Utilizing Mixer Torque Rheometer Data for Studying the Impact of Filler Ratio and Process Parameters on Granule and Tablet Properties

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Tiivistelmä:

High shear -märkärakeistuksessa on useita lopputulokseen vaikuttavia prosessiparametrejä, ja optimaaliset parametrit vaihtelevat riippuen formulaatiosta. Laktoosimonohydraatti (LMH) ja mikrokiteinen selluloosa (MCC) ovat yleisesti märkärakeistuksessa käytettyjä täyteaineita, joilla on erilaiset fysikaaliset ominaisuudet. Niitä käytetään usein formulaatiossa yhdessä. Nestemäärä (L/S -suhde, liquid-to-solid ratio) on yksi märkärakeistuksen kriittisistä parametreista. Sekoitusmomenttireometriä (MTR, mixer torque rheometer) voidaan käyttää sopivan nestemäärän arvioimiseksi ennen rakeistusta. Tämän tutkimuksen tavoitteena oli selvittää, miten MTR:n tulkinta ja rakeistuksen prosessiparametrit vaikuttavat rakeiden ja tablettien ominaisuuksiin formulaatioissa, joissa on käytetty LMH:ia jaa MCC:tä eri suhteissa.

Tutkimus tehtiin plaseboformulaatioilla koesuunnittelun avulla, jossa oli 3 muuttujaa (LMH:MCC suhde, L/S-suhde ja nesteen lisäysnopeus) kahdella tasolla. Lisäksi tehtiin 3 identtistä keskipistetoistoa sekä kaksi lisäkeskipistetoistoa, joilla tutkittiin pohjasekoittajan nopeuden vaikutusta. Jokaisesta formulaatiosta tehtiin MTR-kokeet, joissa myös selvitettiin, kuinka nesteen lisäysnopeuden muutos MTR-ajon aikana vaikuttaa tuloksiin. Nestemäärä rakeistusta varten määritettiin MTR-kokeiden perusteella käyttäen momenttikäyrän toista derivaattaa. Märkärakeistus tehtiin 1 kg erissä, rakeet kuivattiin leijupedillä ja rakeista tehtiin tabletteja. Rakeista määritettiin kokojakauma, muoto ja valuvuus, kun taas tableteista vetomurtolujuus, massan vaihtelu, kuluvuus ja hajoamisaika. Lopuksi tehtiin vielä kaksi erää, jotka sisälsivät 7.5 % furosemidia, joista määritettiin annoksen yhdenmukaisuus ja liukenemisnopeus.

MTR-tuloksista ennustetuilla nestemäärillä saatiin tehtyä melko onnistuneita rakeita ja tabletteja. LMH:MCC suhteella oli eniten vaikutusta rakeiden ja tablettien ominaisuuksiin. MCC:n osuuden kasvaessa MTR:n maksimaalinen momentti ja sen saavuttamiseen tarvittava nestemäärä kasvoivat, rakeet olivat isompia ja sileämpiä, rakeiden puristuvuusominaisuudet heikkenivät ja tablettien hajoamisaika piteni. Suurimmalla MCC pitoisuudella (40 % täyteaineista), tabletteja ei saatu puristettua riittävän lujiksi. Myös nestemäärän nostolla oli samansuuntaisia vaikutuksia kuin MCC määrän nostolla, joskaan puristuvuusominaisuudet eivät heikentyneet yhtä selvästi. Nesteen lisäysnopeudella ei tässä tutkimuksessa ollut vaikutusta lopputulokseen, mahdollisesti johtuen siitä, että erot siinä eivät olleet kovin suuria.

Tutkimuksen perusteella matalampi MCC:n suhteellinen osuus (20 % täyteaineista) olisi paremmin soveltuva märkärakeistukseen. Tällä formulaatiolla myös momenttikäyrän toisen derivaatan käyttö MTR:n tulkinnassa vaikuttaa toimivalta. Korkeammalla MCC:n osuudella rakeiden ja tablettien ominaisuudet eivät olleet optimaalisia. Tutkimuksen perusteella ei voi sanoa, johtuuko se vain MCC:n määrästä vai täytyykö tällä koostumuksella MTR käyrää tulkita eri tavoin. MTR on osoitettu hyödylliseksi arvioidessa nestemäärää, ja sen käytön tutkimista on syytä jatkaa. On kuitenkin mahdollista, että sen tuloksia tulee tulkita eri tavoin riippuen formulaation koostumuksesta, eikä yhtenäistä tulkintamallia pysty välttämättä muodostamaan.

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Abstract

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Abstract:

In high shear wet granulation there are many adjustable process parameters, and the optimal parameters vary depending on formulation. Lactose monohydrate (LMH) and microcrystalline cellulose (MCC) are fillers commonly used in blends for wet granulation. They have different physical properties and are often used in a combination. The amount of added liquid, or liquid-to-solid (L/S) ratio is one of the critical parameters in wet granulation. Mixer torque rheometer (MTR) can be used to estimate the required L/S ratio for granulation. The aim of this study was to investigate, how the interpretation of the MTR results and granulation process parameters affect final granule and tablet attributes in different LMH-MCC -mixtures.

The study was performed with placebo formulations using full factorial study design, with 3 independent variables (LMH:MCC ratio, L/S ratio determination point and liquid addition rate) on two levels, plus 3 identical centre point repetitions. Additionally, the impact of impeller speed was studied in two batches. MTR experiments were done with each composition, and the effect of liquid addition rate during MTR was assessed. The L/S ratios for granulations was determined from MTR experiments, using the 2nd derivative of the torque curve. The wet granulation was done in 1 kg batches; the granules were fluid-bed dried and made into tablets. Granule size distribution, flow and morphology were studied from the granules. From tablets, tensile strength, mass variation, friability and disintegration time were measured. In addition to placebo batches, two batches with 7.5 % of furosemide were done, from which dissolution and content uniformity were assessed.

Granules and tablets were successfully prepared using L/S ratios estimated with MTR. The LMH:MCC ratio had a significant effect on granule and tablet attributes. With increasing MCC amount, the maximum torque and the liquid amount required to reach it in MTR were higher, the granule size was bigger, the granules were smoother, tabletability was poorer and tablet disintegration time longer. With maximum amount of MCC (40 % of total filler amount), the tablets failed to reach the required tensile strength completely. Higher L/S ratio had similar effects as higher amount of MCC. Liquid addition rate did not have significant effect on outcome variables in this study, possibly since the range was not very wide.

Based on the study, the lower amount of MCC (20 % of total filler amount) is better for wet granulation. In this formulation using 2nd derivative of the torque curve of MTR was suitable for estimating L/S ratio. The properties of granules and tablets with high amount of MCC were not as good, but it is unclear, whether this is caused by high amounts of MCC as such, or should MTR be interpreted differently. MTR is a useful tool and further studies with different formulations would be beneficial, but it is possible, that the optimal interpretation varies depending on formulation too much to ever achieve a universal model for MTR interpretation.

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1 INTRODUCTION

High shear wet granulation (HSWG) is a wet granulation technique that has been used in pharmaceutical manufacturing for several decades (Iveson et al., 2001). In granulation, the primary powder particles are bound together to form agglomerates, increasing the particle size of the powder. The aim of granulation is to improve processability attributes of a powder mixture, especially flow properties, but also improving compaction properties, reducing dust and improving uniform distribution of an active pharmaceutical ingredient (API). However, since granulation adds several additional steps to the tablet manufacturing process and subjects an API to moisture, heat and handling, it is typically chosen over direct compression only when it is clearly beneficial.

Granule attributes, which contribute to the final tablet quality, can be influenced by various changes in the granulation process or formulation (Iveson et al., 2001; Thapa et al., 2019; Wang et al., 2023). Fillers and binders are the excipients, considered to have the most effect on the result in wet granulation (Morkhade, 2017; Wang et al., 2023). Microcrystalline cellulose (MCC) and α-lactose monohydrate (LMH) are both fillers commonly used in formulations for high-shear granulation (Chitu et al., 2011). LMH is brittle and water-soluble, while MCC is plastic, non-soluble, but highly hygroscopic. MCC has better processability attributes as a powder, but they can be diminished in HSWG, especially if high liquid amounts are used (Shi et al., 2010; Osei-Yeboah et al., 2014).

Combining MCC and LMH in the formulation has been proven to help to produce granules with desirable properties, combining their brittle and plastic deformation behaviour to an advantage (Chitu et al., 2011; Osei-Yeboah et al., 2014; Morkhade, 2017). The optimal amount of MCC in formulation is suggested to be between 10 and 35 % in different studies, while the minimum amount of brittle material is around 40 % (Kristensen et al., 2000; Chitu et al., 2011; Osei-Yeboah et al., 2014).

The relative amounts depend also on the content of the API and its solubility and compressibility properties. Increasing amount of MCC in LMH-MCC mixtures increases binder liquid requirement, granule hardness, granule size and roundness, and improves flowability. High contents of MCC can lead to overly hard granules that are difficult to compress into sufficiently hard tablets (Osei-Yeboah et al., 2014). High MCC content can also lead to prolonged disintegration times, especially with high compaction forces (Wang et al., 2023). Large amount of LMH, on the other hand can lead to overly friable granules (Chitu et al., 2011). The granulation also becomes more difficult to control, as LMH requires much less liquid for granulation, and the granules can transition to over-wetted state with a minor change in liquid content.

Making a successful and consistent formulation requires choosing the right parameters to ensure good quality for the final product. Important process parameters in HSWG are impeller speed, liquid addition rate and method, wet massing time and the total liquid amount, also referred to as liquid-to-solid (L/S) ratio (Thapa et al., 2019). The formation of granules can be examined as three different processes happening partly simultaneously: wetting and nucleation, consolidation and growth and breakage and attrition (Iveson et al., 2001). The liquid saturation of granule is often described in the increasing order: pendular, funicular, capillary, droplet. The optimal point to stop liquid addition is considered to be between funicular and pendular phases (Chitu et al., 2011). The correct amount of liquid can be observed in-line by various methods, including torque measurements, but the methods have their limitations (Hansuld and Briens, 2014). However, transitions from different wettability states can happen fast, and determining the correct amount of liquid can require multiple experiments, consuming time and material. Thus, estimating the correct L/S ratio in advance can help to ensure the quality and repeatability of granulations.

A mixer torque rheometer (MTR) is a tool, used to assess rheological properties of wet masses (Hancock et al., 1992). Previous studies have shown that MTR can be successfully used in estimating the liquid amount for granulation (Chitu et al., 2011; Santomaso et al., 2017; Franceschinis et al., 2020; Kyttä et al., 2020; Junnila et al., 2022). The advantage of using MTR is that it requires relatively small amounts of API (a few grams) and thus, is useful in the early phases of formulation development. The maximum torque value of the MTR curve corresponds to the transition of granules to capillary state (Santomaso et al., 2017). The shape of the torque curve, obtained from the MTR experiments, is affected by the formulation parameters, such as solubility of the API or the excipients (Hancock et al., 1992; Junnila et al., 2022; Mertsalmi, 2025). Higher MCC content increases the maximum torque values, as well as the amount of liquid required, making the changes in the torque more easily distinguishable (Chitu et al., 2011). Several values from the torque curve can be used to identify the optimal L/S ratio. A method that is frequently mentioned in the literature is using the infliction point in the rise of the curve, which can be determined using the second derivative of the curve which changes there from positive to negative (Santomaso et al., 2017; Franceschinis et al., 2020). L/S ratio corresponding to certain percentage from the maximum torque is another way to interpret MTR curve, and L/S ratio at 2/3 of the maximum torque has been shown to predict good values for continuous twin-screw wet granulation, resulting in satisfactory tablet attributes (Junnila et al., 2022).

Even though there are studies using MTR, the best way to determine the L/S ratio from the MTR curve has not been determined, and there are few studies connecting the use of MTR to tablet properties. The aim of this study was to investigate more deeply the connection of the MTR experiments to granule and tablet characteristics, and to provide tools to make the most use of MTR in product development. The use of MTR to predict the optimal liquid amount was investigated with a systematic approach using Design of Experiments (DoE). A full factorial study design was performed, studying the effect of MCC:LMH ratios, liquid addition rates, and

different L/S ratio points estimated the MTR curves in high shear wet granulation on granule and tablet properties.

2 MATERIALS AND METHODS

2.1 Materials

The placebo experiments were done using lactose monohydrate (Pharmatose® 200 M, DFE Pharma, Germany), microcrystalline cellulose (Emocel® 50 M, JRS Pharma, Germany), polyvinylpyrrolidone (povidone, PVP) K30 (Kollidon®, BASF Pharma, USA), croscarmellose sodium (Ac-Di-Sol®, IFF Pharma solutions, USA) and magnesium stearate (Peter Greven, Netherlands). Furosemide (Ipca Laboratories, India) was chosen as a model API. The compositions of different formulations are presented in Table 1.

Table 1. Compositions of formulations used in the MTR and granulation experiments.

Excipient	M20 (%)	M30 (%)	M40 (%)	FURM20 (%)
Lactose monohydrate	75.2	65.8	56.4	69.2
Microcrystalline cellulose	18.8	28.2	37.6	17.3
Povidone	4	4	4	4
Croscarmellose sodium	2	2	2	2
Furosemide	0	0	0	7.5

2.2 Experimental design

A full factorial experimental design was performed with three independent factors on two levels, and with center point repetitions in triplicate (Figure 1). The independent variables chosen for the study design were LMH:MCC ratio (X1), the determination point of L/S ratio from the MTR curves (X2), and liquid addition rate (X3). In addition, the effect of impeller speed was investigated as center point

repetitions on three levels, with the other factors set in the middle values. The dependent outcome measures were mean granule particle size (D_{50}), flowability index, tablet tensile strength at compression pressure of 300 MPa, friability and disintegration time. The experimental matrix is presented in Table 2 and name coding of the batches in Figure 2. The results of the DoE were tested with a formulation with moderate (7.5 %) API load. From the API formulations also uniformity of dosage units and tablet dissolution were assessed.

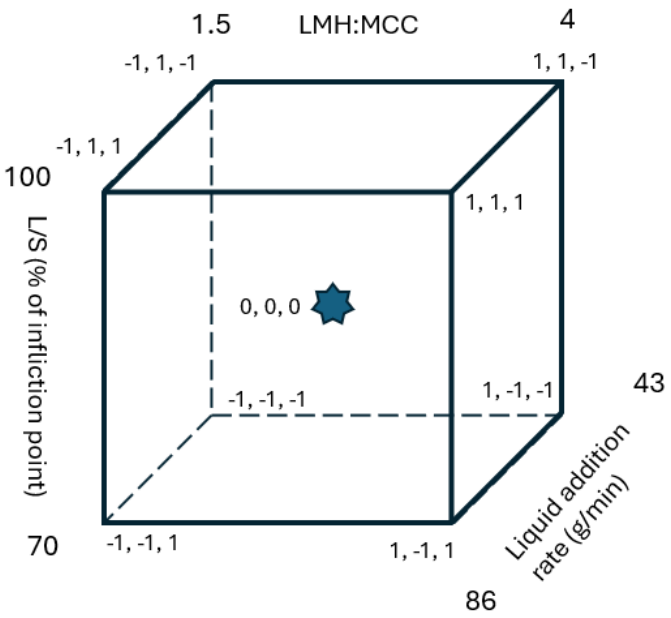


Figure 1. DoE design.

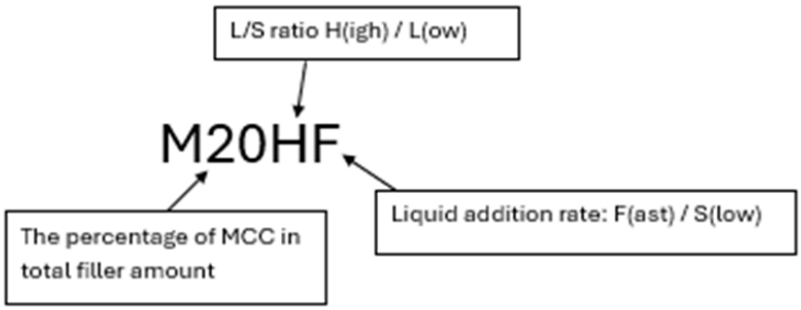


Figure 2. Explanation of the naming of the batches. In the center point batches, the 'I' stands for 'impeller', 'I0' are the center point repetitions A,B and C, and 'F' and 'S' refer to fast and slow impeller speed, respectively.

Table 2. The experimental design matrix, including the main output values. X0 Impeller speed (rpm); X1 LMH:MCC, X2 L/S as point of MTR curve, where the L/S ratio is determined in each formulation: X2*(infliction point - start of rise) + start of rise, (actual L/S ratio); X3 Liquid addition rate (g/min); * Particle size determined by LD (volume %), † Flodex index (d (mm) +/- 2 mm).

Batch	X0	X1	X2	X3	D10* (µm)	D50* (µm)	D90* (µm)	Span*	Flow †	Tensile strength (MPa)	Friability (% loss of w.)	Disintegration time (min)
M20HF	350	4.0	1.00 (0.37)	86	143	337	740	1.8	< 4	2.35	0	5.2
M20HS	350	4.0	1.00 (0.37)	43	215	429	985	1.8	< 4	2.38	0	6.5
M20LF	350	4.0	0.70 (0.27)	86	56	117	556	4.3	< 4	3.11	0	1.2
M20LS	350	4.0	0.70 (0.27)	43	56	117	640	5.0	4	3.41	0.04	1.1
M30I0A	350	2.3	0.84 (0.44)	64.5	145	303	596	1.5	< 4	2.33	0	4.1
M30I0B	350	2.3	0.84 (0.44)	64.5	180	343	784	1.8	< 4	2.10	0	6.1
M30I0C	350	2.3	0.84 (0.44)	64.5	168	333	608	1.3	< 4	1.98	0	10.2
M30IF	500	2.3	0.84 (0.44)	64.5	157	317	583	1.3	< 4	1.81	0	10.8
M30IS	200	2.3	0.84 (0.44)	64.5	150	358	1006	2.4	6	2.35	0	4.3
M40HF	350	1.5	1.00 (0.59)	86	452	826	1369	1.1	5	1.60	0.02	18.5
M40HS	350	1.5	1.00 (0.59)	43	531	885	1388	1.0	5	1.50	0.01	17.0
M40LF	350	1.5	0.70 (0.52)	86	195	417	946	1.8	< 4	1.52	0	14.6
M40LS	350	1.5	0.70 (0.52)	43	265	509	1287	2.0	< 4	1.26	0.02	12.5

2.3 Mixer torque rheometer experiments

Experiments with a mixer torque rheometer (Caleva Process Solutions, UK) (Figure 3) were done to all the blends in the study. The procedure was planned based on preliminary experiments. The first MTR experiments were performed with M20 and M40 formulations, to explore the effects of different liquid addition rates, either 0.5 ml (0.025 g/g) or 1.0 ml (0.5 g/g) per addition. For M30 and API formulations, MTR experiments were performed only with one liquid addition rate (0.5 ml/addition) to determine the L/S ratio for granulation. The powders were weighed in proportions presented in table 1 and mixed in a turbula mixer at 21 rpm for 2 min. The powder blend (20.0 g) was set in a mixing bowl which has two contra-rotating blades. The volume was adequate to cover the blades entirely but not spill out of the mixing bowl. The multiple addition method was used. The powder blend was dry mixed for 30 s, then purified water was added with the chosen rate using a syringe pump. The blend was mixed for 30 s, then the torque recorded for 20 s after each addition. The data was plotted as mean torque of the two identical runs vs. L/S ratio to analyze the torque curves. The second derivative of the torque curve was calculated and plotted against the L/S ratio to help determine the required liquid amount for granulation (see Annex for mean torque curves for all formulations).

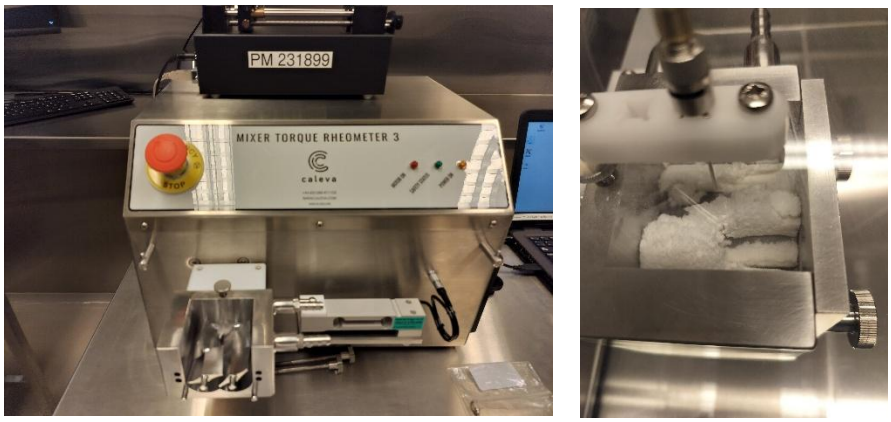
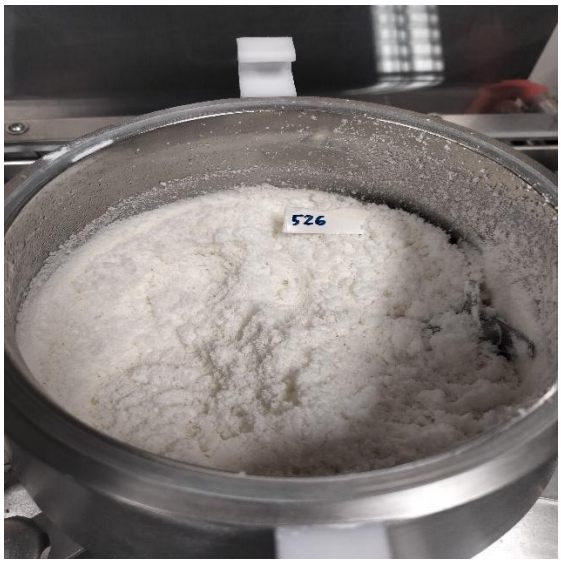


Figure 3. Mixer torque rheometer.

2.4 High-shear granulation

The granules were prepared in 1000 g batches in a randomized order in a high-shear mixer (Glatt TMG, Germany) in a 4 l mixing bowl, equipped with a three-blade impeller and a horizontal four-blade chopper. The powder blend was dry mixed for 60 s with impeller speed 300 rpm and chopper speed 300 rpm. Purified water was used as granulating liquid, and it was added either at 86 g/min, 64.5 g/min or 43 g/min, according to the study design. Water was added through a spraying nozzle. The impeller speed was 350 rpm in all but two center point experiments, in which 200 rpm and 500 rpm impeller speeds were used. Chopper speed was set at 300 rpm in the beginning of granulation, and it was raised to 600 rpm when approximately 1/3 of the liquid had been added, as using the higher speed while the blend was still dry made the blend fly and stick to the lid of the bowl. After the liquid addition was stopped, the wet mass was mixed for 30 s. The appearance of the granulation blend was evaluated as dry powder, after liquid addition, after wet massing and after drying (Figure 4). The granules were wet screened by hand through a 4 mm mesh to improve uniformity of drying, and then dried in a fluid bed granulator (Glatt GPCG1, Germany). The incoming air temperature was set at 60 ˚C, and the air flow was adjusted between 40-80 m^3/h. The moisture content was measured from the powder blend before granulation and granules after drying in a halogen moisture analyzer (Mettler Toledo HX204, Malaysia) with 115˚C 1 d/50 s method. Drying was stopped and the moisture content measured, when the product temperature was approximately 42 +/- 3˚C and outlet temperature 37 +/- 5 ˚C. The drying was considered sufficient, when the moisture content of the dried granules was equal to the initial moisture content of the blend +/- 0.5 % units. The granules were dry screened by hand through a 2 mm screen.

A



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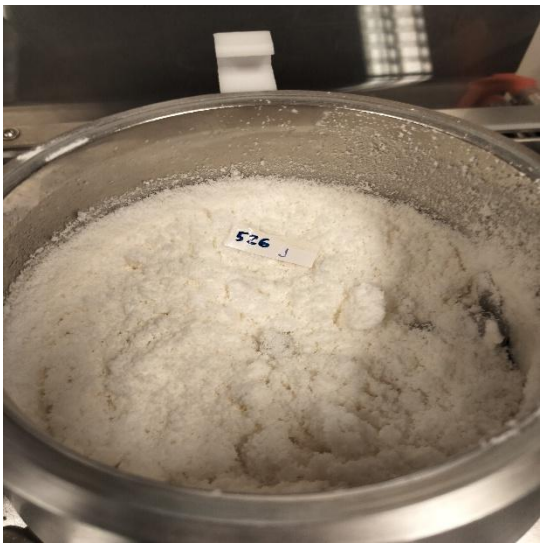


C

D

Figure 4. A blend (M40LF) in a granulator after dry mix (A), after water addition (B), after wet massing (C) and dried screened granules (D).

2.5 Tableting

Before tableting, the granules were blended in a turbula mixer with magnesium stearate (1 % w/w) for 1 minute at 21 rpm. Tableting was performed with a compaction simulator (Styl'One Evo, Medelpharm, France) with round, convex punch-die set 10 mm in diameter and 12 mm curvature radius. The target weight of the tablets was 400 mg, and the fill height of the die was adjusted to achieve it. The die was filled with a force feed shoe. The "Default compression" cycle was used at 30 % compression speed and 10 % feed shoe speed (equipment-specific parameters). A force study was performed within a range of compression force from 5 to 25 kN (corresponding to approximately 50 to 300 MPa) at four levels. Based on the study, a compaction force for preparing a bigger batch of tablets (minimum of 80) was chosen, aiming for a tensile strength of 1.7 MPa (corresponding to breaking force of 140 N). The die fill height was then adjusted again with the chosen force, and a batch of approximately 100 tablets was produced.

2.6 Granule characterization

2.6.1 Granule size distribution

Granule size was analyzed with sieve analysis, using sieve shaker (EasySieve® software, Retsch, Germany) with 1 mm, 710 µm, 500 µm, 250 µm, 125 µm and 90 µm mesh size. Shaking time was 5 min, amplitude 150 mm, and the sample size was 50 g. Granule particle size was also analyzed with a laser diffraction particle size distribution analyzer (Beckman Coulter LS13320, Beckman Coulter Life Sciences, USA) using its Tornado Dry Powder System. The dispersion pressure used was 19.0'' H_2O. Two measurements were made for each sample, each using 10 ml of sample. Fraunhofer theory was used as the optical model to calculate the results. From both measurements, the mean particle diameter (D50) and diameters of 10^{th} and 90^{th}

percentile (D10 and D90) were obtained. Span was calculated from laser diffraction granule size distribution as:

Span = (D90 – D10) / D50. (Equation 1)

2.6.2 Granule morphology

The morphology of the granules was assessed with a scanning electron microscope (JCM-7000 NeoScope Benchtop SEM, Jeol Ltd., Japan). The samples were prepared with platinum sputtering. Images were saved at least with 30-, 100-, 250-, 500- and 1000-fold magnification.

2.6.3 Flow properties

The samples for flow analysis were taken from the granules lubricated with magnesium stearate for tableting. The flow properties were measured with Flodex® flowability index determination (Teledyne Labs, US). The method is based on measuring the free flow of powder or granules through orifices of different sizes (4-34 mm) (Gioia 1980). The measurements were done at 40 % relative humidity. 60 ml of granules were poured into a cylinder with an orifice at the bottom. In this study, the measurements were started using the orifice 8 mm in diameter. The cylinder was lifted straight up by hand, as evenly as possible. The result was considered positive when powder was flowing through the orifice, and there was a clear channel visible on the powder surface. The measurement was repeated three times per aperture size, and if there were both positive and negative results, three additional measurements were performed. The flow index was defined as the aperture size, where half of the results were positive and half were negative +/- 2 mm. Flow is considered acceptable, when the index is 50 to 120 % of the planned tablet punch diameter (Gioia 1980). The method is compatible with US Pharmacopeia (Test <1174> *Powder Flow*).

2.7 Tablet characterization

The weight, thickness and breaking force of tablets were measured with a semi-automated tablet hardness tester (Sotax ST 50, Sotax group, Switzerland) right after compression. In the force study, the sample size was 6 tablets and in the bigger batch 20 tablets. Tensile strength was calculated from measured breaking force, using equation described in US Pharmacopeia (monograph <1217>):

$\sigma_x = \left(\frac{10F}{\pi D^2}\right) * \left(\frac{2.84H}{D} - \frac{0.126H}{W} + \frac{3.15W}{D} + 0.01\right)^{-1}$, where

σ_x = tensile strength

F = breaking force

D = tablet diameter

H = tablet thickness

W = central cylinder thickness (tablet wall height) (Equation 2)

Uniformity of mass was evaluated from 20 tablets according to European Pharmacopoiea 11.8 (Ph. Eur., 2.9.5). Friability was analyzed with a standard method consistent with Ph. Eur. 11.8 (2.9.7) from 16 tablets (approximately 6.5 g) in a drum rotating at 100 rpm for 4 minutes (Sotax FT2, Sotax group, Switzerland). The maximum acceptable loss of weight is no more than 1 %. Disintegration time was analyzed with a method as per the Ph. Eur. 11.8 (2.9.1), with 6 tablets set in the moving disintegration apparatus in 800 ml of water at a temperature of 37 °C, and remaining height and disintegration time were measured automatically (DISI-2A, Charles Ischi AG, Switzerland). Differing from the Pharmacopeial method, if the upper time limit of 15 minutes was exceeded, the time of full disintegration was recorded, but no repeat tests were done.

The uniformity of the dosage units for tablets containing API was determined by content uniformity test. The assay was performed using UHPLC in ammonium phosphate buffer (pH 2.1) with a UV detector (wavelength 250 nm). The results were

interpreted according to Ph. Eur. 11.8 (2.9.40). The dissolution of tablets with API was analyzed using a procedure consistent with US Pharmacopeia (Test <711> *Dissolution*) in a USP II paddle apparatus, with paddle speed 50 rpm in 500 ml of phosphate buffer (pH 5.8). The detection was done using UV fiber optics at 330 nm wavelength.

2.8 Statistical analysis

The data was collected and sorted in MS Excel, after which it was analyzed using JMP 18 (JMP Statistical Discovery LLC, United States). The DoE data was modelled by Least squares – regression method with multiple input variables (X1, X2, X3), using the 'Fit Model' function and 'Factorial to Degree' macros in JMP. These include main effects and polynomial terms, up to a specified degree. The effect of the primary input variables was tested on each output, and the variables with no statistical significance ($p > 0.05$) were removed from the final model. The effect of impeller speed, including only center point repetitions, on output variables was tested separately with linear regression.

3 RESULTS

3.1 Mixer torque rheometer experiments

The torque curves produced by two identical runs were quite consistent, although there was some variation between the runs with more LMH and slower addition rate (Figure 5). There was moderate wall adhesion during some of the runs, especially in formulations containing more LMH. As this happened when the water content was already quite high, it did not affect the torque measurement, when the torque was still rising. Both increasing relative amount of MCC in the formulation, and slower liquid addition rate, resulted in a higher maximum torque and a higher liquid amount

required to reach maximum torque in the MTR (Figure 5). With the faster addition rate, only 12 additions were required before the maximum torque was reached in formulation with the highest LMH content.

Different L/S ratios, which could be considered as optimal liquid amounts, were determined by a few different criteria from the mean torque profile of both runs for each formulation and liquid addition rate (Table 3). The L/S ratios obtained from each torque curve were very different depending on the liquid addition rate used. As mentioned previously, the faster liquid addition rate did not seem reliable for M20 blends. Thus, the L/S ratios for further experiments were chosen to be determined from the curves obtained with the slower addition rate.

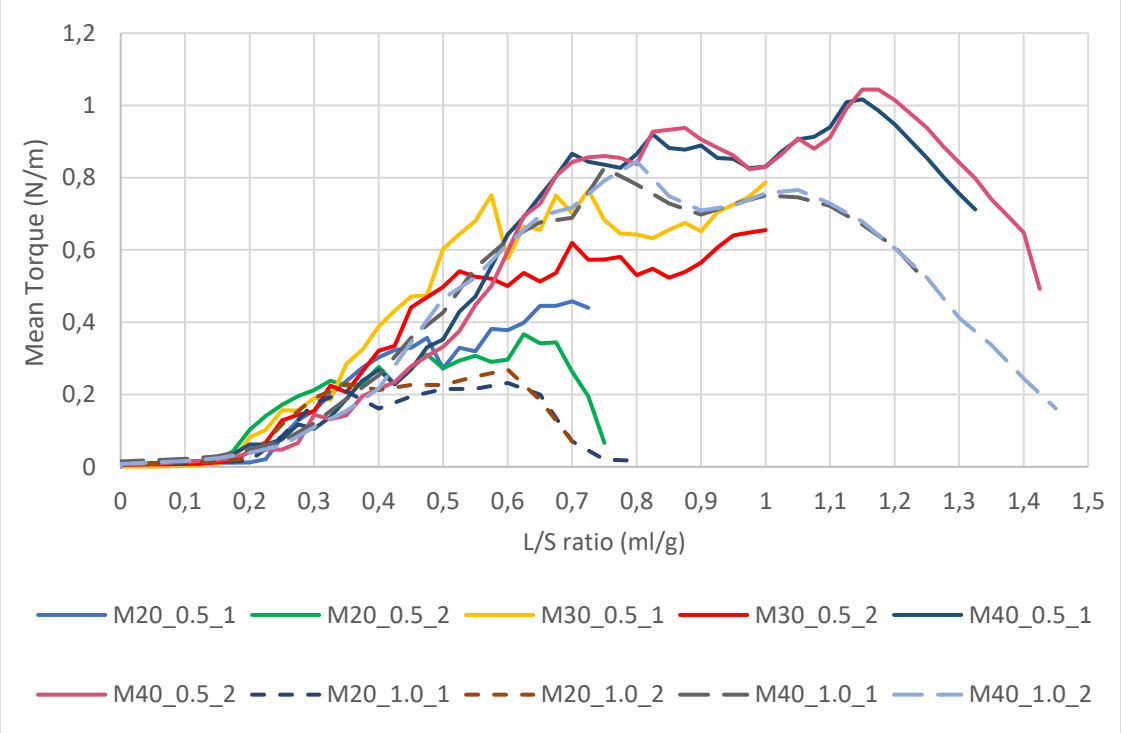


Figure 5. All MTR curves obtained with placebo blends. 0.5 and 1.0 refer to liquid addition rates, and 1 and 2 to the run number.

Based on literature, the infliction point of the curve, where the 2nd derivative turns from positive to negative, was chosen as a starting point. As there could be several

2nd derivative zero points, the ones closest to a shoulder-like bend in the torque curve were chosen. Preliminary experiments suggested that using the infliction point might lead to slightly over granulated mass, so this was chosen as the upper value in the experiments. To ensure large enough difference between batches, the lower L/S ratio was set at the point corresponding to 70 % torque from the start of rise of the curve to the infliction point. The torque was calculated as follows:

(Tq(infliction) – Tq(start of rise)) * 0.70 + Tq(start of rise) (Equation 3)

The L/S ratio corresponding to this torque was determined from the curve. An example of determination of L/S ratio is illustrated in Figure 6.

Table 3. L/S ratios obtained from the MTR curves using different criteria that were considered as possible values. The values eventually chosen as basis for the experiments are highlighted.

	L/S (g/g)					
formulation	M20	M20	M40	M40	M30	FURM20
liq. add. rate	0.5 ml	1.0 ml	0.5 ml	1.0 ml	0.5 ml	0.5 ml
maxT	0.68	0.60	1.15	0.78	1.00	0.58
2/3 maxT	0.38	0.28	0.62	0.55	0.48	0.40
2nd der. neg. to pos.	0.42	0.39	0.75	0.67	0.58	0.42
midpoint	0.39	0.32	0.67	0.57	0.54	0.40
2nd der. pos. to neg.	**0.37**	0.26	**0.59**	0.46	**0.49**	0.38
70 % before 1st infl.	**0.27**	0.23	**0.52**	0.39	**0.40**	0.24
35 % maxT	0.26	0.24	0.51	0.42	0.36	0.22

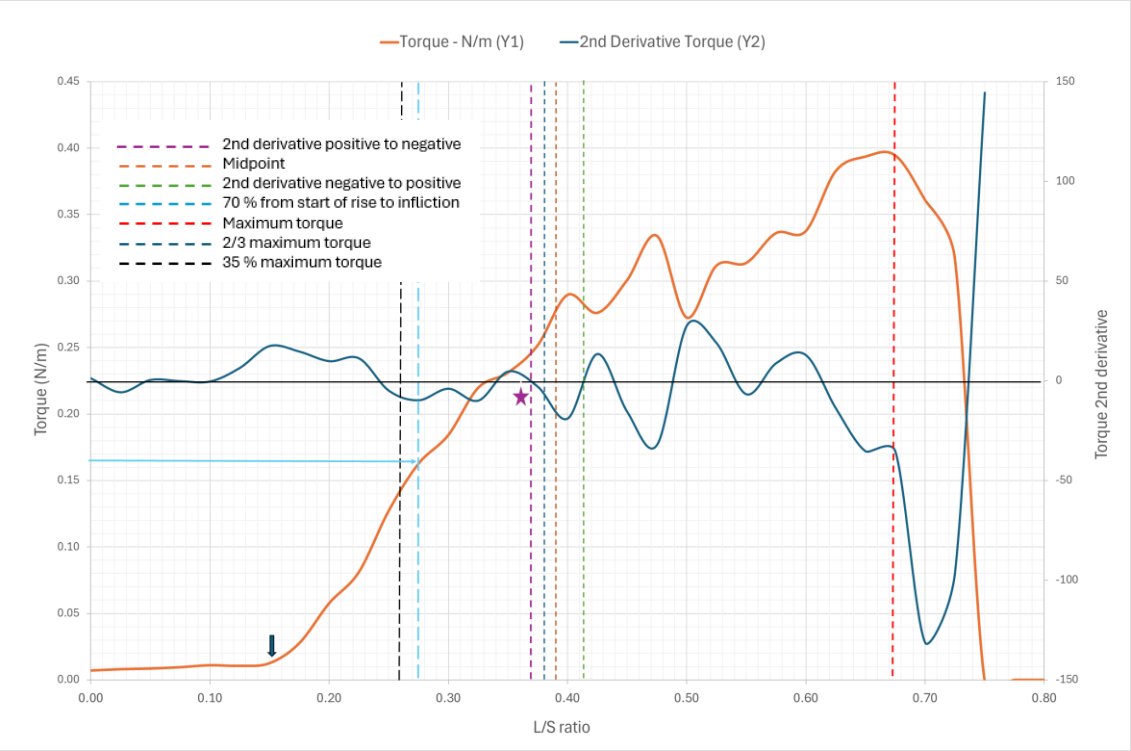


Figure 6. Determining the L/S ratio from MTR curve of M20 formulation. Light blue arrow points from the torque corresponding to 70 % from start of rise (thick arrow) to infliction point (purple star).

3.2 Granulation

Granules were successfully prepared from all batches with final yield varying 69-85 %. In M20 formulations, liquid addition rate had a positive effect on final granule yield ($p < 0.01$, $R^2=0.99$), but this effect could not be seen in all batches together, and no other effects of the input variables on the yield could be observed. There was some minor build up on the walls during granulation, more with increasing L/S ratio. The impeller torque curves recorded during granulations follow similar shapes to those seen in MTR curves of the same blend (Figure 7). There are no clear plateaus to be observed in either of the impeller torque curves.

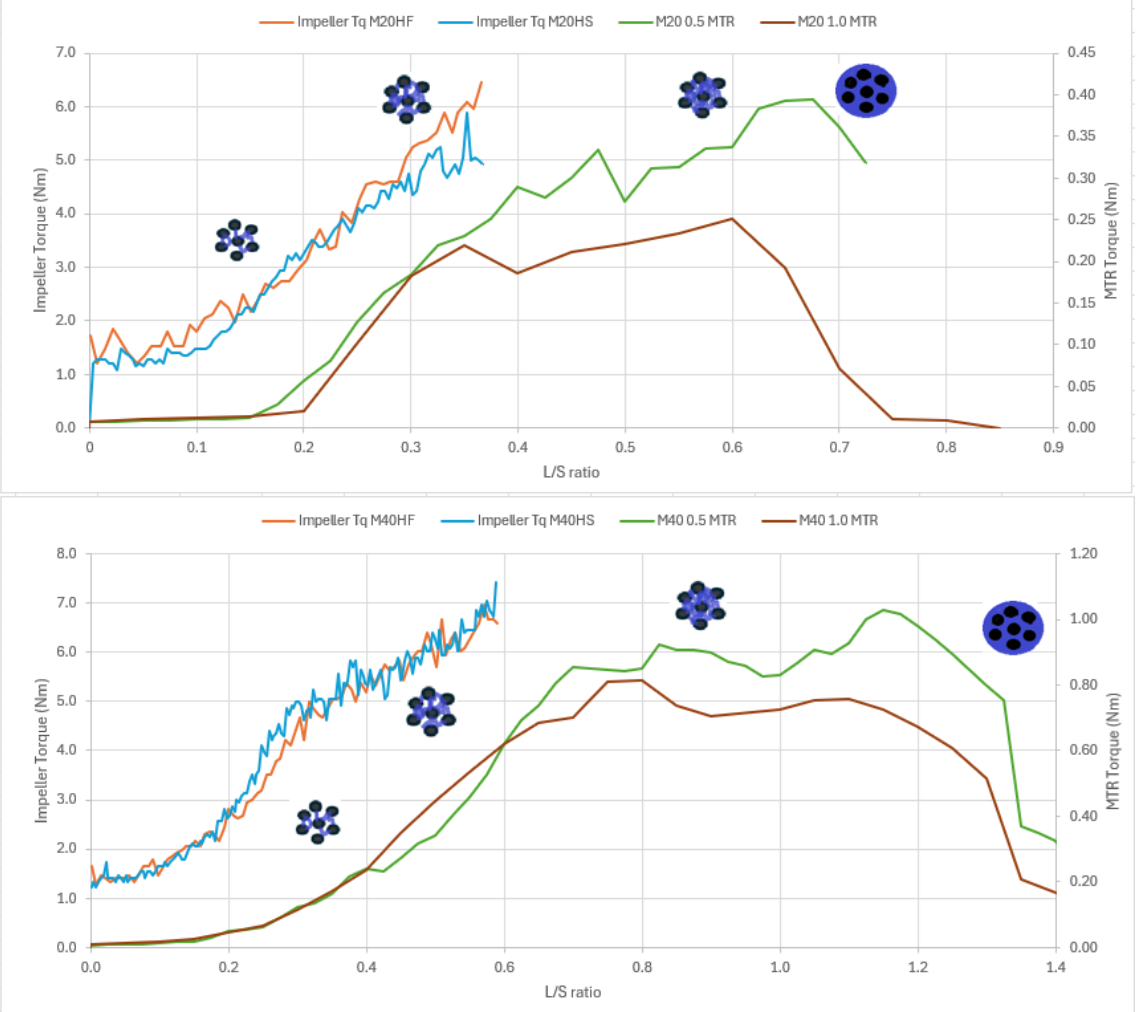


Figure 7. Torque curves from MTR (green and brown)and granulation (orange and blue) (note separate vertical axes) for M20 and M40 formulations with illustration of granule wetting stages (pendular, funicular, capillary and droplet). Adapted from (Chitu et al., 2011; Santomaso et al., 2017).

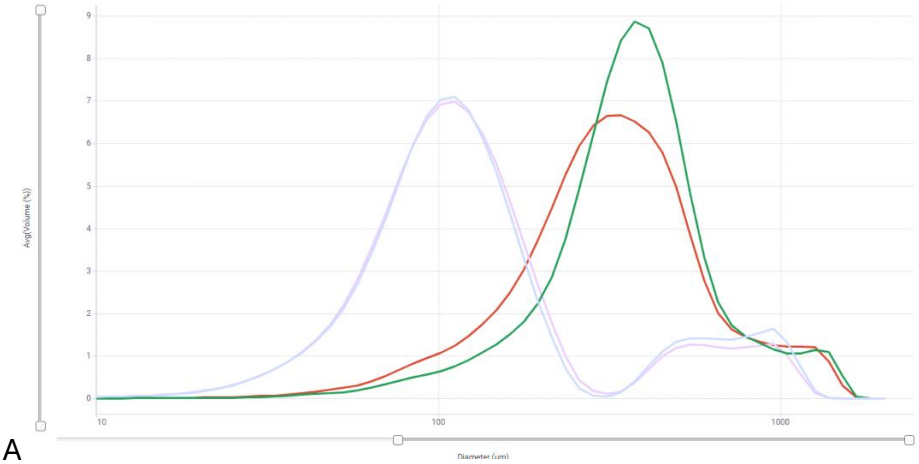
3.3 Granule particle size and particle size distribution

There was clear variability in mean particle size and PSD between batches (Table 4, Figures 8 & 9). In both M20L formulations the mean particle size was small, and the PSD was quite wide (Span 4.3-5.0), with also a considerable step in the distribution curve at the larger diameter end. On the other hand, in M40 formulations, the mean particle size was quite large in all batches, although even larger with increasing liquid amount. In batches with slower liquid addition rates, the peaks of PSD curves

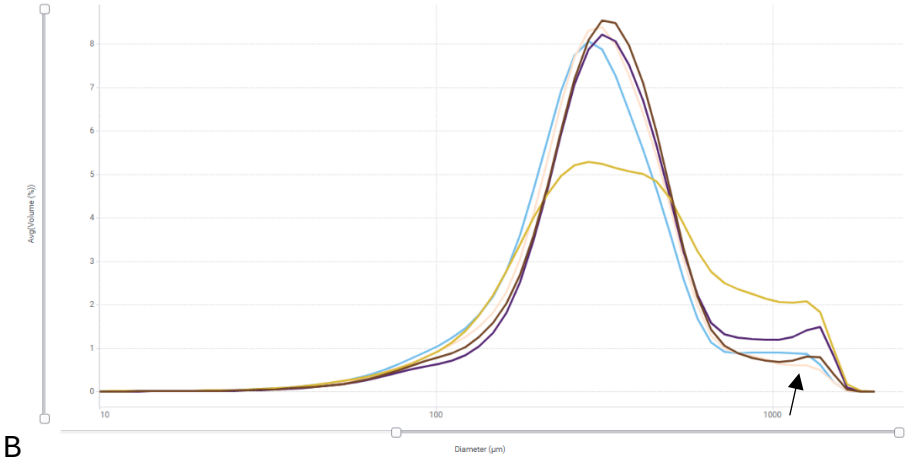
rise slightly sharper. The slower impeller speed also resulted in a little wider PSD (Span 2.4).

Table 4. Granule size distribution D10, D50 and D90 values determined by laser diffraction.

Batch	D10 (µm)	D50 (µm)	D90 (µm)	Span
M40LS	265	509	1287	2.01
M40LF	195	417	946	1.80
M40HS	531	885	1388	0.97
M40HF	452	826	1369	1.11
M30IS	150	358	1006	2.39
M30IF	157	317	583	1.34
M30I0C	168	333	608	1.32
M30I0B	180	343	784	1.76
M30I0A	145	303	596	1.49
M20LS	56	117	640	4.97
M20LF	56	117	556	4.28
M20HS	215	429	985	1.79
M20HF	143	337	740	1.77
FURM20L	82	173	753	3.89
FURM20H	302	598	1230	1.55



A



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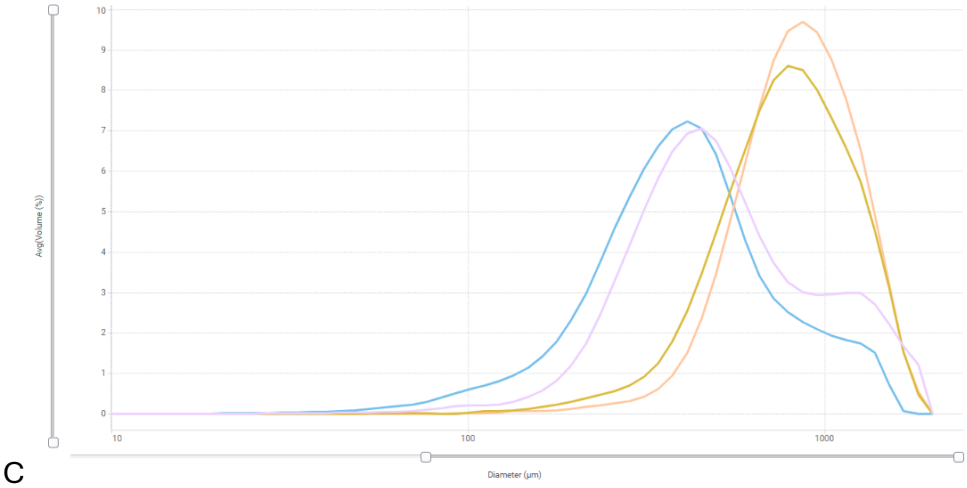
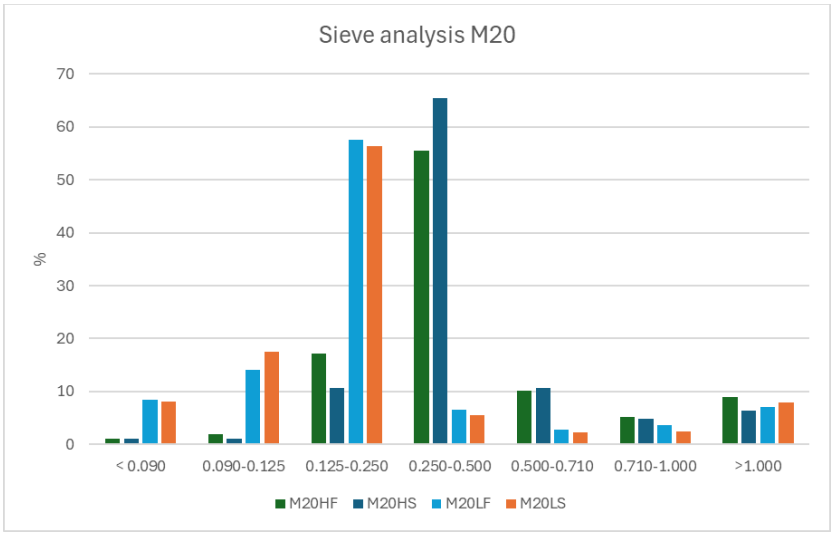
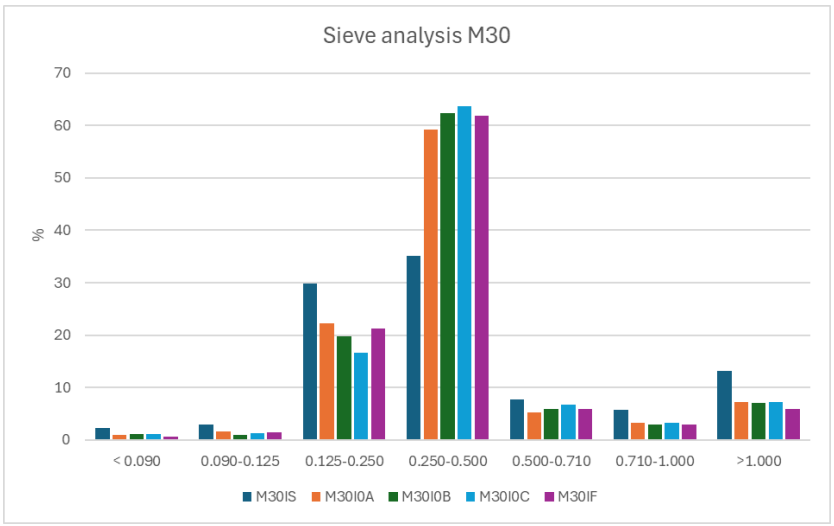


C

Figure 8. Particle size distribution of different formulations determined by laser powder diffraction. A (M20): green M20HS (green), M20HF (red), M20LF & M20LS (pale lines) B (M30): M30IS seen as lower peak with broader PSD (yellow), M30 IF is the pale line with lowest step on the large end (arrow). C (M40): M40LF (blue), M40LS (pink), M40HF (dark yellow), M40HS (peach).





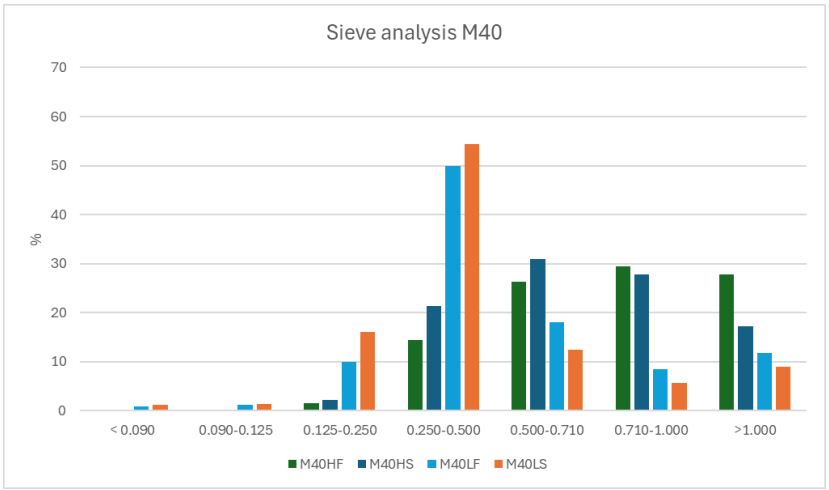


Figure 9. Granule size distribution as determined by sieve analyses.

Data analysis showed that relative amount of LMH:MCC had a significant effect on D10, D50, and D90 values (Table 5 and Figure 10). The effect was less apparent on D90 than on the other values. Higher MCC content also made the granule size distribution narrower. Higher L/S ratio had a narrowing effect on granule size distribution and decreased the portion of smaller granules, with significant effects on D10 and D50. The interaction term of MCC amount and L/S ratio determination point showed a significant effect on span.

The actual L/S ratio corresponding to the variable X2 was different depending on the formulation, so the effect of higher MCC content could have been seen because a higher liquid amount was used in these batches. Therefore, the data was tested also with the actual L/S ratio with X1 and X3. In this model ($p < 0.0001$, $R^2=0.97$), the actual L/S ratio had the most significant effect on D50 ($p < 0.0001$). Both LMH:MCC ($p < 0.01$) and interaction term of (LMH:MCC) * (actual L/S ratio) ($p < 0.05$) also had a significant effect on particle size. Thus, the granule size is affected both by the L/S ratio and the filler ratio as independent variables but also their interaction.

Table 5. Statistically significant effects of variables on particle size. X1 = LMH:MCC ratio, X2 = L/S (point of determination from the MTR curve)

		LDP		SIEVE	
		p	R^2	p	R^2
D10	whole model	< 0.01	0.79	<0.001	0.84
	X1	<0.01		<0.01	
	X2	< 0.01		<0.01	
D50	whole model	< 0.001	0.83	<0.001	0.88
	X1	<0.01		<0.001	
	X2	< 0.01		<0.001	
D90	X1	< 0.05	0.4		none
SPAN	whole model	< 0.001	0.94		
	X1	< 0.001			
	X2	< 0.001			
	X1 * X2	< 0.01			

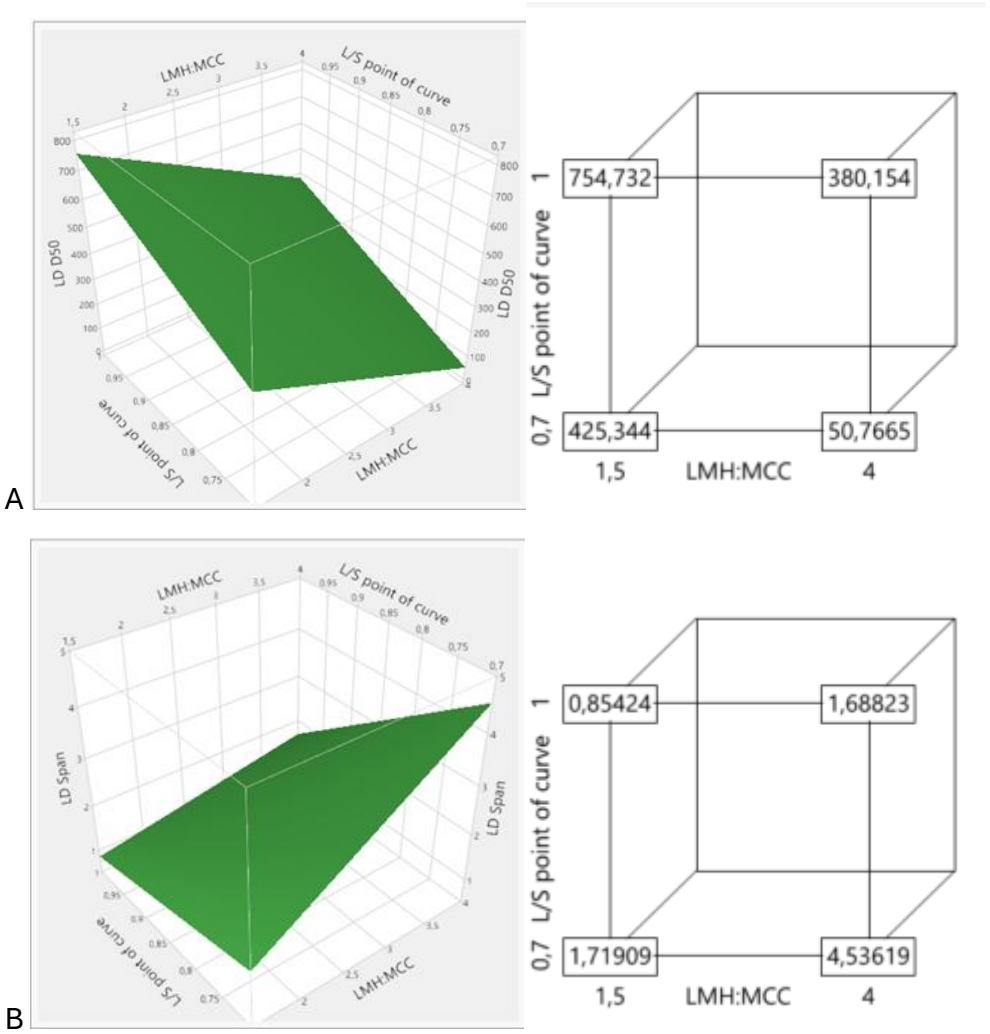


Figure 10. Surface profiles and cube plots of D50 (A) and span (B).

Varying impeller speed had some effect on particle size, but it was not statistically significant (Figure 7B). Mean granule size remained between 300-400 µm regardless of the impeller speed. However, it can be observed from the PSD curves that with higher impeller speed the particle size distribution becomes narrower, especially decreasing the fraction of the large granules.

3.4 Granule flowability

For most granules, the flowability index was 4 +/- 2 or under. The result was 5 +/- 2 in M40 formulations with a higher L/S ratio, and 6 +/- in M30 formulation done with slower impeller speed. Thus, the flow was sufficient in all placebo batches, and the differences between batches were insignificant.

3.5 Granule morphology

The differences in granule sizes that were discussed in previous section can also be clearly seen in SEM images. In the batches with the lowest liquid amount, there is clearly some ungranulated material (Figure 11), which is less frequent as MCC content or liquid amount increases, and is completely absent in M40H batches. In the granules with more LMH, the individual powder particles are distinguishable on the granule surfaces, and the granules are more edgy and porous. The granules with more MCC, on the other hand, are more spherical and smoother on the surface. With the slowest impeller speed, it can be observed that the granules are of more varying shapes and sizes than those made with higher impeller speeds Figure 12). Yet there are no apparent differences in appearance between the granules made with impeller speed 350 rpm or 500 rpm.

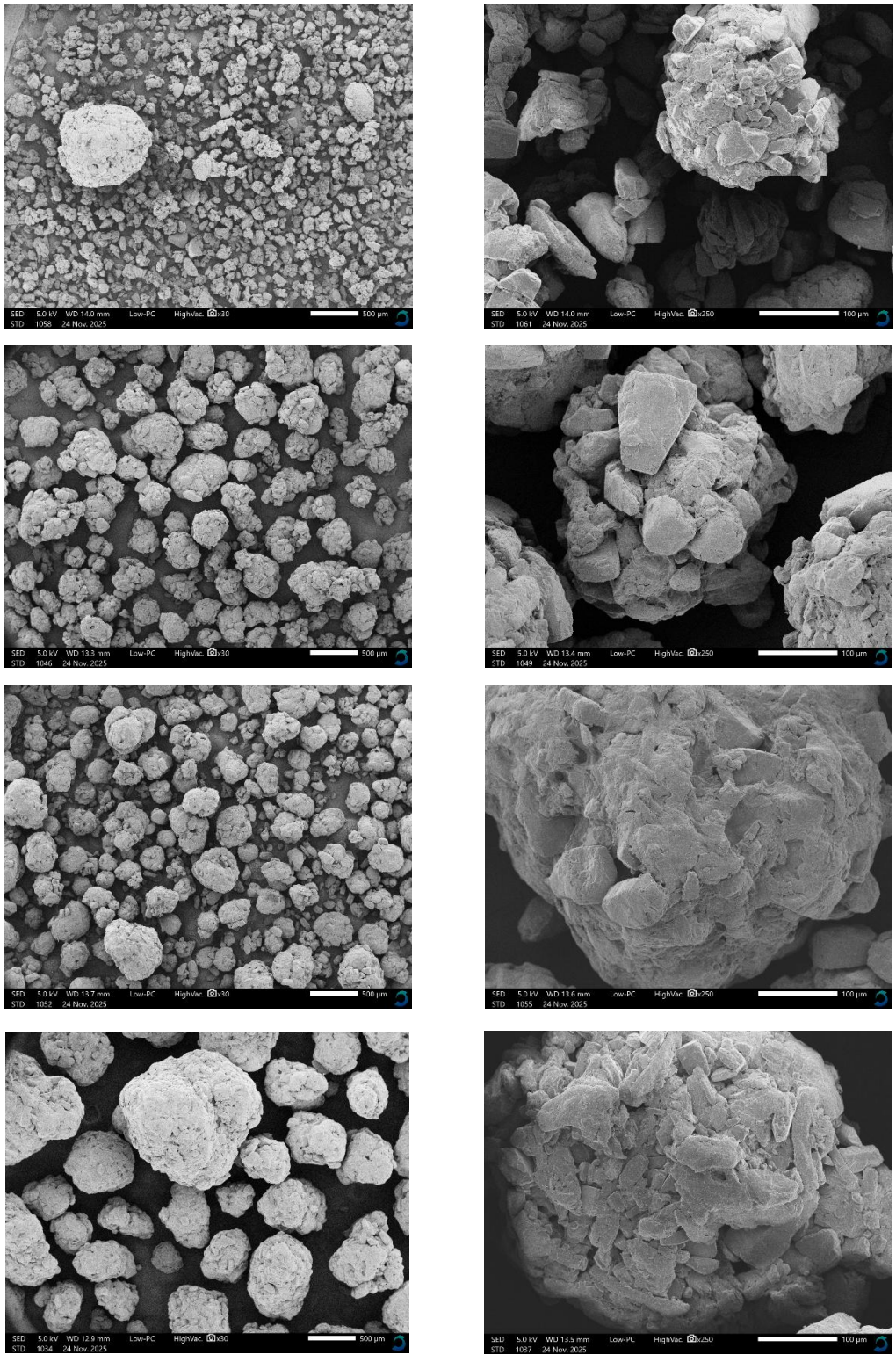


Figure 11. SEM images (top to bottom): M20LS, M20HS, M40LS, M40HS, with 30x magnification on the left and 250x magnification on the right.

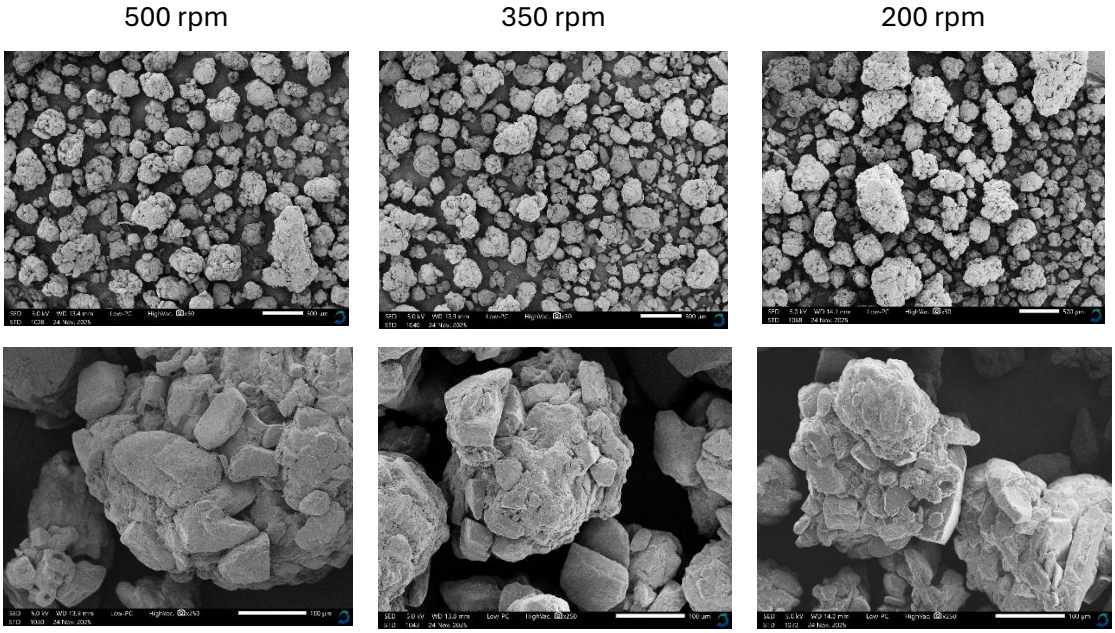


Figure 12. SEM images of center point batches with different impeller speed, with 30x (top) and 250 x (bottom) magnification.

3.6 Compaction properties

All lubricated granule batches were successfully compacted into tablets. However, all the batches with the highest MCC content failed to reach the tensile strength of 1.7 MPa, which can be considered an industry standard minimum (Figure 13). The M40 batches with the slower liquid addition rate (longer granulation time) had the weakest tabletability, although the difference was not statistically significant. MCC content and the interaction term of MCC content and L/S ratio had a significant effect on tensile strength (Table 6 & Figure 14) with higher MCC content decreasing tensile strength, especially with increasing water amount. The tensile strength of tablets compacted with the highest compaction force (300 MPa) in the force study was chosen for modelling, so that to compare the tablets compacted with similar force, and the differences were clearer with higher force.

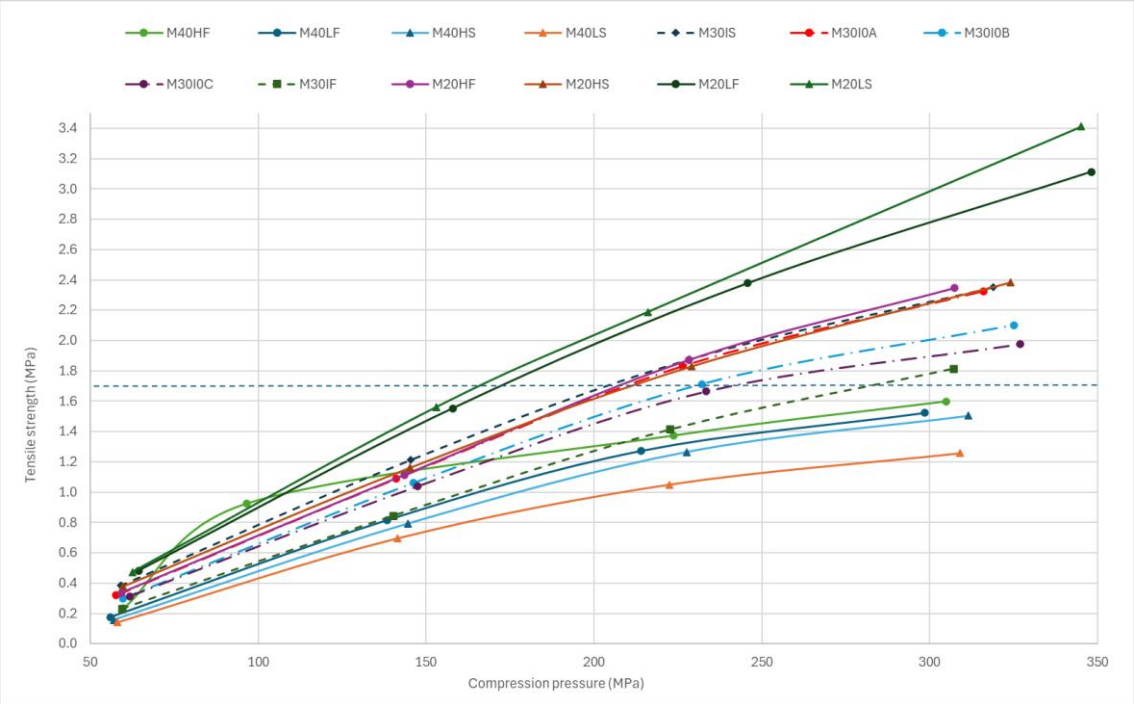


Figure 13. Force study compaction profiles of different batches. The dashed line represents the target minimum tensile strength of 1.7 MPa.

Table 6. Statistical significance of variables on tensile strength at compression pressure 300 MPa. X1 = LMH:MCC ratio, X2 = L/S (point of determination from the MTR curve)

	p
whole model, $R^2 = 0.91$	< 0.001
X1	< 0.001
X1*X2	< 0.01
X2	0.08

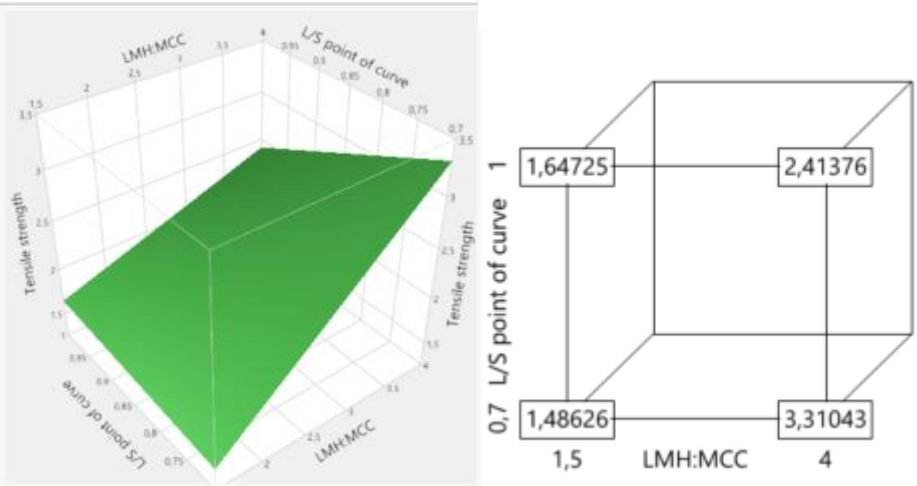


Figure 14. Surface profile and cube plot for tensile strength.

In center point repetitions, the compaction pressure required to reach the target tensile strength increased with increasing impeller speed. Between these batches a statistically significant effect of impeller speed on tensile strength could be observed ($p < 0.05$, R^2=0.81) only when comparing tensile strength at compaction pressure around 230 MPa but not at 300 MPa.

3.7 Disintegration time

Average disintegration time varied from 1.1 min to 18.5 min between batches (Figure 15). The fastest disintegrating tablets were the ones with lower MCC content and lower L/S ratio. Only MCC content had a statistically significant effect on disintegration time ($p < 0.01$, $R^2 = 0.70$). There was a lot of variation in center point disintegration times, and the tested tablets were compressed with different compression forces. Longer disintegration times were clearly connected to higher compression force (Figure 16). Correcting disintegration time dividing it by compression force improved the reliability of the model, and a statistically significant impact of L/S ratio could be observed ($p(\text{model}) < 0.001$, $R^2 = 0.83$; $p(\text{LMH:MCC}) < 0.001$, $p(\text{L/S / compression force}) < 0.05$). Increasing impeller speed appeared to prolong the disintegration time, but the effect was not statistically significant.

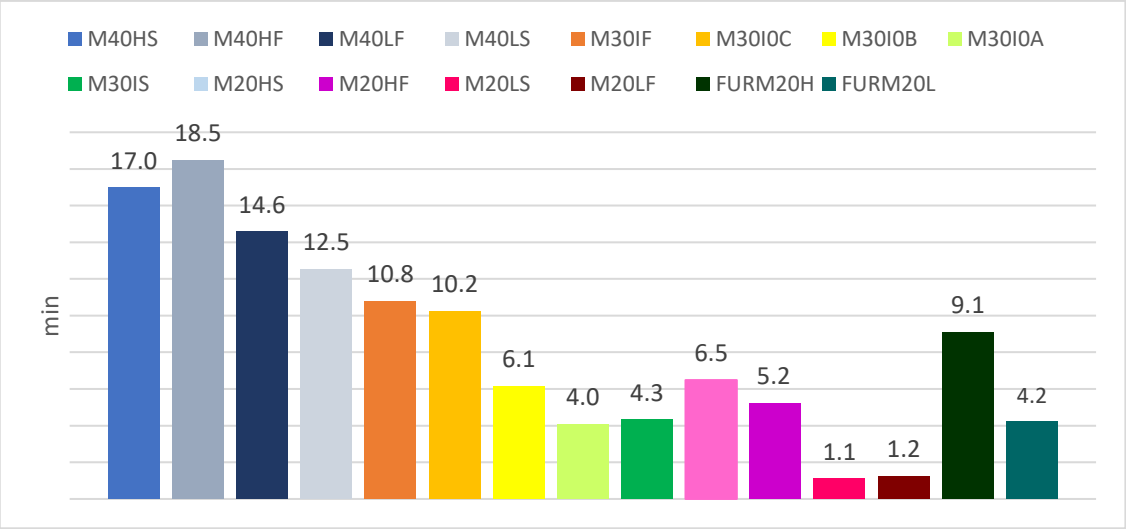


Figure 15. Average disintegration times (min) of tablets (n=6) from each batch.

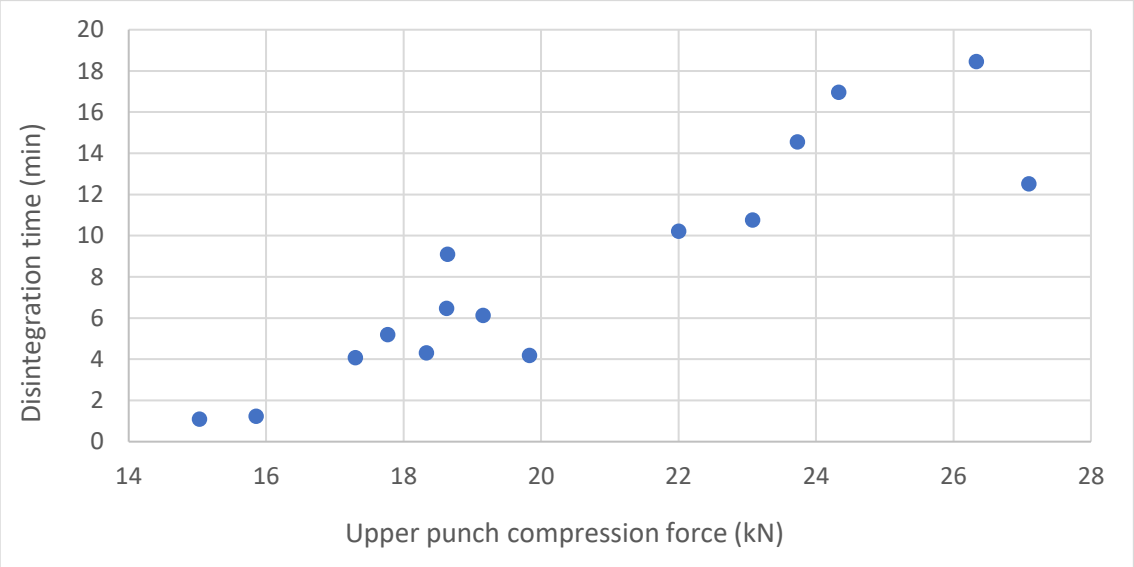


Figure 16. Relationship of disintegration time and the used compression force.

3.8 Other outcome measures

The mass uniformity of all tablets was within the acceptable limits, and there were no tablets outside the acceptable range of +/- 5 % from the mean. Therefore, there was no variability to be observed between batches. Friability was also minimal in all batches (< 0.05 % weight loss).

3.9 Modeling

To get an idea of the overall result of the experimental design, D50, tensile strength and disintegration time were modelled together against independent variables X1 (LMH:MCC) and X2 (L/S determination point). The model cannot be considered statistically reliable, as not all the independent variables had a significant effect on outcomes, as summarized in Table 7. However, it is a way to visualize and guide the decisions during formulation development. The desired for the outcome measures were put into the model and they were 200-550 µm for D50, 2 MPa for tensile strength, and at maximum 15 min for disintegration time. According to the model, the most optimal zone would be at LMH:MCC ≥ 2.5 and L/S ratio at 85-100 % of the infliction point. The contour profile based on this model is presented in Figure 17. Tensile strength is the most limiting outcome measure in increasing MCC content. On the other hand, with a higher LMH amount, too low L/S ratio can lead to ungranulated fines as L/S ratio decreases. The most optimum inputs proposed by the model were X1 = 3.8 (LMH:MCC) and X2 = 0.97 (L/S value 97 % from start of rise of the torque curve to 2nd derivative zero point) , predicting D50 = 355 (CI 200-510) µm, Tensile strength (at 300 MPa compression pressure) 2.4 (CI 2.2-2.7) MPa and disintegration time 5.4 (CI 1.1-9.7) min.

Table 7. Summary of the significance of the factors in the model. The red color marks the factors that are not statistically significant.

	R^2	*p (model)*	*p(X1)*	*p(X2)*	*p(X1*X2)*
Whole model			< 0.0001	< 0.01	< 0.01
D50	0.85	< 0.01	< 0.01	< 0.01	> 0.05
Tensile strength	0.95	< 0.0001	< 0.0001	< 0.01	< 0.01
Disintegration time	0.81	< 0.01	< 0.01	> 0.05	> 0.05

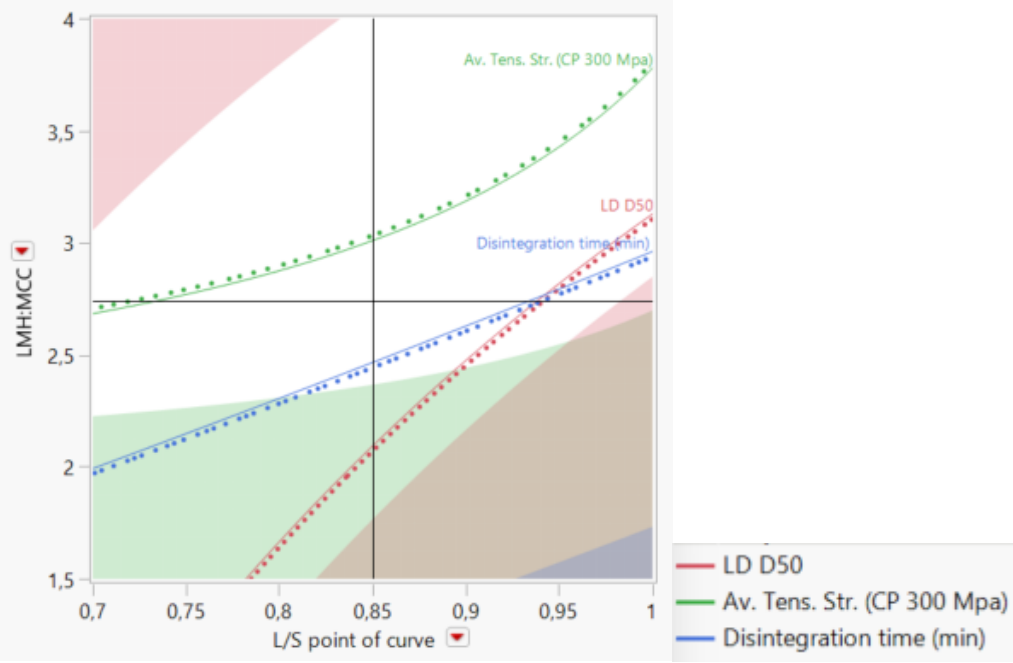


Figure 17. Contour profile based on the combined model, as an example how the experimental data can be utilized in process design. Target area is the white area, and in the shaded areas the outcome values are outside of the targets set at 200-550 µm for D50, at minimum 2 MPa for tensile strength, and at maximum 15 min for disintegration time. The dotted lines give a sense of direction as the dots are in the direction of higher response values.

3.10 Validation experiments with furosemide

Based on the results of the placebo experiments, formulations with relative MCC amount of 20 % seemed to provide the best compaction properties and disintegration. Therefore, this was chosen as a basis for the API experiments. The MTR curves of blends containing 7.5 % furosemide vs. placebo were quite similar, although an earlier and steeper rise could be observed on the curve with API (Figure 18). Two different liquid amounts were chosen for granulation experiments to assess the suitability of criteria for determination of the L/S ratio based on MTR. As the lower liquid amount resulted in a lot of ungranulated powder in the placebo experiments, the lower value was chosen slightly higher – at 80 % torque from start of rise to the infliction point. Thus, the final L/S ratios in furosemide batches were 0.38 (FURM20H) and 0.30 (FURM20L). As liquid addition rate did not have much effect on the critical outcomes, the center point liquid addition rate was chosen.

Furosemide experiments were performed before the final statistical analysis of the DoE data was completed, so their design was not based on the final modeling.

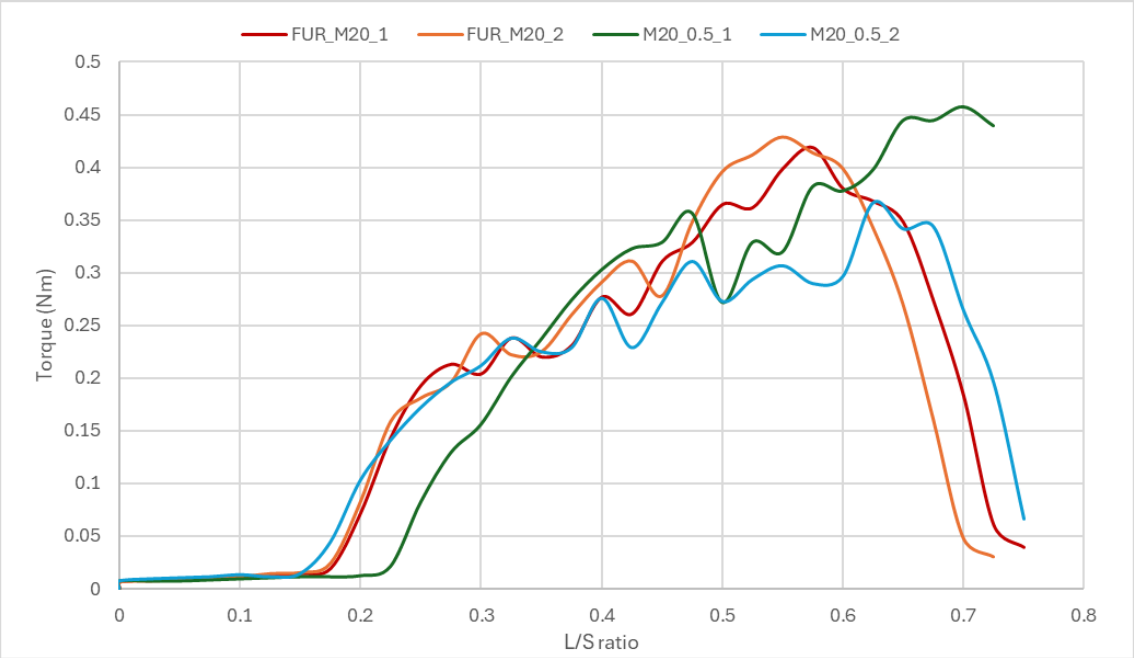


Figure 18. MTR curves of 7.5 % furosemide formulation (red and orange) and placebo (blue and green) with similar filler ratio (M20). Both runs are presented for each formulation.

During granulations, there was clearly more lump formation with furosemide than there was in placebo batches, which was also indicated by clearly lower yields (mean yield 77 % and 61 %, for placebo M20 and furosemide respectively). Furosemide granules were bigger than placebo granules, and there were more of the granules in the larger fractions and less in fines (Figures 19 & 20 and Table 4). The granule size was higher with higher L/S ratio also in furosemide batches. As in placebo formulations, the granule size distribution of the batch with lower liquid amount was wide (span = 3.9). Based on SEM imaging, presence of furosemide did not seemingly affect the appearance and shape of the granules, but the wider granule size distribution and large granules could be observed (Figure 21). As there was little difference in flowability of placebo granules, the flowability analysis was not performed on the furosemide granules.

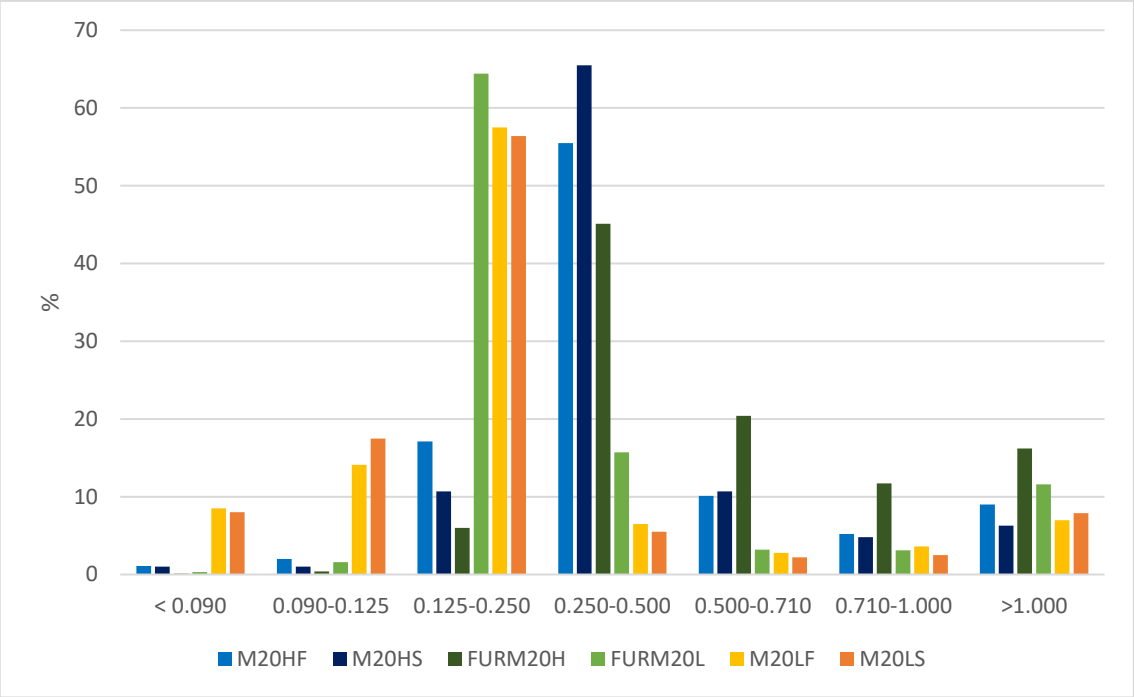


Figure 19. Granule size distribution based on sieve analysis of furosemide-containing granules, compared with placebo granules with the same LMH : MCC ratio.

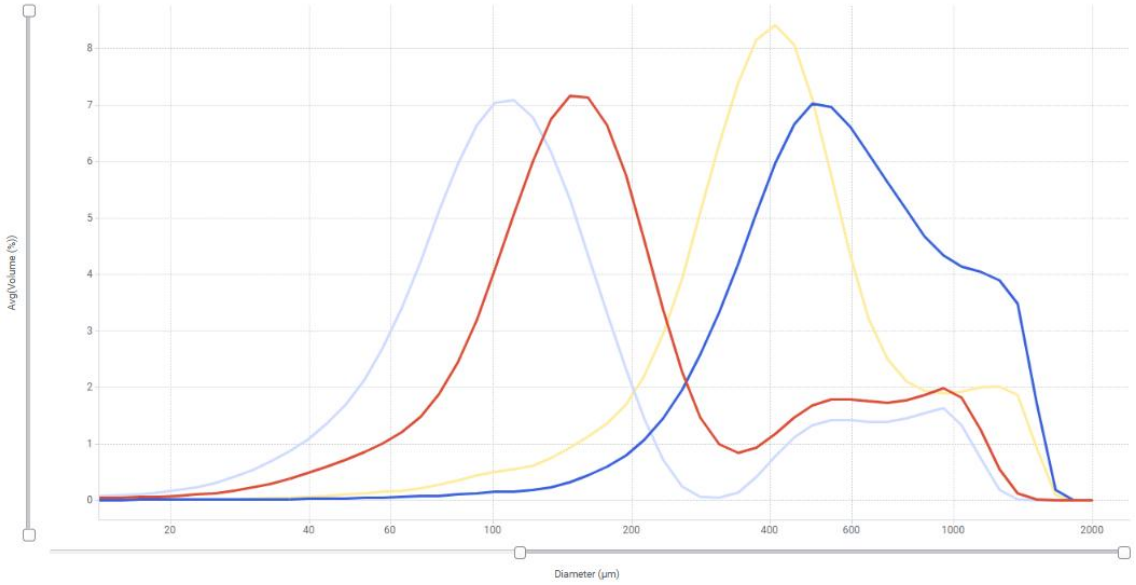


Figure 20. PSD from lased diffraction of furosemide (blue (H) and orange(L)) and placebo (yellow (H) and light blue(L)) granules.

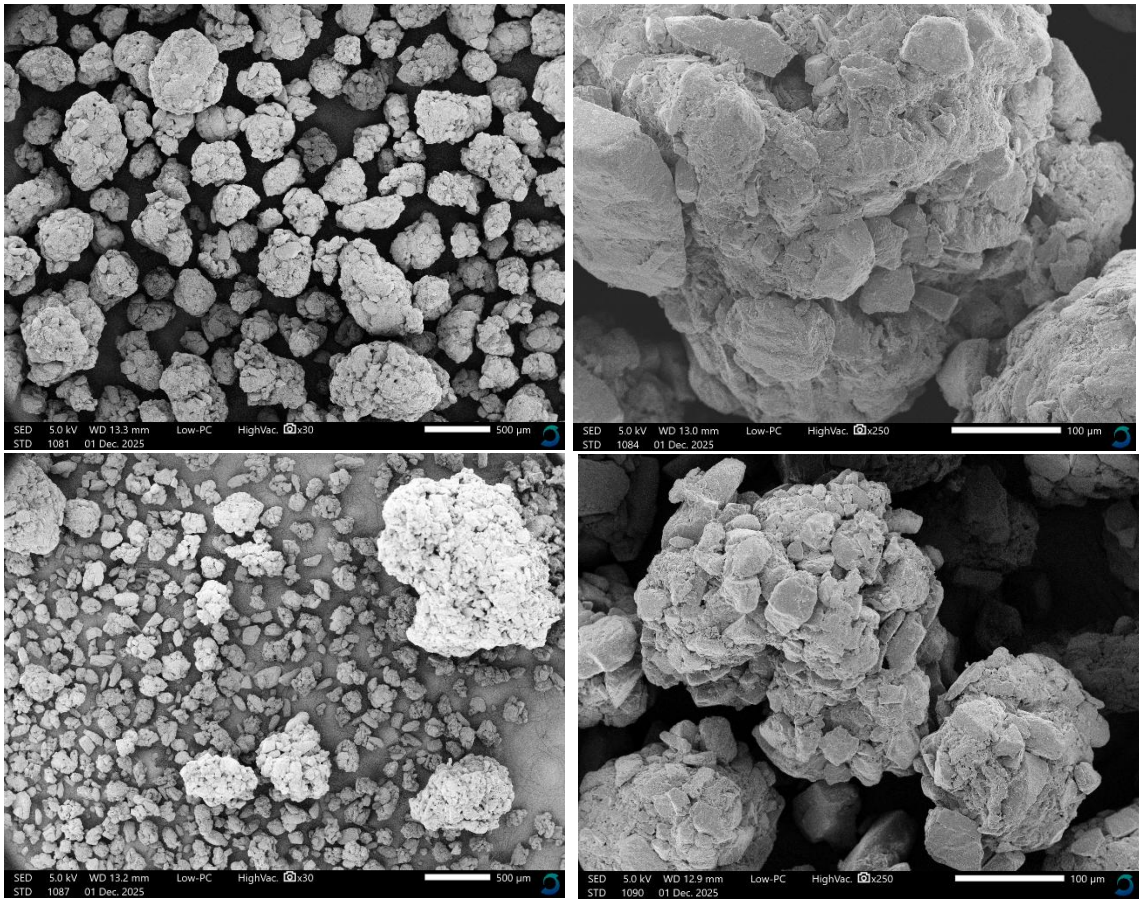


Figure 21. SEM images of furosemide granules with high (upper images) and low (lower images) L/S ratio taken with 30 x and 250 x magnifications.

Tablets produced from both furosemide granule batches were acceptable by their physical attributes. Both batches were compressed with 19 kN compression force (230 MPa compression pressure), and the final tensile strength was around 1.9 MPa. Compaction profiles of furosemide granules did not differ much depending on L/S ratio and were close to the profiles of M20H placebo granules (Figure 22). Disintegration times of furosemide tablets were higher than those of placebo, yet still within acceptable limits (Figure 15). Friability and mass variation were within limits as well.

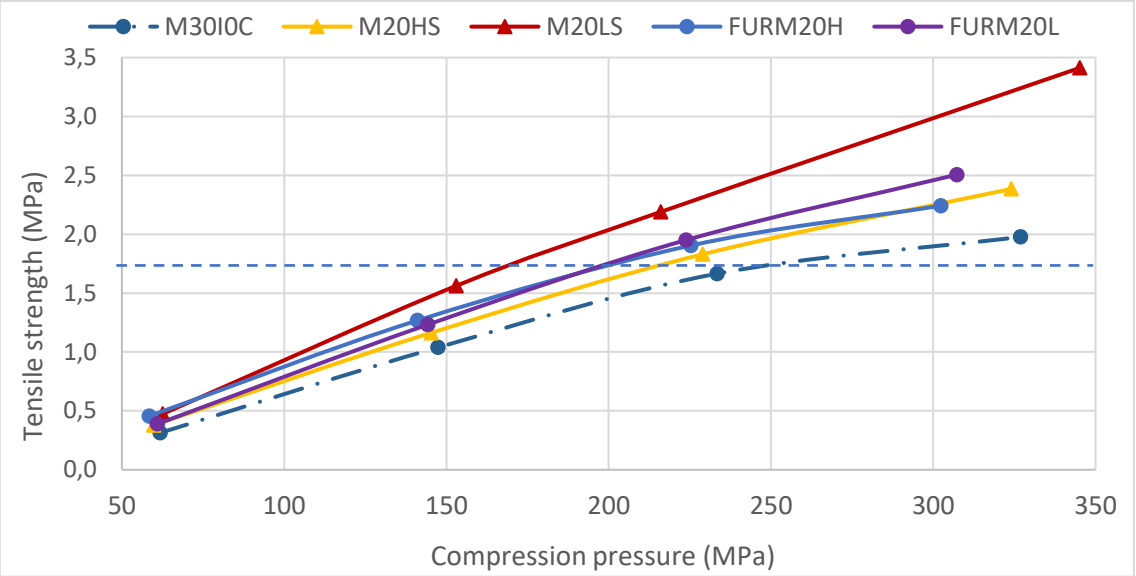


Figure 22. Compaction profiles of furosemide granules (blue and purple) compared to some of the placebo batches. The dashed line represents the desired minimum tensile strength of 1.7 MPa.

In chemical analysis, the content uniformity of both batches was within the acceptable limits (acceptance value, AV ≤ 15), although, in the tablets from the batch with lower L/S ratio, there was a bit more variation, with mean API content a bit higher than the target (Table 8). In the dissolution test, the API was released with a successful rate from both tablets, although the one with lower liquid amount dissolved faster (Figure 23). However, these tablets also disintegrated faster, which can explain much of the difference.

Table 8. Uniformity of content of furosemide tablets. * The values are calculated based on weight-corrected content.

	FURM20H	FURM20L
Mean tablet weight (mg)	403.6	411.3
% of label claim (30 mg)*		
mean	100.8	106.3
min	99.6	105.0
max	102.0	108.3
SD	0.80	0.94
AV	0.69	7.11

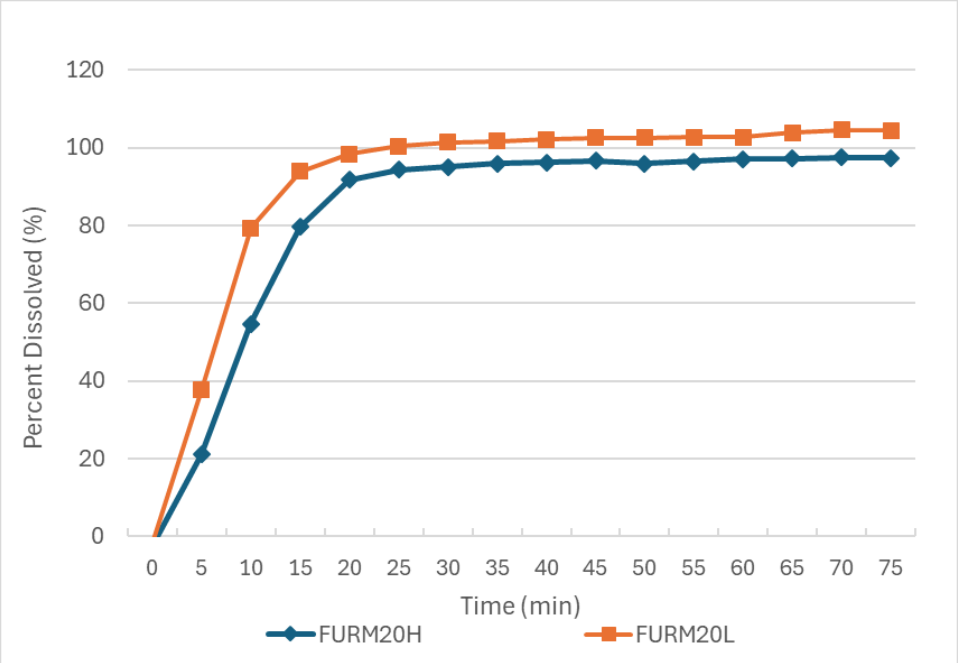


Figure 22. Average dissolution of furosemide tablets, n = 6 for each batch. USP II paddle apparatus, 500 ml of phosphate buffer (pH 5.8) 50 rpm.

4 DISCUSSION

In general, the results of this study reinforce the idea that MTR experiments are useful in guiding towards the right liquid amount for wet granulation. Increasing

amount of MCC led to higher maximum torque values and required higher liquid amount to reach it, as expected based on previous studies (Chitu et al., 2011; Mertsalmi, 2025). The shapes of the curves varied with formulation and liquid addition rate. Although some sort of “shoulder” could be distinguished from nearly all the curves, it is not very exact way to determine infliction point (Annex). 2nd derivative of the curve helps to observe the points where the rise of the torque curve accelerates or slows down. Therefore, using the 2nd derivative helps to study the torque curve more precisely. It should be noted that there can be several points where the 2nd derivative turns from positive to negative, and the 2nd derivative curve should be examined together with the torque curve, when determining the optimal L/S ratio.

The slower addition rate affected strongly the shape of the curve and gave generally higher L/S ratio values. This highlights the importance of specifying the liquid addition rate used in MTR, when comparing results of different experiments or developing a process. In this study the MTR results with lower amount of MCC and 1.0 ml addition, L/S ratio would have been 0.26, which based on the granulation done, seems quite low. There are also very few measurements before the peak is reached in a blend with high amounts of water-soluble components. Therefore, a faster addition rate might be less reliable, at least in a formulation with a high content of water-soluble ingredients. For the M40 formulation, L/S ratio would have been 0.46 with 1.0 ml addition. It is not possible to say, based on this study, whether this would have been appropriate, as it is lower than the range used in these experiments.

The particle size of the granules varied considerably between different batches. The granule size was clearly larger with higher MCC content and higher L/S ratio. The effect of MCC content on granule size is partly inconsistent with other studies, as granule size has also been reported to be larger with more brittle excipients (Chitu et al., 2011; Osei-Yeboah et al., 2014; Wang et al., 2023). This may be due to

differences in other process or formulation parameters or the experimental setting. There are no definite limits for granule particle size, as long as there is sufficient flow and not too much segregation, and the mass and content uniformity are adequate. In the lower end, the particle size very close to the particle size of starting material means that there are ungranulated fines, of which some were seen in M20L batches. In plastically deforming granules, large granule size can be one of the reasons for decreased tabletability, as there is less bonding area between the particles (Osei-Yeboah et al., 2014). This could have been part of the problem with tabletability of M40 batches.

Both batches with API fulfilled the requirements for the content uniformity, but there was more variability, and the mean API content was higher than the target in the ones with lower L/S ratio. This batch had also wider granule size distribution, suggesting the distribution of API could have been somewhat uneven between different size fractions of the granules.

In this study, there were no significant differences in flowability or tablet mass variation, indicating that variations in granule size distribution did not affect die filling. Good flow in all batches was not surprising, as enhancing flow properties is one of the main reasons for granulation. It should be noted that the uniformity of mass can vary depending on the tableting equipment and process. Here the tableting was done at a moderate speed, but in a rotational tablet machine with high speed, the problems with filling could have become detectable.

High amount of MCC led to loss in the tabletability of the granules, as they failed to reach required tensile strength. This is consistent with previous studies, as it has been shown that granules with similar composition can lose their tabletability at relative MCC amount of ≥ 40 % and when the L/S ratio exceeds 0.30 ml/g (Osei-Yeboah et al., 2014). When MCC amount is kept at maximum of 20 % and it is combined with a brittle filler, the risk of overgranulation is lower. The tensile

strengths of tablets in all M40 tablet batches were similarly poor, and they were compressed with same force. The mean disintegration time was over 15 min only in M40 batches with higher water amount, indicating that these were perhaps the densest of the granules. Disintegration time varied a lot depending on the compaction force used. Using the same compaction force on all formulations could have shown the effect of studied parameters more clearly. Here, adjusting the compaction force for every batch was done to get the tablets with as similar tensile strengths as possible.

Liquid addition rate did not have statistically significant effect on any of the outcome measures. Slower liquid addition prolongs granulation time, which could have resulted in differences in the final granules. The shape of the water spray from the nozzle also changed with different liquid addition rates, which could have affected the water distribution and shape of the granules. The range of liquid addition rates included in this experimental design might have been too small to be able to detect the differences. It is interesting that liquid addition rate in MTR did, on the other hand, make a clear difference. This could be explained by the fact that in MTR the mixing happens with low shear forces compared to HSWG, where effective mixing compensates for the differences in liquid addition. In MTR also the total wet mixing time increases even more, as there are mixing periods between each addition, which can cause the differences between torque curves. It is possible that effects of varying liquid addition rate could have been more detectable with other formulation composition. For this kind of formulation and process, these results suggest that liquid addition rate can be quite freely adjusted based on total liquid amount and keeping the granulation time reasonable.

The effect of impeller speed was investigated just at the center point, and as there were only a few repeats and some deviation between results, there were little effects that were statistically significant. However, trends such as wider granule size distribution, poorer flow, better tabletability and faster disintegration could be

seen with lower impeller speed. With the higher impeller speed, the tabletability was quite poor, and high compression pressure was required to reach sufficient tensile strength. Higher impeller speed helps to distribute the liquid more evenly, reducing formation of over-wetted lumps, and it adds the collision of the particles, increasing granule density (Benali et al., 2009). The effect of the impeller speed can, however, vary depending on formulation. With more brittle ingredients, such as lactose or brittle API, or less or different binder there can be more breaking than densification (Iveson et al., 2001). Impeller speed is considered a critical process parameter in HSWG, and it would be important to optimize it with further experiments (Thapa et al., 2019; Liu et al., 2022).

There was only one type of formulation studied, which was a deliberate exclusion, to have the focus on the LMH:MCC ratio and to keep the number of experiments realistic. Using another type, or different amount of binder, or different APIs, the MTR results and their interpretation can be entirely different. The number of experiments was quite small regarding statistical significance of the data. In retrospect, some of the variables, such as L/S ratio, could also have been defined differently and more clearly, so that they would be better suited for statistical analysis. The DoE could have been performed with a different design, such as Box Behnken or central composite design, which could have provided better data for modeling.

There was some room for bias in interpreting MTR results, as the L/S values were determined from the torque curve by hand. The determination was also done in a quite complicated way, through first determining the infliction point, then desired torque and then the L/S ratio. Using a simpler way to determine the L/S ratio could work as well, although the values obtained are slightly different. For example, using 70 % of the L/S ratio (instead of torque) from start of rise to infliction point would have given L/S ratio 0.30 in M20 placebo formulation, and 0.46 in M40 formulation as the lower value. In retrospect, one could presume that these would have

provided different results in the experiments. More straightforward or more clearly defined interpretation of MTR results could be better in practice in the future.

5 CONCLUSIONS

The experiments have shown that MTR interpretation can vary depending on many factors. Therefore, if MTR is used, parameters for the MTR procedure and interpretation of the results should be clearly defined, if the results of different experiments were to be compared. Based on this study, in a formulation with used composition, around 20 % MCC content, and the L/S ratio corresponding to 90 % to 100 % of the torque from start of rise to infliction point, should be a good basis for formulation for HSWG and tableting. The study has been valuable in showing the translation of the choice of the liquid amount based on MTR, into tablet attributes. If just granule size distribution, shape and flow had been studied, the important differences, such as in tabletability, between the batches would not have been detected. The experiments with API have shown that the optimal L/S ratio zone can be quite narrow, with broader granule size distribution and risk of segregation on one end and prolonged disintegration time on the other. The results of this study can be useful when planning a formulation with moderate API load that is planned to be wet granulated, if the API is compatible with the used excipients. This can reduce the number of experiments during formulation development, although there are still many parameters that might be necessary to adjust, depending on API properties or target product profile. It would then be interesting to see next, how these parameters would work in a formulation with, for example, different APIs, API load, or another brittle filler instead of LMH. As the differences that some of these factors show in MTR have already been studied in another Master's thesis (Mertsalmi, 2025), combining the information provided by these two studies could be the next step. As scale up is a critical step in HSWG, another interesting question would be if the established parameters would work in bigger scale. Ideally, if

experiments with other formulations would support these results, more precise general guidelines for interpreting the MTR curve could be developed.

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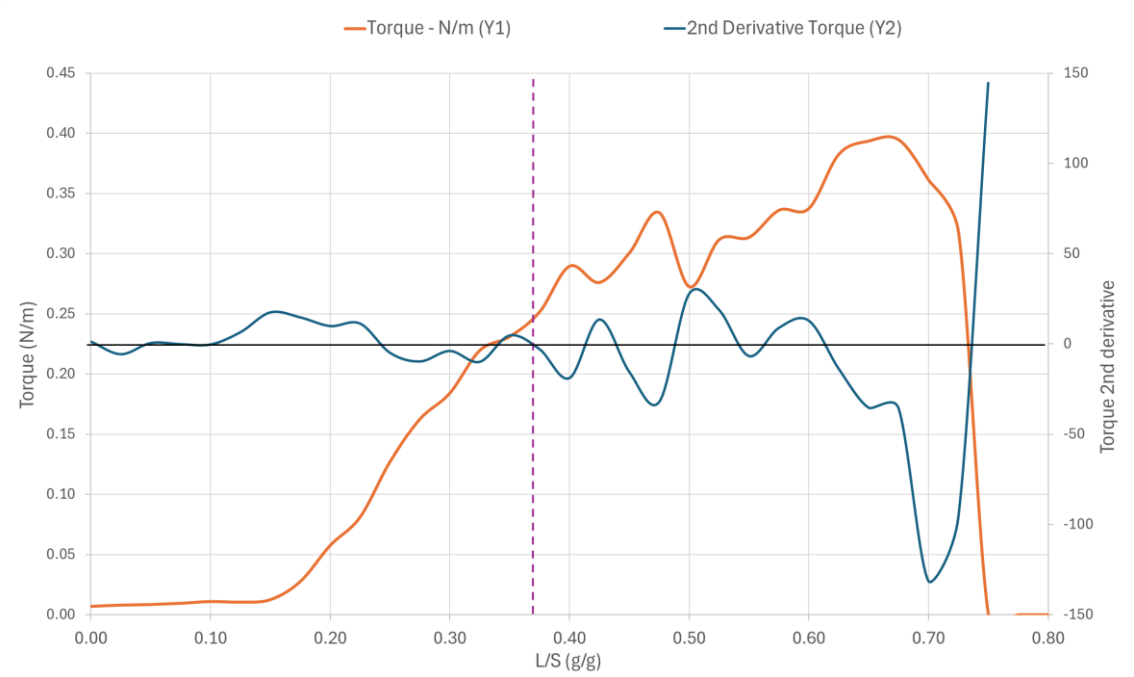
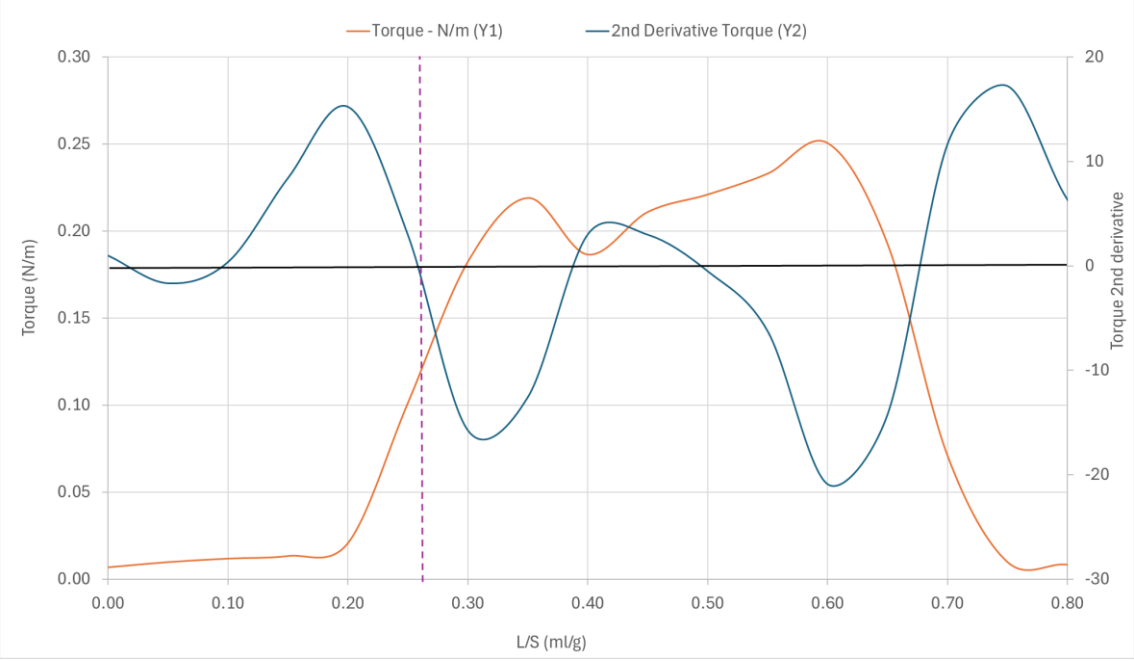
8 ANNEX

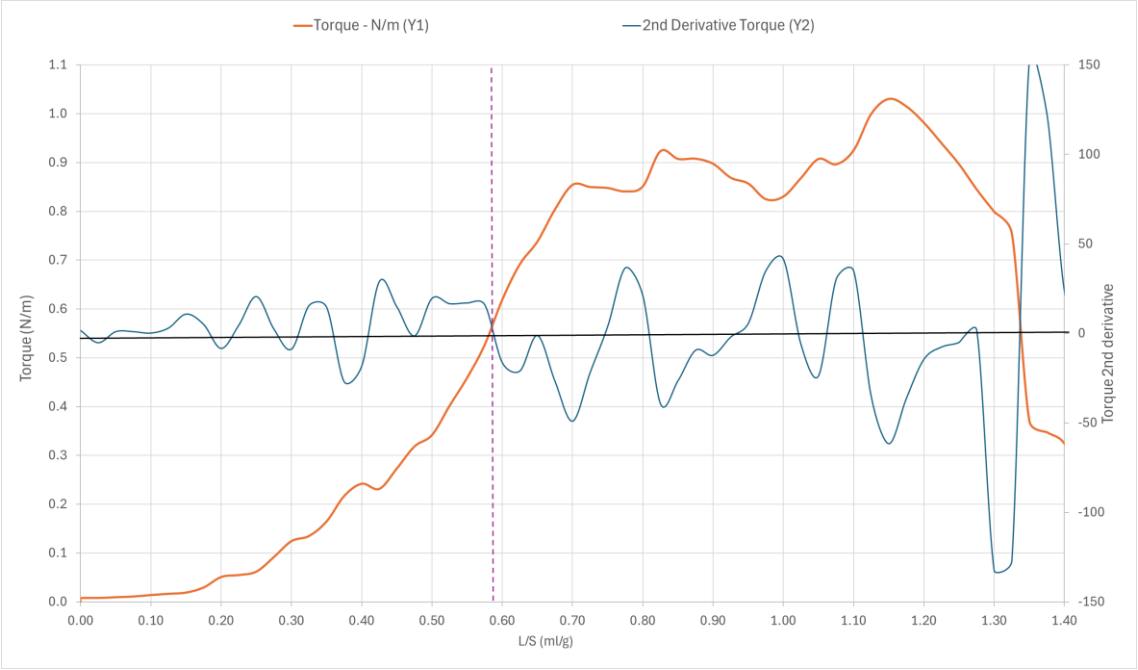
MTR mean torque curves with 2nd derivative curves and the 2nd derivative zero point (purple line)



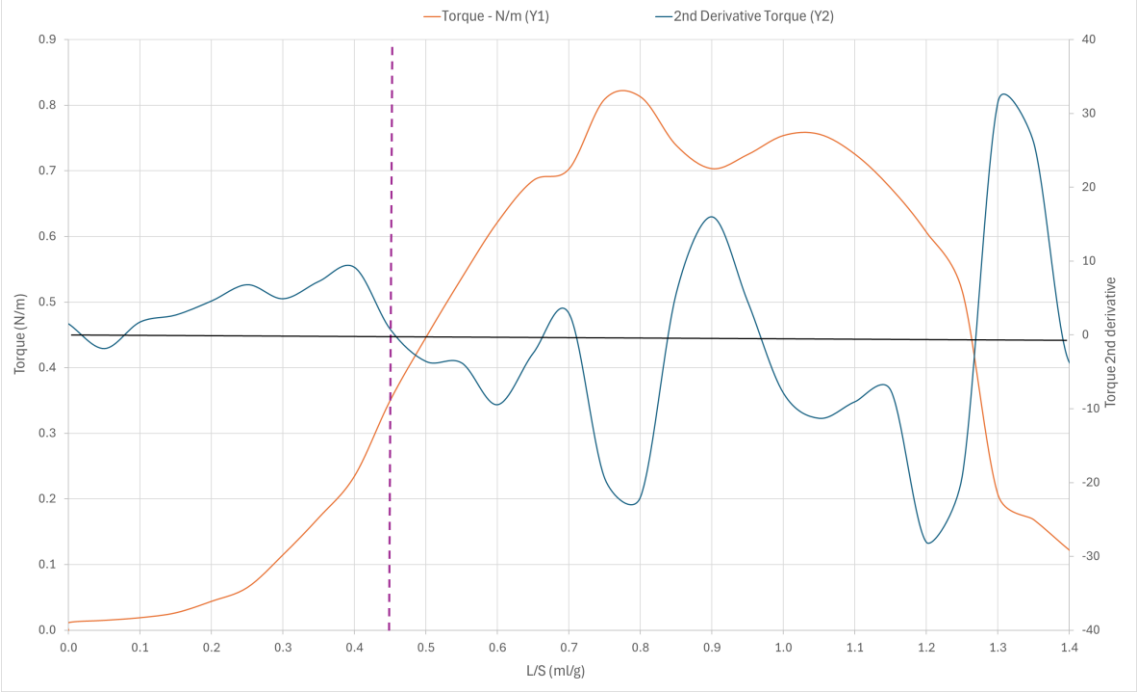
A) M20 0.5 ml per addition



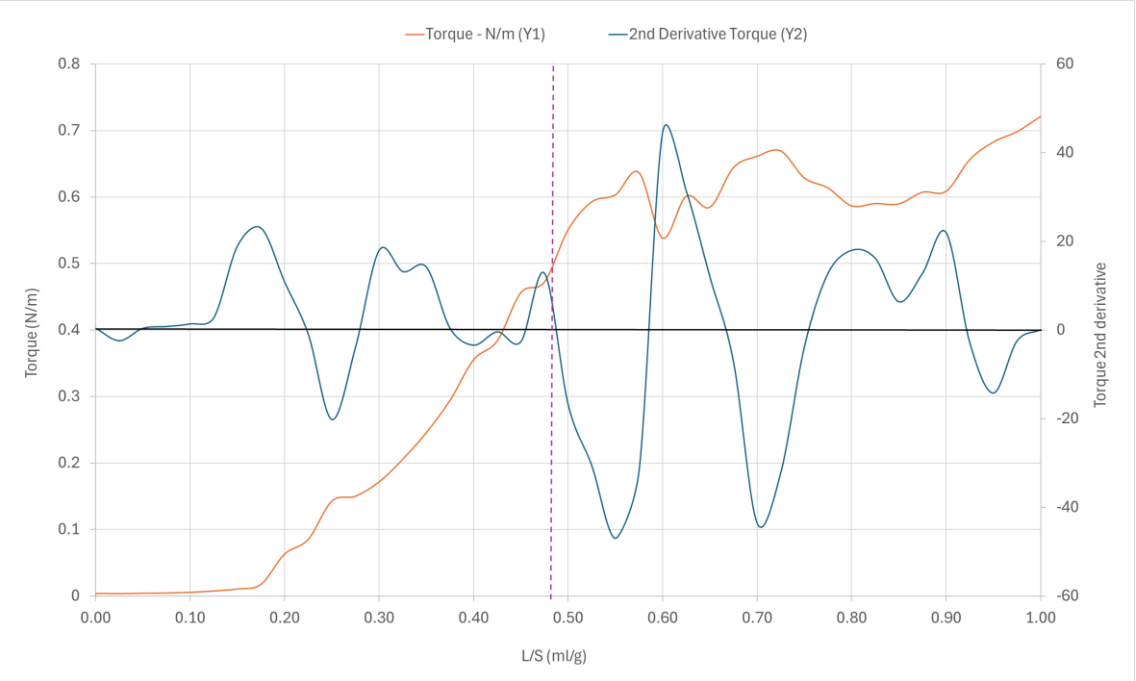
B) M20 1.0 ml per addition



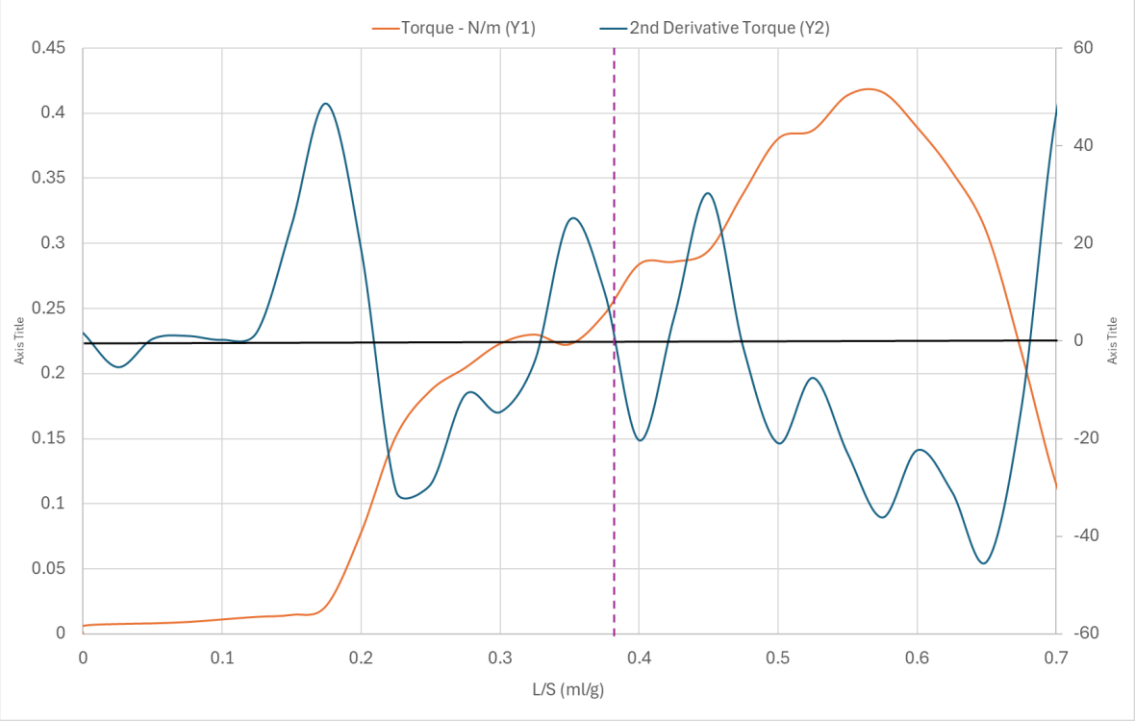
C) M40 0.5 ml per addition



D) M40 1.0 ml per addition



E) M30 0.5 ml per addition



F) FURM20 0.5 ml per addition