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Accelerate pre-clinical developments and improve oral bioavailability with lipid-based formulations and encapsulation technology combination

Dr. Camille Dumont
Manager, Customer Applications – Application Lab

Lonza Capsules & Health Ingredients
France
camille.dumont@lonza.com
+33631704240

Dr. Camille Dumont is a Customer Application Manager at Lonza CHI Applications Lab. This service partners with customers to solve their drug delivery challenges by relying on a strong expertise in formulation and encapsulation technologies, and by providing customized capsules for proof-of-concept evaluation.

Camille has a Msc in Chemistry and a PhD in Pharmaceutical Sciences obtained from the University of Lyon. She has many years of experience in developing solutions for the pharmaceutical industry, with particular expertise in lipid-based formulation and oral bioavailability enhancement of small and large molecules.

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Introduction

Owing its convenience, oral administration is patients' preferred route of delivery for therapeutic molecules. However, most New Chemical Entities (NCE) exhibit physico-chemical properties limiting their absorption in the gastro-intestinal (GI) tract. Indeed, according to Pharmacircle data from March 2022, almost 70% of identified molecules face solubility issues in aqueous GI fluids. Therefore, they require formulation strategies to boost their solubility in biorelevant conditions and meet their therapeutic effect.

Numerous options exist to enhance oral bioavailability of these poorly water-soluble (PWS) drugs [1]. Among them, lipid-based formulations (LBF) represent an interesting approach for their ease of development and manufacturing. Although LBF are mostly known for their ability to increase oral bioavailability of grease ball like Active Pharmaceutical Ingredient (API) (high log P[1], low melting point), recent publications indicate promising results to also increase oral bioavailability of brick dust like small molecules (high log P, high melting point) as well as macromolecules such as peptides and proteins.

As LBF are composed of liquid or semi-solid excipients into which API are either dissolved or dispersed, capsules are the most convenient dosage forms for their administration.

This paper covers the benefits of the LBF and capsules combination in dosage form developments, an efficient technology platform to bring efficient and differentiated products to the market.

1. LBF for oral bioavailability enhancement of therapeutic compounds

a. Lipid excipients

Lipid excipients comprise a wide range of materials such as vegetable oils (mostly triglycerides), fatty acid esters of alcohol (e.g., glycerides: fatty acid esters of glycerol; polyoxylglycerides: fatty acid esters of polyethylene glycol (PEG)) and ethoxylated lipids (e.g. ethoxylated castor oil; fatty acid ester of ethoxylated sorbitan) [2]. These materials are defined by their amphiphilicity or Hydrophilic Lipophilic Balance (HLB) which enables their classification as oils, surfactants and co-surfactants. LBF are isotropic mixtures of these components with the potential addition of solvent(s). The ratio of each category of these excipients will influence the behavior of LBF such as dispersing or self-emulsifying properties in gastro-intestinal fluids, as well as digestion propensity [3].

From a regulatory point of view, compendial monographs are available for pharmaceutical grade lipid excipients and their precedence of use in US marketed drug products can be verified for instance through the quarterly updated US FDA "Inactive Ingredient Database".[4].

[1] Log P is the log of the concentration ratio of a compound between octanol and water.
It is widely used as an indicator of hydrophilicity or lipophilicity of pharmaceutical compounds.

1. LBF for oral bioavailability enhancement of therapeutic compounds

b. Poorly water-soluble drugs

Based on their physicochemical properties PWS drugs can be sub-categorized in 2 families: «grease ball» drugs refer to API with solvation-limited solubility whereas the solubility of «brick dust» drugs in biorelevant fluids is limited by strong solid-state forces [5]. Numerous PWS drugs from both subcategories formulated in LBF obtained marketing authorization, some of them are reported in Table 1.

Drug name	Marketed dosage form	Therapeutic class	Mw (g/mol)	Log P	Mp (°C)
Bexarotene	Targretin®	anti-cancer	348	6.9	230
Cetirizine	Zyrtec®	Antihistamine	389	3.0	110–115
Cyclosporine A	Neoral®	immunosuppressant	1203	3.64	148–151
	Gengraf®				
Doxercalciferol	Hectorol®	Vitamin	413	6.3	138–140
Dronabinol	Marinol®	Cannabinoid	314	7.3	200
Dutasteride	Advodart®	antiandrogenic	529	5.5	242–250
Enzalutamide	Xtandi®	Androgen receptor inhibitor	464	3.8	201
Fenofibrate	Fenogal®	antilipemic agents	361	4.9	79–82
Ibuprofen	Advil®	NSAID	206	3.5	75–78
Isotretinoin	Absorica®	Retinoid	300	5.7	189–190
Levothyroxine	Tirosint®	Hormone	777	1.15	235
Loratidine	Claritin®	Antihistamine	383	4.8	134–136
Naproxen	Aleve®	NSAID	230	3.3	152
Nimodipine	Nimotop®	Calcium channel blocker	418	3.4	125
Nintedanib	Ofev®	Kinase inhibitor	540	3.7	244–251
Progesterone	Prometrium®	Hormone	314	3.6	128–132
Sirolimus	Rapamune®	Immunosuppressant	914	4.9	188–185
Saquinavir	Fortovase®	Protease inhibitor	671	4.0	350
Testosterone undecanoate	Restandol Testocaps®	Hormone pro-drug	457	6.7	39–42
Valproic acid	Depakene®	Anticonvulsant	144	2.5	222

Table 1: *Non-exhaustive list of commercialized LBF, Data from www.drugbank.com and https://www.chemsrc.com/*

1. LBF for oral bioavailability enhancement of therapeutic compounds

i. Grease balls

The obvious interest of LBF with grease ball API is their ability to present the drug in a solubilized or partially solubilized state in the GI tract [6]. Well-designed LBF maintain this solubilized state upon dispersion of the formulation in the GI fluids and action of the digestive enzymes on the formulation components. Moreover, depending on the constituting excipients, LBF may limit food effect and favor lymphatic absorption by by-passing first path metabolism [7].

Developments of LBF to increase oral bioavailability of PWS drugs start with a solubility screening of the API in excipients so as to cover the lipid space [8]. Pseudo ternary phase diagrams with materials exhibiting the best solvent properties ensure homogeneity of the formulations in the capsules and upon dilution in biorelevant media. Additional tests, such as affinity of the API for the formulation (partition coefficient between the LBF and release medium) or evaluation of the LBF capacity to maintain the API in a solubilized state during simulated *in vitro* digestion can be performed to secure LBF design [9,10].

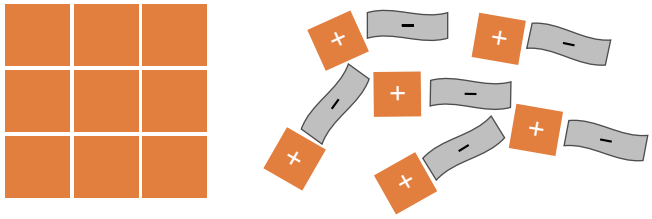
An interesting aspect of LBF is that they are constituted of few components, with sometimes single excipients able to fulfill drug product requirements. Moreover, easy production of small scale batches make LBF an attractive solution to increase testing capacity, reduce amount of API in development phases and accelerate pre-clinical developments. In addition, LBF help contain the safety risk of highly potent APIs as the drug is dissolved/dispersed in a liquid phase during manufacturing.

ii. Brick dusts

The strong solid state organization limiting the solubility of brick dust API in aqueous intestinal fluids also prevents their good dissolution in lipid excipients. Therefore LBF option is only selected with these API when the dose is low or when there is a possibility to use multiple dosage units.

However, lipophilic salts (or hydrophobic ion pairs, HIP) of drugs, which tend to exhibit lower melting point than the free base or the traditional salts, enable the transformation of brick dust into grease ball by disruption of the strong API packing, as schematized in Figure 1. Indeed, promising studies with API such as cinnarizine [11], itraconazole [11], erlotinib [12] or lumefantrine [13] have shown an increased solubility in lipid excipients. This increased affinity for lipid excipients enables the development of LBF with reduced doses, implying a decrease in adverse effects, improvement of patient compliance and reduced costs of production

In addition, from a regulatory point of view, lipophilic salts do not alter the chemical structure of the therapeutic molecule and fall under section 505(b)2 of FDA applications. [14].



API crystalline free base Lipophilic API salt

Figure 1: *Schematic representation of the change in the solid state organization of a crystalline API free base and the lipophilic salt of the same API with an anionic counter-ion*

1. LBF for oral bioavailability enhancement of therapeutic compounds

c. Macromolecules: peptides and proteins

Contrary to PWS small molecules that are formulated in LBF, most peptides and proteins are soluble in biorelevant media. On the other hand, their potent therapeutic effect is limited by strong proteolytic degradation along the GI tract, and low permeability across the intestinal barrier. However, several recent studies have shown multiple benefits from combining peptides and proteins with particular LBF, Self-Emulsifying Drug Delivery Systems (SEDDS), which instantaneously form emulsions upon contact with aqueous media.

As a matter of fact, digestive enzymes are not soluble in lipids. Then, LBF prevent peptides and proteins from being degraded as long as they remain embedded in the oily droplets formed upon SEDDS dispersion [15,16]. To favor this behavior, the affinity of these drugs for lipophilic environment should be adjusted, and the formation of lipophilic salts may also be relevant in this case [5,17–20]. The selected counter-ion will play a role in the drug loading, retention of the drug within the oily droplets and the overall efficacy of the formulation [17,21].

Furthermore, lipid excipients based on medium chain fatty acids are well-known for their ability to improve intestinal permeation [22]. Indeed, they can interact with the intestinal epithelium via several mechanism of action such as fluidization of the epithelial membrane or transient opening of tight junctions [23,24]. Indeed, excipients such as sodium caprate (C_{10}) or Labrasol®, composed of glycerides and PEG esters of caprylic and capric acid were shown to promote *in vitro*, *ex vivo* and in vivo permeation of macromolecules [25–27].

Benefits from using LBF to improve oral bioavailability of macromolecules have been confirmed by in vivo preclinical studies with octreotide and exenatide [5,28]. Interest for this strategy was further reinforced by FDA approvals of Rybelsus® (NovoNordisk) in 2019, an oral tablet of semaglutide containing SNAC (sodium salcaprozate, a fatty acid derived permeation enhancer) and Mycapssa® (Chiasma) in 2020, an oral capsule based on octreotide in oily solution and containing caprylic acid as permeation enhancer [29].

2. Capsules: dosage-form of choice for LBF

a. Soft and hard capsules

Excipients used in LBF are either liquid or semi-solid, for which the simplest and most common vessels are soft and hard capsules [30,31].

Soft capsules (or softgel) are sealed soft gelatin shells which elasticity is obtained by addition of a plasticizer. They are produced, filled and sealed on line using a rotary die process before being stored from 6 to 15 days in specific environmental conditions for gelatin stabilization. Softgel production is a meticulous operation which requires highly trained operators either in the lab or on production scale.

On the other hand, hard capsules are ready-to-fill two-parts containers (body and cap), available in severable standardized sizes and delivered in pre-locked position to be easily fed in capsule filling machines. Main characteristics of soft and hard capsules are detailed in Table 1. It appears from the listed features that hard capsules offer an easier and cost-effective solution to internalize LBF encapsulation process compared to softgel.

Features		Soft capsules	Hard capsules
Technical data	**Size**	Depends on manufacturers	Standardized to fit with commercialized machines
	Composition	Gelatin Plant-based polymers	Gelatin Plant-based polymers
Compatibility with formulations	**Viscosity**	Limited process temperatures prevent viscosity adjustments by heating	Adapted to a wide range of viscosity (0.01-1 Pa.s)
	Suspensions – impact of particle size	Limited to low particle size (risk of bad sealing)	Adapted to a wider range of particle size
	Suspensions – impact of concentration	Up to 45-45% solid content without impact on sealing	Up to 50–55% solid content
	API migration to shell	Risk with hydrophilic compounds, particularly during production	No
	Hygroscopic compounds	Depends on polymer type	Depends on polymer type
	Oxygen permeability	Good in specific temperature and RH conditions	Depends on polymer
Encapsulation process parameters	**Filling**	Simultaneous shell formation and filling	Ready-to-fill vessels
	Process temperature	<35°C for gelatin softgels	Up to 70°C
	Ease of internalization	No, require experienced operators to formulate gelatin – most productions are outsourced	Yes, at all manufacturing scales
	Duration	6 to 15 days	Up to 4 hours
	Production line surface requirements	Encapsulation area supplemented by gelatin film production area (including viscosity adjustments and pigments addition) and drying zones (basket and tunnels)	~200 m²

Table 2: *Soft and hard capsules characteristics*

2. Capsules: dosage-form of choice for LBF

Hard capsules are available in gelatin or plant-based polymers such as hydroxypropylmethycellulose (HPMC) from wood pulp or pullulan from tapioca fermentation, with the potential addition of gelling agents. Polymers and their formulation influence the behavior and characteristics of the capsules, as summarized in Table 3. In particular, the dissolution profile of an encapsulated compound may vary depending on the pH of the dissolution medium. For example, while the *in vitro* dissolution profiles of acetaminophen, a water-soluble model compound, encapsulated in gelatin and HPMC capsule (Vcaps® Plus) conform to USP monograph (more than 75% of API released within 45 minutes) in pH 1.2, 4.5 and 6.8, it is strongly affected by pH when the API is encapsulated in pullulan-based capsules (Plantcaps®), Figure 2.

Therefore the choice of capsules will depend on multiple parameters such as compatibility with the fill formulation, targeted release profile and patient preference considerations.

Polymer	Gelatin	HPMC	Pullulan
Lonza Capsugel® capsule type	Hard gelatin capsule	Vcaps® Plus	Plantcaps®
Origin	Animal (porcine, bovine, fish)	Vegetal (cellulose)	Vegetal (starch)
Gelling agent	No	No	Yes
Moisture content at 50% RH	13–16%	3–9%	10–14%
Oxygen permeability	Low	High	Low
Risk for chemical crosslinking	Yes	No	No
Water vapor permeability	Neutral once equilibrated	Low	Low
Acceptance as described in Pharmacopeias	EP, USP/NF, JP	EP, USP/NF, JP	EP, USP/NF, JP

Table 3: *Main features of gelatin, HPMC and pullulan based hard capsules*

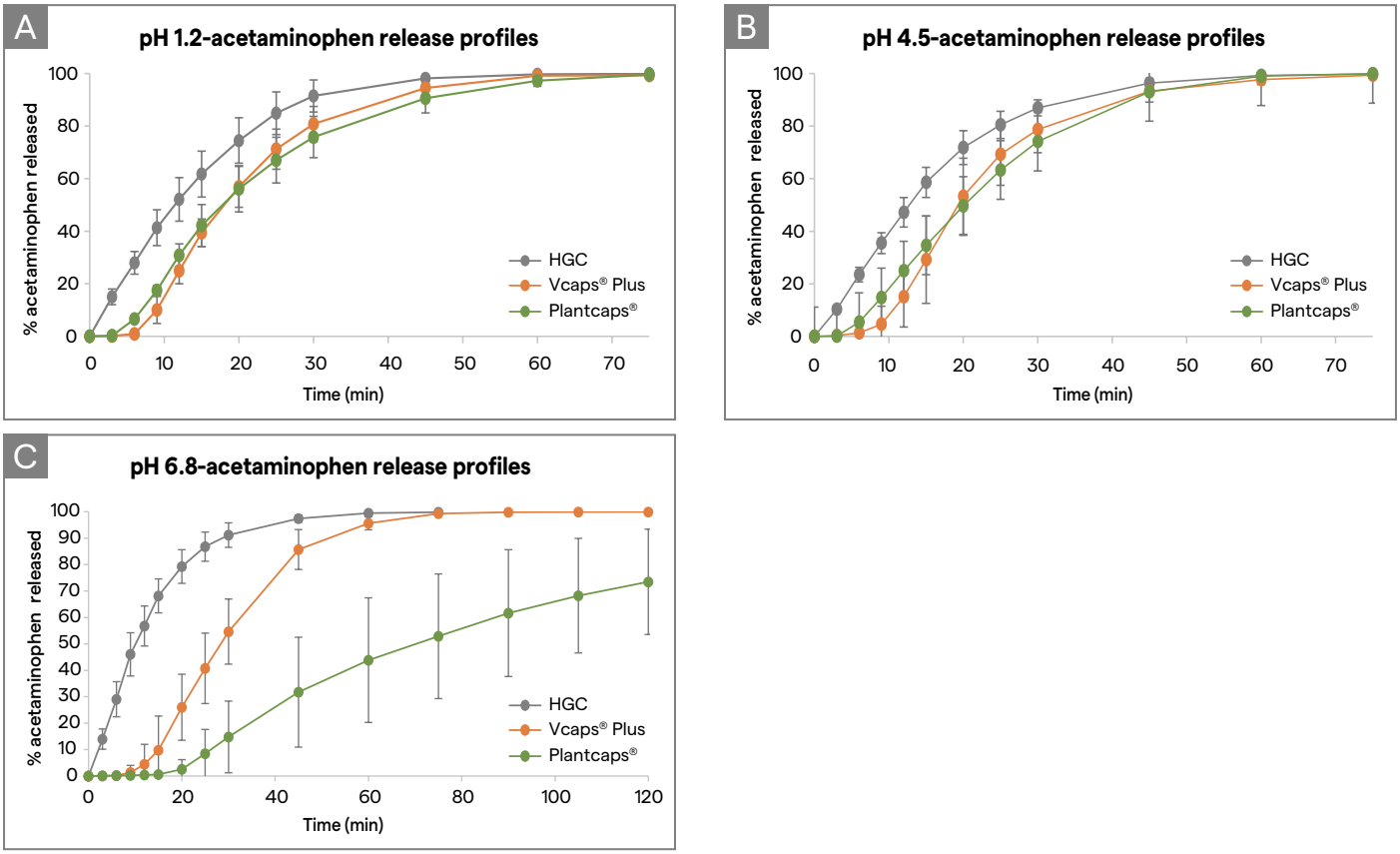


Figure 2: *Dissolution profiles of Acetaminophen (385 mg, 100%) filled in size #0 hard gelatin capsule, Vcaps® Plus and Plantcaps® in pH 1.2 (A), pH 4.5 acetate buffer (B) and pH 6.8 (C), n=6*

b. Lipid/capsule compatibility studies

Dissolution profile can be strongly altered by incompatibility between the capsule shell and the fill formulation. As gelatin-based capsules have historically been used to encapsulate LBF, many compatibility results are available in the literature. They confirm absence of interactions in most cases. However, gelatin is highly susceptible to crosslinking in presence of particular components such as aldehydes or peroxides which may be present in some lipid excipients or be formed during the manufacturing process if exposed to dioxygen. Furthermore, the encapsulation of hygroscopic formulations can fragilize the capsules by absorbing water which acts as plasticizer in gelatin-based capsules.

On the other hand, HPMC-based capsules are not susceptible to crosslinking and are compatible with most lipid excipients. Moreover, their lower water-content ensures stability of hygroscopic fills and moisture sensitive ingredients [32].

As humidity plays as major role in capsule-based dosage form stability, compatibility studies between the capsule and its content are conducted for several weeks in various controlled humidity environments through visual observations, quantification of water uptake, mechanical resistance evaluation and dissolution behavior [32,33]. Table 4 and Table 5 display non-exhaustive lists of pure lipid excipients known to be compatible with gelatin or HPMC-based capsules respectively. It is however important to realize that a pure excipient which is not compatible with a capsule can still be used diluted in a LBF and that compatibility studies between capsules and formulations should be conducted for each new formulation development.

Role	Chemical name	Marketed name (Company)	HLB	Compatibility reference
Oily vehicle	Medium chain triglycerides	Labrafac®WL1349 lipophile (Gattefossé) Kollisolv® MCT 70 (BASF) Crodamol™ GTCC (Croda) Miglyol® 812 N (IOI Oleo GmbH)	1	[32]
	Caprylic/ capric triglycerides	Miglyol®812 (Sasol)	1	[34]
Co-surfactant	Propylene glycol monolaurate 90% (Type II)	Lauroglycol®90 (Gattefossé)	3	[34]
	Polyglyceryl-3 oleate	Plurol® oleique CC497 (Gattefossé)	3	
Surfactants	Lauroyl Polyoxyl-32 glycerides	Gélucire®44/14 (Gattefossé)	11	I31]
	Caprylocaproyl polyoxylglycerides	Labrasol® (Gattefossé)	12	[34]
	Polyoxyl 35 Castor Oil	Kolliphor®ELP (BASF)	12–14	[34]
	Polyoxyl-40 hydrogenated castor oil	Kolliphor®RH40 (BASF)	14–16	[34]
	Polysorbate 80	Tween™80 (Croda) Montanox™80 (Seppic)	15	[34]

Table 4: *Non-exhaustive list of lipid excipients compatible with hard gelatin capsules*

Role	Chemical name	Marketed name (Company)	HLB	Compatibility reference
Oily vehicle	Medium chain triglycerides	Labrafac®WL1349 lipophile (Gattefossé) Kollisolv® MCT 70 (BASF) Crodamol™ GTCC (Croda) Miglyol® 812 N (IOI Oleo GmbH)	1	[32]
	Glyceryl monolinoleate	Maisine®CC (Gattefossé)	1	[32]
	Glyceryl tricaprylate/Tricaprate	Captex®300 (Abitec)	1	[32]
	Caprylic/ capric triglycerides	Miglyol®812 (Sasol)	1	[34]
Co-surfactant	Propylene glycol monolaurate 90% (Type II)	Capmul®PG-12 (Abitec) Lauroglycol®90 (Gattefossé)	3	[34]
Surfactants	Linoleoyl macrogolglycerides	Labrafil® M 2125 CS	9	[32]
	Caprylocaproyl polyoxyl-glycerides	Labrasol® (Gattefossé)	12	[34]
	Polyoxyl 35 Castor Oil	Kolliphor®EL (BASF) Super Refined™ Etocas™ 35 (Croda)	12–14	[34]
	Polysorbate 80	Tween™80 (Croda) Montanox™80 (Seppic)	15	[34]

Table 5: *Non-exhaustive list of lipid excipients compatible with hard HPMC capsules*

c. Capsules for controlled release profiles

Due to their fast disintegration in gastric environment, all gelatin, HPMC and pullulan based capsules enable a fast release of their content in the stomach. However, some API require a controlled release in the GI tract, either to target enhanced absorption in the intestine or to prevent degradation in gastric environment. To answer this need, particular capsules with delayed release were developed such as the DRcaps™ exhibiting a very limited dissolution in gastric conditions (less than 10% acetaminophen release from size #1 HPMC capsules after 120 minutes in pH 1.2).

If extended gastro-resistance is needed, it is possible to use DUOCAP® capsule-in-capsule method, such as DRcaps®-in-DRcaps® [35,36], represented in Figure 3, or to coat capsules with functional polymers enabling enhanced controlled of the dissolution profiles. However, regarding the second option, the additional coating step needs to be operated in a very narrow process window to ensure homogeneous coating without damaging capsules and their content by too high levels of humidity, solvents or heat and maintain processability on encapsulation machines [37].

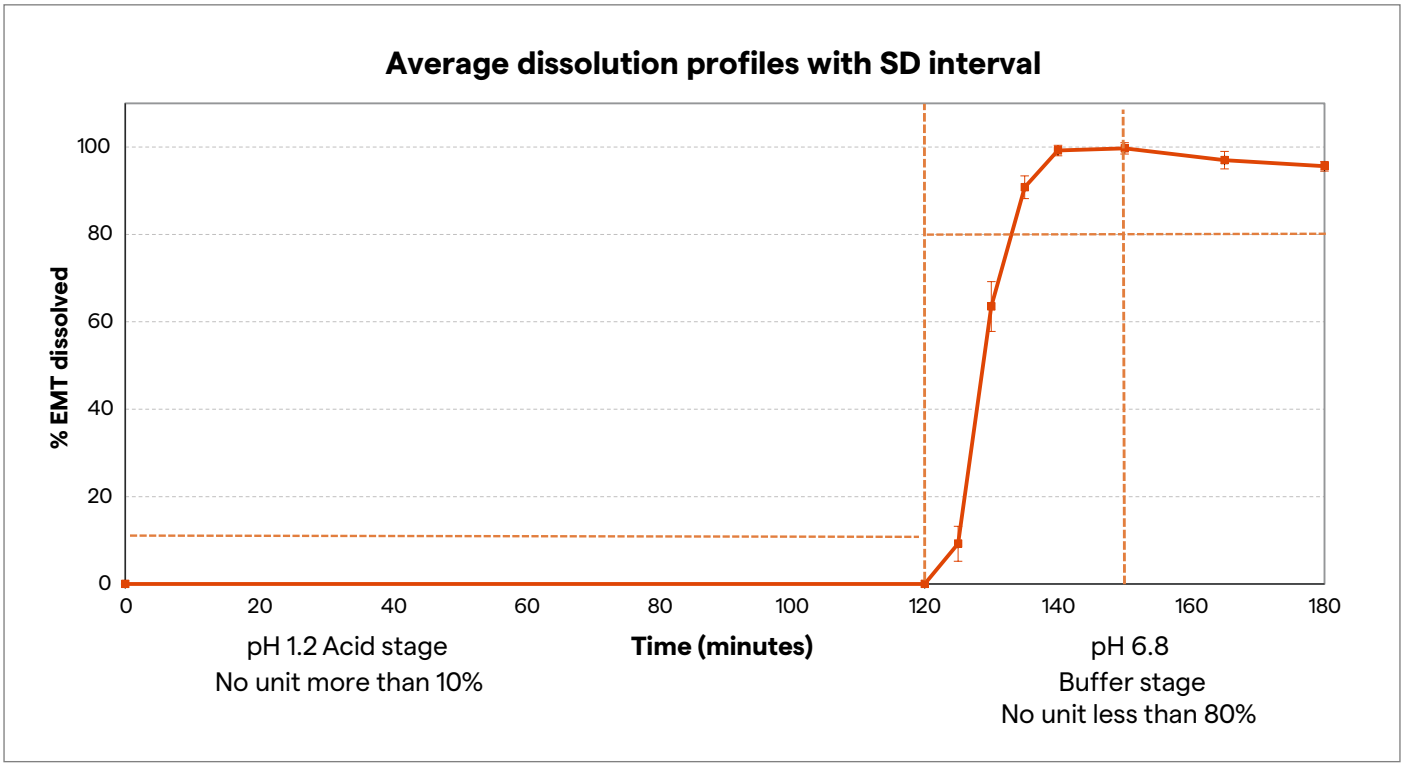
Figure 3: *DUOCAP® technology*

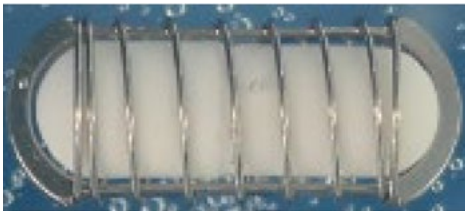
2. Capsules: dosage-form of choice for LBF

Lonza has developed a new ready-to-use enteric capsule, Enprotect®, which only releases its content when reaching the upper pH of the distal part of the intestine, see Figure 4. Its efficacy was proven *in vitro* using the SHIME® (Simulator of Human Intestinal Microbial Ecosystem) model [38] and *in vivo* on healthy volunteers with MRI observations confirming the targeted release in the intestine and highlighting the lack of influence of gastric residence time on capsule performance [39].

Therefore, Enprotect® enables full protection of acid-sensitive molecules such as proton pump inhibitors, but also peptides and proteins, sensitive to pH and gastric enzymes, as well as microbiome.

This capsule was developed through a new technology platform enabling the possibility to generate capsules with uniform functional external layer with preserved machinability on filling equipment. This technology platform opens the gate to a wide range of possibilities, in particular the opportunity to target specific GI zones like colon for specific therapeutics such as Crohn disease [40].





Capsule after 120 min in HCl 0.1N (no deformation)

Capsule after 5 min in pH 6.8 showing start of release

Figure 4: *Enprotect capsule aspect in pH 1.2 and 6.8 and dissolution profile of acid-sensitive model API (esomeprazole) filled in NGE capsule*

d. Licaps design to facilitate encapsulation process

A wide range of capsule filling equipment adaptable to liquid or semi-solid LBF from small to commercial scale are commercially available. They operate on the same principle: formula, maintained in heated tank under nitrogen, is dosed into Licaps capsule with a precise ceramic pump. Filled capsules are then locked before being sealed.

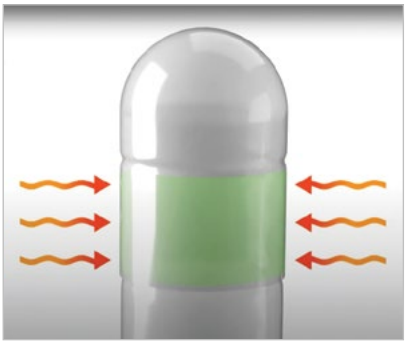
Two methods can be used to ensure sealing of the capsules: banding, which consists in the application of polymer (e.g., gelatin) band on the region of the body and cap overlap, and sealing with LEMS® (Liquid Encapsulation Microspraying Sealing) technology where a solution is sprayed in the overlap region to enable body and cap fusion after application of gentle heating. Whereas the first method require careful adjustment of polymer viscosity and positioning of the band, the second method is easily adaptable to all capsule sizes and guarantees strong capsule sealing.

Sealing method is facilitated by the use of capsules with the patented Licaps® design presenting a 4 times larger seal zone than traditional capsules, Figure 5, and compatible with all standard filling equipment.

Filled and sealed capsules are let to equilibrate for one hour in ambient conditions followed by 20 minutes under vacuum to anticipate leak issues. Capsules are then sorted and packaged in boxes before final packaging in bottles or blisters. A schematic representation of an encapsulation line is represented in Figure 6.

Starts with a specially designed capsule, with a 4x larger seal zone compared to traditional banding method

Sealing fluid is applied



Gentle heat fuses the cap and body together, protecting against leaks

Figure 5: *Sealing liquid or semi-solid filled capsules with Licaps® design*

2. Capsules: dosage-form of choice for LBF

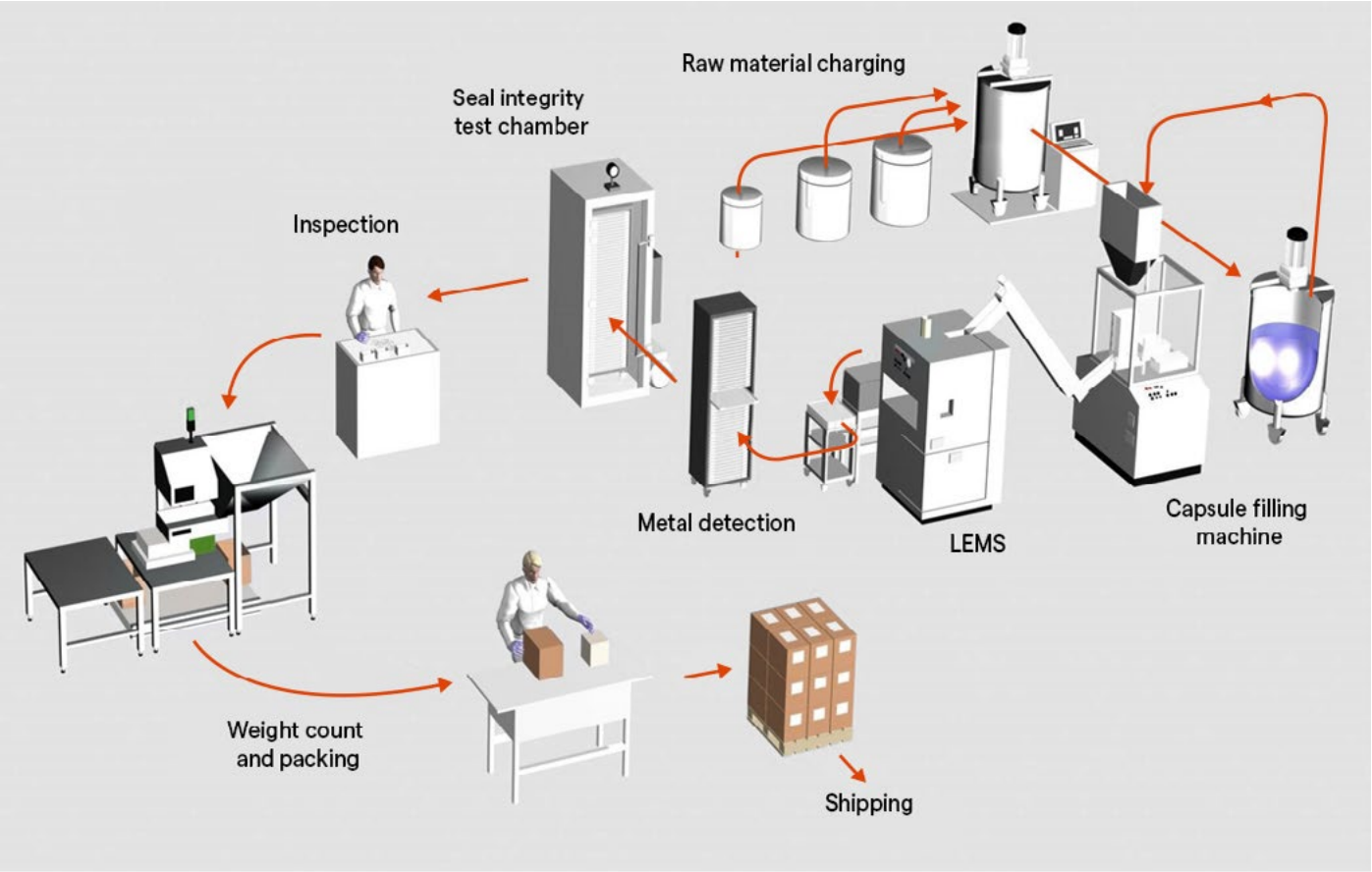


Figure 6: *Schematic representation of an encapsulation line using Licaps® sealing technology with (1) formulation preparation, (2) tank containing formulation under agitation and nitrogen, (3) filling and (4) sealing zone, (5) equilibrating zone, (6) vacuum testing zone, (7) capsule sorting area, (8) counting and packaging, (9) labelling and (10) storage, adapted from [31]*

3. Conclusion

In virtue of their diverse pharmaceutical benefits including ability to dissolve PWS drugs, increase lymphatic absorption, decrease food effect as well as their capacity to increase macromolecules protection against proteolytic degradation and enhance their permeation across the intestinal barrier, LBF represent a smart approach to enhance oral bioavailability of numerous APIs. Combined with hard capsules, they offer a wide range of possibility to easily develop oral dosage forms with controlled release profiles and precise dose uniformity.

Furthermore, combination of LBF and encapsulation technology enables rapid preclinical developments with ready-to-use excipients and capsules, promoting increased small scale trial capacity and facilitated implementation on adapted lab-scale and manufacturing-scale filling machines.

4. Glossary

API = Active Pharmaceutical Ingredient;

GI = Gastro-Intestinal;

HIP = Hydrophobic Ion Pair;

HPMC = Hydroxypropyl methycellulose;

LBF= Lipid-Based Formulations;

log P = octanol/water partition coefficient;

LS = Lipophilic Salt;

NCE = New Chemical Entity;

PEG = Polyethylene glycol;

PWS = Poorly Water-Soluble;

RH = Relative Humidity;

SEDDS = Self-Emulsifying Drug Delivery Systems

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Contact us or your Lonza Capsules & Health Ingredients sales representative **for more information**

United States: 888-783-6361 / solutions@lonza.com
EMEA: +33 389 205725 / solutions.emea@lonza.com
South East Asia: +66 2-260-3812 or +62 21 875 2226 / solutions.apac@lonza.com
China: +86 21 6305 8866 / contact.cn@lonza.com
Japan: +81-42-700-6700 / solutions.jp@lonza.com
India: +91 124-6052900 / contact.india@lonza.com
Australia: +61294212700 / solutions.apac@lonza.com

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