



Bead milling in pharmaceutical industry

This case study pertains to a pharmaceutical unit operation called milling. To successfully crack the problem statement, the contestants are expected to know fundamentals of chemical engineering especially particle size reduction and flow dynamics. The case study also expects contestants to search literature for clues.

Milling is a unit operation to control the particle size by transforming solid particles into smaller ones by applying forces such as shear, compression, friction, collision, or impact. The bead mill is an apparatus that agitates the beads in a cylindrical vessel to disperse minute particles in a slurry. The motion of the bead induces shear and impact on the particles. One of the major factors affecting the particle size is the size and material of bead chosen for milling. It affects the frequency of impact between the bead and the final particle size to be achieved. Fine drug particles are especially desired in formulations designed for parenteral, respiratory and transdermal use.

In this case study, contestants are tasked with optimizing the milling operation, particularly selecting the material of bead, duration of operation and shaft kinetics. Additionally, they need to address challenges related to process scalability, transfer limitations, formulation considerations, product stability and contamination risks control. Moreover, researching literature for valuable insights and potential solutions will be critical to devising an efficient and effective milling process. The winning

solution should offer a robust and scalable approach that ensures consistent product quality, reduced manufacturing costs, and enhanced patient safety.

Literature for reference:

<https://doi.org/10.1016/j.minpro.2016.02.009>

[https://doi.org/10.1016/S0032-5910\(01\)00406-5](https://doi.org/10.1016/S0032-5910(01)00406-5)

<https://doi.org/10.1002/ceat.200390029>

Instructions:

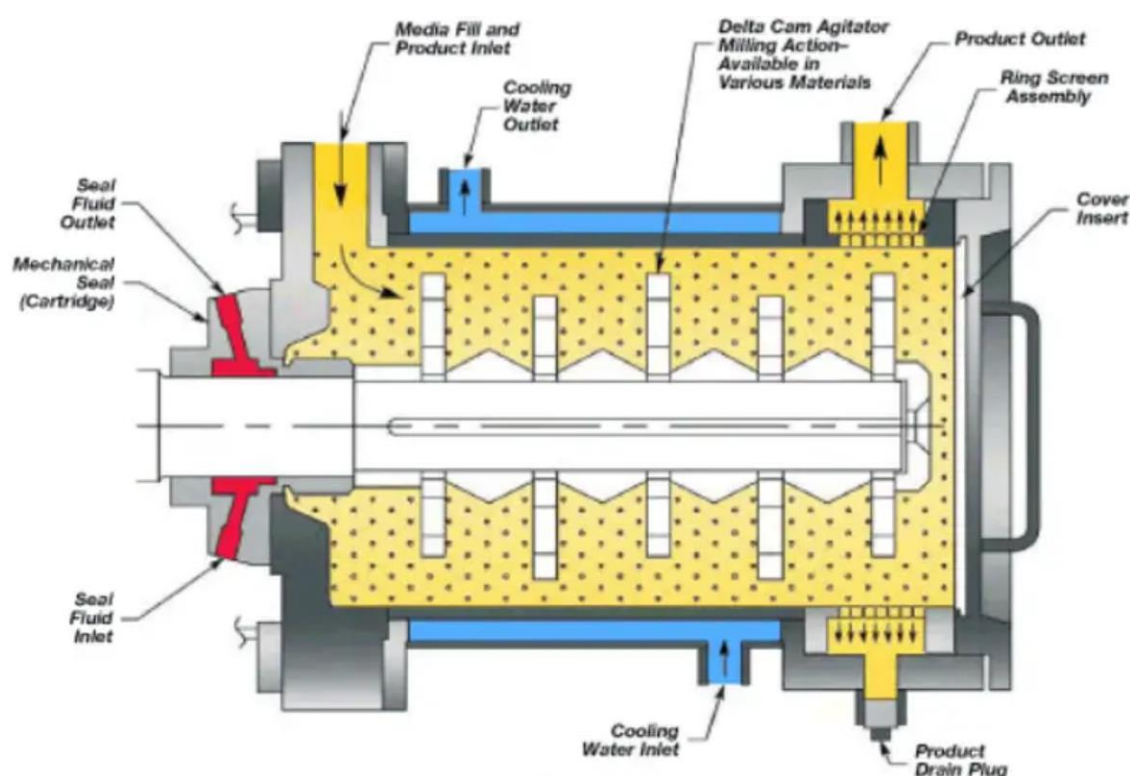
Please ensure conciseness in your responses, with each answer limited to a maximum of 350 words.

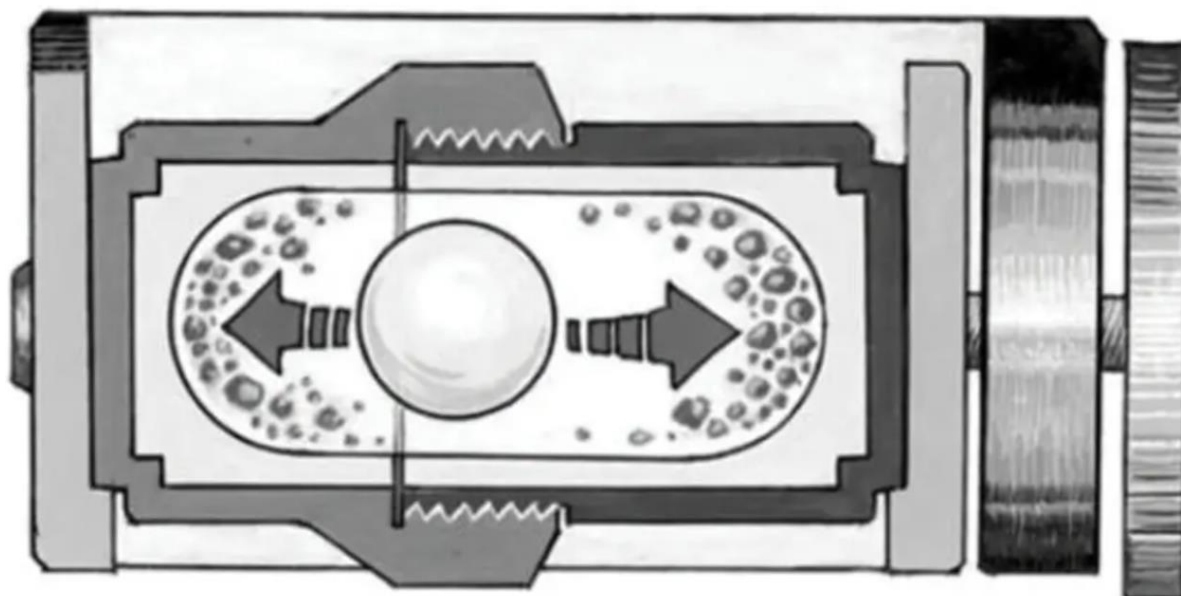
Include illustrative diagrams and graphs where necessary to enhance understanding.

Begin each new question on a separate page.

Kindly address all the questions in the specified order.

All questions are mandatory.





Questions to be answered:

- For the detail provided below:

Parameter	Initial size (μ)	Target size (μ)	Size achieved (μ)
d10	1.5	0.16-0.18	0.166
d50	4	0.5-0.7	0.505
d90	6.5	1.3-1.6	1.9

List down the parameters that can be modified to achieve d90 within the desired range given the following operating conditions:

Batch Size	500 ml
Agitator Speed	1250 RPM
Flow Rate	650 g/min
Chamber Details	650 ml
Working Temperature	20-25 °C
Working Pressure	Ambient
Bead size	0.3 mm
Bead MOC	Zirconium

Please provide the equations/methodology used to conclude on the same.

- For the detail provided below:
Slurry A with initial viscosity 5mPa.s, and, below details:

Parameter	Initial size (μ)	Target size (μ)	Size achieved (μ)
d10	2	0.16-0.18	0.2
d50	4	0.5-0.7	0.65
d90	8	1.3-1.6	1.7

Slurry B with initial viscosity 200 mPa.s, and, below details:

Parameter	Initial size (μ)	Target size (μ)	Size achieved (μ)
d10	1.5	0.16-0.18	0.18
d50	3.5	0.5-0.7	0.76
d90	6.5	1.3-1.6	1.44

Operating Conditions:

Batch Size	16 L
Agitator Speed	1250 RPM
Flow Rate	250 g/min
Working Temperature	20-25 °C
Working Pressure	Ambient
Bead size	0.4 mm
Bead MOC	Zirconium

-Optimize the operating conditions to achieve the target particle size for both the slurries A and B.

-What is the role of viscosity in particle size reduction? Provide the equations/methodology used to conclude on the same.

-How will the equations/methodology change if working temperature is changed to 45-50°C.

- Recommend the type (MOC, size, and, % solid fraction) of beads to be used for the below particle size reduction if the slurry is Non-Newtonian Thixotropic viscous slurry (Viscosity > 100mPa.s):

Parameter	Initial size (μ)	Target size (μ)
d10	10	1.3-1.6
d50	15	2.5-2.8
d90	35	3.7-4.0

- Enlist the scale independent and dependent parameters for bead mill operation. For operating conditions optimized in problem 1, finalize the operating conditions to scale up from batch size of 500 ml to 25 L. Given, viscosity of slurry is >100 mPa.s, and the slurry is Non-Newtonian Thixotropic in nature. Please provide the equations/methodology used to conclude on the same.
- For bead mill operation, a shaft is connected to the gear box. This shaft/agitator is responsible for supplying the necessary input kinetic energy.
 - Identify the parameters that shall affect the selection of O-ring to be used for rotation of the shaft.
 - Quantify the conditions that shall lead to wear & tear (particle generation) in the O-ring. You can use any research literature, mechanistic model or simulation tool to validate your results.

- c. Re-evaluate the selection criteria if lubricant cannot be used between O-ring & shaft.
- d. Re-quantify the conditions that shall lead to wear & tear (particle generation) in the O-ring for problem 5(c). You can use any research literature or simulation tool to validate your results.