TECHNICAL INFORMATION

Specific Excipient Requirements in Continuous Tablet Manufacturing

Abstract

Continuous Manufacturing Technology continues to gain importance in pharmaceutical manufacturing.

Although traditional processes like direct compression, roller compaction, or wet granulation are used within the continuous lines, the requirement for ingredients may differ from traditional batch processing.

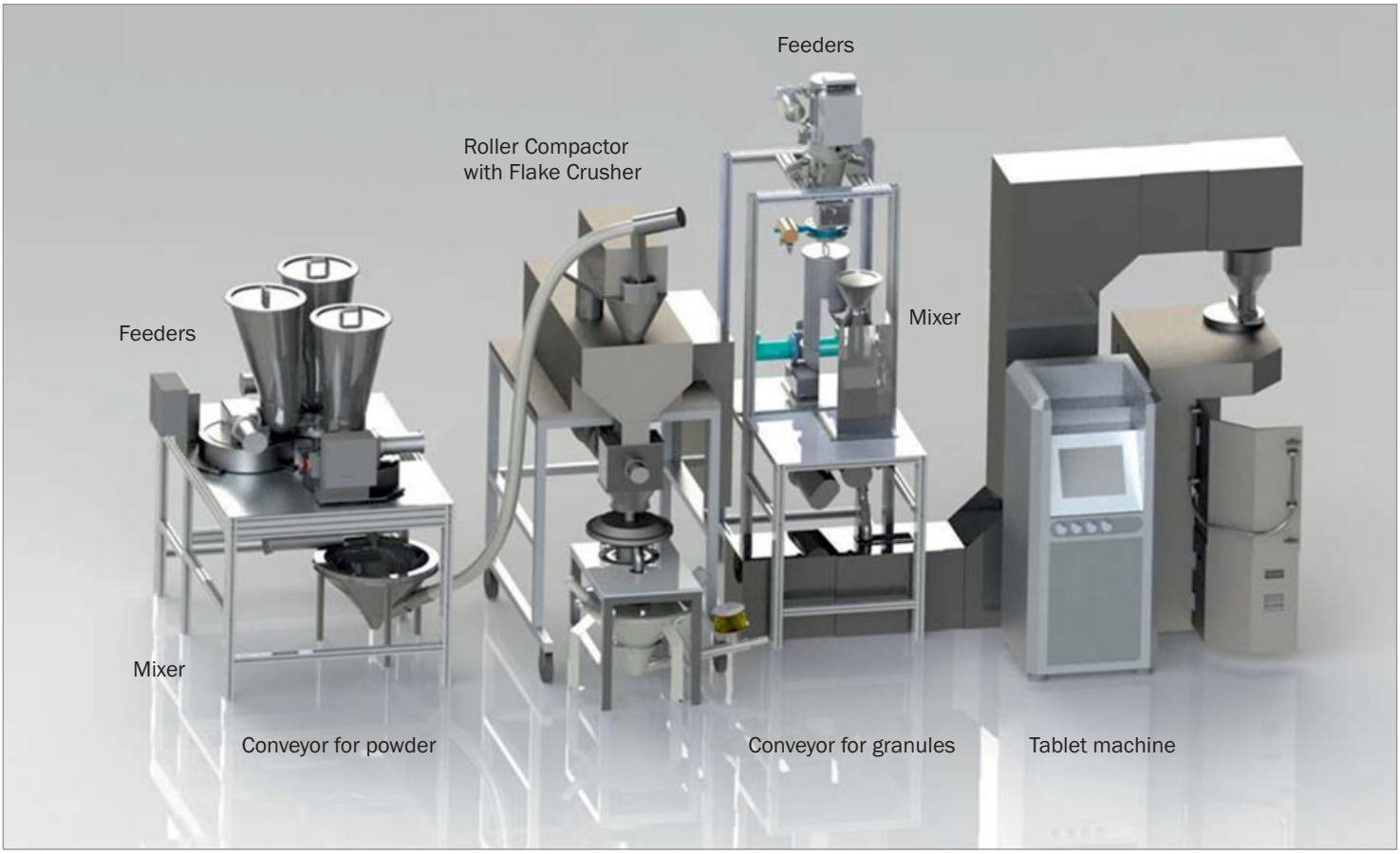
This whitepaper analyzes the various steps of a continuous process in the light of excipient properties.

The evaluation shows that multifunctional excipients such as **PROSOLV® SMCC** and **PROSOLV® EASYtab SP** may be particularly well-suited for continuous processes.

Introduction

While the actual granulation and tableting steps within a continuous process have great similarity with traditional processes, the major difference lies in the feeding and mixing of the ingredients, as well as in the inline monitoring of the blend uniformity. This article aims to identify specific requirements resulting from these differences.

Picture 1 shows the set-up of the research production line used at the University of Eastern Finland in Kuopio. The line consists of a primary feeding and blending unit with three feeders, a roller compactor, a secondary feeding and blending unit for the addition of extragranular ingredients and a tablet press. The content of active ingredient in the powder blend is constantly monitored by NIR measurement. In addition, segmented conveyor systems enable an off-line analysis of samples representing well-defined time intervals of the blender's output.



Pic. 1 Continuous Tablet Manufacturing Line
[Courtesy of University of Eastern Finland, Kuopio]

Specific Excipient Requirements in Continuous Tablet Manufacturing

Feeding

The initial step of the continuous process is feeding the individual ingredients into a continuous blender. A typical tablet formulation consists of at least one active pharmaceutical ingredient (API), a filler/binder, a disintegrant, and a lubricant. Often, flow aids, anti-adherants, and additional dry binders are present, as well. Thus, even a simple formulation consists of at least four ingredients to be accurately fed into the system. The functional contribution of tableting excipients in the tableting blend, in the compaction process, and in the final tablet is shown in Table 1.

		Filler	Binder	Glidant	Disintegrant	Lubricant
Powder	Flowability	x		x		(x)
	Compactability	x	x			
	Homogeneity	x				
Tablet	Mass/Volume	x				
	Toughness	x	x			
	Uniformity	x		x		
	Dissolution				x	
Tabletting	Reduced Wall Friction					x
	Reduced Punch Adhesion					x

Tab. 1 Excipient Functionality

Traditional tableting excipients usually only cover part of these required functionalities. Cost and space limitations may, however, dictate a certain maximum of feeding hoppers to be used in the equipment. The use of multifunctional excipients may, therefore, be advantageous. Table 2 provides an overview of some commercially available, co-processed excipients and the range of functionalities covered by the same.

As shown by this overview, **PROSOLV® EASYtab SP** especially stands out in terms of combining all the required functionalities into a single excipient. **PROSOLV® EASYtab SP** is a co-processed, high functionality excipient containing microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate, and sodium stearyl fumarate in a composite structures.

Using **PROSOLV® EASYtab SP**, the number of necessary feeder units can be reduced to just two, namely one for the active ingredient and one for the excipient composite.

Product	Manufacturer	Functionality			
		Filler/Binder	Glidant	Disintegrant	Lubricant
Cellactose 80	Meggle	Lactose Powdered Cellulose	–	–	–
Ludipress	BASF	Lactose PVP	–	cPVP	–
PROSOLV® EASYtab SP	JRS PHARMA	MCC	Colloidal Silica	SSG	SSF
PROSOLV® SMCC	JRS PHARMA	MCC	Colloidal Silica	–	–

Tab. 2 Functionality of Co-processed Excipients

Blending

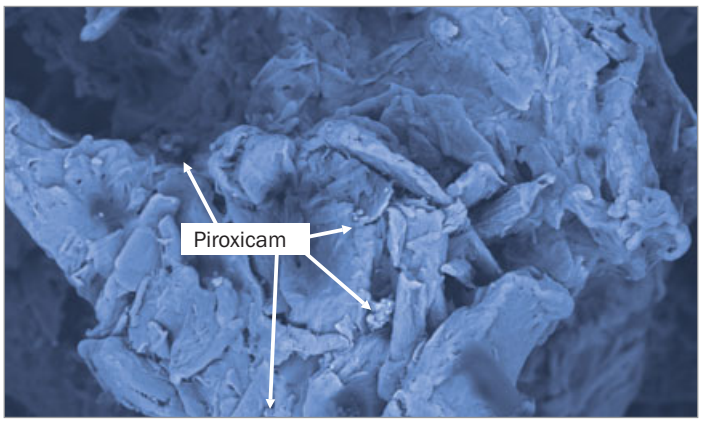
Achieving a good blend uniformity is essential for any tableting process, be it batch or continuous. In continuous processes, blending is particularly demanding, because in comparison to batch processes, dwell-times in the blender are limited. The blending advantages of **PROSOLV®** products are outstanding, due to their unique surface structure, enabling good homogeneity even for low dose APIs via interactive blending. (Picture 2)
A previous study [1] demonstrated, for example, that the content uniformity of low-dose, micronized piroxicam could be substantially improved by using **PROSOLV® EASYtab SP** instead of the corresponding blend of individual excipients. (Table 3)

Reference

[1] JRS Technical Information
Piroxicam Tablets in
Direct Compression with
PROSOLV® EASYtab SP

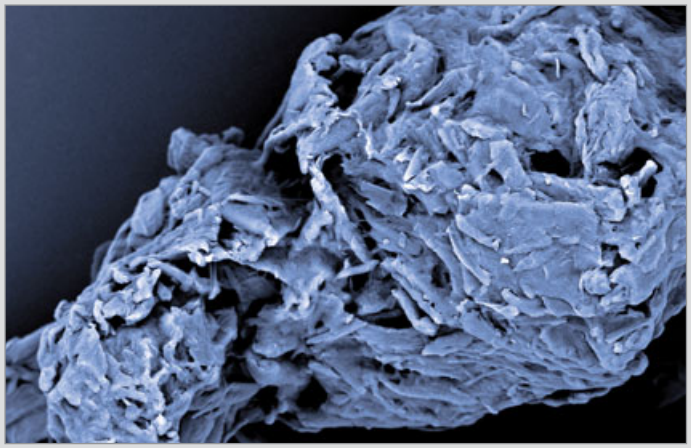
Properties	PROSOLV® Easytab SP Formulation 1	Blend of Individual Excipients
Tablet Weight	200 mg	200 mg
Tablet Hardness	70 N	70 N
Disintegration Time	7 sec.	9 sec.
Friability	0.02 %	0.02 %
Tablet Weight Uniformity, RSD	0.26 %	0.37 %
Tablet Hardness Uniformity, RSD	3.59 %	5.19 %
Active Content Uniformity, RSD	**1.62 %**	**19.59 %**

Tab. 3 Comparison of Tablet Properties of a 10 mg Piroxicam Formulation Prepared with **PROSOLV® EASYtab** or the Corresponding Physical Mixture, Respectively [from 1]
Reference: JRS Technical Information (Page 4)

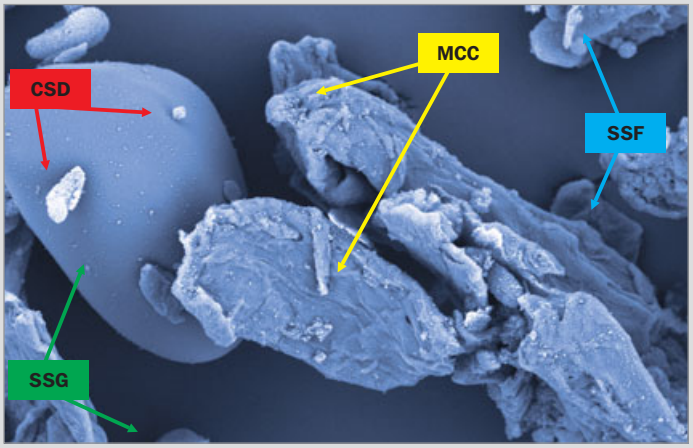


Pic. 2 SEM of a Blend of Piroxicam and **PROSOLV® EASYtab SP**. API Particles are Embedded in the Surface Structure of the Excipient [from 1]

PROSOLV® EASYtab SP



Pic. 3 **PROSOLV® EASYtab SP**
Homogeneous, Monoparticulate Composite of Microcrystalline Cellulose (MCC), Colloidal Silicon Dioxide (CSD), Sodium Starch Glycolate (SSG), and Sodium Stearyl Fumarate (SSF).



Pic. 4 **Physical Blend** of the Four Components.
Heterogeneous Mixture with Risk of Segregation.
No Improvement of Surface Area and Structure.

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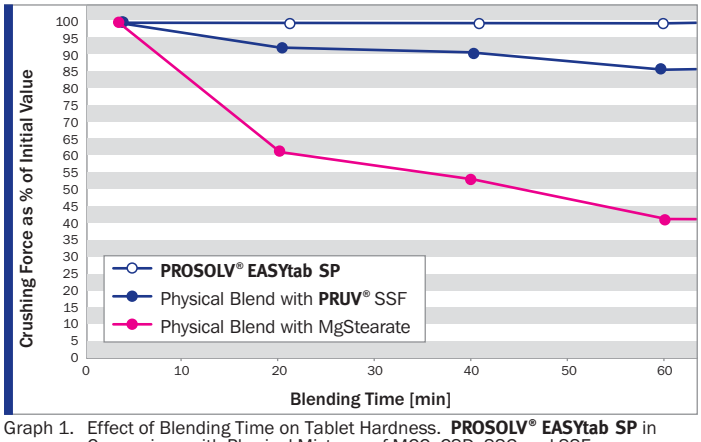
Enhanced Lubrication Robustness

Another critical aspect of blending is the risk of overlubrication resulting from excessive blending. For this reason, continuous blenders usually have a second addition port, enabling the operator to add the lubricant at the final stage of the blending process. In cases where the process involves a granulation step (roller compaction or wet granulation), the lubricant is added during a secondary blending step, during which the extragranular ingredients and, finally, the lubricant are added. In both cases, however, this may lead to insufficient distribution of the lubricant, thus negatively affecting its performance.
It is, therefore, advantageous to select lubricants for continuous manufacturing, which are less sensitive to blending times and conditions.



Graph 1. Effect of Blending Time on Tablet Hardness. **PROSOLV® EASYtab SP** in Comparison with Physical Mixtures of MCC, CSD, SSG and SSF or Magnesium Stearate, Respectively, as a Lubricant.

Graph 1 shows the effect of lubricant blending times on tablet hardness. The magnesium stearate-based formulation exhibits a substantial drop in tablet hardness with increasing blending times. By contrast, the decline in crushing strength is only moderate for the corresponding formulation using **PRUV®** sodium stearyl fumarate as a lubricant. **PROSOLV® EASYtab SP**, due to its composite structure, shows no hardness loss over time at all.

Conclusion

PROSOLV® EASYtab SP presents a set of properties that make it well-suited for continuous processing. Its multifunctionality enables production with just two feeders, since it acts as a filler/binder, flow aid, disintegrant, and lubricant at the same time.

PROSOLV® EASYtab's unique surface structure and good flowability enable fast and segregation-free blending with APIs.

Its all-in-one structure, using sodium stearyl fumarate as a lubricant, provides outstanding robustness in terms of blending times.

To learn more, visit www.jrspharma.com

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