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Review

Application of Life Cycle Assessment in the pharmaceutical industry: A critical review

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ABSTRACT

The pharmaceutical industry presents unique challenges and opportunities for mitigating global environmental impacts. This paper reviewed studies utilizing Life Cycle Assessment (LCA) to quantify and analyze how the pharmaceutical sector affects the environment, from active pharmaceutical ingredients (APIs) to drug formulation, packaging and transportation, and end-of-life disposal. The reviewed LCA literature indicated that the leading contributors to this industry's environmental impacts were energy consumption, particularly electricity use, and chemical application. However, the toxicity impacts should demand equal attention given the potentially severe effects of certain active compounds on human health and ecological systems. We also identified process optimization opportunities, such as transitioning from batch to continuous manufacturing platforms, adopting green chemistry principles, and implementing process intensification techniques. The review further suggested gaps in current research, such as drug recycling, biopharmaceuticals, supply chain strategies, etc. Moreover, we pointed out the current limitations in LCA studies, such as limited system boundaries, unclear data presentation, databases for biopharmaceuticals, etc. Emphasizing the critical need for sustainable development, we stressed the importance of an urgent transition toward cleaner energy sources. We also advocated for using more eco-friendly chemicals across the pharmaceutical life cycle to realize cleaner production in the pharmaceutical industry.

Nomenclature

4-DEL	4-D-erythrolactone	HDPE	High-density polyethylene
		IA	Isostearic acid
ABR	Antibiotic resistance	IRR	Internal rate of return

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Nomenclature

ADM	Animal-derived material	ISO	International Standard Organization
AHP	Analytic hierarchy process	kPt	Kilo Point

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Nomenclature			
Alu	Aluminum	LCA	Life Cycle Assessment
AO	Anodic Oxidation	LCI	Life Cycle Inventory
AOX	Adsorbable organic halogens	LCIA	Life Cycle Impact Assessment
API	Active pharmaceutical ingredient	LVP	Large-volume injectable
BDD	Boron-Doped Diamond	mAb	Monoclonal antibody
BDS	Bulk drug substance	MMO	Mixed metal oxides
BP	Batch processing	MWW	Municipal wastewater
CF	Carbon footprint	NCC	Nanocrystalline cellulose
CO_2	Carbon dioxide	NSAID	Nonsteroidal anti-inflammatory drug
CP	Continuous processing	OPA	1,2-Phthalic dicarboxaldehyde
DP	Drug product	PEF	Product environmental footprint
EA	Exergy analysis	PESTLE	Political, Economic, Social, Technological, Legal and Environmental
EFB	Empty fruit bunch	PET	Polyethylene terephthalate
ELCA	Exergetic life cycle analysis	PP	Pesticides and pharmaceuticals
ENR	Enrofloxacin	PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
EoL	End-of-life	PVC	Polyvinyl chloride
FB	Fed-batch	PVDC	Polyvinyl Dichloride
FEP	Freshwater Eco-toxicity Potential		
GHG	Greenhouse gas	UV	Ultraviolet
		WWT	Wastewater treatment

1. Introduction

The continuous growth in the demand and sales of pharmaceuticals has been increasing the related environmental impacts (Kong et al., 2021; Siegert et al., 2020b). The particularity of pharmaceutical production includes a series of interrelated processes, such as bulk drug synthesis, pharmaceutical preparation, pharmaceutical packaging and transportation, which all span the global economy and have impacts across regions and economic sectors. Similarly, pharmacy synthesis uses numerous inputs and outputs, produces toxic by-products, and involves extensive energy and resource use (Ahsan et al., 2020). As complex and high-value-added products, pharmaceutical chemicals often have a much greater environmental footprint per kilogram than basic chemicals due to the complicated chemistry of active pharmaceutical ingredients (APIs), which necessitate sophisticated multistep manufacturing methods (Belkhir and Elmeligi, 2019; Cespi et al., 2015; Debaveye et al., 2016). The cumulative energy demand (CED) of pharmaceutical chemicals can be 20 times higher than that of essential chemical goods, and their global warming impact (GW) is up to 25 times higher (Wernet et al., 2010). Therefore, manufacturing pharmaceuticals is a labor- and resource-intensive process with potentially severe environmental impacts (Parvatker et al., 2019). For example, the United States healthcare sector accounted for 9–10% of total national emissions of greenhouse gases (GHG), with the production of prescription medications accounting for around 10% of those emissions (Eckelman and Sherman, 2016). According to similar studies, pharmaceuticals in Australia, the United Kingdom, and Canada were responsible for 19–25% of GHG emissions from public health services (Eckelman et al., 2018; Malik et al., 2018).

The pharmaceutical sector is also associated with other environmental concerns beyond energy consumption and emissions. Large volumes of water, for example, may be necessary for some manufacturing processes, and their discharge could have an eco-toxicological impact. In Germany, the German Environment Agency reported that 269 primary chemicals and the metabolites and transformation products of those compounds may be discovered in various environmental compartments (Schulte et al., 2022). Because of their biological activities, pharmaceuticals in the environment may affect hormonal balances, metabolism, or even some development processes (Schulte et al., 2022). Notably, as the world's top producer and exporter of raw materials used in antibiotics production since 2009, China produced 0.12 million tons of antibiotics in 2013 and exported 0.03 million, which took up around 70% of the global market (Guo et al., 2012). As a result of this high production, a large amount of antibiotic mycelial residues (AMRs) were formed. If these residues are improperly handled and released into the environment, they risk breeding antibiotic-resistant bacteria (Pruden et al., 2013; Xu et al., 2007).

On this account, several initiatives have been undertaken to enhance the sustainability of pharmaceutical manufacturing and minimize the environmental footprint of the pharmaceutical industry. Such initiatives included adopting sustainable manufacturing processes based on green chemistry and green engineering concepts (Koenig et al., 2018; Milanesi et al., 2020); gradually transitioning from the batch-producing platform to the continuous one to construct production processes with improved mass/energy efficiency (Lee et al., 2015; Martin et al., 2018); and exploring numerous tactics for process intensification such as microreactor technology, reactive distillation, amorphization, sonocrystallization, and so on (Cheow and Hadinoto, 2012; Feng et al., 2019; Mitic and Gernaey, 2015). However, due to the non-negligible environmental burdens of upstream processes, such as the production of input chemicals and background energy (Ortiz de García et al., 2017), it is vital to quantify the resource consumptions (i.e., mass and energy) and environmental emissions of a manufacturing process (Wang et al., 2021).

Life Cycle Assessment (LCA) is the standard method to assess the biophysical and socioeconomic impacts of products and services across their life cycles (Peña et al., 2021). LCA quantifies impacts across various impact categories such as resource depletion, climate change, toxicity, and impacts on human health, among other things (Peña et al., 2021; Santos et al., 2019). Additionally, LCA could identify the leading causes of the environmental impacts of a product or process, allowing stakeholders to take focused action to lessen those impacts and better understand trade-offs (Ott et al., 2014).

So far, LCA has been used in several phases of the pharmaceutical production process. For instance, LCA has been applied to assess the environmental impact of various operational conditions in bioreactors (Bunnak et al., 2016; Renteria Gamiz et al., 2019), support solvent and enzyme selection based on sustainability (Alder et al., 2016; Brunet et al., 2014; Kim et al., 2009) and lower the environmental impacts in waste treatment (Henderson et al., 2008; Brunet et al., 2014; Raymond et al., 2010), However, environmental management research in the pharmaceutical industry remains limited, as mainly aimed at single-stage problems (Massoud et al., 2015). However, the complexity of pharmaceutical production and the intermittent discharge of pollutants have made multi-objective environmental management an unavoidable problem (Massoud et al., 2015; Milanesi et al., 2020). Incorporating LCA into pharmaceutical manufacturing could facilitate environmental impact hotspot identification and aid decision-makers in the careful selection of optimized solutions from a range of available options during pharmaceutical production (Budzinski et al., 2022; Hadinoto et al., 2022; Yang et al., 2021). Therefore, creating and upgrading environmentally friendly industrial processes as soon as possible is urgent, allowing for increased overall sustainability.

We provide in this review a comprehensive assessment of the application of LCA within the pharmaceutical sector. We initially examined LCA applications in pharmaceutical production, including the synthesis of Active Pharmaceutical Ingredients (APIs) and supplementary chemical components, pharmaceutical formulations, and

biopharmaceuticals. Subsequently, we reviewed the optimization prospects across the entire pharmaceutical production lifecycle. Then, we focused on packaging, transportation logistics, and the environmental implications of drug usage and disposal stages. As far as we are concerned, this is the first literature review on LCA in the pharmaceutical industry that has been published.

2. Methods

2.1. Literature screening

To identify LCA literature within the pharmaceutical industry, we conducted a wide-ranging search using multiple academic platforms: the Elsevier ScienceDirect platform for research journals, Web of Science platform for SCIE Science Citation Index Abstracts database , Scopus and Google Scholar, based on the PRISMA methodology (Moher et al., 2009). The PRISMA method is an evidence-based set of guidelines designed to improve the quality and transparency of reporting in systematic reviews and meta-analyses (Moher et al., 2009). The method offers users a four-phase flow diagram to visualize each step of the literature screening process and better understand the methodology and outcomes (Moher et al., 2009, 2015; Shamseer et al., 2015).

Our search focused on the keywords "Life Cycle Assessment", "Pharmaceutical" and "APIs" in titles and abstracts, targeting research articles published from 2003 to August 2023. Further into specialized fields of pharmaceutical research, we also employed the following key phrases: "Life Cycle Assessment in Pharmaceutical Package" (or "Life Cycle Assessment in Drug Package"), "Biopharmaceutical Life Cycle Assessment", "Life Cycle Assessment in antibiotics" and "Life Cycle Assessment in veterinary drugs", "End of Life for Pharmaceutical". These terms helped explore LCA research within the domains of pharmaceutical packaging, biopharmaceuticals, antibiotics, and veterinary drugs. Ultimately, using the PRISMA method (Moher et al., 2009, 2015; Shamseer et al., 2015), the search and screening yielded a total of 37 papers (Fig. 1 and Table 1) covering six distinct aspects within the pharmaceutical industry: synthesis of APIs (and other pharmaceutical chemicals), pharmaceutical preparation, biopharmaceuticals, drug production cycle and process optimization, pharmaceutical packaging and transportation, pharmacy use and disposal.

2.2. Literature evaluation

Based on the retrieved literature and our understanding of the various stages in the pharmaceutical industry, we have divided the entire pharmaceutical life cycle into three major stages: production, packaging and transportation, use and end-of-life. Accordingly, this review organized materials to cover the full life cycle, including all production, packaging/transportation, and disposal phases. However, LCA research on drug recycling is limited and warrants further attention from the research community. Fig. 2 depicts the number of papers in each part and their publication years. As shown in Fig. 2(a), LCA studies within the pharmaceutical sector have increased since 2019, signaling growing awareness of its significant environmental impacts. Fig. 2(b) suggests a focus on production processes (54% total), including active pharmaceutical ingredients (APIs) synthesis (16%), pharmaceutical preparation (11%), biopharmaceuticals (11%), and production cycle/process optimization (16%). Drug packaging and transportation accounted for 19%, while utilization and end-of-life phases constituted 27%.

In examining the referenced studies, we noted that most (20 out of 37) chose a "cradle-to-gate" approach in their LCA research. Eight

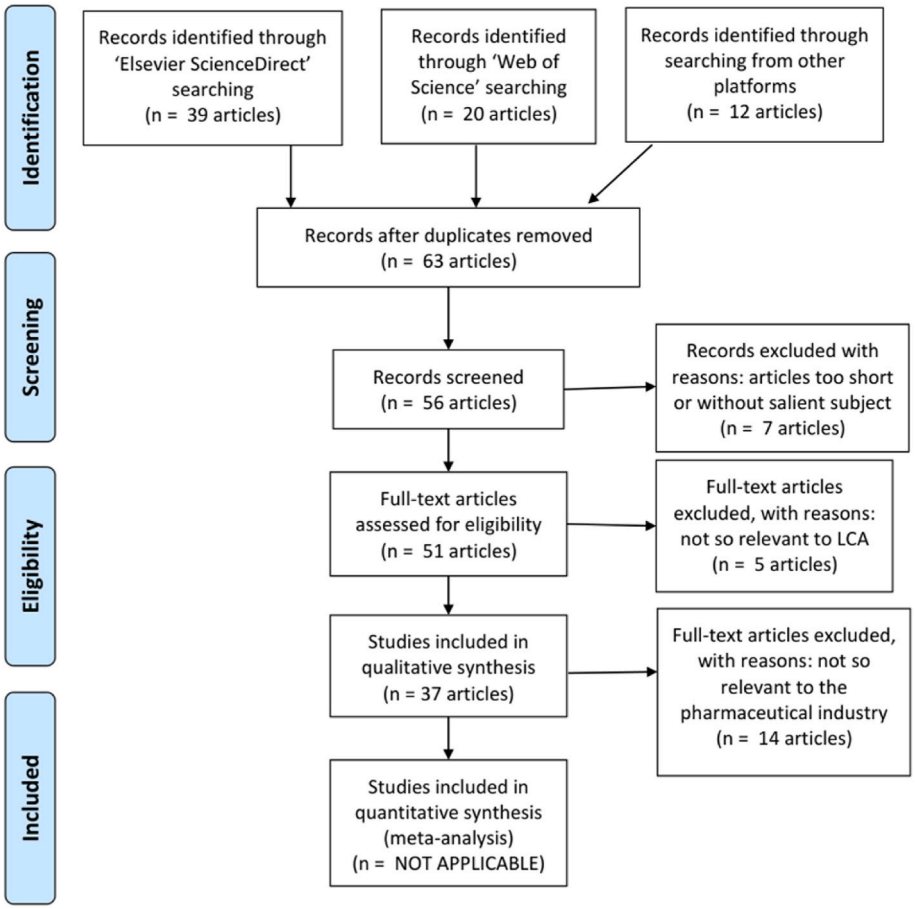

Fig. 1. The process of collecting pharmaceutical and LCA documents literature by the PRISMA method.

Table 1
General Information of the total 37 retrieved papers.

Subjects	Title	System Boundary	Authors (Year)	DOI
LCA on APIs Synthesis	Case study on environmental safety and sustainability of pharmaceutical production based on life cycle assessment of enrofloxacin	Cradle-to-gate	Kong et al. (2021)	10.1016/j.jece.2021.105734
	Life cycle assessment of fine chemical production: a case study of pharmaceutical synthesis	Cradle-to-gate	Wernet et al. (2010)	10.1007/s11367-010-0151-z
	Cradle-to-Gate Greenhouse Gas Emissions for Twenty Anesthetic Active Pharmaceutical Ingredients Based on Process Scale-Up and Process Design Calculations	Cradle-to-gate	Parvatker et al. (2019)	10.1021/acssuschemeng.8b05473
	EHS & LCA assessment for 7-ACA synthesis A case study for comparing biocatalytic & chemical synthesis	Gate-to-gate	Henderson et al. (2008)	10.1089/ind. 2008.4.180
	Cradle-to-gate life cycle assessment of a liquid pharmaceutical product through analysis of chemical production pathways	Cradle-to-gate	Güneş and Şengül (2022)	10.1007/s10098-022-02283-4
	Application of Life Cycle Assessment and Machine Learning for High-Throughput Screening of Green Chemical Substitutes	Cradle-to-gate	Zhu et al. (2020)	10.1021/acssuschemeng.0c02211
LCA on Pharmaceutical Preparation	Selecting optimal pharmaceutical excipient formulation from life cycle assessment perspectives: A case study on ibuprofen tablet formulations	Cradle-to-gate	Wang et al. (2021)	10.1016/j.jclepro.2021.126074
	Life Cycle Environmental and Cost Implications of Isostearic Acid Production for Pharmaceutical and Personal Care Products	Cradle-to-gate	Riazi et al. (2019)	10.1021/acssuschemeng.9b02238
	An integrated analytic hierarchy process and life cycle assessment model for nanocrystalline cellulose production	Cradle-to-gate	Teh et al. (2019)	10.1016/j.fbp. 2019.08.003
	Comparing the environmental impacts of paracetamol dosage forms using life cycle assessment	Cradle-to-gate	Sharma et al. (2022)	10.1007/s10668-021-01948-2
LCA on Biopharmaceuticals	Enzymes for pharmaceutical applications—a cradle-to-gate life cycle assessment	Cradle-to-gate	Kim et al. (2009)	10.1007/s11367-009-0081-9
	Environmental sustainability assessment of the manufacturing process of a biological active pharmaceutical ingredient	Cradle-to-gate	Renteria Gamiz et al. (2019)	10.1002/jctb.5975
	Life-cycle and cost of goods assessment of fed-batch and perfusion-based manufacturing processes for mAbs	Cradle-to-gate	Bunnak et al. (2016)	10.1002/btpr.2323
	Streamlined life cycle assessment of single use technologies in biopharmaceutical manufacture	Cradle-to-gate	Budzinski et al. (2022)	10.1016/j.nbt. 2022.01.002
LCA on Production Process Optimization	Cradle-to-grave life cycle assessment of an ibuprofen analgesic	Cradle-to-grave	Siegert et al. (2020b)	10.1016/j.scp.2020.100329
	LCA approach to the analysis of solvent waste issues in the pharmaceutical industry	Cradle-to-grave	Raymond et al. (2010)	10.1039/c003666 h
	Life cycle assessment of pharmaceuticals: the ciprofloxacin hydrochloride case	Cradle-to-gate	Yang et al. (2021)	10.1007/s11367-020-01841-6
	On the simulation, economic analysis, and life cycle assessment of batch-mode organic solvent recovery alternatives for the pharmaceutical industry	Cradle-to-grave	Savelski et al. (2017)	10.1007/s10098-017-1444-8
	Life Cyle Cycle Assessment Based Environmental Performance Comparison of Batch and Continuous Processing: A Case of 4-D-Erythronolactone Synthesis	Cradle-to-gate	Lee et al. (2016)	10.1021/acs.oprd.6b00275
	Exergetic sustainability assessment of batch versus continuous wet granulation based pharmaceutical tablet manufacturing: a cohesive analysis at three different levels	Cradle-to-gate	De Soete et al. (2013)	10.1039/c3gc41185 k
LCA on Pharmaceutical Packaging and Transportation	Comparison of environmental sustainability of pharmaceutical packaging	Cradle-to-gate	Raju et al. (2016)	10.1016/j.pisc.2016.06.058
	Life cycle assessment of pharmaceutical packaging	Cradle-to-gate	Bassani et al. (2022a)	10.1007/s11367-022-02062-9
	Assessing the sustainability of a manufacturing process using life cycle assessment technique—a case of an Indian pharmaceutical company	Cradle-to-gate	Sharma et al. (2020)	10.1007/s10098-020-01865-4
	Application of Eco-Design and Life Cycle Assessment Standards for Environmental Impact Reduction of an Industrial Product	Cradle-to-grave	Navajas et al. (2017)	10.3390/su9101724
	Life cycle assessment of a large volume parenteral for hospital use	Cradle-to-grave	Hernandez et al. (2023)	10.1016/j.resconrec.2023.107120
	Environmental life cycle assessment of nutraceuticals: A case study on methylcobalamin in different packaging types	Cradle-to-grave	Cooreman-Algoed et al. (2023)	10.1016/j.scitotenv.2023.164780
	Ecodesign approach for pharmaceutical packaging based on Life Cycle Assessment	Cradle-to-gate	Bassani et al. (2022b)	10.1016/j.scitotenv.2021.151565
LCA on Use and End-of-Life of Drugs	Modeling the use and end-of-life phase of pharmaceuticals in support of a life cycle inventory analysis – Case study on different antibiotics in Germany	Gate-to-grave	Schulte et al. (2022)	10.1016/j.scp.2021.100589
	Addressing the use and end-of-life phase of pharmaceutical products in life cycle assessment	Gate-to-grave	Siegert et al. (2020a)	10.1007/s11367-019-01722-7
	Predicting the environmental emissions arising from conventional and nanotechnology-related pharmaceutical drug products	Cradle-to-grave	Jung et al. (2021)	10.1016/j.envres.2020.110219
	Environmental performance of rainbow trout (*Oncorhynchus mykiss*) production in Galicia-Spain: A Life Cycle Assessment approach	Cradle-to-grave	Sanchez-Matos et al. (2023)	10.1016/j.scitotenv.2022.159049
	Life Cycle Comparison of Environmental Emissions from Three Disposal Options for Unused Pharmaceuticals	Gate-to-grave	Cook et al. (2012)	10.1021/es203987 b
	Extensive comparison of methods for removal of organic halogen compounds from pharmaceutical process wastewaters with life cycle, PESTLE, and multi-criteria decision analyses	Gate-to-grave	Do Thi et al. (2023)	10.1016/j.jenvman.2023.118593

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Table 1 (*continued*)

Subjects	Title	System Boundary	Authors (Year)	DOI
	Comparative life cycle assessment (LCA) study of heterogeneous and homogenous Fenton processes for the treatment of pharmaceutical wastewater	Gate-to-grave	Rodríguez et al. (2016)	10.1016/j.jclepro.2016.02.064
	Life Cycle and Economic Analyses of the Removal of Pesticides and Pharmaceuticals from Municipal Wastewater by Anodic Oxidation	Gate-to-grave	Surra et al. (2021)	10.3390/su13073669
	Life cycle assessment and costing of urine source separation: Focus on nonsteroidal anti-inflammatory drug removal	Gate-to-grave	Landry and Boyer (2016)	10.1016/j.watres.2016.09.024
	Is it better to remove pharmaceuticals in decentralized or conventional wastewater treatment plants? A life cycle assessment comparison	Gate-to-grave	Igos et al. (2012)	10.1016/j.scitotenv.2012.08.096

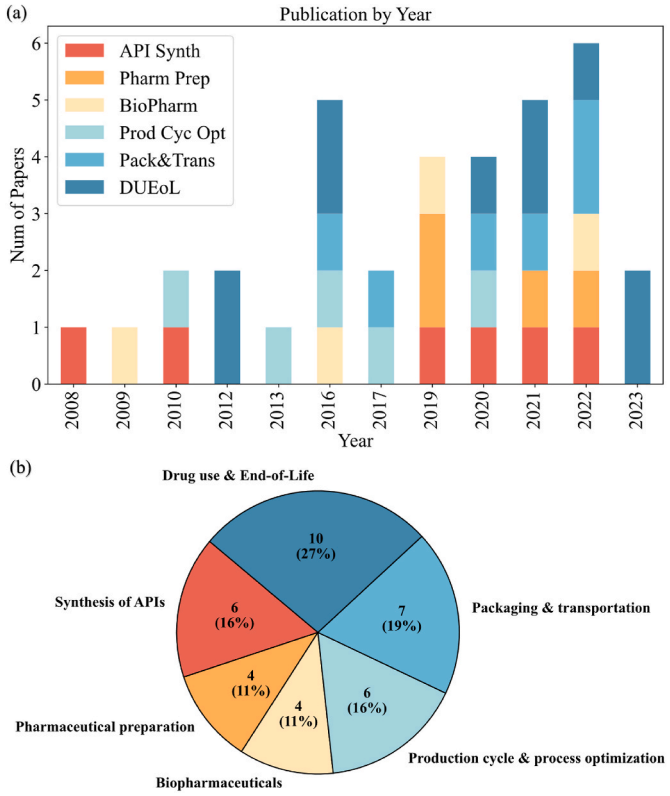

Fig. 2. (a) The number of papers published each year using LCA for Pharmaceuticals; (b) the number and percentage of publications using LCA in different fields/stages of Pharmaceuticals.

studies adopted a "cradle-to-grave" framework, another eight utilized a "gate-to-grave" approach, and only one study applied a "gate-to-gate" framework, as detailed in Table 1. Not surprisingly, pharmaceutical usage and end-of-life studies predominantly chose "gate-to-grave" or "cradle-to-grave" boundaries. The choice of different system boundaries often reflects the unique subjects and focal points of each LCA study. A comprehensive LCA ideally spans from "cradle-to-grave", or even further, adopting a "cradle-to-cradle" perspective. Studies employing a "cradle-to-gate" approach, typically seen in pharmaceutical manufacturing analyses, might omit the assessment of the end-of-life stage. This indicates the need to broaden system boundaries and strengthen uncertainty analysis to better understand the impact of varying parameters on the LCA results (Barahmand and Eikeland, 2022). Additionally, even with the same boundary, treatment stages could vary due to different pharmaceutical manufacturing or recycling methods.

Hence, LCA practitioners should carefully define the system boundary and clearly explain the rationale for their choice. Regarding impact categories and values, it was observed that many studies refrained from providing explicit numerical values for the impact categories discussed. Instead, they resorted to graphical comparisons or analyses of distributions across impact categories, factors, stages, or product types to identify environmental hotspots. The absence of specific impact values might stem from their minimal significance, data unavailability, irrelevance of certain categories, or a study focus elsewhere. In such cases, LCA researchers might consider emphasizing a "comparative LCA" approach in the titles or abstracts to clarify the analytical framework or narrowing the focus to a limited number of impact categories with available data for enhanced clarity.

3. LCA on pharmaceutical production and process optimization

3.1. LCA on APIs synthesis

The synthesis of APIs typically marks the first phase of pharmacy production (Wernet et al., 2010). This process involves a series of reaction steps and the utilization of various reagents, often resulting in greater energy consumption (particularly in terms of electricity) and a larger environmental footprint than conventional chemicals (Wernet et al., 2010).

Many researchers have studied the environmental impact of API synthesis, and most of these papers found that energy and resources were the largest impact sources. An LCA study was conducted by Wernet et al. (2010) on the cradle-to-gate production process of a specific API, finding that pharmaceutical production had much more significant environmental impacts than essential chemical production on a kilogram-per-kilogram basis, with most of the impacts coming from production and use of energy. In addition, Parvatker et al. (2019) performed a cradle-to-gate LCA for 20 anesthetic APIs based on multiple strategies including process scale-up. They accurately calculated the resources and energy needed for producing API, indicating that the intricacy of pharmaceutical manufacturing boosted GHG emissions. Kong et al. (2021) further analyzed the production of enrofloxacin (ENR), finding isopentanol solvent and electricity to be the most significant sources of environmental degradation. They proposed process improvements such as solvent substitution, energy source optimization, and combinatorial analysis, which were found to reduce environmental damage and toxicity levels significantly.

In a targeted investigation into pharmaceutical production, Güneş and Şengül (2022) probed the environmental risks associated with the synthesis of APIs, focusing on the production and wastewater generation of a liquid pharmaceutical product. Their study covered an analysis of the upstream API supply chain and the Freshwater Eco-toxicity Potential (FEP), coupled with a quantitative examination of raw material needs for 17 upstream chemicals. The findings were revealing: the two APIs within the liquid product exhibited higher freshwater eco-toxicity potential than other high-production-volume chemicals. This increasing FEP was directly associated with specific organic and inorganic compounds, such as benzoic acid, aniline, benzaldehyde, and sodium. API chlorhexidine gluconate was identified as the most significant contributor to the FEP. The analysis thus showed the environmental challenges tied to specific pharmaceutical products, drawing attention to the need for more sustainable production pathways.

Further illuminating the environmental concerns within the pharmaceutical manufacturing process, a study by Zhu et al. (2020) analyzed the production process of sitagliptin. The production of sitagliptin can cause serious environmental issues owing to hazardous chemical components, energy-intensive infrastructure, and complex waste treatment. The study highlighted the environmental harm from specific chemicals, particularly trifluoroacetic anhydride. They used high-throughput screening and deep-learning neural networks to find greener alternatives, identifying 1,2-ethanediyl ester as a more sustainable option. This research emphasized the need for greener production methods in API manufacturing, such as adopting clean energy and environmentally friendly chemicals to reduce environmental impacts.

The research above highlighted that producing APIs created significant environmental challenges due to high energy usage, reliance on harmful chemicals, and waste. Thus, optimizing API production methods through cleaner energy sources, sustainable chemical use, and more efficient processes is essential. Concurrently, adopting green chemistry principles and innovative technologies, such as deep-learning models for selecting greener chemicals, could mitigate the environmental impact of pharmaceutical manufacturing.

3.2. LCA on pharmaceutical preparation - excipients & dosage forms

The environmental considerations of pharmaceutical manufacturing extend far beyond the synthesis of APIs (Wang et al., 2021). Indeed, the transformation of APIs and some commonly used excipients into various dosage forms contributes significantly to the overall environmental footprint of pharmacy production.

Isostearic acid (IA) is a widely used chemical raw material and excipient in pharmaceutical processes. The environmental and economic performance of IA made from renewable materials, such as soybean oil and tall oil, was examined by Riazi et al. (2019) in their study. Using various life cycle impact assessment categories, chemical process simulation models, and experimental and patent data, they discovered significant discrepancies in the two sources' impacts on climate change. The CO_2 equivalent per kilogram of IA was more critical in the soybean oil process (1.9–3.8 kg/kg of IA) than in the tall oil process (1–1.5 kg/kg of IA) (as shown in "Climate change" on a logarithmic scale in Fig. 3(a)). Yet, both sources performed lower impacts than synthetic lubricants. Interestingly, the study also unveiled contrasting economic implications. While soybean oil offered a lower unit production cost, it yielded lower profits and return on investment than tall oil-based lubricants. Nevertheless, the potential for soybean oil as a "green" material for IA production remained encouraging in that chemical loading reduction would not only lower raw material costs but also reduce the acidification and ecotoxicity impacts of SOFA-based isostearic acid. This made soybean oil an appropriate source of isostearic acid produced on the margin to satisfy the increasing need.

As a newly developed renewable bionanomaterial made from cellulosic sources such as agricultural waste, nanocrystalline cellulose (NCC) has numerous possible uses in pharmaceutics and the production of pharmaceutical excipients. Teh et al. (2019) compared three distinct process pathways to determine the optimum choice for NCC synthesis from EFB: (i) Acid Hydrolysis with chlorine bleaching, (ii) Acid Hydrolysis with chlorine-free bleaching, and (iii) TEMPO-Oxidation. They found that Acid Hydrolysis with chlorine-free bleaching had the lowest total environmental impact. An integrated analytic hierarchy process (AHP) model integrating LCA was then used to evaluate fungible options based on environmental, technical, and economic criteria. Due to better technical and economic qualities, the investigation concluded that Acid Hydrolysis with chlorine bleaching was the best option.

In a study conducted by Wang et al. (2021), the environmental impacts of ibuprofen tablet production were evaluated using two different excipient formulations. The researchers analyzed each production stage

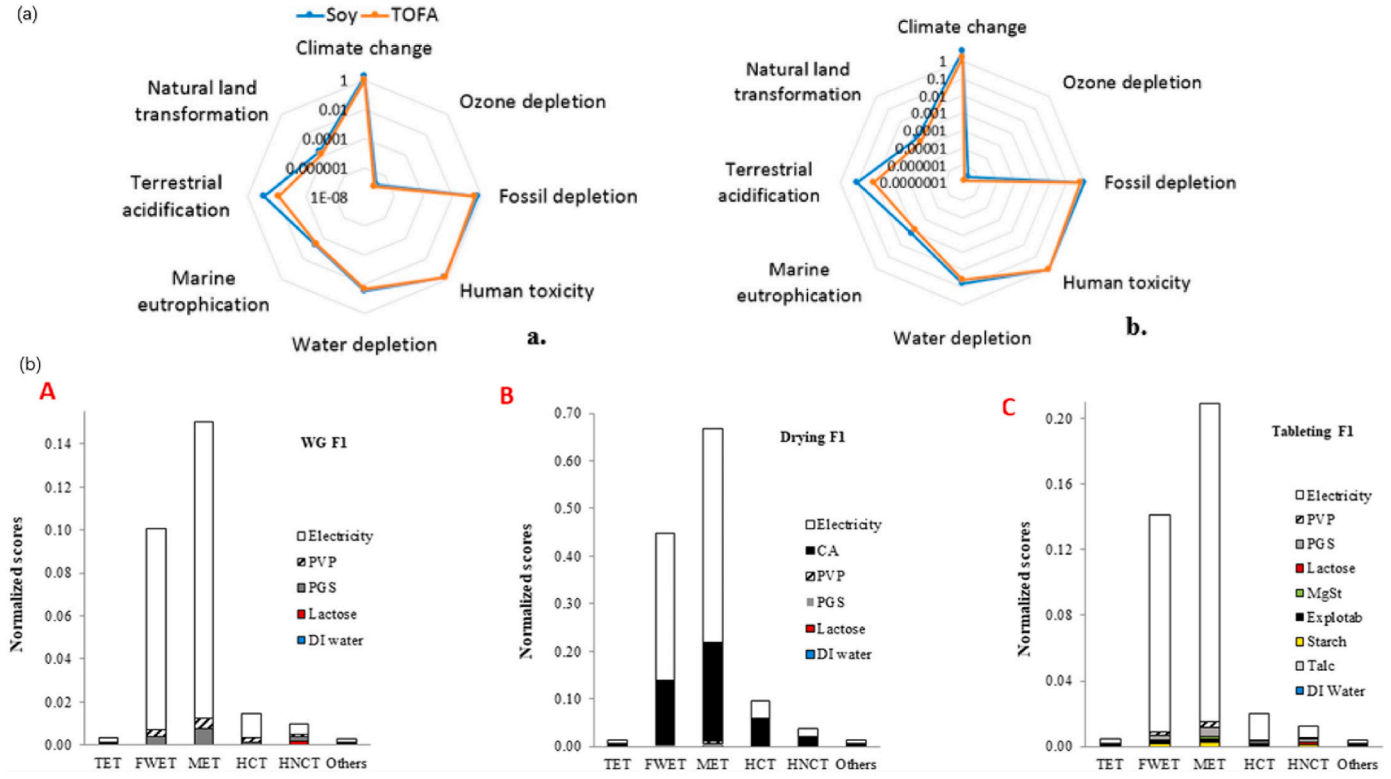

Fig. 3. (a) LCA results of the synthesis of IA, displayed on a scale of logarithms, based on mass/economic allocation, illustrating the comparison of the environmental impact of the soybean oil process and the tall oil process. Adapted with permission from Bahar Riazi et al. Copyright 2019 ACS Publications. (b) LCA results of an ibuprofen tablet production regarding the environmental impacts of the three steps (wet granulation, drying, and tableting) indicate the dominance of electricity consumption. Adapted with permission from Danping Wang et al. Copyright 2021 Elsevier.

through a comprehensive cradle-to-gate LCA, including wet granulation, drying, and tablet compaction. Their findings suggested that the environmental impacts of ibuprofen tablet production were chiefly driven by process-level energy consumption, especially the electricity used in drying, as shown in Fig. 3(b). Furthermore, they observed that creating diverse excipients resulted in varying environmental footprints, subject to the raw materials and manufacturing procedures. In their LCA study, Sharma et al. (2022) compared the environmental impacts of producing paracetamol in two forms: tablets and syrup. The study found that syrup production significantly contributed to climate change (90%) and had over 50% impact across various categories, including fossil depletion, freshwater consumption, and photochemical ozone formation. Tablet production, however, had significant impacts, mainly on human toxicity, ionizing radiation, and metal depletion.

The above research further implied that beyond the synthesis of APIs, the scope of pharmaceutical LCA research extended to the production of upstream chemicals and pharmaceutical excipients. The environmental impacts could differ significantly when the same API was formulated into different dosage forms or when different excipients were utilized to create identical dosage forms. The studies further supported the argument that energy consumption remained the primary factor influencing environmental impact during pharmaceutical preparation. However, despite the currently published literature, there still was a significant gap in more inclusive LCA studies focusing on different excipients. For instance, future research could extend to various aspects of excipients, including but not limited to diluents (lactose, starch, microcrystalline cellulose, etc.), lubricants (calcium stearate, magnesium stearate, etc.), binders (polyvinylpyrrolidone, povidone, etc.), preservatives (phenol, parabens, etc.), wetting agents (sorbitol, propylene glycol, etc.), suspension and emulsifying agents, sustained-release agents (ethylcellulose, polymethyl methacrylate, etc.), stabilizers, osmotic agents (mannitol), colorants and flavorings, and so on.

3.3. LCA on biopharmaceuticals

Recently, biopharmaceuticals have gained widespread attention due to their pronounced therapeutic specificity, high pharmacological activity, and reduced toxicity or side effects (Jones et al., 2022). Nevertheless, their production and preparation came with challenges, including intricate purification processes and topics related to stability and perishability, during which environmental impacts can be an issue (Jones et al., 2022).

The rapid growth of biologics in multiple therapeutic domains has shifted the environmental dynamics of pharmaceutical production for some companies. A simplified cradle-to-gate LCA on the production of a biological bulk drug substance (BDS) was conducted by Budzinski et al. (2022). As a result, the electricity required to operate the plant was shown to be the most significant contributor to biopharmaceutical companies' life cycle environmental impact. Therefore, it was proposed that operational modifications can boost process efficiency and reduce plant operation times, regarded as critical strategies for mitigating environmental impact.

Bunnak et al. (2016) presented a framework that combined an LCA and economic analysis of manufacturing-related variables. The study focused on production scale-up to design a more economical, reliable, and sustainable manufacturing pipeline for monoclonal antibodies (mAbs). A comparison of the two often employed upstream topologies for producing mAb, namely fed-batch (FB) and perfusion-based procedures, was conducted to show the framework's effectiveness. The findings showed that the cost of goods for a typical perfusion process was comparable to that of an FB method, but its environmental impact was more significant. This was attributed to its greater consumption of water, energy, and CO_2 emissions, i.e., 35% more consumed water, 17% more demanded energy, and 17% more CO_2 emitted than the FB process. In this study, water consumption became the most critical environmental factor, particularly when scaling up processes.

With primary and modeled data, Renteria Gamiz et al. (2019) performed an LCA on Infliximab, a monoclonal antibody. The zymolysis and its raw materials supply chain exerted the most significant environmental impact. This was because of the need for chemicals and complicated components such as animal-derived materials (ADMs) in culture medium. A comparison of infliximab and ustekinumab (a biopharmaceutical made without ADMs) revealed that doing away with these components might cut the overall resource consumption of the manufacture of monoclonal antibodies by up to 7.5 times. Furthermore, the heating, ventilation, and air conditioning system was identified as a major electricity consumer, contributing to roughly 75% of the overall plant electricity usage.

Kim et al. (2009) estimated the environmental impact of three immobilized enzymes used in pharmaceutical products through a cradle-to-gate LCA. The research included enzyme manufacturing and purification, energy generation, raw material production, waste disposal, and transportation. Their results showed that the non-renewable energy consumption of the three immobilized enzymes ranged from 117 to 207 MJ/kg, with the global warming potential ranging from 16 to 25 kg CO_2 equivalent per kilogram. Support production accounted for around 31%–67% of total energy consumption in each impact category. In comparison, soybean protein and yeast ions contributed approximately 64%–72% of total photochemical smog-forming. In addition, a hypothetical analysis even suggested that switching petroleum-based to bio-based glycerin could significantly reduce warming impacts, with a proportion ranging from 11% to 44%.

From the studies above, it became evident that the biopharmaceutical process potentially involved high consumption of water and raw materials. A significant challenge for transitioning towards energy-efficient, sustainable practices in the industry was electricity usage. This was applied to both the direct operation of pharmaceutical equipment and supporting systems such as air conditioning and humidity control. In addition, biopharmaceuticals can also involve more organic wastes, some of which involve the disposal of animal and cell tissues (Ma and Li, 2024). Therefore, the disposal and inappropriate treatment of biological tissues may be more complicated and bring new environmental concerns (Hidalgo et al., 2018; Ma and Li, 2024; Yamano-Adachi et al., 2020). Thus, beyond the quest for cleaner energy, greener compounds, and proper waste treatment, enhancing process efficiency and minimizing operational times may be vital strategies for mitigating the environmental impacts (Budzinski et al., 2022; Bunnak et al., 2016; Kim et al., 2009; Renteria Gamiz et al., 2019).

However, to summarize, current LCA studies on biopharmaceuticals still lack comprehensive analysis and deep insights. For instance, the effects of sourcing and transporting raw materials, such as culture media, reagents, and buffer solutions, still need thorough investigation. Additionally, the specialized cold chain logistics for storing and transporting vaccines and drugs have significant environmental impacts, as do the added equipment and consumables needed for injections (Bertesteanu et al., 2014; Nijholt, 2015). Furthermore, the lack of detailed and up-to-date LCI background databases limits the widespread application of LCA, especially when it involves biologics and organic compounds (Leceta et al., 2014; Xia et al., 2020). The limited availability of data makes the LCA modeling and calculations challenging and introduces uncertainties (Parvatker and Eckelman, 2019; Xia et al., 2020). The same challenge exists in the modeling of complex processes of chemical pharmaceuticals, due to the highly complex nature of pharmaceutical simulations (Luo and Ierapetritou, 2020; Parvatker et al., 2019; Pranav et al., 2022; Xiao et al., 2003). Therefore, we encourage professionals and stakeholders in these fields to actively develop effective and accessible databases.

3.4. LCA on production process optimization

3.4.1. Identification of hotspots in production process

LCA is a versatile tool for assessing the environmental impact of both

specific production stages and the entire pharmaceutical production lifecycle. It can thereby give key insights into optimizing production processes to be more eco-friendly.

Siegert et al. (2020b) conducted a complete cradle-to-grave LCA study of the analgesic Eudorlin®Extra (a tablet of ibuprofen), including API manufacturing, galenic formulation, packaging, distribution, utilization, and end-of-life. The authors filled data gaps in the upstream by calculating LCI data for each input material used in the manufacturing process. As a result, the production stage dominated the environmental profile: more than 73% percent in GWP and even 99.9% for Ecotoxicity, and for some impacts such as Abiotic Depletion and GWP, the distribution process contributed more than 20%, while the stage of use and end-of-life were slight (less than 2%) in this study.

Yang et al. (2021) evaluated the environmental impacts of ciprofloxacin hydrochloride manufacture. Their focus extended from the synthesis of API to formulation production and drug packaging. They determined the significant materials and phases in the pharmaceutical production life cycle and developed methods to reduce wasteful energy and material usage. The findings revealed that the manufacturing of APIs contributed the most to the environment, making up 42.9%, 41.9%, and 15.2% of the total environmental impact, respectively. Crucially, their analysis identified polyol solvent and electricity as the primary drivers of environmental damage, particularly affecting human health, natural resources, and ecosystems. Strategies such as solvent substitution and transitioning from coal-based to natural gas electricity generation led to remarkable reductions in the ecological impact on human health. For instance, in synthesizing APIs, the ecological index scores for human health decreased by 8 kPt following the switch to an alternative solvent. It dropped by 4 kPt after substituting coal-based power with natural gas, and saw a reduction of 12 kPt as a result of concurrent optimization efforts.

3.4.2. Solvent recovery

Solvent usage is an important environmental concern as it often constitutes up to 90% of the total mass of API production (Raymond et al., 2010). In addition, producing virgin solvents and handling solvent waste generated much higher life cycle emissions than equivalent operations for ordinary chemicals (Raymond et al., 2010; Savelski et al., 2017). Raymond et al. (2010) investigated the influence of solvent recovery and reduction approaches on the environmental impact of API synthesis using three case studies from pharmaceutical companies: Pfizer, Bristol-Myers Squibb, and Novartis. They discovered that solvent production and waste combustion contributed significantly to a pharmaceutical API's life cycle emissions. In some circumstances, integrating a solvent recovery system may generate a net reduction in the total energy consumption of processes. While introducing a solvent recovery or reduction system did lead to a modest increase in energy consumption and associated emissions, these were negligible compared to the substantial reductions achieved in both virgin solvent use and waste incineration. However, assessing the environmental benefits of such a system solely from a gate-to-gate perspective was insufficient. Given that solvent manufacture and disposal were the primary contributors to emissions in all three base case scenarios they examined, a comprehensive cradle-to-grave analysis was essential to fully implementing environmental benefits.

Using LCA, Savelski et al. (2017) assessed three different solvent waste streams and looked at design options for their purification and potential reuse in the production of pharmaceuticals. A modular multi-campaign solvent recovery skid could, therefore, economically recover solvents from low-volume streams while reducing operating costs and total emissions by 86.3% and 85.3%, respectively. The payback period for a solvent recovery system investment was calculated to be 4.5 years, and the internal rate of return (IRR) was over ten years. According to the LCA results, using a solvent recovery system impacted human health, ecosystems, and resources by 82.4%, 85.1%, and 87.1%, respectively.

3.4.3. Continuous vs. batch production

Continuous processing offers numerous benefits by enhancing production in various ways as a hallmark of process intensification and a core aspect of green engineering research within the pharmaceutical industry. By potentially reducing solvent usage, lowering production costs, and enhancing both quality and safety standards, continuous processing could be a transformative approach in advance of the production stage and from an environmental perspective. Illustrating this point, Lee et al. (2016) compared the environmental consequences of batch (BP) and continuous (CP) processes on the synthesis of 4-D-erythrolactone (4-DEL) at a trial plant scale. They evaluated the manufacturing system with a cradle-to-gate LCA. According to the outcomes, CP outperformed BP in reducing the environmental burden of 4-DEL production. The improvements were significant: with reductions in cumulative mass intensity, global warming potential, human toxicity index, and water depletion index by 30.1%, 57.5%, 9.37%, and 41.7%, respectively (as shown in Fig. 4). These gains were primarily attributed to efficiencies in less equipment cleaning and smaller factory floor space utilization.

Further enriching the topic of continuous versus batch production, De Soete et al. (2013) quantified the environmental sustainability of batch and continuous pellet production of ConsiGma™ tablets at the Janssen-Cilag SpA drug factory. They used Exergy Analysis (EA) and Exergetic Life Cycle Analysis (ELCA) at three distinct levels to detect and identify resource depletion within the supply chain of pharmaceuticals. Their results illuminated that transitioning from traditional batch production to continuous production would reduce resource consumption at the process, plant, and total industrial levels by 10.2%, 15.2%, and 2.2%, respectively. The reductions were even more pronounced when focusing on DP production processes, reaching 34.0%, 25.9%, and 14.7% at the corresponding system borders. Moreover, they found that the API dose was the parameter most acutely linked to environmental burden and that a shift to continuous production could diminish the carbon footprint by 2.0% at the industrial level.

Existing studies uniformly confirmed the superiority of continuous production over batch production in conserving raw materials and energy. However, moving from batch to continuous pharmaceutical production can present extensive technical or cost challenges in some cases (Costandy et al., 2019; Kumar et al., 2020). For example, batch procedures in biopharmaceuticals required less accurate and robust controls to produce the same product than the continuous ones (Kumar et al., 2020). Thus, optimizing batch modes to minimize raw materials and energy consumption could be a viable path worth exploring.

Table 2 summarizes the major environmental impacts arising from pharmaceutical production processes, including those related to process optimization, as well as potential improvement strategies to mitigate these impacts. Notably, material and energy usage along with pollutant emissions during pharmaceutical production are intricately linked to working conditions like temperature, humidity, and cleanroom standards (Molavi et al., 2020; Zhu et al., 2023). Despite being energy-intensive, these conditions have received scant attention in LCA studies. However, with adequate data availability, working conditions could be incorporated into the LCI to enable an evaluation of their environmental impacts.

4. LCA on Pharmaceutical Packaging and transportation

In addition to the production of APIs and formulations, drugs need to be packaged and transported before being used by hospitals and patients, and this process also contributes to non-negligible environmental impacts. As the pharmaceutical industry intensifies its focus on sustainability, the impacts of medicinal packaging are coming under increased attention (Raju et al., 2016). LCA research has shown that polymers such as HDPE, PVC, and PET tend to outperform traditional materials such as glass and metal in terms of environmental sustainability. As described in Table 3, energy consumption (especially the use

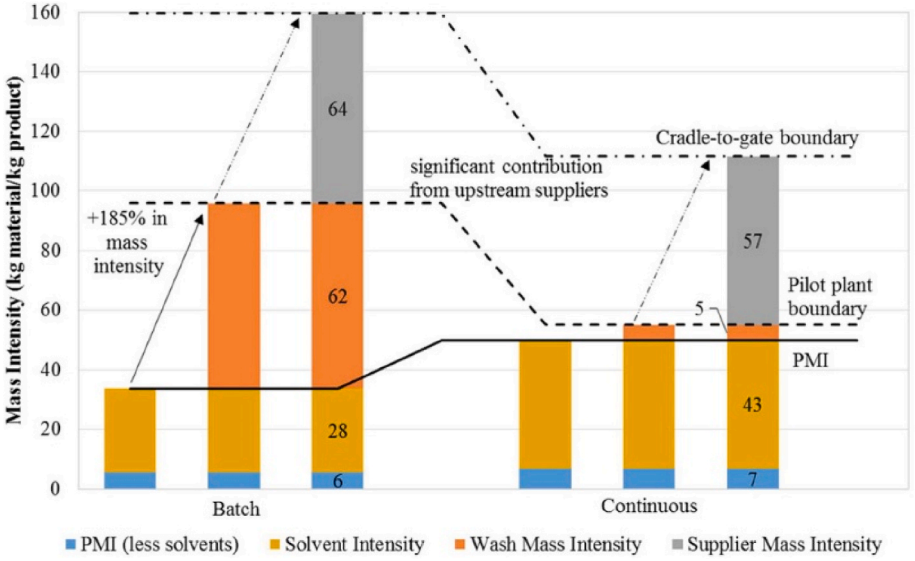

Fig. 4. LCA results of BP and CP on the synthesis of 4-DEL, focusing on the mass intensity, indicating that CP can observably reduce the environmental burden compared to BP. Adapted with permission from Lee et al. Copyright 2016 ACS Publications.

Table 2
Summary of the investigations from literature in the stage of pharmaceutical production.

The most significant environmental impacts	Improvements to reduce environmental impacts	References
a) Energy (electricity, water, etc.) consumption and chemical use b) Manufacture, use and disposal of solvents c) Emissions of greenhouse gas and wastewater	Improvements in energy structure: Application of clean energy for power generation	Kong et al. (2021) Yang et al. (2021)
	Improvements in chemicals and solvents: a) Solvent substitution and recovery b) Seeking environmentally friendly chemicals c) Selection of greener raw materials in biopharmaceuticals	Kim et al. (2009) Kong et al. (2021) Raymond et al. (2010) Riazi et al. (2019) Savelski et al. (2017) Yang et al. (2021) Zhu et al. (2020)
	Changes in processes and products: a) Selection of appropriate excipients and dosage forms b) Turn to continuous production c) Optimization of process efficiency and operational time d) Selection of appropriate methods and pathways for pharmaceutical synthesis	Budzinski et al. (2022) De Soete et al. (2013) Güneş and Şengül (2022) Henderson et al. (2008) Lee et al. (2016) Riazi et al. (2019) Sharma et al. (2022) Siegert et al. (2020b) Teh et al. (2019) Wang et al. (2021)

Table 3
Summary of the investigations from literature in the stage of pharmaceutical packaging and transportation.

The most significant environmental impacts	Improvements to reduce environmental impacts	References
The consumption of energy and resources during packaging production, as well as the untimely transportation strategies	Well-organized transportation means and routes	Bassani et al. (2022b) Cooreman-Algoed et al. (2023)
	Selection of appropriate packing materials	Bassani et al. (2022a) Cooreman-Algoed et al. (2023) Navajas et al. (2017) Raju et al. (2016)
	Application of eco-design of packaging	Bassani et al. (2022b)
	Optimization of the electricity mix	Hernandez et al. (2023) Sharma et al. (2020)
	Adoption of renewable energy sources and energy-efficient industrial processes	Hernandez et al. (2023)

of electricity and natural gas) during packaging often generates a significant environmental footprint.

Bassani et al. (2022a) conducted an extensive LCA study on three forms of pharmaceutical packaging, including blisters, sachets and bottles most often supplied in European community pharmacies. They undertook the analytical assessment of 23 alternative packaging options, varying in both size and material composition. The results showed many consequences among the different packaging options for the same medication, with blisters being more damaging than bottles and sachets. A critical point of concern was the production phase of these materials, with aluminum having extremely high consequences, notably on acidification, and PVC having large implications on considerable fossil depletion. PVC, PVC/PVDC, and OPA/Alu/PVC were determined as the forming films with the lowest environmental implications. As a result, there was still much space for advancement in terms of eco-design for pharmaceutical packaging, especially for blisters, for which PVC was more environmentally friendly than sachets.

Raju et al. (2016) used cradle-to-gate LCA to compare the environmental impact of PVC and aluminum blister packaging for tablets. The study found that PVC blisters generally had a lower impact than aluminum, mainly due to the high environmental cost of aluminum foil production. Another study by Sharma et al. (2020) confirmed that

blister packaging was a significant environmental hotspot in the production of paracetamol tablets due to the intensive resource use of the packaging material. Additionally, the study identified that the sieving process greatly contributed to land use and metal depletion, accounting for over 80% of the impact in these areas. This highlighted the need to improve the electricity mix to reduce environmental impact. The study also found that steam production was a major contributor to most impact categories and suggested switching to more sustainable methods such as solar-based steam generation. Navajas et al. (2017) showed that replacing glass containers with PET reduced the environmental impact of cough syrup packaging in Spain by 35.1%.

Hernandez et al. (2023) performed a cradle-to-grave LCA on medical large-volume injectables (LVPs). They found that the environmental impacts were significantly tied to the energy demands of packaging production mainly due to the requirements of electricity and natural gas (as shown in Fig. 5(a)), which were consumed to run the plant and provide steam to autoclaving treatment, respectively. A crucial tactic to lessen the effects was the adoption of renewable energy sources and energy-efficient manufacturing techniques in LVP production.

The environmental impact of pharmaceutical transportation is crucial and, as highlighted by Cooreman-Algoed et al. (2023), can sometimes surpass that of packaging or the drugs themselves. Their study (see Fig. 5(b)) assessed the supply of 1.2 mg of daily methyl-cobalamin supplements to Belgian consumers in different

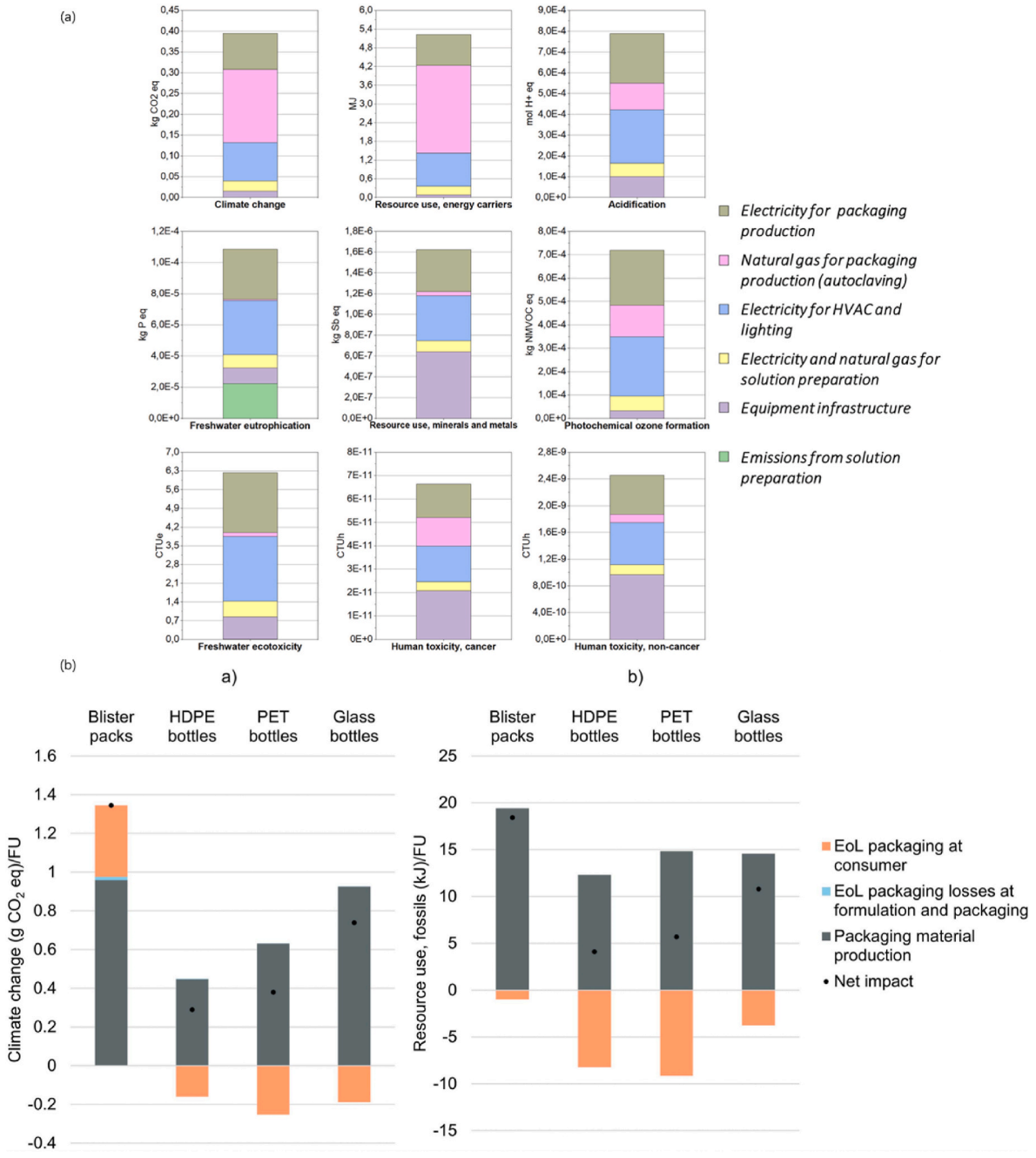

Fig. 5. (a) The environmental impact of energy requirements, operation and infrastructure in packaging during the production of a large volume parenteral for hospital use, emphasizing that energy requirements, especially electricity and natural gas contributed more to the environmental impacts. Adapted with permission from Carlos Hernandez et al. Copyright 2023 Elsevier. (b) LCA results of chewable methyl-cobalamin supplements in four packaging types indicate the non-negligible environmental impacts of pharmaceutical transportation. Adapted with permission from Cooreman-Algoed et al. Copyright 2023 Elsevier.

packaging types, including blister packs and HDPE, PET, and glass bottles. Surprisingly, they found that even though supplements comprised only 1% of the package's weight, transporting consumers to pharmacies and transporting the methyl-cobalamin powder accounted for most of the overall carbon footprint (CF). Supplements in HDPE bottles had the lowest impact (6.3 g CO_2-eq), while those in PET bottles, glass bottles, and blister packs had a larger impact (1%, 8%, and 35%, respectively). Blister packs had the highest footprint for other categories, such as fossil resource footprint, acidification, and water consumption, while HDPE and PET bottles had the lowest. The differences in the carbon footprint were due to energy use and emissions from solvent production. Therefore, choosing the right packaging type for pharmaceuticals and supplements was essential for reducing environmental impact.

Given the environmental challenges of packaging and transportation, eco-design of packaging and strategies for transportation are essential. Bassani et al. (2022b) presented an eco-design method relying on LCA for pharmaceutical packaging to assess opportunities to enhance the environmental sustainability of packaging. The use of smaller-size packaging, eliminating unnecessary components and empty spaces, could lower material and production costs as well as transportation impacts. Other eco-design suggestions included choosing modes of transportation with lower environmental impact when considering the location of packaging production and using electric vehicles for pharmacy distribution, among other things. The LCA-based eco-design method could provide a strong foundation for measuring environmental impacts, covering the entire life cycle of packaging, from material selection to the end user. To summarize the section's findings, the most significant environmental impacts and correlating modifications are listed in Table 3. In addition, a considerable research direction in the transportation part of the LCA study is to include the specialized cold chain logistics for storage and transportation, the impact of regional supply chains, and so on.

5. LCA on use and end-of-life of drugs

In addition to the environmental impact of pharmaceutical production and consumption, drug residues present an often-overlooked hazard to ecosystems and human health (Rana et al., 2019). These residues, which may end up in waterways, soil, or even the atmosphere, can lead to a range of adverse outcomes, such as antibiotic resistance, endocrine disruption, and harm to aquatic life (Destrieux et al., 2017; Rana et al., 2019; Yu et al., 2022), and so on. Consequently, LCA offers a comprehensive understanding of how drug residues interact with the environment and helps devise effective and environmentally responsible disposal strategies.

5.1. Impact of API flows emissions

Siegert et al. (2020a) provided a simplified inventory model for the use and end-of-life (EoL) phase of pharmaceuticals. They estimated API flows and their subsequent environmental emissions. Applying this model to an LCA for orally administered ibuprofen, the study identified and quantified 11 potential API flows and emissions across various forms of the drug. The results showed that most (73.1%) of ibuprofen was metabolized. At the same time, the remaining unmetabolized portion made its way into sewage treatment plants, where it underwent further degradation, accounting for 13.94% of the original amount. Additionally, 8.35% of the unmetabolized ibuprofen was released into surface waters, while negligible amounts were emitted into the air (0%) and contributed to sewage sludge (0.36%).

5.2. Impact of nanotechnology on drug emissions

Aquatic habitats are seriously threatened by prescription medicines and their metabolites entering the environment (Jung et al., 2021). As some research has proved, nanotechnology in pharmaceuticals may be a potential solution for toxicity reduction. Nanotechnology was used by the pharmaceutical products Lipidil 145 One® and Ecocaps to increase the absorption and bioavailability of the medicine in humans compared to the regular product Lipidil® 200. Jung et al. (2021) applied a combined methodology of in-vitro drug release experiments and physiologically based biopharmaceutics modeling to evaluate the environmental emissions of three fenofibrate formulations, including Lipidil® 200, Lipidil 145 One®, and Ecocaps. According to the study, Lipidil 145 One®, a product connected to nanotechnology, reduced overall medication emissions by 27.5% with a nanomaterial percentage of roughly 0.5%. As the prototype of the formulation, Ecocaps comparatively reduced fenofibrate emission by 42.5% and introduced no nanomaterials into the environment, as illustrated in Fig. 6(a). In a simplified LCA, the lower dosage for Ecocaps and the lower drug-to-metabolite ratio led to a decrease in the effects of fenofibrate over its entire life cycle. Specifically, the study observed an 18% decline in global warming potential, a 61% drop in eco-toxicity, and a 15% reduction in human toxicity.

Nano pharmaceuticals offer advantages such as reduced demand for raw materials thanks to smaller quantities of active ingredients, high potential for enhanced biodegradability, and greater precision in drug delivery (Chapman, 2005; Jones et al., 2022; Molavi et al., 2020). These properties could synergistically mitigate drug overuse and consequently reduce environmental burden; however, more evaluations regarding ecotoxicity and long-term impacts are essential to assess their environmental impact compared to traditional pharmaceuticals definitively.

5.3. Impact of antibiotics

Schulte et al. (2022) pioneered an LCI model for assessing pharmaceutical use and the end-of-life phase to better understand the environmental consequences of pharmaceutical use and disposal. They examined different antibiotics in Germany, mainly focusing on amoxicillin, ciprofloxacin, and clarithromycin. According to the model, sewage treatment effluent was found to be the main pathway for pharmaceutical emissions into the environment. The emissions through this route varied among the antibiotics studied, accounting for 39.5% in the case of clarithromycin and going up to 67% for amoxicillin. Furthermore, the research found that ciprofloxacin had a significant propensity to accumulate in sewage sludge, with a portion of 24.3% of its total emissions. In contrast, clarithromycin demonstrated the highest rate of biodegradability, measured at 15.8%. One noteworthy aspect of this study was its call for greater consideration of overlooked transformation processes in future assessments, specifically for hydrolysis. These neglected aspects are essential for a more comprehensive understanding of how antibiotics interact with and impact environmental systems.

Aquaculture systems may release veterinary medications and antibiotics into the environment, endangering aquatic life and contributing to antibiotic resistance and buildup. An LCA study of antibiotics for rainbow trout raised in a small plant in Galicia, NW Spain, was conducted by Sanchez-Matos et al. (2023). The impact category of antibiotic resistance (ABR) enrichment was considered to investigate the possible effects of antibiotic discharge in freshwater microbiota. It was discovered that the primary driver of the ABR enrichment category was the release of amoxicillin to recipient water bodies. New antibiotic alternatives should be researched to lessen the influence of antibiotic discharge on ABR enrichment in freshwater bodies.

5.4. Pharmaceutical disposal

Proper disposal of unused or unmetabolized drugs is vital because pharmaceuticals continue to impact the environment long after they have been consumed. Cook et al. (2012) employed LCA to compare three disposal options: incineration following pharmacy take-back, wastewater treatment after being flushed down the toilet, and either

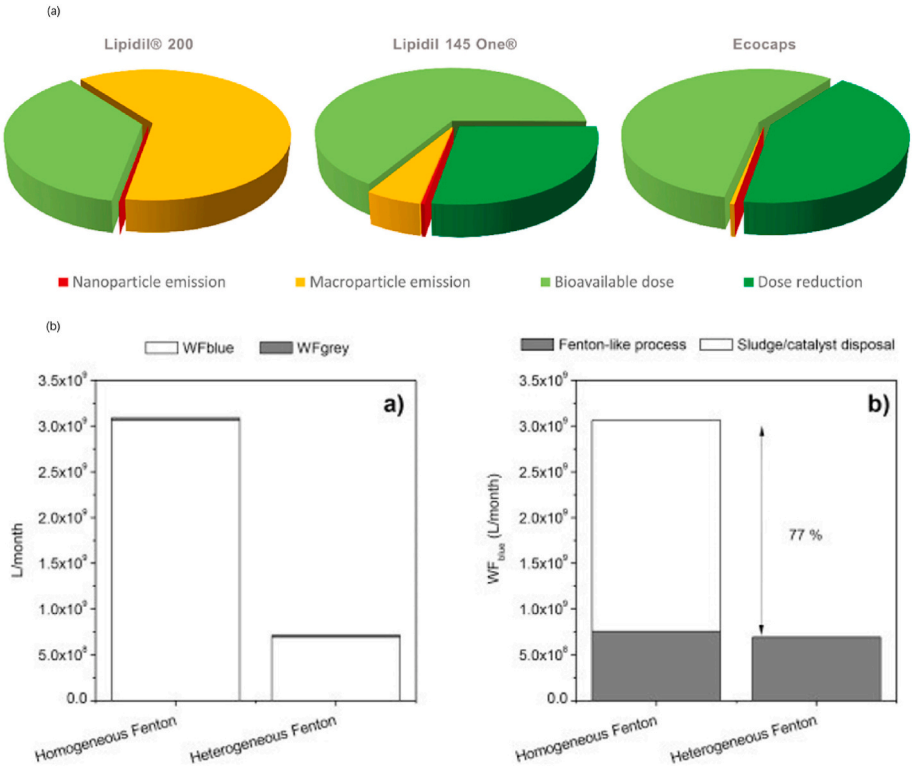

Fig. 6. (a) LCA results of the emission of three formulations of fenofibrate into the environment, indicating that nanotechnology pharmaceutical products Lipidil 145 One® and Ecocaps can effectively increase bioavailability and reduce fenofibrate emission to the environment. Adapted with permission from Fabian Jung et al. Copyright 2021 Elsevier. (b) LCA results of homogeneous and heterogeneous Fenton processes for wastewater treatment, indicating the super ability of heterogeneous Fenton processes to reduce the water footprint. Adapted with permission from R. Rodríguez et al. Copyright 2016 Elsevier.

landfilling or incineration after trash disposal. Both API emissions and non-API emissions were estimated for each option. The study revealed a hybrid scenario, which featured 50% of the unused drugs being returned to pharmacies for incineration and the remaining 50% being disposed of as regular trash. The results showed that it had the potential to reduce API emissions by 93%. However, the hybrid scenario greatly increased non-API emissions: over 300% higher than 100% trash disposal. Perhaps most alarmingly, the study found that if 50% of unused pharmaceuticals were flushed down the toilet instead of trashed, emissions would rise across the board compared to 100% trash disposal.

5.5. Wastewater treatment of the pharmaceutical industry

5.5.1. Mitigating chemical waste in pharmaceutical wastewater

Responsible recycling and disposal of pharmaceutical wastewater are crucial to minimize chemical waste, as uncontrolled hazardous waste discharge can severely impact the environment. (Do Thi et al., 2023). Do Thi et al. (2023) used LCIAs to examine the environmental impacts of adsorbable organic halogens (AOX) in pharmaceutical wastewater. Their study showed that distillation-based separation of AOX chemicals had the most significant positive impact on climate change and outperformed air stripping, steam stripping, and combustion by 6.3%, 29.1%, and 52.0%, respectively, on the PEF single score. Using PESTLE (Political, Economic, Social, Technological, Legal and Environmental) analysis, the authors found that the best AOX disposal scenario involved onshore wind turbines for electricity, which could reduce carbon emissions by about 64.87% compared to fossil fuel alternatives.

Rodríguez et al. (2016) conducted an LCA to evaluate the environmental sustainability of wastewater treatment in the pharmaceutical sector in Toledo, Spain. They compared homogeneous and heterogeneous Fenton processes and found that chemical use and heat demand had the most significant environmental impacts. However, the heterogeneous Fenton process proved to be the more environmentally friendly option, reducing the water footprint by over 77% compared to the homogeneous process, as can be found in Fig. 6(b).

5.5.2. Centralized wastewater treatment

Surra et al. (2021) conducted an LCA study on pesticides and pharmaceuticals (PP) found in the wastewater of a Portuguese treatment plant. The results showed that PP presence raised the environmental impact of municipal wastewater treatment (MWW) by 85%, 60%, and 90% in the impact categories of Human Carcinogenicity, Non-Carcinogenicity, and Freshwater Toxicities, respectively. The authors then evaluated the environmental and economic effects of installing an Anodic Oxidation (AO) unit to remove PPs, comparing Boron-Doped Diamond (BDD) and Mixed Metal Oxides (MMO) anodes. Despite increasing the overall environmental impact by 95%, they found some impacts could be offset using biogas co-generation at the plant. This could reduce reliance on non-renewable energy. However, the environmental costs of the AO technology, particularly for unit construction and electrode production, often outweighed its environmental benefits. While MMO was economically advantageous, it had a larger environmental impact than BDD, making the latter more eco-friendly.

5.5.3. Urine source separation over centralized wastewater treatment

Urine source separation can reduce environmental pollution from medications while improving nutrient recovery. Landry and Boyer (2016) used LCA to compare the environmental and economic impacts of managing NSAIDs and nutrients through urine source separation versus centralized wastewater treatment (WWT). They found that urine source separation reduced environmental impacts by 90% compared to centralized wastewater treatment. This reduction was mainly due to reduced potable water use for flushing, lower electricity consumption at wastewater plants, and nutrient recovery through struvite precipitation.

Centralized treatment with ozone had the highest eco-toxicity due to the ozonation process and infrastructure.

5.5.4. Decentralized treatment of pharmaceuticals at hospitals

Pharmaceuticals may enter the environment insufficiently degraded, either eliminated unchanged after consumption or as metabolites passing through standard wastewater treatment. Mitigation strategies include directly removing pharmaceuticals at the source or enhancing treatment facility processes post-consumption. Igos et al. (2012) studied the decentralized treatment of pharmaceuticals in hospitals using full-scale and pilot plant options. They compared these systems with the older and modern centralized treatment facilities using LCA. Their results indicated that ozonation and activated carbon were more effective than UV treatment. However, the LCA models evaluating drug toxicity produced unclear results, which warrant cautious interpretations. Despite these limitations, this study provided valuable insights into decentralized or on-site wastewater treatment methods. Table 4 summarizes the key environmental impacts and potential improvements identified in this research.

6. Summary and outlook

LCA has gained recognition for assessing the environmental impact across the pharmaceutical life cycle, from API production to packaging, transport, usage, and disposal. It was also used in biopharmaceuticals to identify key environmental hotspots in the production process (Budzinski et al., 2022; Jones et al., 2022). Several studies integrated LCA with other methods, such as Exergy Analysis, Chemical process modeling, and Eco-design (De Soete et al., 2013; Navajas et al., 2017; Parvatker et al., 2019). This indicated the compatibility of LCA with various approaches. Recent LCA studies revealed that energy consumption (especially electricity), and chemical consumption (i.e., raw materials and solvents) significantly impacted drug production and packaging. Therefore, the current pharmaceutical industry needs to adopt renewable energy sources and more efficient chemicals to reduce environmental impacts. In addition, LCA could help identify strategies to optimize pharmaceutical processes. For instance, moving from batch processing to continuous manufacturing could save materials and improve energy efficiency (De Soete et al., 2013; Lee et al., 2016), offering a model for broader adoption in the industry.

Further LCA research is needed in the packaging and transportation stage to explore specialized logistics for storing and transporting biopharmaceutical raw materials and products. However, global and regional pharmaceutical supply chains can bring unique challenges to LCA studies due to varying regional regulations and data availability. Moreover, understanding the environmental impact of pharmaceuticals at their end-of-life phase was important, especially considering drugs that were not fully metabolized by the human body and ended up burdening wastewater treatment systems (Jung et al., 2021; Schulte et al., 2022; Siegert et al., 2020b). This indicated the need for efficient treatment methods, such as decentralized systems designed explicitly for pharmaceutical waste. As mentioned before, proper waste management of biological and chemical byproducts is also a concern (Deschamps et al., 2012). Thus, exploring how to use waste from the pharmaceutical industry could also align with the principles of a circular economy (Peña et al., 2021). However, current LCA research in the pharmaceutical field still lacked a comprehensive analysis of material and energy usage in the design and operation of manufacturing systems, which required further study.

It is noteworthy that while energy consumption and chemical use are often highlighted as the primary impacts of pharmaceutical products, the toxicity of active drug compounds can also pose risks to human and aquatic life during the disposal phase. Currently, the bulk of LCA research within the pharmaceutical sector tends to concentrate on isolated phases of a drug's lifecycle, typically adopting either a "cradle-to-gate" or "gate-to-grave" system boundary, as analyzed in the literature evaluation part. Although a limited number of studies have examined the entire lifecycle of pharmaceuticals from production through disposal, using a "cradle-to-grave" approach, they generally focused on suggesting improvements and corresponding reductions in environmental impacts related to energy and downplayed other significant impacts. Consequently, there is a clear need for additional research to more thoroughly evaluate and compare the importance of other crucial impact categories, such as toxicity (eco-, human-), in future LCA studies. We also encourage more researchers to undertake "cradle-to-grave" LCA studies within the pharmaceutical industry. Furthermore, exploring the metabolic pathways of different drugs in various populations and the specific characteristics of drug metabolites warrants more in-depth investigation. Such research would enable a more precise assessment of the environmental impacts of these metabolites.

In recent years, there has been growing interest in recycling expired drugs. These recycled drugs have proven effective and safe corrosion inhibitors because their active ingredients can adhere to metal surfaces through weak or strong chemical bonds (Vaszilcsin et al., 2019). For instance, Hameed et al. found that expired drugs such as Megavit zinc and Ranitidine can effectively inhibit the corrosion of steel and aluminum in a hydrochloric acid environment (Hameed, 2009; Hameed et al., 2021). The effectiveness depended on the drug concentration, temperature, and the nature of the bond with the metal surface. Using expired drugs as eco-friendly corrosion inhibitors reduces pharmaceutical waste and traditional corrosion-inhibiting materials can be saved. However, no LCA studies have yet been conducted on using expired drugs in this way. This suggests future research needs to assess their environmental impact and broaden the scope of life cycle stages within the pharmaceutical sector.

In the end, serving both as an extensive evaluation of LCA applications in the pharmaceutical sector and a call to action, we hope this work could press the industry towards placing a higher emphasis on sustainable practices and integrating environmental considerations early in the product and process design stages.

Table 4
Summary of the investigations from literature in the use and end-of-life of drugs.

The most significant environmental impacts	Improvements to reduce environmental impacts	References
a) Release of pharmaceutical waste and metabolites into the environment b) Hazardous waste flows in pharmaceutical wastewater	Possible hydrolysis of antibiotic contaminant	Schulte et al. (2022)
	Proper recycling and disposal of wastewater	Do Thi et al. (2023)
		Landry and Boyer (2016)
		Rodríguez et al. (2016)
		Surra et al. (2021)
	Development and application of new antibiotic alternatives	Sanchez-Matos et al. (2023)
	Selection of safe and appropriate disposal schemes for unused/unmetabolized drugs	Cook et al. (2012) Igos et al. (2012)
	Employment of Nano-pharmaceuticals	Jung et al. (2021)

CRediT authorship contribution statement

Zhengyun Chen: Writing – original draft. **Justin Z. Lian:** Writing – original draft, Supervision, Conceptualization. **Hengyi Zhu:** Writing – review & editing. **Jiawei Zhang:** Writing – review & editing. **Yulong Zhang:** Writing – review & editing. **Xinyu Xiang:** Writing – review & editing. **Dechun Huang:** Writing – review & editing. **Kristie Tjokro:** Writing – review & editing. **Valerio Barbarossa:** Writing – review & editing. **Stefano Cucurachi:** Writing – review & editing, Supervision,

Conceptualization. **Bin Dong:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

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