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Continuous twin screw granulation of controlled release formulations with various HPMC grades

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Abstract

HPMC is a popular matrix former to formulate tablets with extended drug release. Tablets with HPMC are preferentially produced by direct compression. However, granulation is often required prior to tableting to overcome poor flowability of the formulation. While continuous twin screw granulation has been extensively evaluated for granulation of immediate release formulations, twin screw granulation of controlled release formulations including the dissolution behavior of the formulations received little attention. Therefore, the influence of the HPMC grade (viscosity and substitution degree) and the particle size of theophylline on critical quality attributes of granules (continuously produced via twin screw granulation) and tablets was investigated in the current study. Formulations with 20 or 40% HPMC, 20% theophylline and lactose were granulated with water at fixed process parameters via twin screw granulation. The torque was influenced by the viscosity and substitution degree of HPMC, but was not a limiting factor for the granulation process. An optimal L/S ratio was selected for each formulation based on the granule size distribution. The granule size distributions were influenced by the substitution degree and concentration of HPMC and the particle size of theophylline. Raman and UV spectroscopic analysis on 8 sieve fractions of granules indicated an inhomogeneous distribution of theophylline over the size fractions. However, this phenomenon was not correlated with the hydration rate or viscosity of HPMC. Controlled release of theophylline could be obtained over 24 h with release profiles close to zero-order. The release of theophylline could be tailored via selection of the substitution degree and viscosity of HPMC.

KEYWORDS: HPMC, continuous production, twin screw granulation, theophylline, controlled release

List of abbreviations

C%	Compressibility index
d_{50}	Median particle size
ffc	Flowability index
L/S	Liquid-to-solid
LOD	Loss on drying
PCA	Principal component analysis
PVP	Polyvinylpyrrolidone
V_0	Bulk volume
V_{1250}	Tapped volume
HPMC	hydroxypropylmethylcellulose
a_{50}	median aspect ratio
d_{50}	median particle size
GSD	granule size distribution
PCA	principal component analysis
PC	principal component

1. Introduction

Hydroxypropylmethylcellulose (HPMC) is widely applied in oral, ophtalmic and topical pharmaceutical formulations. In oral products, HPMC is applied as binder, film coating and hydrophilic matrix former. As matrix former, it sustains drug release resulting in a prolonged therapeutic effect, minimization of side effects, reduced administration frequency and improved patient compliance. Hydrogen bonding between HPMC and water forms a gel layer at the surface of a wetted tablet, controlling the drug release via diffusion through and erosion of the highly viscous polymer matrix. The matrix forming and drug release mechanisms have been thoroughly studied by several research groups [1-3]. HPMC has a polymeric backbone of cellulose substituted with hydroxypropyl and methyl groups. The ratio of hydroxypropyl and methyl substitutions is referred to as the degree of substitution and will determine the characteristics of the polymer (e.g. solubility, hydration rate). Additionally commercially available HPMC grades differ with regard to molecular weight and therefore viscosity.

HPMC is the most popular hydrophilic matrix former for production of controlled release tablets as it is non-ionic, stable over a broad pH range, enzyme resistant, odourless and tasteless, extensively studied and understood, non-toxic and cost-effective [4-8]. Moreover the available variety of HPMC grades with different substitution degrees and viscosities make it a versatile matrix former for controlled release of a wide range of drugs with varying solubilities and doses [8]. Tablets with HPMC can be produced by direct compression but often granulation is necessary [4, 9]. High shear and fluid bed granulation were successfully applied to improve the flowability of formulations with HPMC [4, 5, 9, 10-16], often requiring hydro-alcoholic granulation liquids as granulation with water yielded lumps as well as fines due to the irregular wetting of the formulation.

Twin screw granulation is an emerging continuous granulation technique that can be implemented in a fully continuous from-powder-to-tablet manufacturing line. This concept offers economic advantages, improved product quality and a lower environmental impact [17, 18, 19, 20]. However, up to now only two studies addressed continuous granulation of formulations with HPMC [21, 22]. Whereas these studies used the same HPMC grade and investigated the influence of process parameters, in current study the impact of formulation variables on critical quality attributes of granules and tablets was studied. Three HPMC grades (in two concentrations), varying in substitution degree and viscosity, and two theophylline grades, varying in particle size, were included in the formulations.

2. Materials and methods

2.1. Materials

Anhydrous theophylline, in a micronized and powdered grade, was used as model drug and was kindly donated by BASF (Ludwigshafen, Germany). Three HPMC grades (90SH-4000-SR, 90SH-100000-SR and 60SH-4000) were kindly donated by ShinEtsu (Tokyo, Japan). The substitution types (according to the USP and Ph. Eur.) and viscosities of these HPMC grades are included in Table 1. Magnesium stearate (Fagron, Waregem, Belgium) and α-lactose monohydrate (Pharmatose 200M, DMV-Fronterra, Veghel, The Netherlands) were used as lubricant and filler, respectively.

2.2. Methods

2.2.1. Preparation granules

Theophylline (20% w/w), HPMC (20 or 40% w/w) and lactose were preblended in a tumbling mixer (Inversina Bioengineering, Wald, Switzerland) for 10 minutes at 25 rpm. An overview of the formulations is shown in Table 2. Subsequently they were transferred to the loss-in-weight feeder (DDW-MD2-DDSR20, Brabender, Duisburg, Germany) of the ConsiGma™-1 (GEA Pharma Systems, GEA Pharma Systems, Wommelgem, Belgium) system. This system is a laboratory-scale continuous granulator with an integrated fluid bed dryer intended for early R&D work. The granulation unit consists of a co-rotating twin screw granulator without a die plate and has a length-to-diameter ratio of 20/1. The barrel can be divided in a feed segment with conveying elements and a work segment where the powder is intensively mixed with the granulation liquid by kneading elements. A PT-100 temperature sensor was integrated in the work segment of the barrel and linked to a feedback control system which regulates the temperature in the barrel jacket and compensates for temperature increase during the process due to friction. Torque was monitored by a built-in torque gauge at 1-second intervals. All torque values were smoothed by application of moving average (over a period of 5 measurements). Water as granulation liquid was pumped into the barrel just before the first kneading element via a double liquid addition port (internal diameter 0.8

mm), injecting granulation liquid on top of each screw. For all experiments the distance between liquid addition and the first kneading element was kept constant. Granulation of the formulations was performed at constant process parameters (screw speed 900 rpm, throughput 10 kg/h, barrel temperature 25 °C) using a fixed screw configuration consisting of two kneading blocks with each 6 kneading elements at an angle of 60°. This screw configuration was schematically presented by Vanhoorne et al. [22]. The liquid-to-solid (L/S) ratio was varied between 0.08 and 0.18 with intervals of 0.02. After stabilization of torque at least 100 g granules were collected at the outlet of the granulator at each L/S ratio, while 1000 g granules was collected at an L/S ratio considered optimal for each formulation. The optimal L/S ratio (listed in Table 2) was dependent on the HPMC grade and percentage HPMC included in the formulation. The granules were tray dried in an oven at 40 °C for 24 h. After drying, the granules processed with an optimal L/S ratio were milled through a 1000 µm grater screen with square impeller at 900 rpm using the Quadro comil (U10, Quadro, Ontario, Canada) incorporated in the ConsiGma™-25 line.

2.2.2. Preparation of tablets

The milled granules were blended with 0.5% magnesium stearate in a tumbling blender for 2 minutes at 49 rpm (T2F, W.A. Bachofen, Basel, Switzerland) before tableting. Tablets were prepared in manual mode at a speed of 230 tablets per minute on the Modul™ P tablet press (GEA Pharma Systems Courtoy™, Halle, Belgium). The press was equipped with 10 pairs of round flat-faced bevel-edged Euro B punches (GEA Pharma Systems, Halle, Belgium) (diameter 12 mm) and an overfill cam of 16 mm. The paddles in the feed frame were rotating at 15 and 20 rpm. Filling depths between 5.75 and 7.50 mm were used, dependent on the density of the samples. Tablets were compressed at 7 different main compression pressures in order to assess the tabletability of the granules: 60, 110, 150, 190, 260, 330, 410 MPa after precompression at 15 MPa. Tablets compressed at 190 and 330 MPa were selected for friability and dissolution testing.

2.2.3. Characterization methods

2.2.3.1.　　　Laser diffraction

The particle size distributions of all starting materials were measured in duplicate by laser diffraction (Mastersizer S long bench, Malvern Instruments, Worcestershire, UK) and the average particle size distributions were calculated via the Mastersizer 2000 software. The dry dispersion technique was applied using a 1000 mm lens at a jet pressure of 3.2 bar (Malvern 220 Instruments, Worcestershire, UK). The results were expressed as volume diameters d_{10}, d_{50} and d_{90}. The span was calculated as $(d_{90}-d_{10})/d_{50}$ and was an indication of the width of the particle size distribution.

2.2.3.2.   Loss on drying

The residual moisture content of the milled granules was determined via loss-on-drying using a moisture analyzer (Mettler LP16, Mettler-Toledo, Zaventem, Belgium) including an infrared dryer and a balance. A sample of 5 g was dried at 105 °C until the weight was constant for 30 s.

2.2.3.3.   Particle size and shape analysis

The granule size and shape of all granules was analyzed before and after milling via dynamic image analysis using the QICPIC[TM] system (Sympatec, Clausthal-Zellerfeld, Germany) equipped with a vibrating feeder system (Vibri/L[TM]) for gravimetrical feeding of the granules. Samples of 20 g were measured in duplicate. Averaged granule size distributions are shown, as the measurements were done in duplicate and the respective results did not differ from each other. Windox 5 software (Sympatec, Clausthal-Zellerfeld, Germany) was used to calculate the median granule size (d_{50}) as the equivalent projected circle diameter based on a volume distribution. The amounts of fines and oversized granules were defined as the fractions <150 μm and >1500 μm, respectively. The yield of the process was defined as the percentage of granules between 150 and 1500 μm. The aspect ratio (i.e. the ratio of the minimal Ferret diameter to the maximal diameter orthogonal to it) of the granules was determined to evaluate the shape of the granules. The median aspect ratio (a_{50}) of the granules was calculated by the Windox 5 software.

For analysis of drug content in the granules by Raman and UV spectroscopy, different size fractions of the milled granules were isolated by sieve analysis using a Retsch VE 1000 sieve shaker (Haan, Germany). Granules were placed on the shaker during 10 min at an amplitude of 2 mm using a series of sieves (150, 250,

500, 710, 1000, 1400 and 2000 µm). The amount of granules retained on each sieve was determined and isolated.

2.2.3.4. Flowability testing

The flowability expressed as the flowability index (ffc) of the milled granules was measured in duplicate by ring shear testing (Type RST-XS, Dietmar Schulze Schüttgutmesstechnik, Wolfenbuttel, Germany). The powders were tested using three consolidation stresses (250, 525 and 800 Pa) at a preshear of 1000 Pa.

Additionally, the compressibility index (C%) was calculated from the bulk and tapped densities of the milled granules. The bulk volume (V_0) of 30 g milled granules was measured in a 100 ml graduated cylinder as well as the tapped volume after 1250 taps (V_{1250}) in a tapping machine (J. Englesman, Ludwigshafen, Germany). Experiments were performed in duplicate. Bulk and tapped densities were calculated as 30 g/V_0 and 30 g/V_{1250}, respectively. The compressibility index was calculated from the bulk (ρ_i) and tapped (ρ_f) densities using the following equation: C% = [(ρ_f - ρ_i)/ ρ_f]*100.

2.2.3.5. Friability analysis

The granule friability of the milled granules was determined in duplicate using a friabilator (PTF E Pharma Test, Hainburg, Germany) at a speed of 25 rpm for 10 min, by subjecting 10 g (I_{wt}) of milled granules together with 200 glass beads (mean diameter 4 mm) to falling shocks. Prior to determination, the granule fraction <250 µm was removed to assure the same starting conditions. Afterwards, the glass beads were removed and the weight retained on a 250 µm sieve (F_{wt}) was determined. The friability was calculated as [(I_{wt} – F_{wt})/I_{wt}]*100.

2.2.3.6. Raman spectroscopy

Raman spectroscopy was applied on isolated sieve fractions to evaluate the distribution of theophylline over the sieve fractions. Raman spectra (Raman Rxn1, Kaiser Optical Systems, Ann Arbor, United States) of the samples were recorded (n = 5) using exposure times of 5 s with 3 accumulations. All spectra were recorded with a resolution of 4 cm^{-1}. The spectral region between 300 and 1500 cm^{-1} was selected for evaluation. Principal component analysis (PCA) was applied on the

spectra with Simca 13.0.3 software (Umetrics, Umeå, Sweden). Data were corrected by standard normal variate preprocessing and center-scaled prior to analysis. Standard normal variate preprocessing was applied to eliminate the additive baseline offset variations and multiplicative scaling effects in the spectra which may be caused by small variations in distance between the Raman probe and the sample and possible differences in product density.

2.2.3.7.   UV spectroscopy

The isolated sieve fractions were dissolved in water (1 mg/ml), diluted 20 times and measured by UV spectroscopy (UV-1650PC, Shimadzu Benelux, Antwerp, Belgium). The theophylline content in these samples was derived from their absorbance at 272 nm.

2.2.4. Evaluation of the tablets

The hardness, thickness and diameter of the tablets (n = 10) were determined using a hardness tester (Type HT 10, Sotax, Basel, Switzerland) and the tensile strength of the tablets was calculated according to the formula of Fell and Newton [23]:

Tensile strength = $2F/\pi dt$

Where F, d and t denote the diametral crushing force, tablet diameter and tablet thickness, respectively.

The tablet friability of tablets compressed at 190 and 330 MPa was determined using a friabilator (PTFE, Pharma Test, Hainburg, Germany) as described in the European Pharmacopoeia at a speed of 25 rpm for 4 min. The percentage weight loss was expressed as the tablet friability.

Dissolution tests were performed (n = 3) in 900 ml demineralized water using the paddle method (VK 7010, Vankel, Cary, NC, USA). The temperature of the dissolution medium was maintained at 37 ± 0.5 °C, while the rotation speed was set at 100 rpm. Samples of 5 ml were withdrawn after 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h. The drug content in these samples was derived from the absorbance of the samples at 272 nm using a UV spectrophotometer (UV-1650PC, Shimadzu Benelux, Antwerp, Belgium).

3. Results and discussion

Evaluation of the granulation process

3.1.1. Torque

Since HPMC swells upon hydration, excessive torque values might limit the processing of formulations with HPMC. Although inclusion of 40% HPMC in the formulations resulted in higher torque values compared to 20% HPMC, the torque was lower than 10 Nm for all experiments, which was far below the maximal torque (20 Nm) tolerated by the granulator.

Increasing the L/S ratio resulted in higher torque values until a critical L/S ratio was reached where torque became independent of L/S ratio. This is illustrated in Figure 1 for F9 where the L/S ratio was increased up to 0.18. Reports on the influence of L/S ratio of immediate release formulations on torque are contradictory, indicating linear or inverse relationships depending on the formulation [24, 25, 26]. Nevertheless, the results in current study were compatible with the regime map presented by Tu et al. on an immediate release formulation with microcrystalline cellulose (MCC), a component also known to swell upon hydration, reporting that the torque increased until a critical L/S ratio was reached and then decreased [27]. First the torque increased at higher L/S ratios due to interparticle bond formation but after reaching a critical L/S ratio over-wetted malleable particles were formed resulting in lower torque readings.

Longer runs (at least 10 min) were performed using the optimized L/S ratio was selected for each formulation (Table 2). The torque of these runs was compared to evaluate the influence of viscosity and the substitution degree of the HPMC grade on torque. The effect of these variables was most obvious with the formulations containing 40% HPMC. Inclusion of HPMC grades with a high viscosity and a high degree of hydroxypropyl substituents increased the torque. As viscous materials caused frictional resistance of the material to flow, the torque during granulation of F8 was higher compared to F7 (Figure 2). This is similar to literature reports on high torque values recorded during twin screw granulation with viscous liquids [24, 25]. Granulation of a formulation with HPMC substitution type 2208 (F7) resulted in higher torque values than with HPMC substitution type 2910 (F9) (Figure 2). The former type has more hydroxypropyl substituents and consequently swells faster upon hydration in the granulation process. This resulted in faster formation of a highly viscous gel structure, yielding high torque values. The particle size of the theophylline grade did not influence the torque.

3.2. Influence of formulation variables on granule quality

Overall the granule size distribution (GSD) was broad which is a common observation for twin screw granulation, independently of the formulation [17, 24, 26, 27 28, 29, 30, 31, 32, 33, 34]. These multimodal distributions can potentially result in segregation during downstream processing and have a negative effect on the drying uniformity. Efforts have been made to obtain monomodal GSD after continuous granulation through optimization of the feeder performance, screw design, binder addition, liquid pump, nozzle design and operation at low filling degree [22, 28, 30, 35, 36]. However, for granulation of HPMC bimodal distributions were also reported on high shear granulation which was attributed to the specific granulation mechanism of HPMC [11]. HPMC grades used as matrix former quickly absorb water and develop a gel layer during granulation. This hinders uniform distribution of granulation liquid in the powder bed. Moreover the viscous gel layer is resistant against shear forces and consequently limits breakage of the granules, resulting in a bimodal distribution [11]. Thus, obtaining a monomodal GSD by twin screw granulation is even more challenging for controlled release formulations with HPMC compared to immediate release formulations.

The GSD (d_{50}, fines and oversized fraction) was evaluated in function of the L/S ratios and formulation parameters (substitution degree, viscosity and concentration of HPMC, particle size of theophylline). The d_{50}, fines and oversized fraction in function of L/S ratio are shown in Figure 3 and Figure 4. Increasing the L/S ratio yielded granules with a higher d_{50}, fewer fines and more oversized granules. The formulations with HPMC substitution type 2910 (F3, F6 and F9) required more water for efficient granulation compared to HPMC type 2208 (F1 vs. F3, F4 vs. F6 and F7 vs. F9 in Figure 3). At a specific L/S ratio the granules with HPMC grade 2910 contained more fines and less oversized granules compared to the granules with HPMC grade 2208. This is linked to the higher hydrophilicity and faster polymer hydration of HPMC type 2208, which has less methoxy substituents than HPMC type 2910. This allows a faster interaction with water during twin-screw granulation, hence more bonds are formed between water and HPMC type 2208, yielding larger granules at a specific L/S ratio.

The molecular weight (and therefore the viscosity) of the polymers did not influence GSD (F1 vs. F2, F4 vs. F5 and F7 vs. F8 in Figure 4). The influence of the viscosity of cellulose-ether derivatives during twin screw granulation of immediate

release formulations was studied in literature by varying the amount of binder in the granulation liquid. In these studies more binder resulted in larger granules which was linked to the higher binder viscosity [24, 36]. However, the viscosity of cellulose-ether derivatives used as binders in immediate release formulations is 100 to 100000-fold lower than the grades used for controlled release purposes. In addition, in immediate release applications the polymeric binder is often added to the process as an aqueous dispersion (i.e. via the granulation liquid), while HPMC in sustained release formulations can only be added dry (i.e. mixed with the other powder components prior to the addition of granulation liquid). Hence, the granulation behavior of cellulose-ether derivatives as binders in immediate release formulations cannot be compared to that of cellulose-ethers used as matrix former in sustained release formulations.

While granule growth was affected by the substitution degree of HPMC during twin screw granulation, the viscosity of HPMC and not the substitution degree influenced GSD during high shear granulation [9]. This difference is likely due to the difference in residence time between continuous (5 – 20 s) and high shear granulation (tens of minutes) as the substitution degree (and thus hydration rate) only influences granule growth when the contact time between water and polymer is short [24, 26, 32, 36].

Inclusion of a higher HPMC concentration in the formulation required more water to obtain granules with a similar GSD. This is illustrated in Figure 5 for the formulation with HPMC type 2910 and was attributed to the high water binding capacity of HPMC.

To evaluate the influence of raw material variability on processability, granule and tablet critical quality attributes, two theophylline grades (F1-3: micronized, F4-6: powdered grade) were included in the formulations. The particle size distributions of all starting materials were summarized by their d_{10}, d_{50}, d_{90} and span (Table 2). The particle size of micronized theophylline was significantly smaller than of the powdered grade. However, the primary particle size of theophylline starting material did not influence the GSD of the formulations. This is in agreement with research of El Hagrasy et al. on immediate release formulations, reporting limited differences in GSD among formulations with different lactose grades at low L/S ratios [32]. At higher L/S ratios a direct correlation between the primary particle size of lactose and GSD was established by El Hagrasy et al. [32]. Furthermore, Fonteyne et al. linked the primary particle size of theophylline to differences in the GSD [37]. In the current study the inclusion of a high percentage of HPMC, which in addition to its function

as matrix former also acts as binder, probably eliminated the effect of primary particle size on GSD.

For each formulation an optimal L/S ratio was selected based on the GSD results: yielding granules with less than 10% fines, less than 52% oversized granules and a d_{50} between 1300 and 1600 µm. As the GSD was broad, milling was necessary to narrow down the GSD before tableting. Therefore, a large fraction of oversized granules was tolerated in these samples. After milling, the samples were further analysed with regard to flowability, friability, distribution of theophylline over the sieve fractions and finally tableted. The yield of the process before milling varied between 40 and 49% which was mainly due to an extensive oversized fraction. This fraction was eliminated by milling, resulting in a yield varying between 78 and 86%.

The median aspect ratios varied between 0.57 and 0.63 (Figure 6). This is slightly lower than typically reported for immediate release formulations [17, 21, 24]. The aspect ratios of the formulations with HPMC substitution type 2910 were higher compared to formulations with HPMC substitution type 2208, although the differences were minor. As the viscous gel layer of HPMC type 2910 formed slower due to the lower number of hydrophilic substituents, granules containing type 2910 are more deformable during the granulation process, yielding a higher aspect ratio. No correlation between the median aspect ratios and the applied L/S ratio was detected.

Thompson et al. reported the formation of elongated noodle-like granules (3-10 mm) during granulation with HPMC type 2208, even with formulations containing only 5% HPMC. In the current study a similar screw design was used but no elongated granules were formed with either HPMC grade. This confirmed previous research of our group, studying the influence of process parameters on the granulation behaviour of a formulation with HPMC type 2208, where no elongated granules were formed [22]. Thus, granule shape was not an issue for granulation of formulations with different types of HPMC.

All granules were classified as passable and easy-flowing according to the C% and ffc values, respectively [38]. The friability of the granules was low, varying between 8.1 and 13.9 % (friability lower than 30% is considered acceptable, using the applied method).

The content uniformity of theophylline over 8 sieve fractions was evaluated by Raman and UV spectroscopy for all formulations. The results of the Raman analysis were summarized in a PC 1 vs. PC 2 scores plot of the first and second principal components (PC), explaining 54 and 25% of variation in the dataset, respectively (Figure 7). The spectra of the fines fraction (< 150 µm) were clustered in the negative

part of PC 2 while the spectra of fractions 150 - 250 µm and 250 - 500 µm were clustered in the positive part of PC 2. The other size fractions (500 - > 2000 µm) were distributed homogeneously over the PC 1 vs. PC 2 scores plot. Comparison of the spectra of lactose and theophylline to the loading plot of PC 1 and PC 2 learned that PC 1 represented variation due to baseline offset variations while the maxima and minima of the PC 2 loading plot were characteristic for theophylline and lactose, respectively (Figure 8). This signified that theophylline was underdosed in the fines fraction (on average 15% less theophylline) and overdosed in the fractions 150 - 250 µm and 250 - 500 µm (an excess of 7 and 6%, respectively). The uneven distribution of theophylline over the size fractions was present in all formulations, independently of the viscosity and substitution degree of HPMC. Comparable observations were made after batch granulation of immediate release formulations [39, 40]. These studies pointed at differences in primary particle size between drug and fillers to explain preferential granule growth and consequently inhomogeneous drug distribution over the size fractions. Despite the similar primary particle size of lactose and powdered theophylline in formulations F4-6, theophylline was not evenly distributed over the size fractions of these formulations. This was also observed by Fonteyne et al. after continuous granulation of an immediate release formulation [37]. However, no explanation was found for the observations. Thorough characterization of the starting materials (e.g. solubility, solubility rate, wettability) could help to reveal the granulation mechanism leading to uneven API distribution over the size fractions of granules produced by twin screw granulation.

3.3. Influence of the formulation variables on tablet quality

The tensile strength of the milled formulations tableted at 7 main compression pressures was measured. The particle size distributions and moisture content of the different formulations were similar and could not bias the comparison of the formulations. A linear relationship between tensile strength and main compression pressure was established for all formulations. No differences in tensile strength were detected between the formulations containing 20% HPMC, whereas the viscosity and substitution degree of HPMC influenced the tensile strength of the formulations containing 40% HPMC (Figure 9). F7, containing an HPMC grade with a lower viscosity, showed a lower tensile strength than F8, containing an HPMC grade with a higher viscosity. Similar observations were made after high shear granulation of HPMC with different viscosities [9]. This was attributed to the stronger plastic

deformation during compression of HPMC grades with a high viscosity [9]. Comparing F7 (containing HPMC type 2208) and F9 (containing HPMC type 2910), it is clear that the substitution degree of HPMC also affected the tensile strength of formulations containing 40% HPMC. HPMC type 2208 contains more hydrophilic substituents that can form hydrogen bonds during compression, yielding harder tablets. This in agreement with research on the compaction behavior of HPMC with different substitution degrees after direct compression and batch granulation [4, 9, 41, 42, 43, 44]. The particle size of theophylline starting material did not influence the tensile strength.

Considering the linear relation between tensile strength and main compression pressure, the friability of tablets compressed at an intermediate (190 MPa) and high (330 MPa) main compaction pressures was determined. The friability of all tablets was low, varying between 0.05 and 0.16%. The tablets compressed at a higher main compression pressure were harder and consequently less friable. No correlation between HPMC or theophylline grade and the friability of the corresponding tablets was detected.

The influence of viscosity and substitution degree of HPMC on the drug release rate after direct compression and batch granulation was already extensively studied [4, 9, 12]. However, a comparative study between twin screw granulation and high shear granulation demonstrated that granules produced by twin screw granulation were denser and that the drug release rate from tablets derived from these dense granules was slower [34]. Therefore the influence of viscosity and substitution degree of HPMC on drug release was investigated after twin screw granulation in the current study.

The release of tablets compressed at 190 MPa and 330 MPa was measured but the main compression pressure did not significantly influence the release, a similar observation was already reported after high shear granulation [43]. Inclusion of 20% HPMC type 2208 resulted in controlled release of theophylline over 24 h, while complete drug release was obtained after 16 h with 20% HPMC type 2910 (F4 vs. F6 in Figure 10). The viscosity of HPMC also influenced the release rate of theophylline, a higher viscosity resulting in a slightly slower release (F4 vs F5 in Figure 10). At 40% polymer load, the drug release was only affected by the viscosity of HPMC and not by its substitution degree. Incomplete release (80%) of theophylline was obtained after 24 h with the highest viscosity HPMC grade (F8), while F7 (HPMC type 2208) and F9 (HPMC type 2210) showed identical dissolution profiles and complete release after 24 h. These dissolution profiles also approached zero-order kinetics. Thus, at low polymer load the faster hydration of HPMC type

2208 resulted in a faster formation of the matrix and at both polymer loads the higher viscosity of HPMC formed a more tortuous and resistant barrier to diffusion and erosion, resulting in slower release rates. These results are in accordance with dissolution studies of HPMC after direct compression and batch granulation [4, 9, 12, 14, 41, 43, 45, 46]. The particle size of theophylline starting material did not influence the release of the formulations.

4. Conclusions

HPMC was identified as versatile matrix former for manufacturing of controlled release formulations via twin screw granulation using water as granulation liquid. The torque during processing was linked to viscosity and hydration rate of HPMC, but the recorded torque values did not limit the process. HPMC type 2910 required more water during granulation to obtain a similar granule size distribution compared to HPMC type 2208 which was attributed to its lower hydrophilicity. Although theophylline was not homogenously distributed over the size fractions (with a lower theophylline content in the fines fraction), this phenomenon was not correlated to the hydration rate or viscosity of HPMC. The release of theophylline was independent of the compression pressure but could be steered by the viscosity and substitution degree of HPMC to obtain sustained release over 24 h.

Acknowledgement

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Tables

Table 1   Overview and characterization of the starting materials.

Product	Substitution type[a]	Viscosity (mPa*s)	d_{10} (µm)	d_{50} (µm)	d_{90} (µm)	span	True density (g/cm³)
HPMC Metolose 90SH-4000-SR	2208	4000	18.8	80.4	208.5	2.4	1.32
HPMC Metolose 90SH-100000-SR	2208	100000	14.5	49.7	287.6	5.5	1.32
HPMC Metolose 60SH-4000	2910	4000	16.6	42.6	253.2	5.6	1.29
α-lactose monohydrate	-	-	6.6	41.4	113.8	2.6	1.46
Micronized theophylline	-	-	0.52	8.6	25.6	2.9	1.49
Powdered theophylline	-	-	4.5	41.7	95.0	2.2	1.48

[a]Substitution type according to the USP and Ph. Eur.

Table 2   Composition of the granulated formulations.

Formulation	Theophylline (%)		HPMC (substitution type – viscosity)			lactose	Optimized L/S ratio
	micronized	powdered	2208-4000	2208-100000	2910-4000		
F1	20	-	20	-	-	60	0.10
F2	20	-	-	20	-	60	0.10
F3	20	-	-	-	20	60	0.12
F4	-	20	20	-	-	60	0.10
F5	-	20	-	20	-	60	0.10
F6	-	20	-	-	20	60	0.12
F7	-	20	40	-	-	40	0.12
F8	-	20	-	40	-	40	0.12
F9	-	20	-	-	40	40	0.16

Table 3   Overview of the bulk and tapped density, compressibility index (C%), friability and flowability index (ffc) of the milled granules.

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	C%	Friability (%)	ffc
F1	0.47	0.62	23.1	11.5	5.6
F2	0.48	0.60	20.5	7.7	5.2
F3	0.50	0.62	20.5	13.9	6.1
F4	0.49	0.61	20.2	11.2	5.2
F5	0.45	0.60	24.4	8.9	4.4
F6	0.49	0.63	21.6	8.1	6.5
F7	0.42	0.57	25.6	11.9	4.4
F8	0.40	0.54	26.4	8.5	4.3
F9	0.41	0.53	22.7	9.2	5.4

Figure 1   Torque profiles in function of L/S ratio for formulation F9.
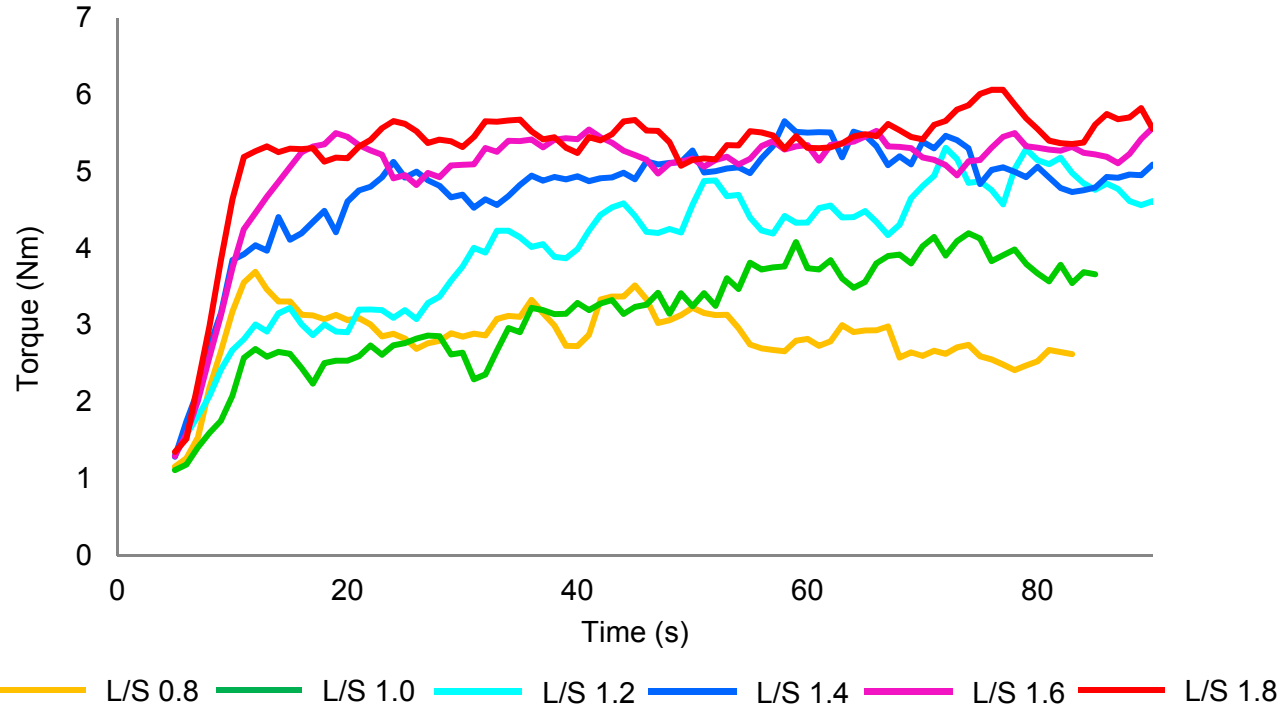
Figure 2   Torque profiles of F7, F8 and F9 granulated with optimized L/S ratios.
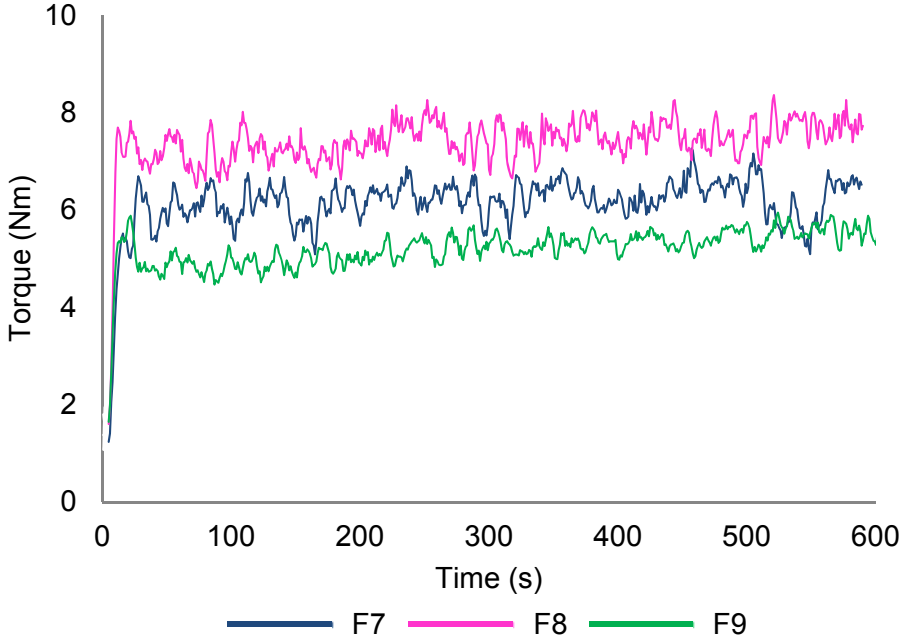
Figure 3   Influence of HPMC substitution degree on granule size distribution: d_{50}, fines fraction and oversized fraction of F1 and F3 (formulations with micronized theophylline and 20% HPMC), F4 and F6 (formulations with powdered theophylline and 20% HPMC) and F7 and F9 (formulations with powdered theophylline and 40% HPMC) as a function of the applied L/S ratio.

Figure 4   Influence of HPMC viscosity on granule size distribution: d_{50}, fines fraction and oversized fraction of F1 and F2 (formulations with micronized theophylline and 20% HPMC), F4 and F5 (formulations with powdered theophylline and 20% HPMC) and F7 and F8 (formulations with powdered theophylline and 40% HPMC) as a function of the applied L/S ratio.
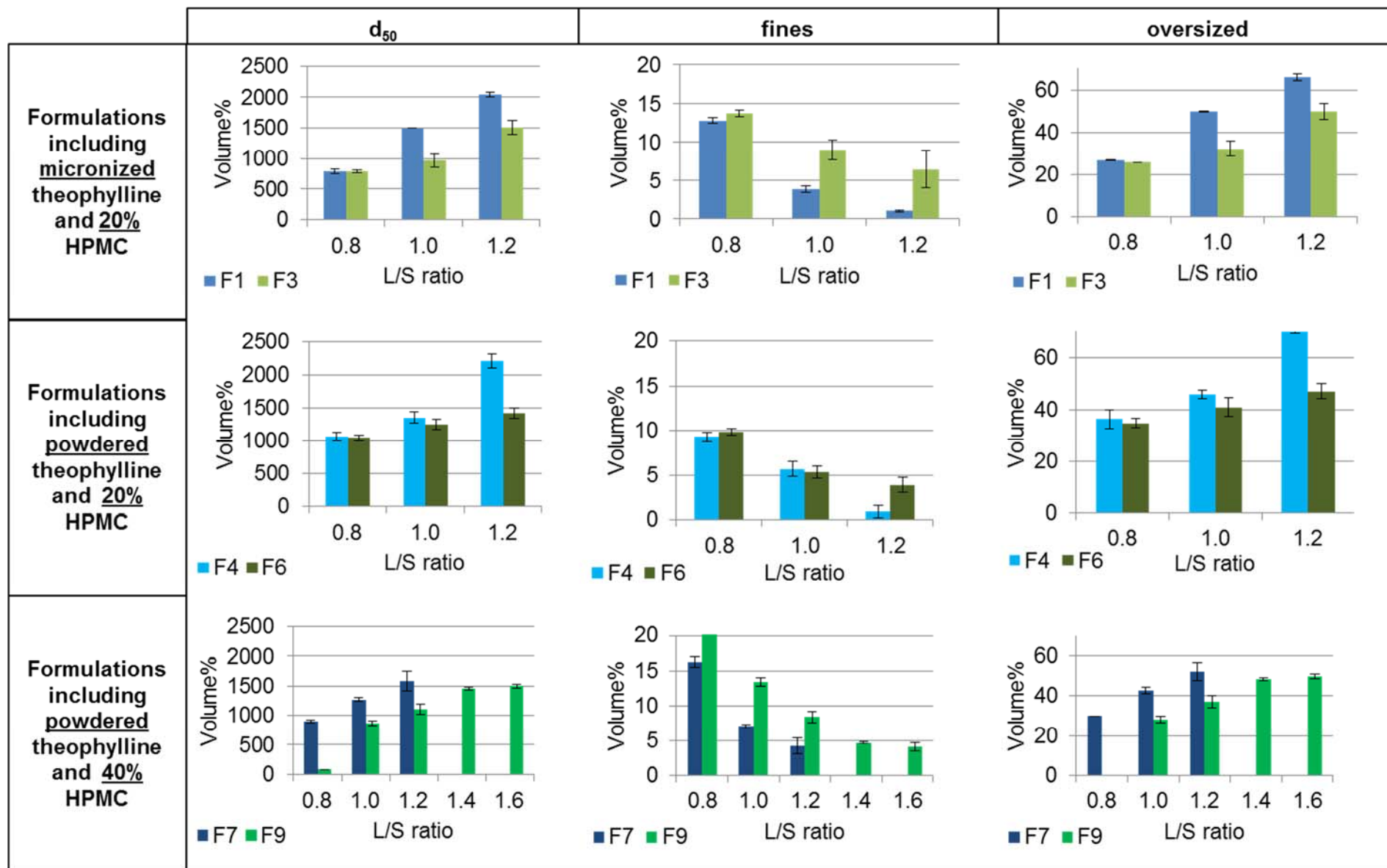
Figure 5   Influence of HPMC concentration on granule size distribution: d_{50}, fines fraction and oversized fraction of F6 and F9, containing 20 and 40% HPMC, respectively.
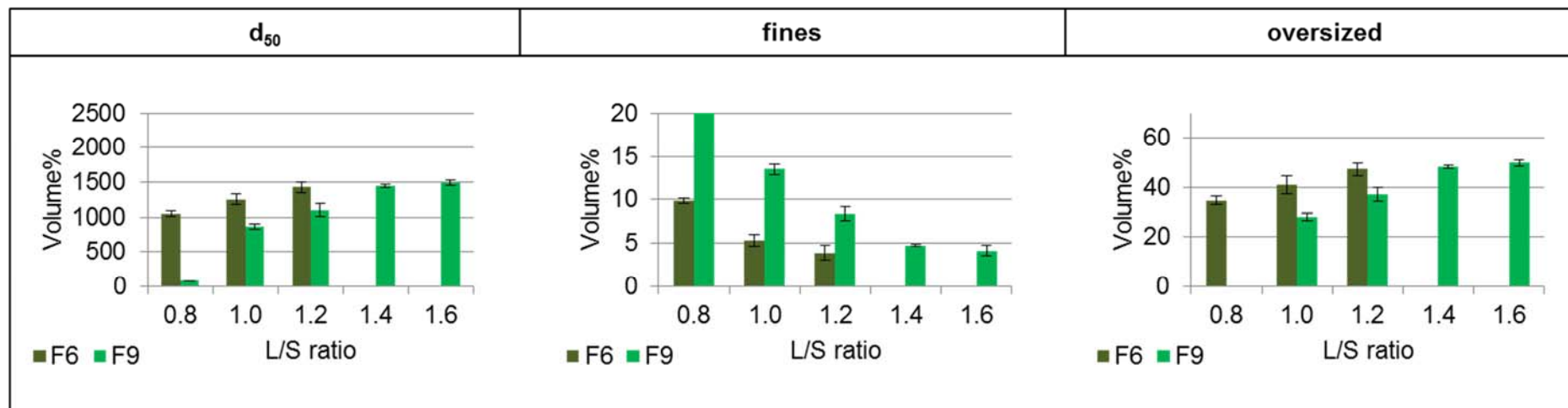
Figure 6   Aspect ratios at varying L/S ratios.
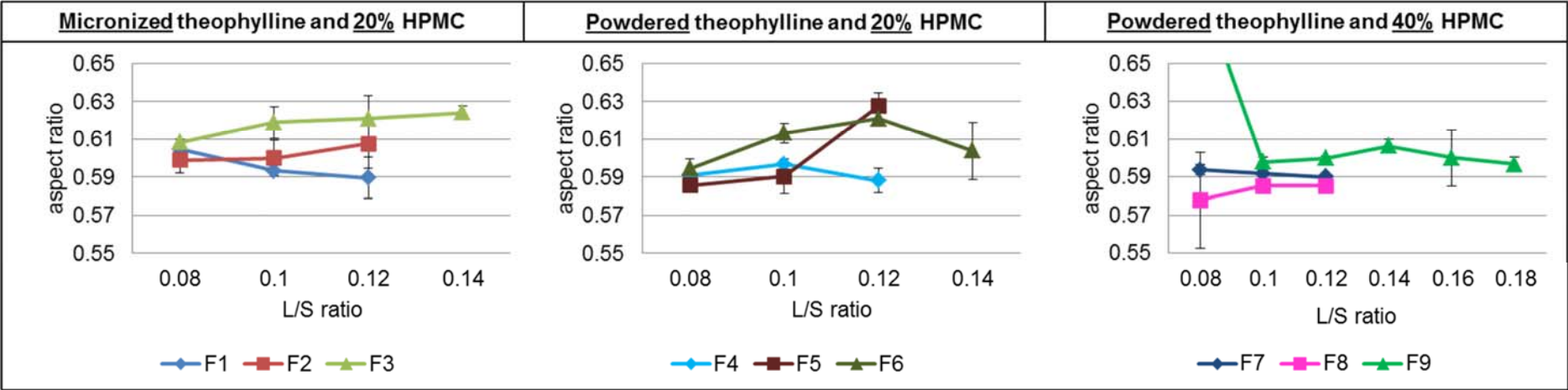
Figure 7   PC1 vs. PC2 scores plot obtained after PCA analysis on 8 sieve fractions of all formulations.
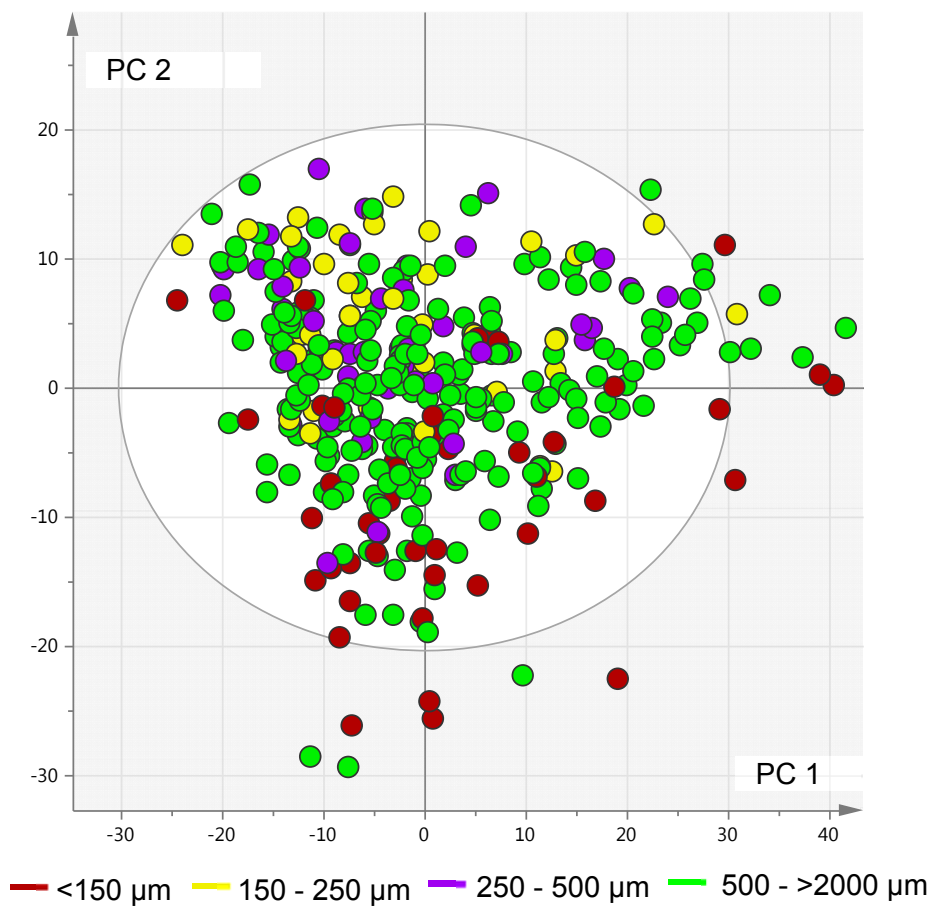
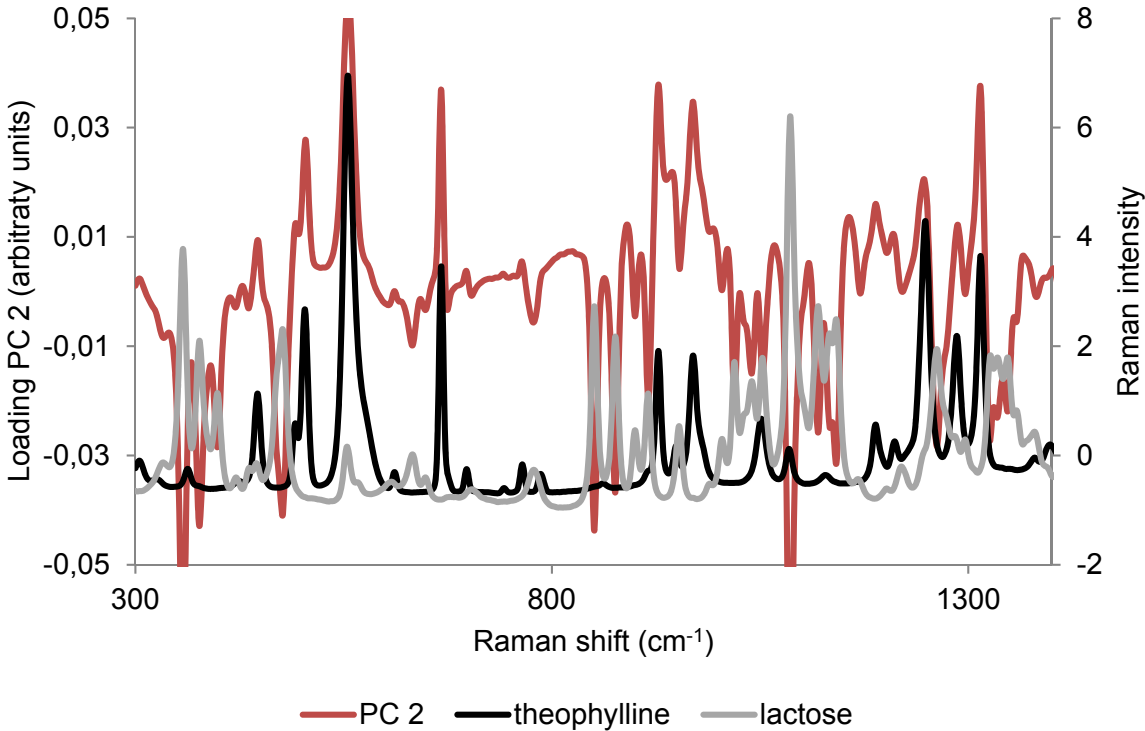Figure 8   Raman spectra of pure lactose and theophylline and loading plot of PC 2 after PCA analysis.

Figure 9   Tabletability of (A) F4 - 6 (containing 20% HPMC and 20% powdered theophylline) and (B) F7 - 9 (containing 40% HPMC and 20% powdered theophylline).
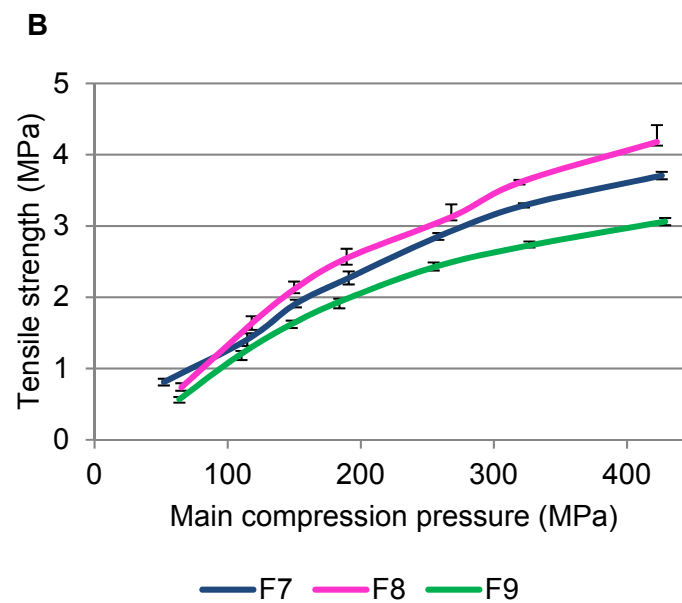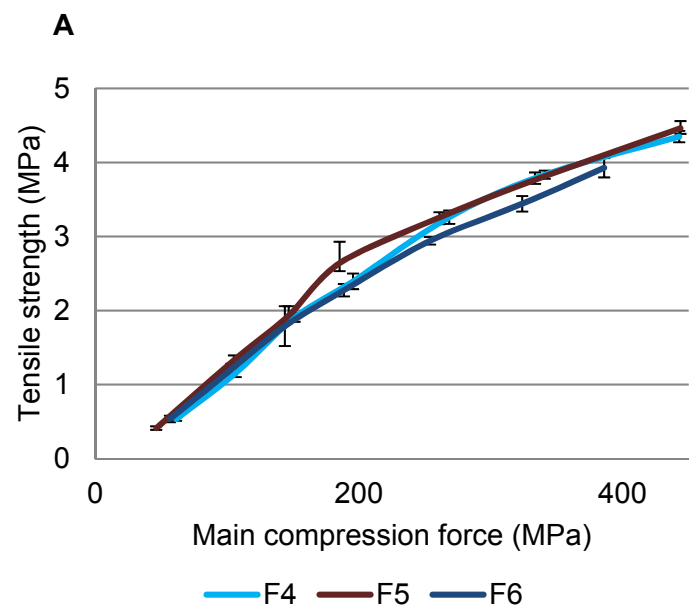
Figure 10   Dissolution profiles of (A) F4 - 6 (containing 20% HPMC and 20% powdered theophylline) and (B) F7 - F9 (containing 40% HPMC and 20% powdered theophylline).