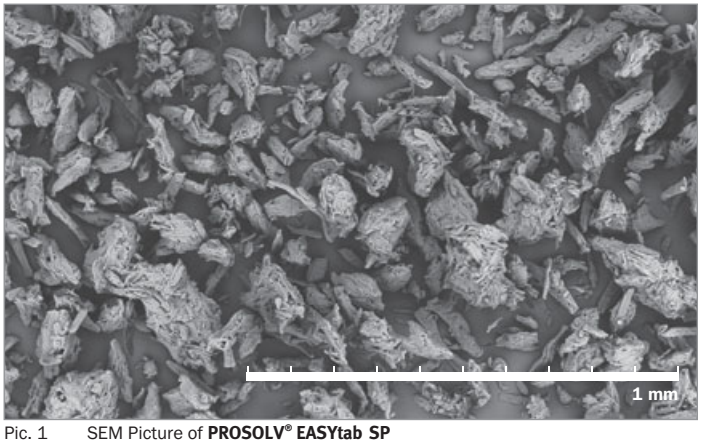
TECHNICAL INFORMATION

The Performance of **PROSOLV® EASYtab SP** in Four Medium-Dose, Direct Compression Formulations with Morphologically Challenging Model APIs

Abstract

In the present study, the performance of **PROSOLV® EASYtab SP** was tested in four DC formulations with different model APIs. Each of the selected APIs presented a particular challenge in terms of producing tablets with suitable hardness, weight uniformity, content uniformity and/or reliable dissolution profiles. **PROSOLV® EASYtab SP** was shown to perform considerably better than the corresponding physical mixture of its components for all formulations tested.



Pic. 1 SEM Picture of **PROSOLV® EASYtab SP**

Introduction

PROSOLV® EASYtab SP is a ready-to-use tablet excipient composite, comprised of microcrystalline cellulose as filler/binder, colloidal silicon dioxide as flow aid, sodium starch glycolate as disintegrant and sodium stearyl fumarate as lubricant. **PROSOLV® EASYtab SP** is specifically designed for use in direct compression.
In direct compression formulations, the active ingredient can often present challenges in terms of achieving powder blends with decent flowability, compactability and homogeneity. These problems can cause insufficient tablet hardness, poor weight and/or content uniformity and inconsistent drug release. The impact of adverse API properties grows with increasing concentration in the formulation. For the purpose of this study, four medium-dose formulations of APIs were selected, each of which presented its individual morphological challenge. (See overview in Table 1)

In each case, the functional performance of the **PROSOLV® EASYtab SP** formulations were compared to simple dry blends of the individual components.

Parameters measured in this study were: Compaction force, ejection force, tablet disintegration time, content and weight uniformity as well as API dissolution. **PROSOLV® EASYtab SP** formulations were simply blended with the API for 18 minutes. For the physical blends, the API was blended with microcrystalline cellulose, sodium starch glycolate, and silicon dioxide for 15 minutes. Sodium stearyl fumarate was then added and blended for an additional three minutes.

API	Solubility	Particle Size / Shape	Main Challenge
Propanolol HCl	high	fine	flowability, weight uniformity
Diclofenac	low	coarse / spherical	demixing, content uniformity
Atenolol	high	flaky	mixing properties, uniformity
Hydrochlorothiazide	low	even, flat surface	uniformity of lubrication, dissolution

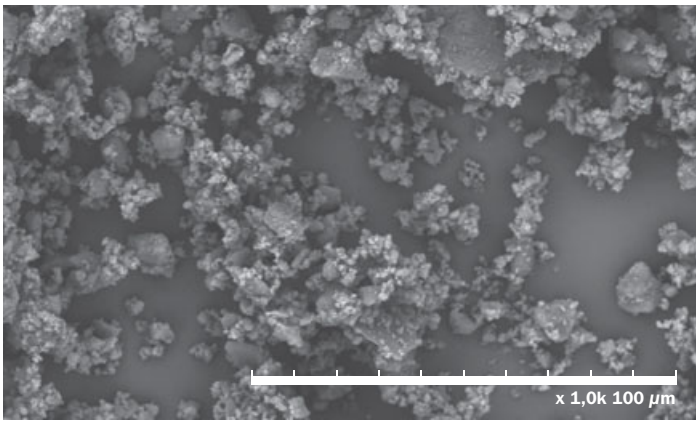
Tab. 1 Properties of selected model APIs

Case Study – Propranolol Hydrochloride

High Solubility, Fine Particle API

Parameter	Formulation 1 PROSOLV® EASYtab SP		Formulation 2 Dry Blend	
	mg	%	mg	%
Propranolol HCl	40.00	20.00	40.00	20.00
PROSOLV® EASYtab SP	160.00	80.00	–	–
VIVAPUR® 102	–	–	154.40	77.20
Colloidal Silicon Dioxide	–	–	3.20	1.60
EXPLOTAB® Sodium Starch Glycolate	–	–	1.60	0.80
PRUV® Sodium Stearyl Fumarate	–	–	0.80	0.40
Total	200.00	100.00	200.00	100.00

Tab. 2 Propranolol Hydrochloride Formulation



Pic. 2 Propranolol Hydrochloride

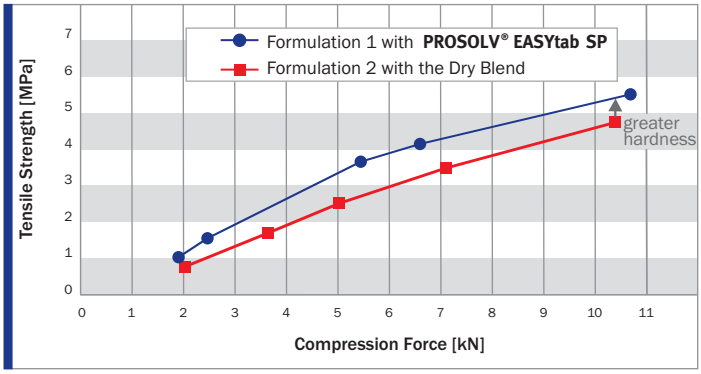


Fig. 1 Compressibility of Propranolol Hydrochloride

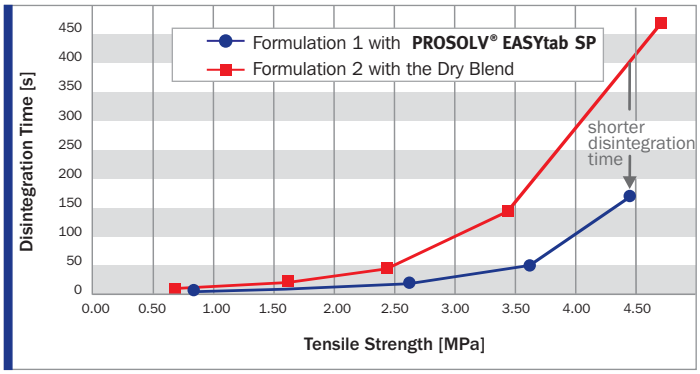


Fig. 2 Disintegration of Propranolol Hydrochloride

20 – 30 % better compressibility

Shorter disintegration times

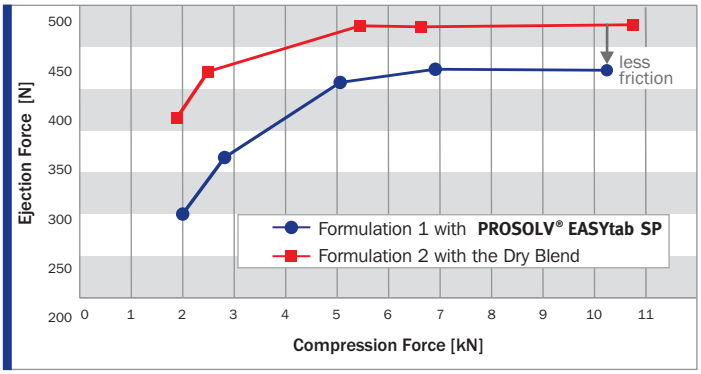


Fig. 3 Ejection Forces of Propranolol Hydrochloride

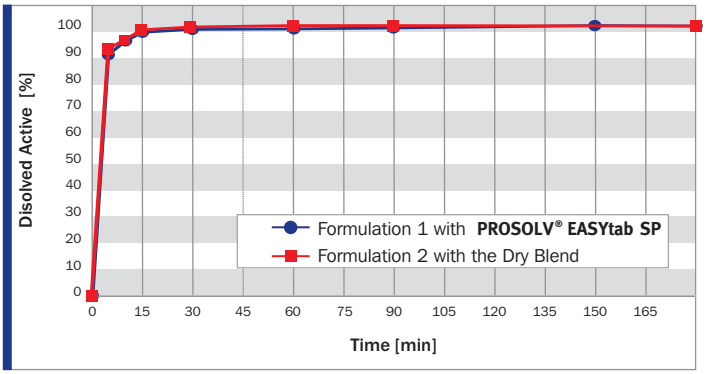


Fig. 4 Dissolution of Propranolol Hydrochloride (USP - Apparatus II, 50 rpm Deionized H_2O)

30 – 40 % lower ejection forces

Equivalent dissolution times. Dissolution test – pass USP-NLT 75 % in 45 min (100 % in 15 min)

Uniformity	Relative Standard Deviation	
	Formulation 1 PROSOLV® EASYtab SP	Formulation 2 Dry Blend
Tablet Hardness Uniformity	2.38 %	3.85 %
Tablet Weight Uniformity	0.16 %	0.54 %
API Content Uniformity	**1.29 %**	4.47 %

Tab. 3 Propranolol Hydrochloride – Formulation Uniformity

The uniformity values above in Tab. 3 demonstrate that **PROSOLV® EASYtab** is capable of overcoming the negative API properties in terms of flow.

Conclusions

Compared to the physical mixture **PROSOLV® EASYtab SP** shows:

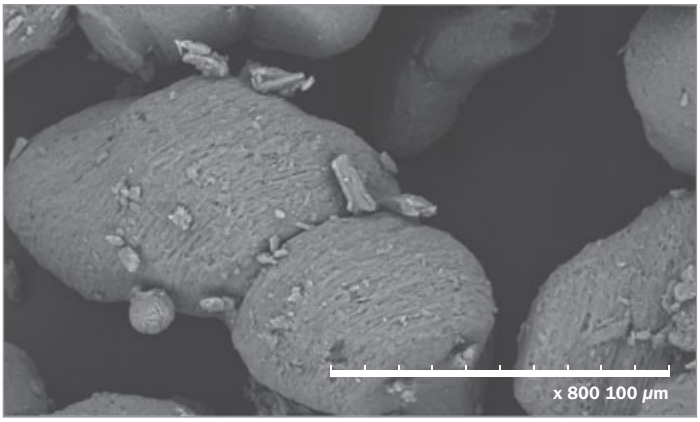
- 20 – 30 % better compressibility (Figure 1)
- 30 – 40 % lower ejection forces (Figure 2)
- Shorter disintegration times (Figure 3)
- Equivalent dissolution times. Dissolution test – pass USP-NLT 75 % in 45 min (100 % in 15 min, Figure 4)
- Improved tablet hardness, weight and content uniformity (Table 3) in spite of poor API flow.

Case Study – Diclofenac Sodium

Low Solubility,Coarse API

Parameter	Formulation 1 PROSOLV® EASYtab SP mg	%	Formulation 2 Dry Blend mg	%
Diclofenac Sodium	25.00	12.50	25.00	12.50
PROSOLV® EASYtab SP	175.00	87.50	–	–
VIVAPUR® 102	–	–	168.86	84.43
Colloidal Silicon Dioxide	–	–	3.50	1.75
EXPLOTAB® Sodium Starch Glycolate	–	–	1.76	0.88
PRUV® Sodium Stearyl Fumarate	–	–	0.88	0.44
Total	200.00	100.00	200.00	100.00

Tab. 4 Diclofenac Sodium Formulation



Pic. 3 Diclofenac Sodium

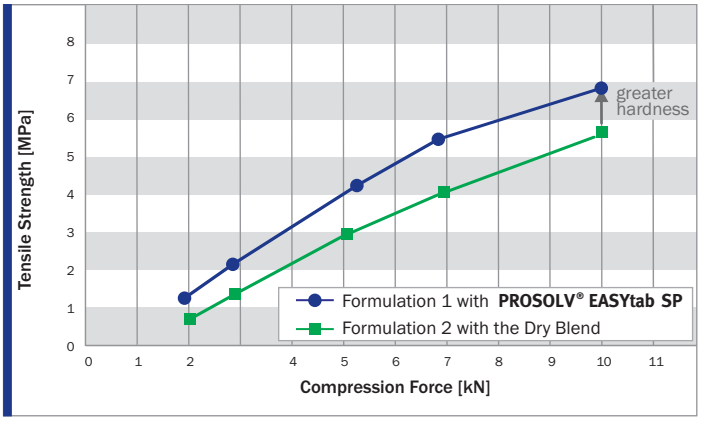


Fig. 5 Compressibility of Diclofenac Sodium

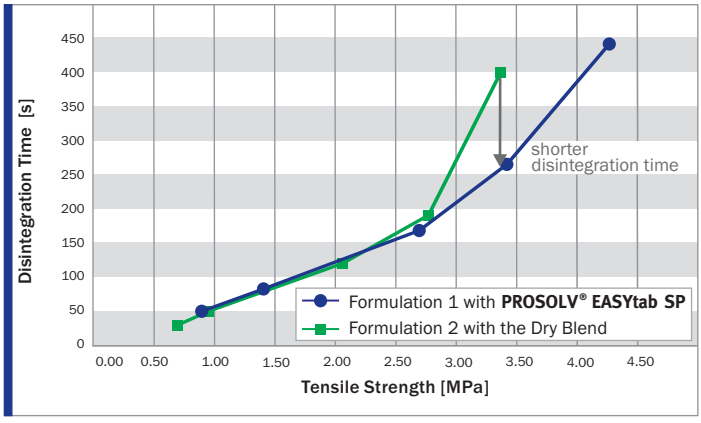


Fig.6 Disintegration of Diclofenac Sodium

30 – 35 % better compressibility

Shorter disintegration times

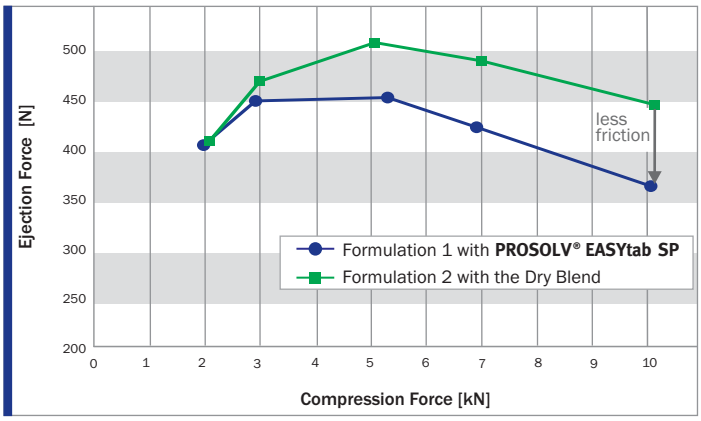


Fig. 7 Ejection Forces of Diclofenac Sodium

20 % lower ejection forces; especially at high compression forces

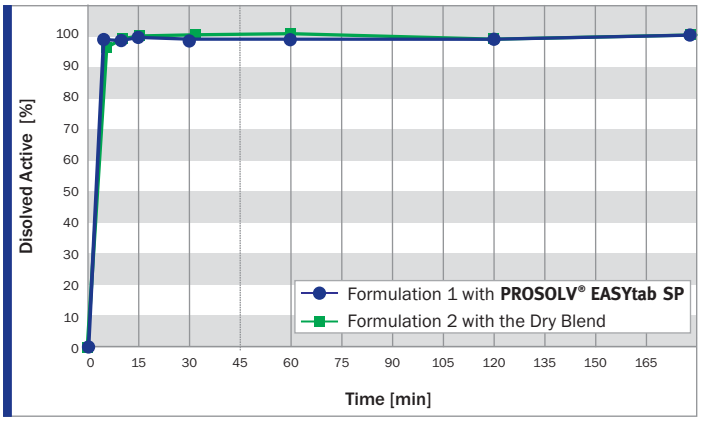


Fig. 8 Dissolution of Diclofenac Sodium (USP - Aparatus II, 50 rpm Deionized H_2O)

Equivalent dissolution times. Dissolution test – pass USP-NLT 75 % in 45 min (100 % in 5 min).

Uniformity	Relative Standard Division	
	Formulation 1 PROSOLV® EASYtab SP	Formulation 2 Dry Blend
Tablet Hardness Uniformity	1.77 %	4.18 %
Tablet Weight Uniformity	0.23 %	0.52 %
API Content Uniformity	**1.02 %**	2.70 %

Tab. 5 Diclofenac Sodium – Formulation Uniformity

Tablet and content uniformity due to the API's size and shape are improved by **PROSOLV® EASYtab**.

Conclusions

Compared to the physical mixture:

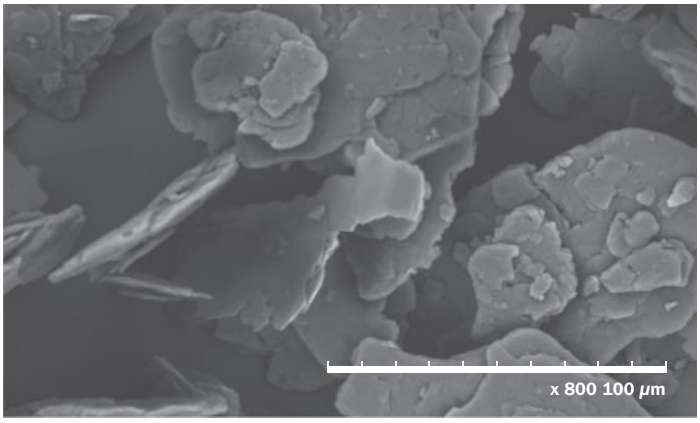
- 30 – 35 % better compressibility (Figure 5)
- 20 % lower ejection forces; especially at high compression forces (Figure 6)
- Shorter disintegration times (Figure 7)
- Equivalent dissolution times Dissolution test – pass USP-NLT 75 % in 45 min (100 % in 5 min, Figure 8)
- Improved, weight and content uniformity in spite of demixing tendency (Table 5)

Case Study – Atenolol

High Solubility, Flaky

Parameter	Formulation 1 PROSOLV® EASYtab SP		Formulation 2 Dry Blend	
	mg	%	mg	%
Atenolol	50.00	25.00	50.00	25.00
PROSOLV® EASYtab SP	150.00	75.00	–	–
VIVAPUR® 102	–	–	144.74	72.37
Colloidal Silicon Dioxide	–	–	3.00	1.50
EXPLOTAB® Sodium Starch Glycolate	–	–	1.50	0.75
PRUV® Sodium Stearyl Fumarate	–	–	0.76	0.38
Total	200.00	100.00	200.00	100.00

Tab. 6 Atenolol Formulation



Pic. 4 Atenolol

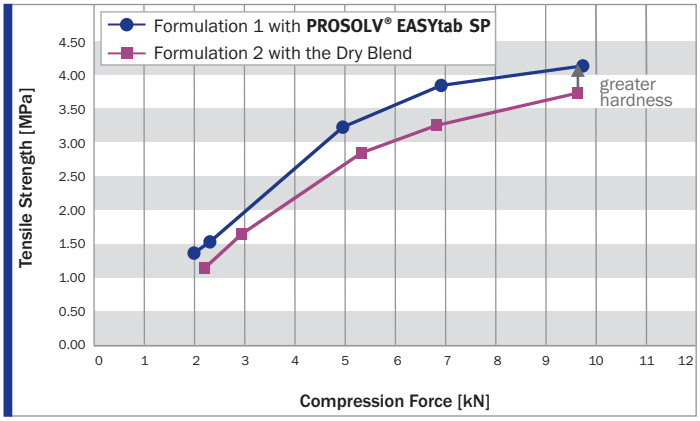


Fig. 9 Compressibility of Atenolol

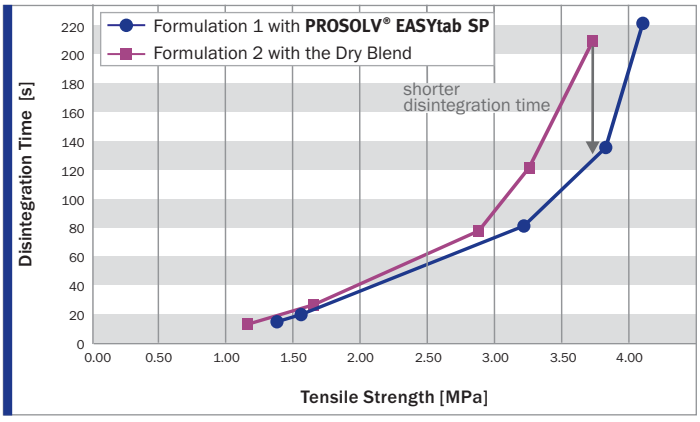


Fig. 10 Disintegration of Atenolol

20 % better compressibility

Shorter disintegration times

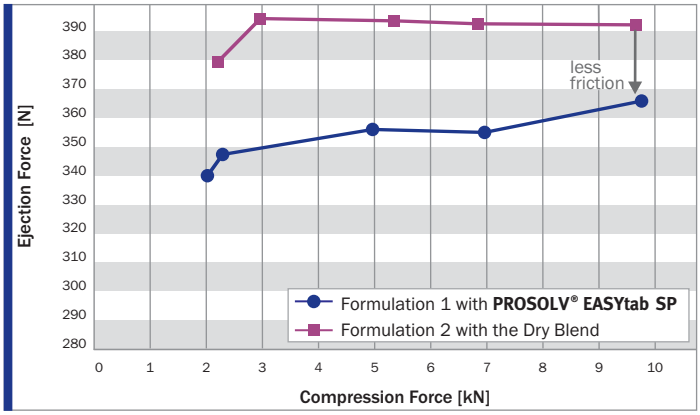


Fig. 11 Ejection Forces of Atenolol

10 – 15 % lower ejection forces

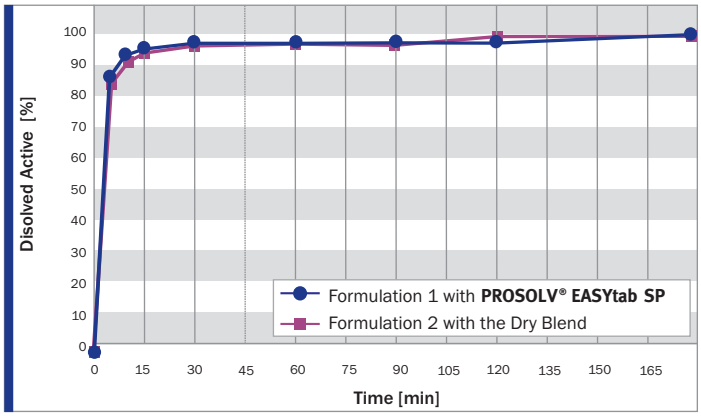


Fig. 12 Dissolution of Atenolol (USP - Aparatus II, 50 rpm Deionized H_2O)

Equivalent dissolution times. Dissolution test – pass USP-NLT 75 % in 45 min (95 % in 15 min).

Uniformity	Relative Standard Divisoion	
	Formulation 1 PROSOLV® EASYtab SP	Formulation 2 Dry Blend
Tablet Hardness Uniformity	1.99 %	2.47 %
Tablet Weight Uniformity	0.26 %	0.75 %
API Content Uniformity	**0.74 %**	7.93 %

Tab. 7 Atenolol – Formulation Uniformity

The flaky structure of the API leads to content uniformity issue which is addressed by **PROSOLV® EASYtab**.

Conclusions

Compared to the physical mixture **PROSOLV® EASYtab SP** shows:

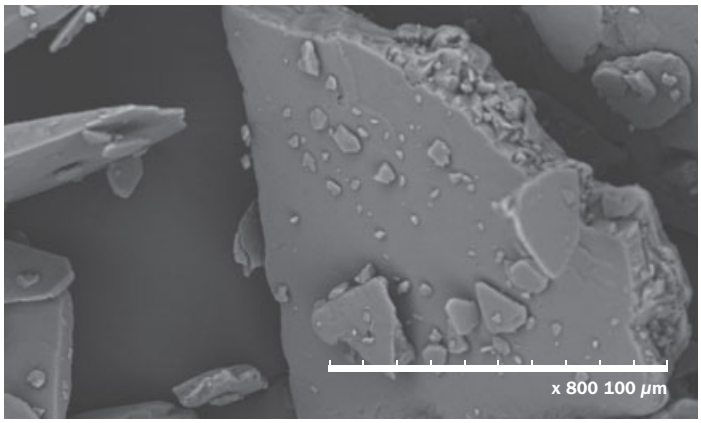
- 20 % better compressibility (Figure 9)
- 10 – 15 % lower ejection forces (Figure 10)
- Shorter disintegration times (Figure 11)
- Equivalent dissolution times. Dissolution test – pass USP-NLT 75 % in 45 min (95 % in 15 min, Figure 12)
- Improved hardness and weight uniformity (Table 7)
- 10 times better content uniformity (Table 7) in spite of challenging structure of the API.

Case Study – Hydrochlorothiazide

Low Solubility, Plate-like Structure

Parameter	Formulation 1 PROSOLV® EASYtab SP mg	%	Formulation 2 Dry Blend mg	%
Hydrochlorothiazide	25.00	12.50	25.00	12.50
PROSOLV® EASYtab SP	175.00	87.50	–	–
VIVAPUR® 102	–	–	168.86	84.43
Colloidal Silicon Dioxide	–	–	3.50	1.75
EXPLOTAB® Sodium Starch Glycolate	–	–	1.76	0.88
PRUV® Sodium Stearyl Fumarate	–	–	0.88	0.44
Total	200.00	100.00	200.00	100.00

Tab. 8 Hydrochlorothiazide Formulation



Pic. 5 Hydrochlorothiazide

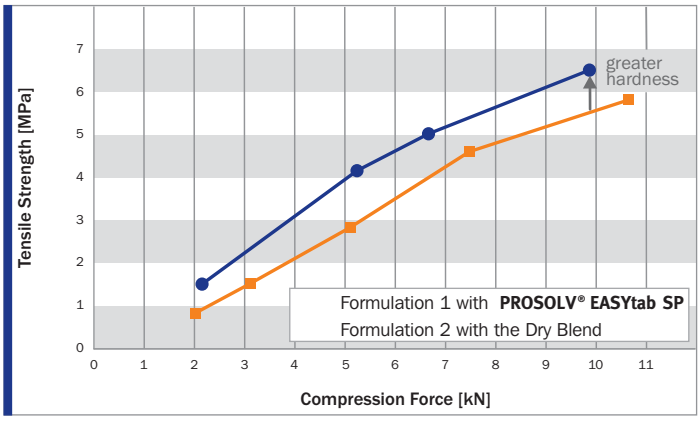


Fig. 13 Compressibility of Hydrochlorothiazide

20 – 30 % better compressibility

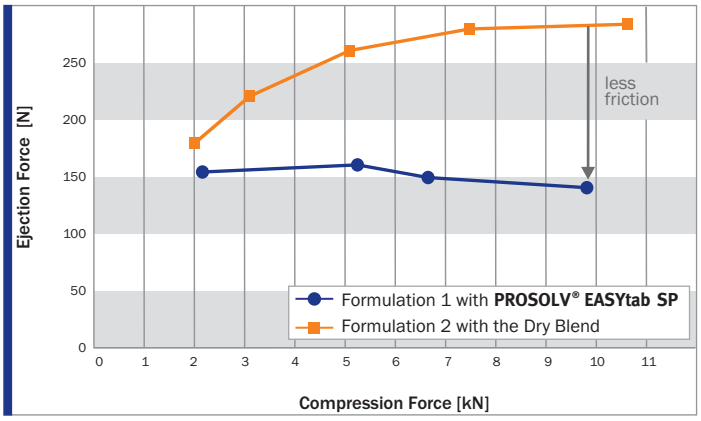


Fig. 15 Ejection Forces of Hydrochlorothiazide

25 – 50 % lower ejection forces; especially at high compression forces

Uniformity	Relative Standard Deviation Formulation 1 PROSOLV® EASYtab SP	Formulation 2 Dry Blend
Tablet Hardness Uniformity	1.88 %	4.33 %
Tablet Weight Uniformity	0.26 %	0.41 %
API Content Uniformity	1.00 %	3.93 %

Tab. 9 Hydrochlorothiazide – Formulation Uniformity

Improved tablet hardness, weight and content uniformity (Table 9)

Dissolution Comparison with Hydrochlorothiazide

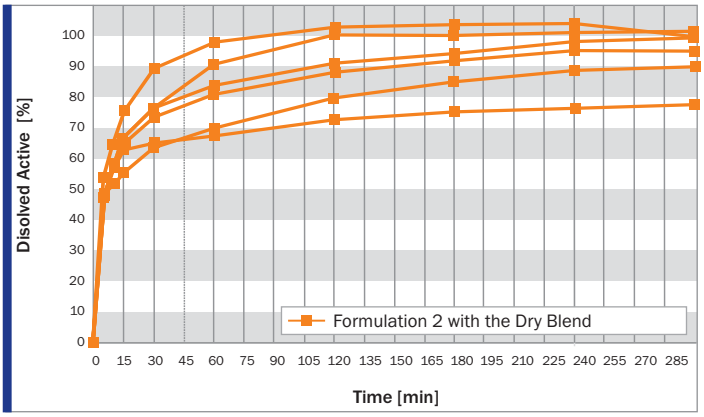


Fig. 16 Dissolution of Hydrochlorothiazide with the Physical Mixture – 6 Tablets (USP - Apparatus II, 50 rpm Deionized H_2O)

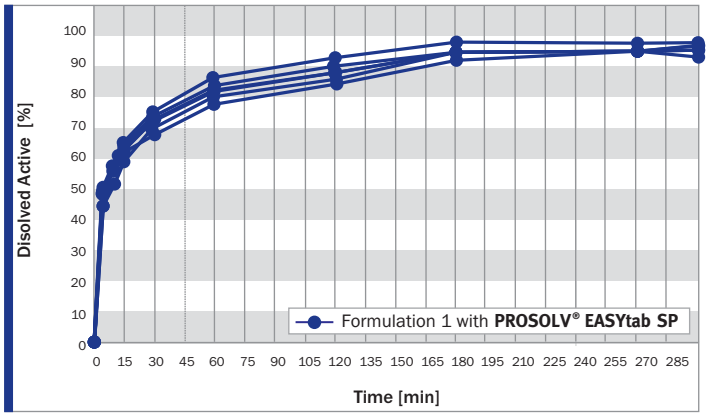


Fig. 17 Dissolution of Hydrochlorothiazide with **PROSOLV® EASYtab** – 6 Tablets

Dissolution test of six randomly selected tablets with Formulation 2 (Figure 16):

- Four tablets pass the USP-NLT 75 % in 45 min, two failed
- Inconsistent dissolution results
- High standard deviation in the dissolution rate (30 %)
- Low formulation robustness

Dissolution test of six randomly selected tablets with Formulation 1 **PROSOLV® EASYtab SP** (Figure 17):

- All tablets pass the USP-NLT 75 % in 45 min
- Very low standard deviation in the dissolution rate (8 %)
- Superior formulation robustness

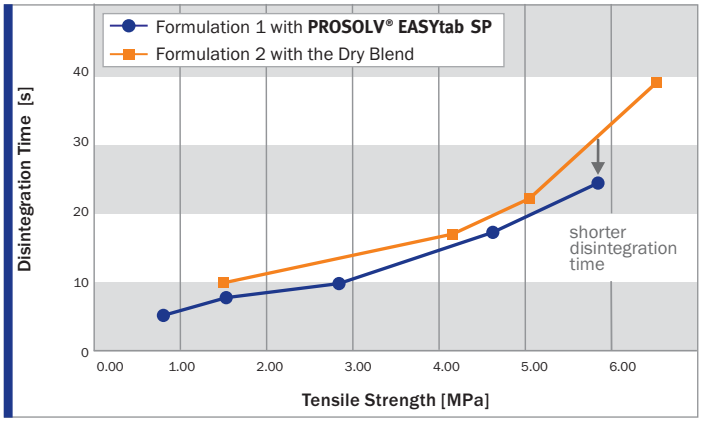


Fig. 14 Disintegration of Hydrochlorothiazide

Shorter disintegration times

Conclusions

Compared to the physical mixture **PROSOLV® EASYtab SP** shows:

- 20 – 30 % better compressibility (Figure 13)
- 25 – 50 % lower ejection forces; especially at high compression forces (Figure 14)
- Shorter disintegration times (Figure 15)
- Improved hardness, weight and content uniformity (Table 9)
- Highly consistent dissolution rates, as composite structure prevents accumulation of lubricants on the plate-like API surface. (Figure 17)

Overall Summary:

Compaction **Lubrication Efficiency** **Disintegration**	In all cases, **PROSOLV® EASYtab SP** showed better compactibility resulting in 20 - 35 % harder tablets, lower ejection forces, and shorter disintegration times compared to the dry blend of the single components.
Dissolution Behavior	In the case of Propanolol HCl, Diclofenac Sodium, and Atenolol, the dissolution profiles of **PROSOLV® EASYtab SP** and traditional formulations were equivalent, passing the USP, NLT 75 % in 45 min requirement. For Hydrochlorothiazide, the **PROSOLV® EASYtab SP** formulation showed highly reproducible dissolution results and better formulation robustness compared to the traditional blend prepared using the individual ingredients.
Blend Homogeneity **Tablet Uniformity**	In all cases **PROSOLV® EASYtab SP** showed much better uniformity in terms of tablet hardness, weight and API content.
Tablet Coatability **Tablet Physical Appearance**	**PROSOLV® EASYtab** also produced smoother tablet surfaces which lead to better film coating adhesion and a more pronounced logo embossing. (Additional technical information available).

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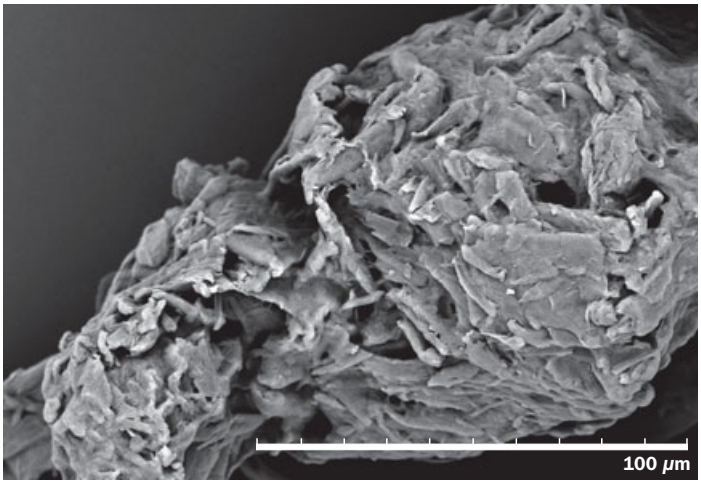
10 Reasons to Choose **PROSOLV EASYtab®** All-in-one Composite

1. Coprocessed all in one ready-to-use composite for direct compression and continuous processing.
2. Superior API content uniformity.
3. Up to 40 % harder tablets with less friability compared to physical blend
4. Outstanding logo definition and film adhesion to the core.
5. Shorter development times
   - Faster market entry
   - Less experiments needed
6. Three times faster tableting increases your capacity without additional investments.
7. Wide range of pharma and nutra grades.
8. Upcoming monograph reduces time effort for registration.
9. The use of only one instead of 4 excipients cuts down handling, storage and QC costs.
10. Global service network with local technical and operational support



Product Overview **PROSOLV EASYtab®**

Grades	Developed for	Filler/Binder	Flow Aid	Disintegrant		Lubricant	
		Microcrystalline Cellulose	Colloidal Silicon Dioxide	Croscarmellose Sodium	Sodium Starch Glycolate	Sodium Stearyl Fumarate	Magnesium Stearate
PROSOLV® EASYtab SP	Phr. Eur., NF, JPE	x	x		x	x	
PROSOLV® EASYtab SP LM	Phr. Eur., NF, JPE	x	x		x	x	
PROSOLV® EASYtab Nutra CM	Russia, Brazil, EU, and USA	x	x	x			x
PROSOLV® EASYtab Nutra GM	China, Korea	x	x		x		x
PROSOLV® EASYtab Nutra CP	USA	x	x	x		x	

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