

## FREQUENTLY ASKED QUESTIONS

PuroMill™ Pharmaceutical is a novel polymeric milling media developed to enable the preparation of pure drug nanoparticles that support formulation development in pharmaceutical and biopharmaceutical applications.

### Using the Media

#### **What is PuroMill™?**

PuroMill is an advanced polymeric milling media compatible with high-energy media milling for the preparation of pure drug nanoparticles. PuroMill media is composed of highly crosslinked copolymer beads that pose many benefits to pharmaceutical formulation development.

#### **Who should use PuroMill™?**

Small molecule formulation and API development teams at pharmaceutical companies, CMOs and CDMOs who need to reduce compounds to nanoscale to enhance bioavailability for enteral, parenteral, injectable and topical dosage forms.

#### **How do I determine if PuroMill™ is right for my pharmaceutical molecule?**

In general, if your compound is a crystalline small molecule with low water solubility, it is likely compatible with nanoparticulate dispersion formulation approaches. In this case, PuroMill provides excellent particle size reduction into the nano domain without product contamination. Additionally, Many OEMs for mill equipment provide testing labs to help determine feasibility of certain compounds.

#### **What type of pharmaceutical products can PuroMill™ be used for?**

PuroMill is suitable for all drug delivery systems including oral, ocular, pulmonary, transdermal, nasal and parental.

#### **What biopharmaceutical processes can PuroMill™ be used for?**

PuroMill is suitable for biological cell disruption as an advanced alternative to high-pressure homogenization or chemical disruption techniques.

#### **Will using PuroMill™ in my process allow scalability?**

Yes. PuroMill has demonstrated to scale very well from the smallest lab-scale nanoparticle media mills to the largest production-scale mills. Scaling is generally related to maintaining a consistent energy density within the agitated media bed during scale-up.

# Using PuroMill™ Media cont'd

## Is PuroMill™ suitable for both dry milling and wet milling?

Generally, PuroMill is recommended for wet media milling applications using agitated media mills. In some cases, dry milling may be feasible.

## Performance & Characteristics

### Will using PuroMill™ in my process allow consistent reproducibility?

Yes. PuroMill milling media is produced under tight specification parameters and strict cGMP guidelines. The beads have a very specific particle size range and allow consistent batch-to-batch reproducibility.

### Does PuroMill™ contain impurities?

PuroMill pharmaceutical-grade media is highly purified during manufacturing to ensure potential contaminants (both particulates and volatiles, such as monomers or solvents) are reduced to the lowest attainable levels. We recommend that customers evaluate all final products prepared using PuroMill to ensure trace impurities are within acceptable limits.

### Does PuroMill™ generate impurities?

As with any milling media, PuroMill can experience abrasion. Impurity levels are related to milling energy input (media load in the mill and RPM), product viscosity, product density and total milling time. However, impurity levels associated with PuroMill, including leachables, extractables and insoluble impurities, are generally below levels of detection. It is, however, the responsibility of the customer to ensure that drug products produced with PuroMill have appropriate safety and efficacy characteristics.

### What microbial limits tests does PuroMill™ media undergo?

All PuroMill pharmaceutical-grade milling media is tested under USP <61> Microbial Limit Tests and USP <85> Bacterial Endotoxin Tests to enable use for oral and parenteral dosage forms.

### Can PuroMill™ be used with viscous suspensions?

Yes. Despite its lower density, PuroMill can be used effectively for processing viscous suspensions by maximizing media mill agitation speeds to promote effective media separation during milling.

### Will PuroMill™ cause excessive wear to milling equipment?

No. In fact, unlike ceramic media, PuroMill can be used in conventional stainless steel equipment or pharmaceutically acceptable alloys without measurable wear to milling equipment surfaces (e.g., agitator or chamber).

### PuroMill™ is a low-density media. Doesn't that make it more susceptible to hydraulic packing?

No. As with any milling media, the operational parameters of nanoparticle milling (e.g., flow rate, RPM, media load, product viscosity, etc.) need to be established and optimized experimentally. PuroMill can be used at maximum media loads and RPMs without hydraulic packing, provided product flow rate and viscosity are optimized.

### What temperature range is ideal for PuroMill™ operation?

PuroMill does not have temperature limitations. However, most drug formulations will have temperature limits before they experience Ostwald Ripening. Because of this, temperature parameters are generally between 5°C and 40°C. However, temperature limits for each compound should be determined experimentally.

### How does the low density of PuroMill™ affect comminution time when compared to YTZ or other media?

PuroMill can achieve comparable particle size reduction efficiency to YTZ media by operating nanoparticle media mills at higher media load and agitation speeds.

### In what other ways does PuroMill™ differ from YTZ or other media?

PuroMill does not undergo hydrothermal degradation, which is often associated with YTZ media and YTZ ceramic mill components, making it particularly applicable to pharmaceutical applications that require hot water or steam-based sanitization /sterilization cycles.

# About the Technology

## How does PuroMill™ polymeric media produce effective particle nanonization?

PuroMill is composed of optimized, monodisperse copolymer beads that have exceptional wear resistance and provide excellent milling efficiency. Similar to conventional media, the mechanism of particle size reduction with PuroMill is based upon shear and impact forces resulting from media collisions during high-energy agitation within a media mill. Unlike denser ceramic media, PuroMill can withstand higher media load and agitation speeds without unacceptable media attrition, resulting in maximum stress intensity and stress frequency during milling.

## How is the uniform particle size of PuroMill™ media achieved?

PuroMill milling media is produced using Purolite's proprietary copolymer synthesis and purification technologies that enable production of consistent, monodisperse media bead distributions.

## What is the benefit of PuroMill™'s uniform particle size?

The narrow distribution size of PuroMill™ media results in more uniform milling and better batch-to-batch uniformity of your final product. During production, the monodisperse size eliminates screen plugging.

## What type of media mills, nanoparticle media mills or ball mills can utilize PuroMill™?

Low-density PuroMill is recommended for use in high-energy mills with agitation speeds ranging from ~ 5 m/sec. to over 20 m/sec. PuroMill is compatible with all mill designs, including horizontal and vertical mills. Most applications favor the use of wet milling approaches, but PuroMill may also be used in dry milling applications. In specialty applications, very small (e.g., 50 µm) PuroMill media can be used in rotor-stator equipment with tip-speeds over 35 m/sec. to produce nanoparticles as small as 10 nm.

## What percent capacity of the empty mill volume should be filled with PuroMill™ for most effective operation?

PuroMill is generally used in mills at higher media loads than conventional ceramic media. Media loads of 90% – 99% are recommended to maximize milling efficiency.

## What agitator speeds are recommended with PuroMill™?

PuroMill can be used in media mills at much higher RPM or "tip-speeds" than conventional ceramic media, without excessive media attrition or heat generation. Tip-speeds of 15 – 20 m/sec. are generally recommended.

## Will anything cause PuroMill™ media to degrade prematurely?

Yes. Consideration should be given when using PuroMill at extreme processing temperatures and certain organic solvents.

# The Basics

## Is PuroMill™ media reusable?

Yes. Due to its excellent wear-resistance, PuroMill can be used multiple times, depending upon the application.

## Can PuroMill™ be cleaned and sterilized?

Yes. PuroMill media has been developed to withstand moist heat sterilization techniques, such as autoclaving or SIP (e.g., 121°C for 20 min.). Also, PuroMill can be cleaned by flushing with water or with the use of common CIP detergents to enable media reuse.

## What is the shelf life of PuroMill™ media?

PuroMill pharmaceutical-grade media is viable for 5 years from its production date.

## What grades of PuroMill™ are available?

PuroMill is offered as either a pharmaceutical-grade media or an industrial-grade media. PuroMill Pharmaceutical-grade is manufactured and tested in an ISO-8 cleanroom governed by a quality system conforming to ISO 9001:2015 and cGMP Part II requirements.

## How is PuroMill™ sold?

PuroMill is sold by weight and a variety of packaging options are available, ranging from 1 kg to 50 kg quantities. Given the low bulk density (0.61 kg/L) of PuroMill, it is important to consider the required amounts to charge the media mill on a volumetric basis.

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