An Executive Summary

# The Evolution of Cellulose in Tableting Technology


**Anthony Carpanzano**
*Director of R&D*
JRS Pharma

**Gernot Warnke, PhD**
*Global Head of R&D*
JRS Pharma


## How the evolution from traditional powdered cellulose to microcrystalline cellulose to a new generation of co-processed high functionality excipients can benefit tableting processes including continuous manufacturing applications.

### Overview

The development of co-processed, multifunctional excipients has enabled formulators to address multiple challenges with a single excipient, resulting in enhanced production and better finished product quality. This paper explores how the evolution from traditional powdered cellulose to microcrystalline cellulose (MCC) to a new generation of co-processed high functionality excipients can benefit tableting processes.

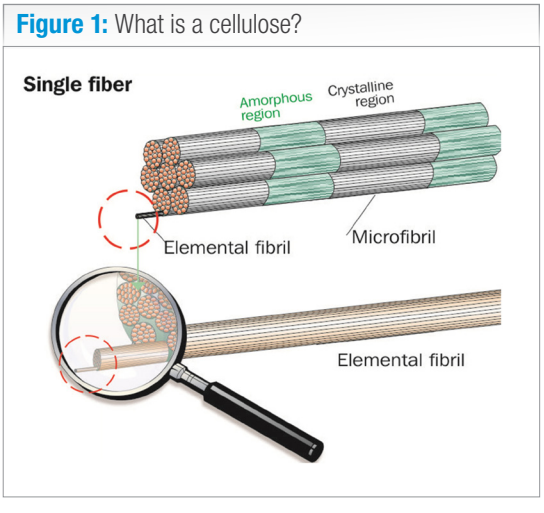
### What Is Cellulose?

Cellulose is one of the most abundant organic compounds on earth. This polysaccharide is a chief constituent of plant fiber. Cotton fiber, for example, is composed of approximately 90% cellulose, and wood is composed of 40–50%. Cellulose, the main structural component of plant cell walls, helps makes plants stable, elastic, and resilient to external influences.

The basic building block of cellulose is glucose. Glucose monomers are connected through ß(1-4) glycosidic bonds. The degree of polymerization in cellulose ranges from 200 to 1500 glucose monomers.

Single polysaccharide chains bundle together in parallel arrays to form cellulose microfibrils, a process that is mediated by hydrogen bonding. This creates a three-dimensional network that is essentially a crystalline substance, though both amorphous and crystalline regions are present (**Figure 1**). Crystal defects are common in cellulose molecules.

**Figure 1:** What is a cellulose?



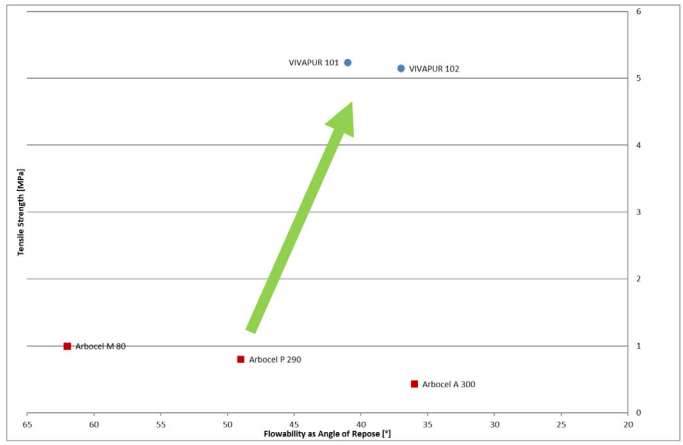


SPONSORED BY

JRS PHARMA The Global Excipient Maker JRS FAMILY A Member of the JRS Group

Pharmaceutical Technology

**Figure 2:** Microcrystalline cellulose improves tabletability.




The conversion of powder cellulose into microcrystalline cellulose dramatically improves the tabletability

Numerous industries take advantage of cellulose's unique structural properties and functionality for host of potential applications, resulting in the commercial production of approximately 100 billion tons of cellulose each year worldwide.

## Microcrystalline Cellulose: Special Grades Address Pharmaceutical Challenges

Powdered cellulose can be made by mechanical fragmentation milling (e.g., as with ARBOCEL® from JRS Pharma). Raw material suppliers can further improve the functional properties of powdered cellulose by combining mechanical and chemical treatments to create microcrystalline cellulose (MCC), which offers additional benefits over powdered cellulose. For instance, JRS Pharma uses mechanical fragmentation followed by partial acid de-polymerization to produce VIVAPUR® MCC and EMCOCEL® MCC.

For drug makers, converting powdered cellulose to MCC in this manner significantly improves tabletability. JRS Pharma, elucidated this benefit by comparing the flowability and tabletability of three different grades of powdered cellulose, MCC, and silicified MCC. The tensile strengths of tablets made with these materials were plotted against the corresponding flowability values (expressed as angle of repose). The resulting "Compactability Map" shows that the MCC had superior flowability and significantly better tabletability as compared to powdered cellulose (**Figure 2 and 3**).

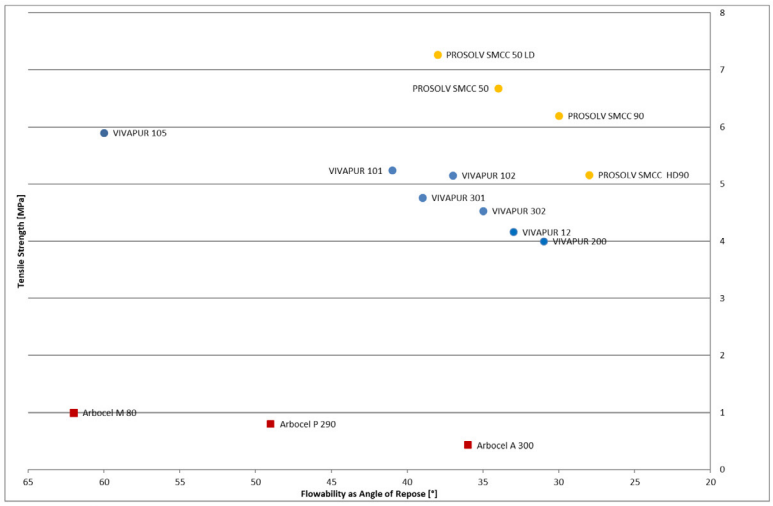
By varying the processing parameters, several grades of MCC can be made, which can help address specific challenges faced by pharmaceutical developers. For example:

- **High-density MCCs** (e.g., VIVAPUR® 301 and 302) can improve powder flow, boost content uniformity when working with high-density APIs, be useful as a carrier for capsule filling, and increase finished product batch weight.
- **Low-moisture MCCs** (e.g., VIVAPUR® 103, 112, 14 and 200 XLM [extra-low moisture]) help with the compression of water- or moisture-sensitive, and hygroscopic APIs. Note that low-moisture MCCs are not anhydrous as are some excipient compounds, but are merely dried to a lower moisture content during production and thus start their shelf lives at a lower value on the moisture adsorption curve than other forms of MCC.
- **Coarse particle size grade MCCs** (e.g., VIVAPUR® 102 SCG [special coarse grade], 12, 14, 200 and 200 XLM) are useful as binders for coarse APIs, improve powder flow, and reduce dust because particles are large.
- **Fine particle size grade MCCs** (e.g., VIVAPUR® 105) are good binders for chewable tablets because they will not have a gritty mouthfeel since particles smaller than about 50 μm are not sensed as gritty in the mouth. They also contribute to better content uniformity for fine particle size APIs by broadening the particle size distribution and boost compactibility in high-dose formulations.

## Optimizing Microcrystalline Cellulose for Direct Compression

Taking the evolution of cellulose-based excipients further, JRS Pharma has improved MCC for direct compression by coprocessing colloidal silicon dioxide and MCC in a spray-drying process. The process, which creates PROSOLV® silicified microcrystalline cellulose (SMCC), begins with a high-purity pulp. The material goes through

**Figure 3:** PROSOLV® SMCC is more compactable than microcrystalline cellulose.




**Silicification leads to an improvement of both compactability and flowability of MCC**

**Figure 4:** Tablets made with PROSOLV® SMCC versus microcrystalline cellulose and colloidal silicon dioxide.

**PROSOLV SMCC promotes interactive blending and, thus, content uniformity.**

**Tablets with blue pigment as model, fine particle size API:**

**PROSOLV SMCC 90 (left)**
**MCC+CSD (right)**

a shredder where the pulp is reduced to smaller more processable pieces, followed by an acid hydrolysis reaction to break down the pulp into its component parts. These initial steps are the same ones used to make MCC, but the material goes through several additional steps to create SMCC. It is then washed and filtered to isolate and neutralize the crystalline cellulose. Colloidal silicon dioxide is added and dispersed in the aqueous MCC suspension; it is intimately mixed with the MCC in a manner that cannot be achieved through simple blending of the two materials. Last, the material is spray dried and the result is PROSOLV SMCC, which is almost dust free and flows significantly better than non-direct compression grade MCC.

PROSOLV SMCC® is 30–50% percent more compactible than MCC (see **Figure 3**). Therefore, the same hardness as observed with MCC tablets can be achieved with less compaction force. This results in more porous tablets which enables faster, more complete drug dissolution.

PROSOLV also has approximately five times the surface area of MCC, which in terms of blend quality, promotes better blending, homogeneity, dispersion, and overall content uniformity. **Figure 4** compares tablets made with PROSOLV SMCC 90 (left) and MCC+CSD (right). Blue pigment was added to the blending as a demonstration of content uniformity. In this example, PROSOLV SMCC 90 promotes interactive blending and clearly creates a more uniform blend.

## Case Study: Low-Dose L-Thyroxine Formulation

A client was making a generic low-dose levothyroxine product but was having content uniformity problems. The original product was made with an MCC/lactose wet granulation process. In an attempt to improve content uniformity, the company tried a direct compression blend with MCC 102, with little benefit.

The client then tried a direct compression formulation with PROSOLV SMCC 90 (102 grade) and saw immediate improvement in content uniformity.

To achieve even better results, the company made a pre-blend of the API with 15% of the PROSOLV SMCC 90 requirement and then geometrically blended it with the bulk of the PROSOLV. Content uniformity again improved as did %RSD.

Going a step further, the client used the same pre-blend of the API with 15% of the PROSOLV SMCC 90 requirement. They then blended it with PROSOLV 50 and PROSOLV 90 (50% each) to try and minimize the disparities between the particle sizes of the excipient and the API. By using that formula and the geometric dilution, the direct compression process achieved excellent content uniformity of 0.08–0.1% RSD (see **Table I**).

**Table I:** PROSOLV® SMCC—l-thyroxine: low-dose API fomulation study.

| Formula | Process | %RSD |
|---|---|---|
| Original product | MCC/lactose wet granulation | 5 - 8.0% |
| MCC blend | Direct compression blend with PH 102 | 5 - 8.0% |
| PROSOLV® blend | Direct compression blend with SMCC 90 | 2 - 2.5% |
| PROSOLV® pre-blend | Pre-blend with 15% of SMCC 90 requirement | 0.8 - 1.0% |
| PROSOLV® mixed grade pre-blend | Pre-blend with 15% of SMCC 90 requirement; titrated with 50/50 SMCC 90 and SMCC 50 | 0.08 - 0.1% |

**Table II:** PROSOLV® Easytab grades.

| | | Filler / Binder | Glidant | Disintegrant | | Lubricant | | |
|---|---|---|---|---|---|---|---|---|
| EASYtab Grade | Developed for | MCC | CSD | Croscarmellose Sodium | SSG | Palm Kernel Oil saturated, DATEM | PRUV® SSF | Magnesium Stearate |
| SP | Pharma | x | x | | x | | x | |
| NUTRA | EU | x | x | x | | x | | |
| NUTRA CM | Russia, Brazil, EU and USA | x | x | x | | | | x |
| NUTRA GM | China, Korea | x | x | | x | | | x |
| NUTRA CP | USA | x | x | x | | | x | |

**Figure 5:** PROSOLV® Easytab SP: co-processed excipient.

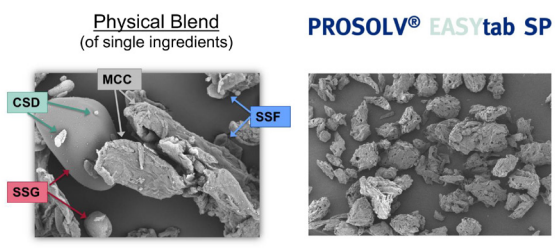



**Table III:** Piroxicam–PROSOLV® Easytab SP tablet properties.

**Case Study: Piroxicam Formulation**

| Properties | PROSOLV® EASYtab SP Formulation 1 | Physical Formulation 2 |
|---|---|---|
| Tablet Weight | 200 mg | 200 mg |
| Crushing Strength | 70 N | 70 N |
| Disintegration Time | 7 sec. | 9 sec. |
| Friability | 0.02 % | 0.02 % |
| Tablet Weight Uniformity, RSD | 0.26 % | 0.37 % |
| Tablet Hardness Uniformity, RSD | 3.59 % | 5.19 % |
| API Content Uniformity, RSD | **1.62 %** | 19.59 % |

Improved API content uniformity &
higher uniformity of tablet weight and hardness

Moreover, eliminating the wet granulation process saved manufacturing time and reduced batch losses.

## All-in-One Excipients for Direct Compression

One excipient that is particularly suitable for direct compression is PROSOLV® EASYtab, a ready-to-use all-in-one excipient. EASYtab (available in several grades, see **Table II**) combines the following ingredients in one excipient (see **Figure 5**):

- Microcrystalline cellulose (filler/binder)
- Colloidal silicon dioxide (glidant)
- Superdisintegrant
- Lubricant

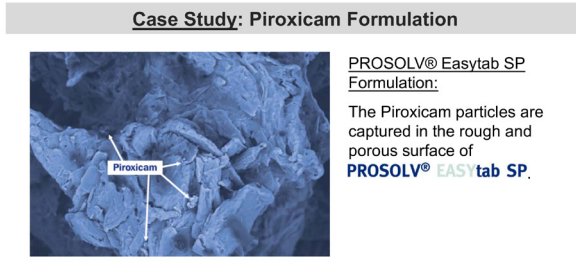
A study was designed to examine the effect of using the all-in-one excipient versus all of the components as separate ingredients in a formulation. The first formula combined 5% piroxicam (a challenging API due to its waxy nature and tendency to clump into agglomerates) with 95% PROSOLV® EASYtab SP. The second formula combined 5% piroxicam with the four separate ingredients present in PROSOLV® EASYtab: VIVAPUR® MCC, CSD, Vivastar P (sodium starch glycolate), and PRUV® (sodium stearyl fumarate) in the same percentages as in EASYtab SP.

While tablet weight, crushing strength, disintegration time, and friablility were all about the same between the two formulations, tablet weight uniformity, tablet hardness uniformity, and API content uniformity were all improved in Formulation 1 because the PROSOLV® EASYtab material enhances blending (**Table III**).

> “Tablet weight uniformity, tablet hardness uniformity, and API content uniformity were all improved in Formulation 1 because the PROSOLV® EASYtab material enhances blending.”

Under scanning electron microscopy (**Figure 6**), one can see that the porous surface of the piroxicam particles trap the piroxicam particles and lead to a very uniform

**Figure 6:** Piroxicam–PROSOLV® Easytab SP blend.




dispersion. The material is also less prone to segregation because of the resulting ordered mixing.

Additional studies suggest PROSOLV® EASYtab does not sacrifice tablet hardness even though it includes a lubricant. Conversely, hardness in tablets made with a physical blend of EASYtab components was lower by comparison, thus indicating that the lubricant (sodium stearyl fumarate) when blended separately, reduced cohesive strength.

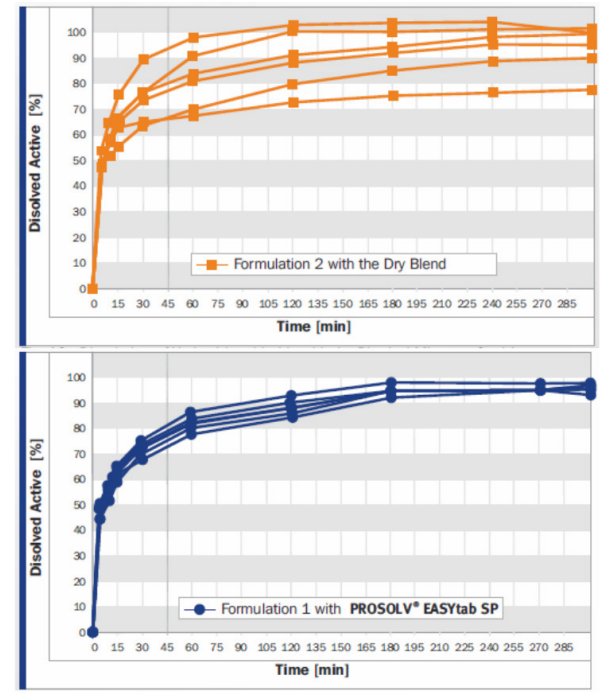
A separate study was done involving Formulation 1 (a blend of 12.5% hydrochlorothiazide and 87.5%

> The PROSOLV® family of high-functionality excipient promotes blending through reduction of the interparticulate cohesive forces which cause fine particles to agglomerate.

PROSOLV® EASYtab) versus Formulation 2 (12.5% hydrochlorothiazide plus a physical blend of EASYtab components). The challenge with hydrochlorothiazide is its crystalline morphology, which is plate-like. These structures, with their flat surfaces and jagged edges, tend to stick together on their flat surfaces and resist dispersion under the relatively gentle conditions of blending. The PROSOLV® family of high-functionality excipients promotes blending through the reduction of the interparticulate cohesive forces which cause fine particles to agglomerate. Formulation 1 had 20–30% better compactibility, slightly faster disintegration, 25–50% lower ejection force (especially at high compression), as well as improved tablet hardness, weight, and content uniformity.

Most interestingly, though, the EASYtab formulation showed far higher reproducibility in dissolution compared to the physical mixture (**Figure 7**).

**Figure 7:** Dissolution profiles of PROSOLV® Easytab SP versus physical blend of hydrochlorothiazide.




Due to their plate-like structure, the HCT particles are readily covered by more or less hydrophobic lubricants, thus exhibiting unpredictable dissolution behavior. In case of EASYtab, the lubricant is an integral part of the excipient composite and does not, therefore, affect the APIs surface hydrophobicity and dissolution kinetics

## Summary

Overall, excipients have come a long way since powdered cellulose, particularly with the introduction of all-in-one excipients such as EASYtab®. Designed for direct compression, this excipient can achieve excellent functional tablet properties that cannot be achieved when adding the same components individually to a formulation. PROSOLV® EASYtab also has some special benefits when used in continuous manufacturing applications, but that's a topic for another day.