_{max}	Maximum desired number of warehouse
Big$M$	A huge number
$B_{p'}$	The volume of one unit of product p'

Decision variables

$Q^{tr_{mw}}_{p'mw}$	Quantity of product p' delivered from internal/foreign producer m to warehouse w on the route r_{mw} at the period t
$Q^{tr_{mc}}_{p'mc}$	

(continued on next page)

(*continued*)

	Quantity of product p' delivered from internal producer/foreign m to the customer $c$on the route r_{mc} at the period t
$Q^{tr_{wc}}_{p'wc}$	Quantity of product p' delivered from warehouse w to customer on the route r_{wc} at the period t
$S^t_{p'w}$	Inventory quantity of the product p' in the warehouse w at the period t
$S^t_{p'm}$	Inventory quantity of the product p' in the internal/foreign producer m at the period t
$S^t_{p'c}$	Inventory quantity of the product p' in the customer c at the period t
$S^t_{p'w}$	Inventory level of product p' in the warehouse w at the period t
$S^t_{p'c}$	Inventory level of the pharmaceutical product p' in the customer c at the period t
$BOQ^t_{p'm}$	Back-order quantity of the product p' in internal/foreign producer at the end of the period t
$X^t_{p'mw}$	Quantity of product p' ordered from internal/foreign producer m by the warehouse w at the period t
$X^t_{p'mc}$	Quantity of product p' ordered from internal/foreign producer m by the customer c at the period t
$Y^t_{p'wc}$	Quantity of product p' ordered from the warehouse w by the customer c at the period t
$W^t_{p'c}$	The amount of waste from the product p' at the customer c at the end of the period t
$U^t_{p'c}$	The amount of late delivery from the product p' at the customer c at the first of the period t
$U_{p'v}$	The amount of product p' transported by airplane v
$\lambda^t_{p'm}$	Production quantity of product p' at the internal/foreign producer m at the period t
$Z^{tr_{mw}}_{p'mwv}$	Shipping quantity of product p' from internal producer m to warehouse w using truck/airplane v on the route r_{mw} at the period t
$Z^{tr_{mc}}_{p'mcv}$	Shipping quantity of product p' from internal/foreign producer m to the customer c using truck/airplane v on the route r_{mc} at the period t
$Z^{tr_{wc}}_{p'wcv}$	Shipping quantity of product p' from warehouse w to the customer c using truck/ airplane v on the route r_{wc} at the period t
$N^t_{p'wm}$	Purchasing quantity of a product p' by warehouse w from internal/foreign producer m at the period t
$N^t_{p'cm}$	Purchasing quantity of a product p' by the customer c from internal/ foreign producer m at the period t
$N^t_{p'cw}$	Purchasing quantity of a product p' by the customer c from the warehouse w at the period t
$A_{p'mw}$	Delivery time of products p' from internal/foreign producer m to the warehouse w
$A_{p'mc}$	Delivery time of products $p'$from internal/foreign producer m to the customer c
$A_{p'wc}$	Delivery time of products p' from warehouse w to the customer c
$\vartheta^t_{p'w}$	Quantity of excess demand for the product p' in the warehouse w at the period t
$\vartheta'^t_{p'w}$	Quantity of excess supply for the product p' at the warehouse w at the period t
$\sigma^t_{p'c}$	Quantity of excess supply for the product p' in the customer $c$at the period t
$\sigma'^t_{p'c}$	Quantity of excess demand for the product p' in the customer c at the period t
g^t_v	A binary variable, equal 1 if truck/airplane v traverses from one level to another level in the network at the period t; 0 otherwise
F_m	A binary variable, equal 1 if internal/foreign producer m is opened; 0 otherwise
F_w	A binary variable, equal 1 if the warehouse w is opened; 0 otherwise
F_c	A binary variable, equal 1 if the customer c is opened; 0 otherwise
$O^t_{wcr_{wc}}$	A binary variable, equal 1 if the warehouse w is assigned to the customer c on the route r_{wc} at the period t; 0 otherwise
$O^t_{mwr_{mw}}$	A binary variable, equal 1 if internal/foreign producer m is assigned to the warehouse w on the route r_{mw} at the period t; 0 otherwise
$O^t_{mcr_{mc}}$	A binary variable, equal 1 if internal/foreign producer m is assigned to the customer c on the route r_{mc} at period t; 0 otherwise
$\nabla^t_{vr_{mw}}$	A binary variable, equal 1 if vehicle v is used on the route r_{mw} at period t; 0 otherwise
$\nabla^t_{vr_{mc}}$	A binary variable, equal 1 if vehicle v is used on the route r_{mc} at period t; 0 otherwise
$\nabla^t_{vr_{wc}}$	A binary variable, equal 1 if vehicle v is used on the route r_{wc} at period t; 0 otherwise

2.3. Proposed mathematical model

$$
\begin{aligned}
Min\,F_1 = {} & \sum_t \Bigg\{ \sum_{p'}\sum_w \alpha^t_{wp'} \times S^t_{p'w} + \sum_{p'}\sum_{m1}\alpha^t_{mp'}\times S^t_{p'm} + \sum_{p'}\sum_{m2}\alpha^t_{mp'}\times S^t_{p'm} \\
& + \sum_{p'}\sum_c \alpha^t_{cp'}\times S^t_{p'c}\Bigg\} + D\sum_{p'}\sum_t\Bigg\{\sum_w\sum_{m1}\frac{\beta^t_{wmp'}}{X^t_{p'mw}} + \sum_w\sum_{m2}\frac{\beta^t_{wmp'}}{X^t_{p'mw}} \\
& + \sum_c\sum_{m1}\frac{\beta^t_{cmp'}}{X^t_{p'mc}} + \sum_c\sum_{m2}\frac{\beta^t_{cmp'}}{X^t_{p'mc}} + \sum_c\sum_w\frac{\beta^t_{cwp'}}{Y^t_{p'wc}}\Bigg\} \\
& + \Bigg\{\sum_{p'}\sum_c\sum_t\Big[\Big(P^t_{p'}\times W^t_{p'c}\Big)+\Big(C^t_{p'}\times U^t_{p'c}\Big)\Big]\Bigg\} \\
& + \Bigg\{\sum_{p'}\Bigg[\bigg(\sum_t L^t_{p'}\times\sum_v U_{p'v}\bigg)\Bigg]\Bigg\} + \Bigg\{\sum_{p'}\sum_t\Bigg[\Bigg(\sum_{m1}\Big(\psi^t_{p'm} \\
& \times\lambda^t_{p'm}\Big)\Bigg) + \Bigg(\sum_{m2}\Big(\psi^t_{p'm}\times\lambda^t_{p'm}\Big)\Bigg)\Bigg]\Bigg\} \\
& + \{\sum_v\sum_{p'}\sum_t[\Bigg(\sum_{m1}\sum_w d_{mw}\Big(\psi^{tr_{mw}}_{p'mwv}\times Z^{tr_{mw}}_{p'mwv}\Big) + (\varphi^{tr_{mw}}_{p'mwv} \\
& \times Z'^{tr_{mw}}_{p'mwv})\Bigg) + \Bigg(\sum_{m2}\sum_w d_{nw}(\varphi^{tr_{mw}}_{p'mwv}\times Z'^{tr_{mw}}_{p'mwv})\Bigg) \\
& + \Bigg(\sum_{m1}\sum_c d_{mc}\Big(\psi^{tr_{mc}}_{p'mcv}\times Z^{tr_{mc}}_{p'mcv}\Big) + (\varphi^{tr_{mc}}_{p'mcv}\times Z'^{tr_{mc}}_{p'mcv})\Bigg) \\
& + \Bigg(\sum_{m2}\sum_c d_{mc}(\varphi^{tr_{mc}}_{p'mcv}\times Z'^{tr_{mc}}_{p'mcv})\Bigg) + \Bigg(\sum_w\sum_c d_{wc}\Big(\psi^{tr_{wc}}_{p'wcv} \\
& \times Z^{tr_{mc}}_{p'mcv}\Big) + (\varphi^{tr_{wc}}_{p'wcv}\times Z'^{tr_{wc}}_{p'wcv})\Bigg)]\} + \{\sum_{p'}\sum_t\Bigg[\Bigg(\sum_{m1}(B^t_{p'm} \\
& \times BOQ^t_{p'm})\Bigg) + \Bigg(\sum_{m2}(B^t_{p'm}\times BOQ^t_{p'm})\Bigg)\Bigg]\Bigg\} + \{\sum_c\sum_t(F_c \\
& \times E^t_c)\} + \{\sum_{p'}\sum_w\sum_t(F_w\times K^t_{p'w})\} + \{\sum_{m1}(\delta_m\times F_m) \\
& + \sum_{m2}(\delta_m\times F_m) + \sum_w(\delta_w\times F_w)\} + \{\sum_{p'}\sum_t[\Bigg(\sum_w\sum_{m1}(\theta^t_{p'wm} \\
& \times N^t_{p'wm})\Bigg) + \Bigg(\sum_w\sum_{m2}(\theta^t_{p'wm}\times N^t_{p'wm})\Bigg) + \Bigg(\sum_c\sum_{m1}(\theta^t_{p'cm} \\
& \times N^t_{p'cm})\Bigg) + \Bigg(\sum_c\sum_{m2}(\theta^t_{p'cm}\times N^t_{p'cm})\Bigg) + \Bigg(\sum_c\sum_w(\theta^t_{p'cw} \\
& \times N^t_{p'cw})\Bigg)]\} + \{\sum_{p'}\sum_t[\Bigg(\sum_w\sum_{m1}\sum_{r_{mw}}(D^t_{wmp'}\times Q^{tr_{mw}}_{p'mw})\Bigg) \\
& + \Bigg(\sum_w\sum_{m2}\sum_{r_{mw}}(D^t_{wmp'}\times Q^{tr_{mw}}_{p'mw})\Bigg) + \Bigg(\sum_c\sum_{m2}\sum_{r_{mc}}(D^t_{cmp'} \\
& \times Q^{tr_{mc}}_{p'mc})\Bigg) + \Bigg(\sum_c\sum_w\sum_{r_{wc}}(D^t_{cwp'}\times Q^{tr_{wc}}_{p'wc})\Bigg) \\
& + \Bigg(\sum_c\sum_{m1}\sum_{r_{mc}}(D^t_{cmp'}\times Q^{tr_{mc}}_{p'mc})\Bigg)]\}
\end{aligned} \tag{1}
$$

The first objective function (1) is the minimization of the total costs in the PSCN consisting of inventory holding, ordering, penalty, tariff, production, transportation, re-ordering, distribution, warehouse, fixed, purchasing, and delivery costs.

In the first bracket, inventory costs of pharmaceutical products are considered at the internal and foreign producer, warehouse and customer. In the second bracket, the costs are based on orders and demands for products from customers and warehouses to internal and foreign producers and from customers to warehouses, which must be paid. In the third bracket, the penalty cost for delaying delivery and deterioration of pharmaceutical products is considered. In the fourth bracket, a tariff cost should be indicated for carrying pharmaceutical products between the levels of the network employed by the air transportation system and delivered to the airport tariff office. In the fifth bracket, the production cost for pharmaceutical products in internal and foreign producers is considered. In the sixth bracket, at different period times and different transport systems (air and land), the cost of sending pharmaceutical products between different routes in the network is considered variable. In the seventh bracket, we will re-order products from internal and foreign producers at the end of the period. In the eighth bracket, the preparing and packaging cost of pharmaceutical products in customers is considered. In the ninth bracket, there is a fixed cost for the opening of internal and foreign producers and warehouses. In the tenth bracket, the purchase of pharmaceutical products by customers and warehouses from internal and foreign producers and by customers from warehouses are carried out. In the eleventh bracket, it shows the fixed cost of delivery of products based on the delivery time between the levels of the network.

$$Min\ F_2=\sum_{p'}\sum_{t}[\left(\sum_{m1}\sum_{w}\sum_{r_{mw}}\left(Q^{tr_{mw}}_{p'mw}\times A_{p'mw}\right)\right)+\left(\sum_{m2}\sum_{w}\sum_{r_{mw}}\left(Q^{tr_{mw}}_{p'mw}\times A_{p'mw}\right)\right)\left(\sum_{m1}\sum_{c}\sum_{r_{mc}}\left(Q^{tr_{mc}}_{p'mc}\times A_{p'mc}\right)\right)+\left(\sum_{m2}\sum_{c}\sum_{r_{mc}}\left(Q^{tr_{mc}}_{p'mc}\times A_{p'mc}\right)\right)+\left(\sum_{w}\sum_{c}\sum_{r_{wc}}\left(Q^{tr_{wc}}_{p'wc}\times A_{p'wc}\right)\right) \tag{2}$$

The second objective function (2) investigates to minimize the delivery time of pharmaceutical products from internal and foreign producers to warehouses and customers, from warehouses to customers.

$$Max\ F_3=R\sum_{v}\sum_{t}\left(\sum_{r_{mw}}\nabla^t_{vr_{mw}}+\sum_{r_{mc}}\nabla^t_{vr_{mc}}+\sum_{r_{wc}}\nabla^t_{vr_{wc}}\right) \tag{3}$$

The third objective function (3) seeks to maximize the reliability of the transportation system of pharmaceutical vehicles that travel from internal and foreign producers to warehouses and customers and from warehouses to customers.

$$\left(\sum_{p'}\sum_{m1}\sum_{r_{mw}}Q^{tr_{mw}}_{p'mw}B_{p'}+\sum_{p'}\sum_{m2}\sum_{r_{mw}}Q^{tr_{mw}}_{p'mw}B_{p'}\right)\leqslant\omega_w\,.\,F_w \qquad \forall w,t \tag{4}$$

$$\sum_{p'}\sum_{w}\sum_{r_{wc}}Q^{tr_{wc}}_{p'wc}\cdot B_{p'}\leqslant\omega_c\cdot F_c \qquad \forall c,t \tag{5}$$

$$\sum_{p'}B_{p'}\times Z^{tr_{mw}}_{p'mwv}\leqslant\ \omega_v\,.\,g^t_v \qquad \forall m,r_{mw},w,v,\ t \tag{6}$$

$$\sum_{p'}B_{p'}\times Z^{tr_{mw}}_{p'mwv}\leqslant\ \omega_v\,.\,g^t_v \qquad \forall m,r_{mw},w,v,\ t \tag{7}$$

$$\sum_{p'}B_{p'}\times Z^{tr_{wc}}_{p'wcv}\leqslant\ \omega_v\,.\,g^t_v \qquad \forall w,r_{wc},v,c,\ t \tag{8}$$

Constraints (4)–(8) investigate the capacity of the warehouse, customer, and vehicle in each period, respectively.

$$\sum_{r_{wc}}O^t_{wcr_{wc}}\leqslant 1 \qquad \forall w,c,t \tag{9}$$

$$\sum_{r_{mw}}O^t_{mwr_{mw}}\leqslant 1 \qquad \forall m1,w,t \tag{10}$$

$$\sum_{r_{mw}}O^t_{mwr_{mw}}\leqslant 1 \qquad \forall m2,w,t \tag{11}$$

$$\sum_{r_{mc}}O^t_{mcr_{mc}}\leqslant 1 \qquad \forall m1,c,t \tag{12}$$

$$\sum_{r_{mc}}O^t_{mcr_{mc}}\leqslant 1 \qquad \forall m2,c,t \tag{13}$$

Constraints (9)–(13) display an allocated route between each warehouse and customer, each internal producer and warehouse, each foreign producer and warehouse, each internal producer and customer, each foreign producer and customer, and each warehouse and customer.

$$\sum_{c}\sum_{r_{wc}}O^t_{wcr_{wc}}\leqslant 1 \qquad \forall w,t \tag{14}$$

Constraint (14) ensures that a warehouse is allocated to only one customer.

$$\eth^t_{p'wm}=\sum_{r_{mw}}Q^{tr_{mw}}_{p'mw} \qquad \forall t,p',m1,w \tag{15}$$

$$\eth^t_{p'wm}=\sum_{r_{mw}}Q^{tr_{mw}}_{p'mw} \qquad \forall t,p',m2,w \tag{16}$$

$$\eth^t_{p'cm}=\sum_{r_{mc}}Q^{tr_{mc}}_{p'mc} \qquad \forall t,p',m2,c \tag{17}$$

$$\eth^t_{p'cw}=\sum_{r_{wc}}Q^{tr_{wc}}_{p'wc} \qquad \forall t,p',w,c \tag{18}$$

$$\eth^t_{p'cm}=\sum_{r_{mc}}Q^{tr_{mc}}_{p'mc} \qquad \forall t,p',m1,c \tag{19}$$

Constraints (15)–(19) determine the number of pharmaceutical products delivered from the internal and the foreign producer to the customer and the warehouse and from the warehouse to the customer.

$$\sum_{w}(Y^t_{p^{'}wc}\times I_{p^{'}}+\vartheta^t_{p^{'}w}-\vartheta^{'t}_{p^{'}w})=\eth^t_{p^{'}cw}\forall t,p^{'},c \tag{20}$$

Constraint (20) indicates balance constraint for warehouse and customer.

$$S^{t-1}_{p'w}+\sum_{v1}\sum_{r_{mw}}Z^{tr_{mw}}_{p'mwv}=\sum_{v}\sum_{c}\eth^t_{p'cw}+S^t_{p'w} \qquad \forall w,m,p',t \tag{21}$$

$$S^{t-1}_{p'w}+\sum_{v2}\sum_{r_{mw}}Z^{tr_{mw}}_{p'mwv}=\sum_{v}\sum_{c}\eth^t_{p'cw}+S^t_{p'w} \qquad \forall w,m,p',t \tag{22}$$

Constraints (21) and (22) show inventory balance constraints in the warehouse.

$$S_{p'w}=Init_{p'w} \qquad \forall w,p' \tag{23}$$

$$S_{p'c1}=Init_{p'c} \qquad \forall c,p' \tag{24}$$

$$F_m\leqslant M_{max} \quad \forall m1 \tag{25}$$

$$F_m\leqslant M_{max}\ \forall m2 \tag{26}$$

$$F_w\leqslant M_{max}\ \forall w \tag{27}$$

$$F_c\leqslant D_{max}\ \forall c \tag{28}$$

Constraints (23) and (24) show the initial inventory in the warehouse and customer. Constraints (25)–(28) indicate the maximum number of used pharmaceutical products in internal and foreign producers, warehouses, and customers.

$$(g^t_{v1}+g^t_{v2})-O^t_{mwr_{mw}}\leqslant 1 \qquad \forall m1,w,v1,v2,r_{mw},t \tag{29}$$

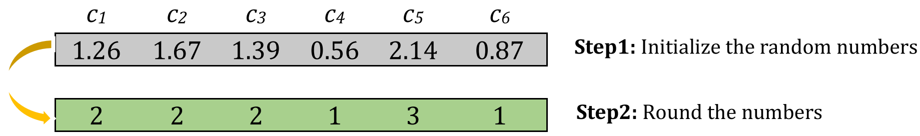

Fig. 2. The utilized procedure to allocate a sort of vehicle system for customers.

$$(g^t_{v1}+g^t_{v2})-O^t_{mwr_{mw}}\leqslant 1 \qquad \forall m2,w,v1,v2,r_{mw},t \tag{30}$$

$$(g^t_{v1}+g^t_{v2})-O^t_{mcr_{mc}}\leqslant 1 \qquad \forall m1,c,v1,v2,r_{mc},t \tag{31}$$

$$(g^t_{v1}+g^t_{v2})-O^t_{mcr_{mc}}\leqslant 1 \qquad \forall m2,c,v1,v2,r_{mc},t \tag{32}$$

$$(g^t_{v1}+g^t_{v2})-O^t_{wcr_{wc}}\leqslant 1 \qquad \forall w,c,v1,v2,r_{wc},t \tag{33}$$

Constraints (29)–(33) exhibit the routes of each vehicle in a sequence, respectively.

$$A_{p'mw}\geqslant \mu_{mwr_{mw}}-BigM(1-O^t_{mwr_{mw}}) \quad \forall m1,w,r_{mw},p',v1,t \tag{34}$$

$$A_{p'mw}\geqslant \mu_{mwr_{mw}}-BigM(1-O^t_{mwr_{mw}}) \quad \forall m1,w,r_{mw},p',v2,t \tag{35}$$

$$A_{p'mw}\geqslant \mu_{mwr_{mw}}-BigM(1-O^t_{mwr_{mw}}) \quad \forall m2,w,r_{mw},p',v1,t \tag{36}$$

$$A_{p'mw}\geqslant \mu_{mwr_{mw}}-BigM(1-O^t_{mwr_{mw}}) \quad \forall m2,w,r_{mw},p',v2,t \tag{37}$$

$$A_{p'mc}\geqslant \mu_{mcr_{mc}}-BigM(1-O^t_{mcr_{mc}}) \quad \forall m1,c,r_{mc},p',v1,t \tag{38}$$

$$A_{p'mc}\geqslant \mu_{mcr_{mc}}-BigM(1-O^t_{mcr_{mc}}) \quad \forall m1,c,r_{mc},p',v2,t \tag{39}$$

$$A_{p'mc}\geqslant \mu_{mcr_{mc}}-BigM(1-O^t_{mcr_{mc}}) \quad \forall m2,c,r_{mc},p',v1,t \tag{40}$$

$$A_{p'mc}\geqslant \mu_{mcr_{mc}}-BigM(1-O^t_{mcr_{mc}}) \quad \forall m2,c,r_{mc},p',v2,t \tag{41}$$

$$A_{p'wc}\geqslant \mu_{wcr_{wc}}-BigM(1-O^t_{wcr_{wc}}) \quad \forall w,c,r_{wc},p',v1,t \tag{42}$$

$$A_{p'wc}\geqslant \mu_{wcr_{wc}}-BigM(1-O^t_{wcr_{wc}}) \quad \forall w,c,r_{wc},p',v2,t \tag{43}$$

Constraints (34)–(43) prove the delivery time of pharmaceutical products from internal and foreign producers to warehouses and customers and from warehouses to customers on a different route.

$$\begin{gathered} BOQ^t_{p'm},X^t_{p'mw},X^t_{p'mc},Y^t_{p'wc},W^t_{p'c},U^t_{p'c},U_{p'v},\lambda^t_{p'm},Z^{tr_{mw}}_{p'mwv},Z^{tr_{mc}}_{p'mcv},Z^{tr_{wc}}_{p'wcv},Q^{tr_{mw}}_{p'mw},\\ Q^{tr_{mc}}_{p'mc},Q^{tr_{wc}}_{p'wc},S^t_{p'w},S^t_{p'm},S^t_{p'c},S^t_{p'w},N^t_{p'wm},N^t_{p'cm},N^t_{p'cw},A_{p'mw},A_{p'mc},A_{p'wc},\\ \vartheta^t_{p'w},\sigma^t_{p'c}\geqslant 0 \end{gathered} \tag{44}$$

$$g^t_v,F_m,F_w,F_d,O^t_{wcr_{wc}},O^t_{mwr_{mw}},O^t_{mcr_{mc}},\ \nabla^t_{vr_{wc}},\ \nabla^t_{vr_{mc}},\nabla^t_{vr_{mw}}\in\{0,1\} \tag{45}$$

Finally, constraints (44) and (45) determine the type of decision variables.

2.4. Linearization process

In the first objective function, the term ordering costs $(\frac{\beta^t_{wmp'}}{X^t_{p'mw}},\frac{\beta^t_{cmp'}}{X^t_{p'mc}},\frac{\beta^t_{cwp'}}{Y^t_{p'wc}})$ make the model non-linear. To linearize it, new positive variables $(\kappa^t_{wmp'},\kappa^t_{cmp'},\ \kappa^t_{cwp'})$ are defined and replace with the nonlinear term. Furthermore, the first objective function (just the bracket of ordering cost) is modified as follows:

$$Min\, F_1=D\{\sum_w\sum_{m1}\sum_{p'}\sum_t\kappa^t_{wmp'}+\sum_w\sum_{m2}\sum_{p'}\sum_t\kappa^t_{wmp'}+\sum_c\sum_{m1}\sum_{p'}\sum_t\kappa^t_{cmp'}$$

$$+\sum_c\sum_{M2}\sum_{p'}\sum_t\kappa^t_{cmp'}+\sum_c\sum_w\sum_{p'}\sum_t\kappa^t_{cwp'}\} \tag{46}$$

Objective functions Eq. (2) and (3), and constraints Eq. (4)–(45)

$\kappa^t_{wmp'},\kappa^t_{cmp'},\kappa^t_{cwp'}\geqslant 0$

3. The solution method

The proposed model was formulated as a MINLP model that cannot be solved by conventional approaches in a reasonable time. First of all, the exact method is described; secondly, we present two new ISEO and HFFA-SA algorithms and three heuristics (H-1), (H-2), and (H-3) approaches to find Pareto solutions. Additionally, these heuristics (H-1), (H-2), and (H-3) are compared to justify the developed algorithms.

3.1. Epsilon constraint method

The Epsilon constraint approach is one of the exact methods for calculating Pareto points in multi-objective optimization problems. Additionally, many successful applications have been reported using this approach. In this approach, an objective function is added to the constraints at each step. The general equations of this approach illustrate as follows:

$$\begin{aligned} &minf_1(x)\\ &x\in X\\ &f_2(x)\leqslant\varepsilon_2\\ &\vdots\\ &f_n(x)\leqslant\varepsilon_n \end{aligned} \tag{47}$$

The steps for solving this approach are as follows (Pérez-Cañedo, Verdegay, & Miranda Pérez, 2020):

- Select one of the objective functions as the main objective function,
- Solve the problem with the selected objective function each time,
- Divide the interval between the two optimal values of the sub-objective functions into a predetermined number and obtain a table of values for $\varepsilon_2,\cdots,\varepsilon_n$,
- Solve the problem each time with the main objective function with any of the $\varepsilon_2,\cdots,\varepsilon_n$ values,
- By making changes in the values (εi) are obtained efficient solutions to the problem.

3.2. Multi-objective optimization

In this sub-section, the PSCN problem has three objective functions. In this condition, the interactions amidst the solutions are indicated by the Pareto optimum set. This set comprises the non-dominated solutions. To illustrate this actuality, consider three solutions: solution *A*, *B*, and *C*. Solution *A* dominates the Solutions *B* and *C* when all the objectives of *A* are not worse than *B* and *C* and it is available at least one of *A* that is more reliable than *B* and C (Samadi, Mehranfar, Fathollahi Fard, & Hajiaghaei-Keshteli, 2018). According to the Pareto optimum set, this paper applies four metrics to appraise the quality of Pareto fronts such as many recent pieces of research e.g. (Deb & Padhye, 2014; Devika, Jafarian, & Nourbakhsh, 2014; Sahebjamnia, Goodarzian, & Hajiaghaei-Keshteli, 2020; Fathollahi-Fard, Ahmadi, Goodarzian, & Cheikhrouhou, 2020). In this respect, the solution representation of utilized multi-

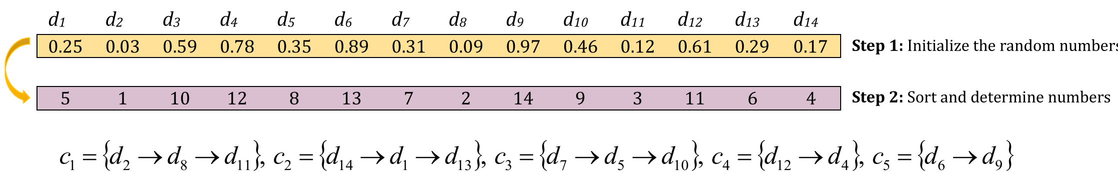

Fig. 3. The utilized method to allocate transportation system to deliver products to customers in each route.

objective metaheuristic algorithms is explained.

3.3. Solution presentation

A scheme should be designed to encode the problem to implement the metaheuristic algorithms (Grobelny & Michalski, 2017). According to this view, a two-stage method called Random-Key is employed (Snyder & Daskin, 2006). Accordingly, this method transforms an unfeasible solution to a feasible one by a set of methods in two stages (Golmohamadi, Tavakkoli-Moghaddam, & Hajiaghaei-Keshteli, 2017). Researchers have used this method in many contexts of engineering design. For more information, refer to references (Quinton, Hamaz, & Houssin, 2019).

Then, a numerical example to encode the solution presentation is exhibited as follows. Six internal and foreign producers (m), three warehouses (w), six customers (c) with two types of vehicles (v) and fifteen pharmaceutical products (p') is considered. First, the sort of utilized vehicle system to transfer each product to customers should be particularized. In this procedure, an array by a length of C is created by a uniform distribution: U (0, c). Then, the sort of vehicle system allocations to carry every product to customers should be interpreted. Furthermore, a set of methods has been displayed in Fig. 2. Hence, the third type of vehicle system is employed for customers c_1, c_2, and c_3. Likewise, the fourth and sixth sort of vehicle systems is used for customers c_4 and c_6, respectively.

Furthermore, an array of the length of D is distributed by U (0,1) to determine the route of the vehicle of products to customers. Next stage, these numbers are classified. Henceforth, these numbers are stipulated to schedule the delivery of products to the customers. Fig. 3 indicates an instance of the utilized arrays of this matrix for algorithms. Especially, based on the maximum optimal total distance travelled, the utilized vehicle capacity, as well as delivered products to the customers' constraints, the route of five utilized vehicle systems for delivered products to the customers, are checked and determined. According to this example, the sixth customers not needed for the routes. These routes are shown as follows:

3.4. Improved social engineering optimization

Even though in recent years several metaheuristic algorithms have been introduced, but researchers nevertheless use traditional algorithms to solve problems. Also, it can be said that over the past two decades, most of the metaheuristic algorithms are population-based and have many steps and parameters that make them difficult to understand and perceive. This research follows an intelligent algorithm like many of the most recent metaheuristic algorithms, and yet very simple, which only includes four steps and three parameters for adjustment. The social engineering optimization (SEO) algorithm was introduced by Fathollahi-Fard, Hajiaghaei-Keshteli, and Tavakkoli-Moghaddam (2018), which has been inspired by the rules of social engineering, an emerging phenomenon in today's real world. Therefore, this algorithm begins with two random solutions called the attacker and defender. Also, search phases are based on the rules of social engineering in which the attacker uses certain techniques to achieve his desired goals. Then, we first introduce the concepts of social engineering and then describe the method inspired by this phenomenon with the description and steps related to it.

In the proposed method, each answer expressing each individual and their characteristics, including their abilities in mathematics, sports, business, etc., expresses the variables of the problem. As mentioned earlier, this algorithm begins with two random solutions, the better solution is called the attacker and the other the defender. Therefore, in order to simulate the learner's training and retraining from the attacker to the defender, a series of random tests are defined for each attribute in which the attacker tests an attribute in the defender and the amount of learning was calculated and the new defender has the highest re-training rate if there is a replacement for the current defender. Further, attacks from the defender are carried out according to the techniques that are available to him. During these actions, the defender is transferred to the attacker's points in order to respond to the attacks and the defender is evaluated and this process is repeated until the end of the strike, and if the defender is more valuable than the attacker, they are replaced by each other and in Ends, a new defender has been used to reboot the algorithm. In this algorithm, like other metaheuristic algorithms, phases of the search are considered. Also, training and retraining of the defender and the attacker from each other forms a local search in the algorithm. In addition, the attacker's attacks on the defender and the response to that focus phase are formed, and eventually, the choice of the new defender will be the phase of diversity for this algorithm.

3.4.1. Initialize the attacker and the defender

The purpose of optimization is to obtain the optimum solution between all available solutions. In this regard, an array should be considered for optimization. In the algorithm, "*chromosome*" represents this array. Here, "*person*" in this algorithm represents this array. Besides, in the genetic algorithm for naming variables, the "*gene*" used to represent it, is employed herein as "*trait*" for persons determining the variables of an array for optimization. In an n-dimensional space for the optimization problem, each person can be defined with the following equations:

$$person=[X_1,X_2,X_3,\ldots,X_{N_{var}}] \tag{48}$$

Hence, the objective function value is calculated as follows:

$$Value=f(person)=f(X_1,X_2,\ldots,X_{N_{var}}) \tag{49}$$

The algorithm begins with two random solutions, the better solution as the attacker and another solution as the defender.

3.4.2. The number of attackers and defenders

In this algorithm, there are two different search factors, which include the attacker and the defender. The number of attackers and defenders as the population is considered in this search space. The number of attackers is randomly chosen from 65% to 90% of the total population. The number of attackers obtained from Eq. (50) is:

$$N_a=floor[(0.9-rand\times 0.25)\times N] \tag{50}$$

where $rand$a random number is among [0,1]. Meanwhile, $floor(0)$mapping a real number is an integer. The number of defenders (N_d)as complementary between (N) and (N_a) is calculated as Eq. (51):

$$N_d=N-N_a \tag{51}$$

Furthermore, the total population (M) is formed by elements of N

and are divided into two subgroups G and Q. Moreover, G and Q sizes are controlled by a predetermined constant ρratio. The group of G is a set of attackers $G = \{G_1, G_2, ..., G_{N_a}\}$. Meanwhile, the group of Q includes defenders$Q = \{Q_1, Q_2, ..., Q_{N_d}\}$. wherein, $M = \{M_1, M_2, ..., M_N\}$. So,

$$M = m_1 = G_1,\ M_2 = G_2, ..., M_{N_a} = G_{N_a},\ M_{N_a+1} = Q_1, M_{N_a+2} = Q_2, ..., M_N = Q_{N_d}$$

3.4.3. Training and retraining

At this stage, we intend to demonstrate the defender's and the attacker's training and retraining. In this process, the attacker will choose the most influential trait. For this purpose, α percent of the traits are randomly chosen and repeated directly in the same trait in the defender. The number of traits for training is given by the formula:

$$N_{Train} = round\{\alpha,\ nVar\} \tag{52}$$

where α is the percent of chosen characteristics and $nVar$ is the total number of traits per person. Hence, N_{Train} is the number of characteristics that are randomly tested in the defender.

3.4.4. Defender and attacker evaluation criteria

In this step, each defender and the attacker have one weight W_a and W_d, that indicates the quality of the solution to the defender d and the attacker 'a' of the population (M). Therefore, equations (53) and (54) have been used to calculate the weight of each attacker and defender.

$$W_a = \frac{K(M_a) - worst_m}{best_m - worst_m} \tag{53}$$

$$W_d = \frac{K(M_d) - worst_m}{best_m - worst_m} \tag{54}$$

where $K(M_a)$and $K(M_d)$ capability is obtained by evaluating the attacker's position and defender and according to the objective function $K(0)$. Values $worst_m$ and $best_m$ are defined as equations (55) and (56):

$$best_m = \min_{i \in (1,2,...,M)} (K(M_i)) \tag{55}$$

$$worst_m = \max_{i \in (1,2,...,M)} (K(M_i)) \tag{56}$$

3.4.5. Spot an attack

At this stage, in order to carry out an attack, this research proposes four various techniques, including obtaining, phishing, diversion theft and pretext. In the following, a random technique is used as a search function. Additionally, only one input parameter called β is required for adjustment. Besides, the arrow sign indicates the way in which the defender moves. In all phrases, def_{new} represents the new defender during the attack, and def_{old}, att indicate the current position of the attacker and the defender, respectively. Therefore, this algorithm gives the user the opportunity to use one of the four suggested techniques for his or her own point of view.

3.4.5.1. Obtaining. At this stage, the attacker disturbs the defender directly to attain desirable purposes. Then, a novel solution is generated and the strategy is based on the following equation:

$$def_{new} = def_{old} \times (1 - sin\beta \times U(0,1)) + \frac{(def_{old} + att)}{2} \times sin\beta \times U(0,1) \tag{57}$$

3.4.5.2. Phishing. To the design of this technique, the attacker tends towards a defender, and the defender moves to a place where the attacker has predicted it. The equations are displayed as follows:

$$def^1_{new} = att \times (1 - sin\beta \times U(0,1)) + \frac{(def_{old} + att)}{2} \times sin\beta \times U(0,1) \tag{58}$$

$$def^2_{new} = def_{old} \times \left(1 - sin\left(\frac{\pi}{2} - \beta\right) \times U(0,1)\right) + \frac{(def_{old} + att)}{2} \times sin\left(\frac{\pi}{2} - \beta\right) \times U(0,1) \tag{59}$$

Eqs. (58) and (59) show two novel defenders by a movement according to the attacker and the defender, respectively. In this regard, the mean distance between the attacker and the defender is the principal part of the movement. Besides, the common position of the attacker in Eq. (58) and the common position of the defender in Eq. (59), are the principal reasons to move the defender in this attack. The movement is according to a random distribution *i.e.* $U(0,1)$and the quantity of β is to accomplish this purpose.

3.4.5.3. Diversion theft. In this section, first of all, the attacker pushes the defender into a place that is, in reality, a deception, and then the defender moves in the attacker's direction and pushes the attacker to his desirable goal. At this stage, only one solution is generated. The equation is shown as follows:

$$def_{new} = def_{old} \times (1 - sin\beta \times U(0,1)) + \frac{\left(def_{old} + att \times U(0,1) \times sin\left(\frac{\pi}{2} - \beta\right)\right)}{2} \times sin\beta \times U(0,1) \tag{60}$$

Eq. (60) tries to propose the movement of the defender by presenting its common position and the mean of distance among the defender and a weighted amount of attacker to accomplish the purpose. The uniform distribution $U(0,1)$and the quantity of β play the principle variety of this movement of the defender in this spotting attack.

3.4.5.4. Pretext. The attacker uses a number of traits that the defender is more inclined to them. And it is expected that this technique will be more than enough to defeat the defender. First, as a diversion theft, the defender first moves forward to the attacker. The equations are displayed as follows:

$$def_{new} = \left(def_{old} \times U(0,1) \times sin\left(\frac{\pi}{2} - \beta\right)\right) \times (1 - sin\beta \times U(0,1)) + \frac{\left(def_{old} \times U(0,1) \times sin\left(\frac{\pi}{2} - \beta\right) + att\right)}{2} \times sin\beta \times U(0,1) \tag{61}$$

3.4.5.5. Respond to attack. The new defender's position is assessed and compared with the previous position. If it was better, it would be replaced and if the final position of the defender was more reliable than the attacker, they would replace.

3.4.6. Adjustment operator

This improved algorithm is introduced with an adjustment operator

For (i=1;i< M_d +1;i++)
  For (j=1; j<n+1; j ++)
    $$d_{i,j}^{0} = p_j^{low} + rand(0,1).(p_j^{high} - p_j^{low})$$
  End for
End for
For (k=1;i< M_a +1;k++)
  For (j=1; j<n+1; k++)
    $$a_{k,j}^{0} = p_j^{low} + rand(0,1).(p_j^{high} - p_j^{low})$$
  End for
End fore

Fig. 4. The pseudo-code of initialization.

For (a=1; a<M+1; a++)
  For (d=1; d<M+1; d++)

$$W_a = \frac{K(M_a) - worst_m}{best_m - worst_m}$$

$$W_d = \frac{K(M_d) - worst_m}{best_m - worst_m}$$

Where $best_m = \max_{i\in(1,2,\ldots,M)}(K(M_i))$ and $\min_{i\in(1,2,\ldots,M)}(K(M_i))$

End for
  End for

Fig. 5. The pseudo-code of calculating the weight of each attacker and defender.

to enhance its efficiency in terms of search precision and running time. This operator is used to make a novel generation. The size of this part is equal to the size of G and Q. This operator creates a new division according to the best person and other random people from G and Q. Also, we assume that $Y_{o,j}^{t+1}$the value of the element j is the number of individuals o, then$Y_{o,j}^{t+1}$ generated based on Eq. (62):

$$Y_{o,j}^{t+1} = \begin{cases} Y_{best,j}^{t} & rand \leqslant \rho \\ Y_{r3,j}^{t} & rand > \rho \end{cases} \tag{62}$$

where r is a random number obtained from equation (63). Where '*rand*' is a random number of uniform distribution and δ a fixed value equal to 1.2. Also, t is the number of iterations.

$$r = rand \times \delta \tag{63}$$

In Eq. (63), parts of the newly created person are updated according to Eq. (64), if the number of other random numbers created is greater than the adjustment rate. The adjustment rate is shown by the BAR and the set is equal to the fixed partition. In Eq. (65) dy, a local search is represented by the training and retraining of the defender and the attacker in each other in this algorithm. 'μ' is an element that controls the penetration of dy in the updating process.

$$Y_{o,j}^{t+1} = Y_{o,j}^{t+1} + \mu(dL_y - 0.5) \tag{64}$$

$$dy = RT(Y_o^t) \tag{65}$$

3.4.7. Choose a novel person as a defender

During this section, the attacker has destroyed the defender and the novel defender is randomly replaced.

For i = 1 to num Q **do**
  Scale=max Step Size(Iter)
  Step Size=exprnd (2*Max Iter)
  DeltaY=RT (StepSize, Dim)
  For j=1 to Dim **do**
    If rand ≥ partition, **then**
      Q (i, j) =Best(j)
    Else
      r_4=round (num Q*rand+0.5)
      Q (i, j) =Population (r_4, j)
      If rand>BAR, **then**
        Q(i, j) = Q(i, j) +scale*(delta Y(j)-0.5)
      End if
    End if
  End for
End for

Fig. 6. The pseudo-code of adjustment operator.

3.4.8. Stop condition

Like other metaheuristic algorithms, the stop condition can be used to maximize the simulation time or find the best solution, or any conditions that are chosen by the user.

3.5. Computational method of ISEO

The computational method for the presented algorithm is as follows:

Step 1: Given M as the number of members of the m-dimensional set, the number of defenders M_d and the number of attackers M_a in the total population is defined as:

$$N_a = floor[(0.9 - rand \times 0.25) \times N] \tag{66}$$

$$N_d = N - N_a \tag{67}$$

where *rand* a random number is between [0,1]. Meanwhile, $floor(0)$mapping a real number is an integer.

Step 2: Initialization is randomly for the defender Eq. (68), the attacker Eq. (69), and for the set of member Eq. (70). In Fig. 4, an initialized pseudo code is presented.

$$Q = \{Q_1, Q_2, \ldots, Q_{N_d}\} \tag{68}$$

$$G = \{G_1, G_2, \ldots, G_{N_a}\} \tag{69}$$

$$M = m_1 = G_1, M_2 = G_2, \ldots, M_{N_a} = G_{N_a}, M_{N_a+1} = Q_1, M_{N_a+2} = Q_2, \ldots, M_N = Q_{N_d} \tag{70}$$

Step 3: At this stage, we intend to demonstrate the defender's and attacker's training and retraining. In this step, the attacker chooses the most influential trait. For this purpose, α percent of the characteristics are elected randomly and repeated directly in the same trait in the defender. The number of traits for training is indicated in Eq. (71).

$$N_{Train} = round\{\propto .nVar\} \tag{71}$$

where α percent is selected traits and $nVar$ is the total number of characteristics per person. Moreover, $N_{Train}$is the number of characteristics that are randomly tested in the defender.

Step 4: Calculate the weight of each defender and attacker from the population of N, which is expressed in pseudo-code in Fig. 5.

Step 5: In order to carry out an attack, this algorithm proposes four various techniques, including obtaining, phishing, diversion theft, and pretext.

Step 6: This improved algorithm is introduced with an adjustment operator to enhance its efficiency in terms of search precision and running time. In the following, we will express its pseudo-code in Fig. 6.

Step 7: In this step, the attacker finally defeats the defender and the new defender is randomly replaced.

```
T1=clock;
Initialize attacker and defender
It=1;
For (i=1;i< M_d +1;i + +)
  For (j=1; j<n+1; j + +)
      d^0_{i,j} = p_j^{low} + rand(0,1).(p_j^{high} - p_j^{low})
  End for
End fore
For (k=1;i< M_a +1;k++)
  For (j=1; j<n+1; k++)
      a^0_{k,j} = p_j^{low} + rand(0,1).(p_j^{high} - p_j^{low})
  End for
End for
        For (a=1; a<M+1; a++)
          For (d=1; d<M+1; d++)
```

$$W_a = \frac{K(M_a) - worst_m}{best_m - worst_m}$$

$$W_d = \frac{K(M_d) - worst_m}{best_m - worst_m}$$

Where $best_m = \max_{i \in (1,2,\ldots,M)} (K(M_i))$ *and*

$$\min_{i \in (1,2,\ldots,M)} (K(M_i))$$

```
        End for
          End for
while solving_time < Max_time
    Do training and retraining;
    Num_attack=1;
    while Num_attack < Max_attack
          Spot an attack;
          Check the boundary;
          Respond to attack;
          if the OF of defender is lower than attacker
            Exchange the defender and attacker position;
          End if
          Num_attack= Num_attack+1;
    End while
              For i=1 to num Q do
                    Scale=max Step Size(Iter)
                    Step Size=exprnd (2*Max Iter)
                    DeltaY=RT(StepSize, Dim)
                    For j=1 to Dim do
                      If rand ≥ partition, then
                          Q (i, j) =Best(j)
                      Else
                          r4=round (num Q*rand+0.5)
                          Q (i, j) =Population (r4, j)
                          If rand>BAR, then
                              Q (i, j) = Q(i, j)+scale*(delta Y(j)-0.5)
                          End if
                      End if
                    End for
                  End for
    Create a new solution as defender;
    It=It+1;
    T2=clock;
    Solving_time=T2- T1;
End while
Return attacker.
```

Fig. 7. The pseudo-code of proposed ISEO.

Step 8: If the stop criteria are met, the process ends, otherwise we will go back to step 3.

Therefore, Fig. 7 indicates a pseudo-code ISEO algorithm.

3.6. Hybrid Firefly and Simulated Annealing algorithms (HFFA-SA)

In this subsection, the Firefly Algorithm (FFA) and Simulated Annealing (SA) algorithm are used, which is explained as another innovation of this paper in this section. Then, by applying the Hybrid FFA-SA (HFFA-SA) algorithm, it will increase the efficiency of the main algorithms because it converts the unfeasible solutions created by the main algorithms into a feasible one. Moreover, the pseudo-code and mechanism of performance of the HFFA-SA algorithm are shown in Fig. 8.

3.7. Heuristic approach

Other contributions of the present paper are to develop several

```
            %%Hybrid FFA-SA algorithm Parameters

MaxIt=500; % Maximum Number of Iterations
MaxSubIt=10; % Maximum Number of Sub-iterations
T0=10; % Initial Temp.
alpha=0.99; % Temp. Reduction Rate
nPop=40; % Number of Fireflies (Swarm Size)
gamma=1; % Light Absorption Coefficient
beta=2; % Attraction Coefficient Base Value
alpha=0.2; % Mutation Coefficient
alpha_damp=0.99; % Mutation Coefficient Damping Ratio
delta=0.05*(VarMax-VarMin); % Uniform Mutation Range
m=2;

 %%Initialization
 %Empty Firefly Structure
Firefly. Position= [];
Firefly. Cost= [];

 %Initialize Population Array
pop=repmat(firefly, nPop,1);
 %Initialize Best Solution Ever Found
Best Sol. Cost=inf;

 %Create Initial Fireflies
for i=1:nPop
    pop(i). Position=unifrnd(VarMin, VarMax, VarSize);
    pop(i). Cost=Cost Function(pop(i). Position);

    if pop(i).Cost<=BestSol.Cost
        Best Sol=pop(i);
    end
end
 %Array to Hold Best Cost Values
Best Cost=zeros(MaxIt,1);
 %Initialize Temp.
T=T0;
 %%Hybrid FFA-SA algorithm Main Loop
for it=1: MaxIt
  for subit=1: MaxSubIt
    new pop=pop;
    for i=1:nPop
        for j=1:nPop
            if pop(j). Cost<=pop(i).Cost
                rij=norm(pop(i). Position-pop(j). Position);
                beta=beta0*exp(-gamma*rij^m);
                e=delta*unifrnd(-1,+1,VarSize);
                e=delta*randn(VarSize);
                new pop(i). Position=pop(i). Position...
                     +beta*(pop(j).Position-pop(i).Position)...
                          +alpha*e;
                New pop(i).Position=max(newpop(i).Position,VarMin);
                New pop(i).Position=min(newpop(i).Position,VarMax);
                New pop(i).Cost=CostFunction(newpop(i).Position);
                if new pop(i).Cost<=Best Sol. Cost
                    Best Sol=new pop(i);
                end
            end
        end
    end

    %Merge
    pop= [pop
         new pop
         Best Sol]; %#ok

    %Sort
    [~, Sort Order] =sort ([pop. Cost]);
    pop=pop (Sort Order);

   %Compare using SA Rule
        for i=1:nPop
            if new pop(i).Cost<=pop(i).Cost
                pop(i)=newpop(i);
            else
                DELTA=(new pop(i).Cost-pop(i).Cost)/pop(i).Cost;
                P=exp(-DELTA/T);
                if rand<=P
                    pop(i)=new pop(i);
                end
            end
    %Truncate
    pop=pop(1:nPop);
    %Store Best Cost Ever Found
    Best Cost(it)=Best Sol. Cost;
    %Show Iteration Information
    disp (['Iteration ' num2str(it) ': Best Cost = ' num2str (Best Cost(it))]);
   %Damp Mutation Coefficient
    alpha=alpha*alpha_ damp;
    %Temp. Reduction
    T=alpha*T;
  end
end
```

Fig. 8. The pseudo-code of the proposed HFFA-SA.

heuristic algorithms to approximate the global optimum solution for the recommended model in a sensible time. Besides, two heuristic algorithms analyzing a distinguished strategy and concentrating on the key parameters of the model are extended. Furthermore, we extend three heuristics (H-1), (H-2), and (H-3) to solve the model. Eventually, these (H-1), (H-2), and (H-3) are compared. According to the presented model, all these heuristics are proposed to better understand the presented model. The gist decision variables are binary variables of the model. *i. e.,*$O^t_{wcr_{wc}}$,$O^t_{mwr_{mw}}$and$O^t_{mcr_{mc}}$ properly. Each of the heuristics presents a similar matrix close to the decision variable. To hold on to the objective function, the routes for vehicles are designed by analyzing the distance among internal and foreign producers, central pharmacies, and warehousesd_{mw},d_{mc}, and d_{wc}as well as the amount of transportation cost for each vehicle in the different routes$\phi^{t\,r_{mw}}_{p'mwv}$, $\phi^{t\,r_{mc}}_{p'mcv}$ and$\phi^{t\,r_{wc}}_{p'wcv}$. In this respect, the following formula is generated for the principle input of heuristics:

$$\alpha^{tr_{mw}}_{p'mwv} = \phi^{t\,r_{mw}}_{p'mwv} \times d_{mw} \forall m1, p', v1, r_{mw}, w, t \tag{72}$$

$$\alpha^{tr_{mw}}_{p'mwv} = \phi^{t\,r_{mw}}_{p'mwv} \times d_{mw} \forall m1, p', v2, r_{mw}, w, t \tag{73}$$

$$\alpha^{tr_{mw}}_{p'mwv} = \phi^{t\,r_{mw}}_{p'mwv} \times d_{mw} \forall m2, p', v2, r_{mw}, w, t \tag{74}$$

$$\alpha^{tr_{mc}}_{p'mcv} = \phi^{tr_{mc}}_{p'mcv} \times d_{mc} \forall m1, p', v1, r_{mc}, c, t \tag{75}$$

$$\alpha^{tr_{mc}}_{p'mcv} = \phi^{tr_{mc}}_{p'mcv} \times d_{mc} \forall m1, p', v2, r_{mc}, c, t \tag{76}$$

$$\alpha^{tr_{mc}}_{p'mcv} = \phi^{tr_{mc}}_{p'mcv} \times d_{mc} \forall m2, p', v2, r_{mc}, c, t \tag{77}$$

$$\alpha^{tr_{wc}}_{p'wcv} = \phi^{tr_{wc}}_{p'wcv} \times d_{wc} \forall m1, p', v1, r_{wc}, c, t \tag{78}$$

$$\alpha^{tr_{wc}}_{p'wcv} = \phi^{tr_{wc}}_{p'wcv} \times d_{wc} \forall m1, p', v2, r_{wc}, c, t \tag{79}$$

where $\alpha^{tr_{mw}}_{p'mwv}$,$\alpha^{tr_{mc}}_{p'mcv}$and$\alpha^{tr_{wc}}_{p'wcv}$, are the principal input of all heuristics. Only the first step of each heuristic is different, and the other steps are the same. The central strategy of them is according to the allocation of internal and foreign producers, central pharmacies, and warehouses. throughout, the first step of heuristics is explained as follows:

- Heuristic 1 (H-1): To set the route of each internal producer and warehouse, the first vehicle is to consider the minimum number of the first row of the matrix indicated based on Eq. (72) in Fig. 8. The other vehicles are chosen by the minimum number of this matrix in the other rows.
- Heuristic 2 (H-2): For the tour of each internal producer and warehouse, choosing the first vehicle is started with the average of each row of the matrix presented in Eq. (73). Similar to H-1, choosing the other vehicles of the route is according to the minimum digit of this matrix in the other rows.
- Heuristic 3 (H-3): A heuristic method is developed to achieve solutions for the PSCN model. Hence, (H-3) based on binary variable relaxation is presented. The suggested heuristic (H-3) is tested for all samples small, medium, and large experiments. In the following, a flowchart of the H-3 approach is indicated in Fig. 9.

To strongly understand the heuristics, a numerical instance for per heuristic is given with details in Fig. 10. In the following, a set of numerical instances indicates the description of the H-2 heuristic in Fig. 10. The rate of transportation cost for four sorts of the vehicle *i.e.* the ground vehicle nine-pharmaceutical products with different period and different routes that their costs are four-unit. For every route as demonstrated before, the first pharmaceutical products are chosen based on chosen rules of H-2. To run the H-2 proposed, amongst all arrays of $\alpha^{tr_{mw}}_{p'mwv}$the matrix, in the first row of each vehicle, the minimum one is chosen. This means that pharmaceutical product 4 for the first sort of vehicle is elected. Henceforward, this method is used for pharmaceutical product 4 as can be displayed in Fig. 10. Likewise, pharmaceutical product 3 is chosen. Then, the column of pharmaceutical product 4 is deleted and then pharmaceutical product 5 is selected by the same procedure similar to earlier. Note that in H-2, the routes are considered based on the capacity of utilized vehicles. According to the limitation of the details of proposed model constraints, the principle decision variable values of the model ($\alpha^{tr_{mw}}_{p'mwv}$) are indicated in Fig. 10.

3.8. Constraint handling strategy

In this paper, most of the constraints are satisfied with the settings of heuristic algorithms, but in order to satisfy other constraints, a penalty

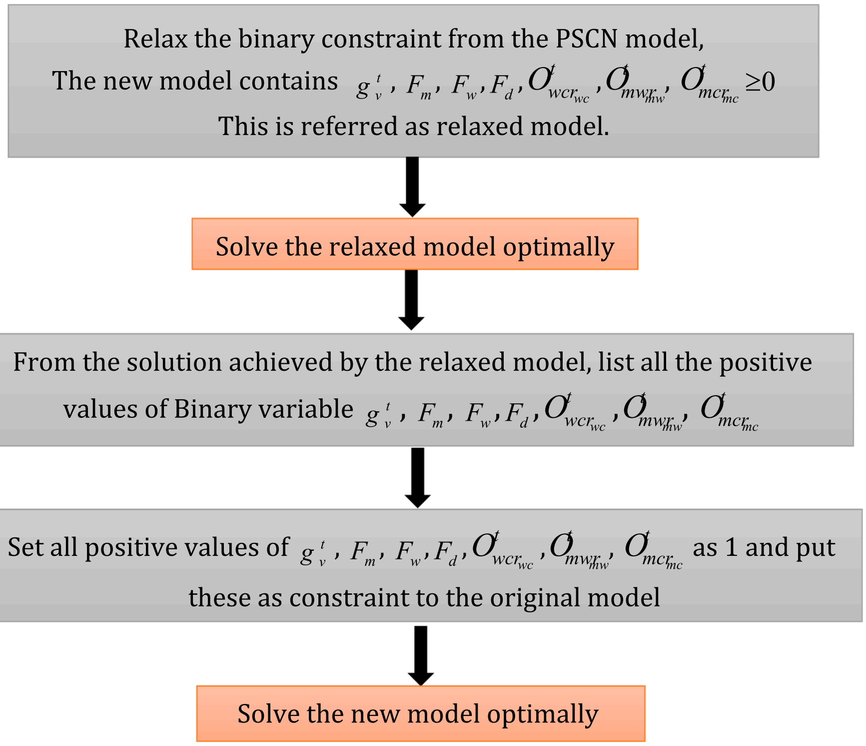

Fig. 9. The flowchart of H-3 approach.

$\alpha_{p'mwv}^{tr_{mw}}$		1	2	3	4	5	6	7	8	Avg.
v=4: nine-pharmaceutical products, three-internal producer, and two-warehouses	1	#	334	265	178	433	211	132	120	239
	2	334	#	118	233	289	278	301	199	250.28
	3	265	118	#	166	251	88	123	244	179.28
	4	178	101	166	#	288	160	219	433	192.14
	5	433	289	251	288	#	112	68	220	237.29
	6	88	278	211	160	112	#	323	267	205.57
	7	132	301	123	291	120	323	#	390	232.57
	8	120	199	244	101	220	267	390	#	220.14

H-2:
The first route: 0→6→1→8→4→2→0
$Z_{9324}^{106} = Z_{9324}^{261} = Z_{9324}^{318} = Z_{9324}^{484} = Z_{9324}^{442} = Z_{9324}^{420} = 1$
The second route: 0→3→7→5→0
$Z_{9324}^{103} = Z_{9324}^{237} = Z_{9324}^{375} = Z_{9324}^{450} = 1$
The other same variables are equal zero.

Fig. 10. A numerical example of H-2.

strategy is used. The considered constraint handling was for capacity-related constraints. For example, warehouse and customer capacity constraints are listed here. The solution process is such that the maximum amount of constraints is calculated. If this value is negative, the number zero is selected as the maximum. Then, according to the dynamics of the proposed method, the calculated total value is multiplied by the number of iterations. Finally, the calculated amount is multiplied by the penalty amount. For more information, you can refer to Khalili-Damghani, Abtahi, and Ghasemi (2015). The main idea of constraint handing is taken from Khalili-Damghani et al. (2015). Constraint handling is provided as dynamic and will change based on the number of iterations. For example, equations (80) and (81) are used to calculate violations of constraints 4 and 5:

$$A_f = O_{wt}^4 = \max_{\forall w,t}\{0, \sum_{p'}\sum_{m1}\sum_{r_{mw}} Q_{p'mw}^{tr_{mw}} B_{p'} + \sum_{p'}\sum_{m2}\sum_{r_{mw}} Q_{p'mw}^{tr_{mw}} B_{p'}) - \omega_w \, . \, F_w \,\} \forall f = 1,2 \tag{80}$$

$$B_f = O_{ct}^5 = \max_{\forall c,t}\left\{0, \sum_{p'}\sum_{w}\sum_{r_{wc}} Q_{p'wc}^{tr_{wc}} . B_{p'} - \omega_c . F_c\right\} \forall f = 1,2 \tag{81}$$

It should be noted that the index f is equal to the number of objective functions. The calculated violation value according to Eq. (82) is equal to the sum of each violation:

Table 2
The instances for experiment problem.

Classification	Instance	m	w	c	v	p'	t
Small	SP1	2	4	3	3	10	1
	SP2	2	4	3	3	15	1
	SP3	3	4	4	3	25	1
	SP4	4	5	4	4	35	2
	SP5	5	5	5	4	45	2
Medium	MP6	6	5	6	5	50	2
	MP7	6	6	6	5	55	2
	MP8	7	6	7	6	65	2
	MP9	7	7	7	6	70	3
	MP10	8	7	8	6	75	3
Large	LP11	8	8	10	14	85	4
	LP12	10	12	12	18	95	5
	LP13	12	16	14	22	140	6
	LP14	14	20	16	26	160	7
	LP15	16	24	18	30	180	8

$$Violation_f = \left(A_f + B_f\right)*iteration \tag{82}$$

It should be noted that in Equation (82), the violation value is dynamic due to the iteration value. In this way, the higher the iteration, the greater the amount of the violation value will be. Therefore, the value of the ultimate objective functions is defined as Equation (82) for penalized chromosomes. As the iteration of the algorithm goes on, the violated chromosome is penalized harder.

The value of the calculated violation in Eq. (83) is dynamic and changes based on the number of iterations.

$$f_c = f_c + penalty*Violation_c \ \forall c = 1, 2 \tag{83}$$

4. Numerical experiments, results, and discussion

Firstly, the experiment problems are created by a method related to the proposed pharmaceutical supply chain network. Regarding the three conflicting objective functions, four assessing metrics are introduced to evaluate the quality of non-dominated solutions of the metaheuristic algorithms. After that, a comprehensive analysis is presented by comparison of the developed three heuristics (H-1), (H-2), and (H-3) and the ISEO and HFFA-SA algorithms based on algorithm parameter values. Consequently, the best trade-off among three objective functions is investigated and the best heuristics by comparison of developed heuristics are selected, as well as the best method for the problem is proposed. The proposed model was tested using GAMS 24.1.3 software and MATLAB R2016b on a computer with Intel (R) Core (TM) i5-2400 2.50 GHz in CPU and 6 GB memory and utilizing Windows 8.1 as an operating system.

4.1. Data generation

As the proposed model in this study is innovative, there are no available benchmarks in the literature to experiments on the proposed pharmaceutical supply chain network problem. An approach is required to generate experimental problems. Fifteen experimental problems involving three classifications including small-scale: SP1 to SP5, medium scale: MP6 to MP10 and large-scale: LP11 to LP15 are proposed. Table 2 indicates the scales of problem instances. The range of the proposed model parameters could be seen in Table 3. Furthermore, Table 4 explains the presented levels along with the factors.

Table 4
Values of parameter setting of the algorithms.

Factors	levels			
	ISEO			
	1	2	3	4
Max Iteration	100	200	300	400
M_a (Number of attacker)	50	100	150	200
M_d (Number of defender)	50	100	150	200
α (Rate of collecting data)	0.2	0.25	0.3	0.35
β (Rate of connecting attacker)	0.5	0.55	0.65	0.7
dy (a local search for the training and retraining)	0.3	0.5	0.7	0.9
W_a (Weight of the each attacker)	0.1	0.15	0.2	0.25
W_d (Weight of the each defender)	0.2	0.25	0.3	0.35
Factors	HFFA-SA			
	1	2	3	4
MaxIt	100	200	300	400
MaxSubIt	10	20	30	40
T0; Initial Temp.	10	15	20	25
alpha; Temp. Reduction Rate	0.8	0.85	0.9	0.99
nPop; Number of Fireflies (Swarm Size)	40	50	60	80
$gamma = 1$; % Light Absorption Coefficient	1	1.5	2	2.5
beta; Attraction Coefficient Base Value	2	2.5	3	3.5
alpha; Mutation Coefficient	0.2	0.25	0.3	0.35
alpha_damp; Mutation Coefficient Damping Ratio	0.8	0.85	0.9	0.99
$delta = 0.05*$(VarMax-VarMin); Uniform Mutation Range	–	–	–	–
m	2	3	4	5

Table 5
The results of calculation and CPU time for small and medium scale test problems.

Classification	Instance	$F1$(dollars)	$F2$(seconds)	$F3$(%)	Time (s)
Small scale	SP1	2134325.06	1914226.39	6.28	4
	SP2	2344336.23	2033153.35	7.42	38
	SP3	2422667.82	2232227.50	9.01	72
	SP4	2735633.09	2345165.08	9.98	97
	SP5	2883218.08	2533240.24	11.25	219
Medium scale	MP6	2923536.35	2772676.42	15.78	711
	MP7	3167883.78	2942562.85	16.33	1617
	MP8	3481249.09	3166451.70	18.08	2884
	MP9	3633129.50	3361545.93	18.89	5936
	MP10	3815435.27	3506547.11	19.17	9826

Table 3
The range of the proposed model parameters.

Parameters	Value/distribution	Parameters	Value/distribution
$\alpha^t_{cp'}\ \alpha^t_{wp'}\ \alpha^t_{mp'}$	$Uniform(100000, 200000)\$$	$\mu_{mwr_{mw}}\ \mu_{mcr_{mc}}\ ,\mu_{wcr_{wc}}$	$Uniform(25, 120)min$
δ^t_w,δ^t_m	100000	D	30
$\beta^t_{wmp'}\ \beta^t_{cmp'},\ \beta^t_{cwp'},L^t_{p'},B^t_{p'm}$	$Uniform(150000, 250000)$	$d_{mw}\ d_{mc},d_{wc}$	$Uniform(45, 1000)km$
$P^t_{p'},C^t_{p'},\psi^t_{p'm}$	$Uniform(50000, 150000)$	$Init^t_{wp'},Init^t_{cp'},I_{p'}$	2000
$\phi^{t\,r_{mw}}_{p'mwv},\phi^{t\,r_{mc}}_{p'mcv},\ \phi^{t\,r_{wc}}_{p'wcv}$	$Uniform(150000, 250000)$	R	550
D_{max},M_{max},W_{max}	50000	$\omega_w,\omega_c,\omega_v$	$Uniform(150000, 250000)$
$D^t_{cmp'}\ D^t_{wmp'},D^t_{cwp'},E^t_c,K^t_{p'w}$	$Uniform(150000, 250000)$	$\partial^t_{p'wm},\partial^t_{p'cm},\partial^t_{p'cw},\varepsilon^t_{p'w}$	$Uniform(20000, 50000)$
$\theta^t_{p'wm},\theta^t_{p'cm},\theta^t_{p'cw}$	$Uniform(200000, 350000)$	Big$M$	1000000

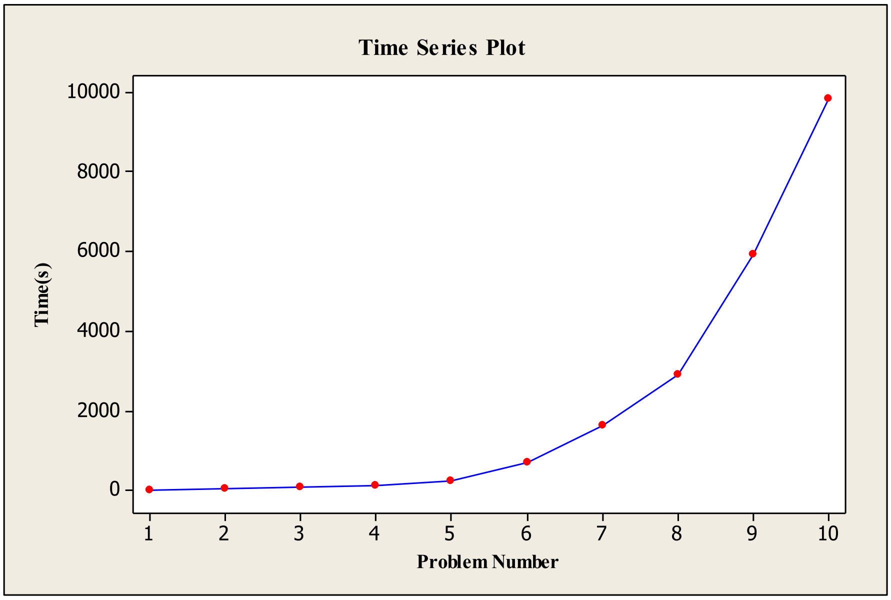

Fig. 11. CPU time of the exact method based on the small and medium problems.

Table 6
The orthogonal array ISEO algorithm.

L32	A	B	C	D	E	F	G	H
1	1	1	1	1	1	1	1	1
2	1	1	1	1	1	1	1	1
3	1	1	1	1	1	2	2	2
4	1	1	1	1	1	2	2	2
5	1	2	2	2	2	1	1	1
6	1	2	2	2	2	1	1	1
7	1	2	2	2	2	2	2	2
8	1	2	2	2	2	2	2	2
9	2	1	1	2	2	1	1	2
10	2	1	1	2	2	1	1	2
11	2	1	1	2	2	2	2	1
12	2	1	1	2	2	2	2	1
13	2	2	2	1	1	1	1	2
14	2	2	2	1	1	1	1	2
15	2	2	2	1	1	2	2	1
16	2	2	2	1	1	2	2	1
17	3	1	2	1	2	1	2	1
18	3	1	2	1	2	1	2	1
19	3	1	2	1	2	2	1	2
20	3	1	2	1	2	2	1	2
21	3	2	1	2	1	1	2	1
22	3	2	1	2	1	1	2	1
23	3	2	1	2	1	2	1	2
24	3	2	1	2	1	2	1	2
25	4	1	2	2	1	1	2	2
26	4	1	2	2	1	1	2	2
27	4	1	2	2	1	2	1	1
28	4	1	2	2	1	2	1	1
29	4	2	1	1	2	1	2	2
30	4	2	1	1	2	1	2	2
31	4	2	1	1	2	2	1	1
32	4	2	1	1	2	2	1	1

Table 7
The orthogonal array HFFA-SA algorithm.

L32	A	B	C	D	E	F	G	H	J	K	L
1	1	1	1	1	1	1	1	1	1	1	1
2	1	1	1	1	1	1	1	1	1	1	1
3	1	1	1	1	1	2	2	2	2	2	2
4	1	1	1	1	1	2	2	2	2	2	2
5	1	2	2	2	2	1	1	1	1	2	2
6	1	2	2	2	2	1	1	1	1	2	2
7	1	2	2	2	2	2	2	2	2	1	1
8	1	2	2	2	2	2	2	2	2	1	1
9	2	1	1	2	2	1	1	2	2	1	1
10	2	1	1	2	2	1	1	2	2	1	1
11	2	1	1	2	2	2	2	1	1	2	2
12	2	1	1	2	2	2	2	1	1	2	2
13	2	2	2	1	1	1	1	2	2	2	2
14	2	2	2	1	1	1	1	2	2	2	2
15	2	2	2	1	1	2	2	1	1	1	1
16	2	2	2	1	1	2	2	1	1	1	1
17	3	1	2	1	2	1	2	1	2	1	2
18	3	1	2	1	2	1	2	1	2	1	2
19	3	1	2	1	2	2	1	2	1	2	1
20	3	1	2	1	2	2	1	2	1	2	1
21	3	2	1	2	1	1	2	1	2	2	1
22	3	2	1	2	1	1	2	1	2	2	1
23	3	2	1	2	1	2	1	2	1	1	2
24	3	2	1	2	1	2	1	2	1	1	2
25	4	1	2	2	1	1	2	2	1	1	2
26	4	1	2	2	1	1	2	2	1	1	2
27	4	1	2	2	1	2	1	1	2	2	1
28	4	1	2	2	1	2	1	1	2	2	1
29	4	2	1	1	2	1	2	2	1	2	1
30	4	2	1	1	2	1	2	2	1	2	1
31	4	2	1	1	2	2	1	1	2	1	2
32	4	2	1	1	2	2	1	1	2	1	2

Accordingly, a maximum of four levels is considered to the algorithm's factors.

4.2. Exact solution results

The results of solving the proposed model in small and medium sizes by the Epsilon constraint approach are provided in Table 5. As can be seen, five instances are given for small and medium problems. As it is clear, the CPU time of the exact approach increases dramatically by increasing problem size.

The first objective function is of cost, its unit is US dollars. The second objective function of time and its unit is in seconds. Finally, the third objective function, which is responsible for maximizing system transportation reliability, is scaleless.

The CPU time of the presented model by the Epsilon constraint approach is shown in Fig. 11. As it is evident, the CPU time of the presented model increases exponentially. Therefore, to solve the proposed problem on a large scale, heuristic and *meta*-heuristic algorithms have to

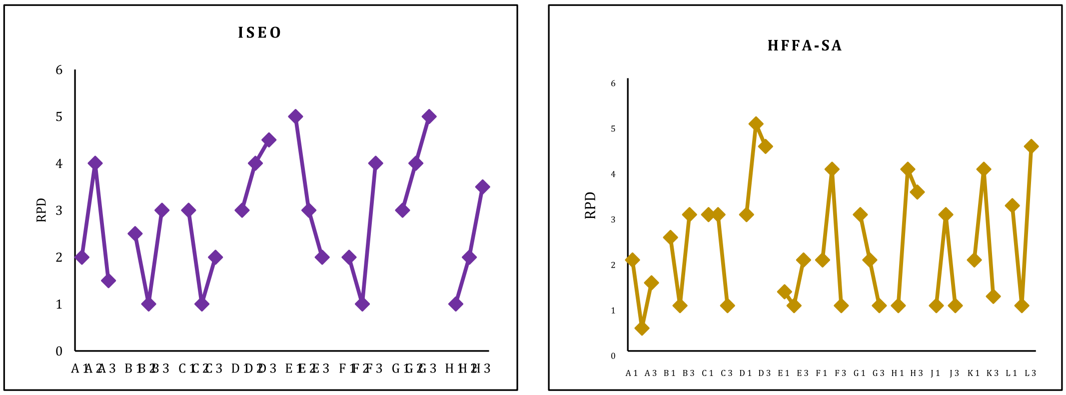

Fig. 12. The RPD ratios of ISEO and HFFA-SA.

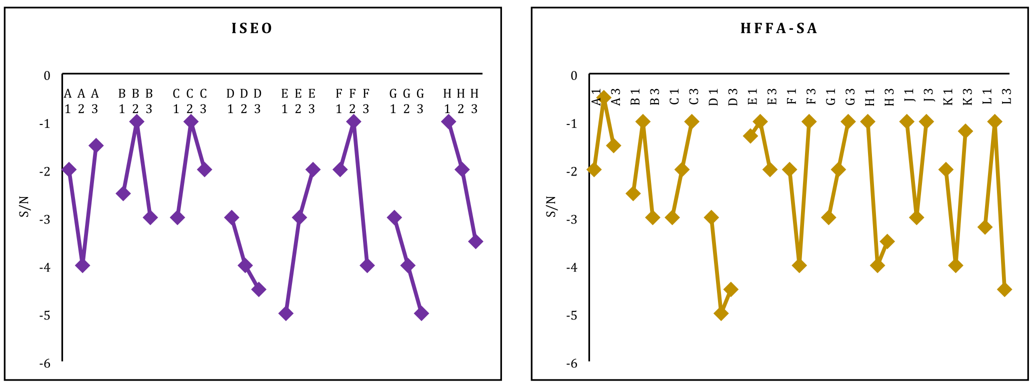

Fig. 13. The S/N ratios of ISEO and HFFA-SA.

use.

4.3. Taguchi method for parameter tuning of metaheuristic algorithms

In this sub-section, the evaluation makes sense when done in a fair environment. For a fair comparison of the proposed algorithms, it is necessary to adjust the input parameters of the algorithms for each model so that it can be effective for solving it [103]. If the parameters of the algorithms are not adjusted well, comparison and solving of the problem with their help will be useless [104]. In this paper, the Taguchi method is used to adjust the parameters of the problem. For more details about the Taguchi method, we have suggested several references such as Sadeghi, Mousavi, Niaki, & Sadeghi, 2013; Candan & Yazgan, 2015; Goodarzian & Hosseini-Nasab, 2019; Orłowska et al. (2020); Goodarzian, Taleizadeh, Ghasemi, & Abraham, 2021. Therefore, the *RPD* and *S*/*N* metrics for the proposed algorithms are calculated, which suggests the best level among the proposed levels for the algorithms. Hence, the number of factors and levels of algorithms are specified in Table 4. Regarding this issue, the Taguchi method decreases the total number of experiments by proposing a set of orthogonal arrays to tune the algorithms in a reasonable time. The Taguchi method for the ISEO and HFFA-SA algorithms proposed the Orthogonal Array L32 with different levels, which in Tables 6 and 7 are provided.

Furthermore, after performing experiments and calculating the evaluation parameters in the Taguchi method to find the effectiveness and efficiency of the levels in each factor, the RPD and S/N figures for each algorithm are drawn separately. Figs. 12 and 13 illustrate the RPD and S/N for the ISEO and HFFA-SA algorithms, respectively.

4.4. Evaluation metrics of Pareto optimum solutions

Especially, the comparison of multi-objective algorithms is complex. In this regard, researchers have proposed several metrics to appraise the quality of Pareto fronts for the algorithms (Devika et al., 2014; Belhaiza, M'Hallah, Brahim, & Laporte, 2019). Hence, four famous evaluation metrics have been utilized. These metrics were employed in the papers (Govindan, Jafarian, & Nourbakhsh, 2015; Sahebjamnia et al., 2020; Goodarzian, Hosseini-Nasab, Muñuzuri, & Fakhrzad, 2020).

- The number of Pareto Solution (NPS) (Govindan et al., 2015; Sahebjamnia et al., 2020),
- Mean Ideal Distance (MID) (Karimi, Zandieh, & Karamooz, 2010; Govindan et al., 2015; Goodarzian, Hosseini Nasab, & Fakhrzad, 2020),
- Spread of Non-Dominance Solution (SNS) (Maghsoudlou, Kahag, Niaki, & Pourvaziri, 2016; Goodarzian, Abraham, & Fathollahi-Fard, 2021),
- Maximum Spread (MS) (Samadi et al., 2018).
- Inverted Generational Distance (IGD) (Li & Zhang, 2008)
- Hyper Volume (HV) (Van Veldhuizen, 1999)

4.5. A balance among the delivery time, total cost, and reliability: Evaluation of heuristics

In this segment, three heuristics in two variants according to the proposed three approaches *i.e.* H-1, H-2, and H-3 are presented to address the experiment problems. The outcomes are shown in Table 8. In this respect, the study compares the heuristics' resolutions to each other, to attain a non-dominated solution to every experiment problem. As a result, the solutions for some experiment problem *i.e. SP2*, *SP5*, *MP10*,

Table 8
The results obtained are the objective functions and CPU time (based on seconds) of the heuristics.

Problem size	Objective function	H-1	CPU	MID	H-2	CPU	MID	H-3	CPU	MID
SP1	F_1	2777431.12	33.1	1	2298341.32	29.5	3	1935429.13	16.3	1
	F_2	2387605.28			1876231.26			1722780.58		
	F_3 (percent)	22.54			22.61			23.76		
SP2	F_1	2886525.59	57.3	1	2447659.02	39.2	3	1967126.16	17.5	3
	F_2	2456761.41			2133157.43			1728781.18		
	F_3 (percent)	24.54			24.76			24.98		
SP3	F_1	2912365.54	69.3	–	2522300.18	55.8	3	2013781.32	28.2	3
	F_2	2754431.23			2380233.76			1856670.14		
	F_3 (percent)	26.00			26.05			26.08		
SP4	F_1	3122541.28	78	–	2734216.12	67.2	–	2047168.81	33.5	3
	F_2	2856612.21			2345172.23			1935781.27		
	F_3 (percent)	26.28			26.64			26.89		
SP5	F_1	3504326.39	89.8	–	2903566.14	76.1	–	2145781.41	45.2	–
	F_2	3293415.17			2733243.84			1978125.04		
	F_3 (percent)	28.75			28.82			28.86		
MP6	F_1	3887665.19	122.8	–	2923544.26	91.2	–	2250212.82	57.3	–
	F_2	3589011.18			2772681.23			2067784.26		
	F_3 (percent)	30.05			31.08			31.75		
MP7	F_1	4116576.12	152.56	–	3280987.53	122.6	–	2658124.06	78.2	3
	F_2	3988033.25			2942871.23			2378123.19		
	F_3 (percent)	31.64			31.84			31.97		
MP8	F_1	4490881.18	197.34	–	3481255.71	162.1	1	2845781.23	85.1	1
	F_2	4190221.25			3216054.12			2670341.56		
	F_3 (percent)	32.95			33.28			33.42		
MP9	F_1	4578823.05	221.31	–	3633133.54	201.3	3	2887651.12	89.3	3
	F_2	4156601.43			3361552.56			2757120.67		
	F_3 (percent)	33.62			33.69			33.74		
MP10	F_1	4838213.61	283.19	–	3915378.31	225.9	3	3156780.68	125.7	3
	F_2	4359080.17			3692551.81			2941383.18		
	F_3 (percent)	33.94			34.11			34.18		
LP11	F_1	5226318.19	296.7	1	4107961.13	256.8	3	3678120.45	166.1	3
	F_2	4668913.17			3880231.87			3256782.19		
	F_3 (percent)	35.95			35.95			36.04		
LP12	F_1	5456218.36	367.1	–	4120431.34	318.2	1	3734780.17	193.2	–
	F_2	4922913.04			3934411.34			3378025.56		
	F_3 (percent)	36.20			36.38			36.76		
LP13	F_1	5956758.12	398.2	3	4596128.45	356.8	1	4067124.27	244.6	3
	F_2	5382112.27			4249867.67			3778901.21		
	F_3 (percent)	36.79			36.97			37.01		
LP14	F_1	6154928.19	573.2	–	4890231.67	473.6	–	4120601.15	367.8	–
	F_2	5689125.74			4393101.18			3967103.67		
	F_3 (percent)	37.05			37.48			37.89		
LP15	F_1	6589120.15	678.3	–	5178932.67	512.3	–	4521670.76	466.7	3
	F_2	6090238.98			4467091.14			4256091.41		
	F_3 (percent)	39.67			40.12			42.61		

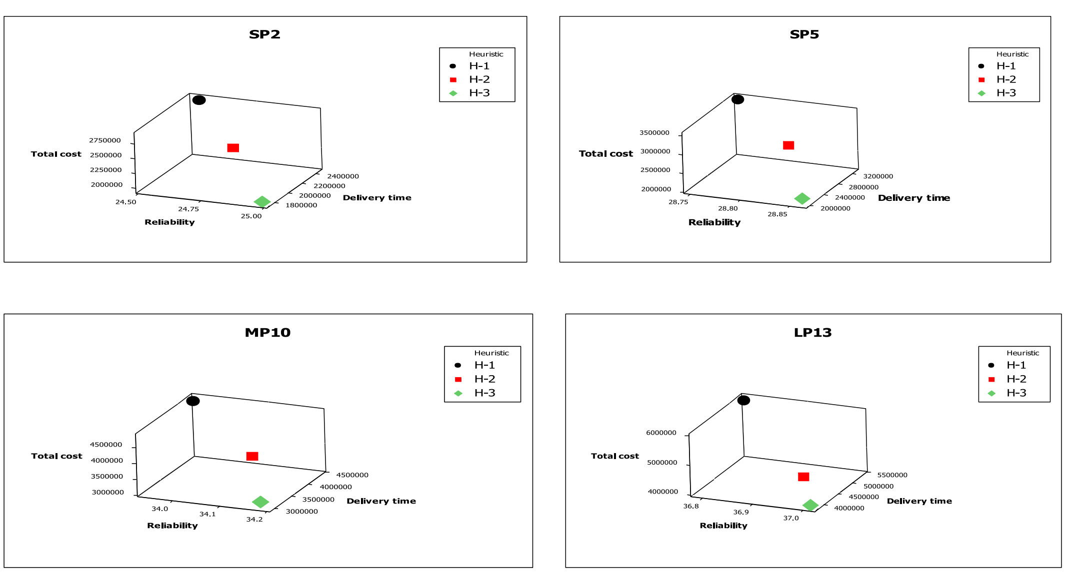

Fig. 14. The non-dominated solutions for experiment problems.

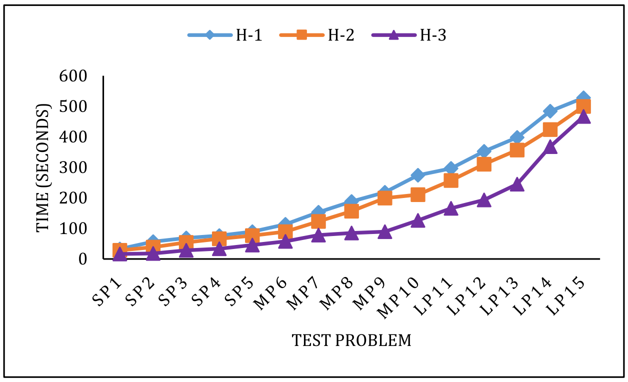

Fig. 15. The behavior of CPU time for three heuristic approaches.

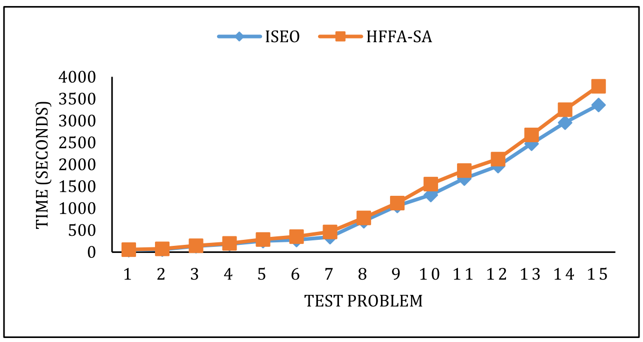

Fig. 16. The behavior of metaheuristics according to the CPU time.

and *LP13* are indicated in Fig. 14. To attain the best trade-off among the non-dominated solutions of heuristics, like the MID metric, the normalized interval among all solutions for every experiment's problem is calculated. Eventually, the solution which has the minimum normalized interval is chosen as the best trade-off among objective functions to include the total cost (F1), the delivery time (F2), and reliability (F3). According to the MID of the suggested heuristics, the outcomes can be explained as follows. In Table 8, first, the solutions of presented heuristics using H-3 performs better than the H-1 and H-2. Next, by concentrating on the average of MID, while the three heuristics has the minimum value of the mean of MID (0.4), the H-2 heuristic has the maximum rate of this mean (1.4), and the H-3 heuristic has the maximum rate of this mean (1.93). We, therefore, conclude that H-3 is more reliable and performs better than the H-1 and H-2 to solve the model.

Further, Fig. 15 displays the behaviour of heuristics as per the computational (CPU) time. According to the mean CPU time for three heuristics, a set of the heuristic utilizing H-1 has a more solution time (221.7473 s) and H-2 (192.56 s) than H-3 (134.1 s). Therefore, between the three heuristics, H-1 has the lowest quality and less reliable.

4.6. Pareto optimum analysis: Comparison of metaheuristics

In this section, suggested four evaluation metrics, two novel metaheuristic algorithms are compared together. Both metaheuristics ISEO and HFFA-SA and their primary solutions are created with an equivalent contribution. Eventually, to improve the efficiency of algorithms, the mean of outcomes for thirty run times is proposed. The behavior of algorithms in terms of CPU time is indicated in Fig. 16. In Fig. 16 and Table 9, it is clear that ISEO is swifter than the HFFA-SA. Thus, the solution time of ISEO is lesser than HFFA-SA for different scale problems. Furthermore, ISEO has the least means of solution time (1120.59 s). The HFFA-SA has the highest rate for this part (1250.761 s).

The capability and performance of the proposed metaheuristic algorithms are tested by evaluating the comparison metrics *i.e.* NPS, MID, SNS, MS, IGD, and HV for achieving Pareto sets for every experiment problem. The outcomes are indicated in Tables 10–15.

According to Tables 10–13, In the NPS metric, the number of non-dominated solutions in the objective function space overcomes all other solutions. It is obvious that the higher the number of non-dominated solutions on the best front, the higher the efficiency of the algorithm. It should be noted that the lower the value of MID, the better the quality of the algorithm solutions. Based on the non-dominated solutions of MID, the SNS criterion examines the degree of a variety of solutions. The higher the value of SNS is shown the higher the quality of the algorithm's non-dominated solutions population. MS considers the extent of non-dominated solutions. A higher value of this criterion indicates more capability of the algorithm's solutions. Based on the description of the four evaluation criteria, the ISEO algorithm in all four criteria examined shows that this algorithm is more efficient than the HFFA-SA. In multi-objective optimization, two performance criteria are used to compare solutions in terms of Pareto frontal amplitude and convergence. First of all, to determine the degree of convergence of solutions, the IGD criterion is employed. According to the results of Table 14, the rate of convergence to the real Pareto front is higher in the ISEO algorithm than in the HFFA-SA. Secondly, the HV metric calculates the volume (or level) covered by the optimal solutions found relative to a reference point and is an indicator of both convergence and diversity criteria. The reference point can be considered the vector of the worst values of the objective functions. This metric measures the quality of solutions in terms of both the ability to converge and maintain diversity in the population. The higher the value of this metric, it means the better the performance. According to Table 15, the ISEO algorithm is of higher quality than HFFA-SA in the HV metric.

Fig. 17 indicates the non-dominated solutions of the proposed algorithms in *SP*1, *MP*8, and *LP*13 experiment problems. In these figures, ISEO displays the best efficiency and reliability than the other metaheuristics. The other algorithm solutions are near and similar to each other.

Accordingly, to determine a more reliable algorithm, this paper carries out statistical comparisons between algorithms according to the Pareto optimum analyses based on assessment metrics. Hence, the outputs which were indicated in Tables 10–15 are converted into a common metric *i.e.*, Relative Deviation Index (RDI) by using the following formula (Devika et al., 2014):

$$RDI = \frac{|Alg_{sol} - Best_{sol}|}{Max_{sol} - Min_{sol}} \times 100 \tag{84}$$

Where Alg_{sol} is the objective value achieved based on the assessment metric of the metaheuristic, Max_{sol} andMin_{sol} are the maximum and the minimum values between all values consequence of algorithms respectively. $Best_{sol}$ is the best solution between procedures; in another expression, it is one of the $Max_{sol}$and Min_{sol} based on the essence of metrics (Hatami, Ruiz, & Andrés-Romano, 2015; Goodarzian & Hosseini-Nasab, 2019; Fakhrzad & Goodarzian, 2019). The lower the amount RDI attains, the higher the quality and efficiency of the algorithm. As a result, to assess modified metaheuristics, the means plot and Least Significant Difference (LSD) are used. The outputs of the means plot and LSD are indicated in Fig. 18. Regarding Fig. 18(a), according to the NPS, firstly, it shows that the ISEO algorithm is more reliable than HFFA-SA that obtained the most suitable solution time. Between these metaheuristics, the introduced ISEO algorithm is the most efficient than HFFA-SA. Briefly, the suggested ISEO indicates the best efficiency in the NPS metric. Fig. 18(b) displays that the ISEO algorithm is forcefully better than HFFA-SA. Although HFFA-SA indicates weak efficiency, ISEO is strongly better than HFFA-SA in the MID metric. Then, this point of view in MS metric is correct. However, HFFA-SA indicates the worst behaviour in the MS metric (Fig. 18(c)). The outputs of the SNS metric

Table 9
The outcomes of the objective functions and CPU time (based on seconds) of the metaheuristics.

Problem size	Objective function	ISEO	CPU	HFFA-SA	CPU
SP1	F_1	5178613.124	46.65	5345341.344	61.87
	F_2	4145191.123		4356128.236	
	F_3 (percent)	32.89		32.14	
SP2	F_1	5245661.23	59.13	5690218.877	78.23
	F_2	4656671.15		5351289.128	
	F_3 (percent)	32.92		32.90	
SP3	F_1	5672981.134	145.17	6378975.811	156.43
	F_2	4992123.228		5838703.544	
	F_3 (percent)	34.48		34.08	
SP4	F_1	5853291.123	196.32	6830341.673	208.17
	F_2	5256334.185		6189452.566	
	F_3 (percent)	37.75		36.51	
SP5	F_1	9857455.566	268.67	11832231.78	279.45
	F_2	8547611.19		10332439.4	
	F_3 (percent)	37.85		36.89	
MP6	F_1	12156611.76	289.12	15823544.716	378.45
	F_2	10855621.19		16772268.123	
	F_3 (percent)	45.75		45.28	
MP7	F_1	14554302.71	345.34	16767887.21	462.56
	F_2	12012231.61		19342566.23	
	F_3 (percent)	45.94		45.84	
MP8	F_1	16890655.29	714.67	23981255.71	794.21
	F_2	13467711.15		21566454.789	
	F_3 (percent)	46.95		45.98	
MP9	F_1	18677125.162	1056.34	29176613.529	1145.34
	F_2	15893252.671		24661552.566	
	F_3 (percent)	47.00		46.11	
MP10	F_1	19233701.814	1236.23	34578991.451	1678.78
	F_2	17765541.523		26187651.532	
	F_3 (percent)	47.25		47.19	
LP11	F_1	22567651.763	1678.26	39804561.801	1866.38
	F_2	19567480.156		28489831.267	
	F_3 (percent)	53.75		52.11	
LP12	F_1	25567781.892	1945.34	32267731.234	2265.12
	F_2	21587781.456		29034411.934	
	F_3 (percent)	53.98		53.61	
LP13	F_1	28756211.231	2578.54	34566088.123	2777.4
	F_2	23347845.781		31126543.634	
	F_3 (percent)	55.62		55.52	
LP14	F_1	28567732.897	2856.43	39523231.232	3491.31
	F_2	25687901.754		33043241.145	
	F_3 (percent)	56.94		55.72	
LP15	F_1	33465439.236	3254.21	4528765198.5	3828.5
	F_2	28714432.311		37564811.152	
	F_3 (percent)	58.84		57.29	

Table 10
The outcomes of NPS's for proposed algorithms.

Experiment problem	HFFA-SA	ISEO
SP1	4	8
SP2	6	7
SP3	6	10
SP4	7	11
SP5	5	12
MP6	8	10
MP7	7	11
MP8	5	11
MP9	6	10
MP10	5	9
LP11	5	7
LP12	5	8
LP13	5	7
LP14	6	9
LP15	7	9

Table 11
The outcomes of MID's for suggested algorithms.

Experiment problem	ISEO	HFFA-SA
SP1	904.025	1009.211
SP2	648.671	978.240
SP3	774.601	944.100
SP4	831.167	1127.611
SP5	917.241	1355.417
MP6	1075.050	1418.080
MP7	489.215	1755.601
MP8	568.610	2010.640
MP9	1765.871	1988.715
MP10	1510.410	2055.891
LP11	1674.756	2203.333
LP12	2019.369	2489.341
LP13	2025.700	2742.025
LP14	2365.008	2563.409
LP15	1936.000	2089.341

are distinctly contrary to the three explained metrics. Hence, ISEO is more reliable than HFFA-SA. The proposed ISEO is more trustworthy than HFFA-SA. Between both proposed metaheuristics, not only ISEO is more efficient than HFFA-SA but it also shows the most competent efficiency between all algorithms for SNS metric (Fig. 18(d)). Based on Fig. 18(e) and (f), in terms of IGD and HV, the results of the ISEO algorithm has high efficiency and also it is more priority than HFFA-SA.

4.7. Sensitivity analyses

To identify the behaviour of the PSCN model along with the real savings of the problem proposed more efficiently, a number of sensitivity analyses have been performed on the important parameters of the model. In this regard, a medium test problem such as MP6 considering six internal and foreign producers, five warehouses, five types of vehi-

Table 12
The outcomes of MS's for presented algorithms.

Experiment problem	HFFA-SA	ISEO
SP1	4,732,147	5,183,225
SP2	5,102,311	5,432,721
SP3	5,231,773	5,577,716
SP4	7,400,149	8,056,415
SP5	11,329,216	12,005,413
MP6	11,164,064	13,643,871
MP7	9,730,189	12,116,213
MP8	20,065,885	21,126,876
MP9	20,005,167	22,556,005
MP10	22,644,230	25,685,706
LP11	25,672,367	27,651,410
LP12	28,846,211	30,231,746
LP13	28,993,015	30,469,199
LP14	31,225,156	35,615,279
LP15	32,566,980	38,822,911

Table 13
The outputs of SNS's for proposed algorithms.

Experiment problem	HFFA-SA	ISEO
SP1	787525.4	824413.6
SP2	713518.5	733619.3
SP3	527143.2	535316.9
SP4	574610.7	591537.7
SP5	741753. 2	765440.3
MP6	968547.4	972542.2
MP7	1245953.1	1386346.5
MP8	2225664.9	2758079.4
MP9	2409308.1	2845619.5
MP10	2714505.3	2795330.6
LP11	3712364.2	3792505.8
LP12	4017116.6	4276416.6
LP13	4264419.3	5153206.3
LP14	4164825.6	4597561.1
LP15	3566845.5	3642609.3

Table 14
The outputs of IGD's for proposed algorithms.

Experiment problem	ISEO	HFFA-SA
SP1	0.0384	0.0532
SP2	0.0392	0.0582
SP3	0.0401	0.0612
SP4	0.0422	0.0657
SP5	0.0434	0.0682
MP6	0.0456	0.0721
MP7	0.0478	0.0756
MP8	0.0489	0.0812
MP9	0.0492	0.0824
MP10	0.0494	0.0856
LP11	0.0532	0.0878
LP12	0.0678	0.0912
LP13	0.0732	0.0936
LP14	0.0821	0.0956
LP15	0.0876	0.0978

cles, six customers, and fifty patients is elected. To manage the PSCN model, H-3 and ISEO as the most efficient heuristic and *meta*-heuristic algorithm respectively in this paper are considered. A set of changes containing the distance between levels in the network (d_{mw}, d_{mc}, d_{wc}), inventory holding cost $(\alpha^t_{wp'}, \alpha^t_{mp'}, \alpha^t_{cp'})$, reliability rate of vehicles (R), and travel time $(\mu_{mwr_{mw}}, \mu_{mcr_{mc}}, \mu_{wcr_{wc}})$ for extended PSCN model are analyzed. Each analysis is divided into six samples numbered as S1 to S6. Eventually, all outcomes based on H-3 and ISEO are provided in Table 16 and also in Fig. 19 as well as all outcomes in Fig. 20.

According to the distance between levels in the network, inventory holding cost, reliability rate of vehicles, and travel time parameters, sensitivity analyses have been represented by raising the amount of

Table 15
The outputs of HV's for proposed algorithms.

Experiment problem	HFFA-SA	ISEO
SP1	1.36	2.34
SP2	1.45	2.67
SP3	1.67	3.24
SP4	1.79	3.45
SP5	1.82	3.78
MP6	1.93	4.01
MP7	2.01	4.34
MP8	2.23	4.68
MP9	2.35	4.89
MP10	2.56	5.34
LP11	2.69	5.88
LP12	2.78	6.21
LP13	2.85	6.45
LP14	2.93	6.67
LP15	3.02	7.21

these parameters. Details are summarized in Table 16. To recognize the behavior of three objective functions *i.e.* total cost, delivery time, and reliability, simultaneously, the values are considered in these comparisons as illustrated in Figs. 19 and 20. Regarding the results of Figs. 19(a) and 20(a) show that by the raising amount of the distance between levels in the network parameter the three objective functions be raised. In this regard, although by the increasing amount of the inventory holding cost parameter the first objective function is increased, these changes are no effect on the second and third objective functions in Figs. 19(b) and 20 (b). Therefore, the behavior of the three objective functions is clear in Figs. 19(c) and 20(c). By increasing the number of the reliability rate of vehicles, the behavior of the total cost and reliability is raised, but the delivery time is decreased. Then, regarding this issue, the speed of delivery time for sending pharmaceutical products is decreased based on increasing transportation [system reliability along with raising transportation costs. Finally, in terms of Figs. 19(d) and 20(d), by maximizing the travel time, every three objective functions have remained without change and these increases are no effect on the total cost, delivery time, and reliability.

The effect of the change in the value of the parameters on the feasibility of the model is shown in Table 17. Therefore, the lower limit and the upper limit of the parameter deviation are calculated as long as the model remains feasible.

For this purpose, the parameters are divided into different categories. For example, the first line indicates that changes in the range of -15% up to $+ 26\%$ in the amount of Inventory holding cost keep the solution space of the proposed model feasible. This category contains the parameters $\alpha^t_{wp'}$, $\alpha^t_{mp'}$and$\alpha^t_{cp'}$. The last line also indicates that changes in the range of -27% up to $+ 39\%$ in the amount of demand keep the solution space of the proposed model feasible. This category also contains the parameters$\partial^t_{p'wm}$, $\partial^t_{p'cm}$ and$\partial^t_{p'cw}$. It should be noted that after running the proposed model for all parameters, the maximum changes for the Upper bound and Lower bound for each category of parameters are reported in Table 17.

5. Conclusion, managerial implications, and future studies

In the present paper, a novel production–distribution-inventory-location-allocation-routing model and associated solution for the PSCN problem of pharmaceutical products was developed by considering the delivery time and reliability with multi-modal transportation. The proposed model was formulated as a MINLP model with reliability. Adding the multi-modal transportation of various sorts of utilized vehicles to transfer the pharmaceutical products to customers, was the principal contribution of the three-objective pharmaceutical supply chain model distinguished by three objectives. Three new heuristics (H-1), (H-2), (H-3) and two new, ISEO and HFFA-SA algorithms to find optimal solutions are developed. The efficiency of the ISEO algorithm is better, as it

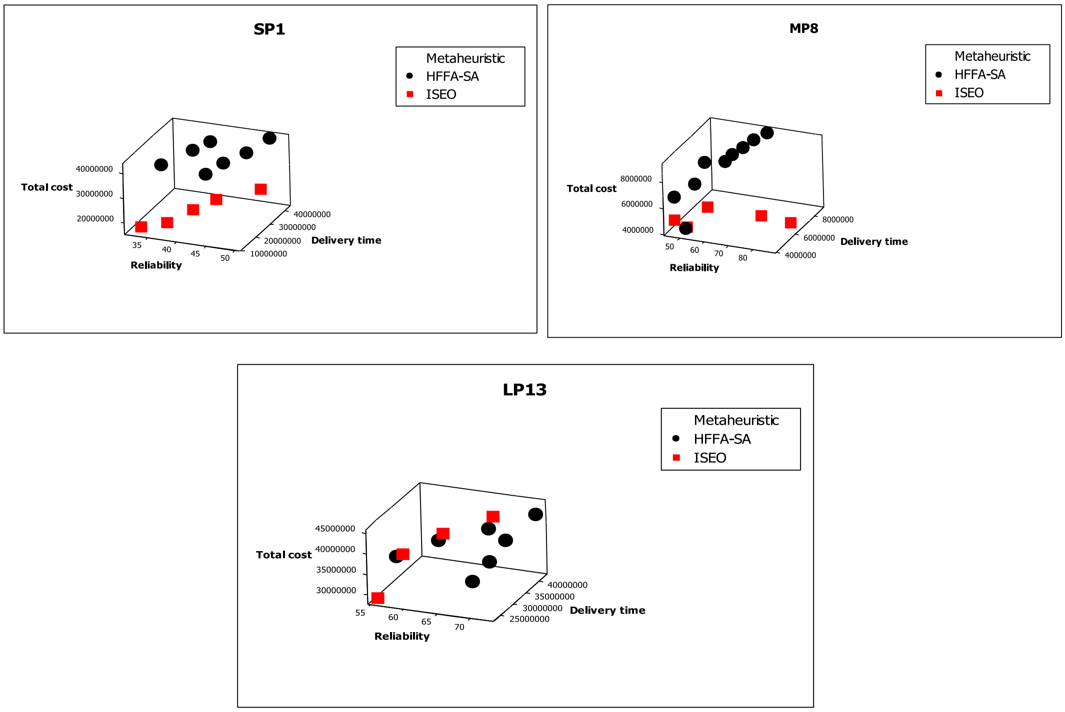

Fig. 17. Pareto frontier of presented metaheuristics algorithms.

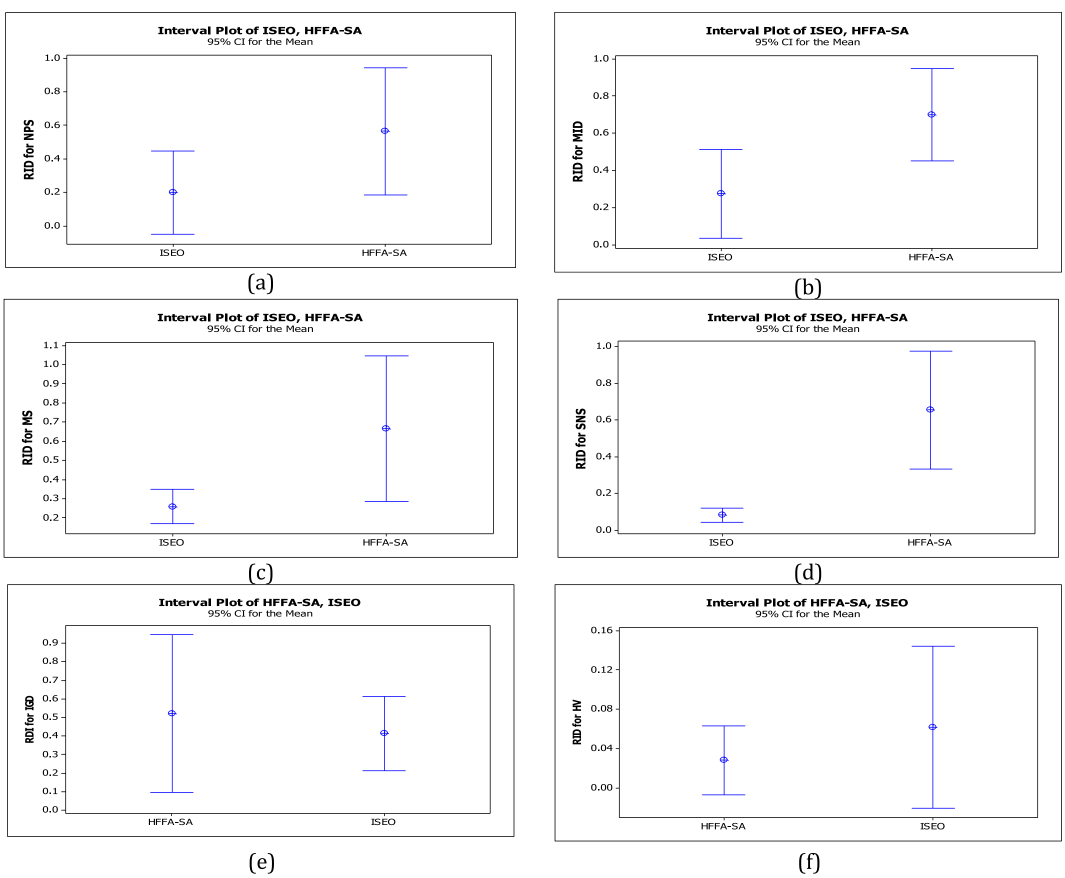

Fig. 18. ANOVA plots for the evaluate metrics in term of RDI for algorithms.

utilizes a new position mechanism. This improved algorithm is introduced with an adjustment operator to enhance its efficiency in terms of search precision and running time, as the main aim was to better balance the convergence speed and local optima avoidance of the ISEO. Besides, numerical experiments were conducted to test the validity of the suggested problem, two presented heuristics, and an extended

Table 16
The sensitivity analyses based on the results of H-3 and ISEO.

The sensitivity analyses on the distance between levels in the network					
Samples		d_{mw}, d_{mc}, d_{wc}	Total cost	Delivery time	Reliability
S1	H-3	45 km	2923544.26	277268.123	27.87
	ISEO		12156611.76	10855621.19	25.98
S2	H-3	150 km	4323169.31	356912.456	28.92
	ISEO		21072109.23	15789123.31	27.45
S3	H-3	300 km	5621812.81	462814.511	30.31
	ISEO		29651245.19	19356284.45	29.74
S4	H-3	400 km	6389126.17	523219.702	32.51
	ISEO		37278823.13	25701240.18	31.85
S5	H-3	500 km	7145618.27	592802.19	33.95
	ISEO		49192629.28	31562719.21	33.27
S6	H-3	1000 km	8547544.26	762113.322	35.79
	ISEO		67195623.52	45691218.23	35.11
The sensitivity analyses on the inventory holding cost					
	Samples	$\alpha^t_{wp'}, \alpha^t_{mp'}, \alpha^t_{cp'}$	Total cost	Delivery time	Reliability
S1	H-3	100000$	2923544.26	277268.123	24.32
	ISEO		12156611.76	10855621.19	23.75
S2	H-3	115000$	3427128.43	277268.123	24.98
	ISEO		17325723.12	10855621.19	23.88
S3	H-3	140000$	4278122.34	277268.123	25.97
	ISEO		21872312.25	10855621.19	25.23
S4	H-3	160000$	4928890.81	277268.123	26.31
	ISEO		25762323.65	10855621.19	26.10
S5	H-3	180000$	5226671.26	277268.123	28.61
	ISEO		29782109.23	10855621.19	27.28
S6	H-3	200000$	5880121.45	277268.123	30.79
	ISEO		32784523.19	10855621.19	28.64
The sensitivity analyses on the reliability rate of vehicles					
	Samples	R	Total cost	Delivery time	Reliability
S1	H-3	0.450	2923544.26	277268.123	16.27
	ISEO		12156611.76	10855621.19	14.64
S2	H-3	0.550	3145812.32	258912.249	23.67
	ISEO		13152833.71	9651281.21	20.78
S3	H-3	0.650	3367128.45	227268.123	28.91
	ISEO		15461289.19	9155621.19	25.09
S4	H-3	0.750	3578011.18	197268.433	33.14
	ISEO		17569023.16	8855621.21	31.68
S5	H-3	0.850	3678544.26	177268.567	38.94
	ISEO		19156611.76	8255011.23	36.87
S6	H-3	0.950	3923544.37	143468.455	45.23
	ISEO		21780923.16	6518011.34	40.56
The sensitivity analyses on the travel time					
	Samples	$\mu_{mwr_{mw}}, \mu_{mcr_{mc}}, \mu_{wcr_{wc}}$	Total cost	Delivery time	Reliability
S1	H-3	25(second)	2923544.26	277268.123	21.32
	ISEO		12156611.76	10855621.19	20.64
S2	H-3	45	2923544.26	277268.123	23.41
	ISEO		12156611.76	10855621.19	21.70
S3	H-3	65	2923544.26	277268.123	25.61
	ISEO		12156611.76	10855621.19	24.41
S4	H-3	85	2923544.26	277268.123	28.61
	ISEO		12156611.76	10855621.19	26.71
S5	H-3	95	2923544.26	277268.123	29.42
	ISEO		12156611.76	10855621.19	29.31
S6	H-3	120	2923544.26	277268.123	32.34
	ISEO		12156611.76	10855621.19	30.55

metaheuristic algorithm for the small, medium, and large size of the problem. According to the numerical experiments, the following conclusions could be made; Firstly, though H-3 is faster than H-1 and H-2, the quality of H-3 solutions is higher than that of H-1 and H-2; Secondly, though the ISEO algorithm is efficient than other algorithms, the quality of the ISEO algorithm is higher than that of other algorithms when large-scale problems. Afterwards, the significance of identifying a compromising solution is explained by examining the trade-offs through Pareto analysis in relevance to the considered examples. Observations reveal that a significant amount of the total costs and delivery time of pharmaceutical products reduction can be achieved at the expense of a minimal increase in the reliability of transportation systems in the PSCN much to the interest of internal and foreign producers and hospitals and pharmacies.

The managerial implications related to the transportation costs and the rate of reliability of vehicles observed for different configurations of the common problem are derived as follows. Firstly, for the small, medium, and large-size problems, the rate of reduction in total costs of the PSCN according to the decreasing delivery time of pharmaceutical products and the increase in the reliability of the vehicles, is found to increase initially and later the rate of reliability in the different sizes of problems decreases drastically. Secondly, the insights achieved by

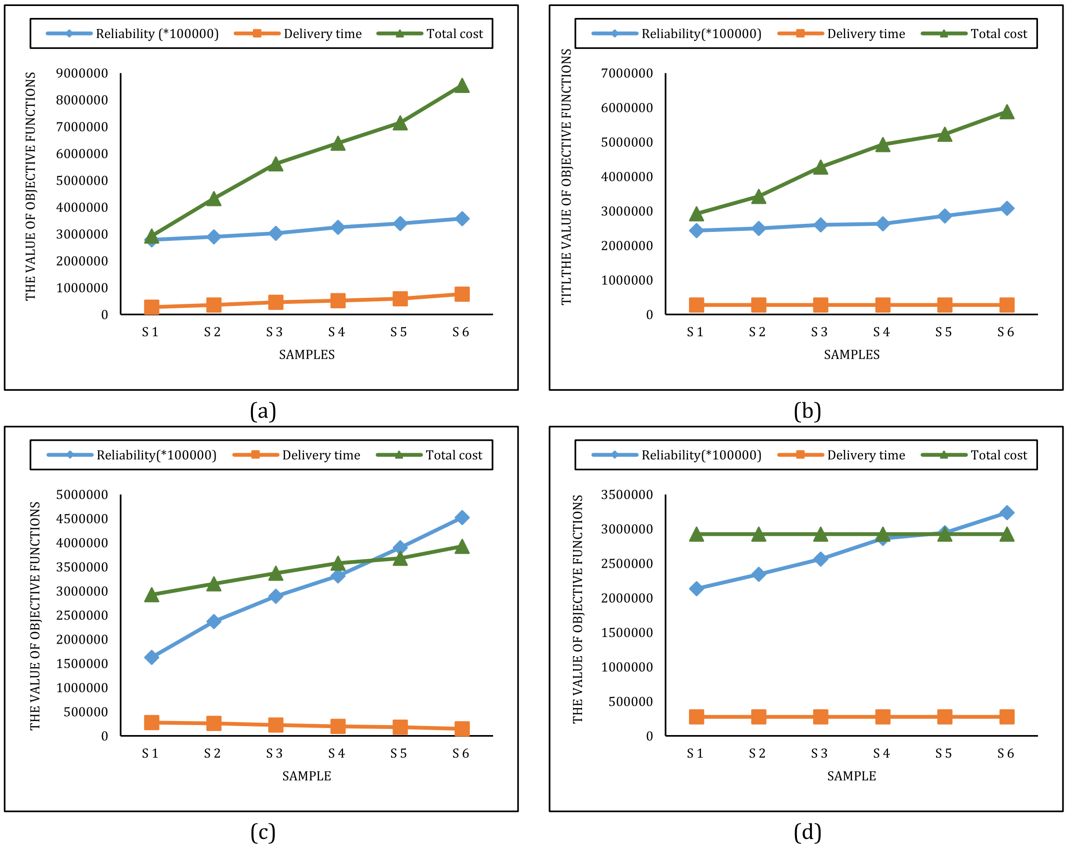

Fig. 19. The behavior of objective functions in the sensitivity analyses based on the H-3.

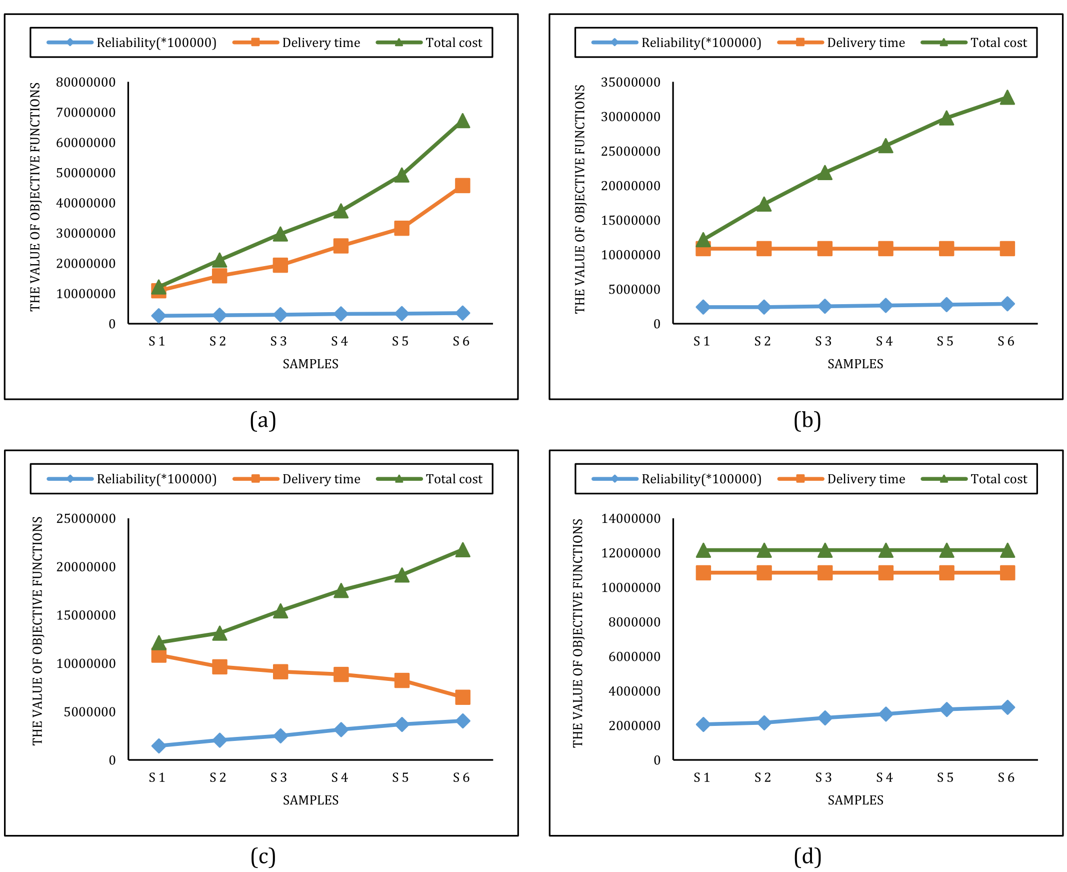

Fig. 20. The behavior of objective functions in the sensitivity analyses based on the ISEO.

Table17
Analysing the change of parameters on the feasibility of the model.

Type of parameters	Lower bound	Upper bound
Inventory holding cost	15%−	26%+
Order cost	23%−	28%+
Penalty cost	13%−	17%+
Production cost	24%−	32%+
Transportation cost	34%−	41%+
Back-order cost	18%−	28%+
Delivery cost	15%−	14%+
Purchase cost	19%−	33%+
Travel time	28%−	44%+
Demand	27%−	39%+

capturing the impact of variation in allocation, distribution, inventory holding, and production level on the available cost in the PSCN and increasing reliability for users of the transportation system on the different route, are of crucial value for internal and foreign producers to decide the adequate level of allocation, distribution, inventory holding, and production of pharmaceutical products. Subsequently, this proposed model helps internal and foreign producers in staying well informed concerning the achievable levels of penalties thresholds, while ensuring a check on costs, delivery times, and reliability of vehicles. The present paper provides a numerical example to display the pros and cons of raising the warehouse, distribution center, and the sorts of transportation system capacities. The aforementioned trade-offs are instrumental for internal and foreign producers while making an intuitive selection of a reliability strategy for pharmaceutical products according to the penalties.

In future works, one can consider a multi-objective metaheuristic algorithm such as multi-objective Grey Wolf Optimizer, Multi-objective Stochastic Fractal Search, Fast PGA, NSGA-II, MOGA, etc. to attain Pareto solutions. Furthermore, several parameters of the model such as demand and cost can be considered stochastic, robust, or fuzzy to cause the application closer to actuality. Besides, the interested scholars could utilize the Lagrangian Relaxation Algorithm, logic-based benders decomposition, branch-and-price, or branch-and-price-and-cut algorithms to solve the proposed problem in future studies. In addition, the presented mathematical model by adding other objective functions such as sustainability in the PSCN, maximization of product quality level, and minimization of customer dissatisfaction of pharmaceutical products will be developed for future research. Finally, Blockchain technology will be utilized in the PSCN in future studies.

CRediT authorship contribution statement

Fariba Goodarzian: Conceptualization, Methodology, Validation, Formal analysis, Writing - original draft. **Vikas Kumar:** Writing - review & editing, Supervision. **Peiman Ghasemi:** Validation, Software.

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