White Paper: Solvent Considerations in Solid-Dose Manufacturing

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Solvent Considerations in Solid-Dose Manufacturing

Solid-dose tablet and capsule manufacturing is a mainstay of the pharmaceutical industry, as it results in a consistent, effective, and economical platform for drug delivery. Not only are tablets and capsules convenient and easy for consumers to handle, they are also very stable and have a high throughput, offering benefits to both consumers and pharmaceutical companies alike. Technological advances, combined with increasingly potent active pharmaceutical ingredients (APIs), have resulted in the availability of complex delivery systems such as controlled- and extended-release tablets and capsules that enhance therapeutic efficacy while minimizing adverse events.[1] Although the number of novel APIs available for development has decreased, the complexity of solid-dose formulations has dramatically increased. Moreover, as complex, brand-name medications reach the end of their product lifecycle, generic equivalents will need to be produced that meet the same technology-enhanced high quality standards. This paradigm necessitates a greater flexibility on behalf of the manufacturer in order to meet the production requirements of a wide range of drug formulations while maintaining efficient and cost-effective manufacturing processes.

For many pharmaceutical companies, both large and small, this has meant moving away from all-inclusive, in-house operations and partnering with Contract Development and Manufacturing Organizations (CDMOs) to meet these new development and manufacturing challenges. The approach to pharmaceutical production itself has also shifted in certain areas, including the mindset around solvent-based technologies. Organic solvents were once commonplace in pharmaceutical manufacturing; from the synthesis of active pharmaceutical ingredients to the formulation of drug products.[2] Concerns surrounding workplace and environmental safety resulted in a move to water-based processing for wet granulation and coating during the formulation of relatively simple API-containing solid-dosage forms. However, in light of the aforementioned advances in solid-dose technology, the pendulum is once again swinging. Certain product characteristics, as well as practical production considerations, may preclude the use of water and necessitate the introduction of organic solvents to facilitate development and manufacturing. For example, the production of moisture-sensitive products can require solvent-based systems. In addition, the application of a polymer-based coating for modified-release tablets or pellets could take up to 4 to 5 times longer using an aqueous-based compared with a solvent-based platform, as more energy is required to evaporate water than organic solvents. Furthermore, the deterioration of moisture-sensitive drugs during granulation or coating processes could be increased with aqueous systems.

While these examples serve to demonstrate the practical need for solvent processing in pharmaceutical production, they do not negate the safety concerns that need to be addressed. Residual solvents have no therapeutic benefit and may pose hazardous to human health and the environment. Moreover, the presence of even small amounts of these chemicals may influence the efficacy, safety, and stability of the pharmaceutical products. Although there has been a shift away from the use of the highly toxic solvents, rigorous quality assurance processes and regulatory requirements remain integral in the manufacturing of pharmaceutical agents to ensure quality, consistency, and minimal environmental impact.

If you are looking to outsource your solvent-based solid-dose manufacturing, important considerations should be addressed when researching potential CDMOs to ensure that they can safely and efficiently meet all related needs. Although these considerations are not intended to replace the quality assurance standards that you have in place, they provide a guide to increase the confidence you have in your manufacturing partner.

It goes without saying that your CDMO of choice should have a documented history of solvent-based technology that results in consistent pharmaceutical products manufactured in a safe, certified environment.

Solvent-based capabilities

- ✓ Solvent capabilities in both granulation/coating solutions used in production
- ✓ Solvent-based production processes include:
    - o Wet/high-shear granulation
    - o Fluid bed processing, including granulation, particle coating, and Wurster coating
    - o Tablet coating in side-vented pans (eg, used for osmotic delivery systems)

A low-risk solvent-based manufacturing approach starts with the specialized equipment used and the environment in which production is performed. A good rule of thumb is that anything that comes into contact with solvent vapor needs to have solvent-capable (XP) properties.

Equipment installation in a dedicated production space

- ✓ Proper installations should be engineered to meet all established requirements to minimize risks to all stakeholders (eg, the worker population, the customer) and the environment

- ✓ Equipment should be installed in a room designed to meet stringent Class 1 Division 1 standards for optimal risk mitigation; surrounding areas should also meet these standards
- ✓ All controls need to be sealed and/or flushed with air

Dedicated, solvent-capable equipment

- ✓ Solvents should be run only in XP equipment. This includes pumps, mills, and ancillary equipment in the immediate surrounding area
- ✓ Appropriate preventive maintenance should be performed on all solid-dose equipment to ensure that it operates at designed levels
- ✓ Continued engineering support ensures that the equipment's utilization can be maximized throughout its lifetime

Effective methods of solvent abatement

- ✓ Effective means must be employed to abate the exhaust air, which is highly solvent laden, to meet all appropriate regulatory standards for the site
- ✓ A thermal oxidizer in order to physically burn the solvents or scrubbers to remove the solvents from the exhaust gases

Quality-based requirements

- ✓ Residual solvent levels must be assured using appropriate testing to meet USP Guidelines[3]
- ✓ Manufacturers should be in regular contact with state and federal authorities to ensure appropriate emission licensure

In conclusion, solvent-based technology represents an important function in the manufacturing of solid-dose pharmaceutical formulations. CDMOs with a well-engineered and well-executed approach to handling solvents allow for the efficient and safe production of highly effective therapeutic formulations that may otherwise be unavailable to patients in need. When choosing a CDMO, it is important to explore the options available before committing to a partner. Begin by gaining an understanding of their specific capabilities and expertise, and thoroughly review the variables that are important for safe and efficient production processes.

References

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