



制粒过程影响质量和重复性重要因素



BOSCH

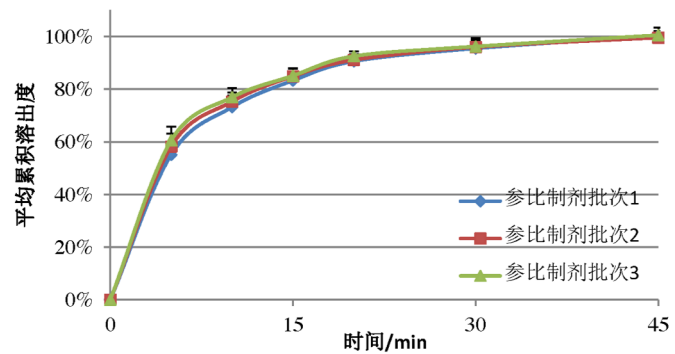
博世 科技成就生活之美



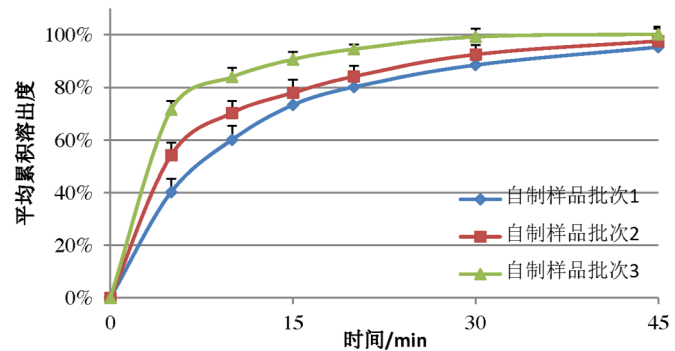
关注内容

- 仿制药一致性评价
- 批间差异
- 过程受控性
- 质量重复性重现性
- 过程周期时间
- 物料损失
- 能耗
- 环境影响

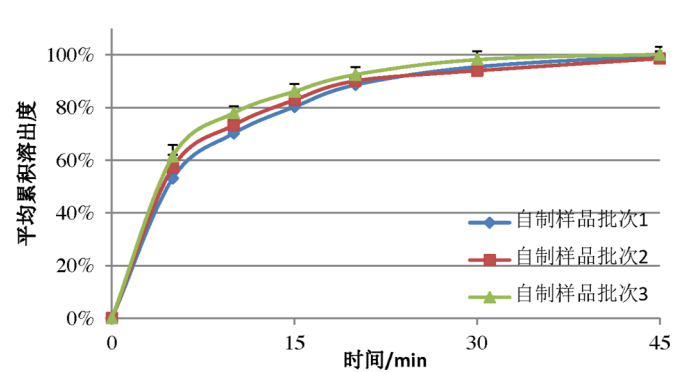
参比制剂溶出曲线对比



自制样品溶出曲线对比 (1)



自制样品溶出曲线对比 (2)



典型固体制剂布局



干整粒

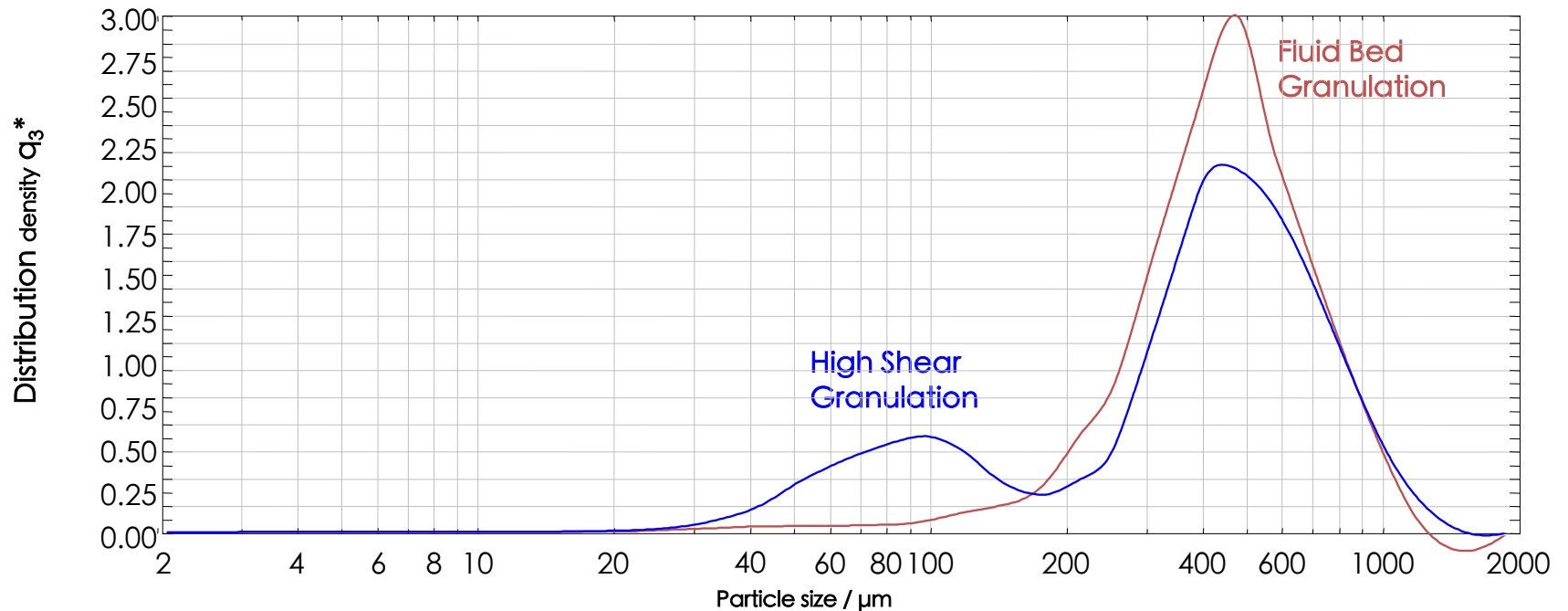
流化床干燥和制粒

湿法制粒

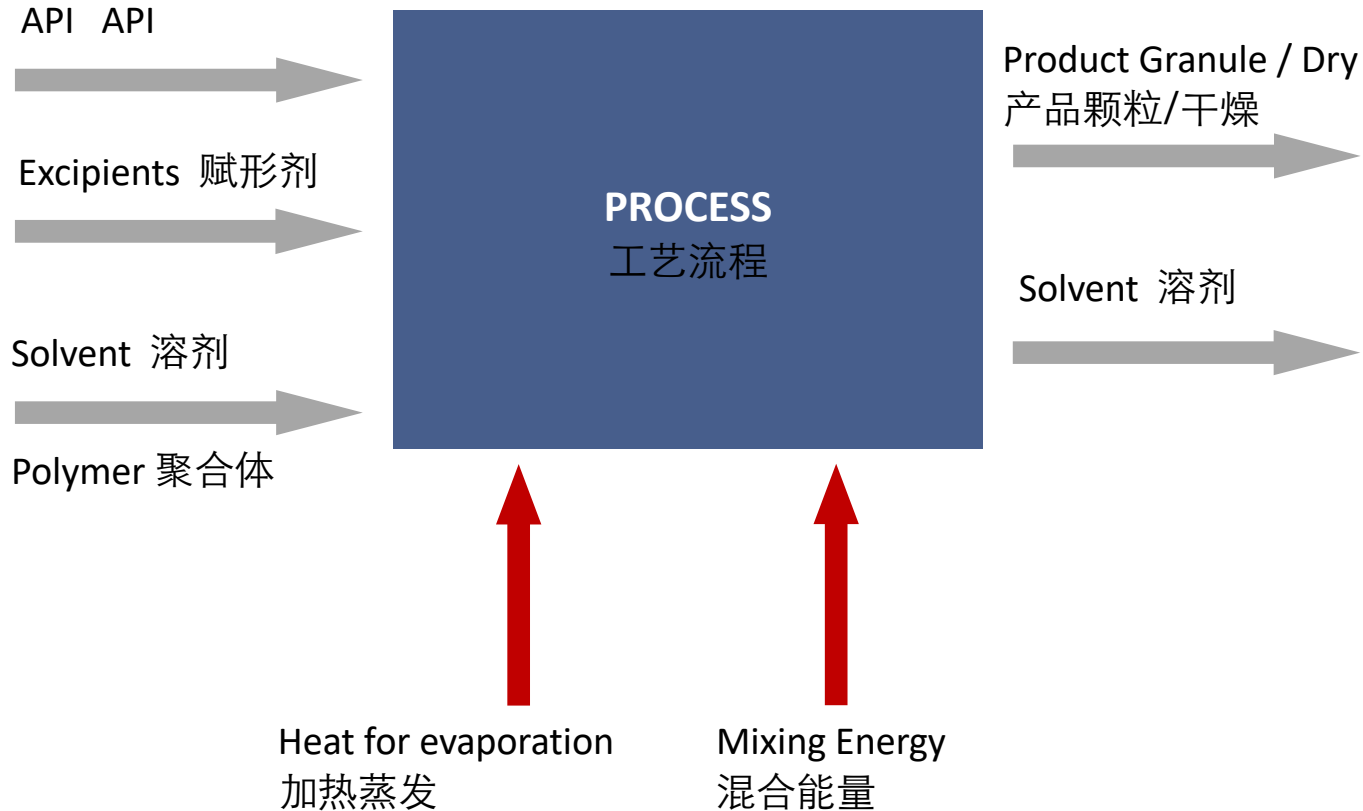
湿法制粒和流化床制粒粒径对比

	Unilab	Mycromix
Bulk density 容积密度 [g/ml]	0.431	0.546
Tap density 振实密度[g/ml]	0.500	0.669
Carr Index	13.8	18.4
Particle size at x_{50} 微粒大小	436 μm	408 μm

Formulation: 86% Lactose, 10% Cellulose, 4% PVP K90



Wet Granulation 湿法制粒

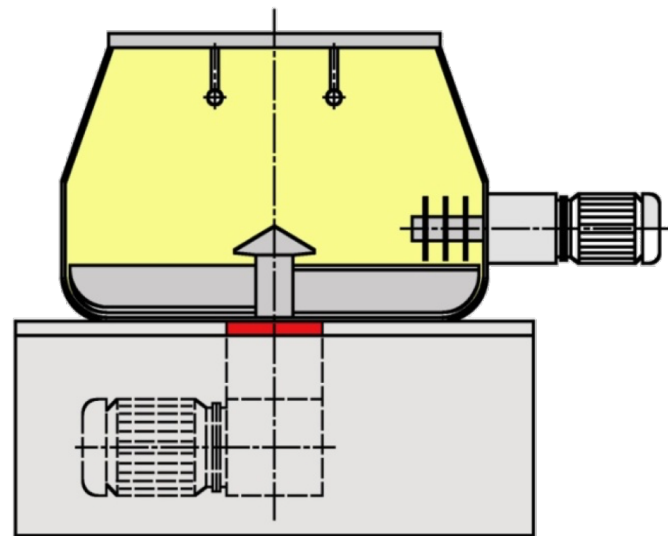




博世Hüttlin



其它技术





Chopper
切刀

Granulation Impeller
制粒叶轮
Gentlewing
搅拌桨

Where does the energy of an impeller go?

搅拌桨的动能用于哪里

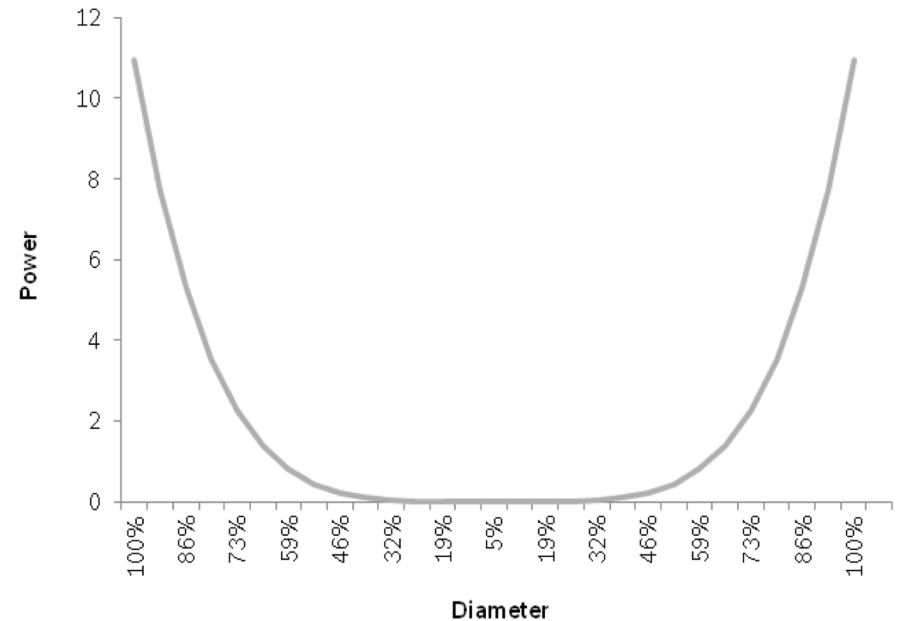
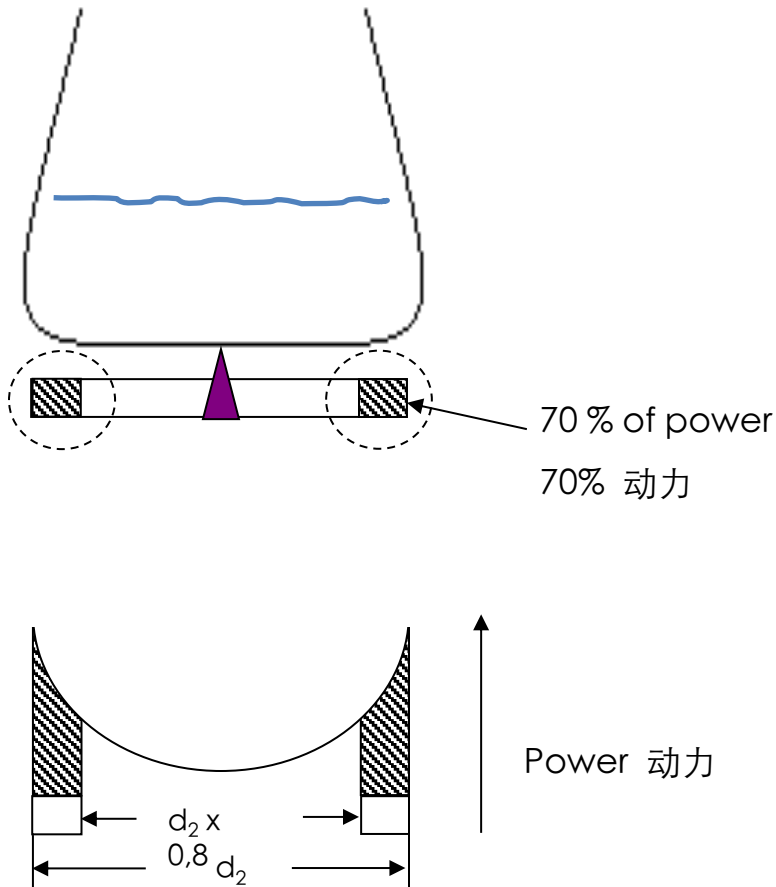
$$P \sim Ne \rho n^2 d^5$$

Ne = impeller geometry in relation to Reynolds number

ρ = density 密度

n = rotational speed 转动速度

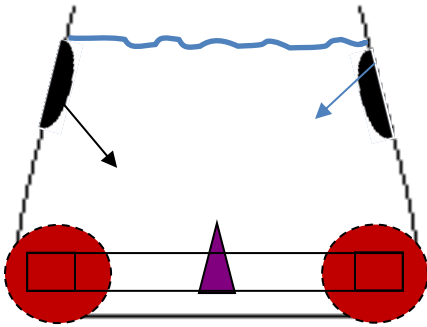
d = impeller diameter 叶轮直径



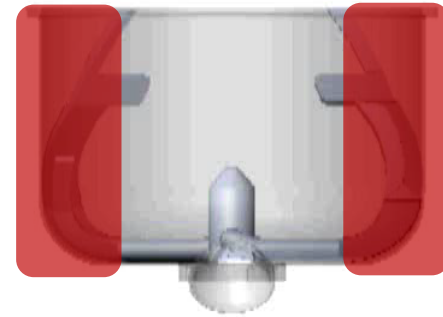
Hüttlin High-shear mixer evolution

Hüttlin 湿法混合制粒机进化

Product build up 产品粘壁

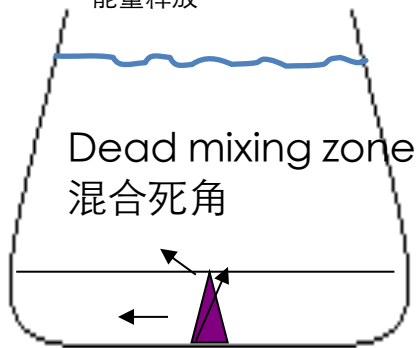


100% Product buildup not possible 产品不粘壁



$P/V = \text{same}$

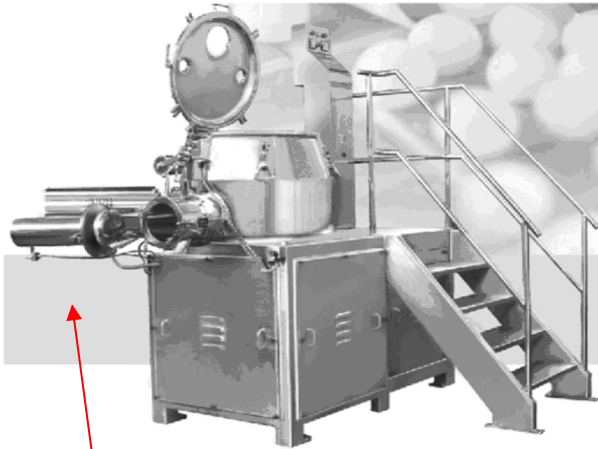
Energy Dissipation
能量释放



Energy Dissipation
能量释放



How Important is the Machine? 选用设备考虑重要因素?



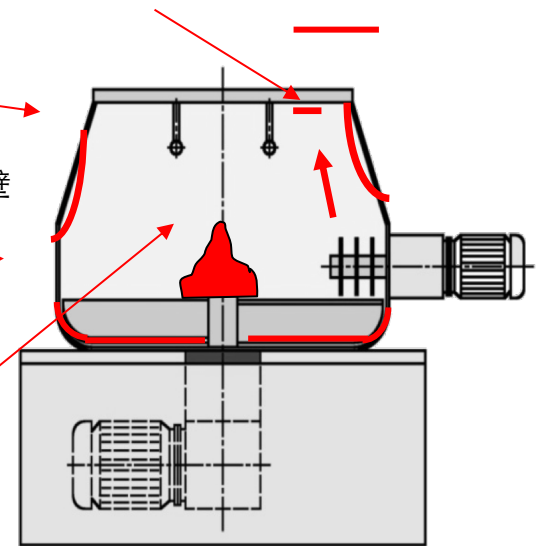
Difficult Product Discharge from the side
侧出料困难

Wet product slung onto lid by chopper
破碎器将湿物料扬至顶盖

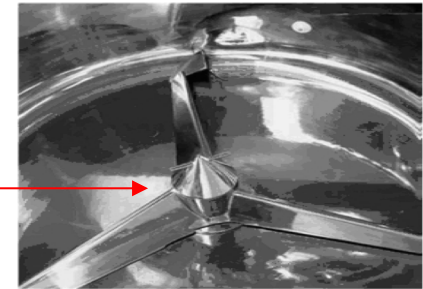
Limited granulation Surface causes product caking / builtup
有限的造粒面积易引起产品结块/粘壁

High tip speeds necessary
桨叶梢速高
local hot vessel surfaces can cause product smearing
Damage

局部容器表面温度过高会造成产破坏
Product loss: Christmas tree effect on impeller
产品损失：湿物料像圣诞树一样积聚在桨叶中央

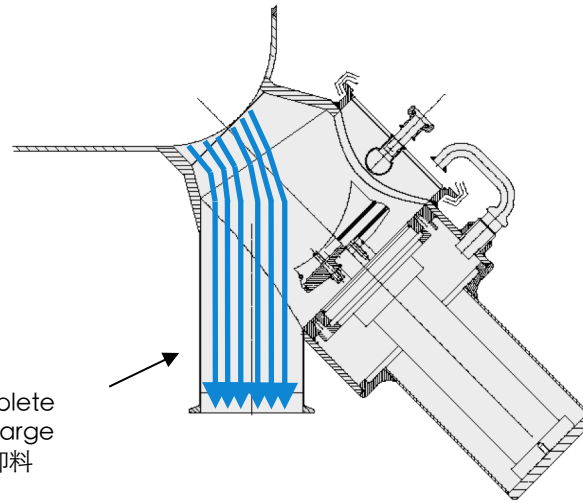
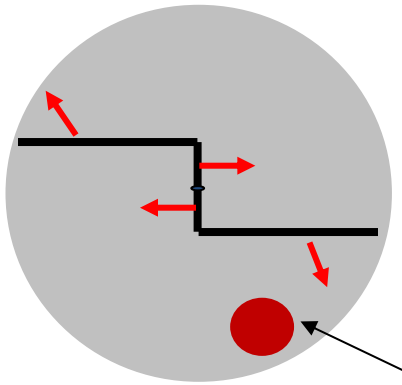


Simple impeller blade
简易的桨叶



Process Step: Discharging HBG | 工序：卸料HBG/HTG I

Choose the right Impeller HTG | 选择合适的搅拌桨



Complete Discharge
完全卸料



- Maximum Granulation Surface | 最大造粒面积
- No Product caking | 产品无结块
- Low tip speeds | 桨叶梢速低
- Cool vessel surfaces | 容器表面冷却
- Eliminate product damage | 减少产品损耗

Basic design | bottom & top drive 基本设计 | 底部&顶部驱动

Hüttlin is the only supplier with... Hüttlin是唯一的供应商

- identical design of product container and Gentlewing
产品容器和搅拌桨同样的设计
- identical processing properties

同样的工艺性能

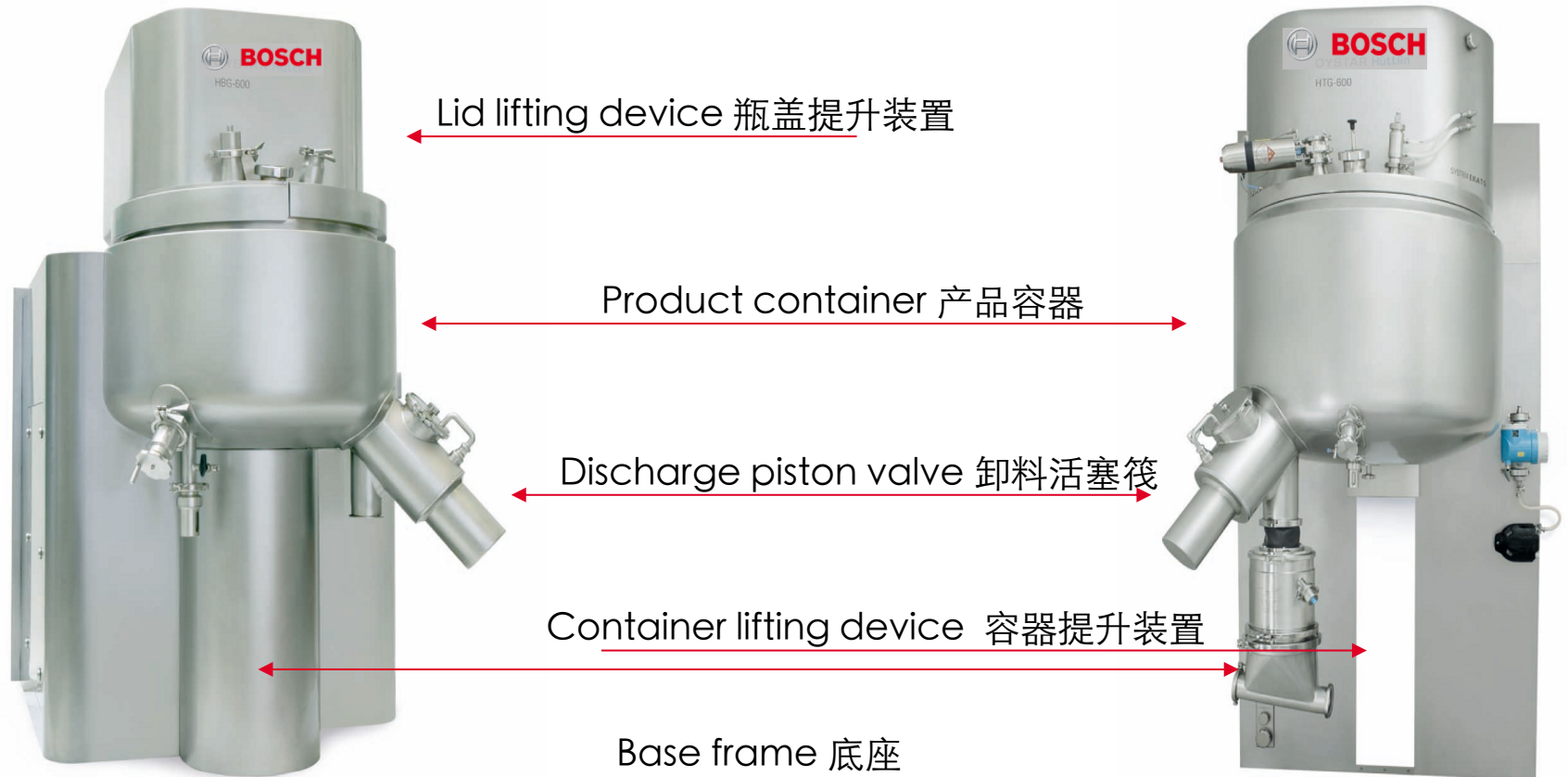
(quality of granules, process times, proc

(颗粒质量, 加工时间, 工艺参数)



High-shear Mixer 湿法混合制粒机

Basic design I bottom & top drive 基本设计I 底部&顶部驱动



High-shear Mixer 湿法混合制粒机

Basic design | bottom & top drive 基本设计 | 底部&顶部驱动

Only Top Drive 只有顶部驱动

- No seals in product contact
产品接触件无密封
- Upgrade to Single pot
升级到单锅装置
- Good accessibility for inspection of container and Gentlewing by lowering product bowl
易于监测物料容器和搅拌桨



High-shear Mixer 湿法混合制粒机

Basic design - bottom & top drive 基本设计-底部&顶部驱动

- Bottom Drive 底部驱动
 - Lid lifts up vertically to improve bowl access
垂直提升盖板易于产品锅的进入
 - Flushed Seal 气流保护密封
 - Gentlewing 搅拌桨
 - Inline operation 在线操作
 - Ultra Clean (option) 在位清洗 (可选)
- Top Drive 顶部驱动
 - Lifting column for product bowl
产品锅提升立柱
 - Flushed Seal 气流保护密封
 - Gentlewing 搅拌桨
 - Inline operation 在线操作
 - Ultra Clean (option) 在位清洗 (可选)



Basic design - bottom & top drive 基本设计-底部&顶部驱动

Gentlewing I Granulation impeller 搅拌桨 | 制粒搅拌桨

- Unique shaped impeller design cover complete product bowlwall
特殊的搅拌桨形状设计完全覆盖物料容器内壁
- Better mixing properties
更好的混合效果
- Gentle product movement
产品移动轻柔
- Complete discharge – no lid opening
出料彻底-无需开盖
- No product sticking at lid, wall and impeller
(no scratching out after discharging!!!)
顶盖板，内壁和搅拌桨无产品附着(出料后无需刮壁)
- Less fine particles
细粉较少
- Less power consumption
能量消耗少
- No dismantling after cleaning
清洁后无需拆卸

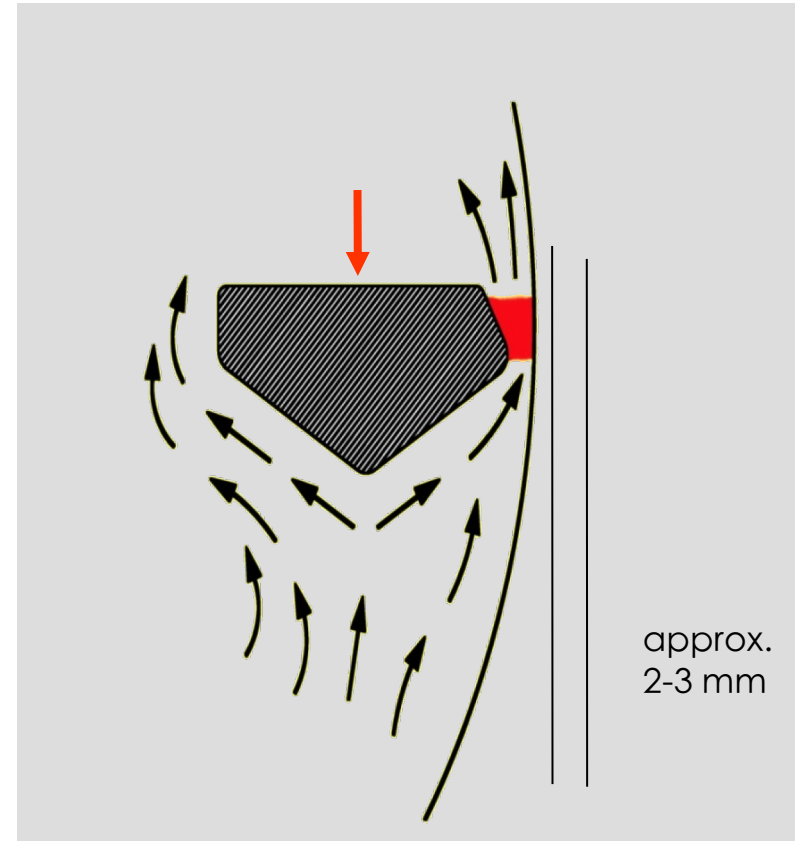


Basic design - bottom & top drive 基本设计-底部&顶部驱动

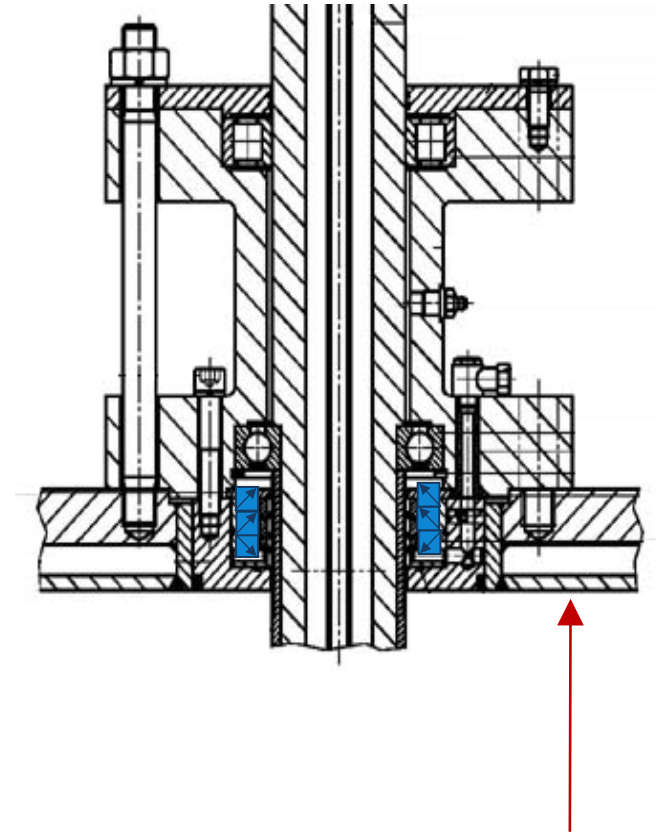
Gentlewing 搅拌桨

- Axial movement of the whole batch ensures a short mixing time with highest homogeneity
所用物料轴向运动确保极高的均匀性和节约混合时间
- Product is pressed into the gap impeller wing / wall by the triangle profile. This results into a high specific power input.
通过三角面产品被压缩至有间隙的搅拌桨翼/内壁，产生高功率输入。
- The small wall distance / triangle wing profile between prevents wall layers of inhomogeneous product
短小的内壁距离/三角翼防止壁层产品不均一

HMG Mix

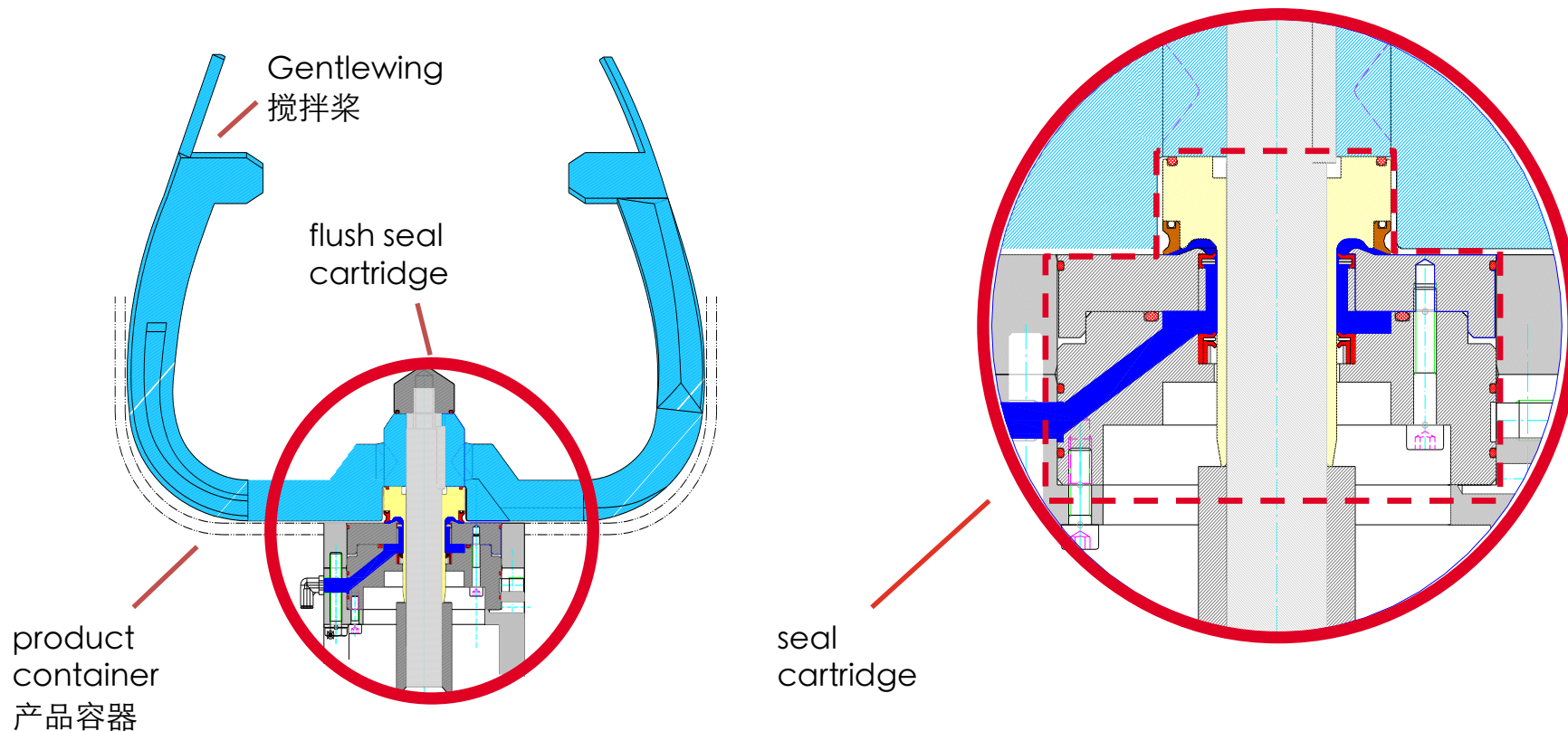


Sealing of Shafts 轴封合



Gas flushed seals are drained with WIP liquid
平齐封合的空气被WIP液体排尽

Flush Seal Cartridge for Gentlewing



Flush Seal Cartridge for Gentlewing...

...gap free avoids product entering

无缺口防止产品进入

Application 应用

- Processes with inertisation

惰性化工艺

- Water based processes

水工艺

abrasion resistant lip seal
抗磨损的密封

lip for gas and CIP water flushing

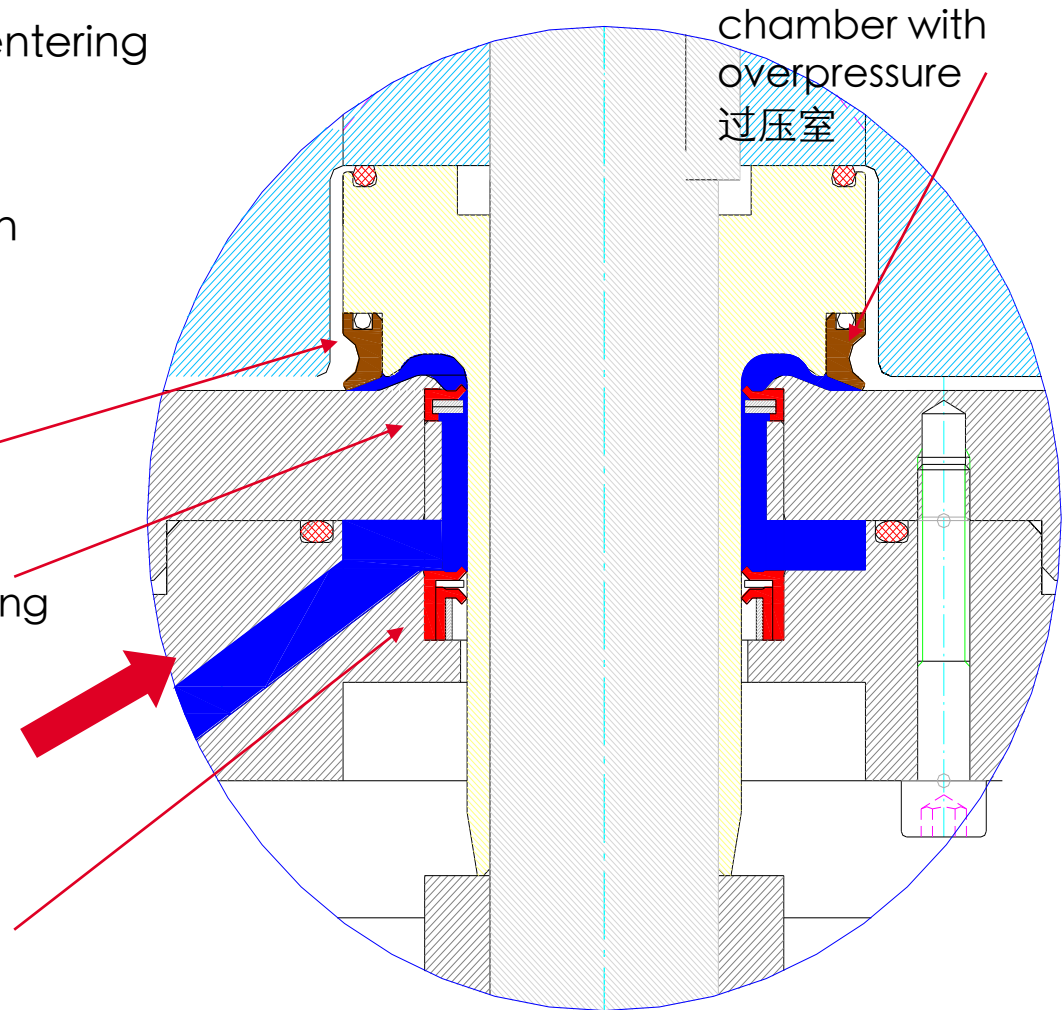
空气和CIP水反吹或清洗

gas and CIP water
flushing

空气和CIP水反吹或清洗

lip seal for vacuum and
overpressure

真空和过压的密封



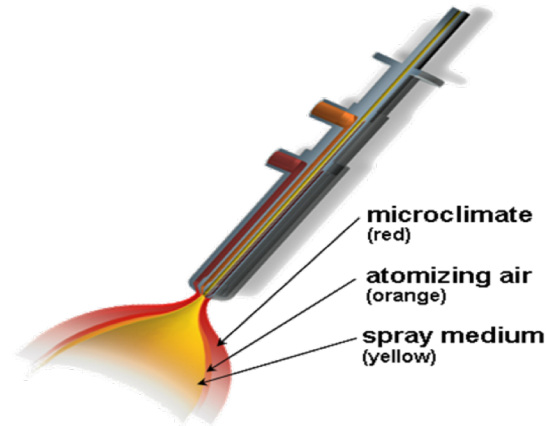
One component nozzle 一元管嘴

- even wetting of the product surface
产品表面加湿均匀
- even distribution of the binder is the result from spraying and axial mixing blade
由于喷液和轴向搅拌桨叶综合作用使粘合剂分布均匀
- easy to clean and dismantle
清洁和安装简易
- wide range of nozzle sizes available
有不同大小喷嘴供选择
- feeding by different pumps
不同泵进料

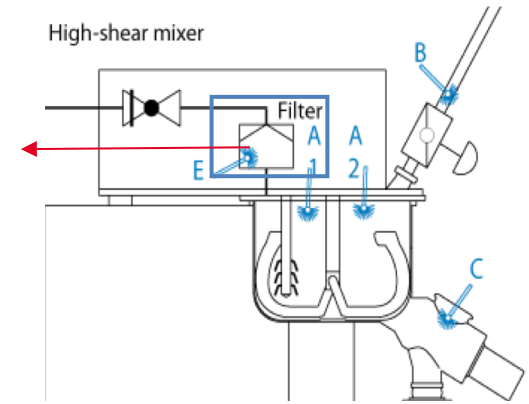
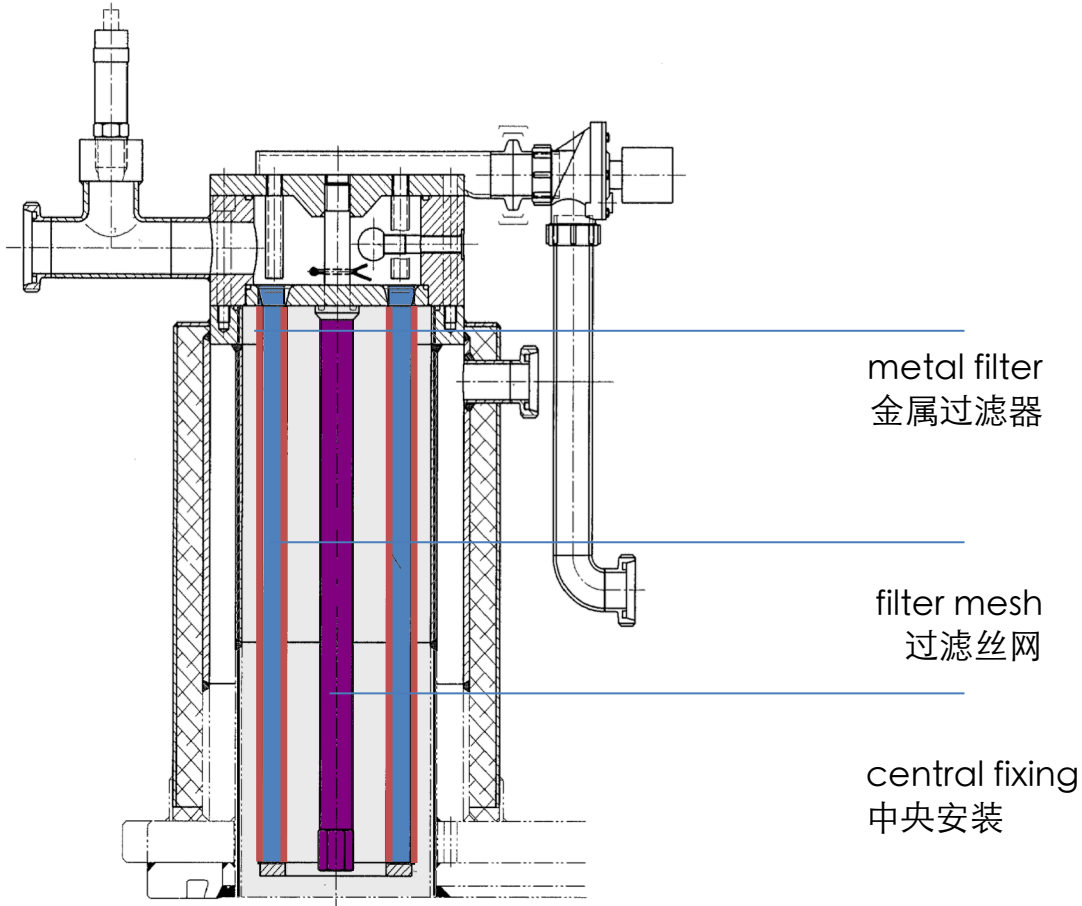


Atomized Nozzle 喷雾管嘴

- very even wetting of the product surface because of atomizing air
因雾化空气产品表面加湿均匀
- even distribution of the binder is the result from spraying and axial mixing blade
由于喷液和轴向搅拌桨叶综合作用使粘合剂分布均匀
- proven in our fluid bed
经我们的流化床验证
- feeding by different pumps
不同泵进料

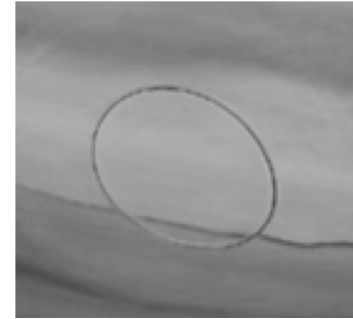
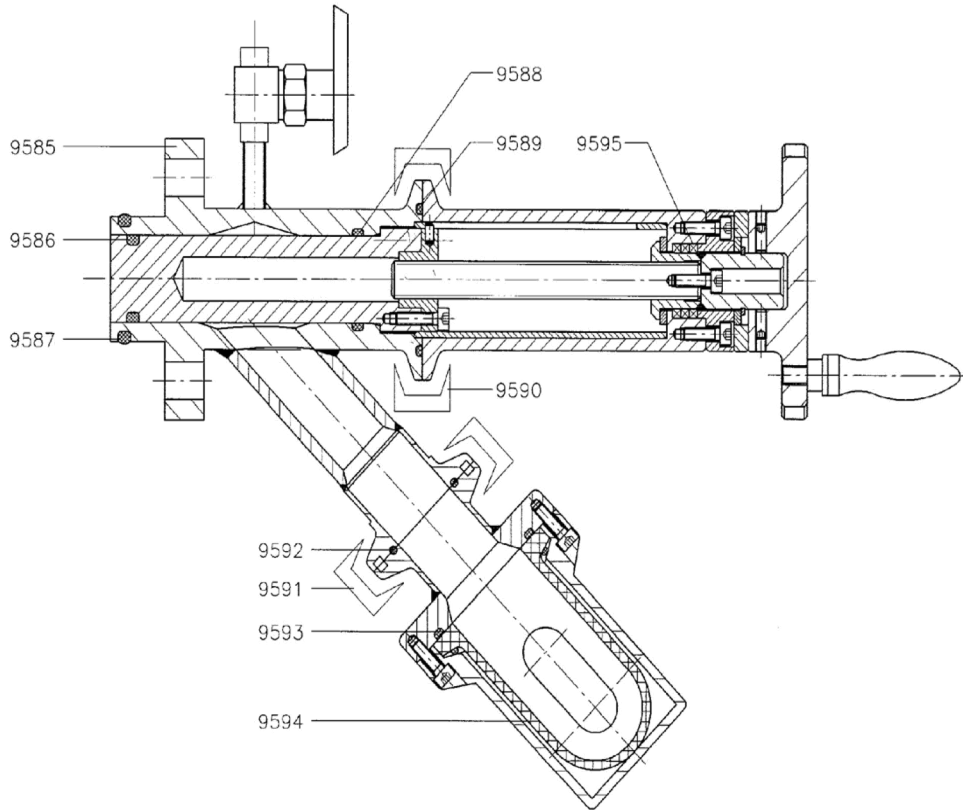


Dust Filter 除尘过滤器

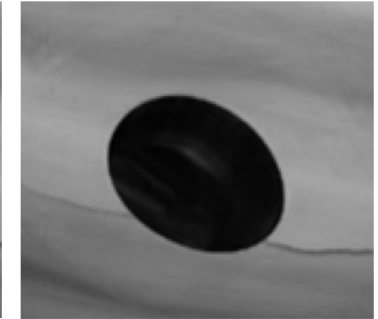


Easy removable filter with integrated WIP nozzle for easy and safe cleaning of filter housing
过滤器拆卸简易，结合WIP管嘴，便于简易且安全的过滤室清洗

Basic design sampler 抽样装置



Closed
闭合的

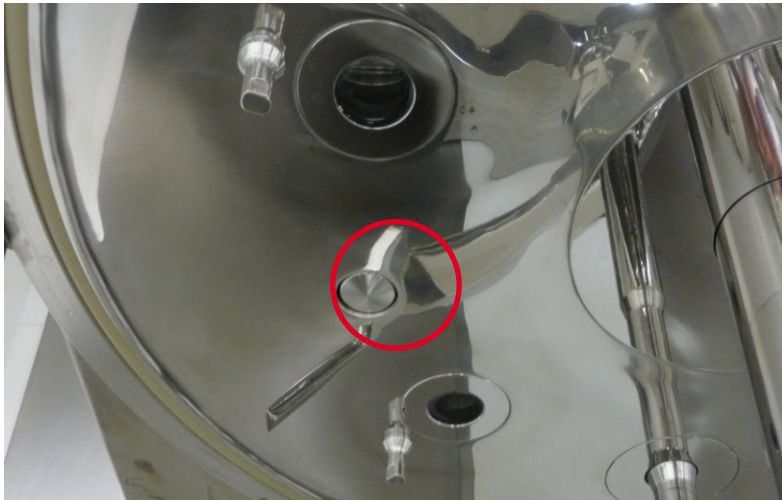


Opened
打开的

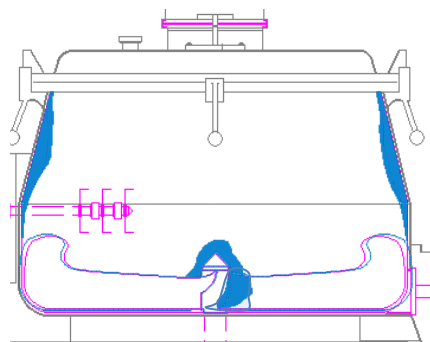


Easy sampling – e.g. to control humidity or quality
简便抽样-控制湿度或质量

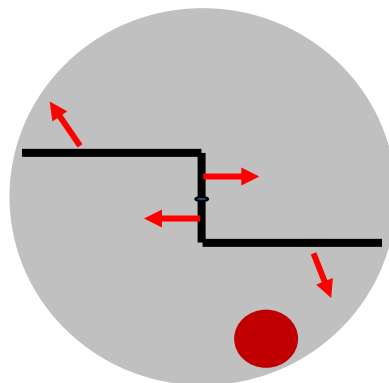
Cleaning - WIP Nozzles HxG
清洁-WIP管嘴 HxG



Heat Transfer 热量转移



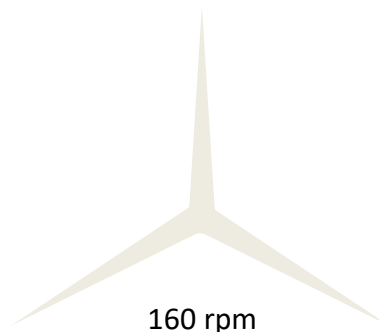
5 Hz



Mixing Granulation
混合制粒



69 rpm



Drying
干燥



160 rpm

进料出料和物料输送

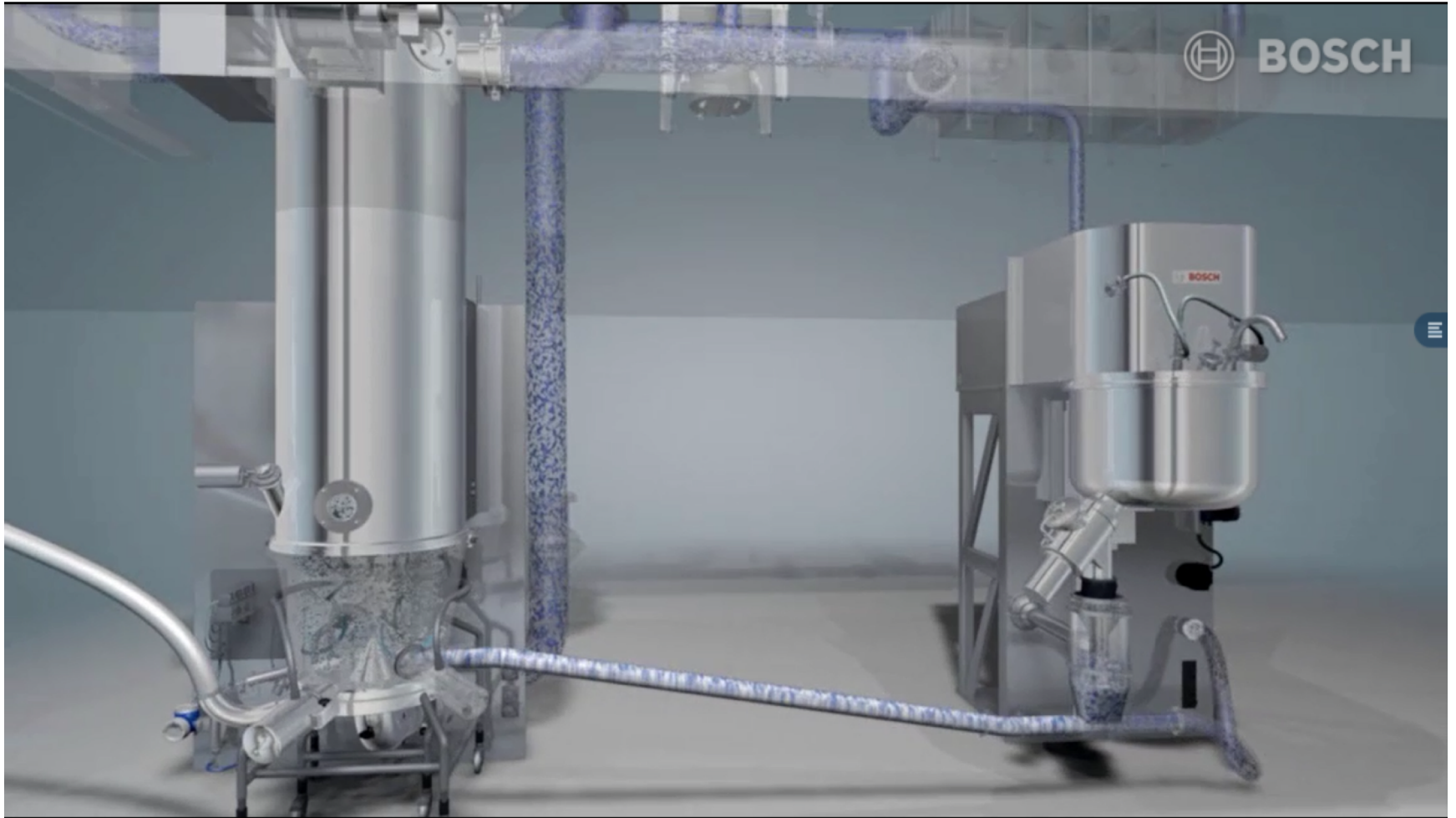


干整粒

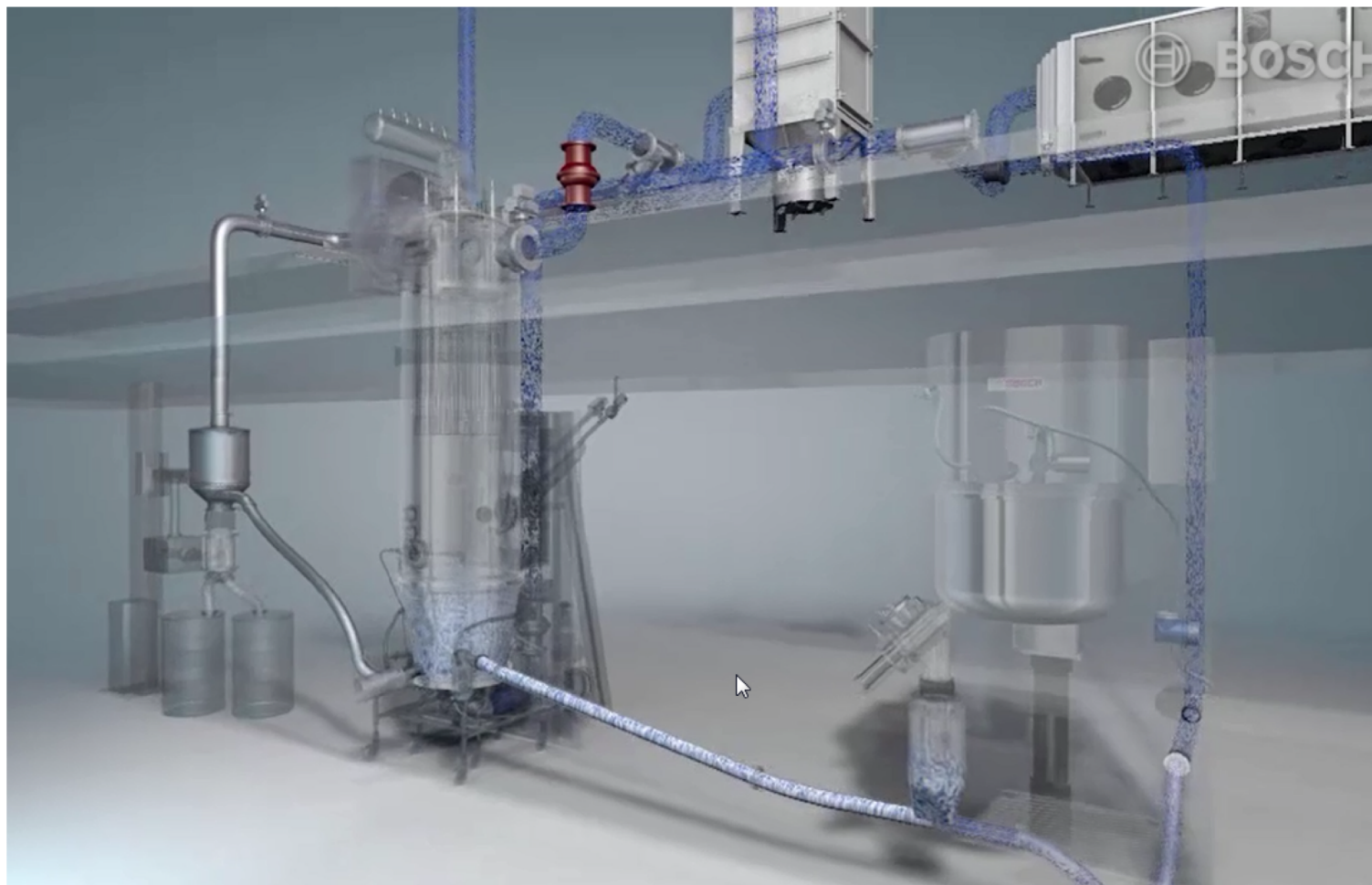
流化床干燥和制粒

湿法制粒

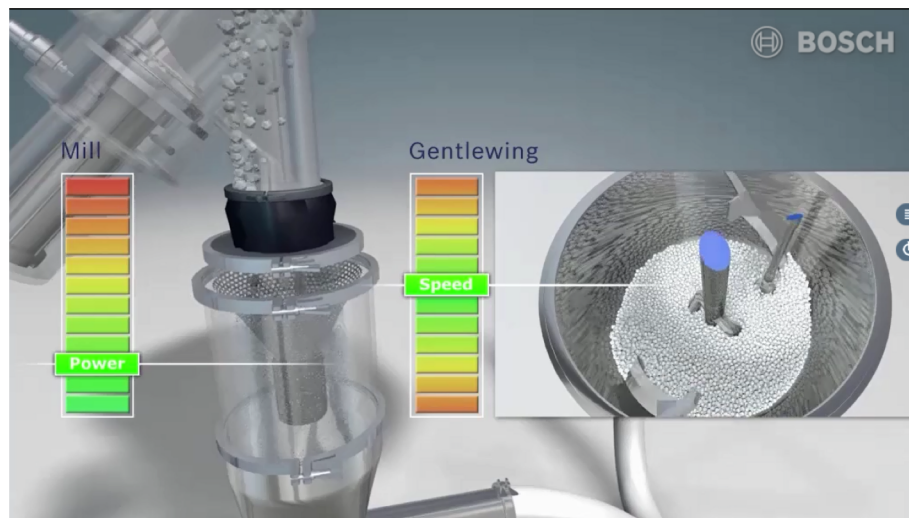
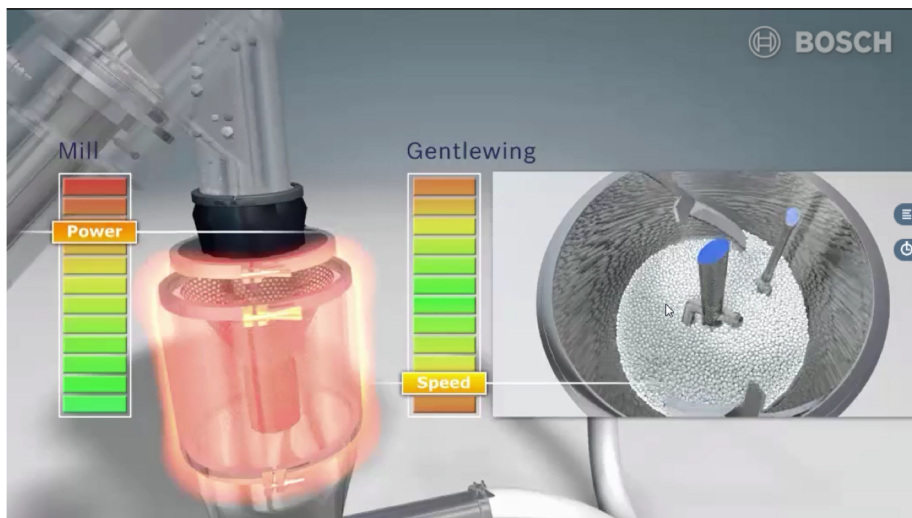
湿法制粒出料和输送



防湿颗粒输送管线堵塞措施



防止湿整粒机出料堵塞措施



Top Drive or Bottom Drive? 顶部或底部驱动

- Top drive and bottom drive technology with identical processing properties

顶部和底部驱动技术具有相同工艺特征

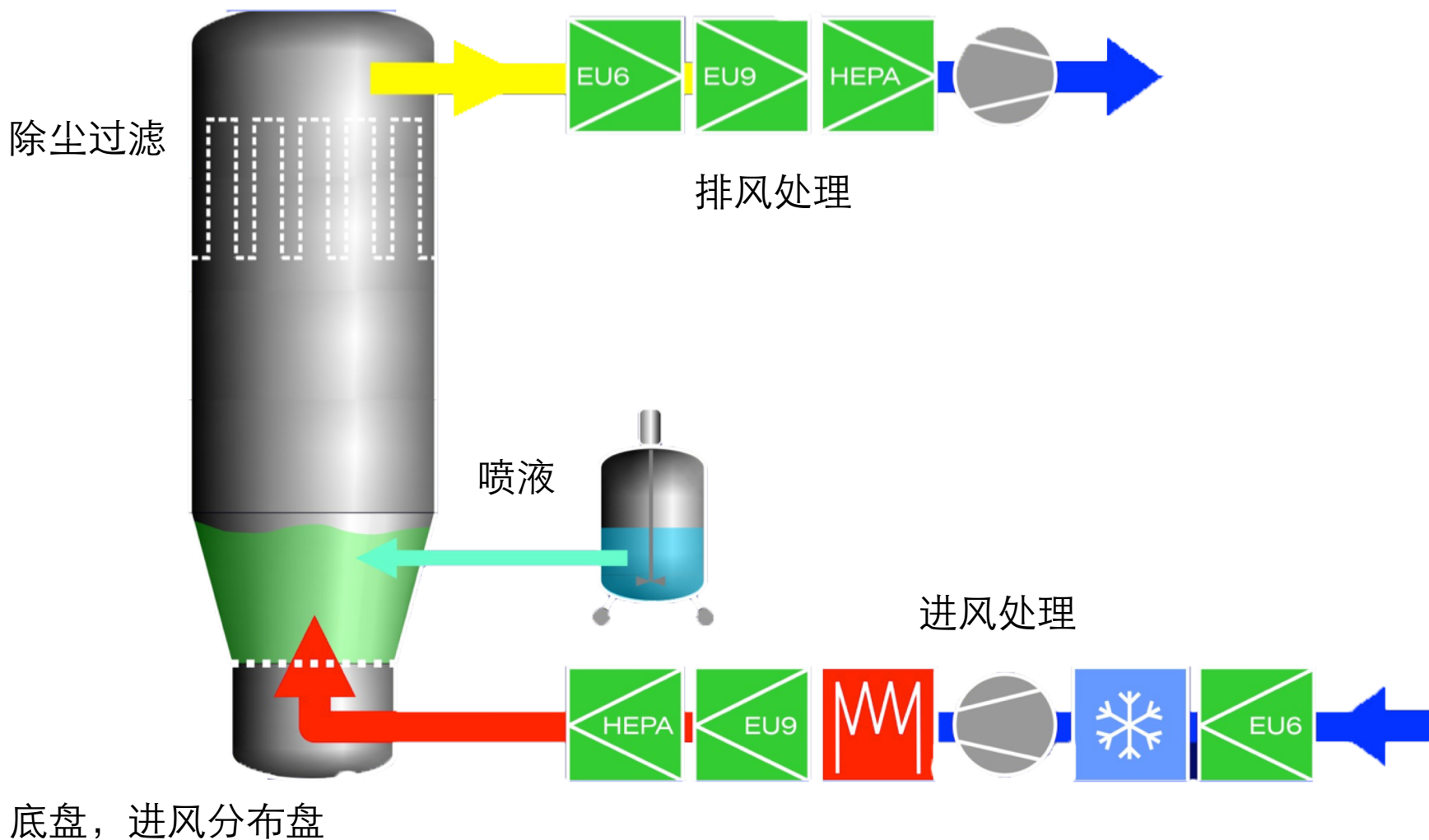


Hüttlin - top drive technology
Hüttlin - 顶部驱动技术

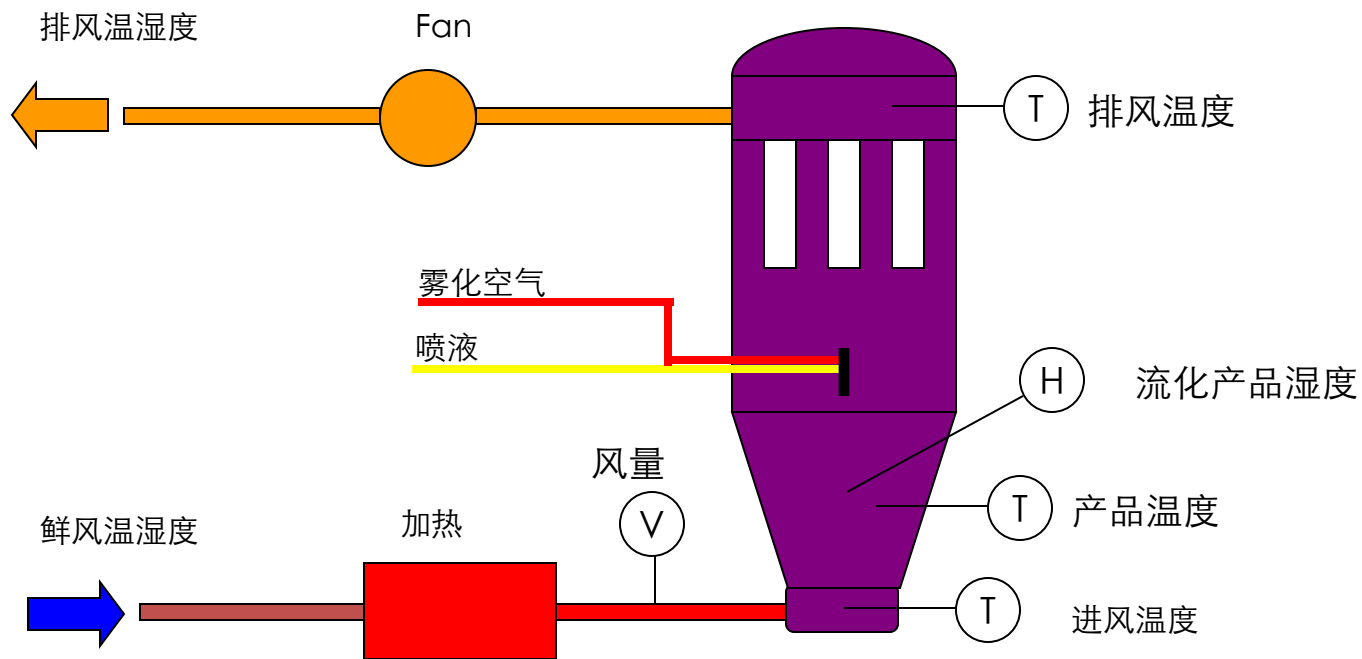


Hüttlin - bottom drive technology
Hüttlin - 底部驱动技术

流化床基本构造

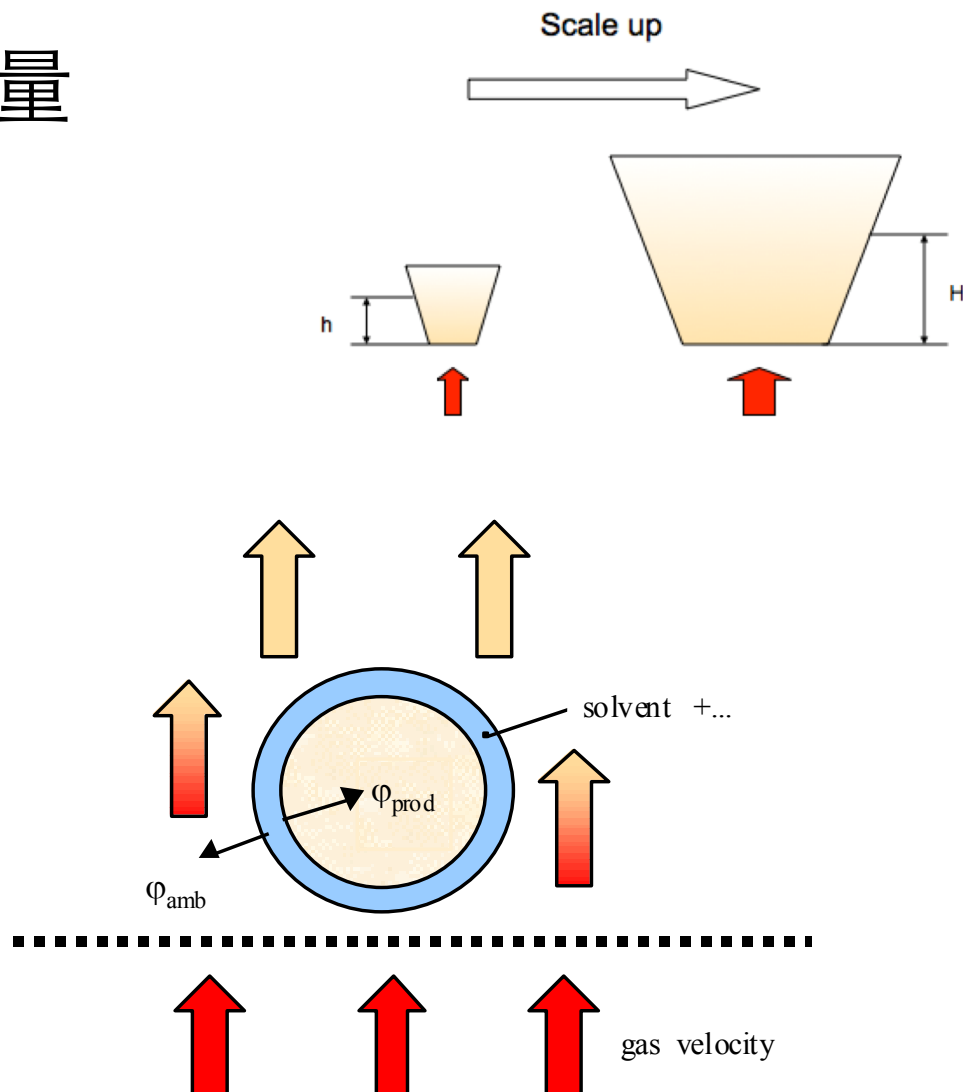


流化床关键工艺参数



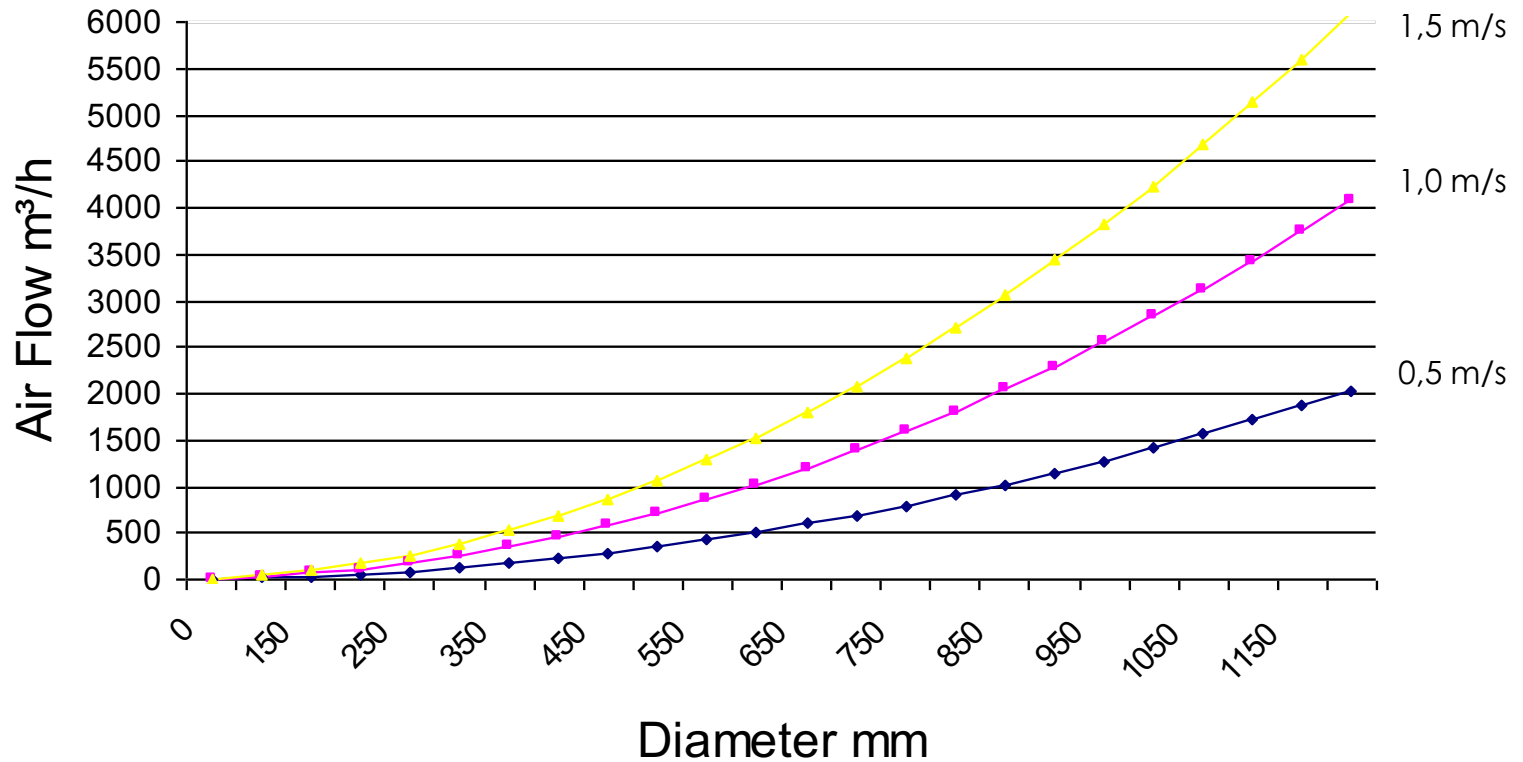
流化床系统关键工艺参数

- 产品流化所需风量
- 进风温度
- 进风湿度
- 产品温度
- 喷液速率
- 雾化空气压力

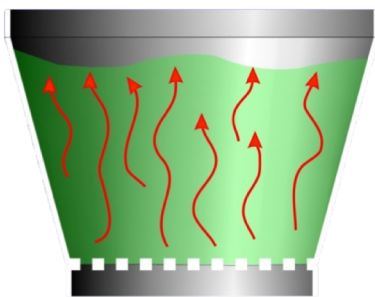


底盘直径 - 风量 - 风速之间的关系

Air Flow at different velocities

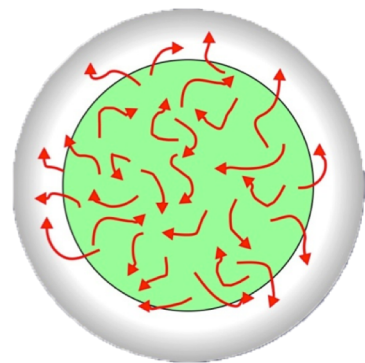


底盘 - 进风分布盘对工艺过程的影响



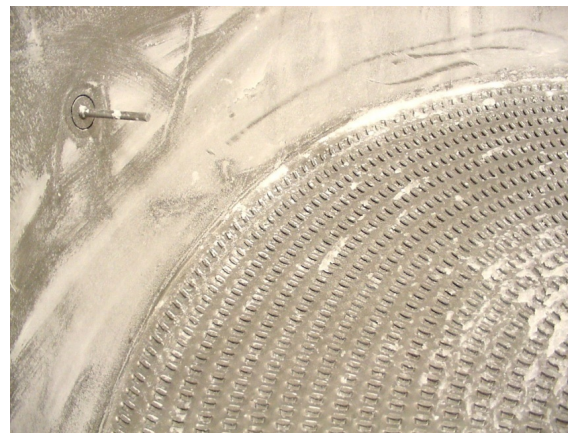
丝网或鱼鳞式底盘：

- 垂直进风；
- 物料运动不受控；
- 产品流化随机不均匀；

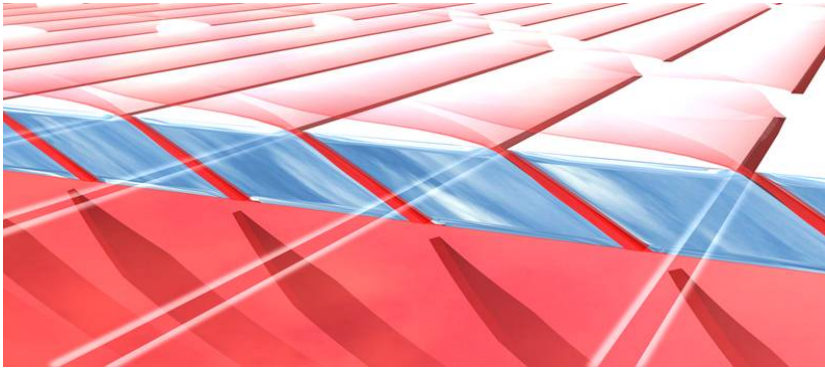


造成：

- 混合效果较差，甚至分层；
- 颗粒粒径不均匀；
- 产品含水量不均匀；
- 细粉含量过多；
- 容易结块；
- 出料复杂，不便；
- 不易清洗和清洗验证。



德国Bosch专利Diskjet底盘 – 进风分布盘



Diskjet构造:

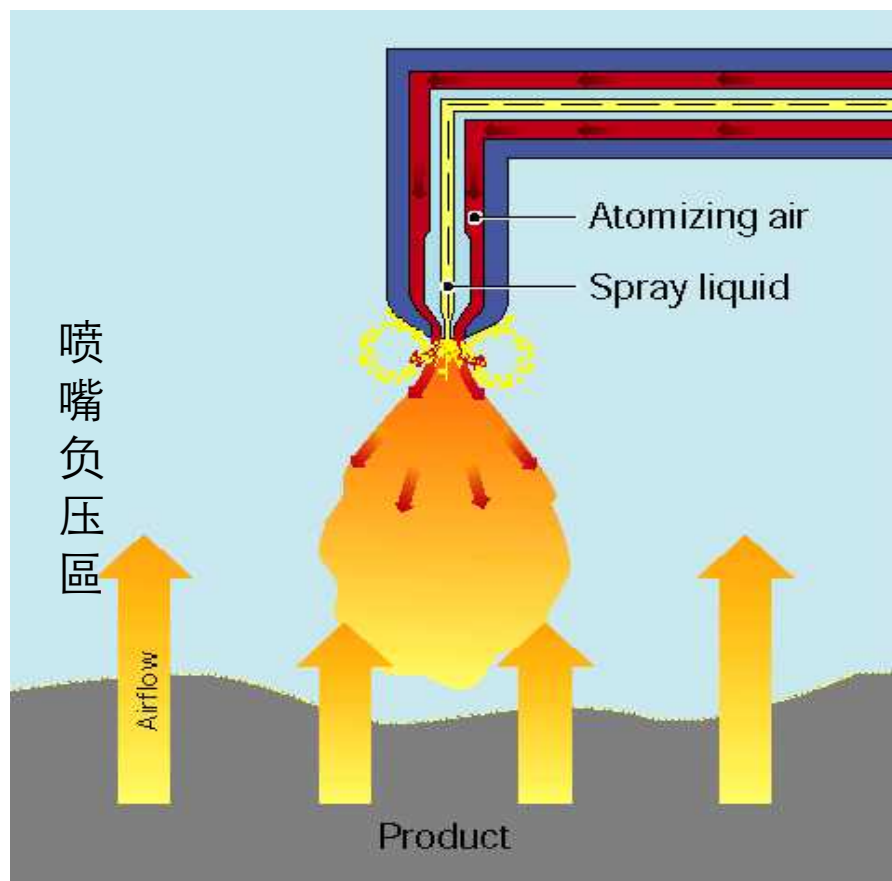
- 激光打孔锥形斜槽，宽度仅为0.15毫米；
- 45度固定角度进风，非垂直；
- 无焊点；
- 物料运动受控，非随机；
- 产品流化均匀，所有物料无静止；
- 表面光滑整洁。



结果:

- 混合效果极佳；
- 颗粒均匀，水分含量均匀；
- 流化制粒，可无需整粒；
- 不易结块；
- 干燥快；
- 出料容易简单；
- 极易清洗和验证；
- 可粉末和微丸包衣。

喷液系统对工艺过程的影响



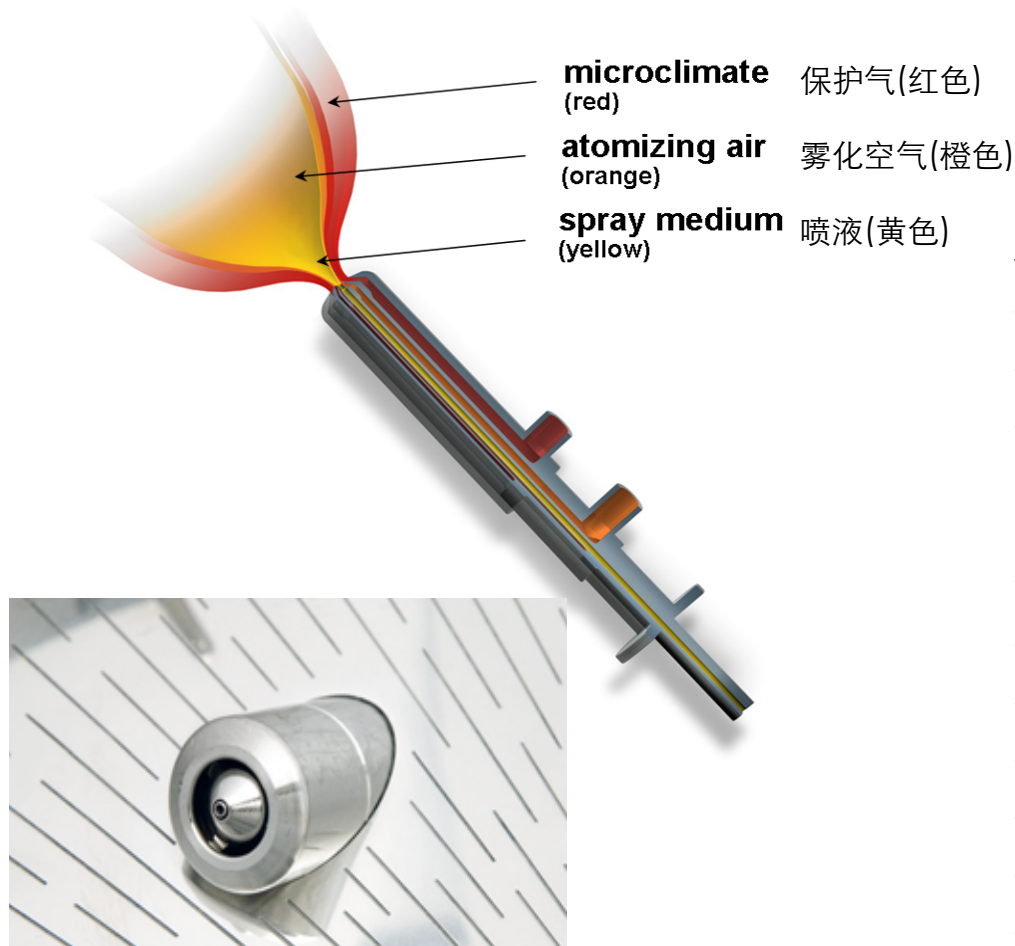
常见的2元喷头：

- 顶喷制粒，喷雾干燥现象；
- 喷嘴周围易积聚物料；
- 多为单喷头；
- 生产过程如喷头堵塞，需停机处理。

造成：

- 因喷雾干燥，较大喷液损失；
- 喷嘴因积聚物，影响雾化效果；
- 制粒不均匀，必须整粒；
- 喷液速率低，过程时间长；
- 不便中途清理喷头；
- 工艺放大困难；
- 顶喷不能包衣。

德国Bosch专利3元喷枪



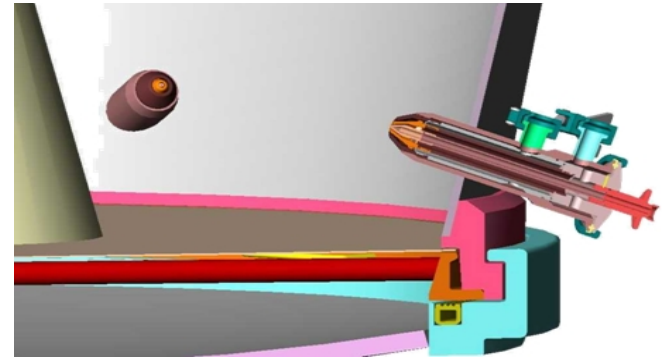
3元喷枪：

- 配备多只喷枪，置于底盘或侧壁；
- 保护气作用，避免喷嘴堵塞；
- 不停机拆换清理喷嘴；

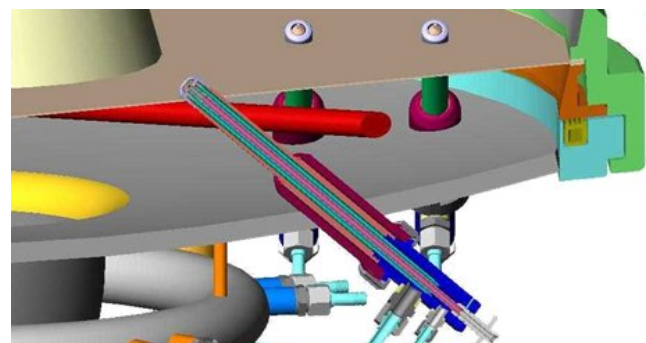
结果：

- 极低的喷液损失；
- 颗粒均匀，无需整粒；
- 喷液速率高，过程时间短；
- 清理喷头便捷方便；
- 底置喷头可制粒和包衣；
- 精确工艺放大计算。

Tangential spray | HDG 侧置切向喷液 | HDG

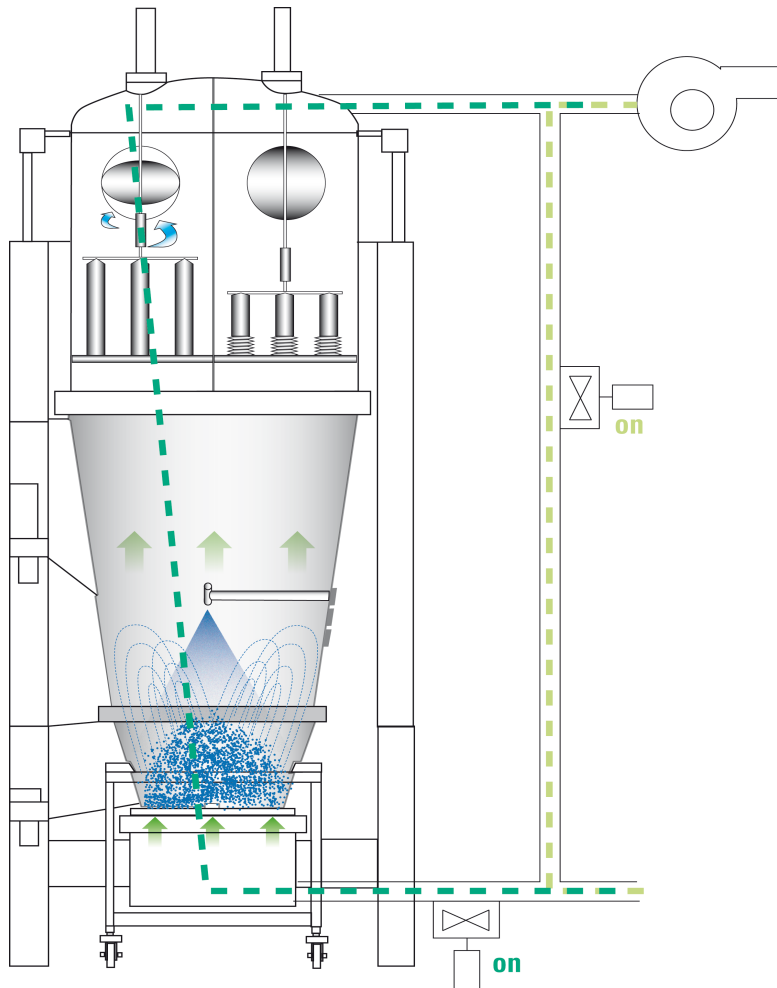


Bottom spray | HDGC 底置喷液 | HDGC



除尘系统对工艺过程的影响

单或双气动抖动除尘



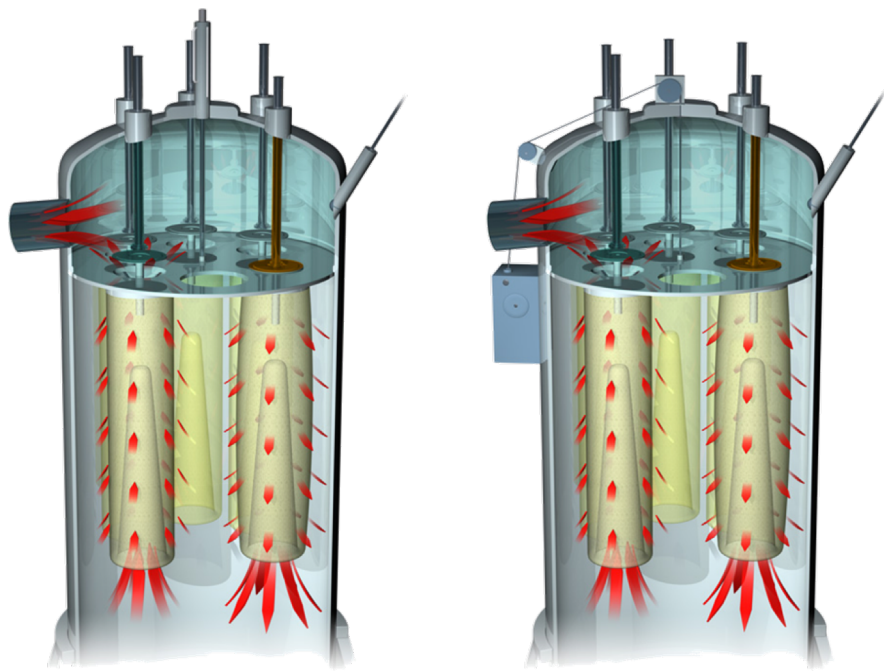
传统单或双气动抖动除尘：

- 单气动抖动在除尘时必须暂停流化态；
- 双气动抖动，轮流除尘；
- 机体较高大；
- 过滤袋为一整体。

造成：

- 干燥周期拉长，效率低；
- 粘附物不易脱离过滤器表面；
- 过滤器易堵塞；
- 如过滤器出现破漏，需整个更换；
- 运作成本较高；
- 程序完毕时大量细粉回落；
- 设备清洁困难。

德国Bosch动态反吹除尘过滤



Bosch动态反吹除尘过滤：

- 多个独立过滤器；
- 连续轮流反吹；
- 逆向反吹；
- 抗静电滤袋或不锈钢材质；
- 自动升降；

结果：

- 有效为过滤器表面除尘；
- 缩短干燥时间；
- 保持过滤器表面干燥；
- 如个别过滤器破漏，只需单一更换；
- 运作成本低；
- 干燥完毕后，附着细粉很少；
- 易清洗。

Standard filter 标准过滤器



抗静电过滤器

Metal filter 金属过滤器



适合CIP在位清洗和致敏性产品

从小试到大生产 – 我们关注一致性



Solidlab 1 (ex Mycrolab)

Unilab

Pilotlab

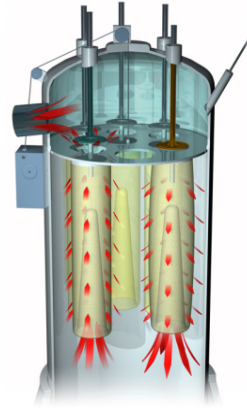
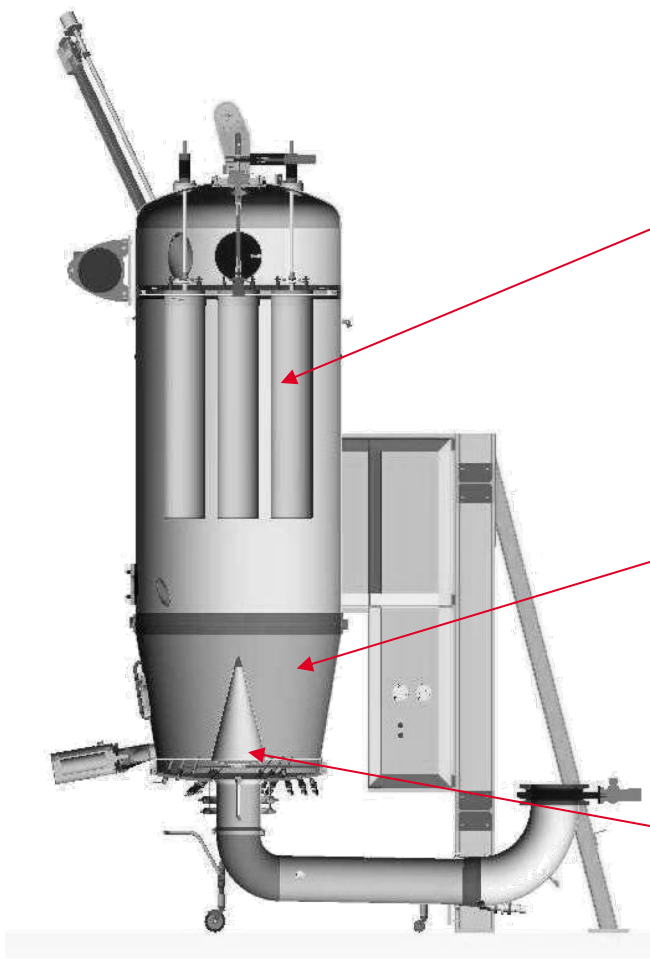
HD

HDG

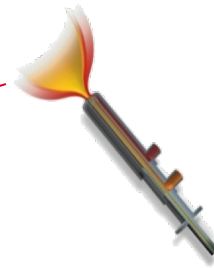
HDGC

HD / HDG / HDGC UltraClean

实现目标的可靠手段



Bag filters - are sequential cleaned for a continuous process
过滤袋连续轮流除尘
No disruption to the fluidized bed
流化床无间断



- Bottom | tangential spray 底置 | 侧置 喷液
- No spray losses 无喷液损失
- Higher spray rates 喷液速度更快
- Better product quality 产品质量更高



- Diskjet 碟片进风
- No wet spots 无潮湿污点
 - Quicker uniform drying 快速均匀干燥
 - Side charging / discharging 侧边进料 / 卸料

Sizes and Capacities 尺寸和容量



		Type 型号	Total volume [l] 总量	Drying 干燥 * [kg]	Granulatin 制粒 g* [kg]	Coating * 包衣 * [kg]
HD HDG HDGC	on trolley	100	256	130	100	80
		200	527	260	210	170
		300	749	375	300	240
		400	937	470	375	300
	slewable	600	1315	660	530	420
		800	1880	900	750	600
		1200	3266	1600	1300	1050
		2000	5029	2500	2000	1600

* minimum load 25%

* at bulk density of 0.5 kg/l
** at bulk density of 0.8 kg/l

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