Co-processed excipients for dispersible tablets – Part 1: Manufacturability

Abstract

Co-processed excipients may enhance functionality and reduce drawbacks of traditional excipients for the manufacture of tablets on a commercial scale. The following study aimed to characterise a range of co-processed excipients that may prove suitable for dispersible tablet formulations prepared by direct compression. Co-processed excipients were lubricated and compressed into 10.5-mm convex tablets using a Phoenix Compaction Simulator. Compression profiles were generated by varying the compression force applied to the formulation and the prepared tablets were characterised for hardness, friability, disintegration and fineness of dispersion. Our data indicates that CombiLac, F-Melt Type C and SmartEx QD100 were the top 3 most suitable out of 14 co-processed excipients under the conditions evaluated. They exhibited good flow properties (Carr's index < 20), excellent **tabletability** (tensile strength > 3.0 MPa **at 0.85 solid fraction**), very low friability (< 1% after 15 minutes), rapid disintegration times (27 – 49 seconds) and produce dispersions of ideal fineness (< 250 µm). Other co-processed excipients (including F-Melt Type M, Ludiflash, MicroceLac, Pharmaburst 500 and Avicel HFE-102) may be appropriate for dispersible tablets produced by direct compression providing the identified disintegration and dispersion risks were mitigated prior to commercialisation. This indicates that robust dispersible tablets which disintegrate rapidly could be manufactured from a range of co-processed excipients.

Keywords: co-processed excipients; dispersible tablets; direct compression; compaction simulator; tablet disintegration.

Introduction

Direct compression **(DC)** is a commonly used method for the preparation of oral solid dosage forms such as tablets. Benefits include avoiding process steps such as wet or dry granulation, providing less variable dissolution profiles compared to granulation methods, reduced wear and tear of punches, improved stability of API and reduced microbial contamination [1]. **The greatest challenge associated with the development of tablets using DC is often the sub-optimal compression and flow properties of the active pharmaceutical ingredient (API), especially if the drug loading in the formulation is very high. [2]. As such, the feasibility of the DC route is highly dependent on the physicochemical properties of the API which determine its flow and compression behaviour [3]. Nevertheless, excipients can profoundly affect or even dominate compaction properties of**

the formulation, especially when these constitute a large proportion of the tablet [4]. When the loading and properties of the API allow for DC, selection of excipients becomes a key consideration in the development of tablets by DC. To ensure formulation success, it is necessary to fully characterise and comprehend the flow and compression properties of the excipients [4]. At present, conventional grades of excipients do not always exhibit the necessary flowability, compressibility, high dilution potential and homogeneity to accommodate different APIs DC [1,5].

The extensive development process for a new product typically involves multiple investigations using a range of excipient material grades and suppliers. One way to ease the development process could be to use co-processed excipients that are suitable for commercial scale manufacture [1,6,7]. Co-processed excipients are the combination of two or more excipients, prepared by processes such as spray drying, wet granulation and co-crystallisation [5,8]. Co-processing of excipients physically modifies the individual materials without altering their chemical structure. Co-processed excipients may be advantageous in a number of ways: (1) providing improved functionality in comparison to physical mixtures of individual excipient components [9]; (2) combining a range of different materials such as plastic and brittle deforming materials, which prevents storage of excess elastic energy during compression, hence reducing the risk of capping and lamination during compression [10]; and (3) accelerating the speed that new products can enter the market without the need for extensive and expensive testing [11]. One drawback of co-processed excipients is that they are not always recognised by the different pharmacopoeias [1].

An area where co-processed excipients may have a particular advantage is in the development and manufacture of dispersible tablets. Dispersible tablets are intended to be dispersed in a liquid (typically water) before administration giving a homogeneous dispersion [12]. Dispersible tablets are an invaluable paediatric formulation that benefit from not necessarily requiring specific storage requirements compared to syrups and powders for reconstitution, and are also less susceptible to stability/microbial issues [13]. Dispersible tablets are typically required to rapidly disintegrate (within 3 mins) [12], have acceptable palatability and provide robust, cost-effective manufacturability on a commercial scale. As such, dispersible tablets often contain a large range of functional excipients such as fillers, lubricants, disintegrants, sweeteners, dispersion aids and multiple flavourings. Therefore, co-processed excipients may be a viable option for including in dispersible formulations as they could reduce the number of separate materials required within the formulation, hence reducing extensive stretching experiments required during formulation and process development.

The following study aimed to identify and characterise a range of co-processed excipients that may prove suitable for the preparation of dispersible tablets by DC. **Candidate co-processed excipients for dispersible tablets were selected based on a previous literature review and advice from**

excipient manufacturers [5]. Placebo formulation containing the co-processed excipients were compressed into tablets and characterised against predefined manufacturability criteria, including flow, compression, disintegration and dispersion characteristics. This enabled screening and selection of the most promising co-processed excipients for the preparation of dispersible tablets by DC. This study also explored a range of tablets prepared at different tensile strengths to determine the target tensile strength value to achieve an adequate balance between mechanical strength and rapid disintegration.

Materials and methods

Materials

The excipients investigated in this study were: Avicel® HFE-102 (FMC biopolymers, Philadelphia, Pensylvania, USA), Compressol® SM and Pharmaburst® 500 (SPI Pharma, Septemes Les Vallons, France), CombiLac® and MicroceLac® (Meggle Pharma, Wasserburg, Germany), Di-Pac (Domino Specialty Ingredients, Decatur, Illinois, USA), Ludiflash® and Ludipress® (BASF, Lampertheim, Germany), Emdex® and ProSolv® ODT (JRS Pharma, Cedar Rapids, Iowa, USA), F-Melt® Type C and F-Melt® Type M (Fuji Health Science, Toyama, Japan), Pearlitol® Flash (Roquette, Corby, Northamptonshire, UK), SmartEx® QD50 and SmartEx® QD100 (ShinEtsu, Tokyo, Japan); and StarCap 1500 (Colorcon, Indianapolis, Indiana, USA). Avicel® PH-102 (FMC Biopolymers) was tested as a comparator against the co-processed excipients since it is a highly compressible non-co-processed excipient. Sodium starch fumarate (SSF) was used as lubricant (Pruv®, JRS Pharma, Cedar Rapids, Iowa, USA). Croscarmellose sodium (Ac-Di-Sol®, FMC Biopolymers), crospovidone (Kollidon® CL-SF, BASF) and low-substituted hydroxypropyl cellulose (L-HPC, NBD-22®, ShinEtsu) were employed as disintegrants. All samples were kindly provided by the manufacturers. The individual constituents of the co-processed excipients are presented in Table 1.

Table 1. Individual constituents of the co-processed excipients

Excipient name	**Individual constituents**	**Particle size (µm)** [†]
Avicel PH-102	100% microcrystalline cellulose (reference)	100
Avicel HFE-102	90% microcrystalline cellulose, 10% mannitol	100
CombiLac	70% lactose, 20% microcrystalline cellulose, 10% maize starch	160 (35-65% below)
Compressol SM	Mannitol, sorbitol, <2% silicon dioxide	126
Di-Pac	97% sucrose, 3% maltodextrin	149 (75% above)
Emdex (USP-NF)	92% dextrose, 4% maltose, 4% maltodextrin	190-220

F-Melt Type C	55-70% D-mannitol, 10-25% microcrystalline cellulose, 2-9% xylitol, 5-13% crospovidone, 2-9% dibasic calcium phosphate anhydrous	120.8
F-Melt Type M	55-70% D-mannitol, 10-25% microcrystalline cellulose, 2-9% xylitol, 5-13% crospovidone, 2-9% magnesium aluminometasilicate	122.3
Ludiflash	90% D-mannitol, 5% crospovidone, 5% polyvinyl acetate dispersion	170-210
Ludipress	93% lactose, 3.5% medium-molecular weight povidone, 3.5% crospovidone	200 (40-60% below)
MicroceLac	75% lactose, 25% microcrystalline cellulose	160 (35-65% below)
Pearlitol Flash	80-85% mannitol, 15-20% maize starch	200
Pharmaburst 500	85% mannitol, <10% silicon dioxide, <10% sorbitol, 5% crospovidone	130
ProSolv ODT	60-70% mannitol, 15-30% MCC, <10% fructose and silicon dioxide, 5% crospovidone	52
SmartEx QD 50	D-mannitol, polyvinyl alcohol, low-substituted hydroxypropyl cellulose	57
SmartEx QD 100	D-mannitol, polyvinyl alcohol, low-substituted hydroxypropyl cellulose	86
StarCap 1500	90% corn starch, 10% pregelatinized starch	90

† Particle size as provided by the manufacturer, expressed as median particle size unless otherwise specified.

Manufacturability criteria and testing methodology

The formulations were characterised against the manufacturability criteria specified in Table 2. These criteria were proposed based on the physical properties of dispersible tablets that are required to produce a robust product that also delivers acceptable patient compliance. The criteria that are required to produce a robust product are flowability (of the powder formulation) and tensile strength, ejection shear, and friability (of the resulting tablets); the criteria that are required to provide acceptable patient compliance are disintegration time and fineness of dispersion. Within this study, minimum requirements and ideal specifications were defined to give an idea as to how successful the different co-processed excipients performed. Rationale for the specifications are provided in the next sections along with testing methodologies.

Table 2. Manufacturability criteria

Formulation property	**Ideal specification**	**Minimum requirement**
Flowability (Carr's Index)	< 15%	< 20%
Tensile Strength **(at 0.85 solid fraction)**	≥ 3.0 MPa	≥ 1.5 MPa
Ejection Shear	< 3.0 MPa	< 5.0 MPa
Friability	< 1% in 10 minutes	< 1% in 4 minutes
Disintegration Time	< 60 seconds	< 180 seconds

Dispersibility	Passes through 250-µm screen	Passes through 710-µm screen

Blending

Co-processed excipients were initially investigated without additional excipients added into the formulation. Selected co-processed excipients, which showed good compression properties but poor disintegration, were evaluated with additional disintegrant added to the formulation. Blends containing co-processed excipient and disintegrant were prepared for 15 min at 22 rpm **using a low shear Turbula blender (Turbula T2F, Willy A Bachofen AG Maschinenfabrik).** All formulations were lubricated with 1% w/w sodium starch fumarate (SSF) for 2 minutes at 22 RPM using a low shear Turbula blender**. Details of the composition of the investigated formulations is presented in Table 3.**

Table 3. Composition of formulations prepared by direct compression using co-processed excipients.

Co-processed excipient (%)		Lubricant (SSF) (%)	Additional Excipient (%)	
Avicel PH-102	99	1	-	
Avicel HFE-102	99	1	-	
CombiLac	99	1	-	
Compressol SM	99	1	-	
Di-Pac	99	1	-	
Emdex	99	1	-	
F-Melt Type C	99	1	-	
F-Melt Type M	99	1	-	
Ludiflash	99	1	-	
MicroceLac	99	1	-	
Pearlitol Flash	99	1	-	
Pharmaburst 500	99	1	-	
ProSolv ODT	99	1	-	
SmartEx QD 50	99	1	-	
SmartEx QD 100	99	1	-	
Emdex	94	1	Crospovidone	5
Emdex	94	1	L-HPC	5
Ludipress	96	1	Crospovidone	3
Ludipress	96	1	L-HPC	3
Di-Pac	94	1	Croscarmellose sodium	5
Di-Pac	94	1	L-HPC	5
StarCap 1500	96	1	Croscarmellose sodium	3

Powder flow testing

Analysis of the flow properties of the co-processed excipients was performed by tapped and bulk density (TBD) analysis by USP method <616> using a Tap Density Tester **(Model 50-1300, Varian Inc)**. Carr's index (CI%) values were calculated to identify the flow properties of the particles. Typically, a Carr's index greater than 25 % is considered to indicate poor flowability, although for this study the preferred value was set at 20% to account for the addition of typically poor flowing API into the formulation which is likely to increase the Carr's Index. A Carr's Index of less than 15 % indicates good flowability and so was used indicate the ideal specification [14,15]

Compression assessment

Tablets of 10.5 mm diameter (round, normal concave) and 500 mg ± 5% weight were produced in triplicate at varying compression forces using a Phoenix compaction simulator **(Serial no. ESH996294, Phoenix Materials Testing Ltd), simulating a Fette 1200i tablet press compression cycle.** Each tablet was characterised for weight (**Analytical Balance XS204, 0.01 mg, Mettler Toledo Inc**), thickness (**Digital Caliper, 0.01 mm, Mitutoyo Ltd**) and hardness (**8M Tablet hardness tester, Dr. Schleuniger Pharmatron, Sotax AG**). The compaction and ejection forces were captured by the compactor simulator for each individual tablet and used to determine tablet tensile strength, solid fraction, ejection shear and compaction pressure [16]. **Tensile strength was measured at solid fraction of *ca.* 0.85, since the desired solid fraction for a tablet is typically in the range 0.85 ± 0.05 [3].** Additionally, tablets of target tensile strengths of either 1.5 or 2.0 MPa were produced for disintegration, fineness of dispersion and friability testing against the criteria detailed in Table 2.

Tensile strength provides information about the crushing strength of the tablet. Tablets with tensile strengths above 2.0 MPa are typically thought to be strong enough to withstand typical packaging and coating operations [15,17]. However, it has been shown that tablets with a tensile strength as low as 1 MPa may be suitable when the product is not subjected to considerable mechanical stress and may also provide faster disintegration [17,18]. Considering that drug substances are typically poorly compressible it was decided to set ideal and minimum specification values at ≥ 3.0 MPa and ≥ 1.5 MPa respectively as detailed in Table 2.

Ejection shear is the force required to eject the tablet from the die after compaction. A low ejection shear is preferable because it suggests that there is a reduced likelihood of defects to the tablets and reduced likelihood of damage to the tablet punches, hence reducing manufacturing costs. A maximum ejection shear of 5.0 MPa is thought to be acceptable to minimise tablet defects and punch damage although a value of less than 3.0 MPa is preferable and as such were set as the ideal and minimum specification values respectively when manufacturing tablets at the target tensile strengths of 1.5 and 2.0 MPa [17].

Tablet friability

Friability testing is typically used to test the physical robustness of tablets [19]. Although tensile strength gives an indication of the mechanical properties of the tablets, friability testing is the Pharmacopoeial standard to measure the tablets resistance to mechanical stress. Friability testing is often used to determine whether tablets can withstand the coating process. Although this is less likely to be required for dispersible tablets it was still thought to be a worthwhile test to understand the physical robustness of the tablets produced from the different co-processed excipients. Tablet friability testing was performed by accurately weighing 10 tablets and placing them into a friability tester (Friabilator 108008, VanKel Ltd). Friability testing was performed for either 4 minutes (standard conditions) or 15 minutes (extended conditions) at 25 rpm. Following testing, the tablets were removed, dedusted and weighed to enable the calculation of the % friability. **As per the current Pharmacopoeial standard, tablets need to be less than 1% friable during testing for 4 minutes, which was set as the minimum requirement. Tablets that withstand a longer time of 10 minutes under stress conditions maintaining less than 1% friable were considered ideal in terms of friability.**

Tablet disintegration

Specifications in the USP for products such as Amoxicillin dispersible tablets require disintegration times to be less than 3 minutes at 37 °C. In contrast, guidance from the WHO requires dispersible tablets to disintegrate within 3 minutes at 15-25 °C. In this study, the minimum requirement for disintegration time was set at 3 minutes. However, since a number of currently available marketed dispersible tablets have disintegration times between 30 seconds and 1 minute [20], it was decided that an ideal specification for disintegration time would be less than 60 seconds. The test was performed as per USP <701> except using four tablets instead of six at 37 ± 2 °C using **an automated tablet disintegration tester with discs (DisiTest 50, Dr. Schleuniger Pharmatron, Sotax AG).** Disintegration times (DTs) were reported as the time taken for the last tablet to disintegrate. **The time taken for the last tablet to disintegrate was recorded.**

Tablet fineness of dispersion

Fineness of dispersion tests are performed on dispersible tablets to provide information on the mouthfeel of a dispersion [21]. The test is used to determine if the dispersion passes freely through a 710µm screen, based on USP <2>. **The compendial test establishes that the dispersion is**

acceptable if it passes freely through a 710µm screen, which was set in this study as the minimum requirement. However, it has been suggested that dispersions of reduced particle size may indicate improved mouthfeel compared to formulations that produce dispersions of particles **larger than *ca.* 250 µm [22]. Thus, an additional sieve screen of 250 µm was used in this study and this was set as the ideal specification for fineness of dispersion.** For each formulation, one tablet was immersed in 10 mL of water and allowed to disperse completely. The suspension was swirled to aid tablet dispersion and then poured through the sieve stack with the visual residue left on each screen being recorded.

Results and discussion

Powder flow of co-processed excipients

Data generated from tapped/bulk density is presented in **Table 3** for the individual co-processed excipients. The results **of Carr's index depicted in Figure 1 indicate** that Compressol SM, Emdex, F-Melt Type M and ProSolv ODT all have ideal flowability with **average** Carr's index results less than 15 %. All other co-processed excipients evaluated showed acceptable flow behaviour with Carr's index values between 15 and 20 %, **except StarCap 1500 which had an average Carr's index of 24% indicating poor flow**. Out of all the co-processed excipients tested, Emdex exhibited the best flow with an **average** Carr's index of 11%; this can be explained because of its non-hygroscopic, uniform porous spheres [23,24]. **The Carr's index limits of 15% (ideal specification) and 20% (minimum required) set in this study allows for the expected reduction in flow which typically occurs with the inclusion of an API in a formulation. Co-processed excipients should be investigated with addition of the target API to demonstrate appropriate flow properties of the blend for the development of dispersible tablets via DC.**

Table 4. Results of bulk density, tapped density and Carr's index

Co-processed excipient	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)
Avicel PH-102	0.33 ± 0.02	0.42 ± 0.02	21.77 ± 0.79
Avicel HFE-102	0.37 ± 0.02	0.45 ± 0.02	19.09 ± 0.63
CombiLac	0.46 ± 0.01	0.55 ± 0.01	16.37 ± 0.42
Compressol SM	0.52 ± 0.02	0.61 ± 0.02	13.63 ± 0.11
Di-Pac	0.73 ± 0.01	0.87 ± 0.01	16.48 ± 1.25
Emdex	0.66 ± 0.01	0.74 ± 0.02	11.14 ± 1.15
F-Melt Type C	0.56 ± 0.01	0.67 ± 0.01	16.78 ± 0.19
F-Melt Type M	0.57 ± 0.01	0.67 ± 0.02	14.59 ± 1.05
Ludiflash	0.54 ± 0.02	0.65 ± 0.04	17.02 ± 1.26

Ludipress	0.53 ± 0.01	0.63 ± 0.02	16.20 ± 0.11
MicroceLac	0.48 ± 0.01	0.58 ± 0.01	18.13 ± 0.68
Pearlitol Flash	0.52 ± 0.01	0.63 ± 0.01	16.00 ± 0.18
Pharmaburst 500	0.44 ± 0.01	0.52 ± 0.01	16.93 ± 0.10
Prosolv ODT	0.65 ± 0.01	0.67 ± 0.02	14.93 ± 1.25
SmartEx QD50	0.54 ± 0.01	0.57 ± 0.01	18.84 ± 0.84
SmartEx QD100	0.47 ± 0.01	0.45 ± 0.03	16.95 ± 0.41
StarCap 1500	0.46 ± 0.01	0.60 ± 0.01	24.17 ± 1.18

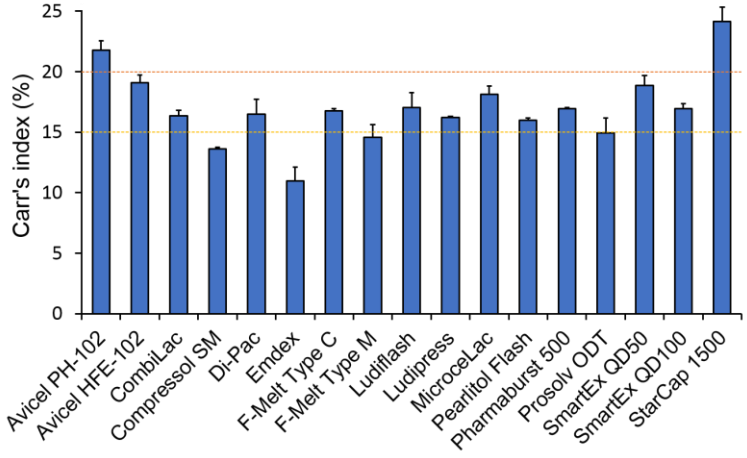

Figure 1. Carr's Index of co-processed excipients. Results expressed as mean **with standard deviation bars** (n=3).

Compression assessment

Tabletability, compactability and compressibility profiles for the co-processed excipients lubricated with 1% w/w SSF are presented in Figure 2, **Figure 3 and Figure 4, respectively**, with the ejection shear results presented in **Figure 5**. Compression profiles for a formulation containing microcrystalline cellulose (Avicel PH102) and lubricant (SSF) were also included to provide a benchmark for excellent compression properties [25]. Tensile strength **at *ca.* 0.85 solid fraction** and ejection shear at the target tensile strength **of 1.5 and 2.0 MPa** are presented in **Table 5**.

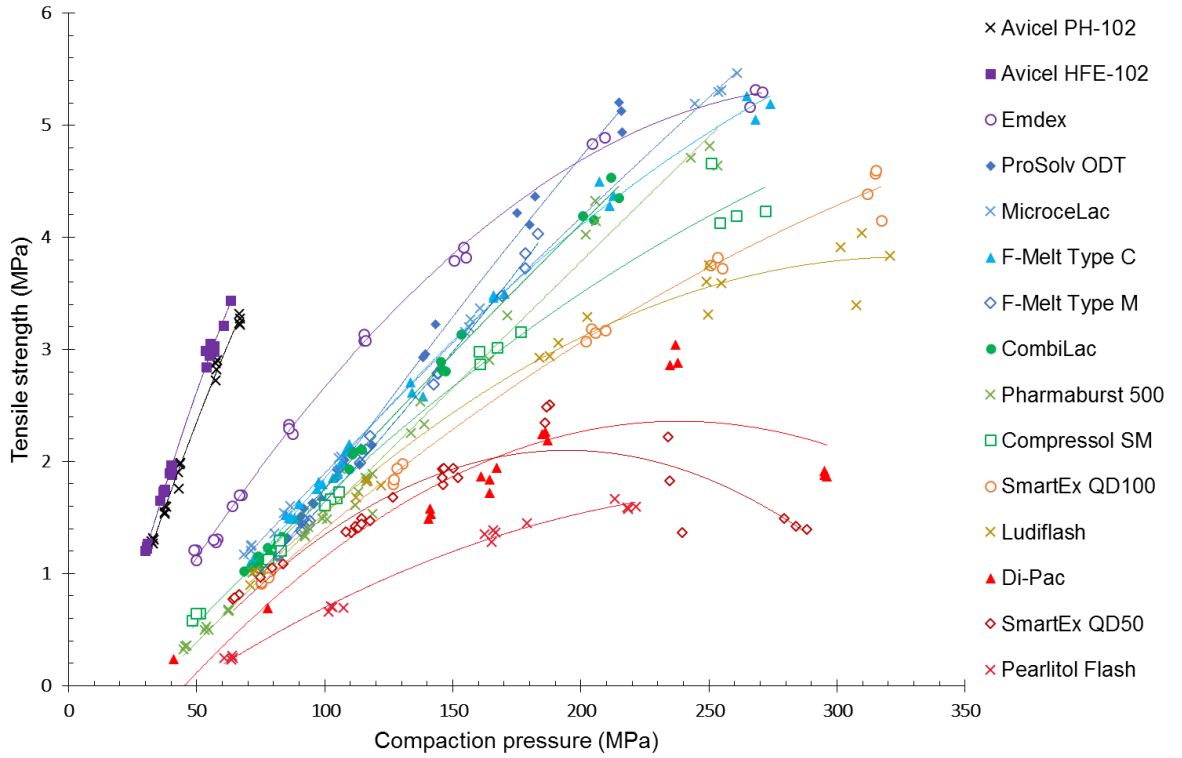

Figure 2. Tabletability profiles (tensile strength as a function of the compaction pressure).

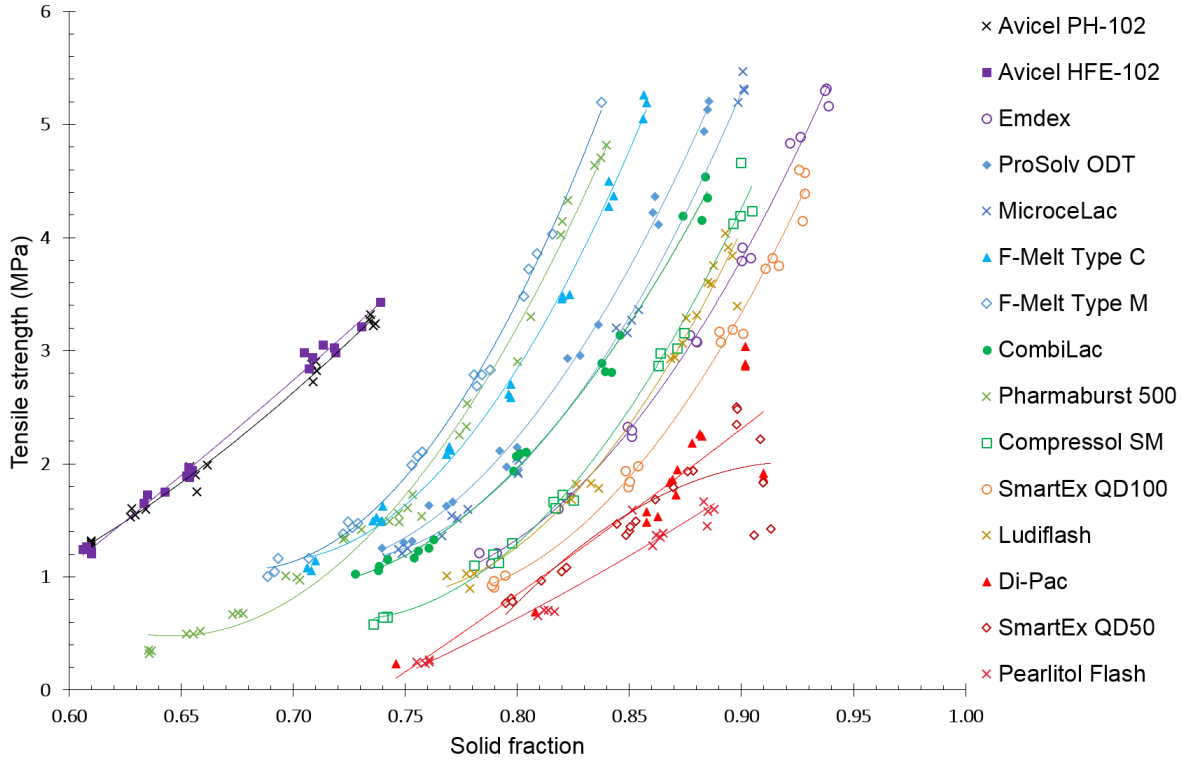

Figure 3. Compactability profiles (tensile strength as a function of the solid fraction).

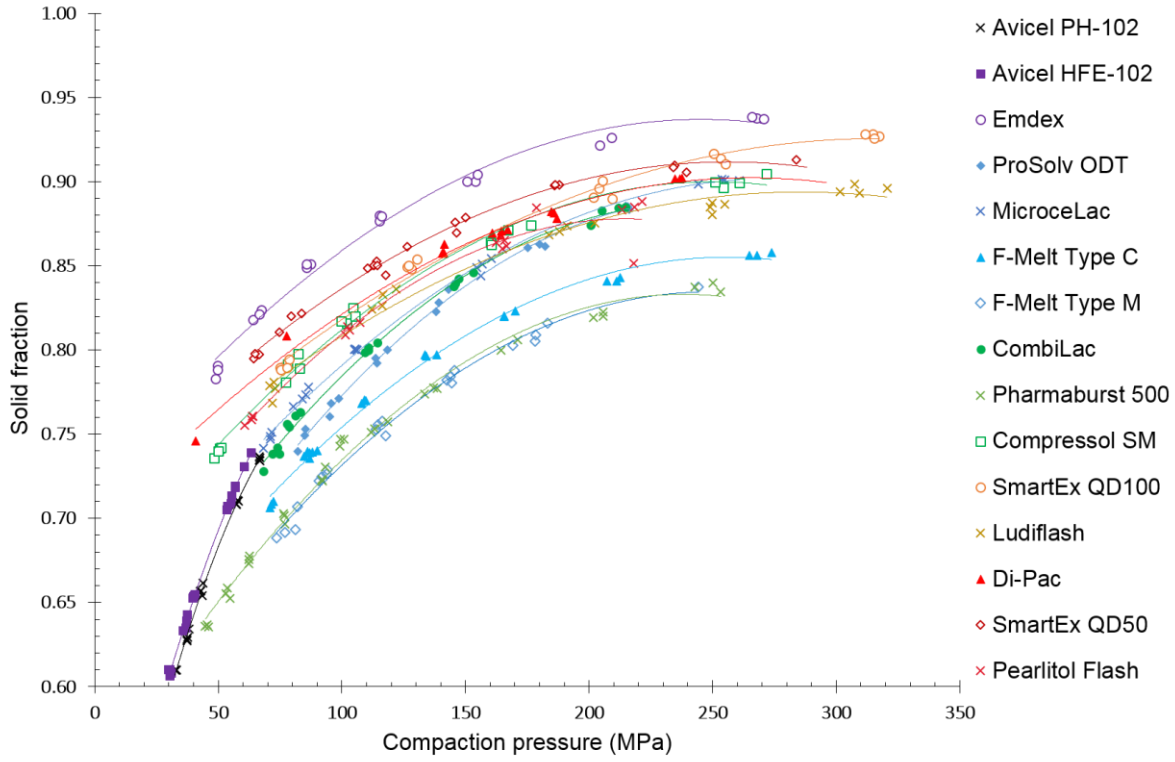

Figure 4. Compressibility profiles (solid fraction as a function of the compaction pressure).

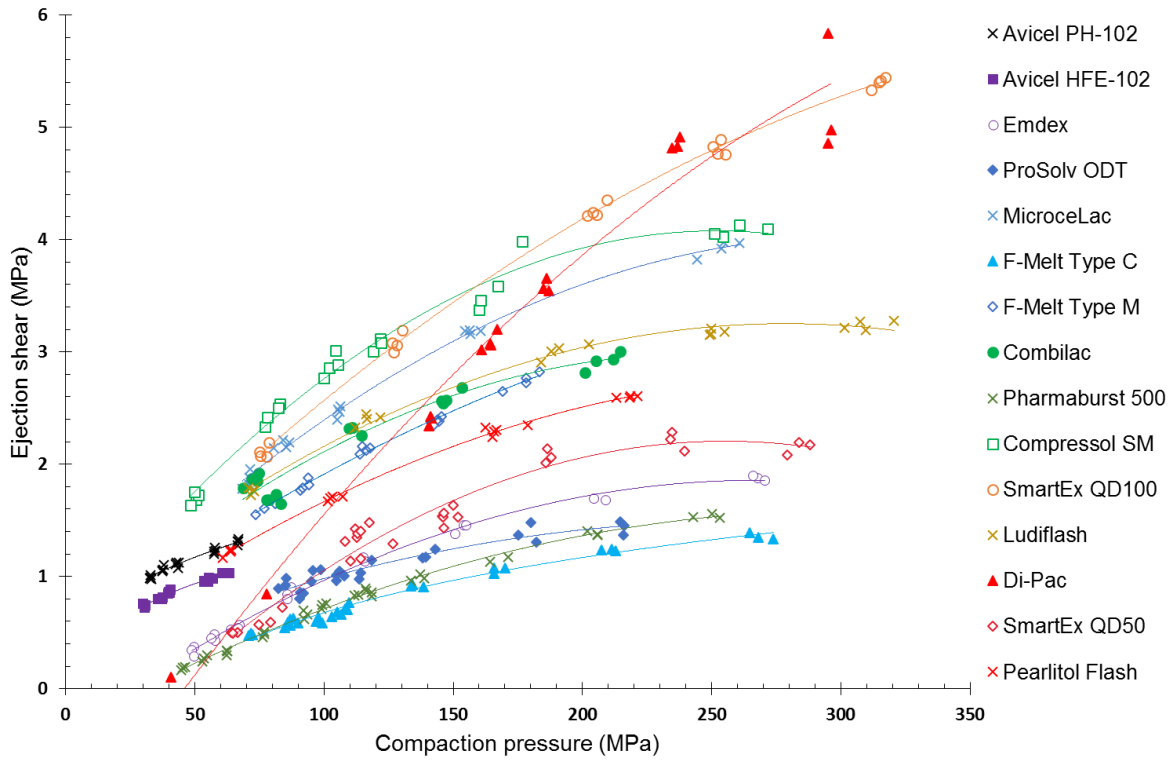

Figure 5. Tablet ejection shear as a function of the compaction pressure

Formulations prepared using Avicel HFE-102, Prosolv ODT, MicroceLac, F-Melt Type C, F-Melt Type M, CombiLac and Pharmaburst 500all showed excellent **compression properties** with tablet tensile strengths **at 0.85 solid fraction** above 3.0 MPa **(ideal specification)**. **Ludiflash, Emdex, Compressol SM and SmartEx QD100 also showed appropriate compression properties with tensile strength at 0.85 solid fraction above the minimum requirement of 1.5MPa.** Formulations containing Di-Pac and SmartEx QD50 provided **tensile strengths at 0.85 solid fraction of 1.40 and 1.43 MPa, respectively, demonstrating poor compression properties** in comparison to other co-processed excipients. **Tablets at a target tensile strength of 2.0 MPa could be achieved with Di-Pac and SmartEx QD50 by increasing the compaction pressure to 160 -180 MPa (solid fraction > 0.85), although** capping occurred for tablets manufactured at higher compaction pressure, which explains the drop in tensile strength shown in Figure 2 **and Figure 3**. Pearlitol Flash **showed the poorest compression properties** of all co-processed excipients investigated, with a tensile strength **at 0.85 solid fraction** of 1.61 MPa. Capping was observed in Pearlitol Flash tablets prepared at high compaction pressures **(220 MPa and above, resulting in solid fraction greater than 0.85)**, hindering the preparation of tablets with target tensile strength of 2.0 MPa and above. **Increased risk of capping and lamination can be expected in tablets with very high solid fraction (i.e. very low porosity) due to localised high-density regions [3].**

Avicel HFE-102 showed particularly superior **tabletability** compared to the other excipients tested, producing very strong tablets at low compaction pressures. Avicel HFE-102 is a mixture of 90% MCC and 10% mannitol produced by spray drying [5]; its compression profile highly resembled that of Avicel PH-102, which could be expected due to high concentration of MCC in both products [25]. Emdex is a dextrate-based co-processed excipients which compresses by plastic deformation mechanism with low elastic energy, demonstrating excellent tabletability [24,26]. Formulations containing Prosolv ODT, MicroceLac, F-Melt Type C and Type M and CombiLac contain a combination of plastic (MCC) and brittle (lactose or mannitol) deforming materials which explains their good **tabletability** [27,28]. Similarly, Pharmaburst 500 and Compressol SM contain sorbitol which will provide good compression through plastic deformation and high mannitol content which will allow consolidation through brittle fragmentation [24,29]; the inclusion of silicon dioxide is thought to offset the hygroscopic nature of sorbitol in these co-processed excipients [30]. Ludiflash and SmartEx QD100 primarily contain mannitol which can be expected to provide brittle fragmentation under compaction leading to friable, weaker tablets compared to plastic excipients such as Avicel PH102 and Emdex [31,32]. However, Ludiflash and SmartEx QD100 still exhibited acceptable **tabletability**. SmartEx QD50 has the same composition as SmartEx QD100 with the difference between grades being the particle size. SmartEx QD100, which contains a larger-sized fraction, showed superior compression properties than SmartEx QD50. Improved **tabletability** of larger particles has been previously attributed to increased fragmentation and better rearrangement

upon compression (compared to smaller fractions), leading to stronger inter-particle bonding, although there may be other unknown differences between the grades not readily disclosed by the excipient supplier [33]. Di-Pac consolidates by both brittle and plastic mechanisms (attributed to the sucrose and maltodextrin components, respectively), which has been reported to overcome the poorer **tabletability** of sucrose [34]; poor **tabletability** of Di-Pac could be ascribed to the much larger proportion of sucrose (97%) than maltodextrin. Poor **tabletability** and capping of Pearlitol Flash could be attributed to the viscoelastic nature of starch, which represents 15-20% of the co-processed excipient, providing good plasticity but high elastic recovery [4,28].

The compactability and compressibility profiles for the co-processed excipients lubricated with 1% w/w SSF resulted in a wide range of solid fractions ranging from 0.6 to 0.95. Emdex formed particularly dense tablets, with a solid fraction greater than other excipients across the range of compaction pressures evaluated. At the target tensile strength of 1.5 MPa, the solid fraction was typically between 0.75 and 0.9 for the co-processed excipients. However, Avicel HFE-102 and Avicel PH-102, which was included as a benchmark for excellent compression properties, compressed into tablets with tensile strength of 1.5 MPa at a lower solid fraction of *ca.* 0.65, demonstrating greater compactability than the other excipients.

Table 5. Summary of compression, friability, disintegration and fineness of dispersion results

Co-processed excipient	Tensile strength **at 0.85 SF** (MPa)	Target tensile strength† (MPa)	Ejection shear† (MPa)	Friability†		DT† (secs)	Dispersion fineness†	
				% 4min	% 10min		710 µm	250 µm
Avicel PH-102	>3.0	1.94	1.15	0.07	0.07	60	Fail	Fail
		1.47	1.04	0.03	0.11	38	Fail	Fail
Avicel HFE-102	>3.0	1.96	1.04	0.04	0.09	56	Fail	Fail
		1.48	0.90	0.02	0.11	35	Pass	Fail
Compressol SM	**2.22**	2.01	3.07	0.17	NM	436	Fail	Fail
		1.50	2.64	0.22	NM	426	Fail	Fail
CombiLac	>3.0	2.10	2.10	0.06	0.27	58	Pass	Pass
		1.49	1.79	0.06	0.30	42	Pass	Pass
Di-Pac	**1.40**	1.84	3.09	0.32	NM	424	Pass	Pass
		1.53	2.39	NM	NM	NM	NM	NM
Emdex	**2.29**	1.96	0.84	0.12	NM	251	Pass	Pass
		1.36	0.57	0.32	NM	194	Pass	Pass
F-Melt Type C	>3.0	1.91	0.66	0.02	0.12	49	Pass	Pass
		1.5	0.57	0.06	0.19	30	Pass	Pass
F-Melt Type M	>3.0	2.15	2.05	0.03	0.33	82	Pass	Pass

		1.43	1.74	0.04	0.21	28	Pass	Pass
Ludiflash	**2.51**	2.07	2.53	0.13	0.59	70	Pass	Fail
		1.45	2.16	0.21	0.72	47	Pass	Pass
MicroceLac	>3.0	2.03	2.52	0.02	0.68	84	Pass	Pass
		1.59	2.28	0.02	0.12	44	Pass	Pass
Pharmaburst 500	>3.0	1.86	0.86	0.06	0.31	36	Pass	Fail
		1.51	0.74	0.08	0.55	26	Pass	Fail
Prosolv ODT	>3.0	1.94	1.01	0.06	NM	259	Pass	Pass
		1.51	0.84	0.09	NM	149	Pass	Pass
Pearlitol Flash	**1.05**	Unable to achieve target tensile strength of 2.0 MPa						
		1.46	2.36	0.15	1.11	49	Pass	Pass
SmartEx QD50	**1.43**	1.88	1.54	0.27	1.25	30	Pass	Pass
		1.44	1.42	0.61	1.78	26	Pass	Pass
SmartEx QD100	**1.86**	1.95	2.63	0.15	0.71	38	Pass	Pass
		1.55	2.08	0.18	0.82	27	Pass	Pass

[†]Average result for tablets manufactured at target tensile strength of 1.5 and 2.0 MPa; NM: Not measured; only excipients which displayed appropriate disintegration (below 3 minutes) and standard friability (< 1% in 4 minutes) were investigated for extended friability (during 15 minutes).

In terms of ejection at the target tensile strengths of 2.0 MPa, only Compressol SM and Di-Pac provide borderline results with values greater than 3.0 MPa. At a target tensile strength of 1.5 MPa, all co-processed excipients provided ejection shear results below 3.0 MPa. SmartEx QD100 and Microcellac also show relatively high ejection shear results when compressing at higher compaction pressures. As such, these excipients may still be suitable for use in preparation of dispersible tablets however with the use of an alternative lubricant.

Tablet Friability

The results for the tablet friability are presented in **Table 5**. All tablets prepared at tensile strengths of 2.0 MPa and 1.5 MPa were less than 1% friable after standard friability testing for 4 minutes, which suggests that co-processed excipients would allow for DC of tablets at a tensile strength of 1.5 MPa whilst maintaining appropriate mechanical properties.

Formulations that displayed passable compression properties (i.e. maximum tensile strength > 1.5 MPa), appropriate disintegration times (below 3 minutes) and less than 1% tablet friability (over 4 minutes) were investigated for extended friability. The advantage of this test is that it will provide an insight into the tablets ability to withstand manufacture, transportation and patient handling. Extended friability also aims to reproduce the mechanical stresses experienced by tablets during a coating

process. All the studied formulations, except for SmartEx QD50 and Perlitol Flash, passed the extended friability test. These results suggest that formulations containing SmartEx QD50 or Pearlitol Flash may be more challenging to coat compared to the other co-processed excipients investigated.

Tablet disintegration

Table 5Disintegration times for all formulations at the two target tensile strengths (1.5 and 2.0 MPa) **are shown in Table 5**. Disintegration times varied from 26 seconds to over 7 minutes.

Target Tensile Strength of 2 MPa

When compressing to a target tensile strength of 2.0 MPa, the formulations yielding the shortest disintegration times contained SmartEx QD50 and QD100, Pharmaburst 500, F-Melt Type C, Avicel HFE-102 and CombiLac; all disintegrating in less than 60 seconds. These were followed by Ludiflash, F-Melt Type M, Avicel PH-102 and MicroceLac, which disintegrated within 60-90 seconds. Both F-Melt products (Type C and Type M), Pharmaburst 500 and Ludiflash contain the disintegrant crospovidone which acts by wicking and swelling mechanisms, drawing water in by a capillary action associated with its porous morphology, resulting in rupturing of interparticle bonds and disintegration [35]. SmartEx QD50 and QD100 contain the disintegrant L-HPC which swells when it encounters water leading to rapid tablet disintegration [36]. PVA in SmartEx products, as well as in Ludiflash, may contribute towards their short disintegration times [37]. The inclusion of silicon dioxide in Pharmaburst 500 and MCC in F-Melt Type C and Type M may also help to reduce the disintegration time for these formulations [38]. The fast disintegration of CombiLac and MicroceLac can be attributed to MCC, which acts by wicking on contact with aqueous fluids [25]; while the quicker disintegration of the former can be ascribed to the additional maize starch (10% w/w) within its composition [39].

The formulations containing Prosolv ODT, Emdex, Di-Pac and Compressol SM displayed long disintegration times of over 3 minutes. This could be expected for Emdex, Di-Pac and Compressol SM since they contain no disintegrant in their composition; although it was unexpected from Prosolv ODT, which contains 5% crospovidone as disintegrant along with 15-30% MCC. **Longer wetting and disintegration times have been previously reported for Prosolv ODT compared to formulations containing other co-processed excipients such as Ludiflash, Pharmaburst 500 or Pearlitol Flash [40,41].**

Target Tensile Strength of 1.5 MPa

A reduced target tensile strength of 1.5 MPa was investigated to determine the effect of hardness on disintegration and the effect on tablet robustness. All formulations manufactured at a lower target tensile strength of 1.5 MPa had faster disintegration times than those with a target tensile strength of 2.0 MPa. This can be explained by the lower compression forces resulting in an increase in the tablet porosity because of weak bonding between the particles. This increase in tablet pore size results in quicker water uptake that leads to disintegration/erosion by dissolution of soluble components and also increased swelling of the disintegrant, hence decreasing disintegration time [42].

As with a target tensile strength of 2.0 MPa, the best performing formulations contained Pharmaburst 500, SmartEx QD50 and QD100, F-Melt Type C and Type M, Avicel HFE-102, Avicel PH-102, CombiLac, MicroceLac and Ludiflash, with disintegration times all below 60 seconds. Pearlitol Flash, which was not possible to compressed into 2.0 MPa tablets, also disintegrated in less than 60 seconds when compressed into 1.5 MPa tablets. ProSolv ODT also provided a disintegration time shorter than 3 minutes, although this formulation still took 2 minutes 29 seconds to disintegrate. Meanwhile, formulations containing Emdex and Compressol SM produced long disintegration times of over 3 minutes.

Tablet fineness of dispersion

All of the formulations except those containing Avicel PH-102, Avicel HFE-102, Compressol SM, Pharmaburst 500 and Ludiflash created smooth dispersions that passed through sieve screens with nominal mesh apertures of 250 and 710 µm. Avicel HFE-102 tablets at 2.0 MPa tensile strength formed coarse dispersions which substantially remained in the 710 µm sieve however when compressed to the lower tensile strength, the dispersions passed through the 710 µm screen but not the 250 µm screen. Similarly, formulations containing Pharmaburst 500 (at either target tensile strength) and Ludiflash (at high tensile strength) passed through the 710-µm screen but not that with a nominal mesh aperture of 250µm; although Ludiflash at 1.5 MPa passed through both sieves. Avicel PH-102 and Compressol SM formed coarse dispersions at both target tablet tensile strengths (1.5 and 2.0 MPa) which failed to pass through both the 250 and 710 µm screens. The results for the tablet fineness of dispersion are summarised in Table 5.

Formulations with additional disintegrant

Some of the excipients investigated offered good tabletability and mechanical strength but slow disintegration. Poor disintegration performance could be overcome by blending of co-processed excipients with additional disintegrants before compression. Potentially, additional disintegrant and API could be added simultaneously to the formulation to minimise processing steps. As proof-of-

concept, some excipients were investigated in formulations containing additional disintegrants. Di-Pac and Emdex provided good friability and dispersibility but the disintegration time was too long for dispersible tablets (i.e. > 3 minutes); thus, these excipients were investigated in formulations containing alternative disintegrants. Moreover, the suppliers of Ludipress and StarCap 1500 recommended the inclusion of additional disintegrants into the formulations.

The disintegrants investigated were Ac-Di-Sol (croscarmellose sodium), Kollidon CL-SF (crospovidone) and L-HPC (NBD-22). Crospovidone acts by a wicking and swelling mechanism, drawing water in by a capillary action associated with its porous morphology, resulting in rupturing of interparticle bonds and disintegration [35]. Croscarmellose sodium works by swelling when in contact with water thereby overcoming inter-particulate forces and bringing about disintegration [43]. L-HPC also swells when in contact with water leading to rapid tablet disintegration [36].

The alternative disintegrants made only minimal differences in the **tabletability** and ejection shear results, as shown in **Table 6** (tabletability profiles not shown). **Emdex and Ludipress showed acceptable tabletability, whereas Di-Pac and StarCap 1500 showed poor tabletability with tensile strength at 0.85 solid fraction below 1.5 MPa, irrespective of the disintegrant included in the formulation.** The addition of crospovidone or L-HPC to Emdex reduced the disintegration time significantly from over 3 minutes to less than 60 seconds. In contrast, the addition of croscarmellose sodium or L-HPC to Di-Pac did not greatly reduce disintegration times, which remained longer than 3 minutes. Similarly, Ludipress and StarCap 1500 exhibited disintegration times longer than 3 minutes, even with additional disintegrants included in the formulation, suggesting that these co-processed excipients are not optimal for use in directly compressible dispersible tablet formulations. The presence of the binder Kollidon 30 in Ludipress may retard disintegration times whereas the highly soluble nature of Di-Pac may increase viscosity of the penetrating fluid thereby reducing water-swelling disintegrant effectiveness [43,44].

Table 6. Summary of results for formulations containing additional disintegrants.

Co-processed excipient	Disintegrant (% w/w)	Tensile strength at 0.85 SF (MPa)	Tensile strength† (MPa)	Ejection shear† (MPa)	Friability†		DT† (secs)	Dispersion fineness†	
					% 4min	% 10min		710 µm	250 µm
Emdex	Crospovidone (5%)	2.81	1.96	1.38	0.15	NM	51	Pass	Pass
			1.51	1.28	0.15	NM	46	Pass	Pass
Emdex	L-HPC (5%)	2.54	1.94	1.22	0.13	0.59	38	Pass	Pass
			1.45	0.88	0.20	0.98	30	Pass	Pass
Ludipress	Crospovidone	2.32	1.98	1.64	0.22	NM	210	Pass	Pass

	(3%)		1.46	1.93	0.24	NM	195	Pass	Pass
Ludipress	L-HPC (3%)	1.98	1.96	2.21	0.14	NM	403	Pass	Pass
			1.55	1.81	0.20	NM	290	Pass	Pass
Di-Pac	Croscarmellose sodium (5%)	1.29	Unable to achieve target tensile strength of 2.0 MPa						
			1.55	3.52	0.34	NM	295	Pass	Pass
Di-Pac	L-HPC (5%)	1.47	1.91	3.71	0.19	NM	396	Pass	Pass
			1.45	2.52	0.29	NM	306	Pass	Pass
StarCap 1500	Croscarmellose sodium (3%)	1.43	Unable to achieve target tensile strength of 2.0 MPa						
			1.44	0.99	0.05	NM	191	Pass	Pass

Conclusion

This study investigated a range of co-processed excipients that may prove suitable for the preparation of dispersible tablets by DC. Formulations containing CombiLac, F-Melt Type C and SmartEx QD100 exhibited acceptable flow properties (Carr's index < 20), **tabletability** (max. tensile strength > 3.0 MPa) and ejection results (< 2.8 MPa at target tensile strengths) in addition to low friability (< 0.2 %), short disintegration times (< 60 seconds at both 1.5 MPa and 2.0 MPa) and good dispersibility (< 250 µm), which suggest that they may be suitable co-processed excipients for use in directly compressed dispersible tablet formulations. Other excipients that may be appropriate include F-Melt Type M, Ludiflash, MicroceLac, Pharmaburst 500 and Avicel HFE-102, providing the identified disintegration and dispersion risks were mitigated prior to commercialisation. The use of additional excipients within the formulation, such as disintegrants, to improve the performance of co-processed excipients was also considered in this research but a more thorough investigation might be necessary in a case by case basis. This study also showed that tablets containing co-processed excipients can be manufactured at a reduced tablet tensile strength of 1.5 MPa to provide shorter disintegration times and finer dispersions whilst achieving acceptable tablet friability **(compared to tablets compressed at 2.0 MPa)**.

Further work such as ascertaining organoleptic properties, API compatibility and stability/storage investigation for these materials may be required before the co-processed excipients could be readily used in directly compressed dispersible tablet formulations. **The physicochemical properties of the API and the required drug loading influence the feasibility of the DC process and thus future studies investigating drug-loaded formulations with co-processed excipients would also be required. Nevertheless, this fundamental investigation associated with the flow, compression and disintegration behaviour of excipients provides excellent information to assist the selection of an appropriate co-processed excipient for tablet formulation design using DC. Co-processed**

excipients with a favourable manufacturability profile for the preparation of dispersible tablets by DC have been highlighted.

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Response to Reviewers' Comments:

Reviewer #1:

The manuscript reports significant amount of data such as hardness, friability, disintegration and fineness of dispersion for 17 different co-processed excipients, intended for dispersible tablets. Therefore, in general, such reporting would be a welcome addition to the journal readership. Unfortunately, the current manuscript reads like a report and would benefit from adding some depth or rigor, including properly explaining a number of issues and outcomes as are numerated below, rather than a research article. Therefore, it would require significant revisions if the authors can accomplish those quickly, before publishing.

The authors would like to thank the reviewer for their thorough revision of our manuscript and the valuable contributions provided. We have undertaken a careful revision of our manuscript and have substantially improved its contents based on the feedback provided by the reviewer. We have addressed each of the issues raised by the reviewer, as outlined below.

Before addressing the reviewer's points, we would like to clarify that the work presented in this manuscript is part of a broader investigation. Our work aimed at the simultaneous assessment of co-processed excipients for their manufacturability (Part 1) and end-user acceptability (Part 2). We have adopted a stepwise approach and hence Part 2 is dedicated to show the in vivo (human panel) data for acceptability while Part 1 shows the in vitro manufacturability data (to narrow down the candidates to be assessed in human panel study).

In addition, we have now done some work using API with the key co-processed excipients identified in this preliminary study. We found that the work presented here was very valuable to us for the initial screening of excipients and selection of the most promising candidate excipients (prior to human panel study and prior to addition of API). Hence, we hope that the reviewer understands the value and impact of this preliminary work.

1. The introduction is brief and on a cursory examination, appropriate. It frequently relies on a few previous "review" articles, which are from groups that may not have extensive academic research background.

We would like to acknowledge the use of previous review articles in some parts of our manuscript instead of primary references; unfortunately, research articles dealing with co-processed excipients are still scarce (which, on the other hand, highlights the value of our manuscript). Nevertheless, we have carefully revised our introduction and have added some valuable primary references, including:

X.H. Li, L.J. Zhao, K.P.F. Ruan, Y. Feng, D.S. Xu, K.P.F. Ruan, The application of factor analysis to evaluate deforming behaviors of directly compressed powders, Pharm. Technol. 247 (2013) 47–54.

A.I. Arida, M.M. Al-Tabakha, Cellactose a co-processed excipient: a comparison study., Pharm. Dev. Technol. 13 (2008) 165–175. doi:10.1080/10837450701831294.

For example, the main premise seems to be in their first paragraph, "…..conventional grades of excipients do not always exhibit the necessary flowability, compressibility, high dilution potential and homogeneity to accommodate direct compression". However, later these so-called necessary properties are almost arbitrarily stated in Table 2, without justification or discussion.

We would like to clarify that the properties listed in Table 2 were not arbitrarily stated but rather carefully selected based on scientific grounds and industry experience. These are criteria recommended by our industry sponsor as well as being based on pharmacopoeial requirements and many drug product specifications.

We believe that appropriate justification and discussion of these items was provided in the methodology section along with the description of the testing methodologies. Examples of the discussion and justification included in the paper, including relevant references to the scientific literature, are provided below:

> *Typically, a Carr's index greater than 25 % is considered to indicate poor flowability, although for this study the preferred value was set at 20% to account for the addition of typically poor flowing API into the formulation which is likely to increase the Carr's Index. A Carr's Index of less than 15 % indicates good flowability and so was used indicate the ideal specification [14,15].*

> *Tablets with tensile strengths above 2.0 MPa are typically thought to be strong enough to withstand typical packaging and coating operations [15,17]. However, it has been shown that tablets with a tensile strength as low as 1 MPa may be suitable when the product is not subjected to considerable mechanical stress and may also provide faster disintegration [17,18]. Considering that drug substances are typically poorly compressible it was decided to set ideal and minimum specification values at ≥ 3.0 MPa and ≥ 1.5 MPa respectively as detailed in Table 2.*

Nevertheless, the discussion and justification of these properties have been revised based on the feedback provided by the reviewer and additional details have been provided for friability and fineness of dispersion. Please refer to the revised document for details.

The introduction also appears to set stage for direct compression (DC) of tablets. However, in any commercial formulation, excipients alone cannot determine DC capabilities and API properties and their loading become more significant determinants. This aspect is missing in substance in the introduction as well as rest of the paper. Overall, this section needs significant upgrade to tell the story why this work is significant and if outcome are indeed meaningful.

We have revised our manuscript to better acknowledge the role of the API and the importance of the physicochemical properties of the API on the feasibility of Direct Compression. For example, we have included the following statements in the introduction: "The greatest challenge associated with the development of tablets using DC is often the sub-optimal compression and flow properties of the active pharmaceutical ingredient (API), especially if the drug loading in the formulation is very high. [2]. As such, the feasibility of the direct compression route is highly dependent on the physicochemical properties of the API which determine its flow and compression behaviour [3]".

We have also included relevant statements in the conclusion to acknowledge that: "the physicochemical properties of the API and the required drug loading often determine the feasibility of DC and thus future studies investigating drug loaded formulations with co-processed excipients would be valuable".

The authors would also like to emphasise that the influence of the API (with potentially poor flow and compression properties) was taken into account in the selection of specifications for the properties listed in Table 2, as detailed in our previous response.

2. Continuing with the major problem with the paper is that all the work is done without even a model API or API based formulation and thus all results are those of a placebo. As an example, a co-

processed MCCC-based excipient such as Prosolv 90 has excellent properties and would meet majority of the requirements of Table 2 when formulated as a placebo. However, even at 40 % API load of poorly flowing cohesive API like micronized acetaminophen, it would fail most of those requirements. The same is most likely true for the results of this paper. The authors must present limited results and associated discussion.

The authors appreciate the insight provided by the reviewer and acknowledge the limitations of our work; however, we believe that this work represent a valuable initial step towards the design and development of dispersible tablets via direct compression by providing in depth characterisation and screening of excipients. Those excipients which showed better manufacturability profile in placebo formulations are more likely to meet the requirements when API is added to the formulation.

We have added a few lines in the conclusion to acknowledge the limitations of our work, suggest future work with addition of API into the formulation and justify the value of the research presented in this manuscript in that "co-processed excipients with a favourable manufacturability profile for the preparation of dispersible tablets by DC have been highlighted".

3. Regarding Table 2, as mentioned before, significant justification must be provided, including at least one realistic formulation. Also, the number of criteria needs to be justified. Is this a fairly comprehensive list? Provide full justification of both the ideal and minimum requirements.

As mentioned in the manuscript "These criteria were proposed based on the physical properties of dispersible tablets that are required to produce a robust product that also delivers acceptable patient compliance. The criteria that are required to produce a robust product are flowability (of the powder formulation) and tensile strength, ejection shear, and friability (of the resulting tablets); the criteria that are required to provide acceptable patient compliance are disintegration time and fineness of dispersion".

The criteria listed in Table 2 is based on Pharmacopoeial requirements of dispersible tablets, including friability, disintegration time and fineness of dispersion, as well as criteria for flowability (Carr's Index) and compressibility (tensile strength and ejection shear). Firstly, compliance with Pharmacopoeial requirements is essential to obtain Marketing Authorisation and thus relevant tests were included. In addition, flowability and compressibility are widely acknowledged in the scientific literature as the two most important criteria for materials intended for direct compression and thus relevant tests were included to measure these properties.

Although certain physicochemical properties of the materials might also be relevant, including bulk density, particle size or brittle fracture index, these fundamental properties would affect flowability and compressibility of the material and thus their impact is considered by measuring other properties such as Carr's index, tensile strength and disintegration time. We believe that the requirements presented in Table 2 are a fairly comprehensive, relevant and manageable list.

As addressed in our previous responses, justification of both the ideal and minimum requirements have been provided in the methodology section for each of the criterion included in Table 2.

4. The details of the instruments used for characterization are missing, including measurement protocols employed. At the least, manufacture, model etc need to be provided.

The information provided in the manuscript for manufacturing and analytical equipment have been thoroughly reviewed and details have been provided where missing.

5. Please justify using Carr Index instead of other measures such as those obtained from shear-testing, which are more realistic. Also justify why just the tablet strength is listed as a criterion because it strongly depends on other inter-related properties such as the compaction force and table porosity. What was kept fixed? All of these are major weaknesses that need to be overcome in a revised version.

Measurements of bulk density, tapped density and calculation of compressibility index are compendial tests and were chosen as preferred methods for this study. These are well established methods, widely used in industry and widely reported by excipients manufacturers, which allows comparison of results with other scientific publications and commonly used excipients.

We have now replaced "maximum tensile strength" by "tensile strength at ~ 0.85 solid fraction", to allow correct comparison between excipients at a fixed solid fraction value. The value of 0.85 solid fraction has been selected since the expected solid fraction for a tablet is normally in the range 0.85 ± 0.05 and this value has been used as a benchmark to compare formulations in previous research, such as: *M. Leane, K. Pitt, G. Reynolds, A proposal for a drug product Manufacturing Classification System (MCS) for oral solid dosage forms., Pharm. Dev. Technol. 7450 (2014) 1–10*.

6. Why bulk density is not considered one the criteria in Table 2?

As mentioned in our response to Question 3, bulk density and other fundamental properties of the material will impact compressibility/tabletability and flow properties and, for the purpose of our research, were sufficiently considered within the measurements of Carr's index, tensile strength and disintegration time. As much as we wanted these criteria to be fairly comprehensive, we thought that a concise list would be valuable.

However, based on the reviewer's suggestions, we have now included results of bulk density (along with tapped density and Carr's index) in the results section. We have also included a statement to clarify that "co-processed excipients should be investigated with addition of the target API to demonstrate appropriate flow properties of the blend for the development of dispersible tablets via DC ". We hope that this satisfies the reviewer's request.

7. Error bars must be provided for Figure 1, otherwise it is hard to conclude that the Carr's Index of F-Melt Type M and ProSolv ODT are less than 15%. Also, what is the physical difference in an excipient having 11% or 15% Carr's Index? From literature, it looks like they should have the similar flow behavior. If bulk density was also used as a criterion, together they will provide better information. In fact, all the results essentially suggest (based on the Carr Index) that these materials are freely flowing. In that case, why bother? The problem with the paper is that the authors are failing to understand these properties in terms of how they change in a realistic formulation that includes an API.

We thank the reviewer for their contribution and we have now included error bars in Figure 1. We have amended the manuscript to clarify that **average** Carr's index F-Melt Type M and ProSolv ODT are less than 15%.

We agree with the reviewer that all co-processed excipients investigated are free-flowing and no significant differences can be concluded solely from the Carr's index results. We still believe this is important to show, thus we included results of Carr's index to prove that all excipients are indeed free flowing. The manuscript then follows onto more significant results, such as disintegration time, which demonstrate greater differences between excipients.

8. Figure 2 should be called tabletability. Compressiblity is a plot of porosity vs compaction pressure. Please read the references (citation 22 and 23) more carefully.

We thank the reviewer for their feedback and have replaced the terms “tablet compression profile” and “compressibility” by “tabletability profiles” and “tabletability” respectively.

9. The discussion of tabletability (compressibility in the manuscript) is poor, please provide an apple to apple comparison. For example, it is not good to compare the tensile strength at a lower compaction force for one sample to the tensile strength at a higher compaction force for another sample. This is in line with a previous comment. Also, a challenging API must be used in a text-book formulation to gain better understanding.

The compression assessment section of the manuscript has been thoroughly reviewed based on the feedback provided. We have included compressibility (solid fraction as a function of compaction pressure) and compactability (tensile strength as a function of solid fraction), in addition to the tabletability data (tensile strength as a function of compaction pressure) initially included. This has resulted in extensive revision of the text to ensure consistency and correctness in the use of these terms throughout the manuscript.

As mentioned in a previous response, we decided to use the value of tensile strength at 0.85 solid fraction to allow a direct “apple to apple” comparison between excipients. We thank the reviewer for their recommendation, which has been used to improve the clarity and rigour of our paper.

Regarding the use of a text-book formulation, investigating drug-loaded formulations was outside the scope of this work, but we value the feedback provided by the reviewer and we have added a line in the conclusion to suggest this approach as future work.

10. Line 226 to Line 228. Please provide references to support this statement. How come the larger particles have a better particle bonding strength?

An explanation of higher compressibility/tabletability in the case of larger particles could be the higher rate of fragmentation. Larger particle fractions have been shown to provide increased fragmentation and better rearrangement of particles upon compression, leading to stronger tablets. This might be applicable to a product such as SmartEx QD50, mainly composed of a brittle material such as mannitol.

A reference was provided to support this statement:
M. Šantl, I. Ilić, F. Vrečer, S. Baumgartner, A compressibility and compactibility study of real tableting mixtures: The impact of wet and dry granulation versus a direct tableting mixture, Acta Pharm. 62 (2012) 325–340.

This reference in turn refers to other examples of previous work showing similar results, such as:
M. Eriksson and G. Alderborn, The effect of particle fragmentation and deformation on the interparticulate bond formation process during powder compaction, Pharm. Res. 12 (1995) 1031–1039.

Nonetheless, there may be other unknown differences between the grades not readily disclosed by the excipient supplier which contribute to the differences in tabletability, as acknowledged in our manuscript.

11. Line 283 to 285, It is interesting to see that Prosolv ODT has a longer disintegration times even though it contains 5% disintegrate. Please explain why it behaves like this.

As acknowledged in the manuscript, this behaviour was unexpected based on its compositions.

However, similar behaviour has been previously reported and we have now included a statement to describe this: “Longer wetting and disintegration times have been previously reported for Prosolv ODT compared to formulations containing other co-processed excipients such as Ludiflash, Pharmaburst 500 or Pearlitol Flash [40,41]”.

12. The conclusions are unsubstantiated based on some of the above comments and lack of rigor. For example, "This work continues to highlight the potential applications of co-processed excipients, compared to traditional physical blends of excipients." Is unjustified based on the results. Nowhere in the paper I can find any baseline cases of "traditional physical blends of excipients".

We thank the reviewer again for their valuable contribution. We have now deleted that sentence and amended the conclusion to be justified by the evidence described in our research.

Reviewer #2:

A well-structured study.

We would like to thank the reviewer for their kind words. We have revised our manuscript and addressed the outstanding points as suggested by the reviewer. Please see below:

Please add compendial status of the copocessed excipients for the ones that are official in the Phamacopoeia.

To the best of the author’s knowledge, Emdex (USP-NF) is the only compendial ingredient from those co-processed excipients investigated in this study. A reference to the USP-NF compendial status of this excipient has been made in Table 1. Other co-processed excipients should be treated as “mixed excipients” from a regulatory perspective, as per the definition in EMEA/CHMP/QWP/396951/2006.

Does the simulator also consider double rotary press?

We used the Phoenix compaction simulator to simulate a Fette 1200i tablet press compression cycle. We have specified this in the methodology section upon revision.

The simulator is a single station press where the movement of the punches represents the movement that would occur on the simulated press based on cam size and shape, providing representative dwell times and compression forces to what is seen on commercial scale rotary presses. As such, the simulator can be used to simulate any rotary (single or double sided) press (including for bi or tri layer tablets).

Are any dissolution studies performed to compare tablets manufactured with traditional excipients and coprocessed excipients? It would be good to have it done. If not, kindly add statement relating

to additional dissolution study comparison for the tablets manufactured with coprocessed excipients and traditional excipients are required.

Dissolution studies were out of the scope of our work. The study of dissolution would be more relevant when APIs are included but we were only looking for the manufacturability piece and not the possible impact on biopharmaceutics at this stage. We believe that the impact of co-processing (compared to traditional blends) would be minimal in terms of dissolution, since dissolution is primarily API dependent when manufacturing using Direct Compression. Also, some dispersible tablets only require disintegration tests for release if they are BCS 1 compounds with high solubility. Therefore, dissolution studies are required on a case-by-case basis.

Nevertheless, based on the reviewer's comments, we have suggested future work investigating drug-loaded formulations (in the conclusion of our manuscript), which would include dissolution studies (as required).

Reviewer #3:

We would like to thank the reviewer for the feedback provided. We have addressed the points made by the reviewer and provided a point-by-point response:

Please add statistical analysis section as I think three tablets were produced on each compression study.

Friability, disintegration time and fineness of dispersion were performed as per compendial requirements and statistical analysis is not applicable. A single result was obtained for friability, although several tablets are used for this test. Similarly, although several tablets are used for disintegration testing, a single value was recorded (the time taken for last tablet to disintegrate); this has been now specified in the methodology for clarity. Fineness of dispersion test is based on a binary outcome (pass/fail) decided by visual inspection and statistics are not applicable.

Results of "maximum tensile strength" have been replaced by "tensile strength at 0.85 solid fraction" in response to reviewers' comments. The values of tensile strength at 0.85 solid fraction are presented as "> 3.0" in most cases, which does not allow to apply statistics. This is because some excipients did not reach values of 0.85 solid fraction at the compression pressure investigated, but higher solid fraction/tensile strength values could be achieved by compressing at greater compaction pressures than those applied in this study. Therefore, statistical analysis of the results obtained in the present study would be meaningless.

The only results for which statistical analysis could be applied are ejection shear results. In general, ejection shear results below 5 MPa are acceptable to minimise tablet defects and punch damage. When ejection shear results are below this threshold, selection of the most appropriate formulation will be based on other properties (such as friability or disintegration). Therefore, when ejection shear results are below this threshold, demonstrating that one excipient produced lower ejection shear than other (even if statistically significant) is meaningless for the purpose of our study. Moreover, given that statistics were not applied to any other test results, the authors considered that applying statistics to these data would not add much value.

Instead, we decided to propose predefined specifications to classify manufacturability criteria as “ideal”, “minimum” or “fail” as shown in Table 2. We believe that these specifications allow appropriate comparison between excipients.

Please add standard deviation values (figure 1-3, Table 3)

We have now included standard deviation bars in Figure 1, as suggested by the reviewer.

Although three tablets were compressed at each compaction pressure, individual values have been presented in Figures 2 to 5, thus error bars are not applicable. Representation of individual values was considered more appropriate than average values to show the variability between replicates in the parameters presented in the x-axis.

Regarding Table 3 (Table 5 after revision), as mentioned in our response to the previous question, standard deviation cannot be calculated for compendial tests such as friability, disintegration time and fineness of dispersion based on the standardised methodology that was followed.

Please add composition of the tablet formulations in a table.

We have added details of the formulation composition as requested. Details of the composition for the investigated formulations is now shown in Table 3.

Please show the relationship between the tensile strength and solid fraction of the formulation in a figure.

The compression assessment section of the manuscript has been thoroughly reviewed based on the feedback provided. We have included compressibility (solid fraction as a function of compaction pressure) and compactability (tensile strength as a function of solid fraction), in addition to the tabletability data (tensile strength as a function of compaction pressure) initially included.

Please add Wetting time, water sorption and water absorption study in method section.

Wetting time, water sorption and water absorption studies were not carried out, so these were not included in the methodology section. A fineness of dispersion test was carried out as per Pharmacopoeial requirements, and this has been described in the methodology.