International Journal of Interdisciplinary Innovative Research & Development (IJIIRD)

ISSN: 2456-236X

Vol. 10 Issue 01 | 2025

Review on Ultrasonic studies of medicinal drugs in aqueous solution at different temperature

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DOI: 10.5281/zenodo.15740748

Abstract

This review explores the application of ultrasonic techniques in pharmaceutical research, particularly focusing on the formulation, characterization, and delivery of medicinal drugs in aqueous solutions at varying temperatures. The principles of ultrasonication, including cavitation and its temperature-dependent effects, are discussed as they influence the physicochemical properties of drugs and delivery systems. Various methodologies, such as nanoparticle preparation and sono-crystallization, demonstrate the enhanced solubility and bioavailability of poorly soluble drugs. Advanced ultrasonic techniques, including focused ultrasonication and temperature-responsive drug delivery systems, present innovative avenues for controlled and targeted therapeutics. The review highlights the significance of ultrasonic treatments in enhancing drug penetration, particularly in challenging contexts such as tumor therapy, while also addressing the need for standardized research parameters and a deeper understanding of molecular mechanisms. Future directions emphasize the integration of computational modeling, exploration of novel drug formulations, and the potential for combining ultrasonic techniques with other advanced delivery strategies to improve therapeutic outcomes. Overall, this synthesis underscores the transformative potential of ultrasonic studies in advancing drug delivery systems within the pharmaceutical landscape.

1. Introduction

Ultrasonic techniques have emerged as valuable tools in pharmaceutical research, offering innovative approaches for drug formulation, characterization, and delivery. The application of ultrasound in the study of medicinal drugs in aqueous solutions has gained significant attention due to its ability to enhance drug solubility, improve dissolution rates, and facilitate controlled release mechanisms. Temperature variations during ultrasonic processing can significantly influence the physicochemical properties of drugs and their delivery systems, making it an important parameter to consider in pharmaceutical development. This review aims to synthesize current knowledge on ultrasonic studies of medicinal drugs in aqueous solutions at different temperatures, highlighting methodologies, applications, and future research directions.

2. Principles and Mechanisms of Ultrasonic Processing in Drug Studies

2.1 Fundamental Aspects of Ultrasonication

Ultrasonic processing involves the application of high-frequency sound waves to generate mechanical and thermal effects in liquid media. When applied to aqueous drug solutions, ultrasonication can induce cavitation, a phenomenon characterized by the formation, growth, and collapse of microbubbles. This process generates localized high temperatures and pressures, which can significantly alter the physicochemical properties of drugs and their carriers.

Ultrasound's ability to propagate through opaque and complex media with minimal energy loss makes it particularly valuable for pharmaceutical applications. Ultrasound can be precisely localized to smaller regions and coupled to systems operating at various time scales, enabling controlled manipulation of drug systems [1]. However, the properties that allow ultrasound to propagate effectively in materials also make it challenging to transform acoustic energy into other usable forms [1]. Recent advancements have addressed this limitation, demonstrating that ultrasonic effects can be harnessed to control chemical and physical systems with remarkable specificity [1].

2.2 Temperature-Dependent Effects in Ultrasonic Drug Studies

Temperature plays a crucial role in ultrasonic drug processing, affecting both the efficacy of ultrasonic treatment and the behaviour of the drugs themselves. In temperature-responsive drug delivery systems, certain polymers

can assume different conformations at varying temperatures, such as an open conformation at sub-physiological temperatures that allows drug encapsulation and a closed conformation at physiological temperatures that prevents unexpected drug release during circulation [2]. This temperature-dependent behaviour can be leveraged alongside ultrasonic stimuli to achieve controlled and targeted drug release.

The relationship between temperature and ultrasonic processing is often reciprocal, as a comparison between classical chemotherapy and thermochemistry shows that temperature can improve therapeutic outcomes by stimulating biological properties [3]. This synergistic effect is particularly relevant in combination therapies where thermal and ultrasonic treatments are used together to enhance drug delivery and efficacy.

3. Ultrasonic Methods in Drug Formulation and Development

3.1 Nanoparticle Preparation Using Ultrasonication

Ultrasonication has emerged as a preferred method for preparing drug-loaded nanoparticles due to its ability to produce uniform particle sizes and enhance drug encapsulation efficiency. Various studies have demonstrated the application of ultrasonication in developing nano formulations for different medicinal drugs.

A thymoquinone (TQ)- and naringenin (NGN)-enriched nanostructured lipid carrier (NLC) was developed via the ultrasonication technique and optimized using a central composite rotatable design (CCRD) [4]. This formulation demonstrated enhanced drug delivery properties, with in vitro drug release studies showing the superiority of the TQ-NGN-NLC compared to the NGN suspension, achieving a cumulative drug release of 82.42 ± 1.88% from the NLC versus 38.20 ± 0.82% from the drug suspension [4]. Additionally, ex vivo permeation studies displayed a 2.21-fold increase in nasal permeation of NGN from the NLC compared to the NGN suspension [4].

Similarly, biocompatible and biodegradable polymeric nano colloids obtained using the ultrasonication method coupled with Layer-by-Layer technology were characterized in terms of size (100 ± 20 nm), physical stability, drug loading (78%), and photoactivation through spectroscopy studies [5]. These nano colloids demonstrated enhanced bioactivity under light irradiation conditions, highlighting the versatility of ultrasonication in developing responsive drug delivery systems.

In another study, an emulsification dispersion-ultrasonic method was employed to prepare doxorubicin (DOX) loaded magnetic solid lipid nanoparticles (mSLNs) [6]. The resultant formulation showed promising drug release characteristics, with in vitro drug release studies indicating that the amount of drug released from DOX-loaded SLN and DOX-loaded mSLN in phosphate buffer saline (pH=7.4) approached 60% and 80%, respectively, after 96 hours of incubation [6].

3.2 Sono-Crystallization for Enhanced Drug Solubility

Sono-crystallization, which combines ultrasonication with crystallization techniques, has been explored as a means to enhance the solubility and dissolution rate of poorly water-soluble drugs. A sono-crystallization approach was used to reduce the particle size of eplerenone (EP), thereby increasing its dissolution rate [7]. EP, which is used for treating hypertension and chronic heart failure, is classified as a BCS class II drug due to its poor solubility and high permeability, which retards dissolution rate and drug absorption, and decreases bioavailability [7]. The sono-crystallization approach successfully addressed these limitations, improving the drug's solubility and dissolution characteristics.

The ultrasound-assisted crystallization process offers significant advantages over conventional crystallization methods, including more uniform crystal size distribution, reduced agglomeration, and enhanced purity. These benefits are particularly valuable for medicinal drugs with poor aqueous solubility, which remains a major challenge in pharmaceutical development.

4. Advanced Ultrasonic Techniques for Drug Delivery Systems

4.1 Focused Ultrasonication for Controlled Drug Release

Recent advancements in ultrasonic technology have led to the development of focused ultrasonication techniques that offer greater precision in drug delivery applications. Adaptive focused ultrasound has been investigated as a potential milling method for rapid small-volume suspensions by identifying the critical process parameters during preparation [8]. This approach allows for precise control over particle size reduction, which is crucial for optimizing drug release profiles.

Using a Design of Experiments (DoE) approach, peak incident power was identified as the most crucial process parameter impacting the milling process for various drug compounds [8]. The study demonstrated that it was possible to decrease the sizes of drug particles to micron range after one minute of focused ultrasound exposure, which was superior compared to other milling techniques (e.g., non-focused ultrasound exposure) [8].

Importantly, adaptive focused ultrasonication proved to be a promising method for rapid homogenization and particle size reduction to micron range for different compounds varying in grindability without altering the crystalline structure [8].

4.2 Temperature-Responsive Ultrasonic Drug Delivery Systems

The combination of temperature and ultrasonic responsiveness in drug delivery systems represents a significant advancement in targeted therapeutics. A temperature- and ultrasound-responsive nano-sized drug delivery system (DDS) introduced a copolymer p-(MEO2MA-co-THPMA) grafted onto mesoporous iron oxide nanoparticles (MIONs) to construct an MPL-p nano-DDS [2]. This innovative system employs a dual-responsive mechanism where external ultrasonic irradiation of the nanoparticles in the targeted organs causes a conformational change of the copolymer and reopens the pores, facilitating controlled drug release [2].

The synergistic effect of temperature and ultrasound responsiveness offers several advantages, including excellent biocompatibility, rare drug release in circulation, and targeted delivery to specific organs without accumulation in others, thereby avoiding related adverse reactions, specifically those affecting the heart [2]. These findings demonstrate the potential of temperature- and ultrasound-responsive drug delivery systems in reducing systemic adverse reactions while maintaining excellent organ delivery efficiency.

5. Applications of Ultrasonic Studies in Drug Delivery

5.1 Enhancement of Drug Penetration and Bioavailability

Ultrasonic techniques have shown considerable promise in enhancing drug penetration and bioavailability, particularly for drugs with poor solubility or limited tissue penetration. The transport of drugs in interstitium relies mainly on the diffusion mechanism to be able to penetrate deeper and reach target cells in the inner regions of tissues such as tumors [3]. Ultrasonic treatments can facilitate this process by temporarily increasing tissue permeability and enhancing diffusion.

In the context of tumour treatment, due to the low drug penetration into the tumour centre, thermal ablation has been used for necrosis of the central areas before ThermoChem therapy [3]. However, perfusion of the region around the necrotic zone is found to be damaged, while cells in the region are alive and not affected by medication therapy, creating a risk of tumour recurrence. Therefore, it is recommended that ablation be performed after the medication therapy [3]. These findings highlight the importance of optimizing the sequence and timing of ultrasonic treatments in conjunction with drug administration.

The improved penetration achieved through ultrasonic techniques is also evident in studies of drug-loaded nanocarriers. Confocal laser scanning microscopy (CLSM) images revealed deeper permeation of naringenin-loaded nanostructured lipid carriers (NGN-NLC) (39.9 μm) through the nasal mucosa compared to the NGN suspension (20 μm) [4]. This enhanced penetration contributes to improved drug bioavailability and therapeutic efficacy.

5.2 Targeted Drug Delivery Using Ultrasound

Ultrasound-mediated targeted drug delivery represents a significant advancement in precision medicine, allowing for site-specific release of therapeutic agents while minimizing systemic exposure and side effects. The ultrasound-assisted transport of drugs or fluorophore-loaded nano agents plays an important role in desirable drug delivery and imaging contrasts [9].

Unlike conventional ultrasound techniques, recent research has explored novel mechanisms of ultrasound-mediated drug delivery. Experimental investigations into the dynamics of interstitial fluid streaming and tissue recovery in ex vivo tissues during and after ultrasound exposures have revealed that biological tissues consist of both a fluid and a solid matrix, and an ultrasound beam compresses the tissues within a small focal volume from all directions, generating macroscopic streaming of interstitial fluid and compression of the tissue's solid matrix [9]. After the ultrasonic exposure, the solid matrix undergoes recovery, leading to a backflow of the fluid matrix [9]. This mechanical effect can be leveraged for enhanced drug delivery in tissues.

The application of ultrasound in targeted drug delivery extends to brain-directed therapies as well. When targeting delivery to the brain, ultrasound promoted the release of loaded drugs in the brain without accumulation in other organs, avoiding related adverse reactions, specifically those affecting the heart [2]. This targeted approach offers significant advantages over conventional systemic drug administration, particularly for conditions requiring precise delivery to specific tissues or organs.

6. Methods and Techniques in Characterization of Ultrasonic Drug Systems

6.1 Analytical Methods for Evaluating Ultrasonic Drug Formulations

The characterization of ultrasonic drug formulations requires a comprehensive set of analytical techniques to assess their physicochemical properties, stability, and release characteristics. Common analytical methods employed in ultrasonic drug studies include spectroscopic techniques, microscopy, thermal analysis, and dissolution testing.

Spectroscopic techniques such as Fourier transform infrared spectroscopy (FTIR) and nuclear magnetic resonance (NMR) are widely used to characterize drug-carrier interactions and confirm successful drug incorporation into delivery systems. Fourier transforms infrared spectroscopy, vibrating sample magnetometer, and photon correlation spectroscopy (PCS) were used to characterize magnetic solid lipid nanoparticles prepared using an ultrasonic method [6].

Microscopic techniques, including scanning electron microscopy (SEM) and confocal laser scanning microscopy (CLSM), provide valuable information about particle morphology, size distribution, and tissue penetration. CLSM images revealed deeper permeation of NGN-NLC through the nasal mucosa in comparison to the NGN suspension, providing visual confirmation of enhanced drug delivery [4].

In vitro dissolution testing is a critical method for evaluating the release characteristics of ultrasonic drug formulations. The in vitro drug release profile showed the superiority of thymoquinone-naringenin-loaded nanostructured lipid carriers (TQ-NGN-NLC) in comparison to the NGN suspension, with a cumulative drug release of 82.42 ± 1.88% from the NLC and 38.20 ± 0.82% from the drug suspension [4]. These release studies provide valuable insights into the potential in vivo performance of ultrasonic drug formulations.

6.2 Temperature-Controlled Studies of Drug Behaviour

Temperature-controlled studies are essential for understanding the behavior of drugs and their delivery systems under varying thermal conditions. To mimic physiological conditions, particles were incubated in artificial saliva at 37°C, with drug release being analyzed via high-performance liquid chromatography [10]. This approach allows for more accurate prediction of in vivo performance under physiological temperature conditions.

The effect of temperature on drug stability and release kinetics is particularly relevant for thermosensitive delivery systems. Amorphous solid dispersions (ASDs) are susceptible to temperature- and humidity-induced phase separation and recrystallization under harsh storage conditions typically encountered in areas with high tuberculosis incidence [11]. Nanoencapsulation represents an alternative formulation strategy to increase aqueous dissolution kinetics while remaining stable at elevated temperature and humidity. The stabilizer layer coating the nanoparticle drug core limits the formation of large drug domains by diffusion during storage, representing an advantage over ASDs [11].

These temperature-controlled studies highlight the importance of considering thermal effects in the development and evaluation of ultrasonic drug formulations, particularly for applications requiring stability under varying environmental conditions.

7. Current Challenges and Future Directions

7.1 Limitations in Current Ultrasonic Drug Studies

Despite significant advances in ultrasonic studies of medicinal drugs, several limitations persist in current research. One major challenge is the standardization of ultrasonic parameters across different studies, making direct comparisons difficult. Variables such as ultrasonic power, frequency, duration, and temperature conditions can significantly impact results, yet these parameters are often inconsistently reported or controlled.

Another limitation is the limited understanding of the molecular mechanisms underlying ultrasonic effects on drug behavior in aqueous solutions. While macroscopic effects such as enhanced dissolution and improved delivery are well-documented, the precise molecular interactions and transformations occurring during ultrasonic treatment remain insufficiently characterized.

The translation of in vitro findings to in vivo applications represents another significant challenge. Although extensive literature has been reported based on implanted ultrasound-responsive hydrogels in various fields, there is a lack of comprehensive review articles showing the strategies to control drug delivery profiles [1]. This gap highlights the need for more systematic approaches to ultrasonic drug delivery system development and evaluation.

7.2 Future Research Directions

Several promising research directions emerge from the current state of ultrasonic studies of medicinal drugs in aqueous solutions. The development of more sophisticated temperature-responsive ultrasonic systems represents

a promising avenue for future research, potentially enabling unprecedented control over drug release profiles based on both thermal and acoustic stimuli.

Integration of computational modeling with experimental approaches could significantly advance the field by enabling prediction of drug behavior under various ultrasonic and temperature conditions. Comprehensive mathematical models that take into account many effective details can serve as reliable guides towards the optimal use of drug delivery systems [3].

The application of ultrasonic techniques to novel drug classes and delivery challenges also presents exciting opportunities for future research. The utility of ultrasonic atomization for the processing of various drug formulations, combined with the ease of production, biocompatibility, and small size of resulting particles, represents a promising approach for delivery of various drugs in clinical applications [10].

Finally, the exploration of combined approaches that leverage ultrasonic techniques alongside other advanced drug delivery strategies could lead to innovative therapeutic solutions. The use of ultrasonic stimuli as triggers for controlled drug release, employed in conjunction with other endogenous (pH, redox, hypoxia, enzyme) or exogenous stimuli (light, magnetic, temperature, radiation), offers potential for developing highly specific and efficient drug delivery systems [12].

8. Conclusion

Ultrasonic studies of medicinal drugs in aqueous solutions at different temperatures have yielded valuable insights into drug behavior and delivery, enabling the development of innovative formulations with enhanced therapeutic properties. The integration of ultrasonic techniques with temperature-responsive systems offers particular promise for achieving controlled and targeted drug delivery.

While significant progress has been made in this field, several challenges remain, including standardization of ultrasonic parameters, elucidation of molecular mechanisms, and translation of in vitro findings to clinical applications. Addressing these challenges will require interdisciplinary collaboration and integration of experimental, computational, and clinical approaches.

Future research directions, including the development of more sophisticated temperature-responsive ultrasonic systems, application of computational modeling, exploration of novel drug classes, and combination with other advanced delivery strategies, hold promise for further advancing the field and addressing unmet therapeutic needs. As ultrasonic techniques continue to evolve, they are likely to play an increasingly important role in pharmaceutical development and precision medicine.

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