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Development and Evaluation of Gilteritinib Nanosuspension by High-speed Homogenization: A Quality by Design (QbD) Approach

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Abstract

Gilteritinib fumarate is a BCS class II drug taken orally. It is a second-generation FLT3 (FMS-like tyrosine kinase 3) inhibitor. It is used for people with relapsed or refractory FLT3-mutated acute myeloid leukemia (AML). Even though Gilteritinib is very important for patients it has a problem that many modern kinase inhibitors have. Gilteritinib does not dissolve well in water and this changes depending on the pH. This makes it hard for the drug to dissolve and can contribute to variable oral absorption. Nanosuspension technology helps by breaking drug particles down to a small size, much smaller than a micron. These tiny particles are kept stable in a water-based liquid. This is a way to make Gilteritinib dissolve faster and more effectively without needing a lot of extra ingredients like lipids or large amounts of surfactants. High-speed homogenization is a "top-down" way to shrink particle size using mechanical force. This method is cheap, economical and does not use organic solvents. When combined with Quality by Design (QbD) framework the work becomes more organized. This framework includes checking risks finding material traits (CMAs) and important process steps (CPPs) using Design of Experiments (DoE) and setting a design space around critical quality attributes (CQAs). This makes the whole process easy to repeat and meets rules. This review looks at why to use these methods, how to use the QbD approach and how to test a Gilteritinib nanosuspension made through high-speed homogenization. Comparative literature on analogous small-molecule kinase inhibitors like gefitinib and ibrutinib were evaluated to inform formulation design, alongside an analysis of critical process parameters, testing protocols, and prospective formulation hurdles specific to gilteritinib.

Keywords: Gilteritinib; Nanosuspension; Quality by Design; High-Speed Homogenization; FLT3 Inhibitor; BCS Class II; Dissolution Enhancement

How to Cite This Article

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Introduction

Gilteritinib is a selective tyrosine kinase inhibitor used to treat FLT3-mutated acute myeloid leukemia. However how well it works is limited because Gilteritinib does not dissolve well in water. Because it does not dissolve easily, it generally cannot be absorbed well by the digestive tract. Instead of entering the bloodstream to work, the solid drug particles pass through the body and exit through waste, leading to very low or no therapeutic effect. These physicochemical limitations necessitate the exploration of approaches designed to enhance drug solubility. Nanosuspension technology is a revolutionary formulation solution designed to overcome the poor water solubility and low bioavailability of hydrophobic drugs. By reducing pure drug particles down to the sub-micron nanometer range (typically between 10 and 1,000 nm), this method drastically increases particle surface area, which helps the drug dissolve faster. To make sure the development goes smoothly Quality by Design framework can be used. This helps to find and control the materials and steps that decide if the final drug is good or not. In this case high-speed homogenization is a method used to shrink the particles so they can be used on a large scale. The QbD approach helps to clearly define the quality of the drug and the steps needed to get there. By using math and statistics like Box-Behnken or central composite methods researchers can test how to use stabilizer and how many times to run the homogenization to keep the liquid stable. These methods help find the time for homogenization and the right force to use.

This keeps the drug crystals safe while stopping the particles from sticking. Also putting these details into a design space helps to understand how different parts of the formula work together to make sure the drug always works the way. With these steps there is still a gap in what is known till now. It is necessary to understand how high-speed homogenization affects Gilteritinib stablility over a time especially to stop particles from growing larger during storage . To fix this it important to study more about how stabilizers and other ingredients work.

Nanosuspension Technology: Rationale

A nanosuspension is a mixture of drug particles. These particles are usually between 100 and 1000 nm in size. They sit in a water-based liquid and are kept from clumping by a polymer or a surfactant. Compared to ways to help drugs dissolve such as solid dispersions or liposomes nanosuspensions have many benefits for a powerful drug like Gilteritinib:

- You can put a lot of drug in the mixer without needing many extra ingredients because the particles are mostly just the drug itself.
- It works whether the drug dissolves in water or oil. This is different from lipid systems that need the drug to dissolve in oil.
- It increases how much drug can dissolve and how fast it dissolves. This happens because the surface area is bigger and the tiny size helps the solubility.
- The final form can be things. A nanosuspension can be given as a liquid. It can be turned into tablets, capsules or powders. There are two ways to make these. "Bottom-up" method use precipitation while "top-down" method use things like media milling or high-speed homogenization. High-speed homogenization is very good for early lab work because it is cheap and does not use solvents and works well with a QbD approach.

Quality by Design Framework

QbD is a science-based way to make drugs consistent, reliable, and safe. When making a Gilteritinib nanosuspension the QbD steps usually look like this:

Quality Target Product Profile (QTPP)

The QTPP is the goal for the product. For Gilteritinib the goal is a Gilteritinib fumarate nanosuspension that dissolves well, has the right particle size, stays stable and can be made in large amounts.

Critical Quality Attributes (CQAs)

Based on the goal the CQAs for a Gilteritinib nanosuspension will likely include:

- Particle size / Z-average diameter
- Polydispersity index (PDI)
- Zeta potential (this shows if the liquid is stable)
- Saturation solubility and how fast it dissolves
- How much drug is in the mix
- If it is even throughout
- How stable the drug stays over time

Risk Assessment

Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs). We often use a fishbone diagram to find which things might change the quality of the Gilteritinib nanosuspension. For high-speed homogenization these are the things to watch:

Critical Material Attributes (CMAs)

- The size of the Gilteritinib particles before we start
- The type and amount of stabilizer (such as polyvinylpyrrolidone/PVP K-30, poloxamer 188 hydroxypropyl methylcellulose/HPMC, polyvinyl alcohol, sodium lauryl sulfate or mixes)
- The ratio of drug to stabilizer
- The type and amount of surfactant used to keep particles apart.

Critical Process Parameters (CPPs)

- How fast the homogenization machine spins (rpm)
- How long the homogenization takes
- How many times to do it
- The shape of the machine parts
- The size of the batch
- The temperature during homogenization
- The order in which we add ingredients and how long we mix them first

Design of Experiments (DoE)

After picking the CMAs and CPPs use a screening design (e.g. Plackett -Burman) followed by optimization design like a 3^2 or 3^3 factorial design, Box–Behnken or central composite design with software like Design-Expert® to map out how the factors affect the results. Look at how homogenization speed, homogenization time and drug: stabilizer ratio change the response. CQAs like particle size, PDI and zeta potential. A strategy similar to the one used for Gilteritinib nanosuspension was adopted. For the gefitinib formulations, a factorial design was executed to monitoring homogeneous pressure, drug-to-stabilizer ratio, and cycle numbers. For the efavirenz nanosuspensions, the study design concentrated on high-speed homogenization variables. Upon concluding these initial assessments, response surface methodology and desirability function optimization were utilized to determine the definitive formulation and map the design space.

Control Strategy

Once an optimized batch is identified within the design space, a control strategy (in-process controls, specifications, and a validated analytical method) is established to ensure the CQAs are consistently met on scale-up — the final step of the QbD cycle.

High-Speed Homogenization: Process Principle

High-speed (rotor–stator) homogenization works by pushing a drug suspension through a gap between a fast rotor and a still stator. This usually happens at speeds between 8,000 and 24,000 rpm. The strong shear, cavitation and turbulence break the drug particles down shrinking them from micrometers to sub-micron size. A normal lab protocol, like the ones I use for nanosuspension studies includes:

1. Mixing the drug powder into a stabilizer solution to make a pre-suspension usually by using magnetic stirring.
2. Running the pre-suspension through high-speed homogenization for a time or number of cycles. The temperature is controlled with external cooling because the shear creates a lot of heat.
3. Sometimes use probe sonication to make the particle size distribution even tighter.
4. Measuring the properties of the resulting nanosuspension. If need turn it into a powder by lyophilization or spray drying so it can be stored for a long time.

Compared to high-pressure homogenization or wet media milling, high-speed homogenization uses equipment and is faster. However high-speed homogenization usually makes the particle sizes more spread out. This is why the QbD/DoE approach is so helpful. It helps to set a process window and systematically reduce the Polydispersity Index (PDI) in a nanosuspension rather than guessing.

Evaluation Parameters for the Nanosuspension

A comprehensive evaluation package, consistent with what has been reported for other kinase-inhibitor nanosuspensions, would include:

Parameter	**Typical Method**	**Purpose**
Particle size/ Z-average	Dynamic light scattering (DLS)	Conforming nano-sized range and uniformity

PDI		
Zeta potential	Electrophoretic light scattering	Predicts physical (colloidal) stability
Drug content	HPLC/UV method	Confirms recovery and uniformity
Saturation solubility	Equilibrium shake-flask method	Quantifies apparent solubility enhancement
In vitro dissolution	USP apparatus, biorelevant/stimulated GI media	Demonstrates improved dissolution rate vs. Plain drug
Crystallinity	Powder X-ray diffraction (PXRD)	Detects amorphization or polymorphic change
Thermal behaviour	Differential scanning calorimeter(DSC)	Assesses melting point depression/amorphouscontent
Morphology	Scanning electron microscopy	Confirms particle shape and surface characteristics
Physical stability	Storage studies (short-term, accelerated ICH conditions)	Monitors size/PDI/Zeta drift and sedimentation
Redispersibility	Visual/instrumental after settling	Confirms ease of resuspension
In vivo pharmacokinetics (Optional)	Animal PK study	Confirms translation of in vitro gains to Cmax/AUC improvement

Other studies on gefitinib nanosuspensions made with high-pressure homogenization and QbD show that particle sizes stay in the hundreds of nanometres. These gefitinib nanosuspensions also show better dissolution than the plain drug. Similarly ibrutinib nanosuspensions made by wet media milling show improvements in how the body processes ibrutinib compared to the original drug. These past examples make it look like this method should work for gilteritinib. However work is needed to be done for gilteritinib especially when picking a stabilizer because gilteritinib is basic and lipophilic. The solubility,dissolution profile and bioavailability of Gilteritinib cannot be assumed a priori; rigorous empirical evaluation is required to substantiate these biopharmaceutical parameters.

Anticipated Challenges Specific to Gilteritinib

- High potency and dosing considerations: People take gilteritinib once every day at specific milligram strengths. Any new way to make gilteritinib must keep the dose accurate and the mixture when turning the nanosuspension into a solid pill.
- Elimination half-life: Since gilteritinib already stays in the body for a long time the main goal is to stop the absorption from changing too much due to how fast gilteritinib dissolves or what a person eats. No alterations to the overall systemic disposition of gilteritinib were targeted.
- Weakly basic character: Owing to the pH-dependent solubility of gilteritinib, the selection of vehicle and stabilizer pH critically governs both the formulation methodology and the subsequent temporal physicochemical stability of the preparation.
- Stability of the nanosuspension: The tiny particles in a nanosuspension have surface energy and like to clump together or grow larger. It is important to find the stabilizer and drying method like lyophilization or spray drying to keep the gilteritinib particles small while they sit on a shelf.
- Scale-up: Moving a lab process for high-speed homogenization to a large factory scale is not easy. To keep the quality the same there is need for a scale-up model. Re-testing of everything at a larger scale is to be done.

Conclusion

Gilteritinib is very helpful for FLT3-mutated AML. Like many new kinase inhibitors gilteritinib has trouble dissolving because of its BCS Class II nature. Using nanosuspension technology made with high-speed homogenization and a Quality by Design framework is a way to help gilteritinib dissolve better. This way avoids using many extra ingredients like lipids or cyclodextrins. Using the QbD method—which includes setting a QTPP finding CQAs picking CMAs/CPPs based on risk using DoE for optimization and setting a control strategy—

gives the strictness and regulatory support needed for medicine. The success of QbD-optimized nanosuspensions for drugs like gefitinib and ibrutinib shows that this should work for gilteritinib. To make it real hard work is to be done. This means testing stabilizers, for gilteritinib using DoE to fix the process checking the properties and stability of gilteritinib and finally proving that gilteritinib actually works better in living subjects.

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