True End-to-End Solutions
From Molecules to Finale Dosage Forms

Interphex Exhibitor Awards 2023

BoMa Paper

Liquid filling of sensitive products with a low to no shear process using Boyle's Law

About Dec Group

Established for over 35 years, the Dec Group are industry leading experts from raw material handling to the final packing process, constantly pushing the boundaries of what can be achieved. Working towards safer more contained environments with a focus on hygiene and sterility, the Dec Group preserve products by taking complex issues and providing productive solutions.

Experience with Dosing

From the development of the first iconic Powder Transfer System (PTS) in the 1980s, dosing has always been at the heart of the group's technology development. Ranging from tons to milligrams and dense powders to viscous liquids, the Dec Group have created solutions to handle any combination of dosing challenges.

Dosing Introduction

Dosing becomes extremely important when it comes to manufacturing drug products as if the drug product mix is not to the desired doses, then potentially lethal consequences can be seen.

Different Forms of Dosing

High to low volume

- High volume dosing when manufacturing commercial drug products or generics, have processes that cater for most expedient transfer of materials to enable maximum throughput – accuracy and handling methods are not usually prioritized.
- Low volume dosing of developmental or NCE products lay on the other end of the product handling spectrum requiring a higher level of care in material handling and a finer degree of accuracy in the delivery of products.

Powder and liquid

- Often different product types require different processes of transfer and dosing. Considerations around the properties of powders and liquids must be understood and a solution assigned to each.
- Powders are commonly dosed using a Dosator or some form of Auger system.
- Liquids are conventionally dosed with a Peristaltic pump or Rotary piston pump, both established and widely used technologies.

Dosing Accuracy

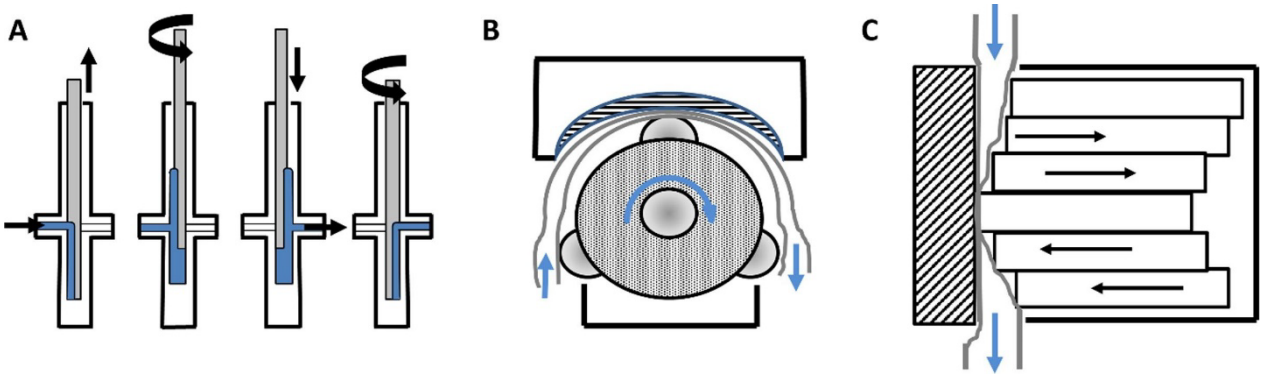
Ranges of dosing

- There is usually a correlation between quantity of product being handled and accuracy required when dosing. The higher the volume handled, the lower the accuracy required. The lower the volume handled the higher the accuracy required when dosing product.
- Methods of dosing product measuring accuracy differ with the changing requirements. Often a balance and manual handling is sufficient to provide results with a given range. However, when it comes to measuring a finer range the use of mechanical aids often replaces manual processes and the common balance is exchanged for alternate methods.

Product sensitivity

- As we see an increase in novel products and processes (ATMPs, C&GT, etc.) within the development space, the understanding of sensitive handling and accurate product make up is becoming more prevalent across the industry.
- Purity considerations for APIs and excipients are amplified, and methods of ensuring this purity are studied and validated to ensure they meet current industry needs.

Available Industry Standards



A - Rotary Piston Pump

A main chamber with a precise piston at its center. By rotating this piston, product is allowed to flow into the central chamber, occupying a fixed volume before continuing the pistons rotation to close off the inlet and simultaneously opening a pathway for the product to leave the chamber.

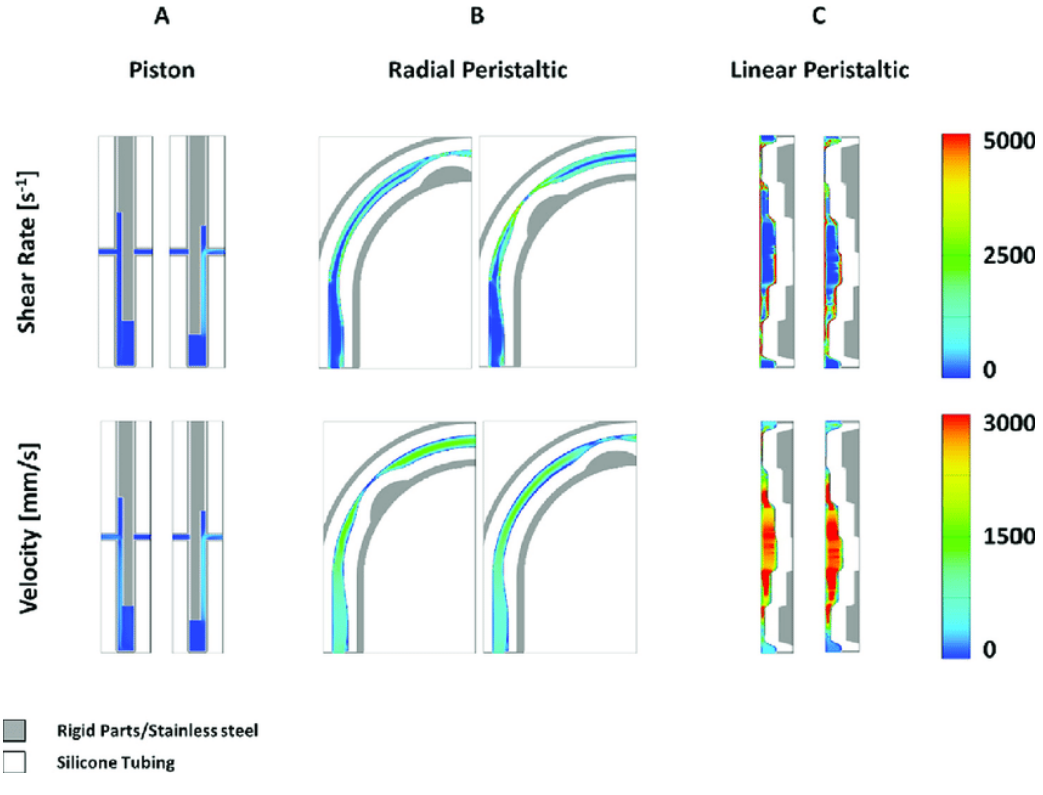
B - Radial Peristaltic Pump

Flexible tubing is placed through a radial disc with notches or rollers placed at specific intervals around its circumference. As the disc rotates it forces the product through the flexible tubing separating the required dose delivering it to its destination.

C - Linear Peristaltic Pump

Taking into consideration similar principals as the radial peristaltic, the linear version uses the same form of product separation but by using a series of actuators that move uniformly to again separate the required dose and allow it to travel onwards to the filling point.

Research published in the European Journal of Pharmaceutics and Biopharmaceutics shows that these dosing methods can cause stress and shear on the product moving through these devices. Tubing detachment, denaturation and aggregation have been observed in some cases when handling sensitive protein formulations.



Issues with Shear when Dosing Sensitive Products

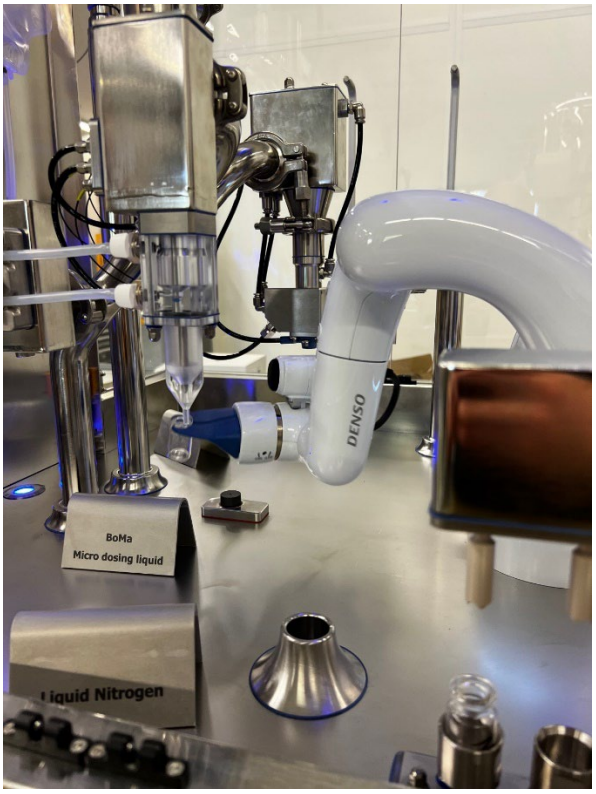
Particulate generation

- All materials shed particles regardless of the material's non-shedding properties, during friction, a small amount of particles is generated. These quantities often have an insignificant impact on a process and are within specified tolerances. However, as products become more sensitive and stability becomes a primary factor in manufacturing, any (even small) particle generation is considered a risk factor in the manufacture of the final dosage form.

Product property changes

- Breakdown or stretching of the drug substance or protein-based formulation can be caused by increased stress and shear during the dosing process. This can cause critical and unwanted change late in the drug manufacturing process.
- A correlation between protein damage and shear/stress in dosing processes has been observed and documented during research studies.

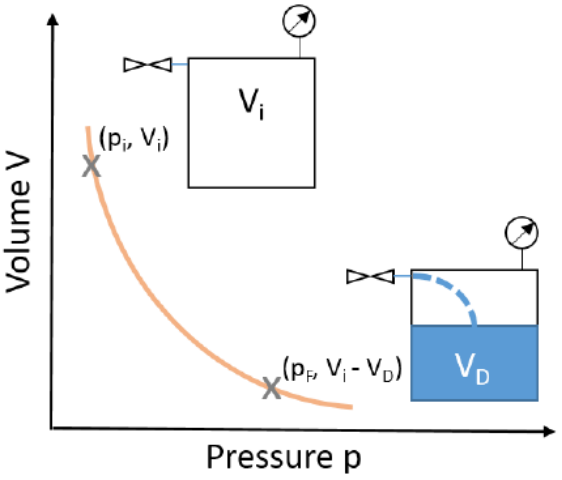
BoMa Dosing System

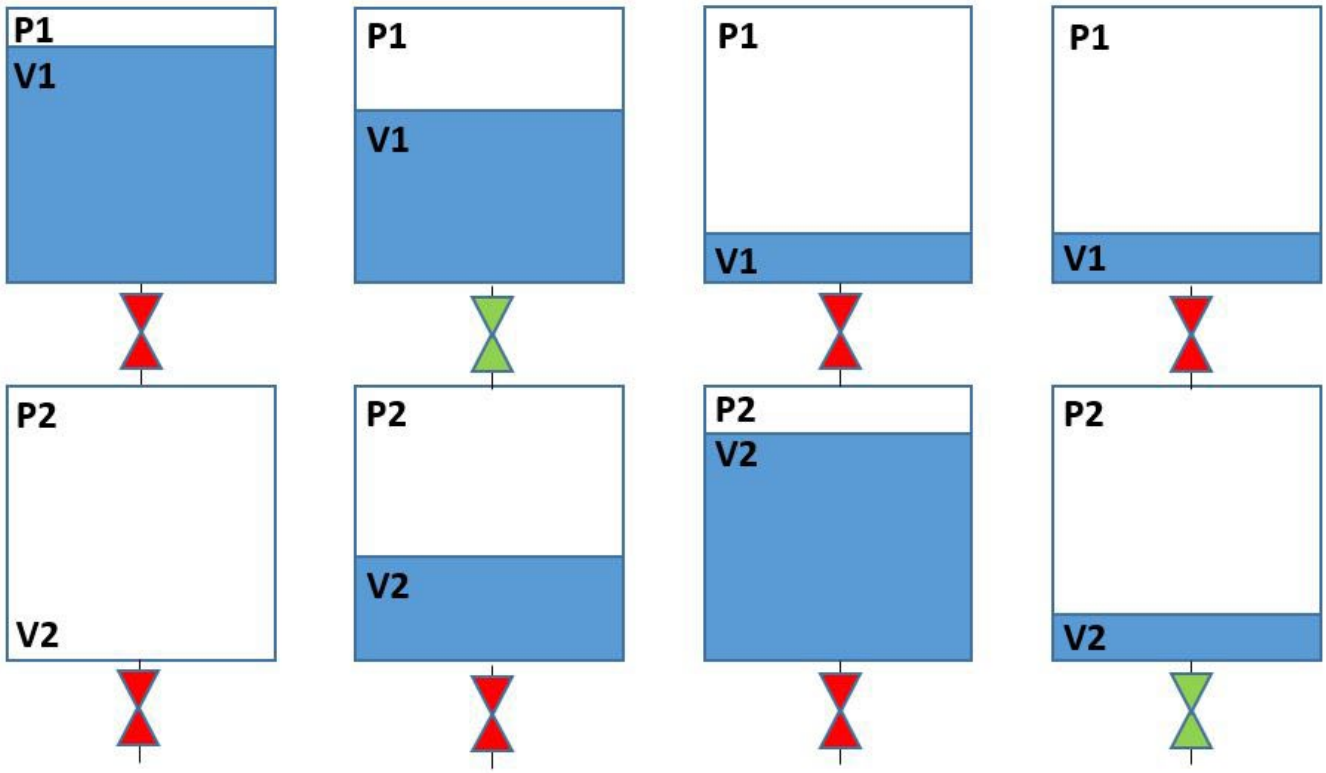


$$P_1 V_1 = P_2 V_2 .$$

Boyle's Law

The absolute pressure exerted by a given mass of an ideal gas is inversely proportional to the volume it occupies if the temperature and amount of gas remain unchanged within a closed system.





Establishment of internal vacuum(Pi) in dosing chamber	Opening of the inlet valve of the dosing chamber	Closing of the inlet valve when the final pressure (Pf) is reached	Opening the outlet valve of the dosing chamber and pressurizing the dosing chamber

How Boyle's Law is an Effective Way to Safely Dose Sensitive Products

Using the BoMa dosing system provides the below benefits when it comes to dosing a range of sensitive products in multiple quantities and in any form.

Liquid or powder

- Boyle's law acts in the same way with powder and liquid as long as the temperature remains consistent
- Transferring product via vacuum allows for a wide range of product densities or viscosity
- Founded on existing principals of dense phase transfer which have been established and demonstrated for decades

Low to no shear

- Fluid product movement with no tube manipulations – limiting the impact on the product flow
- No stress exerted during dense phase transfer, just simple linear motion
- Product structure is maintained

Complete solution developed on a single platform using proven principals

- Product mixing into a single dosing chamber as long as Boyle's Law is upheld
- Primary drug container de-gassing via the same fill point
- Product recirculation
- More and more drugs are suspensions or behave like suspensions meaning that over time the constituents of the liquid move. Some traditional dosing systems have methods of recirculation however there is often a dead leg forcing the user to reject first dispenses. The use of Boyle's Law has no dead legs in the system resulting in the first dispense to be within specification, which is highly advantageous when handling small development batches.
- Using the same recirculation principle, the unit can undergo easy SIP and CIP processes

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