



Liquid Formulations in Licaps® Capsules



A Timely Solution to the Challenge of Poorly Soluble Drug Compounds

CAPSUGEL®
LIQUID GROUP™



Reducing time-to-market can mean millions of dollars, given the increased cost and complexity of drug development, particularly for poorly soluble compounds. Liquid Formulations in Licaps® capsules provide numerous advantages to get your products to market faster.

Formulation Advantages of Liquid and Semi-Solid Formulations in Licaps Capsules

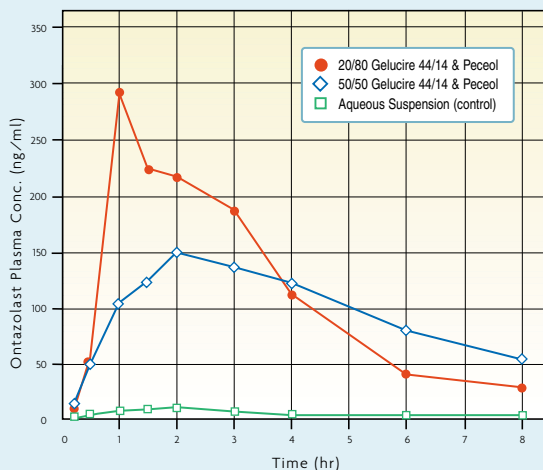
Combinatorial chemistry advances, as well as high-throughput receptor-based screening, often result in the identification of rigid, receptor-specific drug molecules with poor physico-chemical properties, particularly for absorption across the GI tract.

Improved bioavailability of poorly soluble drugs

Maximum bioavailability is achieved by keeping the drug in the amorphous/solubilized state. This prevents the compound from "crashing out" of solution, into an insoluble crystalline form during in-vivo release in the GI tract.

In Vivo Bioavailability

– Rat Model

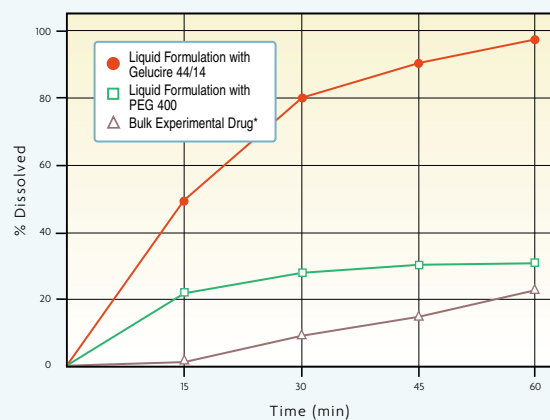


In vivo study in rats show improved bioavailability of two Self-Emulsifying Drug Delivery Systems (SEDDS) compared to aqueous suspension of Ontazolast (100mg/kg).

*Gelucire 44/14: polyglycolized glyceride
Peceol: glyceryl mono-oleate; a pre-digested lipid*

Reference data on file

In Vitro Dissolution



In vitro dissolution profiles of capsule formulations of an experimental drug* show the ability of various solubility-enhancing excipients to substantively impact the dissolution of a poorly soluble active. (USP paddle method at 50 rpm in 37° C water; 0.2% w/v polysorbate in 900 ml water).

In Vivo Bioavailability

– Dog Model

Capsule Formulation	Absolute Bioavailability
Liquid Formulation with Gelucire 44/14	58%
Liquid Formulation with PEG 400	6%
Bulk Experimental Drug*	2%

In vivo bioavailability studies in dogs show a significant bioavailability advantage of the liquid capsule dosage form, in support of the in vitro dissolution data shown above.

In-house formulation and development

- Keep proprietary technical knowledge and related patent opportunities in-house
- The use of scarce amounts of expensive actives is more focused and efficient
- Small-batch manufacturing capability enables rapid production of Phase I trial materials

Wide operating window for temperature-dependent formulations

- Ideal for low-melting point drug molecules
- Can utilize hot melt systems, up to 70° C

* The experimental drug has no ionizable group, with a Mol. Wt. of 496. The aqueous solubility of the compound over a pH range of 1 - 9 is < 1mcg/ml. The log P (partition coefficient, octanol/water) is > 2, and the melting point is 110° C.

Marketing Advantages



- **Improved bioavailability, and subsequent clinical performance, provides stronger competitive advantage**
- Reduced dosage levels could offer less side effects and increased patient compliance
- Extend the product life cycle of existing compounds

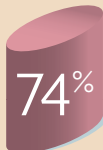


- **Faster development cycle enables earlier market entry, maximizing sales and share position**
- Liquids typically require less processing steps, compared to standard tablet formulations. Consequently, less time is required for process development, documentation, and validation
- Improved bioavailability reduces inter- and intra- patient drug uptake variability; often yielding a dossier that can better meet rigorous regulatory challenges

Percent of consumers who would "definitely or probably buy"



Average response for Consumer Healthcare Branded Concept Tests



Licaps® Purchase Intent After Seeing Product

* Licaps U.S.A. Product Concept Test research, published in January 2002, was conducted in 14 geographically dispersed markets-mall intercepts. Data on file.

- **Positive consumer perception improves patient compliance of liquid-filled dosage forms**

- Liquids are perceived as "Gentle, fast-acting, more natural"
- Supported by heavily advertised OTC shift to liquid-filled analgesics and cough & cold remedies



- **Build a unique brand image**

- Select unique colors for both the cap and body of the capsule, imprinted with logos or brand names
- Utilize a transparent capsule to show an attractive colored liquid fill



Key Applications for Liquid or Semi-Solid Dosage Forms

- Enhancement of bioavailability of poorly soluble drugs
- Improvement of content uniformity
- Reduced risk of cross-contamination of Low Dose/High Potency compounds
- Drugs with moisture-related stability issues
- Low melting point materials
- Modified-release products

Licaps® Capsules

Licaps brand capsules are compatible with a wide range of excipients which may improve bioavailability for poorly soluble drugs. Some key benefits include:

- Unique capsule design maximizes seal integrity to prevent leakage
- Low oxygen permeability
- Can be filled with hot melts (up to 70° C)
- Available in a wide range of capsule sizes



Licaps Capsules Specifications



SIZE	00el	00	0	1	2	3	4
Capsule Volume ml (approx)	1.02	0.91	0.68	0.50	0.37	0.30	0.21
Available Volume ml (approx)	0.89	0.82	0.59	0.43	0.33	0.26	0.18
Weight in mg	130	118	96	76	61	48	38
Tolerance mg	±10	±7	±6	±5	±4	±3	±3
Overall Closed Length mm	25.3	23.3	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
Body Length mm	22.20	20.22	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
Cap Length mm	12.95	11.74	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
External Diameter							
Body mm	8.18	8.18	7.34	6.63	6.07	5.57	5.05
Cap mm	8.53	8.53	7.64	6.91	6.35	5.82	5.32
<i>As specifications are under continuous review, be sure to contact Capsugel for the most up-to-date technical information.</i>							

Liquid Encapsulation Microspray Sealing (LEMS™) Technology

This innovative technology was developed by Capsugel for secure sealing of two-piece capsules. The LEMS production-scale machine, capable of sealing 30,000 capsules per hour, offers these outstanding features:

- Eliminates the need for banding
- Fast installation and start-up
- Cost-efficient manufacturing
- Easy cleaning and size changes



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



LEMS Machine Specifications

Maximum Sealing Capacity	30,000 capsules/hour
Capsule Sizes	00el, 00, 0, 1, 2, 3, 4
Dimensions (approximate):	
Length	1.5 m
Width	0.9 m
Height	1.4 m
Weight (approximate)	670 Kg
Sealing Fluid Utilization	Approximately 50 µL per capsule seal

CFS 1000™ Capsule Liquid Filling & Sealing Machine

The CFS 1000 is specifically designed to allow Formulation Scientists to better exploit the potential of lipid-based formulations for poorly soluble compounds. As a result, the CFS 1000 can significantly reduce your time to produce early phase clinical trial materials. The CFS 1000 features include:

- Development-scale machine with compact design that is perfect for R&D laboratories
- Fully automatic filling and sealing of small batches when minimum quantity of active is available
- Excellent seal integrity
- Scalable to the Capsugel LEMS™ sealing system
- cGMP compliant
- 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

Examples of Excipients Compatible with Licaps Capsules

Akomed® R	Oleic Acid
Castor Oil	Olive Oil
Cetosteryl Alcohol	Poloxamers
Cetyl Alcohol	Polyethylene Glycols
Corn Oil	Silica Dioxide
Cremophor® EL	Softigen® 767
Gelucire®	Softisan®
Hydrogenated Castor Oil	Stearic Acid
Labrafil®	Stearyl Alcohol
Miglyol®	Tween® 80

* Akomed®, Cremophor®, Gelucire®, Labrafil®, Miglyol®, Softigen®, Softisan®, Tween® are the property of the associated companies.

Technical Support

To better assure the success of your product during development, technology transfer and market introduction, Capsugel provides an array of technical support services:

Compatibility Studies

Formulations are evaluated to assess the impact on key mechanical and performance properties of the capsule shell.

Filling & Sealing Trials

Machine trials on both a capsule filling machine, as well as the LEMS sealing machine, are conducted to assist in product development.

Formulation Guidelines

Recommended thermal & rheological characteristics:

- Maximum filling temperature: 70° C
- Viscosity at filling temperature: 100 - 1000 mPa · s
- Particle size of suspended drug: 10 - 20 µm

Excipient Selection Considerations

- Compatible with active ingredient and capsule shell
- Safety and consistency
- Suitable for required bioavailability profile
- Manufacturability and ease of scale-up

Technical papers regarding liquid formulations are available from the Capsugel Library upon request.

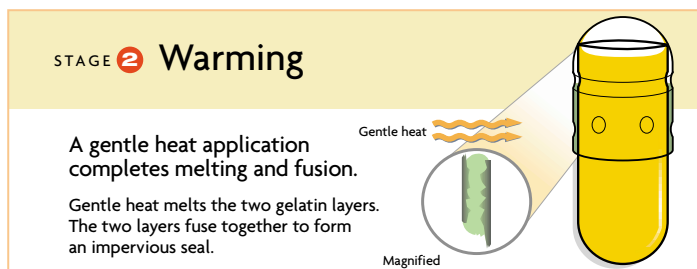
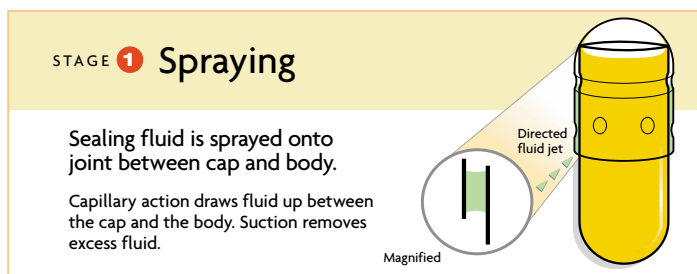
Manufacturing Advantages

- Faster scale-up capability
- In-house manufacturing – less reliance on third-party manufacturers; shorter lead times
- Dust-free production provides for a safer work environment
- Simplified processing with less capital equipment – improves profitability
- Consistent product dimensions facilitate blister packaging



Sealing Process

- As the water/ethanol microspray solution penetrates the cap and body, the melting point of the gelatin 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 two gelatin layers.
- The setting and hardening of the gelatin, often accomplished overnight in open trays, 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 Licaps capsules samples or consultation on your liquid formulations, please contact one of our worldwide sales offices or visit us at www.capsugel.com.

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