gelwoRx™
functional bio-compatibility

gelwoRx™ Dsolve portfolio

Advanced solutions for reduced crosslinking and fast dissolution

White paper

PB LEINER
The Clear Solution

Compared to other oral solid dosage forms, soft gelatin capsules or softgels that contain a liquid formulation of the API or nutritional supplement, can provide important clinical benefits. Furthermore, the outcome of consumer preference surveys has confirmed that clear softgels are the preferred administration form of medicines and supplements.

Gelatin offers a broad spectrum of qualities that make it a natural choice for soft caps. It is universally well-tolerated, and its unique technological and biopharmaceutical properties make it a versatile excipient with excellent biocompatibility.

However, soft gelatin capsules face a major challenge, namely crosslinking. Crosslinking is a natural phenomenon occurring in gelatin that causes a longer dissolution time, a slower rate of drug release, and reduced stability and shelf life.

The gelwoRx™ Dsolve portfolio has been specifically designed to provide **advanced solutions for reduced crosslinking and fast dissolution of soft caps.**

TABLE OF CONTENTS

White paper

Advanced solutions for reduced crosslinking and fast dissolution

Clear benefits:

- Reduced crosslinking speed
- Faster dissolution
- Improved bioavailability
- Improved stability
- Extended shelf life

With advances in research and development in the pharmaceutical area, new drugs based on existing or new chemical entities are constantly being brought to the market. The development of alternative formulations of existing active pharmaceutical ingredients (APIs) is mainly driven by the need to improve patient compliance, stability of formulations or drug bioavailability.

According to estimates, more than 40% of new chemical entities have suboptimal biopharmaceutical properties, mainly related to a low solubility in an aqueous medium, which is an important challenge for the absorption if formulated as an oral dosage form. At the same time, some of the existing APIs or nutritional supplements, when formulated in traditional oral dosage forms such as tablets or hard capsules, present with impaired bioavailability which can result in low efficacy and reduced drug response.

Oral bioavailability optimization is one of the main focus areas and it is also one of the most important drivers in drug and formulation development. Soft gelatin capsules or softgels, which are oral dosage forms that contain a liquid formulation of the API or nutritional supplement, can provide **important clinical benefits** compared to other oral solid dosage forms, particularly for the oral delivery of poorly water-soluble compounds (BCS class II or class IV).

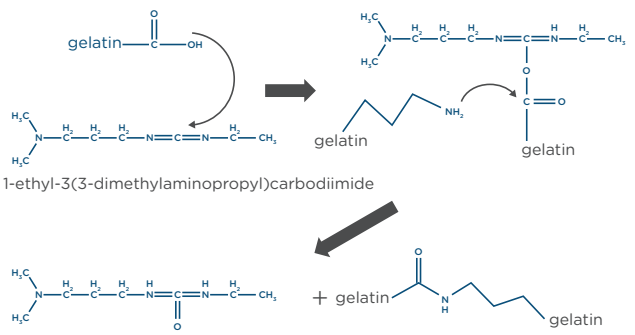
Crosslinking, a natural phenomenon occurring in gelatin
Protein crosslinking is the process of joining two or more protein molecules through intermolecular covalent bonds, promoting the formation of macromolecular structures.

The generation of covalent bonds between proteins can be induced by different routes:
Chemically: caused by chemical crosslinkers or by enzyme catalysis. It is the main responsible route for crosslink formation. Chemical interactions between gelatin and the API, nutritional supplements fills or solvents used for their solubilization (chemically classified as aldehydes, polyphenols, carbohydrates, metal ions, etc.) lead to the formation of firm covalent bonds **(Figure 1).**

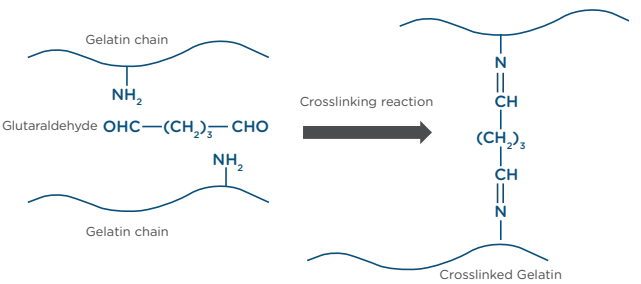
Thermally: exposure to high temperatures (such as storage conditions T > 30°C, relative humidity (RH) > 60%) can cause the formation of covalent bonds, crosslinking within the capsule shell or between the shell and the capsule fill.

Physically: mechanical agitation or photooxidative exposure can form rather weak intermolecular bonds.

Consequently, as the gelatin molecules become larger, polymeric chains develop reduced solubility. While the process occurs in the capsule shell, the solubility of gelatin decelerates and decreases the dissolution of capsules, affecting their stability and fill release.



Chen Et al., Biomed Eng Appl Basis Comm, 2005 (April); 17: 44-49



Rana Imani Et al., Bio-Medical Materials and Engineering 23 (2013) 211–224

Figure 1: Examples of chemical crosslinking of gelatin.
Gelatin has several reactive side groups, such as carboxylic acids, hydroxyl, and amines. The best-known compounds that induce crosslinking reactions with gelatin protein chains are aldehydes. They typically form a crosslink with amino groups of gelatin (e.g. arginine or ε-amino of lysine) via an imine intermediate.

Soft gelatin capsules or softgels, oral dosage forms that contain a liquid formulation of the API or nutritional supplement, can provide important clinical benefits *versus* other oral solid dosage forms.

Crosslinking in soft capsules

While gelatin crosslinking is exploited in the development of new biomimetic tissue scaffolds, it has a negative impact on soft capsules, reducing their stability.

Figure 2 illustrates how external factors, such as increased temperature and relative humidity (left) or chemical crosslinking caused by interaction between capsule fill and shell (right) can induce the formation of an external or internal pellicle – a kind of membrane with a significantly reduced solubility in an aqueous environment. The formation of the pellicle decelerates the capsule shell dissolution and rupture behavior in terms of speed and extent, resulting in a slower drug release and delayed onset of effect.

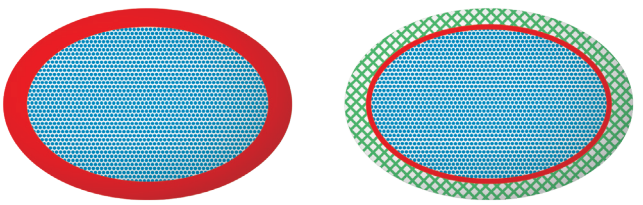


Figure 2: Stability of the soft capsule.

Several characteristics of the gelatin, together with the capsule manufacturing conditions and storage, can influence this crosslinking behavior and bring it to an acceptable level in a controlled way, which will lead to an improved soft capsules product over time.

The gelwoRx™ Dsolve portfolio significantly lowers crosslinking behavior

gelwoRx™ Dsolve portfolio is a range of four pharmaceutical gelatin products – **Dsolve, Dsolve B, Dsolve P and Dsolve xTRA** – especially developed to reduce crosslinking of the soft capsule shell, providing better stability of the oral dosage formulation, faster dissolution of the capsules and rapid drug release, resulting in improved drug bioavailability.

The gelwoRx™ Dsolve portfolio significantly lowers crosslinking behavior, providing a clear solution for soft gelatin capsules

Dsolve PROVEN BENEFITS

Reduced gelatin shell crosslinking

▼

Faster capsule dissolution

▼

Rapid & reliable filling release

▼

Improved stability & increased shelf life of final dosage formulations

Test results show improved performance

Tests have shown improved performance compared to the standard gelatins used in the industry in the presence of a crosslinker. A first step towards achieving a better understanding of crosslinking ability is testing the gelatin. In this regard, PB Leiner has developed an in-house method with a standardized protocol. The results below clearly show that gelwoRx™ Dsolve portfolio products score better than the standard products used in the soft capsule industry for encapsulation. As shown in **figure 3,** in the presence of a crosslinker, gelwoRx™ Dsolve xTRA presented a **45% lower crosslinking tendency** compared to standard soft caps gelatin.

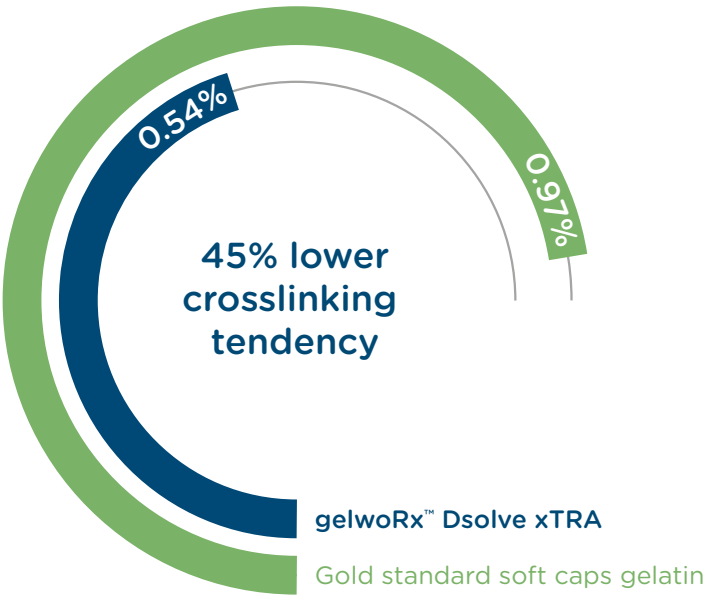


Figure 3: Crosslinking tendency of gelwoRx™ Dsolve xTRA *versus* gold standard soft caps gelatin.

gelwoRx™ Dsolve portfolio: faster dissolution of soft capsules

Lower crosslinking in the capsule shell promotes a faster dissolution of the capsules and rapid drug or nutritional supplement release and faster action. To demonstrate this, tests were conducted on the pilot production of soft capsules with the aim of evaluating their stability.

These soft capsules were submitted to chemical crosslinking, by adding an important amount of crosslinkers in the capsules fill, and to thermal crosslinking by exposing them to a high external temperature of 40°C and high relative humidity of 75% for 6 months **(Table 1).**

The results obtained at 6 months (6M) confirmed that **gelwoRx™ Dsolve significantly outperforms the standard soft capsules gelatin in terms of dissolution (Figure 4).**

Capsule trial parameters	
Machine type	Technophar SGM612
Format	7.5 oval
Filling	PEG400 with added crosslinker
Gel mass	Gelatin, glycerin, sorbitol, water

Table 1: Capsule trial parameter.

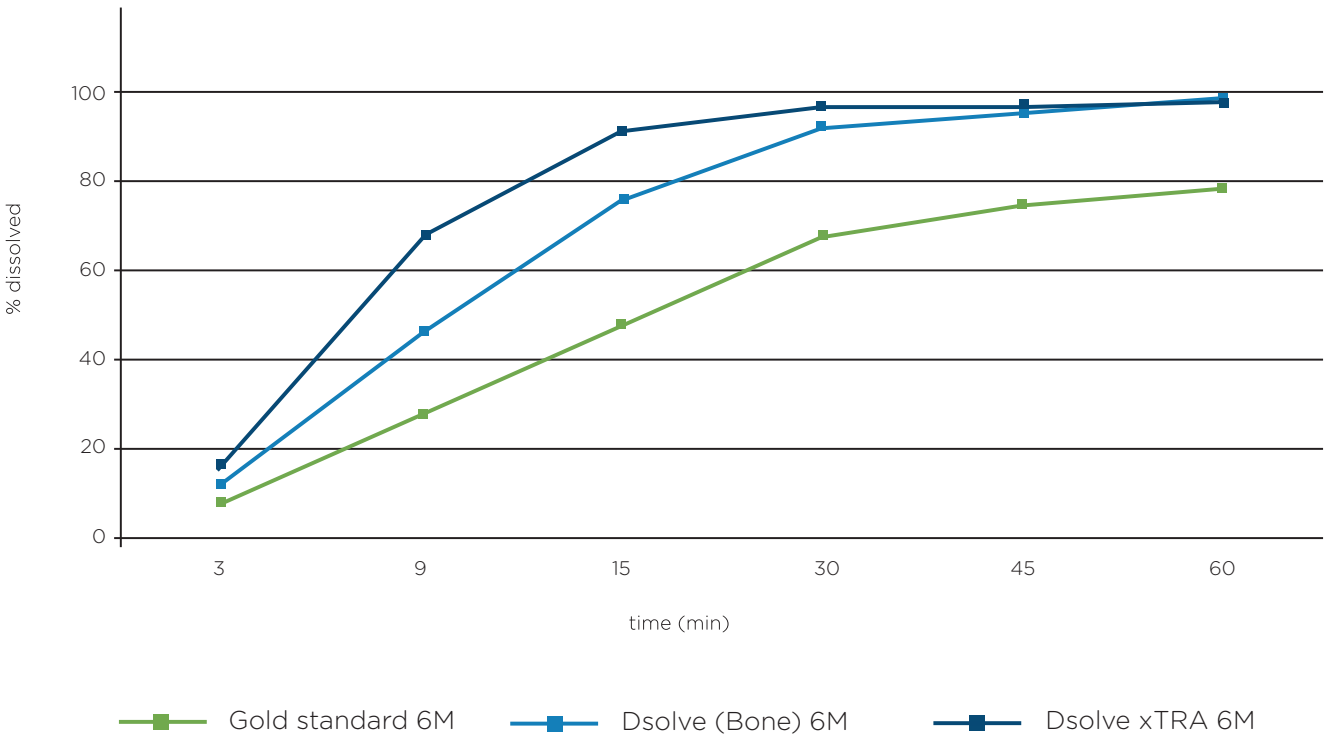
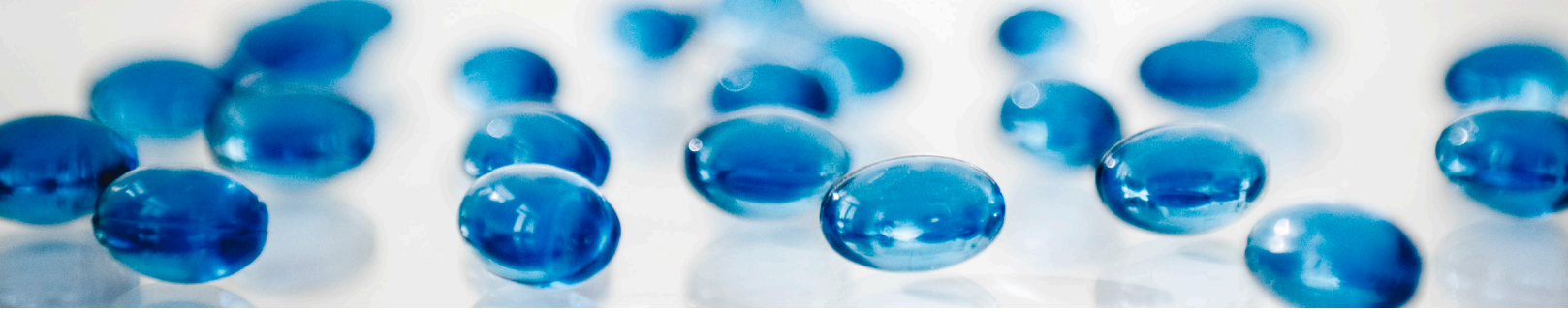


Figure 4: Dissolution rate after 6 months storage (6M) at 40°C/75% RH in the presence of crosslinkers in the capsules filling.



gelwoRx™ portfolio: clear benefits

- Superior dissolution rate
- Faster filling release
- Extended shelf life of final dosage formulations
- Indicated for all soft caps fill that cause crosslinking
- Designed for APIs (Rx and OTC) and nutritional supplements
- Dsolve, Dsolve B and Dsolve P allow for raw material preference choice - Dsolve xTRA allows for even better performance
- Global supply flexibility – production sites located on 3 continents
- Effortless introduction into the current production process

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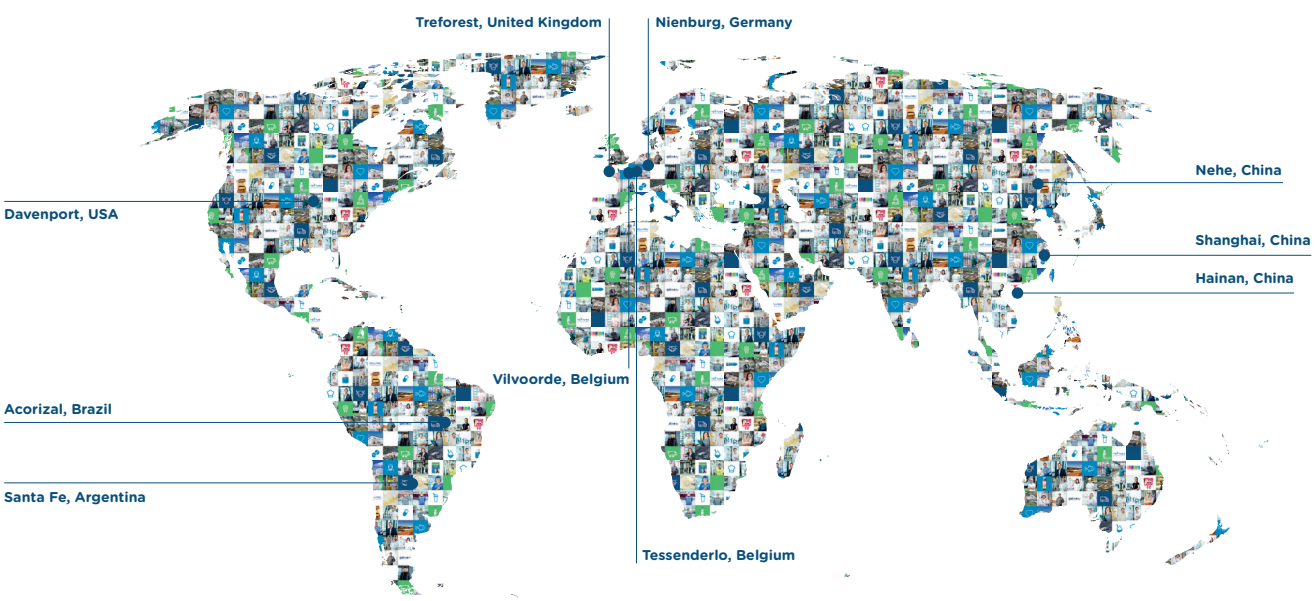
We are here for you, knowledgeable and approachable.



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