Expanding Solutions for Challenging APIs Through Coacervation

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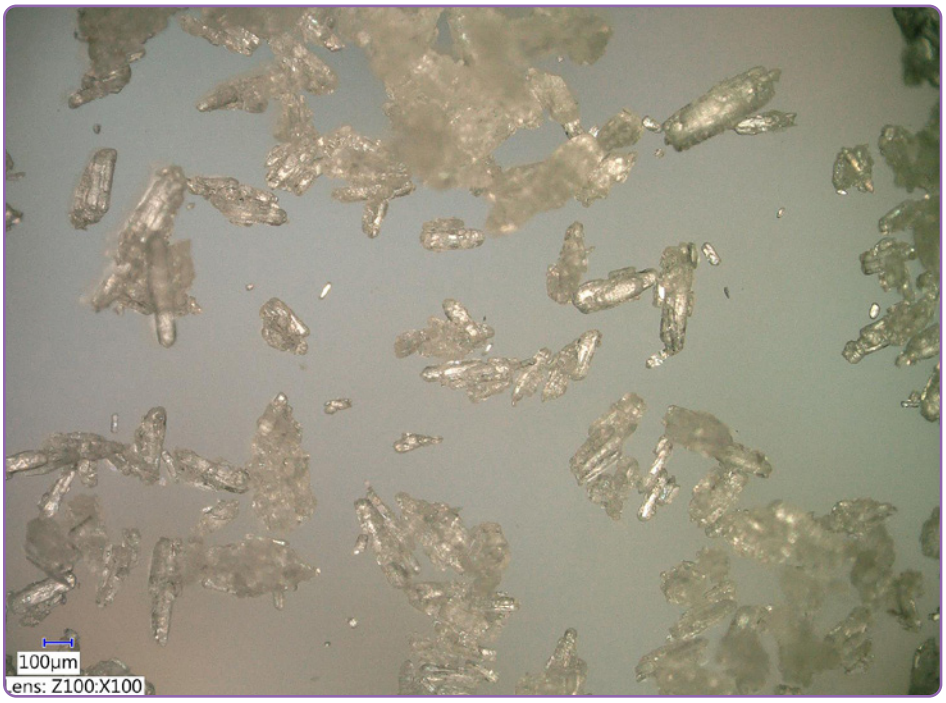
INTRODUCTION

Microencapsulation encompasses a range of sophisticated drug delivery methods that encloses an active ingredient(s) within a protective polymeric material. Drug developers routinely use such techniques to protect sensitive APIs, for taste masking, or to control the release of active materials. A variety of microencapsulation techniques are widely used in the pharmaceutical industry including fluid bed coating, spray drying, solvent evaporation, and more. However, one method—coacervation—offers several unique benefits to developers interested in working with challenging and/or bitter-tasting molecules, managing a product's lifecycle, and even accelerating development timelines.



Ibuprofen's needle-like structure is easily capsulated with Adare's Microcaps platform.

WHAT IS COACERVATION?

Coacervation is a physical–chemical phase separation process in which a polymer or a mixture of polymers is phased out as a liquid phase from a liquid carrier phase to form a solid coat or entrap a substrate (i.e., the pharmaceutical active). This can be accomplished by microencapsulating the core material in either aqueous media or organic solvent media.

One patented technique, the Adare Microcaps® platform, is a particularly versatile method of uniformly and precisely encapsulating drug particles. The platform includes two main coacervation methods, the first of which is a thermal phase separation process. This method uses cyclohexane and ethylcellulose in a manner that takes advantage of ethylcellulose's ability to dissolve under heat within a cyclohexane–ethylcellulose solution. When cooled, it precipitates out and separates from solution as minute particles that subsequently attach to the surfaces of drug particles to create a uniform barrier membrane. Once the solvent is removed, the result is a free-flowing powder containing microencapsulated API that can be as small as 75 µm.

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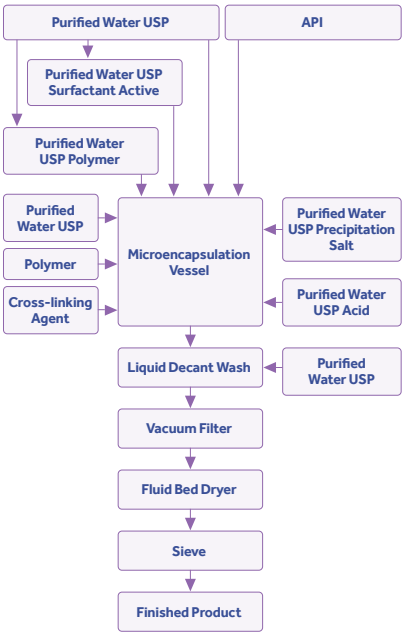
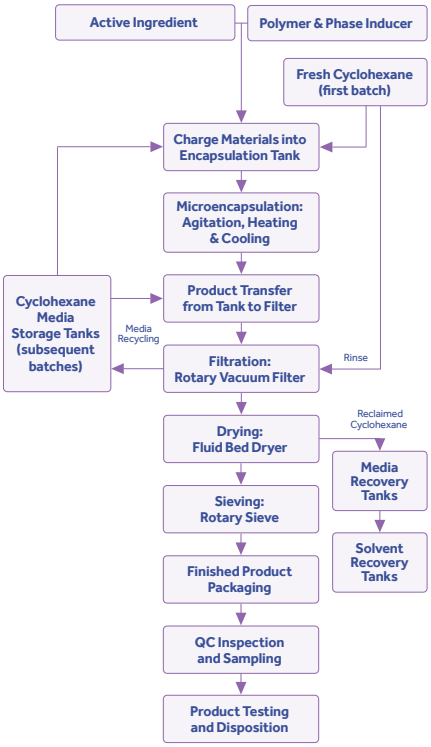
AQUEOUS MICROCAPS® PROCESS



ORGANIC SOLVENT MICROCAPS® PROCESS



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This coacervation technique is useful for encapsulating nearly all water-soluble and most water-insoluble particles.

Uniform coating of a substrate, whether a liquid droplet or solid particle, can also be achieved via a second Microcaps coacervation technique that utilizes an aqueous process. The aqueous process is obviously useful for microencapsulating most poorly water-soluble compounds. This type of process is similar to organic solvent microencapsulation except an aqueous liquid phase is used. In this process, polymer(s) are phased out of solution based upon heat, pH, or other means. Examples of polymers that are suitable for this process include gelatin and cellulose acetate phthalate.

MICROCAPS: ADVANTAGES AND REAL-WORLD EXAMPLES

Numerous drug developers—from well-established big pharma companies to tiny virtual companies—have been drawn to the Microcaps platform for a variety of reasons. Indeed, numerous products are on the market that take advantage of this less well known or "exotic" coacervation method. What follows is a sampling of the unique attributes that the Microcaps® platform offers as well as some real-world scenarios in which this coacervation method greatly benefited a drug development project.

Flexibility and Flowability

One advantage of Microcaps coacervation is that it is a reactor-style production process that suspends the intended particle(s) (e.g., the API) in liquid media. Unlike fluid-bed coating and other mechanical processes, the continuous semi-rigid membrane produced via Microcaps coacervation can coat and encapsulate a particle regardless of its shape or size, even though it is preferable to have small-sized uniform round particles for post-coacervation handling.

For instance, the fluid dynamics of the fluid bed process are not amenable for coating very small particles because of density and other challenges. Conversely, particles from very small, micronized APIs through very large APIs (1,000 µm) are all manageable through this coacervation process to yield aggregate or single-particle Microcaps.

Moreover, the Microcaps process is suitable for working with multiple-active products—even those that would otherwise be reactive in combination formulas. Microcaps coacervation can be used to microencapsulate separately more than one API particles, thus minimizing the contact of incompatible APIs. Nonreactive APIs can be put in the microencapsulation tank together and encapsulated within the same continuous membrane.

The Microcaps coacervation process is flexible in other important ways as well. Unlike some microencapsulation processes, the Microcaps coacervation platform is amenable for coating difficult or irregularly shaped particles such as needle-like particles, which have poor flow, to form individual or free-flowing agglomerates of coated particles. This is achieved during microencapsulation because the drug particles are suspended in a liquid media during coating as compared to spraying coatings in fluidized beds. Historically, it has been very difficult to achieve a consistent microencapsulation coating on needle-shaped particles, which tend to break and create smaller particles. The result of processing these particles by other means (such as a fluid bed for coating) is a powder with very poor flowability. Conversely, powder created through the Microcaps process has excellent flowability properties, even with otherwise undesirable particle shapes.

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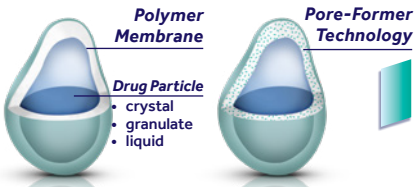
COMPLETE & EFFECTIVE TASTE MASKING



Microencapsulation by coacervation:

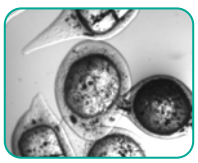
- Uniform coating of a solid particle or liquid droplet with a rigid semi-permeable polymer

Creates a physical barrier:

- Effective taste masking
- Customized release profile
- Turn liquids into powders
- Combine incompatible APIs

Final dosage forms:

- Powder
- Dry syrup
- Orally disintegrating tablets



KCl During Micro-Encapsulation

KCl Microcapsule After Drying

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Example: Improving Powder Flowability; Switching Dosage Forms. A client came to Adare for help improving the flowability of its powder, which was intended as a pediatric formulation. The API had been challenging for the developer because of its very small particle size, needle-like shape, bitter taste, and weight-based dosing requirement.

The Adare team decided to co-process the API and use the Microcaps coacervation process to encapsulate the particles. This combination of techniques not only improved flowability, but also served as a taste-masking technique. Moreover because the production process and the resulting powder were extremely consistent, the client was able to show regulators data indicating that the pediatric product could safely and accurately be dosed with a graduated scoop based on the child's weight.

Adare continues to make commercial batches for the client.

Improving Existing Formulations, Strengthening IP

The previous example touches on another important use for Microcaps: taste masking of extremely bitter compounds for novel dosage forms. The membrane serves as a barrier between the API and the taste buds, creating a more pleasant mouthfeel and eliminating any unpleasant aftertaste. This provides opportunities to turn a traditional tablet format into another delivery format like a sachet or orally disintegrating tablet (ODT), for instance. Regarding ODTs, Microcaps are robust and compressible while maintaining adequate taste masking.

Moreover, controlled release and extended release can be readily achieved with this technology on new or existing APIs, an important tool for patent extension and portfolio lifecycle management. Because the process is so unique, it is difficult to replicate by others and thus is quite strong from an intellectual property (IP) standpoint.

Example: Moving from Tablet to Sachet. A major pharmaceutical company came to Adare with an allergy product that already had achieved significant market success. The client wanted to extend the life cycle of the product by creating a new delayed-release, patient-friendly delivery format intended for the pediatric market. The compound was bitter, however, and though some taste-masking techniques had been tried with the API, patient feedback suggested it needed improvement.

Adare applied its Microcaps technology to create a uniform coating around the bitter particles (15% w/w ethylcellulose) and developed a powder composed of extremely small taste-masked particles (~100 µm). The team also provided options for alternative patient-friendly dosage forms and the client decided to move forward with sachets of the microencapsulated powder in an orally dispersible dry syrup formulation.

With its strong in-house analytical testing capabilities, the Adare team compared the time release of the new formulation to existing delayed-release tablets and found the timing of the API's release was comparable.

With a very short development timeline, the client launched their new pediatric formula very quickly and was able to add IP for its composition and process.

Example: Adding Strengths. A client had a controlled-release product on the market, but wanted to offer the finished product in other strengths as well.

The Adare team was able to work with their API and adapt the formulation for

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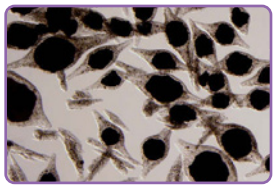

The coacervation process can be used for varying particle shapes. Above and below are API particles both irregularly sized and shaped. The thin transparent outer layer is Adare's Microcaps platform coating.

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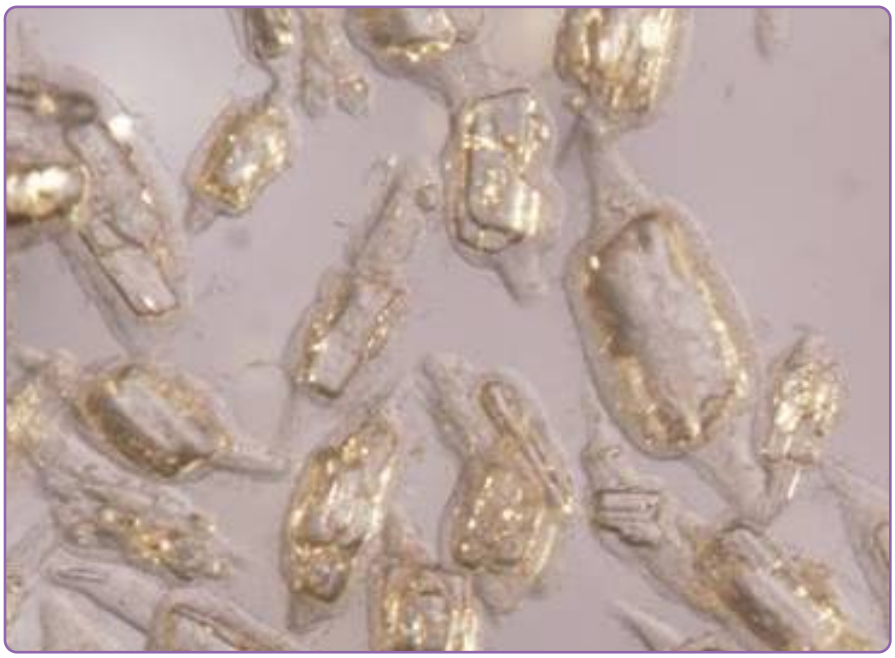
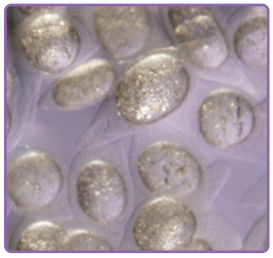
several strengths thanks to the flexibility and adaptability of the Microcaps platform. Adare provided data for the registration process enabling the formulations to come to market quickly, and now supply commercial batches for the client.

Example: A pharmaceutical company came to Adare hoping to create a more convenient and easier-to-swallow version of its formulation. The API, which had a bitter taste and irregularly shaped particles, was not suitable for other microencapsulation methods.





With the Microcaps platform, Adare was able to add taste masking and create uniform-sized particles. The powder was then used to make an ODT. Testing conducted by the client showed bioequivalence with an immediate-release reference product and the product's release was unaffected by administration with and without water.

The client also found in their studies that patients and caregivers widely preferred the ODT to a standard tablet, and the new dosage form increased patient acceptance.

Compressing Development Timelines

The flexibility of the Microcaps platform combined with the expertise of the Adare team means that developers often spend less time working out CMC issues such as content uniformity, impact of particle size and morphology parameters. A client can complete small-scale feasibility work involving the Microcaps coacervation process within a few weeks, depending on the client's needs.

Adare also scales material quickly because of its broad capabilities that range from 1-gallon reactors to 1,000-gallon reactors—all under the same roof. Thus, projects can move from 100-g R&D batches to 1,000-kg commercial batches without a time-consuming technology transfer.

Example: Speed. Dozens of actives have been successfully scaled-up to commercial scale. Processes are routinely transferred back and forth to Adare's sister facility in Pessano, Italy. R&D and manufacturing teams work in close contact during transfers to avoid redundant work, timeline delays, data/information loss, and other headaches and frustrations typical of tech transfer processes.

Co-Processing

Microcaps can be combined with other processing techniques to broaden the delivery options on challenging APIs or to add better process control—essentially, a step to engineer the particles in the desired manner before additional processing. For instance, one can use the Microcaps coacervation process and the fluid bed coating technologies sequentially, or in reverse order, to achieve particles of desired characteristics.

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Adare Pharma Solutions is a global, technology-driven CDMO providing turnkey product development through commercial manufacturing expertise focused on oral dosage forms for the Pharmaceutical, Animal Health and OTC markets. Adare's specialized technology platforms provide taste masking, ODTs, and customized drug release solutions.

With a proven history in drug delivery, Adare has developed and manufactured more than 40 products sold by customers in more than 100 countries globally.

THE ADARE EXPERTS

Kramer

Lai

Craig Kramer is a Senior Manager in R&D Formulations at Adare. He has over 25 years of experience in Microencapsulation with the company both at laboratory and production scales. Craig earned his Associates of Applied Science from The Ohio State University, ATI.

Jin-Wang Lai, PhD, is a Senior Director in R&D at Adare and has contributed to numerous product development projects over the past 16 years. Prior to Adare, he worked for Millennium Pharmaceuticals, Knoll Pharmaceuticals, and Ortho Pharmaceuticals, all in the area of Formulation and Pharmaceutical Sciences. Dr. Lai received his Master and PhD degrees in Pharmaceutics from the University of Georgia and the University of Iowa, respectively.

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The Adare team often uses the Microcaps coacervation process as a foundation for creating novel products. The first step is engineering the particles with the Microcaps platform before taking advantage of other proprietary technologies such as Diffucaps® customized-release technology, MMTS™ Minitabs, sachets, and more.

Example: Combination of Tools 1. Adare scientists applied their expertise to a client's API that had a very small particle size and extremely poor flowability. The molecule was very moisture sensitive and readily degraded in water.

Adare's solution involved co-processing the material, first creating pellets in a non-aqueous, non-solvent extrusion process and then using the Microcaps coacervation system to microencapsulate and taste mask the pellets. The organic-phase Microcaps coacervation was ideal for encapsulating this moisture-sensitive API because the process does not involve water or any concentration of water in the solvent like other coating or granulation processes do.

Example: Combination of Tools 2. Combining the technology of Microcaps and fluid bed Wurster coating allows the ability to coat an API or create a taste-masked granule and further coat it in a fluid bed with other controlled-release polymers such as enteric or other release polymers. These coated particles could then be incorporated into traditional tablets, ODTs, capsules or other dosing mechanism.

Environmentally Friendly. The use of organic solvent in the Microcaps coacervation process is very environmentally friendly, more efficient, and more economical than other processes that burn solvents. With the Microcaps coacervation method, the solvent can be reclaimed, redistilled, and (after testing and release) reused for subsequent batches.

SUMMARY

Coacervation is part art, part science, and when done properly by an experienced and knowledgeable team, it is an elegant solution for a variety of formation issues. Adare's primary method for solvent coacervation platform, Microcaps, is unique in the pharmaceutical industry and provides developers a variety of delivery options including capsules, traditional tablets, ODTs, stick packs, reconstitutable suspensions, and more. The environmentally friendly Microcaps platform is extremely flexible and able to encapsulate challenging APIs, which is useful for addressing poor flowability, very small particle sizes, controlled release, pediatric formulas, taste masking, consistency of bulk density of product, and more.

An added benefit is that at Adare, all work (at all scales) is done in-house, whether it is analytical testing, modeling and simulation, accessing and co-processing with other novel techniques, producing clinical through commercial materials, project management, and regulatory affairs support, filing, and registration. This all-in-one set-up creates flexibility, provides ease-of-scalability, eliminates time-consuming tech transfer, and compresses development timelines.