Why Degas Liquid Drug Products and Biologics at Filling Lines?

Oxygen, carbon dioxide, and other gases dissolved or in micro-bubbles in liquid drug products and biologics can adversely affect many downstream processes, especially after filling lines where these liquids are packaged in vials, syringes, and bags for further inspections or freezing. The following examples illustrate the challenges encountered when filling and packaging non-degassed liquid drug products and therapeutics in containers.

Liquid Drug Products

When filling a pharmaceutical liquid drug products into vials, gas bubbles may be created or exposed, which can be falsely detected as an impurity or a foreign particulate matter by automated optical inspection systems, resulting in high false-rejection rate (rejection of acceptable vials or containers). The presence of particles in a liquid drug product must usually be prevented in order to reduce potential risks to patients of such products. Therefore, vials filled with drug products are usually routinely visually inspected for the presence of particles using fully automated or semi-automated systems such as optical systems. Generally, these systems are often unable to distinguish between a particle and a bubble. Thus, the presence of bubbles in the drug products may lead to an erroneous rejection of containers since the bubbles may easily be mistaken for particles. Thus degassing and de-bubbling the pharmaceutical liquid drug product solution prior to the filling step can eliminate the bubbles which can provoke a false rejection, thereby reducing losses due to discarding drug product or time necessary for further inspection.

Existing drug product filling machines may include a degassing step of the bulk drug product which relies on the application of a vacuum to the bulk drug product in a chamber. After the degassing step the bulk solution is usually transferred to a filling device with the aid of gaseous nitrogen which generally causes a renewed exposure and input of gases such as nitrogen itself. This gas content in liquid drug products, however, may lead to a low accuracy of the filling weight of the liquid drug products contained in a container such as a syringe or a vial. Moreover, this approach is time-consuming as it constitutes a separate, non-continuous step that takes place in addition to the filling process. Additionally, stationary degassing of the bulk solution does usually not completely remove dissolved gases present in the solution. Thus a better solution is needed, which can continuously degas the drug product, in-line with the filling process.

Biotherapeutics

Dissolved gases and bubbles in biologics and therapeutics prior to freezing can significantly impact the protein drug product quality attributes, including formation of visible particles, subvisible particles, soluble aggregates, and changes in target protein concentration due to adsorption of the molecule to various interfaces. During freezing, the dissolved gas in the liquid is rejected (separated) and accumulated ahead of the ice-water interface during solidification, and the resulting bubbles are incorporated into the growing ice crystal. The formation of ice crystals can contribute to cryoconcentration which also affects reaction rates. Although reduction in temperature lowers the rate

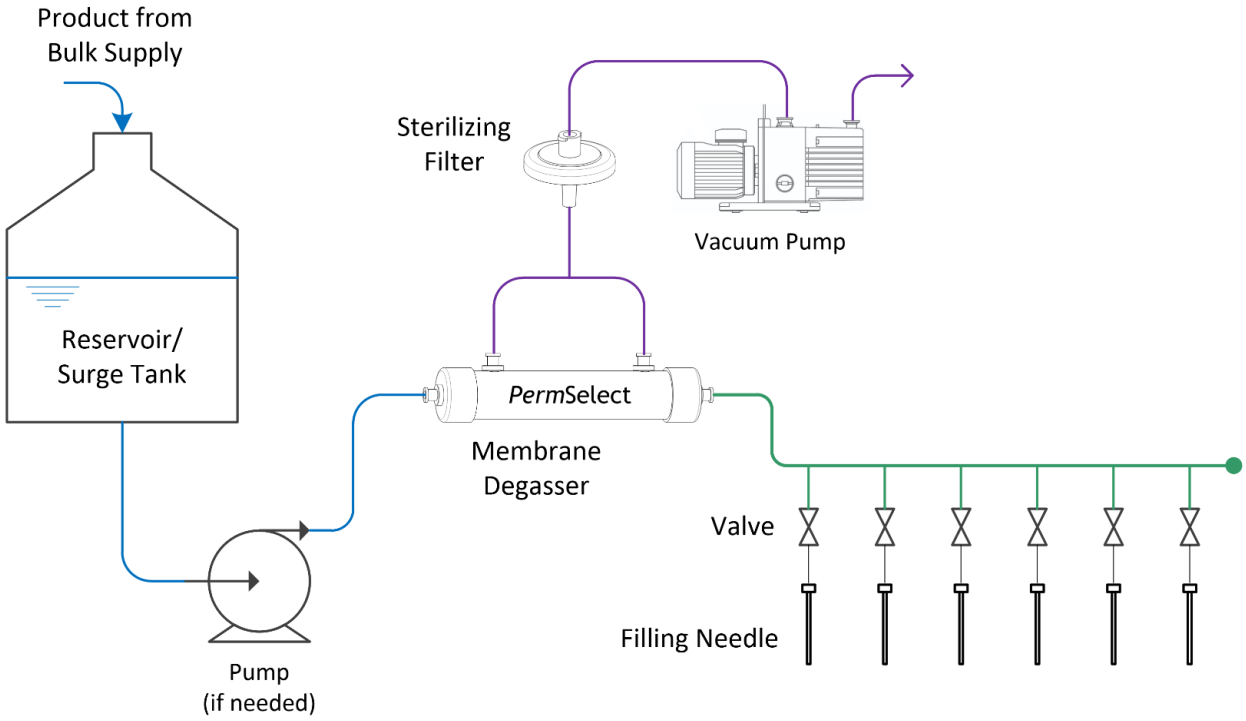
of degradation reactions (the Arrhenius effect), cryoconcentration can counteract that through an increase in the concentration of reactants, specifically oxygen. So reactions such as oxidation can be enhanced, especially when the solubility of oxygen increases as temperature drops while ice formation also excludes gases. Dissolved oxygen at high concentration can be trapped as bubbles along with proteins in the final glassy matrix.

Thus, degassing biologics prior to bagging can reduce or eliminate these problems, plus enable a "crystal clear" frozen liquid without bubbles and possibly fractures.

Continuous Inline Degassing with PermSelect Silicone Membrane Degassers

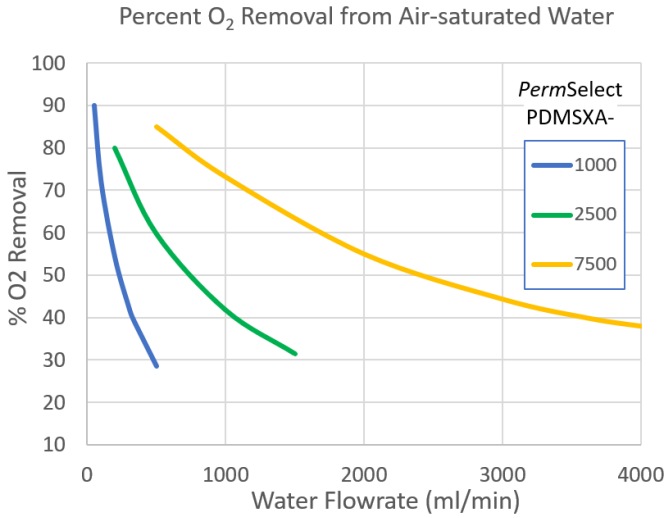
PermSelect silicone membrane degassers are very effective for continuous, inline degassing of liquids including drug products and biotherapeutics. Unlike direct vacuum degassing and ultrasonic degassing of liquids, which are batch degassing approaches, membrane degassing using PermSelect membrane degassers can be accomplished in a continuous mode, inline with other processes such as filtering, dispensing and filling. Moreover our membrane degassers can be implemented as disposable (single use) or reusable in durable settings.

PermSelect silicone membrane degassers can be implemented in line with the filling process as shown below. The PermSelect membrane degasser is placed upstream from the filling needles, and as the drug product flows through the degasser it is continuously degassed with vacuum pulling out dissolved gases and microbubbles across the membrane. A vacuum pump or other vacuum source is used to produce the vacuum supplied to the degasser with a sterilizing filter placed in between the vacuum pump and degasser. A vacuum of 50 to 100 Torr is usually sufficient to properly degas the drug product if the membrane is properly sized.



*Perm*Select

The membrane degasser is selected based on the flow rate at which the drug product is being delivered for filling; the higher the flowrate, the larger the membrane degasser needed to properly degas the drug product. The adjacent graph presents the level of degassing provided by each PermSelect silicone membrane degasser as a function of the flowrate through the degasser. Note that for each degasser the level of O2 removal is higher at lower flow rate. This is because at lower flow rate there is more time for the gases to be pulled out (degassing) as the drug product flows through the degasser.



PermSelect PDMSXA-	Maximum Flowrate for 50% O2 Removal (ml/min)
100	20
1000	250
2500	750
7500	2,500
1.0	3,200
2.1	8,000

The adjacent table provides the recommended flow ranges for each degasser to provide a minimum of 50% O2 removal. So flowing at any lower flowrate will result in improved degassing. It should be noted that there is no minimum flowrate for each degasser and the flow may completely stop and go with no effects on the membrane.

For example, if 1ml vials are filled at a rate of 500 vials per minute, the average flowrate is 500 ml/min which would require a PDMSXA-2500 (from table) to degas with 60% O2 removal (from graph). Higher O2 removal would require a larger degasser, such as the PDMSXA-7500 which would degas to 85% O2 removal at 500 ml/min (from graph).

PermSelect silicone membrane degassers are comprised of thousands of silicone hollow fibers with a diameter of 0.3 mm and a wall thickness of 0.05 mm. The thin wall of the hollow fibers acts as the gas permeable membrane with the liquid drug product flowing on one side of the membrane and vacuum applied to the other. The gas pressure differential enables the transfer of gases across the membrane thus pulling dissolved gasses and microbubbles from the liquid drug product into the vacuum.

PermSelect membrane degassers are made from in FDA compliant materials, including USP Class VI, ISO 10993-5, and FDA CFR 21 compliant materials with low extractables. Prior to shipping, each membrane degasser is individually tested following a rigorous protocol.

Our membrane modules can be sterilized by steam autoclave (including SIP), gamma radiation, EtO and other harsh chemicals.

Contact us at https://www.permselect.com/contact-us or at +1 734 769-1066 to discuss your degassing application.