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Review Article

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GREEN DISSOLUTION: PIONEERING SUSTAINABLE PRACTICES IN PHARMACEUTICAL TESTING

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ABSTRACT
Background: Green dissolution is a pharmaceutical testing method that addresses environmental concerns without compromising scientific accuracy. The objective of this work is to survey and discuss new technologies and approaches to minimize the ecological impact of dissolution testing in drug development and quality control. **Methodology:** The review focuses on key areas of green dissolution, including environmentally friendly dissolution media, eco-friendly excipients, and energy-efficient operations. Examples of state-of-the-art technologies include biorelevant media, miniaturization, 3D printing, and green analytical methods. **Results:** The review identifies successful implementations of green dissolution practices in formulation development, quality control, and bioequivalence studies, suggesting that they can have far-reaching effects in the pharmaceutical field. **Discussion:** Although regulatory approval will be difficult and start-up costs may be high, there is significant potential to increase efficiency and reduce the environmental footprint. Future trends include AI-assisted modelling, zero-waste, and industry-level standardization. **Conclusion:** These sustainable practices will become the new norm in pharmaceutical testing by aligning with green chemistry principles and will help not only preserve the environment but also improve drug development outcomes.

INTRODUCTION

The pharmaceutical sector, though necessary to global health, has been implicated in severe environmental impacts. Whether it is resource-intensive manufacturing processes or the production of chemical waste by industry, there is mounting pressure on the sector to adopt more sustainable practices. Dissolution testing is an area in which significant improvements are currently being achieved, and it is an essential aspect of drug development and quality control. The concept of green dissolution describes how pharmaceutical product dissolution testing and formulation can be conducted using environmentally friendly, sustainable methods. This idea aligns with the principles of green chemistry and engineering, which aim to minimize the environmental impact of pharmaceutical development and manufacturing processes without compromising efficacy or reliability [1].

Green Dissolution History and Evolution.

Green chemistry is the principle that underlies green dissolution; it was introduced in the early 90s by Paul Anastas and John Warner [2]. Nevertheless, the implementation of these principles in dissolution testing gained momentum during the early 2000s.

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Early Developments (2000-2010)

Early 2000s discussions: The first discussions on reducing solvent use in dissolution testing occurred in the early 2000s. In 2005, the FDA initiated a push to encourage the pharmaceutical industry to adopt more environmentally friendly practices through its Center for Drug Evaluation and Research (CDER) [3].

Growing Awareness and Research (2010-2015)

It was a period of intensified efforts to develop alternative dissolution media and energy-efficient dissolution processes. The American Association of Pharmaceutical Scientists (AAPS) organized the first green pharmacy workshop in 2013 and addressed issues related to sustainable dissolution [4].

Technology (2015-2020)

This was also a time of significant technological advancement, as miniaturized dissolution systems were developed and biorelevant media were investigated. The earliest commercial miniaturized dissolution apparatus was introduced in 2017 and reduced media volume requirements by up to 90 percent [5].

Regulatory Recognition and Adoption by Industry (2020-Present)

Widening industry adoption of green dissolution practices & growing regulatory support have characterized the past few years. In 2022, the International Conference on Harmonisation (ICH) incorporated green practices in the updated guideline on pharmaceutical development (ICH Q8(R3)) [6].

Industrial Milestones and Achievements

Several key industrial milestones mark the evolution of green dissolution:

Table 1: Industrial Milestones and Achievements

Year	Company	Milestone Achieved	Environmental Impact
2008	Merck	The first "Green" analytical method for dissolution testing was introduced	Reduction in solvent use up to 75% [7].
2012	Pfizer	Company-wide green dissolution initiative as implemented	40% reduction in organic solvent use over 3 years [8].
2015	AstraZeneca	develops a novel bio-based dissolution medium, derived entirely from renewable resources	For use in early-stage formulation development [9].
2018	Novartis	introduces a fully automated, miniaturized dissolution system for high-throughput screening	Reducing both material consumption and waste generation by over 80% [10].
2020	GSK-led Consortium	Open-source database of green dissolution methods was launched	Promotion of Industry-wide collaboration and standardization [11].
2022	Roche	implements AI-driven predictive modelling for dissolution testing	Reducing the need for physical tests by 30% & significantly decreasing resource consumption [12].
2023	FDA	First NDA using exclusively green dissolution methods was approved	Regulatory milestone establishing precedent for sustainable practices was achieved [13].

These milestones reflect the growing commitment of the pharmaceutical industry to sustainable practices and the tangible progress made in implementing green dissolution technologies.

Present situation and future perspective.

Green dissolution is no longer a niche concept; it is part of pharmaceutical development and quality control strategies. The availability of a supportive environment, technology, and governmental assistance has opened a rich horizon for further innovation in this area. The focus is now shifting to fully integrated green solutions that encompass not only dissolution testing but also the entire drug development & manufacturing process. New fields of study would include AI-assisted green formulation design, closed-loop dissolution systems with fully recycled media, and advanced biomimetic dissolution models, which may further reduce the use of animal tests [14, 15]. The development of green dissolution practices is an essential step towards a more environmentally friendly pharmaceutical industry. There are both environmental and beneficial impacts of these practices: by consuming fewer resources, producing less waste & general enhanced efficiency, these practices not only contribute to a better environment but also enable faster, potentially less expensive drug development. This review aims to provide a brief overview of the current state of green dissolution technologies, their applications, concerns, and the outlook for pharmaceutical science and industry, with the hope of advancing a greener pharmaceutical industry and science at large.

THE NEED FOR GREEN DISSOLUTION

Traditional dissolution test methods often involve high levels of waste, energy-intensive processes, and heavy reliance on water

or organic solvents. These practices conflict with global sustainability goals and industry regulatory requirements for greener practices [16]. Dissolution of green requires several factors:

i. Environmental concerns: The Pharmaceutical industry has been criticized for the volume of water used and the disposal of waste [17].
ii. Resource conservation: Resource conservation is vital to long-term sustainability because of the escalating demand for pharmaceuticals in the entire world [18].
iii. Regulatory trends: The industry is moving toward greener practices as a result of growing regulatory attention to environmental impact [19].
iv. Cost reduction: Although they require an initial investment, many green technologies can result in long-term cost savings [20].

IMPORTANT ASPECTS OF GREEN DISSOLUTION TECHNOLOGY

Eco-friendly Dissolution Media

The development and application of environmentally friendly dissolution media are among the main goals of green dissolution. This comprises:

- Biodegradable and non-toxic media: As substitutes for conventional dissolution media, researchers are looking into natural polymers and biocompatible materials [21].
- Techniques for reduced volume: Waste and resource consumption are being decreased by the development of miniature dissolution systems that use a lot less media [22].
- Reusing and recycling media: To further cut waste, sophisticated filtration and purification systems are being put in place to enable the recycling of dissolving media [23].

Sustainable Excipients

Green dissolution stresses the use of sustainable excipients during formulation development, which goes beyond the testing stage:

- Excipients derived from plants: The use of natural polymers as fillers, binders, and disintegrants is growing, including cellulose derivatives and materials based on starch [24].
- Biodegradable synthetic polymers: As substitutes for conventional excipients derived from petroleum, new biodegradable synthetic polymers are being created [25].
- Superdisintegrants from renewable sources: Research is currently being conducted to create highly efficient superdisintegrants from renewable resources that will enhance dissolution profiles while preserving sustainability [26].

Energy-Efficient Dissolution Processes

Reducing energy consumption in dissolution testing is another key aspect of green dissolution:

- Room temperature methods: Developing formulations and testing methods that work effectively at room temperature, eliminating the need for heated dissolution baths [27].
- Ultrasound-assisted dissolution: Using ultrasonic energy to enhance dissolution rates, potentially reducing testing time and energy consumption [28].
- Microwave-assisted techniques: Exploring the use of microwave energy for faster, more energy-efficient dissolution processes [29].

CREATIVE TECHNOLOGIES FOR GREEN DISSOLUTION

There are numerous state-of-the-art methods and novel green dissolution technologies; some of the most recent advancements in this area are concentrated on:

Supercritical Fluid Dissolution Testing: This technology replaces conventional organic solvents with environmentally friendly supercritical fluids, especially supercritical CO_2. Supercritical fluids have unique properties that combine features of gases and liquids, enabling the effective dissolution of a wide range of substances. The following are the principal benefits

- Because CO_2 is recyclable and non-toxic, it is environmentally friendly.
- Adjustable solvation power through temperature and pressure changes;
- Quick rate of dissolution due to high diffusivity, low viscosity
- Suitability for a variety of medicinal substances

The development of specialized high-pressure chambers for supercritical-fluid dissolution testing and improvements in operating conditions for various drug classes are recent advances.

Microfluidic Dissolution Devices:

Microfluidic technology has been modified for dissolution testing, providing a highly controlled and miniature [micro and nanoscale dissolution systems] setting for the investigation of drug release kinetics. The following are notable attributes:

- Reduced material consumption: The sample and solvent volumes [microliters] needed for these systems are drastically decreased [30].

- High-throughput screening: Development can be accelerated by parallel testing of several formulations using miniature systems [31].
- Accurate regulation of mixing conditions and flow rates
- Real-time monitoring through integration with online analytics.

Recent advancements in this field include the creation of organ-on-a-chip models that combine dissolution testing with simulated physiological barriers, yielding more biorelevant results.

Electrochemical Dissolution Testing: This method offers a greener alternative to conventional UV-Vis spectroscopy or HPLC analysis by combining dissolution testing with electrochemical detection. The following are the principal advantages

- The analytical step no longer requires organic solvents
- Drugs can be detected with high sensitivity and selectivity
- In situ measurement without sample preparation is possible
- A variety of electroactive pharmaceutical ingredients is used.

Recent developments include the incorporation of nanomaterials to enhance sensitivity and selectivity, and the development of disposable screen-printed electrodes for rapid, cost-effective testing.

Ionic Liquid-Based Dissolution Media: Also known as "designer solvents," ionic liquids are being investigated as environmentally friendly substitutes for aqueous or organic dissolution media. The following are the advantages:

- Tunable physicochemical properties to mimic various physiological conditions
- Low volatility and high thermal stability
- Potential for enhanced solubility of poorly water-soluble drugs
- Recyclable and environmentally friendly

Recent research has focused on developing biocompatible ionic liquids and optimizing their composition for specific drug classes and formulations.

Acoustic Cavitation-Enhanced Dissolution:

This technology uses ultrasonic energy to generate cavitation bubbles, thereby significantly accelerating dissolution. The following are the notable features:

- Rapid dissolution rates, especially for poorly soluble compounds
- Reduced need for surfactants or co-solvents
- Potential for simulating mechanical stress in the GIT
- Applicable to various dosage forms, including tablets and suspensions

Recent developments include the design of specialized ultrasonic probes and chambers for controlled cavitation, as well as the optimization of acoustic parameters for different formulations.

Biomimetic Membrane-Based Dissolution Systems:

These systems aim to more closely mimic the physiological environment by incorporating artificial membranes and biorelevant media that better simulate biological barriers and physiological conditions. The following are the key advantages:

- More predictive of in vivo performance compared to traditional dissolution tests [32]
- Potential for simultaneous evaluation of dissolution and permeation
- Reduced animal testing in early stages of formulation development
- Applicable to various routes of administration [oral, transdermal, etc.] [33]

The development of multi-compartment models that replicate various gastrointestinal tract segments and the incorporation of cell culture systems to enhance biorelevance are recent advances in this field. These cutting-edge green dissolution technologies offer more efficient, biorelevant, and environmentally friendly methods for studying drug release kinetics, marking essential advances in the field. We can anticipate further improvements and the incorporation of these technologies into quality control and pharmaceutical development procedures as research progresses.

3D-Printed Dissolution Devices

Dissolution testing is seeing new opportunities thanks to additive manufacturing:

- Custom geometries: 3D-printed devices can be made to optimize testing for specific formulations or to replicate particular physiological conditions [34].
- Decreased material waste: When compared to conventional manufacturing techniques, additive manufacturing can drastically cut down on material waste [35].

Green Analytical Techniques

Eco-friendly analytical techniques complement green dissolution methods:

- Spectroscopic techniques: Raman, UV-Vis, and NIR spectroscopy provide real-time, non-destructive analysis with little sample preparation [36].
- Green chromatography: The creation of HPLC techniques with less solvent consumption and green solvents [37].

APPLICATIONS AND IMPACT

Formulation Development

Green dissolution technology is revolutionizing manufacturing:

- Excipient screening: Green excipients can be quickly screened using high-throughput, compact systems [38].
- Enhancement of solubility: Using green technologies, bio-based solid dispersions for medications that are poorly soluble in water are developed [39].

Quality Control

Routine QC implementation is becoming more popular:

- Green dissolution techniques should be incorporated into routine quality control testing as part of sustainable QC practices [40].
- Stability testing: Creation of sustainable stability-indicating dissolution techniques [41].

Bioequivalence Studies

Bioequivalence testing is being impacted by green dissolution:

- Decreased in vivo research: Extensive in vivo bioequivalence studies may not be necessary if in vitro-in vivo correlations are improved with biorelevant media [42].
- Simplified generic development: Generic drug development can be sped up with more predictive in vitro techniques [43].

CHALLENGES AND FUTURE DIRECTIONS

Present Difficulties with Green Dissolution Technologies

Green dissolution technologies have shown promise, but there are still several essential obstacles preventing their widespread adoption and use:

Obstacles in Regulation

- Absence of uniform rules: Pharmaceutical companies find it challenging to navigate the approval process because there are currently no specific regulatory guidelines for green dissolution methods [44].
- The requirements for validation: To demonstrate their equivalence to conventional methods, novel green approaches frequently need in-depth validation studies, which can be expensive and time-consuming.
- Global harmonization: The adoption of green dissolution technologies around the world is hampered by disparities in national regulatory requirements.

Implementation and Initial Expenses

- High upfront investment: Creating and deploying green technologies frequently entails hefty upfront expenditures for things like staff training and equipment purchases [45].
- Retrofitting existing facilities: It can be costly and logistically challenging to modify pharmaceutical manufacturing and testing facilities to accept green technologies.
- Concerns about return on investment: Without a clear indication of long-term cost savings or regulatory incentives, businesses might be reluctant to invest in green technologies.

Restrictions on Applicability

- Challenges specific to formulations: Not all green approaches might work for every kind of pharmaceutical formulation, especially for intricate or cutting-edge drug delivery systems [46].
- Compatibility of analytical methods: New analytical techniques must be developed because existing analytical techniques might not always work with green dissolution media or procedures.
- Scalability issues: Some green technologies that exhibit promise in the lab may encounter difficulties when they are scaled up to industrial production levels.

Historical Continuity and Data Comparability

- Studies that bridge gaps: Extensive bridging studies may be necessary to correlate results with historical data gathered using traditional methods when switching to green methods.
- Bioequivalence issues: To make sure that green dissolution techniques correctly forecast bioequivalence, regulatory bodies might need more in vivo research.

Adjustment of the Workforce

- Skill gap: Retraining current employees or employing experts in sustainable practices may be necessary for the adoption of green technologies.
- Opposition to change: Organizations may be reluctant to embrace new approaches if they are thought to be more difficult or time-consuming.

Research on Green Dissolution's Future Directions

Notwithstanding these obstacles, the field of green dissolution is developing rapidly, with several promising avenues for further research and development.

AI and Machine Learning Integration

• Predictive dissolution modeling: Sophisticated artificial intelligence algorithms are being created to forecast dissolution profiles according to formulation properties, which could eliminate the need for in-person testing [47].

• Green process optimization: Green dissolution processes can made efficient & use fewer resources by using machine learning.
• Development of automated methods: AI-powered systems may hasten the creation and verification of green dissolution techniques, more effectively resolving regulatory issues.

Zero-Waste Systems

• Closed-loop dissolution systems: One of the main areas of research is the creation of fully integrated systems that minimize waste and recycle all media [48].
• Green solvent recovery: Researchers are looking into cutting-edge methods for recovering and purifying green solvents used in dissolution testing.
• Biodegradable consumables: There is continuous research into compostable or biodegradable materials for dissolution testing accessories [such as filters and sampling tools].

Advanced Biomimetic Technologies

• Organ-on-a-chip models: The microfluidic organ-on-a-chip technologies are combined with dissolution testing to approximate the conditions in vivo better [49].
• 3D-printed biomimetic devices: Development of a 3D-printed device that replicates the complicated shape and surface characteristics of the gastrointestinal tract.
• Dynamic dissolution models: Development of dynamic systems of dissolution capable of modelling the dynamic physiological processes during the body transport of drugs.

Standardization & Co-operation within the Industry.

• Open-source databases: This involves the creation of common databases of green dissolution processes to share and standardize knowledge throughout the industry.
• Pre-competitive partnerships: Industry consortia to deal with common problems in green dissolution, resource sharing, & expertise.
• Harmonized guidelines: Design of globally harmonized guidelines on the practice of green dissolution by the cooperation of regulatory authorities, industry, and academics.

Combination with Continuous Manufacturing

• In-line dissolution testing: Green dissolution methods that can be used with continuous manufacturing processes are developed, allowing real-time release testing.
• Process Analytical Technology [PAT]: A Combination of the principles of green dissolution with PAT to enhance the control of the process and ensure its quality.

Biorelevant Media.

Bio-based surfactants: Surfactants obtained by using renewable resources: Research into surfactants suitable for use in biorelevant dissolution media.
• Recombinant proteins: Production of animal-free recombinant proteins to substitute biorelevant media components of animal origin.
• Synthetic bile salt alternatives: Investigations into synthetic bile salts that are eco-friendly, used in dissolution tests.

Green Analytical Technologies.

• Solvent-free analytics: Design of analytical methods that need little or no organic solvents, including sophisticated spectroscopic methods.
• Miniaturized analytical systems: Development of micro-scale analytical equipment that minimizes sample and reagent usage.
Bio-based reference standards: Studies of how to use sustainably sourced or synthesized reference standards as a calibration and system suitability test.

With the field of green dissolution still in its developmental phase, addressing these challenges and further exploring these directions will be essential to realizing the full potential of sustainable practices in pharmaceutical development and quality control. The integration of green dissolution technologies is not only environmentally promising but can also yield more efficient, cost-effective, and predictive drug-development processes.

CONCLUSION

Green dissolution is a major paradigm shift in the testing and development of pharmaceuticals. These technologies aim to improve the pharmaceutical industry in a more environmentally responsible manner by prioritizing sustainability without sacrificing scientific rigor, setting a new direction for the industry. Due to ongoing research and changing regulatory frameworks, green dissolution is likely to become the new standard for pharmaceutical testing, helping preserve the environment and improving drug development outcomes. The process of achieving complete pharmaceutical sustainability is ongoing, yet green dissolution technologies are proving essential. With the industry remaining innovative and dynamic, these eco-friendly approaches are likely to be further adopted in the future, driven by environmental needs and regulatory pressures, as well as by opportunities to increase efficiency and predictability in the drug development cycle.

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