RXL® Portfolio

Reduced Crosslinking Gelatins

- Improved shelf life
- Compliant fill release
- New formulation opportunities

GELITA

RXL® Portfolio:

Redefining Capsule Technology

The RXL® portfolio includes specially designed Gelatins to reduce crosslinking in softgel capsules. They provide improved stability even under extreme storage conditions with regard to temperature and humidity. These innovative Gelatins allow for the exploration of new challenging capsule fills with reactive fill components. The shelf life of capsules comprising RXL® is significantly extended due to the reliable solubility of the capsule shell.

Gelatin Capsules: Performance Profile

- ***High precision single dosage form***
- ***Protect active ingredients***
- ***Offer high bioavailability***
- ***Present neutral taste and odor***
- ***Promote patient compliance***

Added Value with GELITA's RXL® portfolio

- ***Improved anti-crosslinking properties, adjustable to fill reactivity***
- ***Long-term stability***
- ***Compliant fill release***
- ***Production in compliance with USP/EP* and EDQM certified*****
- ***Easy machinability***
- ***Improved dissolution performance***
- ***Special design of molecular weight profile***
- ***Available from various raw materials***

** w/o Ultra; ** bovine origin*

RXL® PRIME
Improving shelf life and stability

RXL® ADVANCED
Improving shelf life and stability

RXL® PRO
Improving shelf life and stability

RXL® ULTRA
Maximum shelf life and stability

Reduced Crosslinking

Despite its versatility, certain environments — such as high temperatures and humidity — and even components of the filling can cause the gelatin in the capsule shell to react and crosslink.

Stress factors for gelatin capsules

Heat & Humidity
- *Climatic zones II – IV*
- *Seasons*

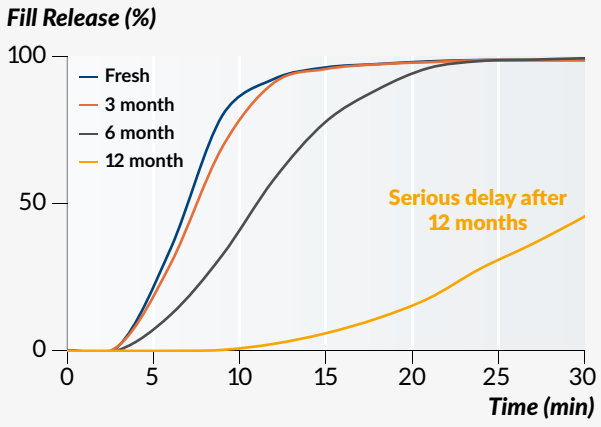
Shelf life & Chemical reactions
- *Fill/Shell components*

Crosslinking occurs when protein molecules (in the shell) interact with compounds containing reactive molecules such as aldehydes, ketones, terpenes and peroxide intermediates. These ingredients are often found in plant and herbal extracts, rich in e. g. polyphenols. Alternatively, minerals or certain vitamins can cause crosslinking, as well as reactive APIs, like e. g. steroid-hormones or certain antibiotics (tetracyclines). With time, soft capsules become increasingly less soluble, which results in longer dissolution times in the gastrointestinal tract and slower fill release rates.

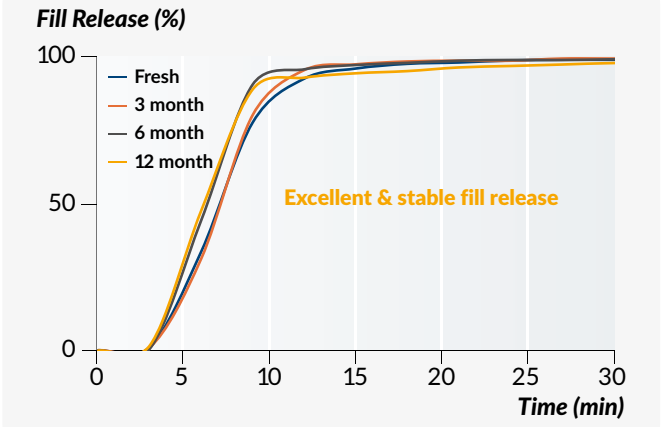
RXL® Stability Studies

- *Fill release during dissolution of soft capsules*
- *Accelerated storage conditions (40°C / 75 % r.h.)*

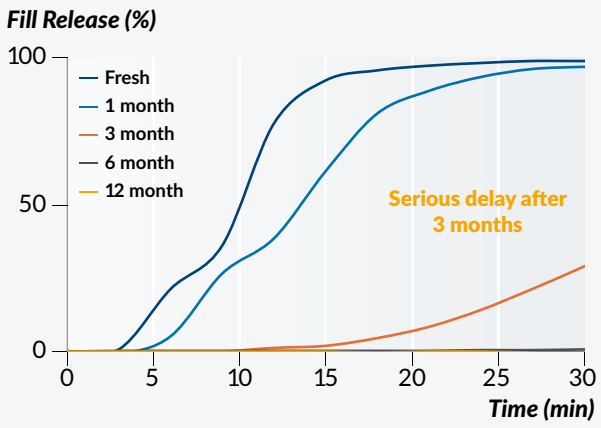
Standard bovine bone softgels



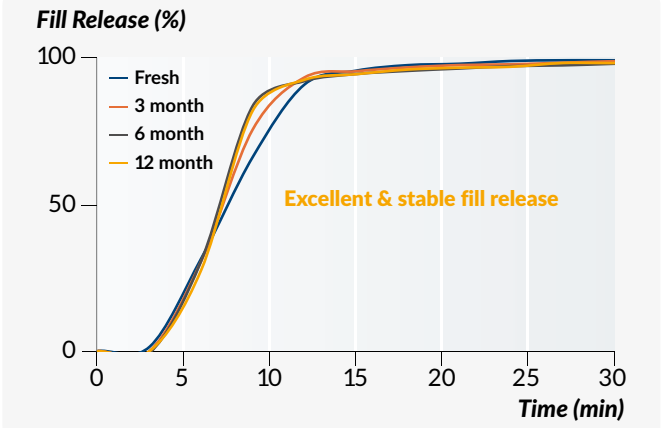
RXL® Prime bovine bone softgels



Standard bovine hide softgels



RXL® Prime bovine hide softgels

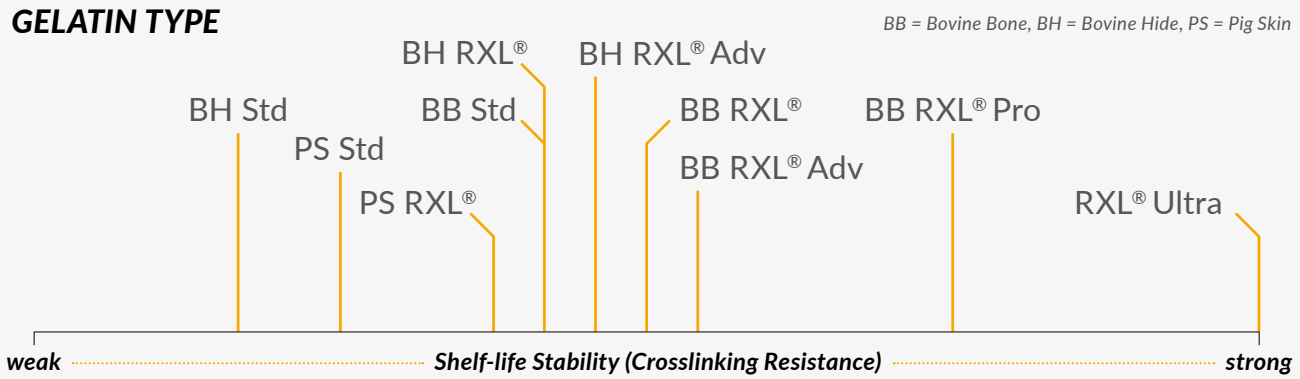


Excellent fill release & reliable performance

Softgels comprising RXL® Prime show significantly improved performance in dissolution while standard bovine bone gelatin capsules show seriously delayed fill release after several months of accelerated storage. Bovine hide gelatin capsules are even more prone to crosslinking and can lead to serious delays in dissolution after a short time. The anti-crosslinking effect of RXL® Prime provides excellent fill release over the whole storage time – for all raw material types!

Quantification of the effect

The RXL® portfolio offers a wide range of anti-crosslinking effect, giving ultimate flexibility for formulators and crosslinking promoting fills.



GELITA Pharma Institute

Managing the fill-shell interaction

CHALLENGING APIS/EXCIPIENTS:

- ***Functional groups***
  - *ketones, formaldehyde, epoxides, isocyanate, carboxyl, …*
- ***Traces of aldehydes can be present in***
  - *fill components like PEG, oils, plant extracts …*
  - *storage environment, packaging material*

GPI PROVIDES KNOWLEDGE AND SUPPORT:

GELITA Pharma Institute provides in-depth knowledge to classify fills and formulations and assign them to the different RXL® qualities. This way, we supply a reliable basis for selecting the optimum capsule gelatin.

RXL® Ultra:

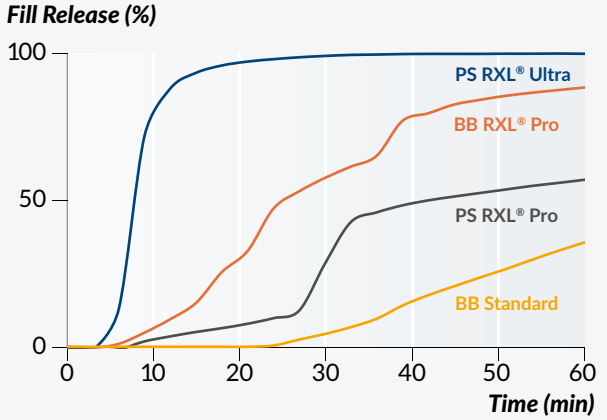
The Benchmark in Anti-Crosslinking Performance

As a new part of the RXL® product family, the modified gelatin RXL® Ultra is the benchmark in anti-crosslinking performance for gelatin-based excipients. While maintaining the known benefits in softgel production for gelatin, RXL® Ultra provides ultimate potential to solve even extreme crosslinking and – in the end – delivers reliable products to the consumer.

No crosslinking even with extreme crosslinking agents

The comparison of soft capsules stored for 8 weeks at 40° C in MCT with a proportion of peppermint oil as an extreme crosslinking agent shows: strong crosslinking with the "gold standard" bovine bone gelatin 160 Bloom, significant crosslinking with the RXL® Pro grades and substantially zero crosslinking with RXL® Ultra.

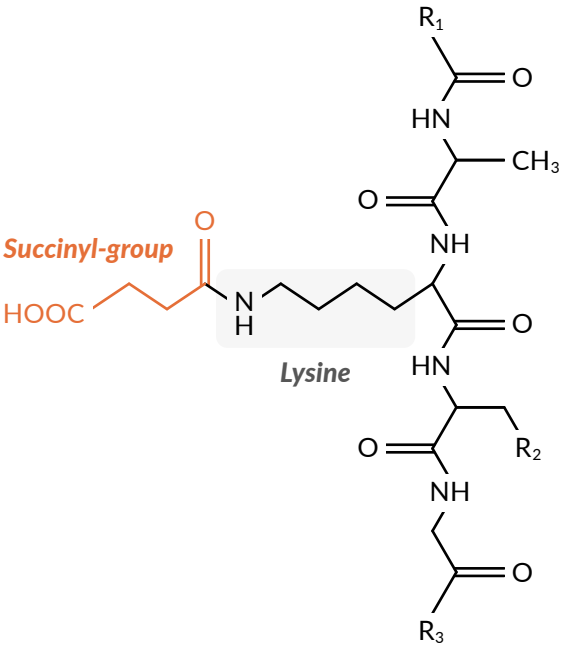
8 weeks, 40°C, MCT & peppermint oil as exemplary extreme crosslinking agent



RXL® Ultra is currently only available in the European Union and for OTC/Rx Products.

THE SCHEME OF THE SUCCINATED GELATIN SHOWS:

– ***The modification at the $-NH_2$ amino group of the lysine side chain blocks crosslinking reactions.***



The RXL® Gelatins portfolio *at a glance*

- *Promotes regulatory and consumer compliance*
- *Improves shelf life and reduces crosslinking*
- *Effect size adaptable to reactivity of fill*
- *Works even at high temperature and humidity conditions*
- *Opens opportunities to encapsulate new fill types (e. g. plant extracts)*
- *Designed for Rx, Gx, OTC and H&N products*

Protected by Patents

E. g.:
- Europe: 1 885 771
- USA: 7,485,323 (Product)
- USA: 7,897,728 (Process)
- China: ZL200680009917.1
- Brazil: PI 0611399-0
- India: 258325

RXL® Gelatin
Types, Pharmaceutical Grade

RAW MATERIAL	Name of gelatin	Bloom [g]	Viscosity 6.67 %/60 °C [mPas]
BOVINE BONE	**RXL® Prime** Bovine Bone Gelatin, 160 Bloom	140 – 180	3.0 – 4.0
	RXL® Advanced Bovine Bone Gelatin, 160 Bloom	140 – 180	2.2 – 3.2
	RXL® Pro Bovine Bone Gelatin, 115 Bloom	92 – 138	1.5 – 2.5
BOVINE HIDE	**RXL® Prime** Bovine Hide Gelatin, 170 Bloom	155 – 185	3.4 – 4.2
	RXL® Advanced Bovine Hide Gelatin, 160 Bloom	150 – 170	2.3 – 3.0
PORCINE SKIN	**RXL® Prime** Porcine Skin Gelatin, 200 Bloom	180 – 220	2.5 – 3.5
	RXL® Advanced Porcine Skin Gelatin, 190 Bloom	160 – 210	2.2 – 2.7
	RXL® Pro Porcine Skin Gelatin, 115 Bloom	92 – 138	1.5 – 2.5
	RXL® Ultra Succinated Porcine Skin Gelatin, 200 Bloom	190 – 220	3.3 – 4.1

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