

Accurate dispensing of biopharmaceuticals

Recent changes in the pharmaceutical industry have made pumps that can accurately dispense small batches a necessity. In the past, piston pumps were often the machine of choice, but recent advances in peristaltic pump technology have changed the range of choices. Peter Lambert and Flemming Joergensen, Flexicon, explain how peristaltic pumps can be used in this demanding market.

The pharmaceutical industry has had to adapt to major changes and challenges over the last decade. The vast number of expiring patents on blockbuster drugs has mainly driven this, forcing the industry to focus more on research and development, particularly with biopharmaceutical products. This trend has highlighted the need for efficient small batch aseptic liquid processing and fill/finish. In addition, the ever-increasing FDA demands, especially regarding cleaning validation, have forced the industry to look for more efficient and safer production technologies.

The traditional filling technologies are piston pumps and time/pressure filling systems, but the new requirements and challenges of the industry have changed the focus to peristaltic filling technology.

Peristaltic pumps are extremely convenient to use. They are often the preferred choice for fluid transfers in all types of environments, from the laboratory to the heavy chemical

industry. On the other hand, piston pumps are also very popular and have proven themselves over the years, but in some applications, the design has several drawbacks. A piston pump has many mechanical parts such as valves and seals that are in direct contact with the product. These parts, which will wear out, need to be taken apart, cleaned and re-assembled between each use. Even the high-end, valve-less piston pumps come in contact with the product and require extreme care to avoid damage.

With peristaltic pumps, the product is only in contact with a piece of tubing that can easily be cleaned or disposed of. This feature makes it an attractive alternative to piston pumps for dispensing biopharmaceuticals/injectable drugs.

Peristaltics save money

For the last few years, the pharmaceutical industry has been searching for ways to reduce the costs of developing and producing new drugs. The concept of disposable or single-use factory is becoming a reality.

Recent peristaltic pump design innovations have been specifically developed for dispensing of injectable drugs. The innovations already contribute to the overall effort to reduce the cost of bringing new drugs to market, and it may change the way they are mass-produced. Most of the existing drugs used today are chemically based, and the promising new drugs being developed are in liquid form, known as biopharmaceutical drugs.

Pulsation-free peristaltic

The key development for making peristaltic pumps accurate occurred twenty-one years ago when Flexicon A/S of Denmark created the "pulsation free" peristaltic pump. Once the pulses were removed, the potential for high accuracy dispensing was possible. Today, and five generations of improvements later, peristaltic dispensing pump accuracy rivals piston pumps down to the micro fill volumes.

Two key design features enable peristaltic pumps to be accurate for dispensing:

- the use of multiple rollers
- the removal of the typical peristaltic flow pulses with offset rollers.

The optimal configuration for a pump head design is to have two sets of six rollers. Each set of rollers is offset with respect to one another. As the product is drawn by two tubes through the pump head, they merge into a single tube via a y-connector. Thereafter, the pulses add up to cancel each other. The resulting pulsation-free flow can then be controlled using precise positioning motor and special software, which enables accurate dispensing.

The peristaltic system – the tubing

There is a huge selection of tubing available made from many materials and in various sizes, many of them made specifically for peristaltic pump use. Nonetheless, to allow for consistent accurate dispensing down to the micro litres, it is imperative that both the

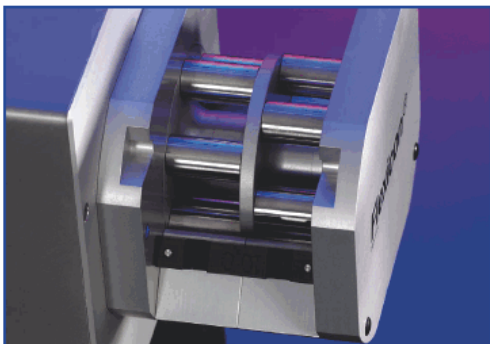


Figure 1. Peristaltic pumps are now a serious alternative to piston pumps for dispensing biopharmaceutical drugs.

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tubing and the pump head be designed from the beginning to work together, and they both must have close dimensional tolerances. Furthermore, the mechanical characteristics of the tubing are critical; after all, the tubing is the pump.

Three key characteristics of good peristaltic tubes are:

- uniform wall thickness
- consistent material hardness
- high mechanical 'memory' after compression.

Finally, and in consideration of dispensing injectables, the silicone tubing must be of the highest quality to meet the FDA's good manufacturing practices requirements (cGMP).

Features and benefits

When compared to other dispensing technologies such as piston pumps, peristaltic pumps offer the following benefits:

- one pump can fill a wide range of fill volumes
- a single peristaltic pump can fill volumes between 0.1 ml to 250 ml, simply by changing the tubing size. More than one piston would be required to meet this fill range.
- fast set-up and calibration
- it can take less than five minutes to load the tubing, purge the system, make one calibration and begin filling.
- no cleaning required/no risk of cross-contamination.

When treated as disposable, peristaltic pumps do not require cleaning. Each batch is produced with a new fluid path or set of contact parts. When filling injectable drugs on a traditional piston filling line, it is the norm to buy dedicated pistons for each product to prevent cross-contamination between batches. Those pistons require cleaning, sterilizing and maintenance.

Cleaning validation

Cleaning validation is a cGMP requirement to demonstrate and document that the equipment used for

processing an injectable drug is clean and free from contaminants.

For a multiple-use filling system such as piston pumps, cleaning validation typically requires two qualified resources up to four months to write up the protocols and execute them. For each subsequent production batch, the cleaning in accordance with the validated procedures has to be maintained and properly documented throughout the pump's commercial life. In addition to these labour costs, you have to add the costs associated with the use of water for injection (WFI), for sterilization using pure steam and, finally, for the cost of detergents.

Flow control

It is very easy to adjust the flow speed via the peristaltic pump interface. This enables adjusting the flow to prevent foaming or splashing of the product. It is also possible to adjust how fast the fill speed is reached using the ramp-up and ramp-down features. This is helpful in optimizing the overall fill time to get more throughput from the filling machine.

Shear sensitive products

The valve system of the piston pump generates high-speed flow through small orifices, and this can potentially damage the product. Even the valve-less piston pumps generate higher pressures, higher shear factors and have a 'dead volume' in

each stroke. Peristaltic pumps are valve-less and only apply a small amount of pressure to move the product.

Matching standards

The typical industry standard for accuracy is $\pm 0.5\%$ of the fill volume. Peristaltic dispensing pumps meet this requirement for fill volumes as small as 0.5 ml while below that fill volume, accuracy can be as good as $\pm 1\%$.

When peristaltic pumps are integrated into high speed filling machines, an automated closed-loop control system of weight-check weight assures that the fill volumes stays within tight tolerances.

Fill time

Typical piston pumps need to cycle through a recovery or suction phase between each dispensing strokes. There is no such downtime with peristaltic pumps, which will dispense immediately upon demand.

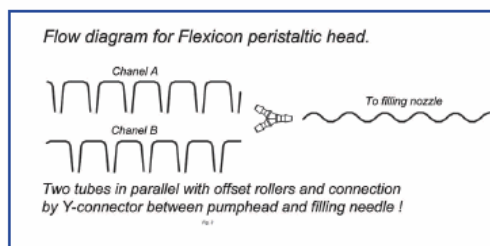


Figure 2. Flow diagram showing how the y-connector in the peristaltic pump evens out flow.

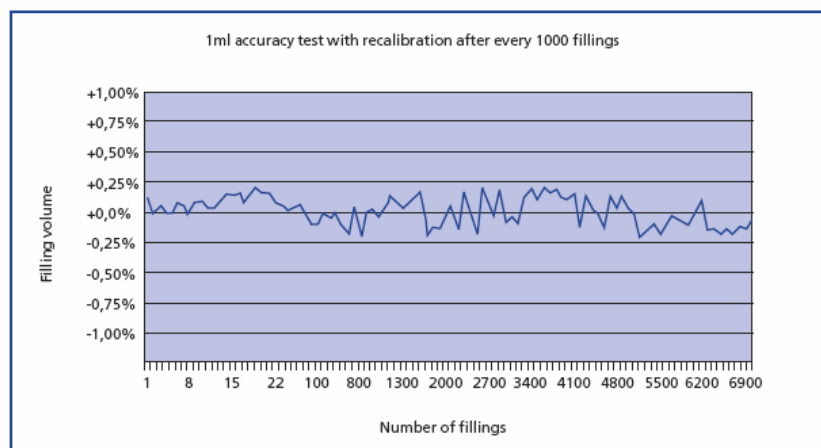


Figure 3. Accuracy for a 1 ml fill using peristaltic pumps.

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| PD12 - Peristaltic Dispenser | Fill volume [ml] | Tube size [mm] | Filling time [sec] |
|---|------------------|----------------|--------------------|
|  | 0,5 | 0,8 | 0,526 |
| | 1 | 1,2 | 0,550 |
| | 2 | 1,6 | 0,526 |
| | 10 | 3,2 | 0,857 |
| | 17 | 4,8 | 0,800 |
| | 30 | 6,0 | 0,909 |
| | 50 | 8,0 | 1,053 |
| | 100 | 8,0 | 1,463 |

Figure 4. Filling time relative to tube size.

The high-end peristaltic dispensing pumps are designed to run at high RPM to minimize fill time. They also have a control system that provides immediate response from a filling machine input signal. Therefore, using a peristaltic dispensing pump instead of a piston pump will not slow down a process.

It is now commonplace to have high-speed filling lines with peristaltic pumps that fill at rates over 400 bottles per minute.

Viscosity limitations

Peristaltic pumps have limited capabilities to dispense viscous products. In general, a product with olive oil viscosity can be dispensed using peristaltic pumps. Slightly higher viscosity products will also work, but with potential loss in accuracy and flow rate.

Piston pumps can generate significantly more pressure to dispense products that are more viscous, while even a high-end peristaltic

dispensing pump cannot. In fact, one of the underlying principles used to achieve accurate dispensing down to the micro fill volumes is to apply very little pressure on the tubing. Those pumps are calibrated to provide approximately 1.3 bar of pressure only.

The future

In recent years, single-use technology has been an efficient method for the biotech companies to develop and bring new drugs to market. Single-use process components such as small reactors, filters, mixers and fluid handling bags have been available for the last few years. The use of peristaltic pumps and single-use tubing is also very common because it allows for simple fluid transfers with no cleaning and no risk of cross contamination.

New drugs and, in particular, biopharmaceutical drugs, are often designed for a specific population and are therefore more likely to be made in relatively small batches when compared to 'chemical' drugs. As the new drugs evolve to have a more specific spectrum of application, the batch sizes will be smaller and the need for efficient product changeovers on the filling lines will be greater.

Many articles have been written about single-use technology and the use of the utility and process equipment for the upstream part of the process. Benefits of single-use include reduced labour, equipment and energy costs, increased plant flexibility, and faster turnaround with significantly less risk of contamination. There is now a requirement for the fill/finish area, or more specifically, the dispensing of the liquid drug into vials and pre-filled syringes to be single-use as well.

Single-use fluid path

The single-use industry has been providing single-use silicone tubing and fittings for peristaltic dispensing with the exception of providing a single-use filling nozzle. In an effort to offer a complete solution to single-use aseptic filling, Flexicon A/S developed a plastic nozzle for single-use.

It is now possible to purchase ready-to-use tubing set assemblies. These include the required pharmaceutical grade silicone tubing, connectors and plastic filling nozzles. The assembly is double bagged and gamma irradiated and comes with a complete validation package.

Various configurations are available that may include a sterile filter, aseptic quick-connect or a product bag. In most cases, tubing and connectors are used to bring the product directly from the product holding tank to the filling nozzle for dispensing on the filling machine, making the entire process single-use. The pharmaceutical industry is implementing single-use technology in both the R&D laboratory and large-scale production of injectable drugs.

Peristaltic pumps have benefited from major technological improvements that have made them very accurate and reliable. Today, they are a serious alternative to piston pumps for dispensing biopharmaceutical drugs, especially in consideration single-use bioprocessing. ■

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Figure 5. The Flexicon DAFFA pump.

