

Why Does 5-FU occlude Infusion Pumps?

From Molecular Structure to Crystallization Mechanism and Pump Occlusion

A Visual 5-Step Explanation

Core Cause: It All Starts with the Molecular Structure

5-Fluorouracil (5-FU) is notorious for occluding elastomeric infusion pumps. Understanding exactly why requires examining the drug at the molecular level — from its crystal lattice to its behavior under clinical conditions. The following five steps explain the complete mechanism.

Step 1 — Molecular Structure: The Root Cause

5-FU is derived from uracil, with the hydrogen atom at the C5 position replaced by a fluorine (F) atom. This seemingly small substitution has profound consequences. The pyrimidine ring retains both an NH group (hydrogen bond donor) and a C=O group (hydrogen bond acceptor), two functional groups that are powerfully attracted to one another.

Key Molecular Features

NH group (hydrogen bond donor) + C=O group (hydrogen bond acceptor) on the same pyrimidine ring. These two groups pull strongly toward each other, acting as the seed for crystallization. The fluorine substitution at C5 enhances the electronegativity of the ring and stabilizes this interaction.

Step 2 — Crystal Structure: Uniquely Rigid

5-FU is unusual among drug molecules in that only a single crystal polymorph has ever been reported. This means it crystallizes in one specific, highly predictable configuration — leaving no room for alternative, less-stable forms.

Within the asymmetric unit, four molecules are connected by hydrogen bonds, forming a planar sheet structure. These 2D sheets then stack on top of one another through π – π stacking interactions, creating an exceptionally rigid 3D crystal lattice.

2D Planar Sheet

4 molecules per asymmetric unit, linked by $\text{NH}\cdots\text{O}=\text{C}$ hydrogen bonds into flat, extended sheets

3D Crystal via π – π Stacking

2D sheets layer on top of each other through aromatic π – π interactions, forming an extremely hard and stable 3D crystal

Step 3 — Low Aqueous Solubility Despite Hydrophilicity

Although 5-FU is classified as a hydrophilic drug, its aqueous solubility is surprisingly low. This apparent paradox is explained by the self-assembly of 5-FU molecules into fibril structures.

The NH and C=O groups drive self-assembly into ordered fibrillar aggregates, even in solution. This fibril formation directly reduces the effective solubility of the drug and is also implicated in reducing its anticancer efficacy — making it both a pharmaceutical and a clinical problem.

Clinical Implication

Fibril formation is not merely a formulation inconvenience. It reduces the bioavailable fraction of 5-FU that reaches the tumor site, potentially compromising treatment outcomes in addition to causing physical pump occlusion.

Step 4 — Three External Factors That Accelerate Occlusion

The intrinsic crystallization tendency of 5-FU is compounded by three clinical and device-related conditions that act synergistically to accelerate pump occlusion:

Step A

Temperature Drop: Body Temperature (37°C) → Room Temperature

As the infusion line exits the patient's body, the solution cools from 37°C to ambient room temperature. This temperature decrease causes a further reduction in 5-FU solubility, pushing the drug past its saturation point and triggering nucleation and crystal growth.

Step B

Low Flow Rate — Extended Residence Time in the Tubing

Elastomeric pumps typically deliver 5-FU at low flow rates of 0.5–2 mL/h. This slow delivery means the drug spends an extended period of time inside the tubing. The prolonged residence time allows local concentration to rise and gives crystals additional time to nucleate and grow.

Step C

Narrow Capillary Cross-Section — Only 50 µm

The restrictor capillary in standard elastomeric pumps has a cross-sectional diameter of only 50 µm. At this scale, even a handful of small crystals is sufficient to cause partial or complete occlusion. There is virtually no tolerance for any particulate matter in the flow path.

Step 5 — The NeoFuser Solution: Wider Channel Architecture

NeoFuser addresses the occlusion problem by fundamentally redesigning the geometry of the flow-restricting element. Its microchannel measures 90 × 100 µm — a rectangular cross-section that is 4.6 times larger in area than the 50 µm capillary used in conventional elastomeric pumps.

Parameter	Standard Pump	NeoFuser Onco
Diameter / Channel Dimensions	50 μm (circular)	90 $\times$ 100 μm (rectangular)
Cross-Sectional Area	$\sim 1,963 \mu\text{m}^2$	$\sim 9,000 \mu\text{m}^2$ (4.6 $\times$ larger)
Tolerance for Crystals	Very Low	Significantly Higher
Occlusion Risk with 5-FU	High	Substantially Reduced

By providing 4.6 times more cross-sectional area, NeoFuser ensures that even when 5-FU crystals do form within the flow path, the channel remains patent and flow is maintained. This geometric advantage directly mitigates the physical root cause of pump occlusion without relying on chemical additives or reformulation.

Summary

The tendency of 5-FU to occlude infusion pumps is not a random or unpredictable event. It results from a convergence of molecular, physicochemical, and device-level factors:

- A bifunctional molecular structure that predisposes the drug to strong intermolecular interactions
- A uniquely stable single crystal polymorph, reinforced by both hydrogen bonding and π - π stacking
- Fibril self-assembly that reduces effective aqueous solubility
- Clinical conditions — temperature drop, slow flow rate, and narrow tubing — that push the drug past its solubility limit inside the pump
- A 50 μm capillary with zero tolerance for particulate matter

The NeoFuser Advantage

NeoFuser's 90 $\times$ 100 μm microchannel is 4.6 $\times$ wider than standard restrictor capillaries, providing sufficient clearance to maintain flow even when 5-FU crystals are present. This engineering solution directly addresses the physical mechanism of pump occlusion.