Technical Information

Kollitab™ DC 87 L

All-in-one direct compression excipient for solid oral dosage forms

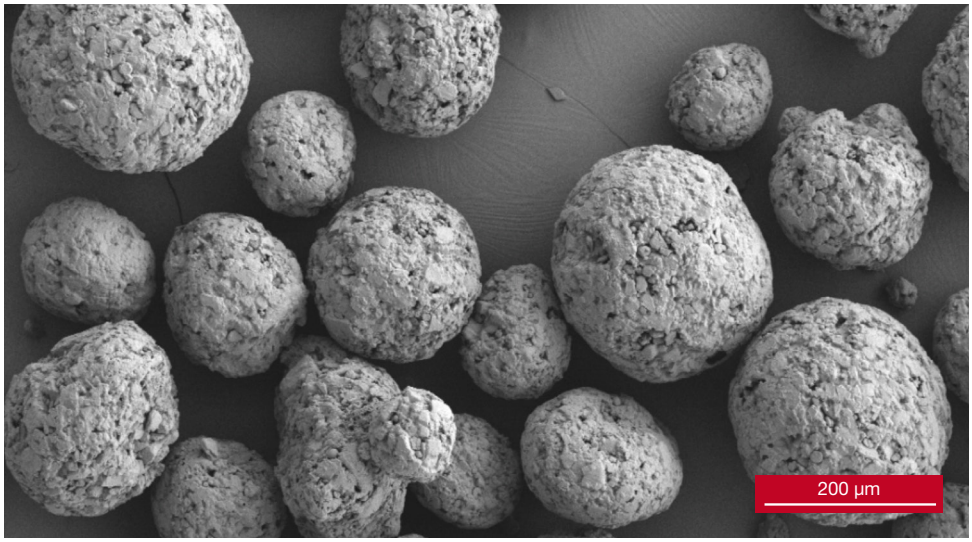

Figure 1. Kollitab™ DC 87 L SEM image (left). Kollitab™ DC 87 L flowing through a funnel (right).

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1. Introduction

Direct compression (DC) formulations typically require multiple excipients to obtain good material flow and compressibility, fast disintegration and efficient lubrication. However, it is often both time-consuming and expensive to determine the proper excipient combinations and concentrations. Even after optimizing the mixture of excipients, the formulation requires several processing steps in order to create the final blend.

Formulations based on coprocessed excipients are a solution to these challenges. Coprocessed excipients combine multiple excipients into a single material to offer an "all-in-one" functionality. Their use reduces the number of excipients required to achieve excellent processability and performance; consequently, they reduce drug product development time, manufacturing complexity, and may significantly expedite time-to-market.

Kollitab™ DC 87 L is an all-in-one lactose-based coprocessed excipient designed for direct compression of solid oral dosage forms. As an all-in-one excipient, it contains all the functionalities required for formulating an immediate release tablet: filler, disintegrant, binder and lubricant. Each ingredient in its composition was expertly selected with the end-use in mind. Furthermore, the manufacturing process was designed specifically to reduce chemical and physical instabilities. The composition can be found below in Table 1. Kollitab™ DC 87 L is composed of four ingredients which are assayed; the results which are listed in the certificate of analysis add up to 100 %.

Kollitab™ DC 87 L is manufactured via aqueous spray drying. A chemical reaction among the ingredients was reduced under the mild processing conditions, and potential incompatibilities were taken into account.

Table 1: Composition of Kollitab™ DC 87 L.

Name	Function	Composition
Lactose *α-Lactose monohydrate[1] – Ph.Eur., USP-NF, JP[2]*	Filler	~87 %
Kollidon® CL-F *Crospovidone – Ph.Eur., USP-NF, JP*	Disintegrant	~9 %
Kollicoat® IR *Polyethylene glycol-polyvinyl alcohol graft polymer – Ph.Eur., USP-NF, JPE*	Binder	~3 %
Sodium Stearyl Fumarate *Sodium stearyl fumarate – Ph.Eur., USP-NF, JPE*	Lubricant	~1 %

[1] The process is optimized to prevent the formation of amorphous lactose, which is undesired due to its instability.

[2] Lactose hydrate

A summary of Kollitab™ DC 87 L components can be found below:

- **Lactose monohydrate** is a water-soluble **filler**. Lactose in general has good compactability, narrow particle size distribution, and provides good blending properties.
- **Kollicoat® IR** is a highly soluble, peroxide-free **binder**. It is commonly used as a film-former, but it also performs extremely well in wet granulation, having similar or even better binding properties than PVP K30.
- **Kollidon® CL-F** is the fine grade of the disintegrant crospovidone. Fine crospovidone particles provide not only fast disintegration, but also excellent compressibility due to their high surface area.

- **Sodium stearyl fumarate** is utilized as a more hydrophilic tablet **lubricant** than magnesium stearate. It has a high degree of API compatibility and robustness to over-lubrication, lessening the impact on drug dissolution and tablet processability when blended for long periods of time. Furthermore, it is suited for high-speed, direct compression of tablets.

Kollitab™ DC 87 L was designed to achieve excellent blend, tableting, and flow properties for manufacturing robust and rapidly disintegrating tablets with high content uniformity.

2. Technical Properties

Kollitab™ DC 87 L is a free-flowing powder comprised of spherical particles produced during the spray-drying process. The median particle size of ~160 µm (Table 2 and Figure 2) and overall morphology is shown in Figure 1.

Table 2: Properties of Kollitab™ DC 87 L (n = 5 batches).

Parameter	Unit of Measure	Typical Values
Air-Jet Sieving:		
250 µm through	wt.-%	95 to 96
160 µm through	wt.-%	47 to 53
32 µm through	wt.-%	2
Volume-based PSD (Laser Diffraction):		
d_{10}	µm	70 to 80
d_{50}	µm	150 to 165
d_{90}	µm	270 to 280
$D_{4.3}$	µm	160 to 170

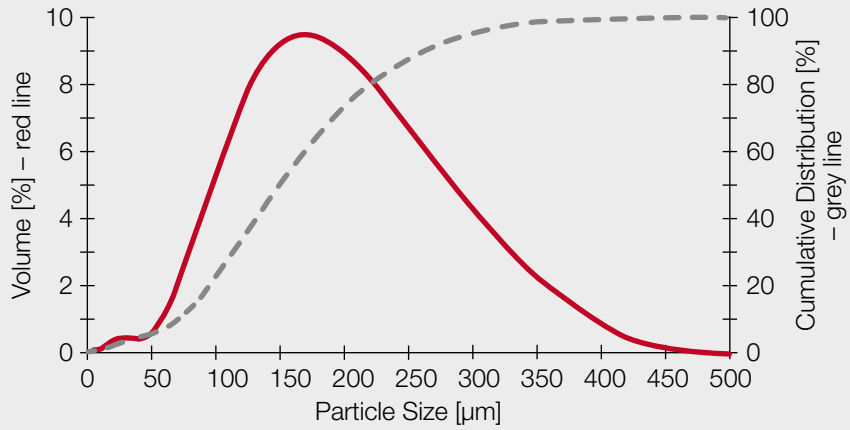

Figure 2: Averaged Particle Size Distribution (PSD) curves of five batches, measured with a Malvern Mastersizer 2000 (Dispersant: 0.5 bar air) in conjunction with a Scirocco 2000 powder feeder (setpoint: 50 %). The solid red line shows the volume fraction values, while the cumulative distribution values are given by the grey dotted line.

Flowability

According to the specifications for the Hausner Ratio and Angle of Repose, Kollitab™ DC 87 L has good and excellent flowing properties, respectively. This ensures high process robustness during blending and compression, and low tablet weight variability.

Figure 3: Kollitab™ DC 87 L flowing through a funnel.

Table 3: Value range for powder characteristics derived from the characterization of five batches of Kollitab™ DC 87 L.

Parameter	Unit of Measure	Typical Values
Bulk Density	g / mL	0.53 to 0.54
Tapped Density	g / mL	0.60 to 0.61
Hausner Ratio	NA	1.11 to 1.15
Angle of Repose	(°)	26.5 to 27.5

Water Sorption

Kollitab™ DC 87 L's manufacturing process was optimized to minimize the formation of hygroscopic amorphous lactose. When opened and exposed to typical 40 – 50 % relative humidity, Kollitab™ DC 87 L has a moisture absorption of less than 3 %, as shown in Figure 4; this is due to the crospovidone. During transport and use, the material is protected from moisture by a thick, double-layer liner.

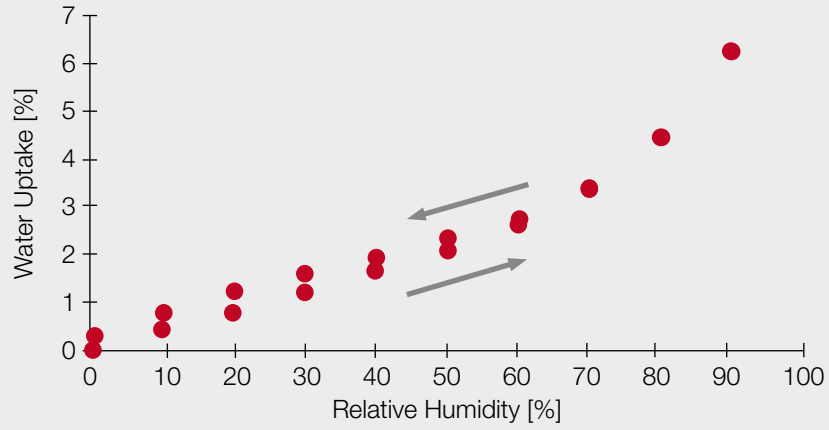

Figure 4: Sorption curve of Kollitab™ DC 87 L measured at 25 °C, determined with approx. 600 mg of sample material.

Compressibility

Kollitab™ DC 87 L can produce high-strength tablets across a broad range of compression forces (low and high), reducing both stress and punch damage from the machine resulting in the reduction of tablet defects.

Figure 5: Tablets of pure Kollitab™ DC 87 L.

Composition	
Kollitab™ DC 87 L	100 %
True Density	1.485 g / cm³

Tableting	
Technology	Compaction Simulator
Type	STYL'One EVO
Punch	10.0 mm
Shape	Round; flat face
Comp. Forces [kN]	6, 9, 14, 18, 23

As a general rule of thumb, the desired tablet strength (in N) is typically a value that is approximately ten times that of the tablet diameter (in mm) or a tensile strength of 1.7 – 2.0 MPa. This value is considered ideal to obtain strong tablets, thus allowing for subsequent processing such as packaging or coating. As shown in Figure 6, strong Kollitab™ DC 87 L tablets can be achieved at low (~9 kN) and high compression forces.

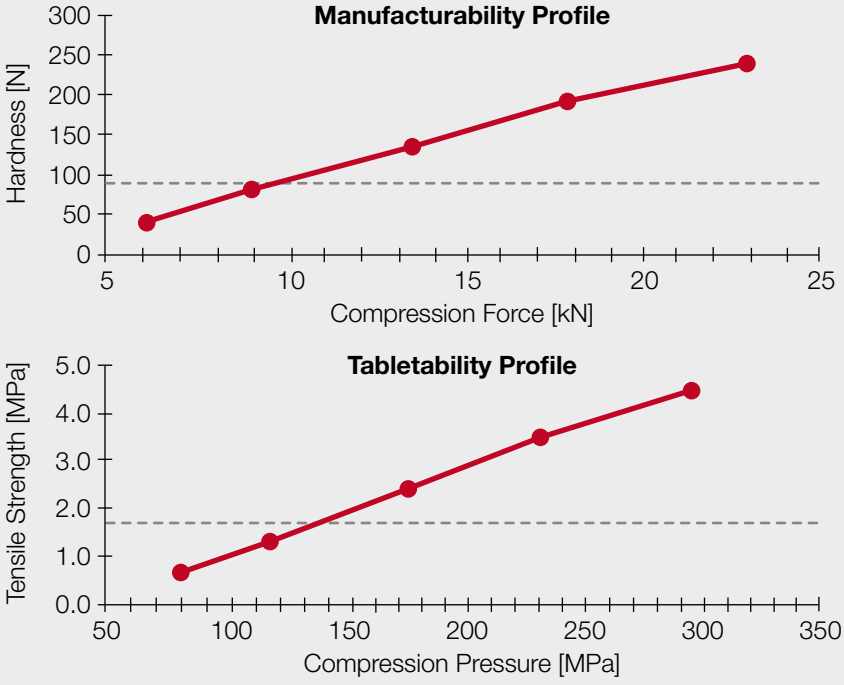

Figure 6: Manufacturability Profile (above) and Tabletability Profile (below) of Kollitab™ DC 87 L tablets.

In accordance with USP chapter <1062>, Kollitab™ DC 87 L tablets show high compressibility and compactability and low ejection force. These are possible due to the binding properties from Kollicoat® IR and Kollidon® CL-F which provide high compactability and compressibility. The complementary lubrication effect from sodium stearyl fumarate reduces ejection force.

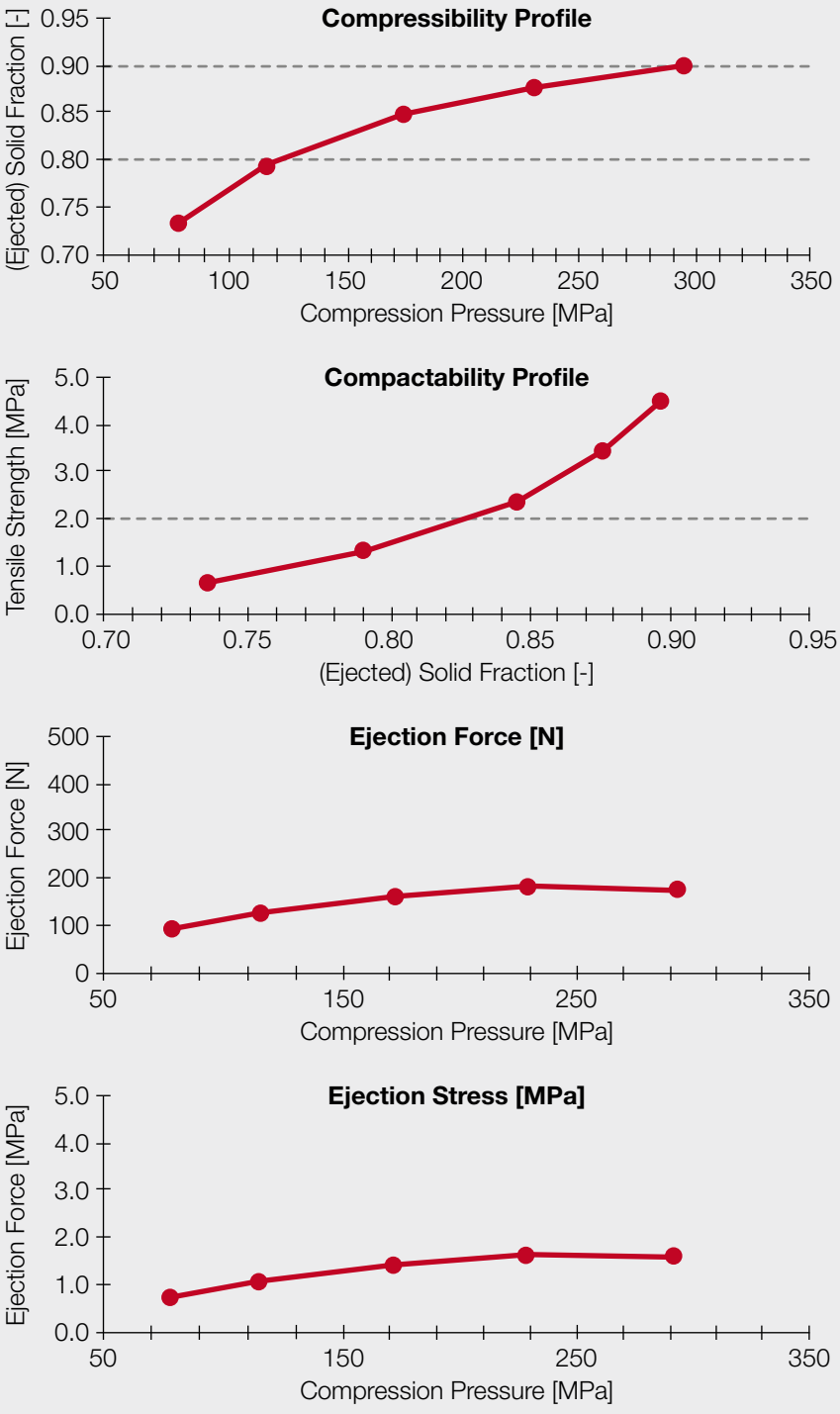

Figure 7: Processability charts of Kollitab™ DC 87 L tablets.

Kollitab™ DC 87 L ensures low tablet weight variability and high tableting performance. As observed in Figure 8, it provides low mass variation in a broad range of compression pressure.

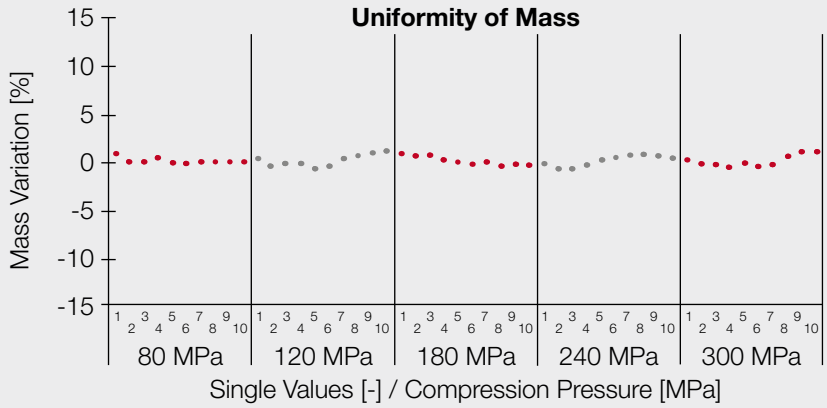

Figure 8: Mass variation (%) of 10 Kollitab™ DC 87 L tablets compressed in a broad range of compression pressure.

Disintegration Time

Kollitab™ DC 87 L achieves fast tablet disintegration for quick and reliable delivery of the intended benefits of the API. This is especially valuable for high-strength tablets that tend to take longer to disintegrate (Figure 9).

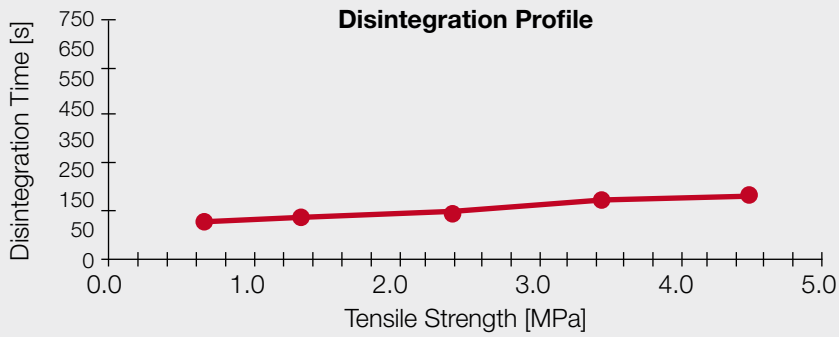

Figure 9: Disintegration time of Kollitab™ DC 87 L tablets in water at 37 °C.

3. Application

Formulation 1:

Aspirin or acetylsalicylic acid (ASA) is a medication used to treat pain, fever, and inflammation and reduces the risk of major adverse cardiovascular events (drugbank.com).

When developing an ASA direct compression formulation, high flowability and compressibility are required to prevent process issues. High strength tablets are required to avoid problems during the coating process, as well as a fast disintegration time to minimize impact on the drug release.

Formulation: »Acetylsalicylic acid 81 mg tablet«

Figure 10: Acetylsalicylic acid crystals (left), and acetylsalicylic acid 81 mg tablets (right).

Tableting Blend	
Acetylsalicylic acid (ASA)	24.5 %
Kollitab™ DC 87 L	75.5 %

Blending
Tumble blender Turbula® T2C 10 min blending time

Sieving (Tableting Blend)	
Oscillating sieving machine ERWEKA AR 400	
Sieve mesh [mm]	0.8
Speed of rotor [rpm]	150 – 250

Tableting	
Technology	Compaction Simulator
Type	STYL'One EVO
Punch	9.0 mm
Shape	round and convex
Comp. Forces [kN]	7.5, 9.3, 11.1, 14.7, 19.1 kN

API Particle Size	
Acetylsalicylic acid crystal	d50: 682 µm
Acetylsalicylic acid crystal (milled)	d50: 280 µm

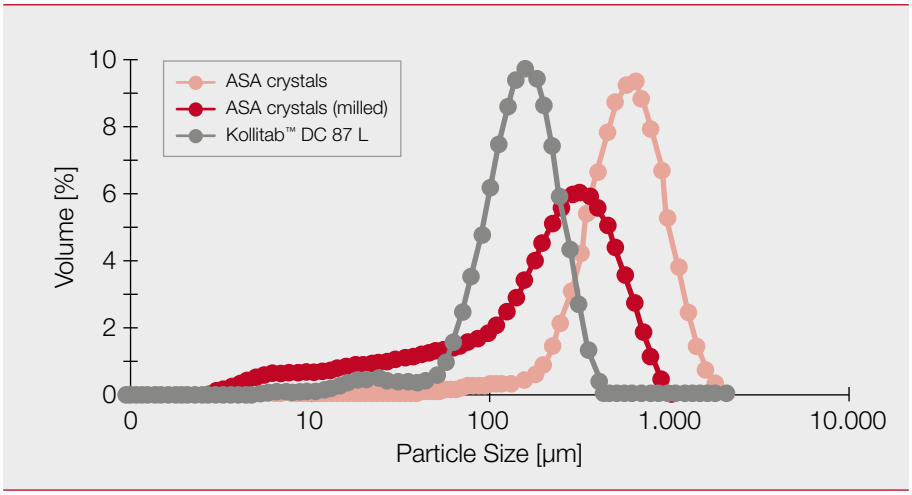

Figure 11: Particle size distribution (laser diffraction) of crystal and milled acetylsalicylic acid (ASA) and pure Kollitab™ DC 87 L.

When adding acetylsalicylic acid to Kollitab™ DC 87 L, an excellent tabletability can be maintained (Figure 12). At a low compression pressure of less than 180 MPa, tablets with a tensile strength of about 2.0 MPa are achieved. There is merely a minor difference between the two ASA grades; tablets of non-milled crystals show slightly lower tensile strength at higher compaction pressures. Independent of tablet strength, tablets with no friability (~0.0 %) were obtained.

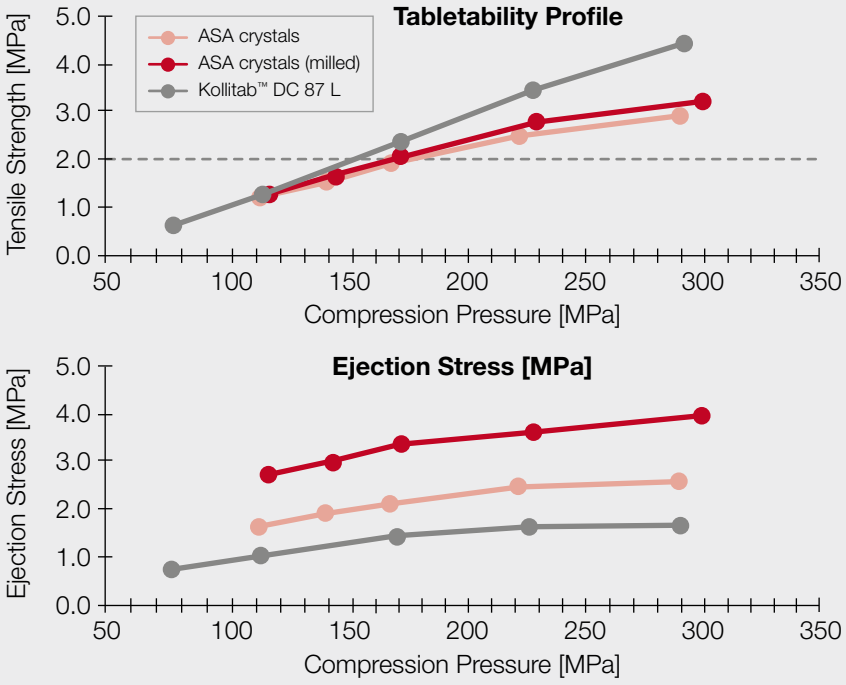

Figure 12. Processability of ASA 81 mg tablets (uncoated).

Adding unlubricated ASA to Kollitab™ DC 87 L leads to an increase of ejection stress, but at an acceptable level that does not impact processability. During drug development, it is important to evaluate the amount of unlubricated surface area that is brought into the formulation, which is dependent on the API's particle size and drug load. Coarse material results in low ejection stress. For high drug load and/or micronized APIs, extra lubricant may be required in the formulation (evaluate case by case).

As shown in Figure 13, ASA tablets had a fast disintegration time of less than 300 seconds regardless of tablet strength or API particle size.

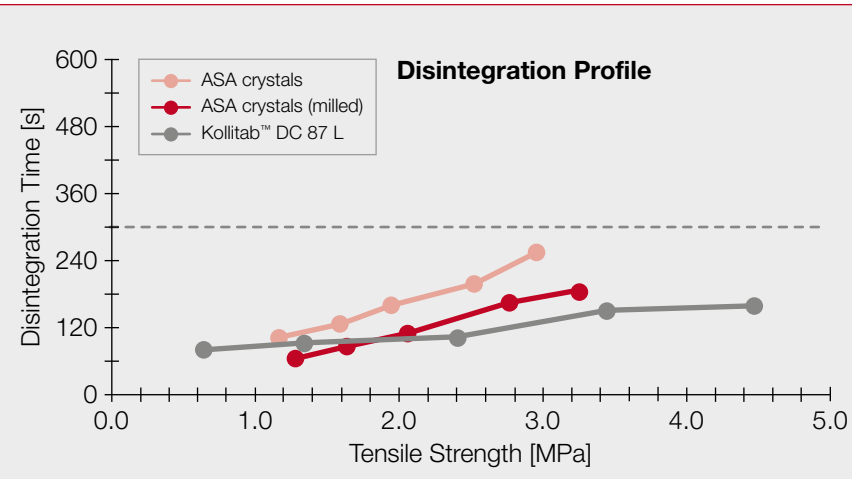

Figure 13. Disintegration time of ASA 81 mg tablets (uncoated) in water at 37 °C.

Formulation 2

Formulation: »Vardenafil tablets«

Vardenafil HCl is a phosphodiesterase-5 inhibitor indicated to treat erectile dysfunction (drugbank.com). It is a fine powder that impacts drug flowability and processability, making it a challenging drug for direct compression.

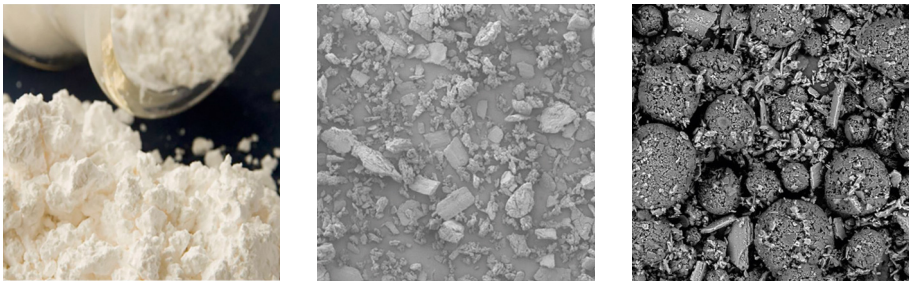

Figure 14: Vardenafil HCl powder (left), vardenafil HCl SEM (center) and Kollitab™ DC 87 L blended with vardenafil HCl (right).

Tableting Blend	
Vardenafil HCl	2 and 8 %
Kollitab™ DC 87 L	98 and 92 %

Blending
V blender for 15 min at 17 rpm

Sieving (Tableting Blend)	
Manual sieving	
Sieve mesh [mm]	0.6

Tableting	
Technology	Direct compression
Equipment	KORSCH XL 100
Punch	9.0 mm
Mass	250 mg

API Particle Size	
Vardenafil HCl	d10: 7 µm d50: 28 µm d90: 112 µm

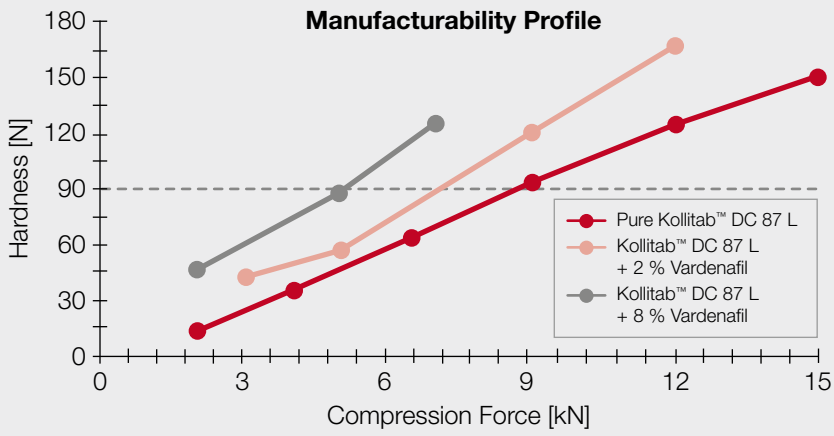

Figure 15: Manufacturability profile of vardenafil HCl tablets (2 and 8 % drug load) and pure Kollitab™ DC 87 L.

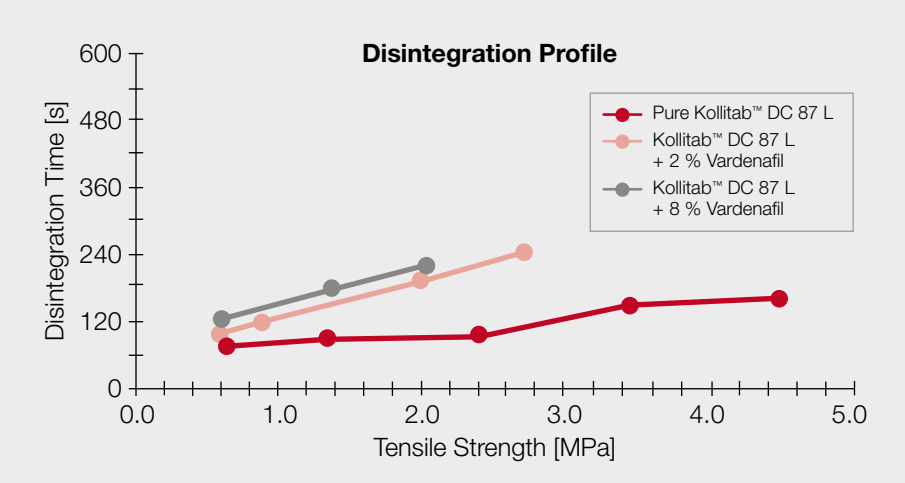

Figure 16: Disintegration time of vardenafil HCl tablets (2 and 8 % drug load) and pure Kollitab™ DC 87 L.

To overcome direct compression challenges presented by cohesive APIs such as vardenafil HCl, Kollitab™ DC 87 L is the ideal solution as it can provide high process consistency. The excellent compressibility of pure Kollitab™ DC 87 L tablets and Kollitab™ DC 87 L + vardenafil tablets at 2 and 8 % drug load can be observed in the manufacturability profile (Figure 15). In addition, Kollitab™ DC 87 L and vardenafil can also produce quickly disintegrating tablets at all compression forces as observed in Figure 16.

Formulation 3:

To better compare the functionality of coprocessed excipients, Kollitab™ DC 87 L and a similar blend of excipients were mixed with 2 % of vardenafil HCl and compressed into tablets.

Formulation: »Lactose blend vs. Kollitab™ DC 87 L blend«

Tableting Blend	
Vardenafil HCl	2 %
Kollitab™ DC 87 L	98 %
Lactose blend*	98 %

Blending
V blender for 15 min at 17 rpm

Sieving (Tableting Blend)	
Manual sieving	
Sieve mesh [mm]	0.6

Tableting	
Technology	Direct compression
Equipment	KORSCH XL 100
Punch	9.0 mm
Mass	250 mg

API Particle Size	
Vardenafil HCl	d10: 7 µm d50: 28 µm d90: 112 µm

Table 4: FT4 powder rheology of Kollitab™ DC 87 L and lactose blend.*

Material	Compressibility % @ 15.0 kPa	Flow Function	Cohesion kPa
Kollitab™ DC 87 L	5.9	37	0.17
Lactose Blend*	9.45	4	2.00

* The lactose blend consisted of the following ingredients: 87 % lactose monohydrate, 9 % crospovidone (Kollidon® CL-F), 3 % copovidone (Kollidon® VA 64**) and 1 % sodium stearyl fumarate.

** For a DC process, Kollidon® VA 64 is recommended as a dry binder. Kollicoat® IR is used as a binder in wet granulation only.

As shown in Table 4, Kollitab™ DC 87 L demonstrated lower compressibility (%), which meant a lower percentage of change in volume as a function of applied force, lower cohesion, and a much higher flow function than the lactose blend*. Based on these results, Kollitab™ DC 87 L was shown not to have a tendency towards agglomeration; instead, this coprocessed excipient remained free-flowing, regardless of the handling conditions (storage, filling/dispensing). In contrast, the lactose blend had a lower flow function, higher compressibility, and cohesion, typical of materials that agglomerate and flow poorly. These results demonstrate the superior functionality and processability of Kollitab™ DC 87 L when compared to a blend composed of similar, individual excipients intended to be used in a DC process.

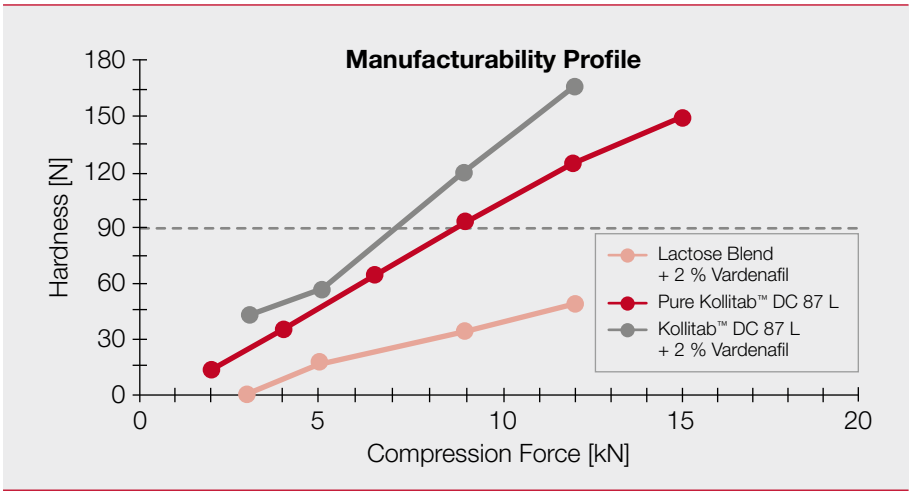

Figure 17: Manufacturability profile of pure Kollitab™ DC 87 L, tablets of vardenafil HCl 2 % drug load with Kollitab™ DC 87 L, and tablets with the lactose blend.

Kollitab™ DC 87 L with 2 % vardenafil produced strong tablets at all compression forces with no ejection problems. On the other hand, the lactose blend and 2 % vardenafil led to delamination and punch sticking, not even achieving the required hardness of 90 N (ten times that of the punch size) as shown in Figure 17. When both materials were blended at 2 % drug load, the addition of Kollitab™ DC 87 L improved vardenafil compressibility and processability via direct compression. In contrast, the individual lactose blend did not offer the same performance, resulting in tablets defects and poor tabletability.

Formulation 4

Formulation: »Valsartan 40 mg«

Valsartan is an angiotensin II receptor blocker used to treat high blood pressure (drugs.com). Valsartan fine particles can be challenging to process via direct compression. For this reason, manipulating valsartan can require additional manufacturing considerations to ensure suitable flowability and compressibility. This study tested valsartan with Kollitab™ DC 87 L in a direct compression process.

Tableting Blend	
Valsartan	20 %
Kollitab™ DC 87 L	80 %

Blending
5 min

Sieving (Tableting Blend)	
Manual sieving	
Sieve mesh [mm]	1.00

Tableting	
Technology	Direct compression
Equipment	Bosch/Syntegon TPR 200
Punch	7.0 mm
Mass	200 mg

API Particle Size	
Valsartan	d10: 60 µm d50: 118 µm d90: 217 µm

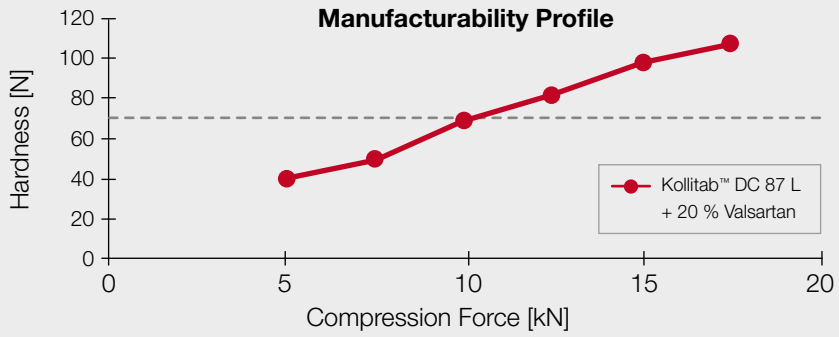

Figure 18: Manufacturability profile of valsartan 40 mg tablets.

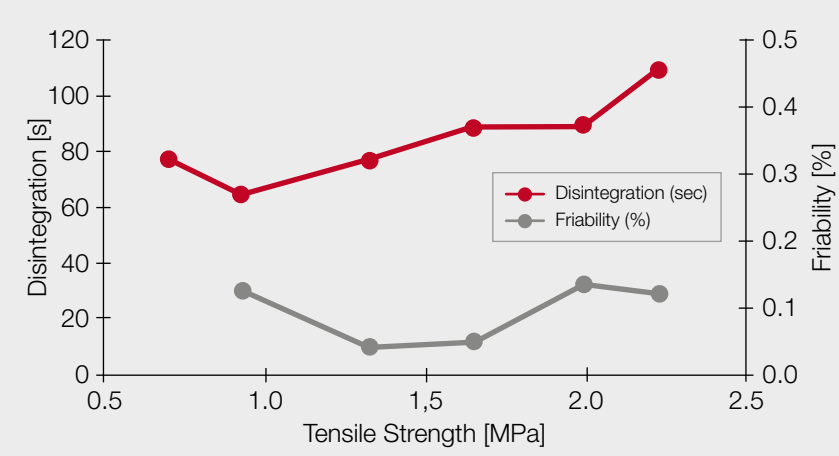

Figure 19: Disintegration time and friability of valsartan 40 mg tablets.

Kollitab™ DC 87 L enabled a successful direct compression formulation with valsartan 40 mg at 20 % drug load. Good compressibility was observed throughout the process, achieving ideal tablet hardness at low compression force (Figure 18). In addition, even for high tensile strength tablets, disintegration time remained under 2 minutes and friability was close to 0.1 % at all tablet strengths (Figure 19).

4. ZoomLab™

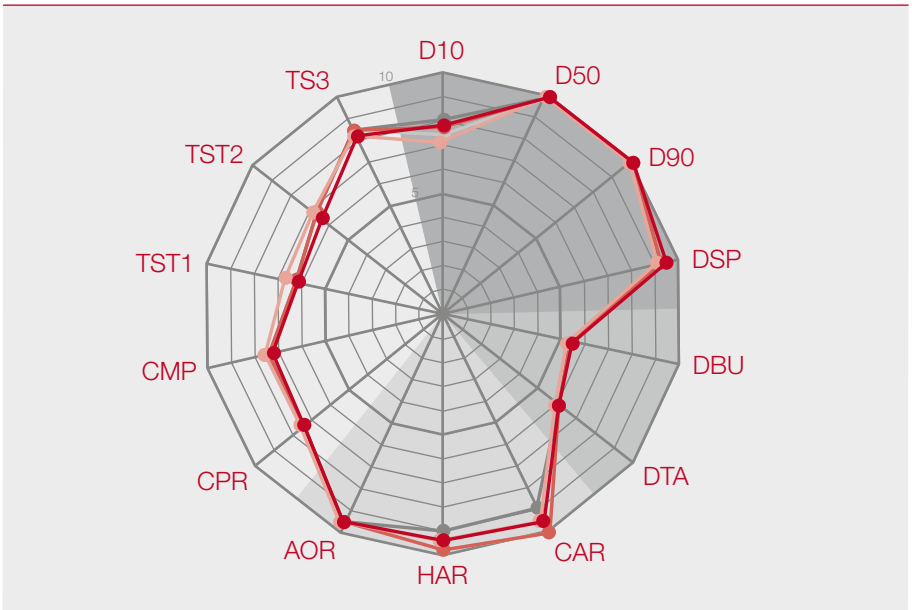

Figure 20: ZoomLab™ spider diagram summarizing Kollitab™ DC 87 L's excellent tableting properties.

ZoomLab™ is the BASF's Virtual Formulation Assistant. It aims to predict formulations and expedite drug development.

Start with an active ingredient, define your target profile, and input your preferences. Include Kollitab™ DC 87 L among the most relevant excipients. Then let the advanced algorithm optimize the formulation.

The parameters evaluated and presented on the ZoomLab™ spider diagram for Kollitab™ DC 87 L (Figure 20) are:

- d10 Value (D10), d50 Value (D50), d90 Value (D90), Distribution span (DSP): refer to particle size distribution – Kollitab™ DC 87 L has a narrow particle size distribution with low fines for better uniformity and reduced process variability. Fine powders are often characterized by insufficient flowability, increased wall adhesion, and dust formation. Very coarse powders can lead to poor content uniformity, slow dissolution profiles, or reduced mechanical strength of tablets.

- Bulk density (DBU), Tapped density (DTA), Carr index (CAR), Hausner ratio (HAR), Angle of repose (AOR): refer to flowability – Kollitab™ DC 87 L has excellent flowability due to its spherical shape, reducing tablet weight variability. The bulk density determines the amount of powder that can fit into a blender, hopper, or die of a tablet press. Large differences between bulk and tapped density are associated with strong interparticulate interactions and poor powder flow.

- Compaction pressure at 0.85 solid fraction (CPR), Tensile strength at 0.85 solid fraction (CMP), Tensile strength at 100 MPa pressure (TST1), Tensile strength at 150 MPa pressure (TST2), Tensile strength at 250 MPa pressure (TST3): refer to powder compressibility – Kollitab™ DC 87 L creates high strength tablets at broad compression forces.

Expedite your formulation using ZoomLab™!

5. Handling and Safety

Refer to the material safety data sheet (MSDS) for instructions on safe and proper handling and disposal. MSDS are available on request and are sent with every consignment.

6. Product Specification

The current version of the product specification is available on BASF WorldAccount and MyProductWorld or from your local BASF sales representative.

7. Regulatory and Quality

Refer to the individual document quality and regulatory product information (QRPI), available on BASF WorldAccount, RegXcellence® and from your local BASF sales representative. **The QRPI document covers all relevant information including retest periods and storage conditions.**

8. PRD and Article Numbers

PRD-No.	Product name	Article numbers	Packaging	Image
30765743	Kollitab™ DC 87 L	**50711206** 1 kg non-GMP sample	2.5 L Plastic Bottle	
		50708787 20 kg Commercial article	60 L Cardboard Box with PE liner