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Research Article

Co-Processed Excipients for Dispersible Tablets–Part 1: Manufacturability

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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 16 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 min), rapid disintegration times (27–49 s) and produced 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.

KEY WORDS: 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

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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, PA, 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, IL, USA); Ludiflash® and Ludipress® (BASF, Lampertheim, Germany); Emdex® and ProSolv® ODT (JRS Pharma, Cedar Rapids, IA, 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, IN, 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, IA, 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 I.

Manufacturability Criteria and Testing Methodology

The formulations were characterised against the manufacturability criteria specified in Table II. 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 is provided in the next sections along with testing methodologies.

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 min at 22 RPM using a low shear Turbula blender. Details of the composition of the investigated formulations are presented in Table III.

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 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 index. A Carr index of less than 15% indicates good flowability and so was used to 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

Table I. Individual Constituent 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% native corn starch	160 (35–65% below)
Compressol SM	80-90% Mmannitol, 10-15% 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

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 Calliper, 0.01 mm, Mitutoyo Ltd.) and hardness (8 M 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 II.

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 and ≥ 1.5 MPa respectively as detailed in Table II.

Ejection shear is the force required to eject the tablet from the die after compaction. A low ejection shear is

Table II. 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 min	< 1% in 4 min
Disintegration time	< 60 s	< 180 s
Dispersibility	Passes through 250-μm screen	Passes through 710-μm screen

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 ten tablets and placing them into a friability tester (Friabilator 108008, VanKel Ltd.). Friability testing was performed for either 4 min (standard conditions) or 15 min (extended conditions) at 25 rpm. Following testing, the tablets were removed, dedusted and weighed to enable the calculation of the percent friability. As per the current Pharmacopoeial standard, tablets need to be less than 1% friable during testing for 4 min, which was set as the minimum requirement. Tablets that withstand a longer time of 10 min 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 min at 37°C. In contrast, guidance from the WHO requires dispersible tablets to disintegrate within 3 min at 15–25°C. In this study, the minimum requirement for disintegration time was set at 3 min. However, since a number of currently available marketed dispersible tablets have disintegration times between 30 s and 1 min [20], it was decided that an ideal specification for disintegration time would be less than 60 s. 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.

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 710-μm screen, based on USP <2>. The compendial test establishes that the dispersion is acceptable if it passes freely through a 710-μm 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 are presented in Fig. 1 and Table IV for the individual co-processed excipients. The results of Carr's index indicate that Compressol SM, Emdex, F-Melt type M and ProSolv ODT all have ideal flowability with average Carr 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 index of 24% indicating poor flow. Out of all the co-processed excipients tested, Emdex exhibited the best flow with an average Carr index of 11%; this can be explained because of its non-hygroscopic, uniform porous spheres [23, 24]. The Carr index limits of 15% (ideal specification) and 20% (minimum required) set in this study allow 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.

Compression Assessment

Tabletability, compactability and compressibility profiles for the co-processed excipients lubricated with 1% *w*/w SSF are presented in Figs. 2, 3 and 4, respectively, with the ejection shear results presented in Fig. 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 V.

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 1.5 MPa. 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-

Table III. 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

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 Figs. 2 and 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].

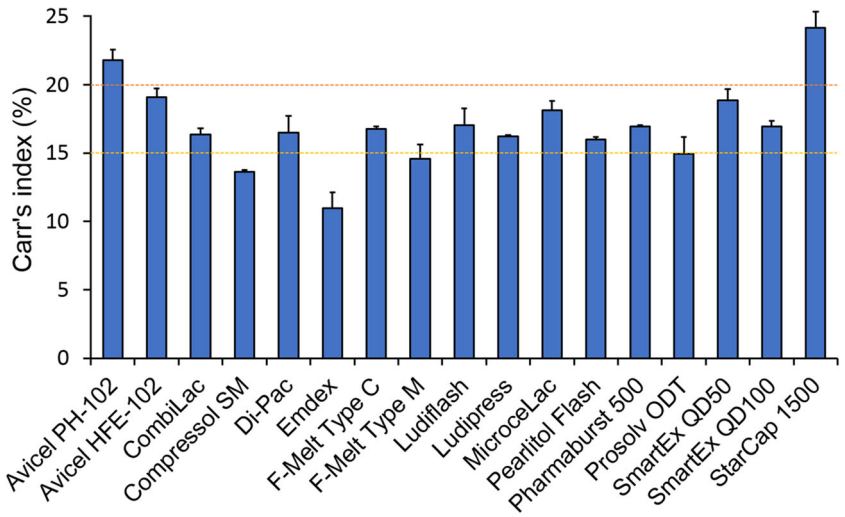

Fig. 1. Carr's index of co-processed excipients. Results expressed as mean with standard deviation bars ($n=3$)

Table IV. 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	0.77 ± 0.02	14.93 ± 1.25
SmartEx QD50	0.54 ± 0.01	0.67 ± 0.01	18.84 ± 0.84
SmartEx QD100	0.47 ± 0.01	0.57 ± 0.03	16.95 ± 0.41
StarCap 1500	0.46 ± 0.01	0.60 ± 0.01	24.17 ± 1.18

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 interparticle 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

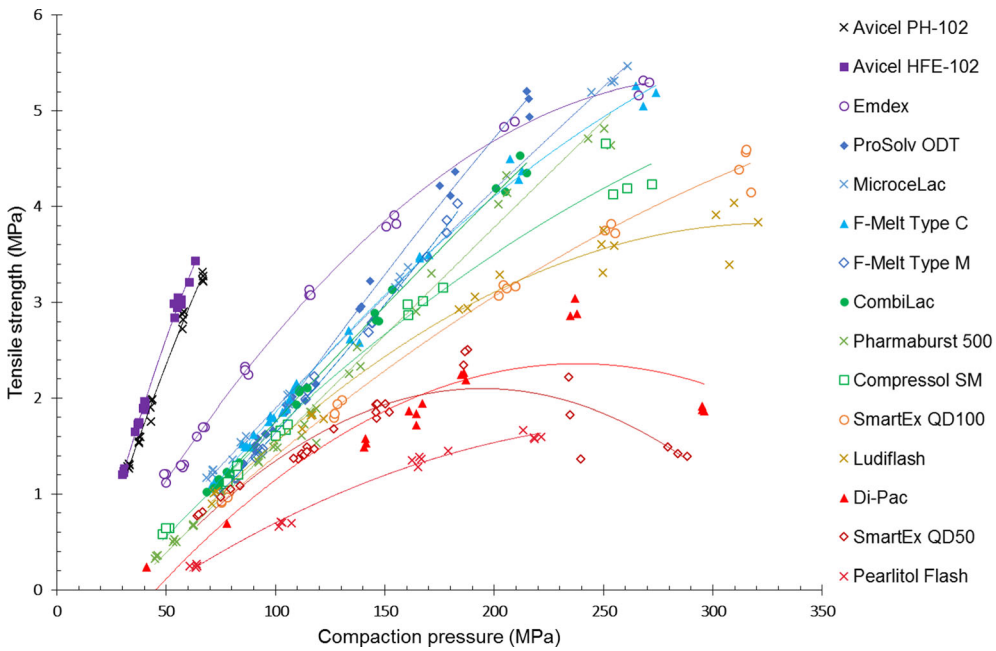

Fig. 2. Tabletability profiles (tensile strength as a function of the compaction pressure)

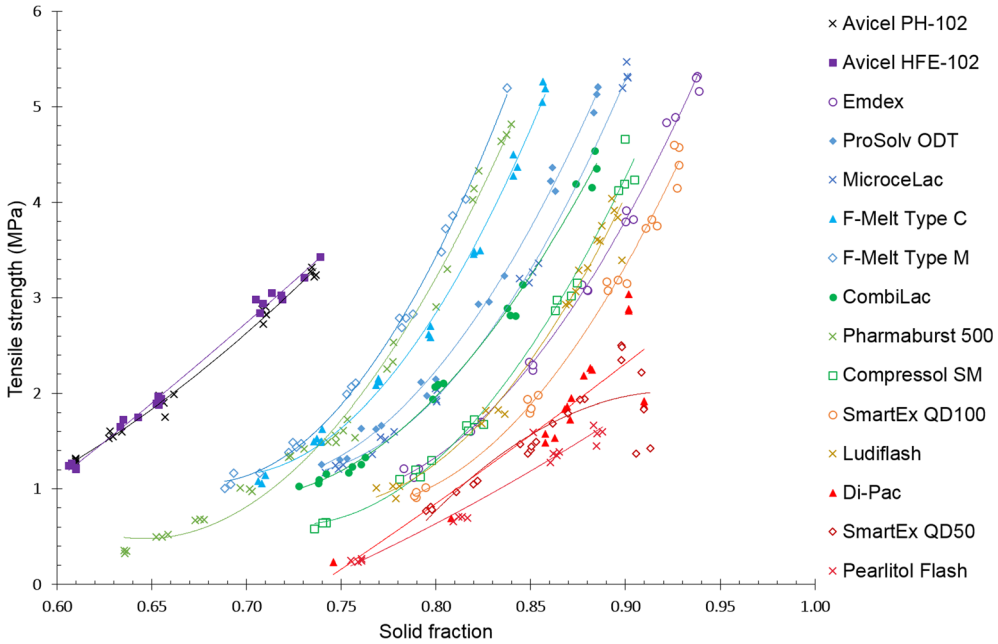

Fig. 3. Compactability profiles (tensile strength as a function of the solid fraction)

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.

In terms of ejection at the target tensile strengths of 2.0 MPa, only Compressol SM and Di-Pac provided 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 showed relatively high ejection shear results

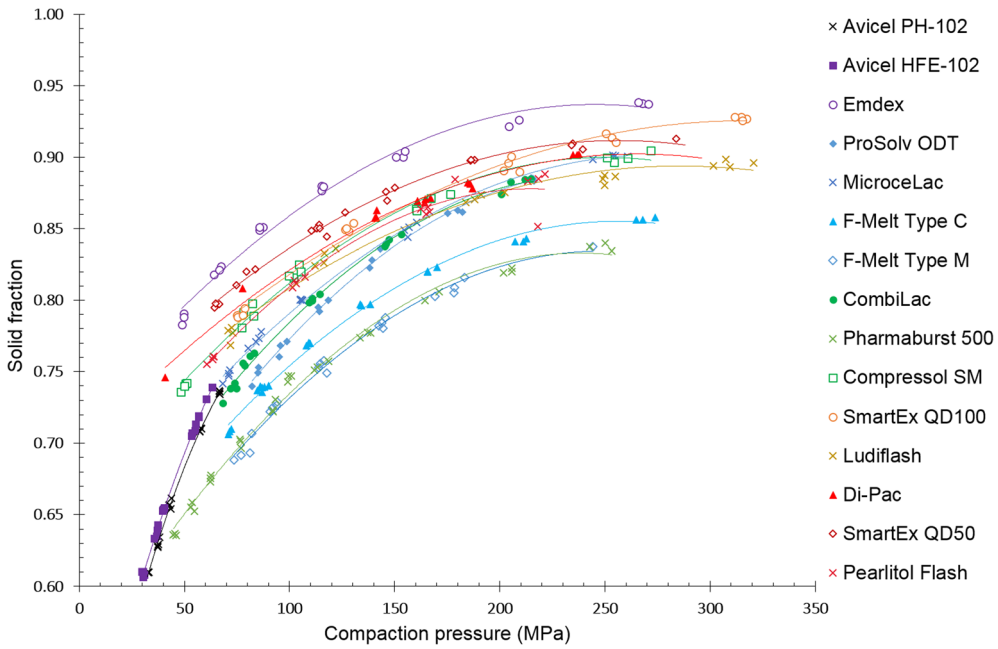

Fig. 4. Compressibility profiles (solid fraction as a function of the compaction pressure)

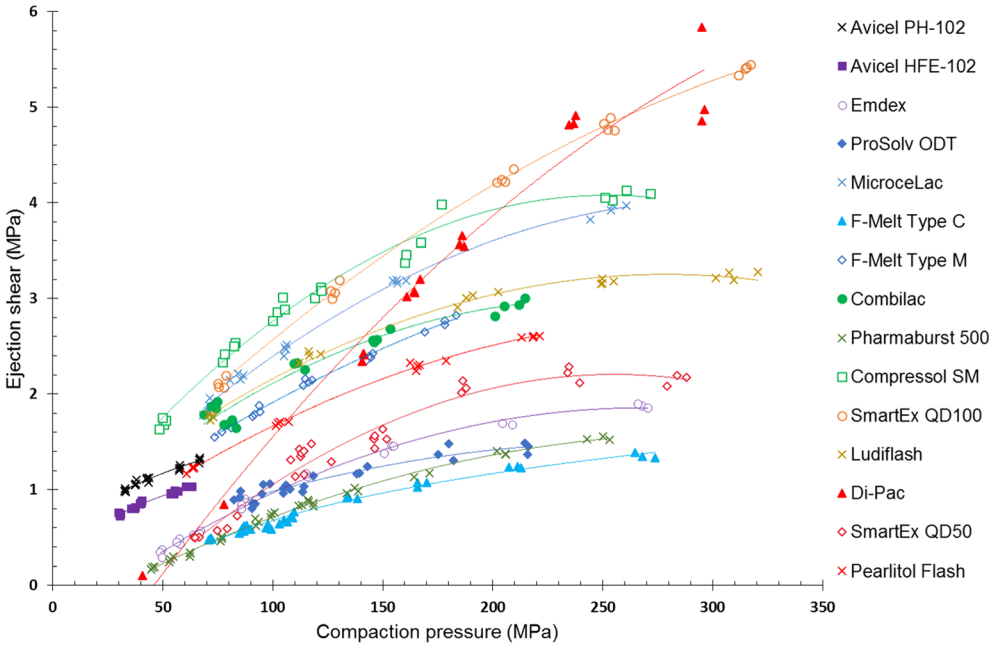

Fig. 5. Tablet ejection shear as a function of the compaction pressure

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 V. All tablets prepared at tensile strengths of 2.0 and 1.5 MPa were less than 1% friable after standard friability testing for 4 min, 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 min) and less than 1% tablet friability (over 4 min) 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

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

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 s. These were followed by Ludiflash, F-Melt type M, Avicel PH-102 and MicroceLac, which disintegrated within 60–90 s. 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 min. 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].

Table V. 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† (s)	Dispersion fineness†	
				% 4 min	% 10 min		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 min) and standard friability (< 1% in 4 min) were investigated for extended friability (during 15 min)

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 increases 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 s. Pearlitol Flash, which was not possible to compressed into 2.0 MPa tablets, also disintegrated in less than 60 s when compressed into 1.5 MPa tablets. ProSolv ODT also provided a disintegration time shorter than 3 min, although this formulation still took 2 min 29 s to disintegrate. Meanwhile, formulations containing Emdex and Compressol SM produced long disintegration times of over 3 min.

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 250 μm; 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

Table VI. 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† (s)	Dispersion fineness†	
					% 4 min	% 10 min		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 (3%)	2.32	1.98	1.64	0.22	NM	210	Pass	Pass
			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

NM not measured

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 V.

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 min); 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 VI (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 min to less than 60 s. In contrast, the addition of croscarmellose sodium or L-HPC to Di-Pac did not greatly reduce disintegration times, which remained longer than 3 min. Similarly, Ludipress and StarCap 1500 exhibited disintegration times longer than 3 min, 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].

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 s at both 1.5 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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