



Liquid Formulations

FOR SOLID ORAL DOSAGE FORMS

CAPSUGEL®
Quality
People and Products Working Together™

Liquid Formulation Development Services

A Host of World-Class Services



OUR COLMAR, FRANCE FACILITY HOUSES PHARMACEUTICAL DEVELOPMENT LABORATORIES AND PILOT PLANT MANUFACTURING

Liquid formulations can address a number of the challenges related to today's drug compounds, including:

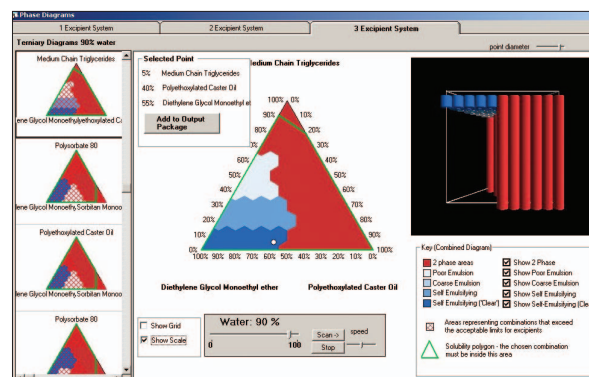
- Low aqueous solubility
- High potency
- Waxy/oily entities
- Cytotoxicity
- Poor/variable bioavailability
- Sub-optimal drug release

At Capsugel, we recognize the complexity and varied approaches needed to solve these issues and offer custom solutions to meet your particular needs. With our state-of-the-art Development Center, Capsugel offers a complete array of services for liquid formulations for both softgel and liquid filled capsules.

Setting a New Standard for Liquid Formulations

Capsugel relies on both conventional and advanced screening capabilities to optimize the performance of drug compounds:

- A sophisticated computer based model, drawing on both public and proprietary technical information, is used to quickly and efficiently develop liquid formulations
- Our scientists have specialized and unique expertise in the field of microemulsions
- Predictive in-vitro testing for drug absorption, including drug efflux and metabolism, is performed on the active ingredient and final formulation



ANALYSIS OF PHASE DIAGRAMS OF EXCIPIENTS IDENTIFIES WAYS TO ACHIEVE STABLE MICROEMULSIONS



No Company Offers You More Options and Solutions for Liquid Formulations than Capsugel

From formulation development and clinical trial batches to final production in softgels or Licaps® liquid filled capsules

Capsugel Contract Research Services

Clinical Development Services



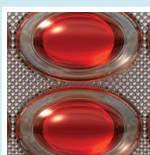
- › Drug candidate assessment
- › Pre-formulation screening
- › Formulation evaluation, development and selection
- › Compatibility studies



- › Clinical trial batches in either softgels or Licaps liquid filled capsules



Scale-up and Commercial Manufacturing



- › Final dosage form development in either softgels or Licaps liquid filled capsules
- › Full-scale production

Capsugel Products for In-House Development

Clinical Development



- › CFS 1000 capsule liquid filling & sealing benchtop machine for R&D labs
- › Licaps capsules for liquids and semi-solids

Commercial Manufacturing



- › Liquid Encapsulation Microspray Sealing (LEMS™) technology for sealing capsules at commercial production rates

Softgels




Beyond just producing softgels in both standard and custom sizes, Capsugel also offers formulation development and technical support.

Softgel benefits include:

- Suitable for oral, topical, ophthalmic and vaginal administration
- Shell composition can be customized to optimize product performance
- Ability to create custom sizes for precise volumes
- Wide variety of customized shapes



Standard Softgel Shapes and Sizes

SHAPE	SIZE	VOLUME
Round 	n° 3	0.18ml
	n° 4	0.25ml
	n° 5	0.31ml
	n° 90	5.54ml
	n° 110	6.78ml
Oval 	n° 2	0.12ml
	n° 3	0.18ml
	n° 4	0.25ml
	n° 5	0.30ml
	n° 6	0.37ml
	n° 7.5	0.46ml
	n° 10	0.62ml
	n° 12	0.74ml
	n° 20	1.23ml
	n° 30	1.85ml
	n° 40	2.46ml
Oblong 	n° 4	0.25ml
	n° 5	0.31ml
	n° 6	0.37ml
	n° 8	0.49ml
	n° 9.5	0.59ml
	n° 11	0.68ml
	n° 12	0.74ml
	n° 14	0.86ml
	n° 16	0.99ml
	n° 20	1.23ml

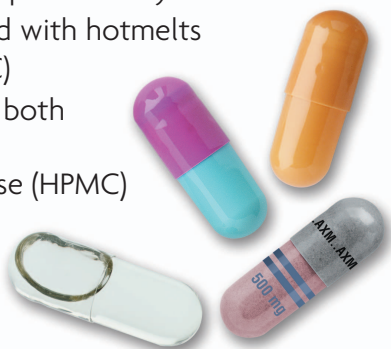
Note: Custom sizes and shapes also available. As specifications are under continuous review, be sure to contact Capsugel for the most up-to-date technical information.

Licaps® Capsules

Designed to contain liquid or semi-solid formulations, Licaps are compatible with a wide range of excipients, which may improve bioavailability for poorly soluble drugs.

Their key benefits include:

- A unique capsule design that maximizes seal integrity to prevent leakage after sealing
- Low oxygen permeability
- Can be filled with hotmelts (up to 70° C)
- Available in both gelatin and hypromellose (HPMC)



Licaps Gelatin Capsule Specifications

SIZE	00el	00	0el	0	1	2	3	4
Capsule Volume ml (approx)	1.02	0.91	0.78	0.68	0.50	0.37	0.30	0.21
Available Volume ml (approx)	0.89	0.82	0.68	0.59	0.43	0.33	0.26	0.18
Weight in mg	130	118	107	96	76	61	48	38
Tolerance mg	±10	±7	±7	±6	±5	±4	±3	±3
Overall Closed Length mm	25.3	23.3	23.1	21.7	19.4	18.0	15.9	14.3
Tolerance mm	±0.3	±0.3	±0.3	±0.3	±0.3	±0.3	±0.3	±0.3
Body Length mm	22.20	20.22	20.19	18.44	16.61	15.27	13.59	12.19
Tolerance mm	±0.46	±0.46	±0.46	±0.46	±0.46	±0.46	±0.46	±0.46
Cap Length mm	12.95	11.74	11.68	10.72	9.78	8.94	8.08	7.21
Tolerance mm	±0.46	±0.46	±0.46	±0.46	±0.46	±0.46	±0.46	±0.46
<u>External Diameter</u>								
Body mm	8.18	8.18	7.34	7.34	6.63	6.07	5.57	5.05
Cap mm	8.53	8.53	7.65	7.64	6.91	6.35	5.82	5.32

As specifications are under continuous review, be sure to contact Capsugel for the most up-to-date technical information.

CFS 1000™ Capsule Liquid Filling & Sealing Machine

Designed to allow formulation scientists the ability to significantly reduce the time it takes to produce early phase clinical trial materials.

With the CFS 1000 you benefit from:

- A development-scale cGMP compliant machine with a compact design that is perfect for R&D laboratories and clinical supply operations
- Fully automatic filling and sealing of small batches when minimum quantity of active is available
- Scalable to the Capsugel LEMS™ sealing system
- Easy size changeovers

CFS 1000 Specifications

Maximum Operating Speed	1,000 capsules/hour
Filling Temperature	20-70° C
Fill Volume Range	0.1 ml – 1.2 ml
Fill Viscosity Range	100 – 1000 mPa · s
Capsule Size Range	Sizes 00el, 00, 0, 1, 2, 3, 4
Minimum Recommended Batch Size	20 – 25 ml



Liquid Encapsulation Microspray Sealing (LEMS™) Technology

An innovative technology, developed by Capsugel, for secure sealing of two-piece capsules, the LEMS production-scale machine offers these outstanding features:

- Capable of sealing 30,000 to 60,000 capsules per hour
- Eliminates the need for banding
- Fast installation and start-up
- Cost-efficient, in-house manufacturing
- Easy cleaning and size changes
- Safer, dust-free production particularly for cytotoxic or high potency drugs



Seal Integrity Evaluation

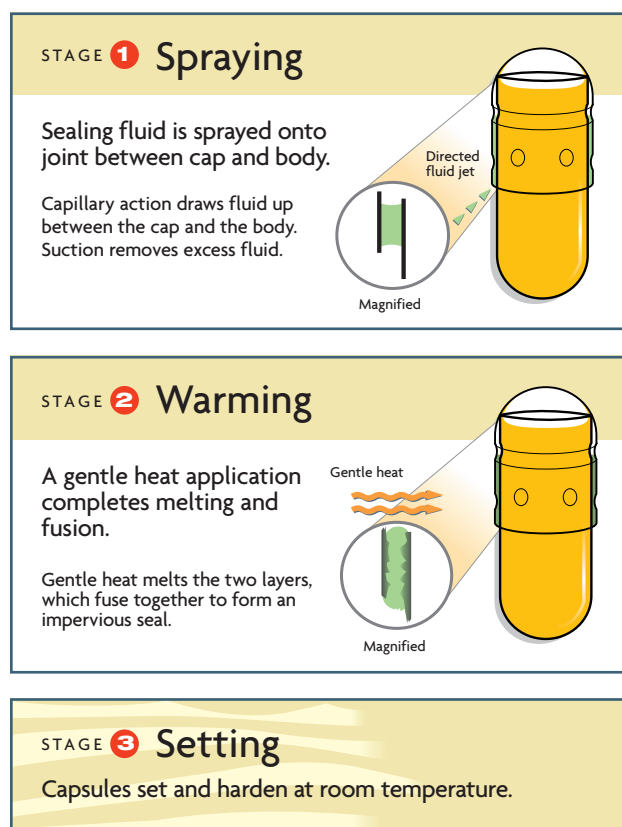


Red dye added to the sealing solution illustrates the extensive actual size of the sealed area.

* See the back page for a detailed illustration of the Sealing Process

Sealing Process for Licaps® Capsules

- As the water/ethanol microspray solution penetrates the cap and body, the melting point is lowered in the sealing area of the capsule. Capsugel supplies Licaps® capsules, which are specially designed to prevent liquid leakage prior to sealing.
- Air heated to 40 – 60° C is gently blown across the capsule to complete the melting and fusion of the body and cap.
- The setting and hardening is often accomplished overnight in open trays, and is completed while the product returns to room temperature. The larger size of the sealed area, compared to traditional banding processes, contributes to a robust, impervious seal.



For consultation on your liquid formulations, please contact one of our worldwide sales offices or visit us at www.capsugel.com.

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