Benefits of Liquid-Filled Capsules for Pharmaceutical Development

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The choice of format for a drug product in development is critically important, as the formulation and manufacturing decisions directly impact timelines; the ideal being minimal delay between availability of the active pharmaceutical ingredient (API) and clinical dosing. Formulation problems can lead to lengthy and costly development delays, and may even jeopardize your entire program. By the same token, precise and expert formulation development and manufacturing can be a contributing factor in whether a drug safely delivers the anticipated dosage, and successfully completes clinical trials within your desired timelines.

Liquid-filled hard-shell capsules (LFCs) offer a number of advantages over tablet and other solid oral dosage formulations, and can help accelerate drug development programs by providing:

1. Simpler, more rapid process for quick entry to the clinic and, with appropriate preplanning, dosage adjustments on the fly
2. Dose escalations possible without increased demand for API
3. Easier scale-up of manufacturing for late-stage trials and commercialization
4. Improved applications for poorly soluble APIs, low-dose and highly potent APIs (HPAPIs), as well as APIs requiring sustained release and/or highly stable environments
5. Customization options and new marketing opportunities

How Liquid Filling Works

The API is suspended or dissolved inside a heated, jacketed kettle via mixing with excipients, as needed. The excipients are selected based on the properties of the API, to resolve the challenges that render the API inappropriate for tablet formulation. These excipients can help improve bioavailability, ensure equal distribution of the active ingredient throughout the mixture, and keep the drug substance contained during manufacturing and packaging.

The formulation travels through heated hoses, if necessary, to maintain optimal temperature of the formulation, then to liquid-filling equipment, where it is filled into two-piece, hard-shell capsules. The capsules come in a variety of sizes, for different applications, dosages, and API concentrations. After filling, the capsules are sealed to prevent leaking, usually with a colored band. When cooled to room temperature, the liquid mixture solidifies to a wax-like consistency, except in the case of vitamin E oil or other fully liquid products.

The simplicity of the process offers many advantages during the different phases of drug development:

Early-Phase Testing

- Speed of development – fewer excipients, simpler process, rapid delivery to clinical site
- Flexibility of manufacture – small batches can be filled by hand
- Ease of dosage adjustment – option of modifying the amount of API in the mixture, or use a different size capsule for the new dosage

Late-Phase Testing

- Ease of scale-up – small to large batches can be filled via the same efficient process
- Rapid availability for clinical trial site
- Ease of dosage adjustment
- Range of dosage options easily produced for different trial arms

Commercialization

- Ease of scale-up without significant change in equipment or process
- Range of dosage options can be manufactured for commercial use
- Variety of band colors for customized marketing opportunities

Logistical Advantages

Simpler, more rapid process

The development of LFCs is less complex than tableting, as the formulations are not required to bind or eject, which can create a significant issue in tablet manufacture. There are less excipients required to ensure smooth movement through the equipment, and the liquid can be transported in a closed system. With less excipients to consider, cross reactivity or incompatibility of excipients with the API or equipment can be mitigated. “Formulation timelines with liquid-filled capsules are extremely quick compared to powder-filled capsules or tablets,” said Ben Reed, Executive Vice President, CDMO Operations, at Altasciences. “What we have seen is that time savings in the beginning directly relate to time and cost savings in the PK studies, and then in the clinic when we produce the GMP supply.”

Dose escalations and scale-up

Dose escalations are more easily planned using LFCs with appropriate preplanning of analytical methods for the expected range of doses. “Using the initial suspension or solution, we can incrementally increase the dosage by using different capsule sizes, without reformulating at a higher concentration of API. This is important because we can save time, and valuable API, which can be useful when only a small quantity of API is GMP-ready”, Reed noted. It is also easier to scale up LFCs from preclinical to clinical to commercial volumes, with fewer steps in the process. “We work with very small batch sizes, right up to 500-liter kettles,” Reed said.

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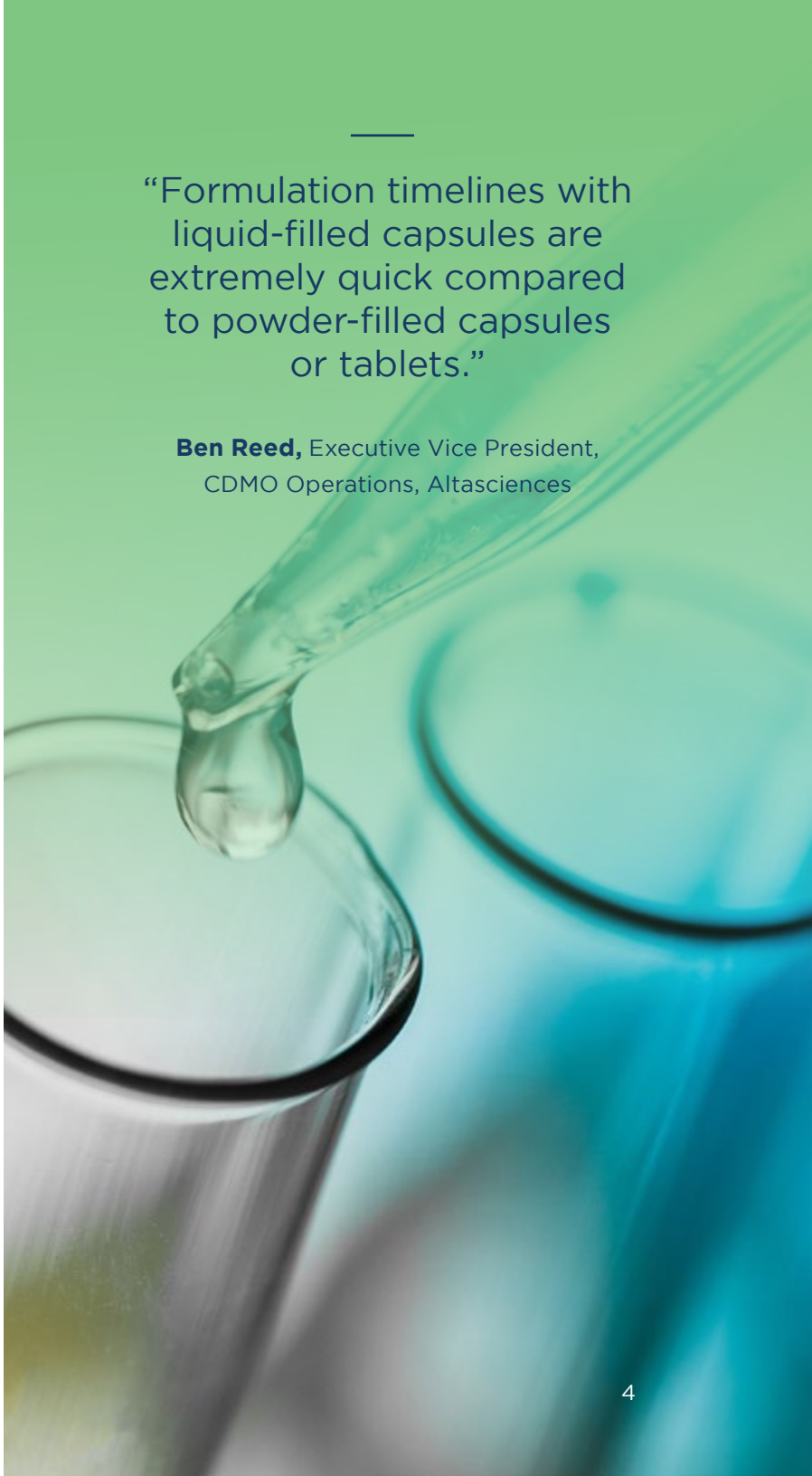
Ben Reed, Executive Vice President, CDMO Operations, Altasciences



"As the final dosage form is not needed until Phase II, we can take advantage of LFCs in the early phases and then consider an alternate dosage form such as tablets, if the client prefers."

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Poorly water-soluble

The bioavailability of poorly water-soluble drugs has been proven to be enhanced by the use of liquid-fill technology[1,2,] while it continues to present an obstacle for tablet formulations. The oral absorption of a drug is directly related to its water solubility and gastrointestinal permeability.

LFCs can provide better therapeutic outcomes by lowering the dose of the product through the use of solubility and bioavailability enhancers. They are also capable of ultra-low dose uniformity (0.25µg/capsule).

In recent decades, updated screening methods and bioavailability enhancements have led to increasing numbers of poorly water-soluble small molecules being considered for development[3], and LFCs are helping deliver on their promise.

Banding Technology

Today, state-of-the art technology and process improvements provide a new level of reliability, with faster and more efficient commercial equipment available for band-sealing of capsules. According to Reed, improvements in band-sealing technology have vastly enhanced the security of LFC shell integrity, and **LFCs have achieved a 97% first-time batch release success rate upon inspection at Altasciences' manufacturing facility.** "As the final dosage form is not needed until Phase II, we can take advantage of LFCs in the early phases and then consider an alternate dosage form such as tablets, if the client prefers."

At Altasciences, band-sealing is the method of choice, as it does not require testing for elemental impurities, and band seals provide tamper evidence for over-the-counter drugs. Additionally, the bands are available in a wide range of colors, offering sponsors product differentiation opportunities.

Improved Applications for Challenging APIs

Low dose/high potency

Compounds in the low dose/high potency category include Schedule I drugs, hormones, and cytotoxic APIs. These products present two main challenges for the manufacture of solid dosage forms, such as tablets:

1. Content uniformity. When working with low dose APIs in solid format, ensuring that each tablet has the same quantity of active ingredient is challenging. By dissolving the active ingredient and creating a solution, improvements in unit dose homogeneity are realized. In a Japanese study, 100% of the capsules investigated met the requirement for content uniformity.[4]

2. Containment of potent drug material during processing. HPAPIs are increasingly numerous in development,[5] with more classes of molecules and new chemical entities being formulated for a broad range of conditions. Liquid-filled capsules provide a safer alternative to powders, in that the HPAPI powder is dissolved in the confines of a closed system, and operators are not exposed to airborne particles during the manufacturing process.[6]

Sustained release and critical stability profile

When formulating LFCs, different solubilizers affect the release properties of the API, allowing better and more consistent options for sustained-release dosing. The excipients used, and polymer composition of the capsule, are customizable to accommodate APIs with different properties and desired dissolution profiles.

The stability of certain APIs can be negatively impacted by environmental conditions during processing, particularly when there is high humidity that may be absorbed by the drug product. The dissolution of the API into a liquid resolves this issue, which is a major impediment to tablet and other solid oral format production.

Customization Options and Marketing Opportunities

The capability to customize is useful for formulating sustained-release drugs, while being an excellent opportunity for filling capsules with two different APIs.[7] Unlike soft gels, hard-shell gelatin capsules offer the possibility of combining APIs, which can be encapsulated in the form of beads, micro tablets, and pellets. In this way, existing medications can be given new life on the market as a combination product. LFCs can also be useful for reformulating existing products for faster onset of action, or better efficacy. Marketing and brand differentiation options become available through these modifications, and through choice of band colors.

Essential capabilities in manufacturing

It is important to choose a CDMO partner with experience in both formulation, manufacturing, and analysis, with the skilled staff and state-of-the-art equipment to handle even the most difficult challenges. As Reed explains, “a deep understanding of the technology and the science, coupled with skilled, experienced operators, are major benefits.”

Having this expertise has helped Altasciences to diagnose issues and avoid roadblocks that can arise with specific small molecule drugs. For instance, in one case, a hydrophobic API was not well suited for the capsule banding material, and an alternative band was developed. In another case, a client had a product that had failed manufacture at numerous CDMOs. The team at Altasciences analyzed the problem and determined that the suspension material was too viscous for capsule-filling using conventional equipment. They engineered custom parts, creating a specialized filling nozzle to efficiently deliver the suspension into the capsule and delivering a reliable product to the client.

Altasciences has the expertise to quickly determine if a particular API is appropriate for LFC formulation, and they can effectively alleviate any issues that may arise during the development and manufacturing process. As an integrated CRO/CDMO, clients can benefit from the company's end-to-end solutions and method transfers spanning formulation, preclinical to early phase clinical trials (including bioanalysis), all the way through to commercialization. **This integrated approach saves clients up to 40% in overall drug development timeline.**

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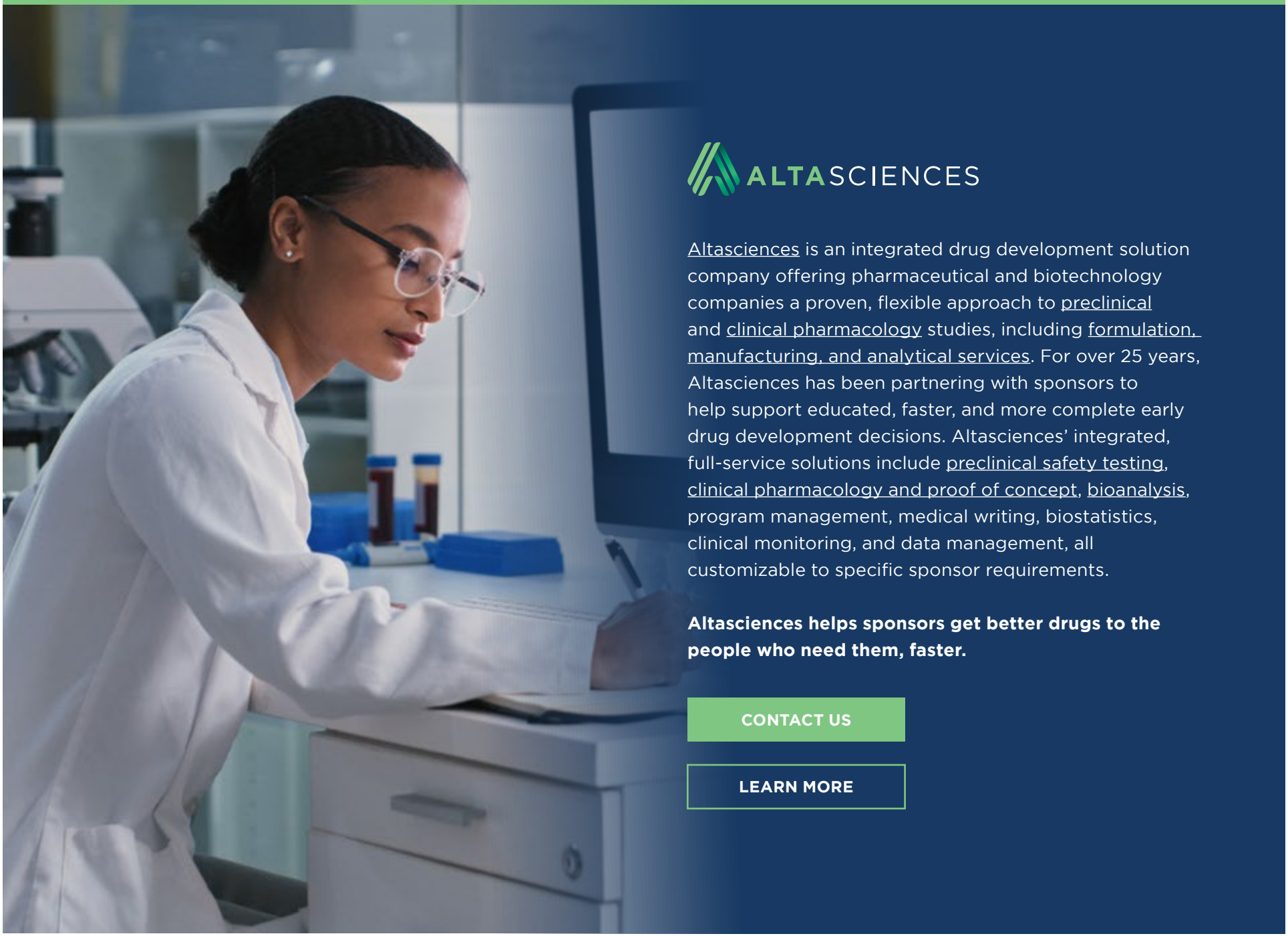

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Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements.

Altasciences helps sponsors get better drugs to the people who need them, faster.

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