Investigating the Role of Ultrasonic Melt Sonocrystallization in the Development of Enhanced Oral Anticoagulant Therapies.

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ABSTRACT:

The present research focuses on the formulation and evaluation of Rivaroxaban crystals using the melt sonocrystallization technique to overcome its poor aqueous solubility and limited oral bioavailability. As a BCS Class II drug, Rivaroxaban exhibits low dissolution rates, which directly impacts its therapeutic performance. Melt sonocrystallization, an innovative crystal engineering method, utilizes controlled ultrasonic energy during the melt phase to induce rapid nucleation and uniform crystal growth, resulting in fine and stable crystalline particles. In this study, rivaroxaban was melted sonocrystallized at optimal circumstances to produce crystals with enhanced solubility and dissolving properties. The produced crystals were evaluated for particle size, shape, crystallinity, and thermal behaviour using a variety of physicochemical techniques. Particle size was significantly reduced, and the rates of dissolving were improved, in comparison to the pure medication. This enhancement is attributed to increased surface area, reduced crystallite size, and modified crystal habit induced by ultrasonic cavitation. Melt sonocrystallization presents a simple, solvent-free, and scalable approach for improving the performance of poorly soluble drugs. The study concludes that this method is a viable alternative for enhancing the bioavailability of Rivaroxaban and potentially other low-solubility therapeutic agents.

KEYWORDS:

Melt sonocrystallization, Rivaroxaban, Solubility, Crystallization, Bath Sonicator.

INTRODUCTION:

The development of particle engineering techniques to modify the drug's micromeritic, biopharmaceutical, and physicochemical characteristics is underway. Numerous techniques for producing particles have been reported, such as sonication, which results in simultaneous crystallisation and agglomeration, spray drying, solution atomisation, extrusion spherization, and spherical crystallisation. But due to stringent environmental concerns around the world, pharmaceutical processing techniques that eliminate organic solvents are preferred. Consequently, a few studies are published on techniques such as melt granulation, melt extrusion, patriation, melt dispersion, melt solidification (MST), and melt sonocrystallization (MSC) technique, respectively. (1)

A few years ago, ultrasound (US) was added to the conventional pharmaceutical technology process to improve the solubility of sparingly soluble drugs. The main purpose of ultrasound was to affect the first nucleation stage of crystallization, which occurs when the metastable zone's breadth is decreased, and nucleation begins at a lower supersaturation level. (2) The US can alter a wide range of materials, resulting in welding, moulding, and plastic deformation. The US can have an impact on technological procedures using pharmaceutical materials since many of them are thermoplastic. High-value items can benefit from sonocrystallization by gaining several attractive properties. (3)

One mechanical impact of ultra sonification is the disaggregation or deagglomeration of particle assemblies. One important phenomenon in ultrasonication is cavitation. Bubbles collapsed at very high temperatures, releasing energy that caused particles to break apart. (4) Since they are similar charge particles, the problem of agglomeration is significantly lessened, and the shock waves can cause the particles to collide with high force. There have been multiple attempts to apply ultrasonic energy during the crystallization process. To produce

deagglomeration and the necessary crystal habit, US energy has been utilized to achieve nucleation at mild super saturation during the crystallization process or terminal treatment. (5)

In addition to directing compaction to produce tablets with increasing hardness and a glassy appearance, ultrasound has been utilized to mill US-compacted matrices to create a new generation of granulates. The active medication is released differently in these powders than in granulates made using a dry, conventional compaction method. The US claimed that compaction altered the physical structures of the medicine or excipients and ultrasonic spray congealing to improve the drug's compaction and release properties. Ultrasound can generate cavitation and substantial molecular motion in liquids or melt mixes in addition to its effects on solids, separating the drop material into several micro drops with a restricted size range. (6)

In the crystallization process or as a terminal treatment to produce deagglomeration and create the required crystal habit, ultrasonication energy has been utilized to achieve nucleation at mild super saturation. The role of ultrasound in crystallization remains unclear despite the proposal of numerous theories on the mechanism of ultrasound on nucleation, cluster formation of molecules before nucleation, and the interfacial impact between crystals and solution. The phenomenon known as acoustic cavitation occurs when ultrasonic waves produce varying-sized air or vapour bubbles that vibrate in unison with the pressure waves. (7)

Cavitation is the process by which cavities are created, then expanded and collapsed to yield very high energy densities. During a single cavitation event, millions of locations within a reactor may experience extraordinarily high temperatures and pressures (few thousand atmospheres of pressure and a few thousand Kelvin of temperature) locally, while the ambient environment stays the same. (8)

Rivaroxaban:

Rivaroxaban is an oral, direct Factor Xa inhibitor that has emerged as a critical agent in the prevention and treatment of thromboembolic disorders, including deep vein thrombosis (DVT), pulmonary embolism (PE), and non-valvular atrial fibrillation. As a novel oral anticoagulant (NOAC), rivaroxaban offers advantages over traditional anticoagulants such as warfarin, including predictable pharmacokinetics, fewer drug and food interactions, and the elimination of routine coagulation monitoring. (9) The formulation of immediate release (IR) tablets of rivaroxaban plays a crucial role in ensuring rapid onset of action, essential for acute clinical scenarios where timely anticoagulation is necessary. This research focuses on the development, evaluation, and optimization of immediate release tablets of rivaroxaban, aiming to enhance its bioavailability and therapeutic efficacy while ensuring safety and patient compliance. By investigating various formulation parameters and excipient compatibility, this study contributes to the advancement of efficient oral delivery systems for Rivaroxaban. (10,11)

Pharmacokinetics: -

1. Absorption:

Bioavailability: Approximately 66–100%, with food increasing absorption (especially for doses greater than 15 mg).

Peak Plasma Concentration: Achieved within 2–4 hours after oral administration.

2. Distribution:

Volume of Distribution (Vd): Approximately 50 L.

Protein Binding: About 92-95% of rivaroxaban binds to plasma proteins, mainly albumin.

3. Metabolism:

Rivaroxaban is metabolized primarily in the liver by the cytochrome P450 enzyme system (CYP3A4), with contributions from CYP2J2 and other enzymes.

4. Elimination:

Half-life: Approximately 5–9 hours, depending on the dose.

Excretion: Primarily excreted via the urine (about 66%) and feces (approximately 33%).

Routes:

~1/3 excreted unchanged by the kidneys.

~2/3 metabolized, then eliminated via renal and fecal/biliary routes.

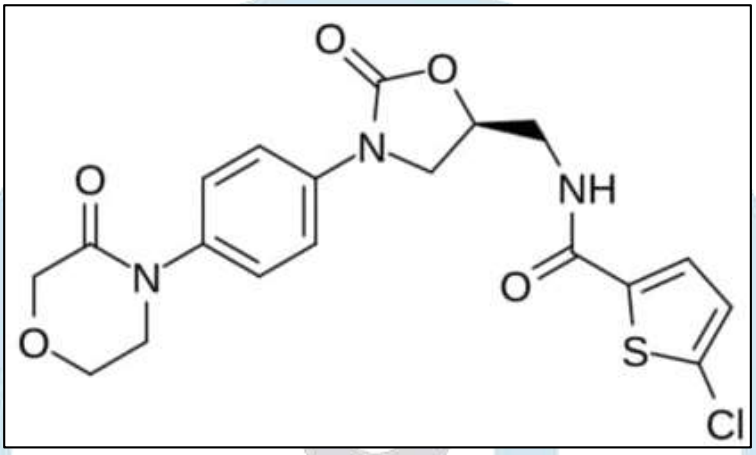

Figure 1: Rivaroxaban

MATERIALS: -

Rivaroxaban (Amepurva Forum Nirant Institute of Pharmacy), Deionized Water (Amepurva Forum Nirant Institute of Pharmacy).

1. Rivaroxaban
2. Deionized Water

1. Rivaroxaban-

Molecular Formula: $C_{19}H_{18}ClN_3O_5S$

Molecular Weight: 435.88 g/mol.

Rivaroxaban:5-chloro-N-([(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl) phenyl]-1,3-oxazolidin-5-yl] methyl] thiophene-2-carboxamide.

Category: Anticoagulant.

Form: Crystalline solid.

Appearance: White to off-white powder. (11)

2. Deionized Water-

It is produced through an ion-exchange process in which contaminating ions are replaced with H^+ or OH^- ions. It is primarily used as a solvent for preparing reagents and for other laboratory operations, where distilled water is

typically used. In this case too purified water derived by other means of purification can be equally suitable when deionised water is specified. (12)

INSTRUMENTATION: -

1) Ultrasonic Bath Sonicator-

An ultrasonic bath sonicator is a laboratory device that uses high-frequency sound waves (typically 20–40 kHz) transmitted through a liquid medium (usually water) to induce cavitation—the rapid formation and collapse of microbubbles. This mechanical energy is used in melt sonocrystallization to enhance nucleation and control crystal growth during the cooling of a melted substance.

The ultrasonic bath typically consists of a stainless-steel tank equipped with piezoelectric transducers attached to its base or sides. These transducers convert electrical energy into sound waves, which propagate through the liquid and reach any sample containers immersed in the bath (e.g., vials or test tubes). The device is controlled via a digital or analog interface, allowing adjustments to sonication time, power output, and sometimes frequency.

In melt sonocrystallization, the compound is first melted often in a paraffin oil bath and then cooled under ultrasonic irradiation provided by the sonicator bath. The ultrasound creates localized pressure changes and energy zones.

This process is especially important in pharmaceutical formulation, where controlling the crystal form and size directly impacts solubility, stability, and bioavailability. (13)

Figure 2: Ultrasonic Bath Sonicator.

Table 1- Features of Ultrasonic Bath Sonicator.

Feature	Description
Frequency Range	Typically, 20–40 kHz
Power Output	Varies from 50 W to 500+ W depending on bath size and model
Tank Capacity	Ranges from small (1–3 L) to large (>10 L), depending on scale of crystallization
Control Panel	May include timers, temperature monitoring, power adjustment
Transducer Type	Piezoelectric crystals bonded to bath surface
Material Compatibility	Stainless steel tank: sample containers must be compatible with ultrasound

2) Paraffin oil bath-

A paraffin oil bath is a laboratory heating device designed to maintain precise and uniform temperatures, especially in processes where water baths are unsuitable due to higher temperature demands or the need for chemical inertness. The heating medium used is paraffin oil, a high-boiling, thermally stable, and non-volatile liquid that offers excellent heat transfer without the risks of evaporation or combustion at elevated temperatures (typically up to 200°C or more).

The instrument consists of a metal or glass container filled with paraffin oil, an electric heating element, and a temperature controller, either digital or analog, often paired with a thermocouple or temperature probe. This setup enables precise temperature regulation, ensuring a stable thermal environment that is critical for sensitive or long-duration experiments. Some models also feature safety enhancements such as over-temperature protection, insulated exteriors, and mechanical or magnetic stirrers to promote even temperature distribution.

In the context of melt sonocrystallization, the paraffin oil bath serves a specialized purpose. It is used to uniformly melt the target compound by immersing the sample—usually contained in a glass vial or test tube—into the hot paraffin oil. The gradual and consistent heat transfer ensures complete melting without thermal degradation. Once the compound is fully molten, the system is allowed to cool in a controlled manner, during which ultrasound is applied using either a probe sonicator or an ultrasonic bath. The ultrasound facilitates nucleation and enhances control over crystal size, morphology, and polymorphic form. This technique is particularly valuable in pharmaceutical development and materials science, where controlling crystallization behavior is essential for product performance and reproducibility.

Figure 3: Paraffin oil bath.

Temperature range: Typically, 30°C to 200°C.

Controller: Digital or analog with PID capability.

Components: Container, heating coil, temperature probe.

Safety: Over-temp cutoff, insulation, stirring options.

Applications: Organic synthesis, thermal analysis, melt sonocrystallization.

METHOD-

The required amount of drug melted in a vessel on a paraffin oil bath maintained at temperature range of 190°C to 193°C.

The molten drug was then poured in a vessel containing deionized water maintained at 50° to 60°C.

The mixture was sonicated for 60 to 90 minutes using ultrasonic bath sonicator at different amplitudes.

The product obtained after solidification of dispersed droplet was separated by filtration and dried at room temperature. (14)

Figure 4: The process of Melt Sonocrystallization.

Table of Ingredients-

Table 2- Ingredients

Drug	Rivaroxaban
Solvent	Deionized Water

Formulation Table-

Table 3 – Various Batches of Melt Sonocrystallization and their various Variables.

Batch Code	Drug (mg)	Time (min)	Bath Power (W)
A1	5	35	50
A2	10	45	50
A3	20	90	150
A4	20	90	150

CHARACTERIZATION OF MELT SONOCRYSTALLIZATION-

The prepared melt sonocrystallization crystals were characterized using standard techniques such as Fourier Transform Infrared Spectroscopy (FTIR) for detecting functional group interactions and confirming hydrogen bonding. Powder X-ray Diffraction (PXRD) to examine crystalline structure.

1. UV Analysis-

Solubility measurements were examined using UV absorbance measurements at 249 nm using a UV spectrophotometer. Also to find out about the unknown structures of the organic groups. (15)

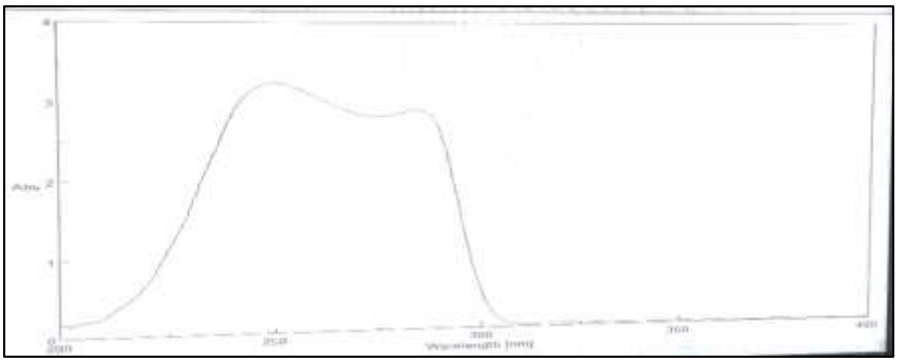

Figure 4 - UV Analysis of Rivaroxaban.

Table 4- Interpretation of UV Analysis of Rivaroxaban

Recorded Range (nm)	Observed Peak (nm)	Functional Group	Organic Group	Interpretation
200-400	~250	π→π* transition (C=C)	Aromatic ring (e.g., benzene)	Strong π→π* absorption, typical for aromatic compounds or conjugated systems.
200-400	~290	n→π* transition (C=O)	Carbonyl compounds	Weaker shoulder peak, may indicate lone pair to π* transitions (e.g., ketones).

The UV-Vis spectrum of Rivaroxaban shows two key absorbance peaks around 250 nm and 290 nm, indicating the presence of conjugated systems. The strong peak at \~250 nm suggests a π→π* transition typical of aromatic rings, while the weaker shoulder at \~290 nm points to a possible n→π* transition, likely from a carbonyl group. This pattern is characteristic of aromatic or conjugated organic compounds, commonly used as standard samples for instrument calibration or validation. (15)

2. FTIR Analysis-

FTIR spectroscopy can be used to study the molecular interactions between the drug and excipients in crystal formulations. By detecting changes in vibrational frequencies, FTIR helps identify potential interactions between the components. (16)

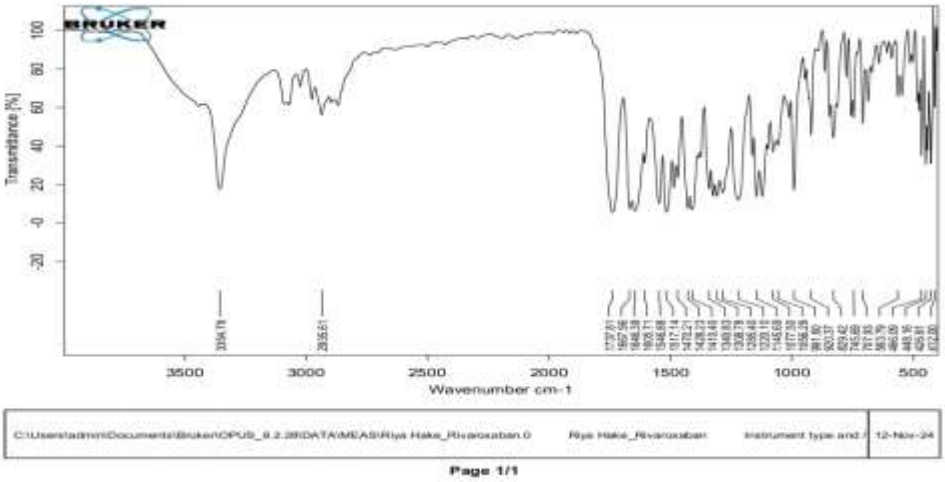

Figure 5- FTIR spectroscopy of Rivaroxaban.

Table 5- Interpretation of IR photometry of Rivaroxaban.

Wavenumber (cm-1)	Type of Vibration	Functional Group /Bond	Interpretation
~3300-3500	N-H stretching	Amide or amine group	Presence of NH group, possibly from amide functionality
~1700-1750	C=O stretching	Carbonyl (ketone, amide)	Strong peak from carbonyl group amide or ester
~1600-1650	C=C stretching /N-H bending	Aromatic ring/amide group	Indicates Aromatic structure and/or secondary Amide
~1250-1350	C-N stretching	Amine or amide	Supports presence of amide group
~1000-1300	C-0 stretching	Ether or ester	Suggests ester or ether linkage
~750-900	C-H bending (out-of-plane)	Aromatic ring	Confirms aromatic substitution pattern

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