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Sustainability in Pharmaceutical Formulation and Processing: Case Studies on Eco-Friendly Micronisation and Nanonisation Approaches

Hien V. Nguyen [1,*], Linh Nguyen-Ngoc Pham [2], Tung Minh Ta [2], Thuy Thi-Nhu Huynh [3]

[1]Faculty of Pharmacy, Van Lang University, Ho Chi Minh City 70000, Vietnam.
[2]Tien Giang General Hospital, Tien Giang 860000, Vietnam.
[3]Faculty of Pharmacy, Nguyen Tat Thanh University, Ho Chi Minh City 70000, Vietnam.

***Correspondence to:** Hien V. Nguyen, Faculty of Pharmacy, Van Lang University, Ho Chi Minh City 70000, Vietnam. E-mail: hien.nv@vlu.edu.vn.

Abstract: The pharmaceutical industry faces growing pressure to adopt sustainable practices throughout the entire product lifecycle, encompassing the design and synthesis of active pharmaceutical ingredients (APIs), manufacturing, distribution, usage, and disposal of pharmaceutical products. Addressing these challenges demands innovative strategies that balance environmental responsibility with economic and operational feasibility. This paper examines key approaches to achieving sustainability in pharmaceutical formulation and processing, including the use of biodegradable materials, minimizing organic solvent consumption, and implementing energy-efficient continuous manufacturing technologies. Through detailed case studies from our research group, we demonstrate the successful application of these principles to develop eco-friendly formulations and optimize manufacturing processes for pharmaceutical micronisation and nanonisation. This work aims to guide further advancements in sustainable pharmaceutical development.

Keywords: Sustainability; Pharmaceuticals; Formulation; Processes; Micronisation; Nanonisation.

1. Introduction

The pharmaceutical industry has long been at the forefront of innovation, driven by the need to develop novel active pharmaceutical ingredients (APIs) and cutting-edge pharmaceutical products to address complex health challenges. However, as the industry matures, it faces mounting pressure to reconcile its rapid innovation cycle with the growing need for sustainability. This pressure stems from both internal objectives and external demands, including regulatory frameworks, corporate social responsibility goals, and increasing public awareness of environmental issues [1].

The pharmaceutical sector is a significant contributor to global greenhouse gas emissions, releasing over 52 million tons of carbon dioxide annually [2]. This footprint is primarily driven by energy-intensive manufacturing processes, the use of hazardous and non-renewable materials, and the generation of substantial waste. From the production phase to post-consumer disposal, APIs and excipients can leach into water systems, persist in the

environment, and disrupt aquatic ecosystems, posing risks to wildlife and human health. Furthermore, the industry's reliance on non-renewable resources for raw materials and energy exacerbates its environmental challenges. These issues are compounded by the use of inefficient, traditional batch manufacturing processes, which often involve significant waste generation and energy consumption. Emissions from production facilities and improper pharmaceutical waste disposal further underline the urgent need for transformative and sustainable solutions.

Despite these challenges, the pharmaceutical sector holds a unique opportunity to lead in sustainability. With established expertise in innovation and process optimization, the industry is well-positioned to set benchmarks for greener practices. Embracing sustainability requires a multidimensional approach that includes the principles of green chemistry, resource optimization, energy-efficient processing, and waste minimization [1]. Specifically, adopting green chemistry principles can mitigate the environmental impact of drug synthesis by reducing hazardous reagents, optimizing reaction conditions, and prioritizing renewable raw materials. Resource optimization involves minimizing raw material consumption and embracing circular economy principles, such as reusing and recycling throughout production. Energy-efficient processing technologies, like continuous manufacturing, can lower the industry's carbon footprint by improving energy utilization, reducing processing times, and enabling real-time quality control. Waste minimization encompasses reducing waste generation and utilizing advanced biodegradable packaging and waste treatment systems to prevent harmful substances from entering the environment.

In this paper, we delve into the critical aspects of sustainability in pharmaceutical formulation and processing, emphasizing practical strategies for implementation. Through two case studies conducted within our research group, we illustrate how sustainable principles can be effectively integrated into pharmaceutical development. These case studies offer novel approaches to eco-friendly formulation and enhanced manufacturing processes with minimized environmental impact, while also aligning with regulatory requirements for pharmaceuticals. Specifically, the first case study on the solid dosage form, prepared using the adsorption method for micronization of active ingredients, distinguishes itself from traditional methods by significantly reducing solvent usage and simplifying processing through a readily scalable wet grinding approach that complies with regulatory guidelines. The second case study on dextran-based nanocarriers for vaccine delivery presents a novel, sustainable alternative to conventional vaccine delivery systems by utilizing a naturally derived, biodegradable polymer with demonstrated biocompatibility and biodegradability, fulfilling regulatory standards for biocompatible and sustainable materials. These case studies provide insights into the formulation of eco-friendly products and the optimization of manufacturing processes that adhere to regulatory frameworks, contributing to the broader dialogue on achieving sustainability in the pharmaceutical industry.

2. Strategies for sustainable pharmaceutical formulations and processing

Sustainable pharmaceutical formulation and processing demand interdisciplinary collaboration and a holistic view of the product lifecycle. By applying green chemistry, green formulation design, and green engineering principles, sustainability can be promoted at every stage of pharmaceutical production—from raw material sourcing to packaging [3, 4]. There are four main approaches to achieving greener pharmaceutical production, as summarized in **Figure 1.**

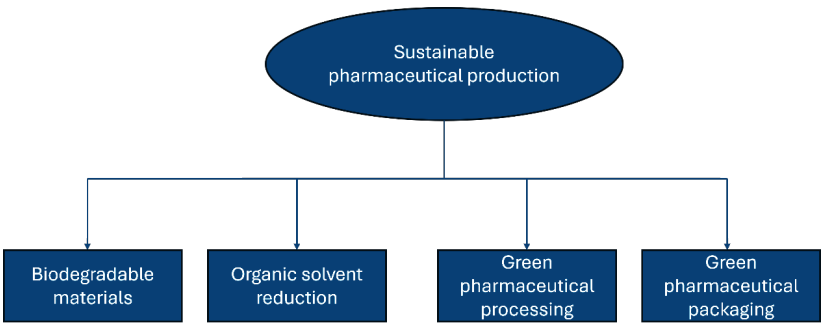

Figure 1. Key strategies for sustainable pharmaceutical production.

One key strategy involves the use of renewable and biodegradable materials. Biobased excipients and natural polymers, such as cellulose, starch, dextran, and chitosan, offer significant environmental benefits by reducing resource extraction, lowering carbon footprints, and improving the biodegradability of pharmaceutical waste. Similarly, plant-based materials from renewable sources (e.g., corn, sugarcane, and vegetable oils) provide eco-friendly options for the pharmaceutical formulation and processing. Beyond their environmental advantages, these materials can also enhance the functionality and performance of drug products, making them a practical and effective choice for sustainable pharmaceutical development [5].

Another important approach is minimizing the use of toxic organic solvents in drug manufacturing. This can be accomplished by modifying processes to use less solvent or replacing them with greener alternatives, such as supercritical carbon dioxide. Supercritical carbon dioxide, used in applications including bioactive extraction and drug adsorption onto carriers, is a sustainable option due to its low toxicity, non-flammability, and moderate critical temperature and pressure [6, 7]. Additionally, developing preparation methods that require fewer organic solvents can maintain drug efficacy and quality while reducing the risk of toxic residues in the final products.

Innovative technologies like continuous manufacturing further contribute to sustainability by improving resource efficiency and reducing waste. Continuous processes, such as hot melt extrusion (HME), can help optimize raw material use, lower energy consumption, and minimize byproduct generation compared to traditional batch operations. HME, which transforms drug-polymer mixtures into solid dosage forms through high temperatures and mechanical shear, also offers enhanced process control, reproducibility, and real-time quality assurance. This technique has been successfully employed in producing several commercial products, such as Oriahnn® (Elagolix/Estradiol/Norethindrone, 2020), Brafttovi® (Encorafenib, 2020), or Lynparza® (Olaparib, 2018) [8].

Green pharmaceutical packaging is another critical aspect of sustainable drug development. Using renewable, recyclable, and biodegradable materials such as bioplastics, recycled paper, and compostable materials, such as polylactic acid (PLA) or polyhydroxybutyrate (PHB), can significantly reduce the environmental footprint of drug products [9]. Optimizing packaging designs—through lightweight materials, minimalist structures, and easily recyclable or compostable formats—further enhances sustainability. For instance, thinner containers, compact labeling, and separable designs reduce resource consumption, lower carbon emissions, and simplify waste management.

By integrating these strategies, pharmaceutical companies can significantly improve the environmental profile of their products while maintaining efficacy, quality, and operational viability. This approach not only benefits the environment but also supports the long-term sustainability of the pharmaceutical industry as a whole.

3. Case study: Enhanced solubility and dissolution of poorly water-soluble drugs by the sustainable adsorption method

The therapeutic efficacy of orally administered drugs is fundamentally linked to their ability to dissolve in the gastrointestinal fluids. Only dissolved drug molecules can permeate the intestinal membrane and enter the systemic circulation to reach their target sites and elicit the desired pharmacological effect. However, studies estimate that up to 40% of currently developed drugs and up to 90% of drugs in the pipeline are poorly water-soluble, exhibiting limited dissolution rates and consequently, reduced drug bioavailability [10]. This poses a major obstacle in achieving optimal therapeutic outcomes, particularly for highly potent drugs where even a small improvement in dissolution can significantly impact clinical efficacy.

Various formulation strategies have been developed to address the challenges of poor solubility and dissolution, including particle size reduction, solid dispersions, salt formation, complexation with cyclodextrins, and the use of surfactants or co-solvents [10]. Among these approaches, solid dispersions have gained significant attention as a promising technique for enhancing the dissolution rate and bioavailability of poorly water-soluble drugs. Solid dispersions involve dispersing the drug in a hydrophilic carrier matrix, typically a polymer, to create a solid-state solution or amorphous form of the drug with an enhanced solubility and dissolution profile compared to the pure drug. Solid dispersions can be prepared using either melting or solvent evaporation methods. In the melting method, the drug and the carrier

are heated above their melting points, mixed, and then cooled to form a solid dispersion. Alternatively, the solvent evaporation method involves dissolving the drug and carrier in a solvent, followed by evaporation of the solvent to obtain the solid dispersion.

While solid dispersions offer advantages, traditional methods for their preparation, especially the solvent evaporation technique, frequently involve large amounts of organic solvents. These solvents can pose environmental hazards due to their volatile organic compound emissions and potential toxicity. Moreover, the removal of residual solvents from the final product can be a costly and time-consuming process, adding to the overall manufacturing expenses. To address these limitations, alternative approaches that minimize or eliminate the use of organic solvents are highly desirable. One such approach is the adsorption method, which offers a more sustainable and cost-effective way to enhance drug dissolution by reducing the amount of organic solvent required [11]. This method involves dissolving the drug in a minimal amount of solvent and adsorbing it onto the surface of a suitable carrier material, thereby increasing the drug's surface area and promoting its dissolution. The preparation of adsorption mixture is graphically illustrated in **Figure 2.**

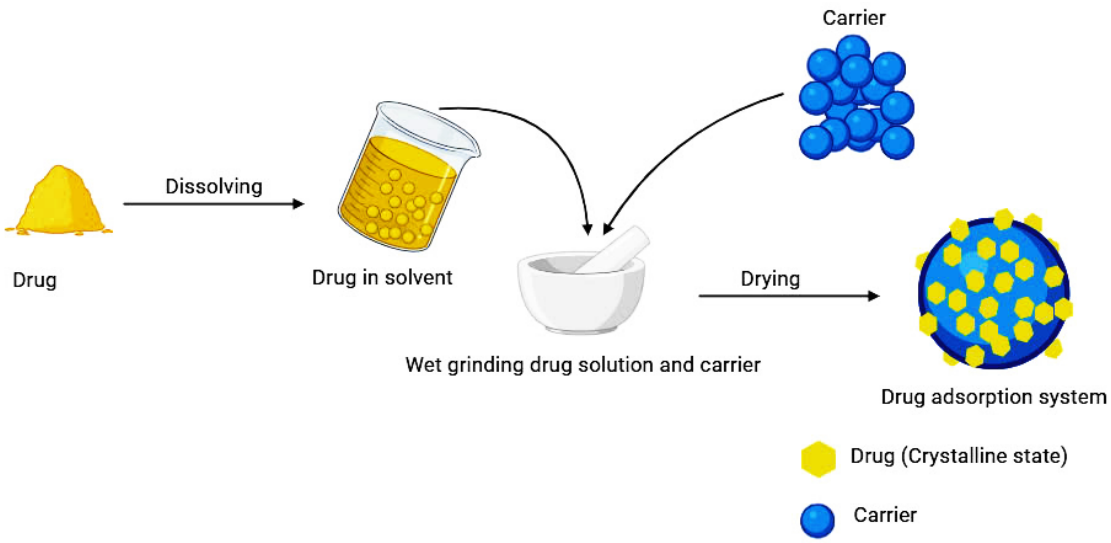

Figure 2. Graphical illustration of the adsorption method for enhanced solubility and dissolution of poorly-water soluble drugs.

Compared to traditional solid dispersions, the adsorption method offers several advantages, including reduced solvent usage, simplified processing, and improved sustainability. Specifically, unlike traditional solid dispersions that require dissolving both the drug and carrier in a solvent, the adsorption method only dissolves the drug, significantly minimizing the amount of solvent needed and promoting a more sustainable approach. Furthermore, the adsorption method employs a simple wet grinding process to adsorb the drug solution onto the carrier, in contrast to the more complex solvent evaporation techniques, such as spray drying, commonly used for solid dispersion preparation. This simple wet grinding process can be readily scaled up to industrial scale using well-established technologies such as fluid-bed coating. In the fluid-bed coating process, the drug dissolved in solvent is sprayed from the top down, while the carrier particles are fluidized in the bottom part of the equipment. This allows for the formation of a uniform layer of drug particles adsorbed onto the carriers with enhanced drug dissolution. The simplified and sustainable nature of the adsorption method also translates to lower costs associated with solvent purchase, handling, and disposal, contributing to the overall cost-effectiveness and sustainability of this approach. The choice of the adsorption carrier is critical to the success of the adsorption method. Our research group investigated different types of carriers and the ratio of drug-to-carrier to enhance the dissolution of celecoxib. It was shown that using lactose monohydrate as a carrier at a 1:1 drug-to-carrier ratio resulted in the highest dissolution rate of celecoxib, which was ten times greater than that of the pure drug (**Figure 3**) [11].

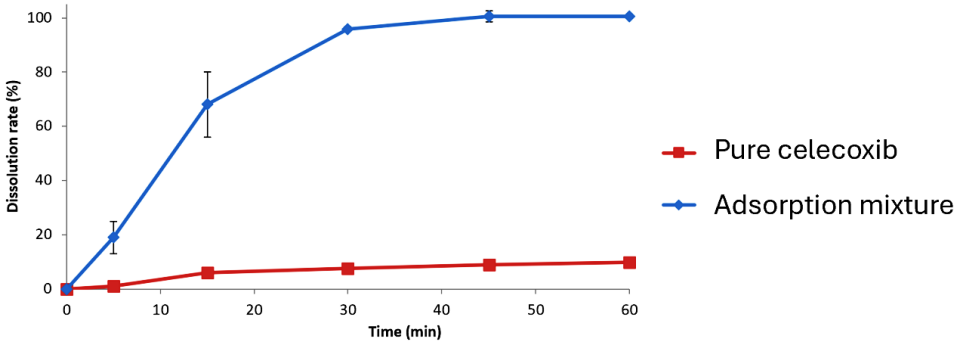

Figure 3. Dissolution profiles of (a) pure celecoxib and (b) adsorption mixture [11].

This strategy was also applied to another poorly water-soluble drug, cilostazol (CLT), which showed a two-fold increase in dissolution after being adsorbed onto silica dioxide (Aerosil®) at a 1:4 drug-to-carrier ratio compared to pure cilostazol (**Figure 4**) [12]. An additional advantage of the adsorption method is that the drug maintains its crystalline state after being adsorbed onto the carrier, which is more physically stable compared to the amorphous state typically obtained when the drug is incorporated into a solid dispersion system. With regards to the mechanism of drug dissolution enhancement, the adsorption method is postulated to improve dissolution by reducing the particle size of the API to the micrometer range and facilitating the formation of intermolecular hydrogen bonds between the drug and the carrier. This suggests the potential to apply this method to enhance the solubility and dissolution of drugs containing hydrogen bond donor or acceptor groups, such as polyphenolic compounds commonly extracted from herbs, including curcumin, rutin, or silymarin. These compounds, known for their therapeutic benefits, often suffer from poor water solubility, making them ideal candidates for adsorption-based solubility enhancement.

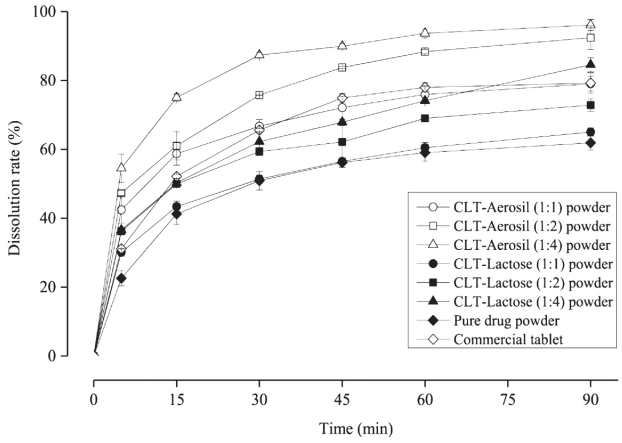

Figure 4. Dissolution profiles of pure cilostazol and the cilostazol-containing adsorption mixtures. Reprinted from [12] with permission.

4. Case study: Application of sustainable dextran-based nanocarriers for enhanced vaccine efficacy

Biodegradable polymers have become a cornerstone in developing sustainable polymeric nanocarriers, providing the dual benefits of environmental compatibility and functional performance. These materials break down into harmless byproducts under physiological or environmental conditions, reducing long-term environmental impact. Using these polymers in nanotechnology is particularly advantageous for drug delivery applications, where controlled degradation ensures precise payload release and minimizes potential side effects. Furthermore, the biodegradability of these polymers aligns with the growing global emphasis on sustainable materials, making them an appealing choice for biomedical and industrial applications. By replacing conventional non-degradable polymers with biodegradable alternatives, researchers are

addressing the critical need for eco-friendly solutions in nanotechnology [13].

Dextran, a naturally occurring polysaccharide, has garnered significant attention as a biodegradable polymer due to its distinctive characteristics. Composed predominantly of glucose units linked by α-glycosidic bonds, dextran exhibits high water solubility and biocompatibility, making it well-suited for biomedical applications. Its versatility in forming stable hydrogels, conjugates, and nanoparticles has been extensively investigated in drug delivery, wound healing, and tissue engineering [14, 15]. Furthermore, dextran can be readily modified chemically, allowing for the introduction of functional groups to tailor its properties for specific purposes. The controlled biodegradation of dextran, facilitated by endogenous enzymes such as dextranase, aligns with the principles of sustainability and mitigates long-term environmental impact. These distinctive features position dextran as a key material in the advancement of biodegradable polymeric nanocarriers.

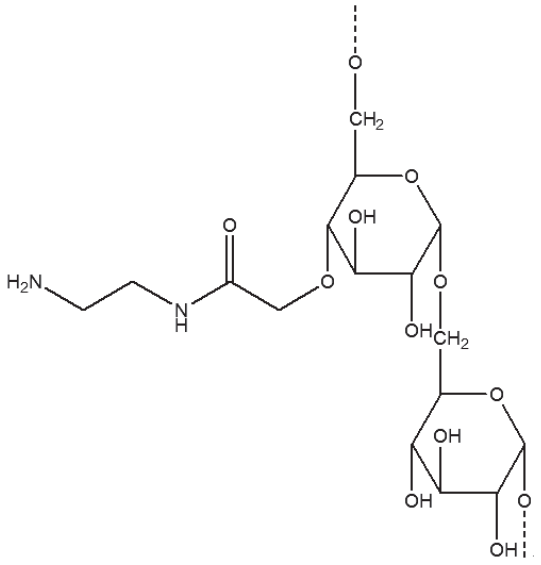

Figure 5. Molecular structure of the amino-dextran.

The development of dextran-based nanocarriers for vaccine delivery has gained significant attention in the scientific community. Our research group investigated the potential of commercially available amino-dextran, whose molecular structure is presented in **Figure 5**. Amino-dextrans are available in various molecular weights and amine functionality levels. The differing amine functionality alters the polymer's charge properties and provides an opportunity to modulate the chemical crosslinking for nanoparticle formation or bioconjugation of active compounds and/or targeting moieties.

The two dextran-based nanocarriers, the amino-dextran nanoparticle and the dextran polymeric conjugate, are graphically illustrated in **Figure 6.** These dextran-based nanocarriers were used to deliver the therapeutic oligonucleotide, cytosine-guanine oligodeoxynucleotide (CpG) via intratumoral administration [16, 17]. CpG was loaded onto the positively charged amino-dextran nanoparticles by either electrostatic adsorption or covalent conjugation. In the polymeric conjugate system, CpG is conjugated to the amino-dextran polymer via a stable or a redox-responsive linkage.

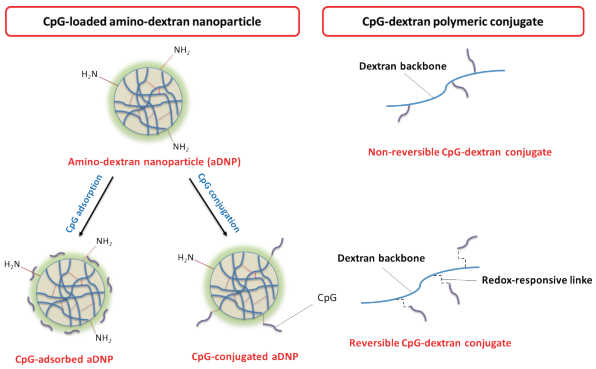

Figure 6. Amino-dextran based nanocarriers for the delivery of CpG oligonucleotide.

The amino-dextran nanoparticles were fabricated via the desolvation method, followed by the immobilization of CpG oligodeoxynucleotides onto the nanoparticle surface. The size and zeta potential of nanoparticles can be controlled to produce uniform spherical particles in the size range of 50 to 300 nm and surface charge of -16.5 to +14 mV (**Figure 7**) [16]. This work represents the first demonstration of developing a dextran-based nanoparticle platform from hydrophilic dextran utilizing the desolvation technique. The amino-dextran nanoparticle exhibited versatility for surface loading due to the free amino groups present on the nanoparticle surface. Notably, CpG-conjugated amino-dextran nanoparticle displayed enhanced cellular uptake and greater immunostimulatory activity in vitro compared to CpG-adsorbed amino-dextran nanoparticle. These observations highlight the significance of CpG immobilization methods in modulating the immunostimulatory properties of CpG-loaded nanoparticles.

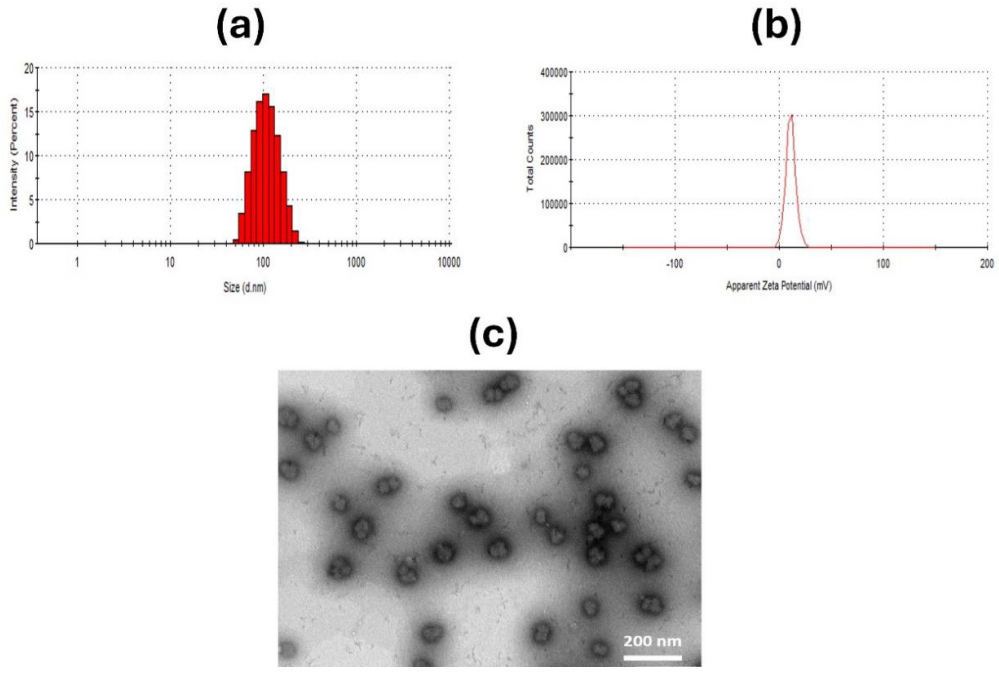

Figure 7. Amino-dextran nanoparticles: (a) particle size distribution, (b) surface charge, (c) transmission electron microscopic (TEM) image [16].

The CpG-dextran conjugates ranged in size from 15 to 30 nm with a net negative charge (**Figure 8**). The CpG-dextran conjugate exhibited enhanced uptake by dendritic cells compared to free CpG in vitro [18]. Notably, the reversible CpG-dextran conjugate demonstrated enhanced tumor growth inhibition and improved mouse survival in vivo compared to the non-reversible counterpart or free CpG. These results revealed that the enhanced anti-tumor immunity of the CpG-dextran conjugate was attributed to the intracellular redox-responsive release of CpG, allowing for better interactions of CpG with its intracellular target [17].

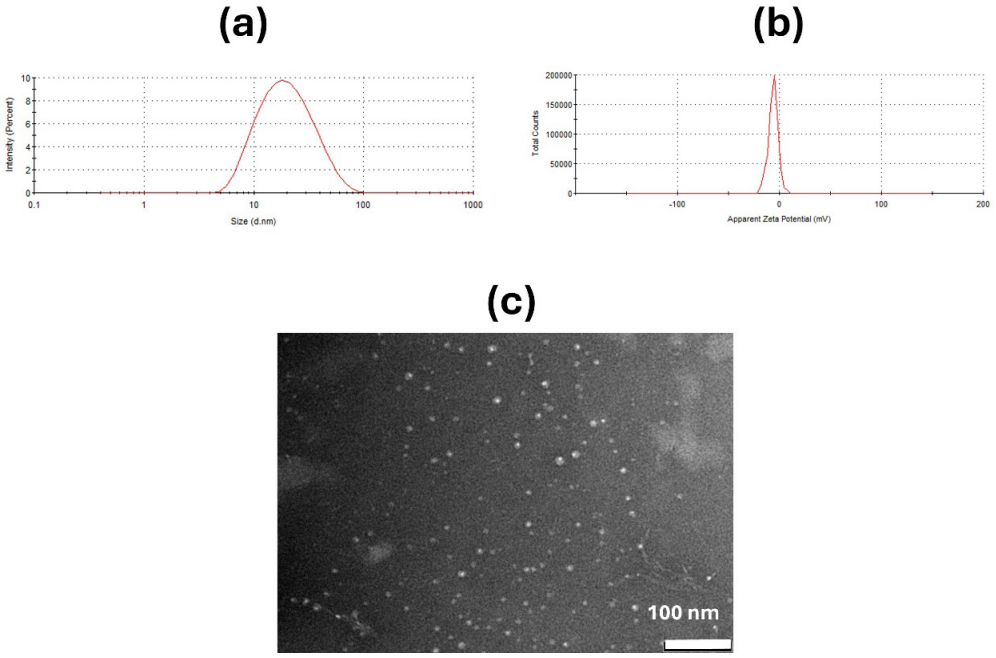

Figure 8. CpG-dextran conjugate: (a) particle size distribution, (b) surface charge, (c) transmission electron microscopic (TEM) image [18].

These findings underscore the immense potential of dextran-based nanocarriers for diverse vaccine delivery applications, with the ability to tailor their physicochemical properties and immunostimulatory capabilities through rational design. The inherent biodegradability and biocompatibility of dextran make these nanocarriers an appealing choice for advancing sustainable and effective vaccine delivery strategies.

Conclusion

This paper has explored the critical aspects of sustainability in pharmaceutical formulation and processing, highlighting practical strategies for implementation and showcasing examples through case studies. The case studies, drawn from our research group's work, provide tangible evidence of how these strategies can be effectively applied to create eco-friendly formulations, enhance manufacturing processes, and minimize environmental impact. While significant progress has been made, the journey towards comprehensive sustainability in the pharmaceutical industry is ongoing. Future research should focus on developing innovative technologies, such as continuous manufacturing platforms and advanced process analytical tools, to further enhance efficiency and reduce waste. Scalability is a critical factor in pharmaceutical manufacturing technology. Accordingly, selecting a suitable manufacturing technology and investigating the critical processing parameters are important for successfully translating from the laboratory to industrial scale. For instance, the fluid-bed coating system can be employed to prepare the adsorption system described in the first case study, while the scalable microfluidic technology can be utilized for nanoparticle preparation in the second case study. In addition, exploring novel biodegradable and bio-based materials for both the drug formulation and packaging will also be crucial for minimizing the industry's environmental footprint. By embracing a holistic approach to sustainability, the pharmaceutical industry can contribute significantly to global environmental protection while ensuring the continued development and delivery of safe and effective medications.

References

[1] M. Sen, A. Rogers, R. Singh, A. Chaudhury, J. John, M.G. Ierapetritou, R. Ramachandran, Flowsheet optimization of an integrated continuous purification-processing pharmaceutical manufacturing operation, Chem. Eng. Sci. 102 (2013) 56-66.

[2] L. Belkhir, A. Elmeligi, Carbon footprint of the global pharmaceutical industry and relative impact of its major players, J. Clean. Prod. 214 (2019) 185-194.

[3] C. Jiménez-González, C. S. Ponder, R. E. Hannah, and J. R. Hagan, Green Engineering in the Pharmaceutical Industry, in: W. Zhang and B.W. Cue (Eds.), Green Techniques for Organic Synthesis and Medicinal Chemistry, John Wiley & Sons, Ltd. New York, 2012, pp. 701 - 714.

[4] Z. Chen, J.Z. Lian, H. Zhu, J. Zhang, Y. Zhang, X. Xiang, D. Huang, K. Tjokro, V. Barbarossa, S. Cucurachi, B. Dong, Application of Life Cycle Assessment in the pharmaceutical industry: A critical review, J. Clean. Prod. 459 (2024) 142550.

[5] B. W. Cue, J. Zhang, Green process chemistry in the pharmaceutical industry, Green Chem. Lett. Rev. 2 (2009) 193-211.

[6] S. O. Essien, B. Young, S. Baroutian, Recent advances in subcritical water and supercritical carbon dioxide extraction of bioactive compounds from plant materials, Trends Food Sci. Technol. 97 (2020) 156-169.

[7] R. L. Matos, T. Lu, G. Leeke, V. Prosapio, C. McConville, A. Ingram, Single-step coprecipitation and coating to prepare curcumin formulations by supercritical fluid technology, J. Supercrit. Fluids 159 (2020) 104758.

[8] V. Vanhoorne, C. Vervaet, Recent progress in continuous manufacturing of oral solid dosage forms, Int. J. Pharm. 579 (2020).

[9] R.A. Ilyas, S.M. Sapuan, H.A. Aisyah, R. Ibrahim, M.S.N. Atikah, H.N. Salwa, M.M. Aung, S.O.A. SaifulAzry, L.N. Megashah, Z.M.A. Ainun, Renewable Sources for Packaging Materials, in: S.M. Sapuan, R.A. Ilyas (Eds.) Bio‐based Packaging: Material, Environmental and Economic Aspects, John Wiley & Sons, Ltd., New York, 2021, pp. 353 - 370.

[10] M. Rodriguez-Aller, D. Guillarme, J.-L. Veuthey, R. Gurny, Strategies for formulating and delivering poorly water-soluble drugs, J. Drug Deliv. Sci. Technol. 30 (2015) 342-351.

[11] H. V. Nguyen, C. Park, E. Oh, B.-J. Lee, Improving the dissolution rate of a poorly water-soluble drug via adsorption onto pharmaceutical diluents, J. Drug Deliv. Sci. Technol. 35 (2016) 146-154.

[12] N. Baek, G.-H. Oh, C. Park, T.T.T. Tran, Y.J. Park, E. Oh, H. Le, T.T.D. Tran, J.-B. Park, B.-J. Lee, Reprecipitation of poorly water-soluble cilostazol crystals using adsorbing carriers for enhanced dissolution and physicochemical modification, J. Drug Deliv. Sci. Technol. 43 (2018) 477-486.

[13] N. Kučuk, M. Primožič, Ž. Knez, M. Leitgeb, Sustainable Biodegradable Biopolymer-Based Nanoparticles for Healthcare Applications, Int. J. Mol. Sci. 24 (2023) 3188.

[14] S. Huang, G. Huang, Design and application of dextran carrier, J. Drug Deliv. Sci. Technol. 55 (2020) 101392.

[15] A. R. Petrovici, M. Pinteala, N. Simionescu, Dextran Formulations as Effective Delivery Systems of Therapeutic Agents, Molecules 28 (2023) 1086.

[16] H. V. Nguyen, K. Campbell, G. F. Painter, S. L. Young, G. F. Walker, Nanoparticle System Based on Amino-Dextran as a Drug Delivery Vehicle: Immune-Stimulatory CpG-Oligonucleotide Loading and Delivery, Pharmaceutics 12 (2020) 124621.

[17] H. V. Nguyen, K. Campbell, G. F. Painter, S. L. Young, G. F. Walker, Redox-responsive CpG-dextran conjugate enhances anti-tumour immunity following intratumoral administration, Int. J. Pharm. 664 (2024) 124621.

[18] H. V. Nguyen, K. Campbell, G. F. Painter, S. L. Young, G. F. Walker, Effect of carrier molecular weight on physicochemical properties and the in vitro immune-stimulatory activity of the CpG-dextran conjugates, Int. J. Pharm. 627 (2022) 122236.