

## REVIEW ARTICLE

**Co-processed excipients for direct compression of tablets****Společně zpracované pomocné látky pro přímé lisování tablet**

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**Summary**

Tablets are the most frequently employed dosage form. Their advantage lies in their availability, easy administration, good stability, and low price. The easiest technology to produce tablets is direct compression, even though the use of the method requires overcoming many obstacles, mainly related to content uniformity and variation of mass, disintegration, dissolution, and radial hardness of tablets. “Co-processed excipients”, containing commonly processed blends of fillers, binders, disintegrants, lubricants, and other excipients are more and more widely used nowadays. These mixtures are manufactured by various technologies, chiefly by spray-drying, fluid bed granulation, wet granulation, melt granulation, dry granulation, and co-crystallisation. This review article lists excipients used usually to constitute co-processed excipients, technologies, and commercially available co-processed excipients for direct compression.

**Key words:** co-processed excipients • direct compression • blends • tablets • physical characteristics

**Souhrn**

Tablety jsou nejpoužívanější lékovou formou. Jejich výhodou je dostupnost, snadné podání, dobrá stabilita a nízká cena. Nejjednodušší technologií pro výrobu tablet je přímé lisování, ačkoliv při použití této metody je nutné překonat určité obtíže, spojené zejména s hmotnostní a obsahovou stejnoměrností, disolucí a radiální pevností

tablet. Společně zpracované pomocné látky obsahující běžně zpracované směsi plniv, pojiv, rozvolňovadel, lubrikantů a dalších pomocných látek, se v dnešní době používají stále častěji. Tyto směsi jsou vyráběny různými technologiemi, zejména sprejovým sušením, granulací ve fluidním loži, vlhkou granulací, granulací tavením, suchou granulací a společnou krystalizací. Tento článek popisuje pomocné látky, které se obvykle používají k vytvoření společně zpracovaných směsí, uvádí výrobní technologie a komerčně dostupné společně zpracované pomocné látky pro přímé lisování tablet.

**Klíčová slova:** společně zpracované pomocné látky • přímé lisování • směsi • tablety • fyzikální vlastnosti

**Introduction**

Since the 1960s, direct compression technology has been increasingly used in tablet manufacture. The principle lies in weighing components followed by blending and tableting. The advantages include chiefly a limited number of manufacturing steps, a shorter time of manufacture, a lower energy demand, and thus reduced costs, lower variability of the production, improved stability of the active substance (API), shorter disintegration and dissolution of manufactured tablets, easier validation of the production, and lower risk of microbial contamination<sup>1</sup>.

Due to the absence of granulation, the possibility to manufacture tablets with a high content of active ingredients (API) is limited. This is called “low dilution potential”. The API has to be both standard and of high quality to allow a high quality of powder (tableting) blend. During the mixing process particles often segregate, which may have negative impact on content uniformity. Powder blend has worse flow properties; this may lead to higher weight variability. Furthermore, powder blend has a higher surface area, requiring the use of a larger amount of the lubricant. The tablets may have lower mechanical resistance, which can be observed during stress testing<sup>2</sup>.

To overcome these disadvantages, the producers decided to develop maximum quality direct compression excipients. Firstly, they introduced better flowing and better compressible mono-excipients<sup>3</sup>. Secondly, co-processed excipients (CPE) were put in practice. CPEs

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contain mostly carriers, binders, and disintegrants, sometimes also surfactants or lubricants. Other substances may be contained as well, e.g. substances for controlled release, flavours, colours, antioxidants<sup>4)</sup> or even the active substance itself<sup>5)</sup>.

In fact, CPEs are solid dispersions manufactured by various granulation processes: spray-drying (SD), co-melting (Co-MELT), co-crystallization (Co-CR), co-milling (Co-MILL), etc. These dispersions have better physical-chemical properties than powder blends manufactured by blending alone. CPEs are characterised by standardized particle size distribution, similar and more spherical particle shape, high density, and high porosity; this results in improved flow and compressing properties as well as higher dilution potential. The required amount of the lubricant is also lower. With the possible exception of API, particular components building solid dispersions do not segregate anymore; the tablets have better disintegration and often better bioavailability. The whole process is less time-consuming<sup>6)</sup>.

In the 2000s, oral dispersible tablets (ODT) have started to play an important role in pharmaceutical technology. Furthermore, some APIs are absorbed as soon as in the oral cavity and reach circulation without the first-pass effect in the liver that follows standard oral administration; the onset of effect comes sooner and is higher. CPE in combination with direct compression proved to be a suitable road in ODT production. CPEs for ODT are usually non-hygroscopic and mask unpleasant flavours satisfactorily<sup>7)</sup>. Beside CPEs for ODT, CPEs for controlled-release drugs entered the market, too. These CPEs contain excipients that form insoluble and swelling or slowly eroding matrices and which were used in granulation and direct compression processes originally. CPEs for controlled release are supposed to lead to standardised dissolution profiles and improved robustness of the production<sup>8)</sup>.

The aim of this article was characterize parameters (composition, technology and evaluation) of selected commercial CPEs accompanied by scans from an electron microscope (JCM-6000 NeoScope™ Benchtop SEM, JEOL, USA) depending on the used technology.

### Most frequent excipients used in CPE

#### *Fillers*

The two most frequent fillers are saccharides and inorganic substances in diverse modifications. Inorganic substances include calcium or magnesium sulphate or carbonate. ODT and pastilles contain well-soluble saccharides and polyols, e.g. saccharose, mannitol, sorbitol, or xylitol. Due to its price, fructose is less popular despite a high sweetening effect. Microcrystalline cellulose (MCC) has excellent compressing properties and acts as a dry binder; furthermore, due to its porous structure, it acts also as a capillary disintegrant. Starch stands on the boundary between a filler, binder, and capillary and swelling disintegrant<sup>9)</sup>. An example of CPE containing both organic and inorganic filler is Avicel®

DG (FMC). Because of a high content of MCC combined with calcium phosphate, it is suitable for dry granulation as well<sup>10)</sup>.

#### *Binders*

When using direct compression, it may be difficult to process binders in low concentration into powder blends. Low concentration, irregular particle shape, and poor flow properties are significant obstacles that stand in the way of blending. Furthermore, binding properties cannot manifest themselves properly in dry state. On the other hand, when using these substances as CPE components, they can be dissolved or dispersed in a liquid, impregnating or penetrating the whole mixture evenly. Produced CPE is both uniform and has improved binding properties.

These binders include substances of natural origins, e.g. guma guar or dextrin; semi-synthetic substances, e.g. carboxymethyl cellulose (CMC), hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC); and synthetic polymers, e.g. polyvinyl alcohol (PVA) and povidone (PVP)<sup>11)</sup>. An example of CPE manufactured by wet granulation (WG) is Compactcel® (Bioground), containing PVP, HPC, and CMC. Compactcel® is added as the dry binder to powder blends to increase compressibility and hardness of tablets that contain a higher share of API<sup>12)</sup>. Composition of individual CPE is described in Table 1.

#### *Disintegrants*

Besides capillary-acting substances mentioned above, disintegrants include “superdisintegrants”, e.g. carboxymethyl starch (CMS), crosscarmellose (SCMC), crosspovidone (CPVP), and low substituted hydroxypropyl cellulose (L-HPC), which have a strong swelling effect<sup>8)</sup>, as well as inorganic substances, e.g. colloidal silica and magnesium aluminometasilicate that both improve hardness and disintegration of tablets by the mechanism of quick hydration and have antistatic and antiadhesive effects. Magnesium aluminometasilicate (Neusilin®) is contained in F-Melt® M, together with mannitol, xylitol, MCC, and CPVP. This quickly-disintegrating CPE is used in ODTs<sup>13)</sup>. Composition of individual CPEs is described in Table 1.

#### *Lubricants and surfactants*

Usually, CPEs do not contain common lubricants, e.g. salts of fatty acids with magnesium or calcium because these lubricants are poorly soluble and dispersible in water and are not readily processed in dispersions. If CPE contains some lubricant at all, mixtures of oils and surfactants or surfactants alone are used; these substances have the ability to improve the wettability of API and thus its bioavailability. Examples include sodium stearyl fumarate (SSF), various types of saturated fat, silicone-coated starch, and fatty acid esters. Their lubricant efficacy is relatively low and the manufacturers suggest admixing a standard lubricant to the blend<sup>10)</sup>. The only CPE so far that uses lubricant properties of magnesium stearate

added in solid state is NU-TAB® (Ingredient Technology, Inc.). Beside saccharose and hydrolysed saccharose, it contains only a small amount of magnesium stearate; in

theory, another lubricant is not necessary. SSF processed by standard dispergation technology is contained in Prosolv Easytab® SP (JRS), where it stands side by side

Table 1. Examples of commercially available CPE for direct compression<sup>30–33)</sup>

Brand name	Manufacturer	Components	Technology
<i>Co-processed excipients based on microcrystalline cellulose</i>			
<b>Avicel DG</b>	FMC	MCC, anhydrous calcium phosphate	SD
<b>Avicel HFE 102</b>	FMC	MCC, mannitol	SD
<b>PanExcea MHC 300G</b>	Avantor	MCC, HPMC, CPVP	SDG
<b>Prosolv Easytab NUTRA</b>	JRS	MCC, colloidal silica, CMC, palm oil, E472e	SD
<b>Prosolv Easytab SP (LM)</b>	JRS	MCC, colloidal silica, CMS, SSF	SD
<b>Prosolv SMCC 50 a 90 (LD, HD, LM)</b>	JRS	MCC, colloidal silica	SD
<i>Co-processed excipients based on lactose</i>			
<b>Cellactose 80</b>	Meggle	lactose, MCC	SD
<b>Ludipress</b>	BASF	lactose, PVP, CPVP	FBC
<b>Ludipress LCE</b>	BASF	lactose, PVP	FBC
<b>Microcelac 100</b>	Meggle	lactose, MCC	SD
<b>RetaLac</b>	Meggle	lactose, HPMC	SD
<b>StarLac</b>	Meggle	lactose, starch	SD
<i>Co-processed excipients based on calcium minerals</i>			
<b>Barcroft CS 90</b>	SPI	calcium carbonate, starch	SD
<b>Celocal</b>	FMC	calcium sulphate, MCC	SD
<b>F-Melt F1</b>	Fuji	calcium phosphate, waxed starch, MCC	SD
<b>Formaxx</b>	Merck	calcium cabronate, sorbitol	Unknown
<i>Co-processed excipients based on saccharides</i>			
<b>Advantol 300</b>	SPI	mixture of polyols	FBG
<b>Advantose FS 95</b>	SPI	fructose, starch	SD
<b>Compressol SM</b>	SPI	mannitol, sorbitol	ME
<b>Di-Pac</b>	Domino Foods	saccharose, dextrin	CoCR
<b>F-Melt C</b>	Fuji	mannitol, xylitol, MCC, calcium phosphate, CPVP	SD
<b>F-Melt M</b>	Fuji	mannitol, xylitol, MCC, CPVP, Neusilin	SD
<b>Ludiflash</b>	BASF	mannitol, PVA, CPVP	WG
<b>Nu-Tab</b>	Ingredient Technology, Inc.	saccharose, hydrolysed saccharose, magnesium stearate	RC
<b>PanExcea MC 200G</b>	Avantor	mannitol, calcium sillicate	WG
<b>Parteck ODT</b>	Merck	mannitol, sodium CCMC	FBG
<b>Pearlitol Flash</b>	Roquette	mannitol, starch, sorbitol	SD
<b>Prosolv ODT G2</b>	JRS	MCC, colloidal silica, mannitol, fructose, CPVP	SD
<b>Smartex QD 50 a 100</b>	ShinEtsu	mannitol, L-HPC, PVA	FBG
<b>Xylitab 100</b>	Danisco	xylitol, polysaccharose	WG
<b>Xylitab 200</b>	Danisco	xylitol, CMC	WG

with MCC, CMS, and colloidal silica to build lubricated CPE<sup>14</sup>). Composition of individual CPEs is described in Table 1.

### Excipients for controlled release

Commercially available CPEs for controlled release contain e.g. highly substituted HPMC or carrubin to form matrix systems. Swellable HPMC is responsible for the formation of a gel coat around the tablet, which causes the API to diffuse slowly into the surrounding environment. Examples include RetaLac<sup>®</sup> (Meggler) that contains HPMC and lactose<sup>15</sup>). Systems based on acrylate polymers are being developed<sup>16</sup>). Composition of individual CPEs is described in Table 1.

### Technology of preparation

CPE technology is based on the fact that a mixture of individual substances is turned into monodispersion that is listed as new entity in pharmaceutical technology because it has a new name and exclusive physical chemical properties. Regulatory authorities approve usually this new entity as a separate excipient. The technology is usually based on dissolving or dispersing individual excipients in liquid, which is removed subsequently; solid dispersion, solid solution, co-crystals, or mixture of these are formed. Another possible way to prepare CPE is a change of consistence, when one of the substances melts or forms a eutectic mixture that is able to dissolve or disperse the other substances if they are present. After cooling, a solid dispersion is formed without need to remove any liquid from the system<sup>6</sup>).

### Spray drying

SD is the most widely used technology in CPE preparation. The principle of the process is based on drying the solutions, rarely emulsions or suspensions of substances (excipients) in fluidized bed in a spray-dryer. This method leads to formation of spherical solid dispersion powder that has good porosity, a relatively good particle size distribution and shape uniformity, with good flow and compressibility properties. Tablets manufactured from such dispersion tend to disintegrate easily. The method has two major disadvantages: it is highly power-consuming and a technical excipient – one or more liquids – has to be used<sup>17</sup>). Many brands of CPE for direct compression are manufactured by SD, e.g. MicroceLac<sup>®</sup> 100 (Meggler) that contains lactose and MCC in its spherical particles<sup>18</sup>). Composition of individual CPE is described in Table 1 and Figure 1.

### Fluid bed granulation

Fluid bed granulation (FBG) is likely the second most frequently used method to produce CPEs. The process is based on spraying the solutions, rarely emulsions or suspensions of individual excipients on a solid material (powder or powder blend) in a fluid bed, using chiefly top spraying. If the substance is sprayed on the solid

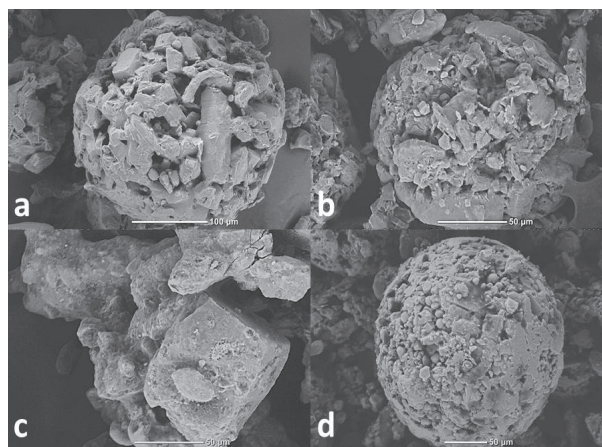


Fig. 1. Spray-dried CPE

a) Cellactose<sup>®</sup> 80, b) MicroceLac<sup>®</sup> 100, c) RetaLac<sup>®</sup>, d) StarLac<sup>®</sup>

particles with a defined shape structure, the process can be described also as fluid bed coating (FBC). FBG results in a granulate, FBC to coated microparticles. Combination of SD a FBG is spray drying granulation (SDG). This method transforms solution or suspension into dry particles that can be dried to spheres in a wide drying range before they are consequently granulated by a binder liquid in one step.

Particles obtained by both FBG/FBC/SDG and SD are similar in shape; however, the former have sometimes lower sphericity, a less regular particle size distribution and worse flow properties. This is caused by the fact that during fluid bed processes, no morphologically uniform monodispersion is formed as the carrier does not undergo significant changes and retains its difference in the resulting particles<sup>19</sup>). CPE prepared by FBC include Ludipress<sup>®</sup> (BASF) containing lactose, PVP, and CPVP<sup>20</sup>). When combined with a suitable retarding excipient, e.g. Kollidon SR, Ludipress<sup>®</sup> can be used as the filler in controlled-release tablets as well<sup>21</sup>). Composition of individual CPE is described in Table 1 and Figure 2.

### Wet granulation

When WG is used to prepare CPE, the process is based on the formation of wet dispersion from individual excipient powders and wetting liquid, drying and sometimes milling. Dried dispersion is usually sieved, which leads to particles with a medium density, a less regular shape, a lower sphericity, a lower porosity, and worse flow properties when compared to particles prepared by SD or in fluid bed<sup>22</sup>). Nevertheless, compressibility is the same or better. The advantage of this method is that it is easily available and it can be used for various purposes; furthermore, individual components do not have to be dissolved or dispersed in the granulation liquid and the total amount of liquid is much lower than in spray-drying or fluid bed<sup>23</sup>). CPE produced by WG include Compactcel<sup>®</sup> SIL (Bioground) containing PVP, HPC, CMC, and

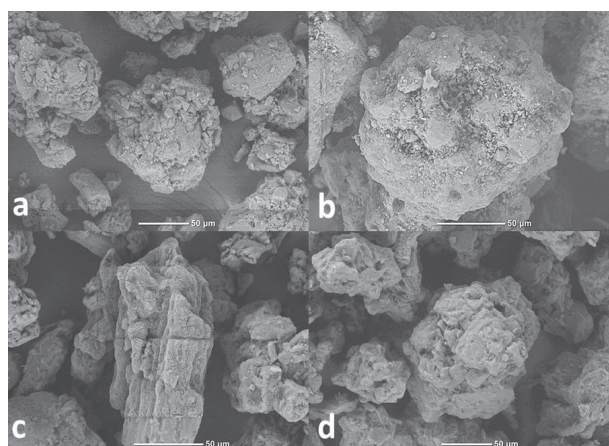


Fig. 2. Fluid-bed granulated CPE

a) Advantol® 300, b) Ludipress® LCE, c) Smartex® QD 50, d) Smartex® QD 100

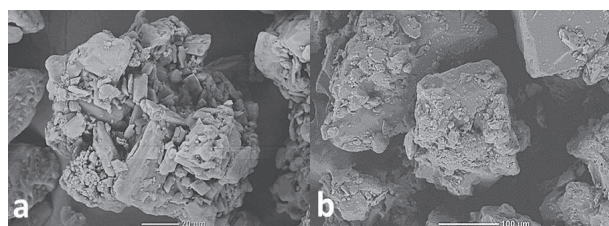


Fig. 3. Wet granulated CPE

a) Ludiflash®, b) Xylitab® 100

colloidal silica. Compactcel® is added to mixtures for direct compression as the dry binder; it can not only improve compressibility and hardness of tablets, but, due to silica, increases disintegration<sup>11</sup>). Composition of individual CPE is described in Table 1 and Figure 3.

### Melt granulation

This progressive method is based on the formation of a solid dispersion from individual components (powders or powder blends) when at least one component of the mixture melts and cools during the mixing which leads to mixed granules. If particular aggregates form without the need for extrusion, the process is described as melt granulation. If the granules form only during the extrusion, the process is described as melt extrusion. In both cases, solidified granules can be sieved to achieve desired particle size distribution. Melt granulation (MG) or extrusion (ME) is advantageous because it does not require the use of liquids. However, some substance with a low melting point has to be used. For melt granulation, “one pot” granulators with their own heat source can be used; similarly, for melt extrusion, extruders with their own heat source are necessary. A granulate produced by MG has similar properties as a granulate produced by wet granulation, while a granulate produced by ME has a more uniform particle shape<sup>24</sup>). CPE produced by melt extrusion contains Compressol® (SPI) manufactured

by Co-MELT of mannitol and sorbitol. It has good flow properties, improved compressibility, and lower hygroscopicity than mixture obtained by mere mixing of both components. Compressol® is suitable for the production of ODT<sup>20</sup>). Composition of individual CPE is described in Table 1 and Figure 4.

### Dry granulation

Roller compaction (RC) is the most frequently used type of dry granulation (DG). The principle lies in processing the solid components (powders or powder blends) into coarse granules, using rotating rollers. The powder gets in between the rollers where it is compressed into compacts which are then milled to form granulated powder that has usually a higher density and a less regular shape than CPE prepared by any other method mentioned previously. The granulate has also poorer flow properties and lower compressibility. In some cases, the hardness of tablets is improved because of wedging of irregular shapes. Rare advantages of rotary compaction include the absence of any liquids or wetting solutions and the possibility to process large amounts of powder at once. However, the whole process is costly and requires specific equipment<sup>24</sup>). CPEs produced by rotary compaction include NU-TAB® (Ingredient Technology, Inc.) mentioned above where magnesium stearate is processed into the CPE in solid state. When compared with monocomponent sugars, the CPE has better flow and compressibility properties and it can be used to manufacture pastilles<sup>25</sup>). Composition of individual CPE is described in Table 1.

### Common crystallisation

Co-CR which is used e.g. in chemical industry in the production of poorly soluble substances can be used to produce CPE as well. The principle lies in the formation of common crystals of at least two substances<sup>26</sup>). A co-crystal can be defined as a stoichiometric multi-component entity of host-guest type; individual substances are usually solid at room temperature. Specific properties of co-crystals are more suitable than those of the mixtures of individual crystals. Co-crystals

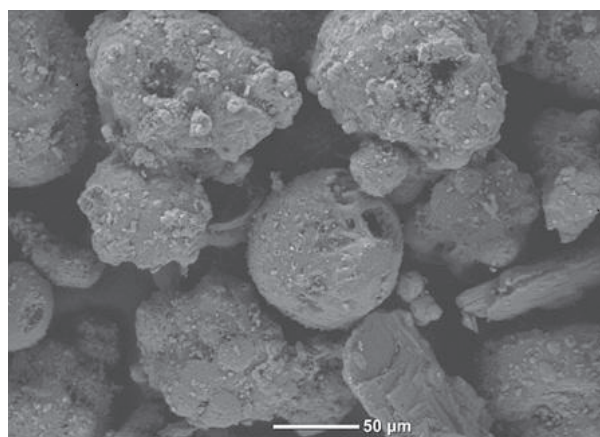


Fig. 4. Melt granulated CPE – Compressol® SM

can be prepared by various technological processes, e.g. Co-CR out of solution, Co-MILL, crystallisation out of Co-MELT, etc.<sup>27</sup>). Co-crystal CPE include DI-PAC<sup>®</sup> (Domino Foods) containing saccharose and maltodextrin crystallized out of common solution. These co-crystals have lower hygroscopicity, good flow properties, good compressibility and hardness of resulting tablets<sup>28</sup>). Composition of individual CPE is described in Table 1.

#### **Other methods**

Recent methods are represented by spray-drying granulation that combines SD and FBG. Firstly, spray-dried powder is formed, then, after transport to fluid bed, FBG ensues. In fact, the principle is based on two connected fluid beds<sup>29</sup>). Other methods used for preparation of CPE “in house“ include common precipitation, common evaporation of solvent, and common dehydration. However, commercially available CPE do not list these manufacturing procedures (see Table 1)<sup>30</sup>).

#### **Impact of use of CPE on physical properties of tablets**

The assessment of quality of particular CPE is advertised by their manufacturers by comparing the properties CPE alone and resulting tablets. The most important ones include content uniformity, mass variation, disintegration, dissolution, mechanical resistance, humidity, and stability<sup>31</sup>).

#### **Content uniformity**

The best way to mix uniformly various substances is to use particles of a similar shape (spherical if possible), a similar density, a similar size, and a similar ratio in the blend<sup>32</sup>). Some producers offer CPEs with various density and particle size distribution; e.g. Prosolv<sup>®</sup> SMCC (JRS), i.e. spray-dried blend of MCC and colloidal silica (silicified MCC) with improved compressibility properties, is available in four types, combining two types of mean particle sizes (50 and 90 µm) and two types of density (low – LD and high – HD)<sup>33</sup>).

#### **Mass variation**

Good mass variation can be achieved when the tableting blend has good flow properties. These properties are defined by parameters calculated from density, i.e. Hausner ratio, Carr compressibility index, flow rate and angle of repose. Generally, CPEs for direct compression have better flow properties than mere mixtures of substances they are prepared from<sup>11,34</sup>).

#### **Disintegration and dissolution**

The dissolution test is very important because it can predict liberation and bioavailability. In development of ODT, disintegration plays also a major role, European Pharmacopoeia sets the limit at 180 s, US Pharmacopoeia at 30 s. In particular, CPEs, besides the composition,

physical properties like surface area or porosity characterise the behaviour of the blend<sup>35</sup>). Logically, more porous material has better wettability, with positive impact on disintegration as well as dissolution. CPEs that were developed to improve dissolution in the oral cavity include Ludipress<sup>®</sup> LCE (BASF) containing lactose and PVP; unlike its predecessor Ludipress<sup>®</sup> it does not contain CPVP that is insoluble in water<sup>36</sup>).

#### **Mechanical resistance**

In tablets, mechanical resistance is tested by friability and radial hardness testing. It depends on the compressibility of the CPE that was used. Predictions on the mechanical resistance of tablets can be made based on the properties of the blend, e.g. porosity, particle size and shape, Carr compressibility index, cohesion index, and sintering force<sup>34</sup>). Some CPEs were developed to achieve improved hardness of tablets. They contain colloidal silica or magnesium aluminometasilicate, e.g. Prosolv<sup>®</sup> (JRS) or F-Melt<sup>®</sup> M (Fuji)<sup>37</sup>).

#### **Stability of dosage form and active substance**

Stability depends mainly on humidity. The use of excipients with a very low content of water is significant if the active substance is prone to hydrolysis. Pharmacopoeial tests include humidity, or loss on drying, and hygroscopicity. However, a lower content of water means usually worse compressibility. Some producers offer CPEs with varying content of water. E.g., Prosolv<sup>®</sup> SMC 90 LM has a lower content of water; guaranteed as loss on drying less than 3 %<sup>6</sup>).

#### **Conclusion**

CPEs have come in focus in the 2000s and have been blooming since. It was the growing popularity of direct compression and ODT that induced the manufacturers to develop new CPEs and market them. This trend seems not to have reached its peak yet and CPE for both direct compression and controlled release is going to grow. This paper describes formulation, preparation and evaluation of CPEs as well as showing scans from electron microscope of frequently used commercially available CPEs.

**Conflict of interest:** none.

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