Thermal mapp routing in pharmaceutical products transportation using machine learning approach: a systematic review

Mapeamento térmico de rotas no transporte de produtos farmacêuticos usando a abordagem de aprendizagem da máquina: uma revisão sistemática

Mapeo térmico de rutas en el transporte de productos farmacéuticos utilizando el enfoque de aprendizaje máquina: una revisión sistemática

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Abstract
The cold chain is crucial to ensure the quality and effectiveness of transported and stored medicines. For this, it is necessary to carry out the thermal mapping of routes for drugs transported between 15°C and 30°C, so that the most assertive decision can be taken without raising costs. This study aims to identify the main factors influencing the thermal mapping of pharmaceutical products in the cold chain and applying the machine learning technique. The method used for this systematic review is the Prisma, where the identification, screening, eligibility, and inclusion stages were analyzed. After analyzing 75 articles, the result shows that only eight papers were consistent with the use of modeling in the medicine cold chain distribution. Thus, it can be concluded that there is an extensive field to be researched regarding the use of prediction algorithms in the cold chain of drugs and vaccines.
Keywords: Cold chain; Medicines; Vaccine; Modeling; Quality control.

Resumo
A rede de frio é fundamental para garantir a qualidade e eficácia dos medicamentos transportados e armazenados. Para isso, é necessário realizar o mapeamento térmico das rotas dos medicamentos transportados entre 15 ° C e 30 ° C, para que a decisão mais assertiva seja tomada sem aumento de custos. Este estudo tem como objetivo identificar os principais fatores que influenciam o mapeamento térmico de produtos farmacêuticos na cadeia de frio e a aplicação da técnica de aprendizado de máquina. O método utilizado para esta revisão sistemática é o Prisma, onde foram analisadas as etapas de identificação, triagem, elegibilidade e inclusão. Após análise de 75 artigos, o resultado mostra que apenas oito artigos foram consistentes com o uso de modelagem na distribuição da cadeia de frio de medicamentos. Assim, pode-se concluir que existe um amplo campo a ser pesquisado quanto ao uso de algoritmos de predição na cadeia de frio de medicamentos e vacinas.
Palavras-chave: Cadeia de frio; Medicamentos; Vacina; Modelagem; Controle de qualidade.

Resumen
La cadena de frío es fundamental para garantizar la calidad y eficacia de los medicamentos transportados y almacenados. Para ello, es necesario realizar el mapeo térmico de las rutas de los medicamentos transportados entre 15 ° C y 30 ° C, para que se pueda tomar la decisión más asertiva sin incrementar los costos. Este estudio tiene como objetivo identificar los principales factores que influyen en el mapeo térmico de productos farmacéuticos en la cadena de frío y la aplicación de la técnica de aprendizaje automático. El método utilizado para esta revisión sistemática es el

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Prisma, donde se analizaron las etapas de identificación, cribado, elegibilidad e inclusión. Después de analizar 75 artículos, el resultado muestra que solo ocho artículos fueron consistentes con el uso de modelos en la distribución de la cadena de frío de los medicamentos. Así, se puede concluir que existe un amplio campo por investigar en cuanto al uso de algoritmos de predicción en la cadena de frío de medicamentos y vacunas.
Palabras clave: Cadena de frío; Medicamentos; Vacuna; Modelado; Control de calidad.

1. Introduction

Proper storage and transport conditions must be maintained to preserve medicines' safety, quality, and efficacy throughout the supply chain. This careful procedure starts at the point of manufacture through the delivery of the products to the final distribution point, typically the person who dispenses or supplies the patient with medication. Planning for the drug supply chain must begin with the product development phases and continue throughout its lifecycle (Health Canada, 2020), including a risk management plan to be taken into account if any failure is set in place (Saint-Lorant, et al., 2014).

Pharmaceutical cold chain logistics is a supply chain system that deals with the stores and transports of medicines from production to the final consumer at the recommended temperature to ensure the quality of these products without changing their integrity (Sinha, et al., 2017). Different from a food cold chain logistics system, medicine cold chain logistics has many characteristics. There are multiple batches, small batches, punctuality, high operating costs, high coordination of all links in the cold chain, unpredictability, customer qualification audits, increased drug quality standards, and complex monitoring requirements. Therefore, it requires several special needs, including high-quality standards, high investment, high precision, continuous supervision, and high quality of human resources (Wen, et al., 2019).

Regarding improving efficiency and cost reduction in the pharmaceutical supply chain, some suggestions are proposed by Burinskiene (2018), such as speeding up the distribution process to pharmacies and investing in paperless and artificial intelligence technologies. Most of the improvement processes will rely on the technologies related to the so-called industry 4.0, which encompasses the use of the internet of things (IoT) and algorithm-based modeling (Kumar, Singh & Layek, 2020).

The temperature ranges allowed during the transport and storage of medicines are linked to each product's stability data and period of use. In the absence of such information, it is necessary to define the temperature ranges around which the product registration holder can harmonize stability studies, storage, and transport requirements and the action to be taken in case of temperature variation. Therefore, transport and storage conditions must be possible to follow, and it is necessary to restrict the information to be achievable in practice (ICH, 2003).

The current ambient temperature scale covers a wide range of temperatures with limited guidelines for storage and transport (Paoli, Bishara & Asselt, 2020). There is a risk of difficulty defining ambient temperature control and management requirements, leading to an overprotective approach. Therefore, such an issue results in very restrictive temperatures during the store and transporting material. Such problems might be resulting in unnecessary storage, costs, and unnecessary workload to manage temperature variations. In this way, the temperature range limits of medicines in a temperature range of 15°C to 30°C must be mapped in their transport routes, ensuring appropriate storage and distribution conditions according to the stability of the raw material, without waste with unnecessary active or passive transport (Brazil, 2020). Brazilian norms are guided by the principle of quality, and follow a robust risk analysis premise.

Several critical literature reviews are found in various areas of the healthcare sector to utilize resources better and improve final patient delivery. Those are facility maintenance management, strategic issues, lean implementation, decision making, cold chain, internal distribution medicines, operations, management function, operations research, outsourcing, and optimization (Yousefli, et al., 2017; Singh, et al., 2016; Costa and Filho, 2016; Malik, et al., 2016; Sharma and Pai, 2015;

Pinna, et al., 2015; Dobrzykowski, et al., 2014; Narayana, et al., 2014; Fakhimi and Probert, 2013; Guimarães and Carvalho, 2013).

Several literature reviews from various areas of the healthcare sector lead to utilize resources better and improve final patient delivery. They cover an extensive array of facility maintenance management, strategic issues, lean implementation, decision making, cold chain, internal distribution drug, operations, management function, operational research, outsourcing, and optimization (Pinna, et al., 2015; Dobrzykowski, et al., 2014; Narayana, et al., 2014; Fakhimi and Probert, 2013; Guimarães and Carvalho, 2013). Although a mathematical optimization model of cold chain logistics distribution is proposed in the food chain logistic distribution (Dou, Liu & Yang, 2020), very few initiatives are found to develop optimization algorithms related to artificial intelligence in the pharmaceutical sector.

Systematic reviews are designed based on predefined eligibility criteria and conducted according to a predefined methodological approach as described in an associated protocol (Moher, et al., 2009). The main characteristics of a systematic review are described by Higgins and Green (2011), as:

• a set of clearly defined objectives with predefined eligibility criteria for studies;

• an explicit and reproducible methodology;

• a systematic search that attempts to identify all studies that would meet the eligibility criteria;

• an assessment of the validity of the included studies results, for example, by assessing the risk of bias; and

• a systematic presentation and synthesis of the characteristics and results of the included studies.

The research question was whether the published research on influencing factors in the thermal mapping of pharmaceuticals in the cold chain using the machine learning approach is sufficient and of quality, as per the Collegiate Board Resolution – RDC no. 430 of 08 October 2020. The present study uses the systematic review approach to define the main factors influencing the thermal mapping of pharmaceuticals in the cold chain.

2. Methodology

Search and study identification

The present study is characterized as bibliographical research with a qualitative approach. In this perspective, the PRISMA method (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) was adopted in this systematic review. The research was divided into four phases: identification, screening, eligibility, and inclusion. Figure 1 presents the flowchart of the methodology used.

Figure 1. Search flowchart based on the PRISMA method.
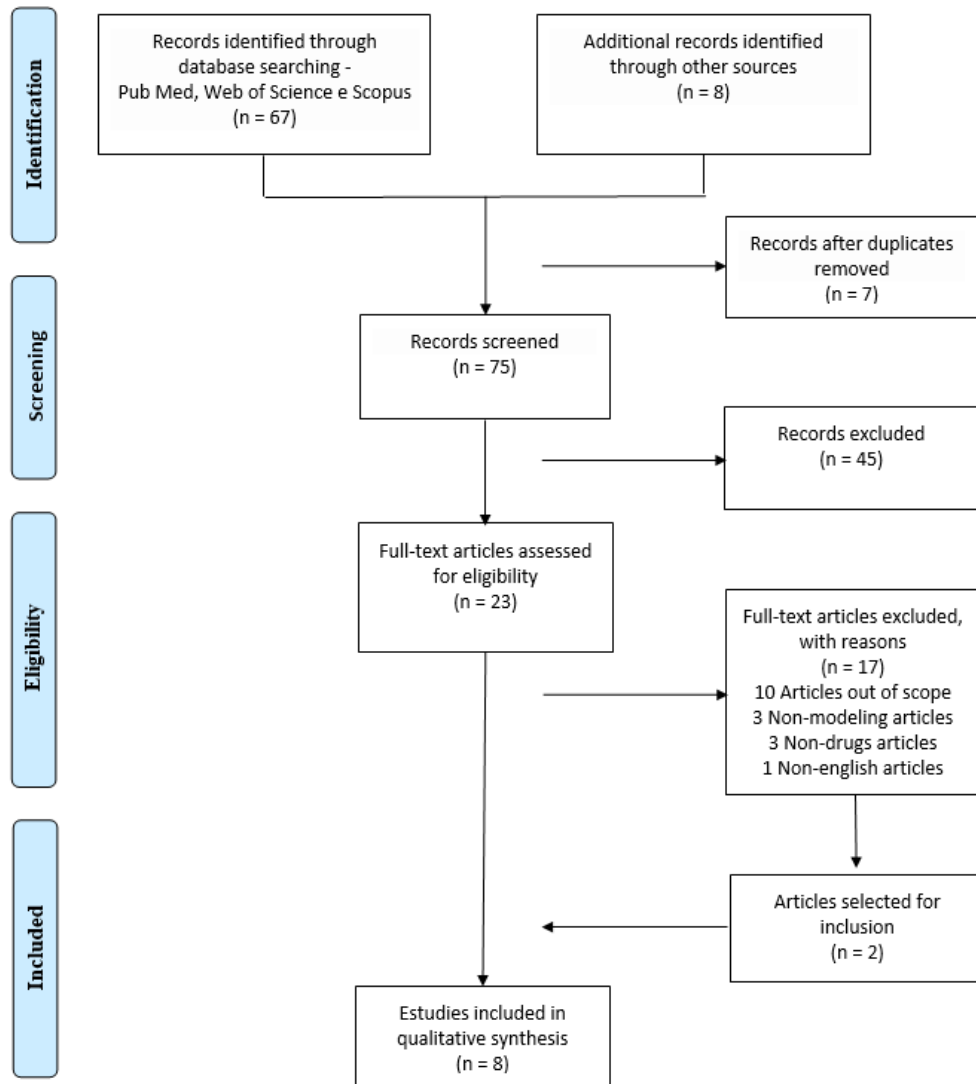
Source: Adapted from Moher, et al., (2009).

In the identification phase, articles were selected from the Pubmed, Web of Science, and Scopus databases. Due to the limited papers, the study accepted the expansion to other research bases considered in the identification, selected in Google Scholar. (Figure 1).

Study selection, characteristics, risk of bias/study quality, and collection outcome data

Three keywords and their respective English versions selected were Cold Chain, Modeling, and Medicines (Table 1). The articles selected by the research databases were not refined by year of publication, as it is a subject studied only in recent years. The articles' titles and abstracts were reviewed in the next screening stage, assessing their characteristics and quality, with regard to the method used and in the treatment of data. In the eligibility phase, the papers were read entirely. In this way, those that addressed the proposed topic were chosen and included in this study's qualitative analysis.

Those that addressed the proposed theme were chosen, and that in their abstract deal with the logistics of controlled temperature products and some form of statistical or algorithmic treatment of the collected data.

Table 1. Information on keywords used and the number of articles found during the literature search.

Database	Keywords	Number of articles
Pubmed	"cold chain", 'modeling' and 'medicines'	53
Web of Science	"cold chain", 'modeling' and 'medicines'	12
Scopus	"cold chain", 'modeling' and 'medicines'	2
Other databases (Google Scholar)	"cold chain", 'modeling' and 'medicines'	8

Source: The autors.

3. Results

During the advanced search in the studied databases, the article's title, abstract, and keywords were the first items analyzed. By the selection method used in this study, 75 articles were initially found, submitted to the following filtering and elimination procedures: duplicate works; works whose title, abstract, or keywords were not aligned with the research topic; papers presented at conferences; and book chapters. At the end of this process, 23 articles were obtained, which were read in full. Of these articles, eight were included in this systematic review as they were closer to the scope of the research. Table 2 shows the selected papers, considering the authors, article title, year of publication, and the main results.

Table 2. Characteristics of the included studies.

Authors	Title	Product	Temperature	Modeling approach	Year of publication	Main results
Donghua Zhang, Tong Han	Analysis of risk control factors of medical cold chain logistics based on ISM model	Medicines	Not identified (the article only informs that it has a controlled temperature)	ISM model (Interpretative structure modeling),	2020	The article analyzes risk elements in the cold drug chain using a modeling approach and builds an interpretation system for risk reduction.
Fabian De Paoli, Rafik H. Bishara, Erik J. van Asselt	How to define the proper ambient temperature range for storage and distribution of pharmaceutical raw materials	The raw material of pharmaceutical products	15–25 ∘C, 2–30 ∘C, and unrestricted (no minimum and maximum temperature limits)	Not identifiable	2020	The article proposes defining subsets of temperature conditions to simplify raw material storage and distribution management.
Yi-hua Chen	Intelligent algorithms for cold chain logistics distribution optimization based on big data cloud computing analysis	Food	Not identified (the article only informs that it has a controlled temperature)	genetic algorithm - API Map-Reduce	2020	The article studies the intelligent algorithm for optimizing cold chain logistics distribution based on big data cloud computing analysis.

Zhi Wen, Huchang Liao, Ruxue Ren, Chunguang Bai, Edmundas Kazimieras Zavadskas, Jurgita Antucheviciene and Abdullah Al-Barakati	Cold Chain Logistics Management of Medicine with an Integrated Multi-Criteria Decision-Making Method	Medicines	Not identified (the article only informs that it has a controlled temperature)	SWARA (step-by-step weight assessment proportion analysis) and CoCoSo (combined compromise solution)	2019	A case study on the selection of drug cold chain logistics providers is presented to demonstrate the applicability of the proposed modeling.
Y.P. Tsang, K.L. Choy, C.H. Wu, G.T.S. Ho, Cathy H.Y. Lam, P.S. Koo	An Internet of Things (IoT)-based risk monitoring system for managing cold supply chain risks	Medicines and food	Multiple temperatures	IBM IoTF and APIs Microsoft Health Cloud – Fuzzy logic	2018	The article proposes an Internet of Things (IoT) based risk monitoring system to control product quality and occupational safety risks in the cold chain.
Atanu Chaudhuri, Iskra Dukovska-Popovska, Nachiappan Subramanian, Hing Kai Chan, Ruibin Bai	Decision-Making in Cold Chain Logistics using data analytics: a literature review	Food	Not identified (the article only informs that it has a controlled temperature)	Not identifiable	2018	The article identifies the various types of data that professionals can collect and analyze across the cold chain, the technology needed to enable data capture, and how to use the data for decision-making.
Jian Li	Optimal design of transportation distance in logistics supply chain model based on data mining algorithm	Not identifiable	Not identified (the article only informs that it has a controlled temperature)	K-means	2018	O artigo utiliza a tecnologia de mineração de dados para seleção de centro de distribuição da cadeia de suprimentos combinado com o algoritmo de agrupamento.
Ashish Kumar Sinha, A. R. Verma, Aditi Chandrakar, Shanta P. Khes, Prem Sagar Panda, Srishti Dixit	Evaluation of cold chain and logistics management practice in Durg district of Chhattisgarh: pointer from Central India	Vaccine	Multiple temperatures	MS Excel	2016	The article studies cold chain equipment using monitoring technology and users' knowledge of cold chain equipment and logistics management.

Source: The autors

Ten (n = 10) of the fifteen selected articles were outside the scope of this research, which focuses on a systematic review of drug cold chain using some form of mathematical modeling. The rest of the studies did not specify any modeling in their results (n = 3), did not address medications as part of the surveys (n = 3), or were in a language other than English (n = 1).

4. Discussion

This systematic review identified eight studies on the drug cold chain using some form of mathematical modeling. Furthermore, the associations found were often small or inconsistent, with few studies related to the factors determined in the survey.

Initiatives to adopt linear modeling (Papageorgiou, Rotstein & Shah, 2001) and apply a multi-objective model that increases demands' coverage and minimizes the total costs using the centroid method to handle demand uncertainty has been explored to solve pharmaceutical logistic issues (Nasrollahi & Razmi, 2021). However, those researches do not focus specifically on an artificial intelligence algorithms solution (Kumar, Singh & Layek, 2020). The authors Chen (2020) and Tsang (2018) understand that processes that use the Internet of Things (IoT) and Cloud Computing are part of the digital transformation of several companies and have become reliable in activities involving the cold chain. These technologies can quickly search real-time dynamic information in a short period, can report on the latest transport operations, warehousing status, real-time routes, and other information for logistics centers and vehicles. Another advantage is getting the calculation results in a short time, thus improving distribution efficiency and increasing economic benefits.

The use of methods and theories that address data mining and even some statistical techniques in the cold chain develop a critical activity to ensure the predetermined metrics by those responsible for transported and stored products with predefined specificities (Li, 2019). Many challenges were observed varying from installing a new distribution center involving supply and demand caused by seasonality, regionality, and unpredictable customer preferences. Also, the challenge varies according to the randomness of product variety, quality, quantity, and delivery date.

Knowledge of packaging and distribution criteria at different temperatures guarantees success in the final result of the cold chain operation (Sinha, et al., 2017 and Paoli, Bishara & Asselt, 2020). It plays an essential role in product quality, efficacy, safety, and stability, especially when immunizing a specific population.

Finally, other authors Zhang and Han (2020), Wen, et al. (2019) and Chaudhuri, et al. (2018), use their studies to associate modeling for decision-making in operations involving pharmaceutical products such as transportation, storage, distribution, and quality. Thus, data analysis makes the results based on reliable research and close to reality, avoiding different types of risk factors at different levels that can lead to product loss due to a lack of acceptance criteria.

None of the factors identified by this systematic review were reported in other reviews. This review found that most studies related to the drug cold chain do not use modeling, where the most frequently observed is statistical methods. The most common results associated with the cold chain identified by this review were related to vaccines or other drugs with similar characteristics: storage and transport temperature of 2 to 8°C. It was impossible to establish strong relationships between the cold chain of medicines using modeling with a specific temperature criterion.

5. Conclusion

Studies on the use of predictive algorithms for the cold chain of medicines are still little addressed by researchers, especially at temperatures between 15°C and 30°C, where they are often neglected and poorly controlled, which may interfere with the product's effectiveness. The nine articles included by the Prisma method are related to the keywords of the research. Still, they were little related to the direct approach, which is cost reduction in decision-making on the type of transport and its respective temperature at the time of collection or delivery of medicines. It highlights once again the need to use technology in routine pharmaceutical logistics processes.

Thus, it can be emphasized that the vast majority of studies addressed in this systematic review are premised on the importance of implicit quality standards in processes related to pharmaceutical logistics. However, the costs of these processes

are equally important for operations to be sustainable since temperature medicines with a range between 15 and 30 °C are generally not of high added value compared to refrigerated ones. Thus, artificially intelligent algorithms methods become increasingly important for this analysis because they form bases for risk analysis widely discussed in the cold chain with their application. For future research, the idea of determining a reliability score as a result of a prediction algorithm may help in decision making in cold chain logistics.

Acknowledgments

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