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Modelling the effect of L/S ratio and granule moisture content on the compaction properties in continuous manufacturing

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ABSTRACT

The pharmaceutical field is currently moving towards continuous manufacturing pursuing reduced waste, consistency, and automation. During continuous manufacturing, it is important to understand how both operating conditions and material properties throughout the process affect the final properties of the product to optimise and control production. In this study of a continuous wet granulation line, the liquid to solid ratio (L/S) and drying times were varied to investigate the effect of the final granule moisture content and the liquid to solid ratio on the properties of the granules during tabletting and the final tensile strength of the tablets. Both variables (L/S and granule moisture) affected the tablet tensile strength with the moisture content having a larger impact. Further analysis using a compaction model, showed that the compactability of the granules was largely unaffected by both L/S and moisture content while the compressibility was influenced by these variables, leading to a difference in the final tablet strength and porosity. The granule porosity was linked to the L/S ratio and used instead for the model fitting. The effect of moisture content and granule porosity was added to the model using a 3d plane relationship between the compressibility constant, the moisture content and porosity of the granules. The tablet tensile strength model, considering the effect of moisture and granule porosity, performed well averaging a root mean squared error across the different conditions of 0.17 MPa.

1. Introduction

As the pharmaceutical industry moves more manufacturing processes from batch to continuous it is important to understand the interplay between the operating conditions across the different unit operations of the process. When a continuous manufacturing process is used, the impact of varying parameters in the units composing the process, such as granulation, drying and tabletting, on the properties of the material during manufacturing and the final product needs to be understood. This understanding should be translated into models which are able to predict the final product properties for different conditions. These models can be used both to reduce the amount of experimental work to optimise the conditions and to design and implement control loops to improve the final product consistency and reduce waste and maximising these advantages of continuous manufacturing (Su et al., 2019).

The Consigma-25 used in this study is composed of 5 main operations: twin screw wet granulation, fluidised bed drying, milling, blending, and tabletting. The Consigma-25 line was chosen due to its integration of both wet granulation and tabletting in a continuous environment and its relative widespread adoption in industry. This study focuses on the effect of the L/S ratio during granulation and the moisture content of the granules after drying on the properties of the granules in the tabletting process and the effect on the final strength of the tablets. The moisture content of the granules was varied by changing the drying time while all other parameters in the dryer were left constant. The L/S ratio was selected as it is the main parameter affecting the granulation step and can be easily controlled by varying the liquid flow while the moisture content was selected as it's a property of the granule that is measured during the process making it a good candidate to be used when implementing control systems that aim to decrease the variability in the final product properties. The moisture content was selected instead of the drying time due to the fact that the time and other drying parameters are usually tailored to achieve a specific moisture target and are affected by other parameters (e.g. L/S ratio, throughput) making the understanding of the impact of moisture content more widely applicable in the field.

The effect of the L/S ratio on granule properties in twin screw granulation has been widely reported in literature in the past few years indicating that in general, an increase in L/S ratio leads to larger and denser granules (Seem et al., 2015; El Hagrasy et al., 2013; Kumar et al., 2014; Lute et al., 2016). Fewer papers have looked at the direct effect of

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the L/S ratio on the tensile strength of the tablets with findings indicating that it is formulation dependant (Gabbott et al., 2016; Megarry et al., 2020). For a similar formulation to this study, it was found that an increase in L/S ratio produced stronger tablets after compression (Megarry et al., 2020).

Other studies (Matsunami et al., 2020; Liu et al., 2019) looked at the impact of various parameters during granulation on both granule and tablet properties. These studies focused on using statistical modelling to locate the ideal operating ranges for the process and focused on the final tablet properties without further analysing the compaction behaviour leading to those properties.

The effect of moisture content on tabletting has been described in the literature both for powders and granules (García Mir et al., 2011; Thapa et al., 2017; Nokhodchi et al., 1995; Sun, 2008; Wade et al., 2013). Usually, an increase in moisture content in the material produced stronger and denser tablet until a threshold moisture where the material becomes too wet, and the final tablets start losing strength. The effect has been mostly studied experimentally and has not been implemented in tabletting models.

Most tabletting models describe the behaviour of the material under compression using two attributes, namely, compressibility and compactability (Wang et al., 2021). Compressibility is the relationship between the applied compaction pressure and the final porosity of the tablet while compactability is the description of the effect of the porosity of the tablet on the tensile strength. The Reynolds (Reynolds et al., 2017) model was selected due to its good performance and simplicity compared to similarly well performing models (Wang et al., 2021).

Overall, although the compression behaviour of materials and how it is impacted by other parameters have both been reported in literature, the combination of both and its implementation in a more mechanistic model has not. Combining and modelling this behaviour could prove beneficial both during the design process and during manufacturing.

This study focuses on to how the L/S ratio and moisture content of the granules affect the final tensile of the tablets by looking at their effect on both the compressibility and compactability of the granules and to implement the effect on to a compaction model to account for changes in conditions before or during manufacturing.

The understanding of the impact of both parameters and the ability to predict the final tablet properties given the parameters used and variables measured during the production process, could lead to a decrease in experimental runs during development and the implementation of control methods able to maintain the tablet properties constant, even when variability is present in the process. To achieve this, the study focuses on generalising the model using relationships between modelling parameters and experimental parameters and findings, allowing it to predict across the range of conditions and therefore making it a more useful tool for optimisation and control implementation.

2. Materials

Microcrystalline cellulose (Chemicel pH 101, Field Group, Nagpur, India, d50 = 50 μm), mannitol (Pearlitol 160C, Roquette, Lestrem, France, d50 = 160 μm), hydroxypropyl cellulose (HPC) (Klucel EXF, Ashland Inc., USA d50 = 45–90 μm) and croscarmellose sodium (Ac-Di-Sol SD-711, FMC International, USA, d50 = 25–55 μm) were used as raw materials. For granulation, a blend composed of 47 % MCC, 47 % mannitol, 3 % HPC and 3 % croscarmellose sodium was blended using a tumbler blender (Inversina 20L, Bioengineering AG, Wald, Switzerland), and water was used as liquid binder. Magnesium stearate (Merck Life Science UK Limited, Gillingham, UK) was used as tabletting lubricant. The moisture content of the blend before granulation recorded via a near infra-red spectroscopy (NIR) probe ((FP710e, NDC Technology, Dayton, Ohio, USA) was 3.5 %.

3. Method

3.1. Experimental

A Consigma-25 (GEA Pharma Systems, Collette™, Wommelgem, Belgium) was used to produce the granules and a directly connected ModulP tablet press (GEA Pharma Systems, Collette™, Wommelgem, Belgium) was used for the tabletting. Fig. 1 shows a block diagram of the process.

3.1.1. Granulation

The Consigma-25 line is composed of a twin screw granulator, segmented fluidised bed dryer, cone mill and helical ribbon blender with a loss in weight feeder to add lubricant. The parameters which were kept constant across experiments are listed in Table 1.

The L/S ratio and cell drying time were varied in the experiments. Three different L/S ratio were tested (0.22, 0.3 and 0.4) at multiple drying times as shown in Table 2. The different times were chosen to obtain a range of moisture contents with further focus on the middle L/S ratio. This approach was taken to maximise the understanding of both L/S ratio and moisture content on the compression behaviour while trying to minimise the number of experiments required. The L/S ratio range was chosen after preliminary granulation tests to produce granules suitable for further processing in the line without causing blockages. The L/S ratio was varied by adjusting the liquid flow while the solid flowrate was kept constant.

For each experiment 3 cells of the fluidised bed were filled and dried continuously, and the moisture content of each cell was recorded after drying and prior to the milling step using a Near Infra-Red (NIR) moisture content probe (FP710e, NDC Technology, Dayton, Ohio, USA). The moisture content from each cell was averaged to obtain the experiment moisture content used for analysis. After the material from all cells reached the tablet press hopper the tabletting process was started.

The NIR probe was calibrated using 5 samples with different moisture content varying from 0 to 15 % using a loss on drying (LOD) measurement (M35, Sartorius GA, Germany). The LOD measurements were run at 110 °C with automatic end point detection using a sample weighting approximately ≈ 3 g. Each measurement was repeated 5 times.

The porosity of the granules after the twin screw granulator was determined using X-ray tomography (μCT 35, Scanco Medical AG, Switzerland) images of granules with a granule size ranging between 1000 and 1500 μm for each L/S ratio. 10 granules per L/S ratio were used to obtain an average granule porosity. The X-ray images were processed using ImageJ and the porosity of the granules calculated. (Monaco et al., 2021).

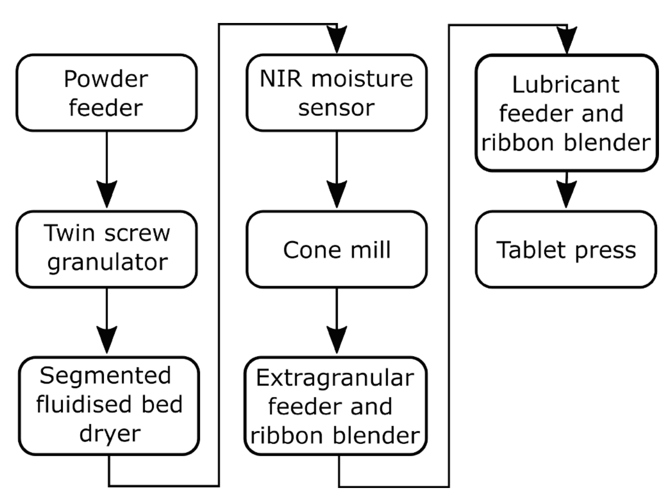

Fig. 1. Process diagram for the Consigma-25.

Table 1
Constant experimental parameters.

Twin screw granulator	
Parameter	**Value**
Screw speed	500 rpm
Powder feed rate	10 kg/hr
Jacket Temperature	25 °C
Fluidised bed dryer	
Drying air temperature	60 °C
Drying air flow	360 m^3/hr
Cell filling time	180 s
Cone mill	
Mill mesh size	1496 µm
Impeller speed	1500 rpm
Milling time	100 s
Lubricant blender	
Lubricant mass added	7 g (1.4 %)
Blending time	60 s
Blender speed	72 rpm

Table 2
Experimental variables.

L/S ratio	Drying times
0.22	400 s, 500 s, 900 s
0.3	450 s, 500 s, 550 s, 600 s, 700 s, 900 s,
0.4	700 s, 800 s, 900 s, 1000 s

3.1.2. Tabletting

Tablets were produced using a 12 mm diameter die, bi convex punches, a tabletting turret speed of 20 rpm and a tablet target mass of 500 mg using the ModulP rotary tablet press (GEA Pharma Systems, Collette™, Wommelgem, Belgium). The compression force was changed from 5 kN to 17.5 kN (44.2 MPa to 154.7 MPa of compaction pressure) in steps of 2.5 kN to produce compression profiles for each experiment. For each compression force 15 tablets were tested after 24hr, using a hardness tester (MultiTest 50, Sotax, Switzerland) to determine their diameter, thickness, and breaking force. The 15 tablets were weighed before testing to obtain an average weight. The tensile strength was calculated using Equation (1) (Pitt et al., 1988 1988).

$$\sigma = \frac{10F}{\pi D^2\left(2.84\frac{H}{D} - \left(0.126\frac{H}{(H-2Hcap)}\right) + \left(3.15\frac{(H-2Hcap)}{D}\right) + 0.01\right)} \tag{1}$$

Where σ is the tablet tensile strength, F is the breaking force of the tablet, D is the diameter, H is the height of the tablet and H_{cap} is the height of the convex cap (1.21 mm for the tooling used in this work). The porosity of the tablets was calculated using the mass and dimensions of the tablets and the true density of the formulation.

3.2. Modelling

A flowsheet model of the tabletting process was developed. gProms Formulated Products 1.6.1 (Siemens PSE, London, UK) was used as the simulation suite. The equations found in Reynolds (Reynolds et al., 2017) were used to describe the tabletting process. The model uses 2 equations. Equation (2) describes the relationship between the final porosity and the tablet compaction pressure based on the material properties.

$$\varepsilon = -1/k_t \ln(P/P_0) \tag{2}$$

ε is the final tablet porosity, k_t is the compressibility constant, P is the applied pressure, and P_0 is the theoretical pressure required to obtain a tablet with zero porosity.

The tablet porosity is then used in Equation (3)

$$T = \overline{T}e^{-k_b\varepsilon} \tag{3}$$

Where T is the tablet tensile strength, $\overline{T}$ is the tensile strength at zero porosity and k_b is the bonding capacity.

The compressibility constant, pressure at zero porosity, tensile strength at zero porosity and bonding capacity are material dependant and could be fitted using the data obtained experimentally. Both gProms formulated products and OriginLab Pro (OriginLab Corporation, USA) were used to fit and analyse the data.

4. Results

4.1. Effect of moisture content

The drying times were varied to obtain granules with different moisture content after the drying step. The average moisture contents for each experiment are listed in Table 3.

The effect of the compaction force on the tablet tensile strength at different moisture content for each L/S ratio is presented in Fig. 2. In general, an increase in moisture content causes an increase in table tensile strength across the 3 different L/S ratio and compression forces. Up to a 200 % increase in tensile strength between the lowest and highest moisture content at the same compaction force is present, with the largest relative differences usually found at lower compaction force while the bigger absolute changes were found towards the higher compaction force. The relationship between compaction force and tensile strength is also linear for most of the experiments apart for the 2 experiments at 0.3 L/S ratio with the highest moisture content which exhibit a plateauing behaviour towards the higher compression force, especially at the highest moisture content of 7.3 %.

To further investigate the mechanism behind the increase in the tensile strength, the effect of the compaction force at different granule moisture content on the final tablet porosity is presented in Fig. 3. An increase in moisture content leads to a decrease in tablet porosity when compressed at the same compaction force across all the L/S ratio, indicating that the moisture is influencing how the porosity changes during the compaction process. Comparing with Fig. 1, it is clear that a lower porosity leads to a corresponding increase in tablet tensile strength. This can be explained as a reduced porosity will increase the contact area between solid particles inside the tablet. As porosity gets lower the force required to further decrease it rises exponentially, this combined with the effect of the moisture content on the porosity leads to plateauing at lower compaction forces for the higher moisture content granules causing the tensile strength to also plateau. This effect is most notable at the higher moisture contents tested.

The decrease in tablet porosity due to increased moisture content has been widely reported by literature (Thapa et al., 2017; Steendam et al., 2001; Gabbott et al., 2016) and has been mostly linked to the change in the plasticity of the granules leading to more deformation under the compaction force which causes a lower final porosity in the tablets. Although reported in other studies, the impact of the moisture on the porosity of the tablets hasn't been implemented in compaction models.

Table 3
Granule moisture content results from experiments.

L/S ratio	Drying time (s)	Moisture content (%)
0.22	400	4.70 ± 0.21
	500	4.39 ± 0.18
	900	4.01 ± 0.17
0.3	450	7.30 ± 0.25
	500	6.20 ± 0.22
	550	5.01 ± 0.20
	600	4.54 ± 0.23
	700	4.43 ± 0.14
	900	4.28 ± 0.15
0.4	700	5.91 ± 0.19
	800	5.20 ± 0.18
	900	4.54 ± 0.11
	1000	3.97 ± 0.13

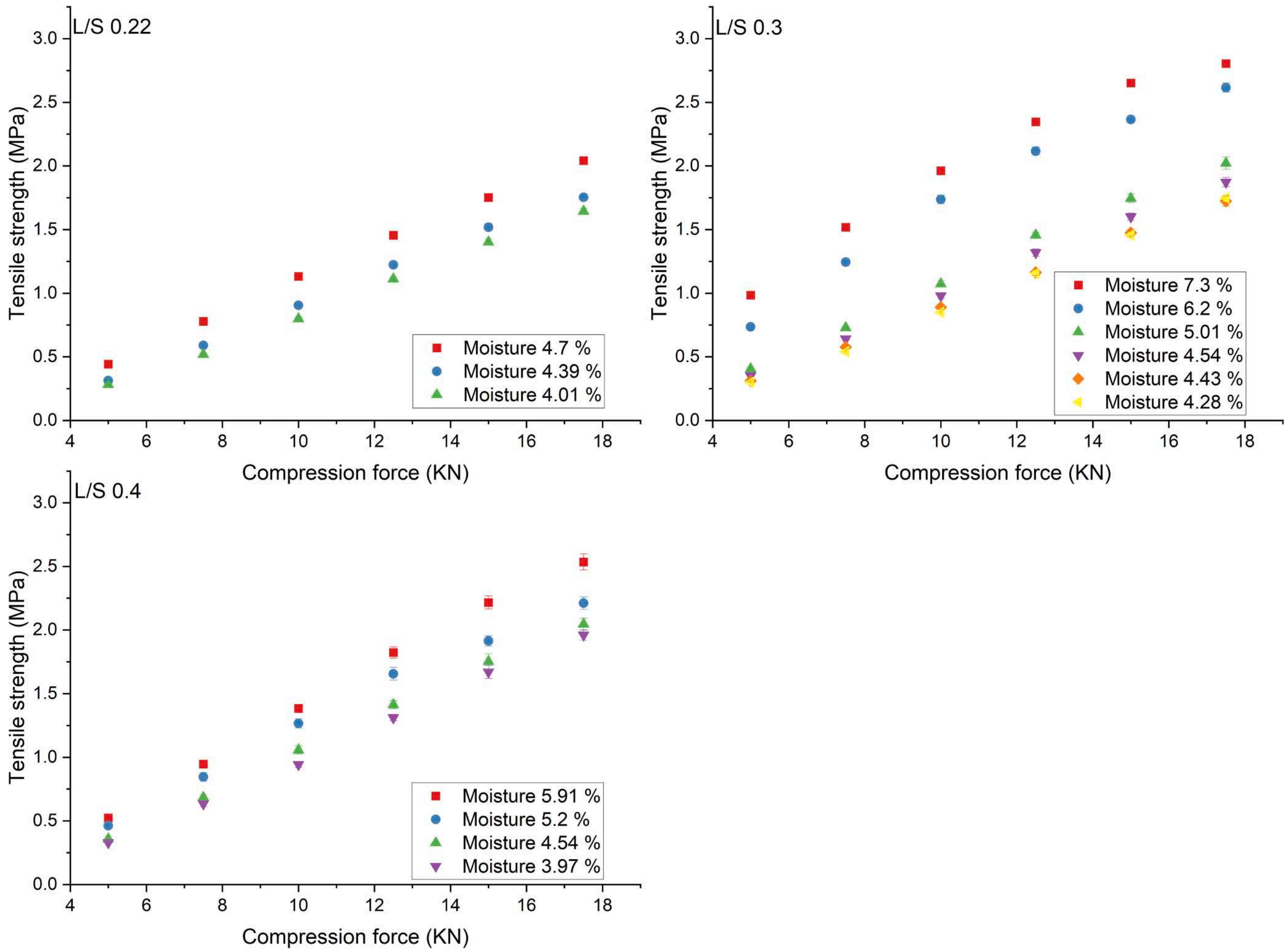

Fig. 2. Tablet tensile strength compaction profile of granules produced at 0.22,0.3 and 0.4 L/S ratios at different moisture contents.

4.2. Effect of L/S ratio

To evaluate the effect of the different L/S ratio on the tablet properties, the data obtained from experiments with equivalent final granule moisture contents were taken in consideration. The moisture content selected was approximately 4.5 % (L/S 0.22: 4.39 %, L/S 0.3: 4.54 %, L/S 0.4: 4.54 %), as data across all L/S ratio was available for comparison. Fig. 4 shows the tensile strength at different compression forces for the 3 different L/S ratio where an increase in L/S ratio causes an increase in the final tensile strength when the moisture content of the granule prior compression is comparable. Similar findings were reported in literature for binary mannitol and MCC formulation (Megarry et al., 2020). The porosity of the tablets is shown in Fig. 5. Overall, the porosity difference across L/S ratios is small in absolute value, in particular between 0.4 and 0.3 while being slightly higher at the lowest L/S ratio at higher compression forces. Overall, the highest L/S ratio always produces the least porous tablet across the compaction force range, which also corresponds to the highest tensile strength. The effect is more obvious on the tensile strength as small changes in porosity lead to large changes in tensile strength due to the exponential relationship between the two. This indicates that the change in tensile strength is mostly related to the difference in porosity of the tablets caused by a difference in the properties of the granules produced at different L/S ratio.

4.3. Effect on compressibility and compactability

To further understand the effect of moisture on the tablet properties the compressibility and compactability were analysed. These two properties directly relate to Equation (2) and (3) with the compressibility being described by Equation (2) while the compactability is described by Equation (3). In Fig. 6 the compactability is shown. As the higher moisture content granules produced the lower porosity and stronger tablets they tend to be towards the top left of the figure. Overall although slight differences were found between the different conditions the data seem to follow this trend. This indicates that the change in granulation condition and granule moisture content affect the strength and porosity of the tablets, but it doesn't not seem to affect the relationship between porosity and tensile strength in the tested ranges. An overall trend for the data was fitted using Equation (2). The model parameters where fitted, with $\overline{T}$ of 6.37 ± 0.19 MPa and k_b 9.81 ± 0.16. The overall quality of the fit was indicated with an R^2 of 0.97. The overall fit values were used for all modelling results to allow for a more general model to be used instead of having different parameter values for each condition. This is in contrast with other studies in the literature where it was noted that the moisture content did affect the compactability behaviour of the materials in a significant fashion (Sun, 2008). The reason for this difference in impact on compactability could be due to the moisture of the granules being mostly present in the granule core and therefore not affecting the interactions between granules during compression as the other studies controlled the moisture content of the material prior compression by varying the storage conditions leading to a more uniform moisture distribution in the material.

In Fig. 7 the compressibility of all experiments is presented. In contrast to the compactability the compressibility is affected by the

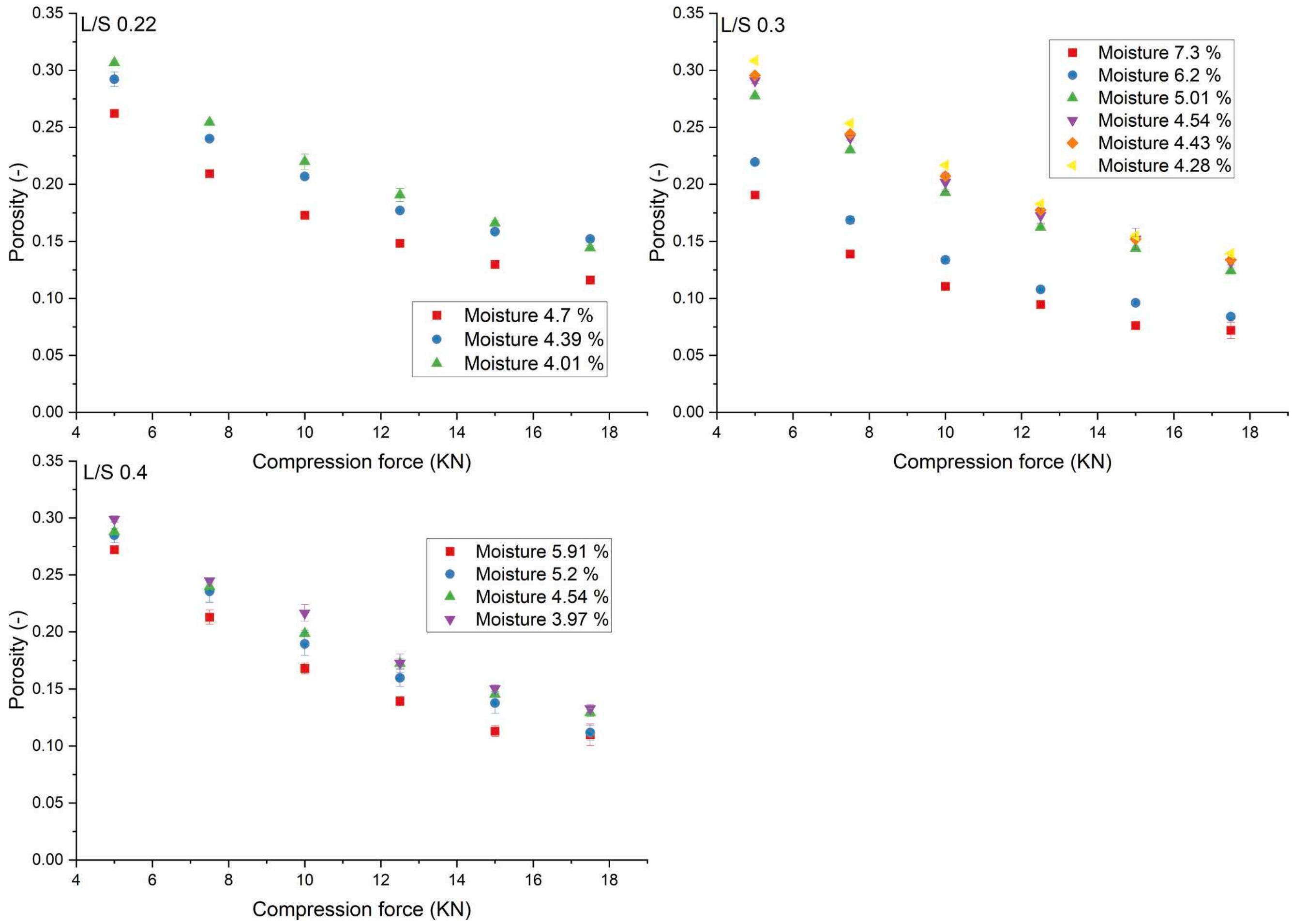

Fig. 3. Tablet porosity compaction profile of granules produced at a 0.22,0.3 and 0.4 L/S ratios at different moisture contents.

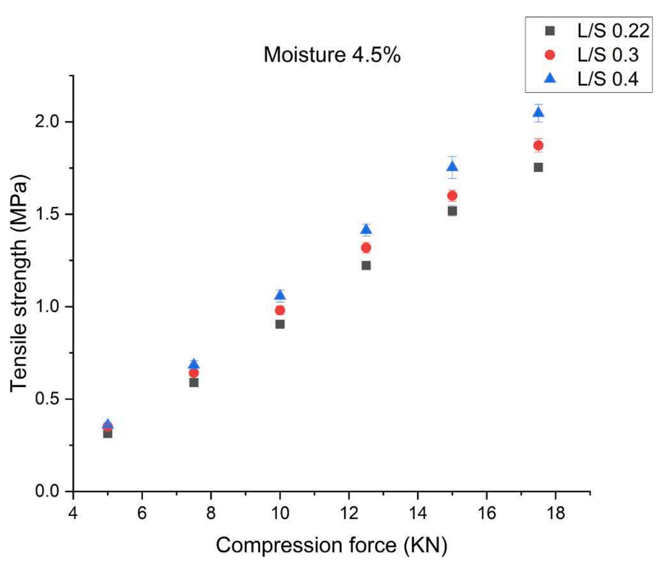

Fig. 4. Tablet tensile strength compaction profile of granules produced at a moisture content of 4.5% at different liquid to solid ratios.

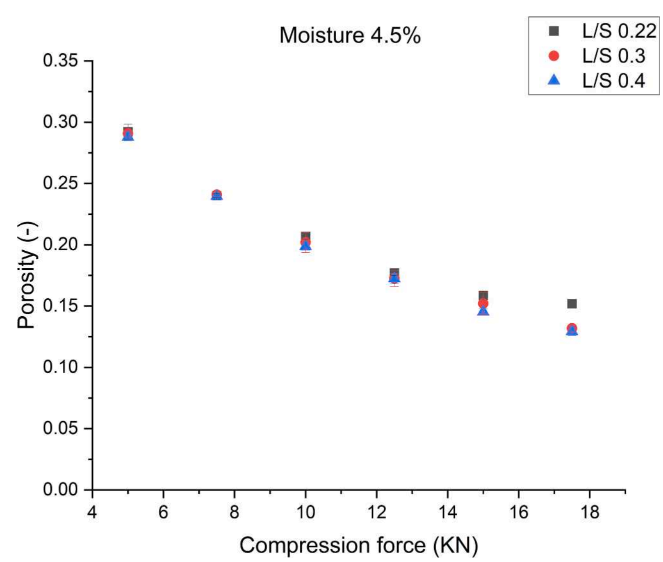

Fig. 5. Tablet porosity compaction profile of granules produced at a moisture content of 4.5% at different liquid to solid ratios.

moisture content as each experiment shows an individual trend. An increase in the moisture content leads to a further decrease in porosity when the same amount of compaction pressure was applied. This agrees with other studies which looked at the effect of moisture content on powder compressibility (García Mir et al., 2011; Wade et al., 2013). For each set of experiments, the data was then fitted using Equation (3) and the values of P_0 and k_t are plotted against the moisture content of the granules in Fig. 8. The resulting P_0 values don't present an obvious trend caused by the change in moisture while the compressibility constant (k_t) generally increases when the granule moisture content is increased. This

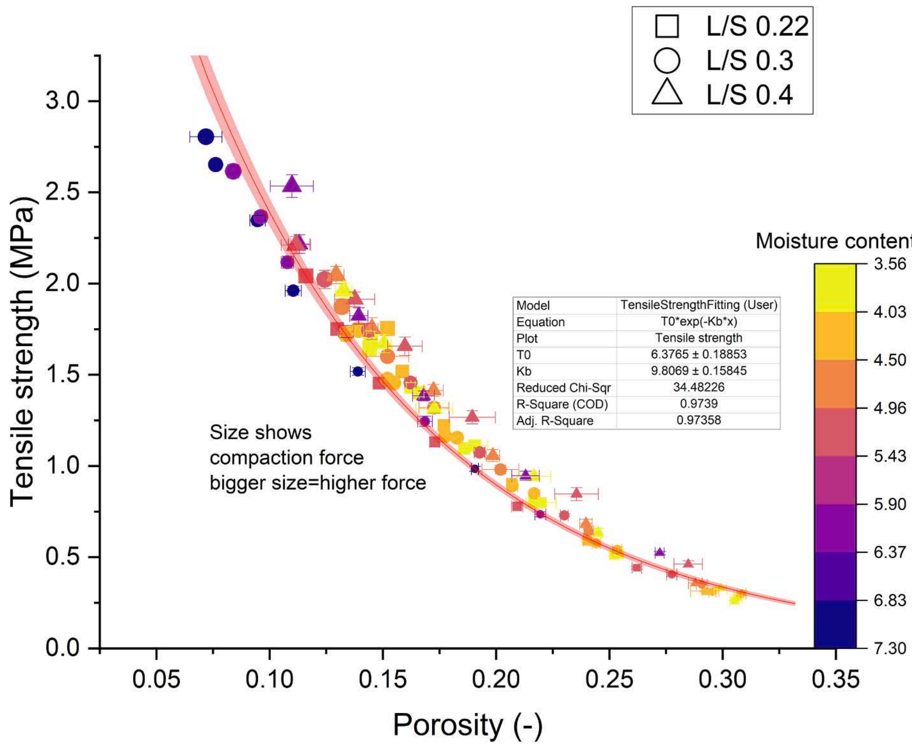

Fig. 6. Compactability data showing the relationship between porosity and tablet tensile strength.

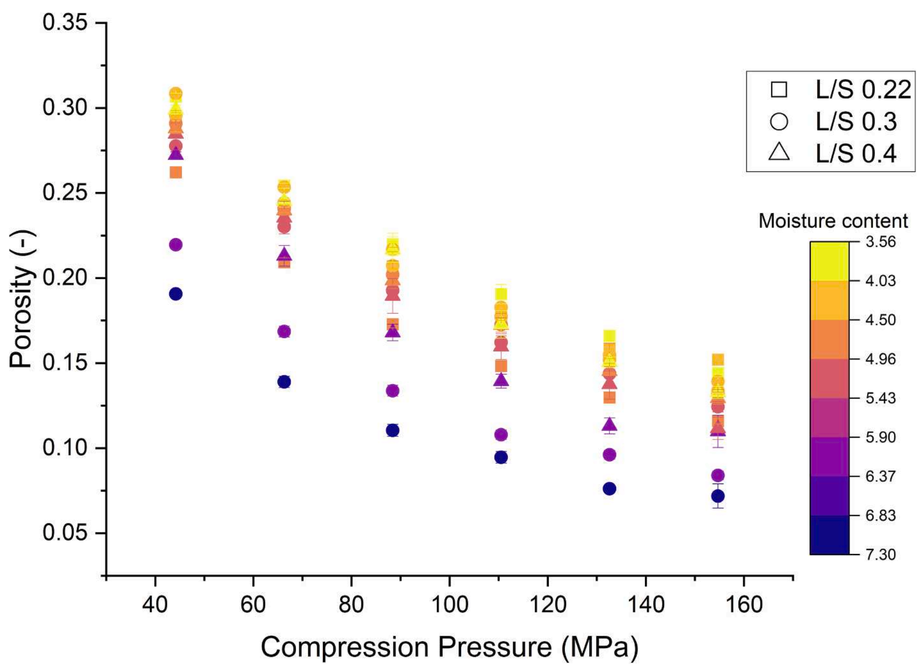

Fig. 7. Compressibility data showing the relationship between compaction pressure and tablet porosity.

agrees with the experimental insight as a higher compressibility constant will lead to a decrease in final porosity for a constant compaction pressure. As P_0 does not show a trend related to moisture content but does exhibit a relationship with L/S ratio the average value of P_0 for each L/S ratio was used to further generalise the model. This makes the compressibility constant the only variable between simulations when the L/S ratio is kept constant which are referred as the single L/S ratio fit. Using the average P_0 value the data was fitted again to obtain the compressibility constant value for each experiment.

4.4. Moisture content model implementation

The porosity of the granules after granulation at different L/S ratios was measured to investigate the possibility of linking the compressibility parameters to a physical property of the granules instead of an equipment parameter. The porosity was also previously found to impact the compression characteristic of materials Xiao et al., 2022. The relationship between the L/S ratio and granule porosity is shown in Fig. 9, a linear relationship was fitted to and added to the flowsheet model

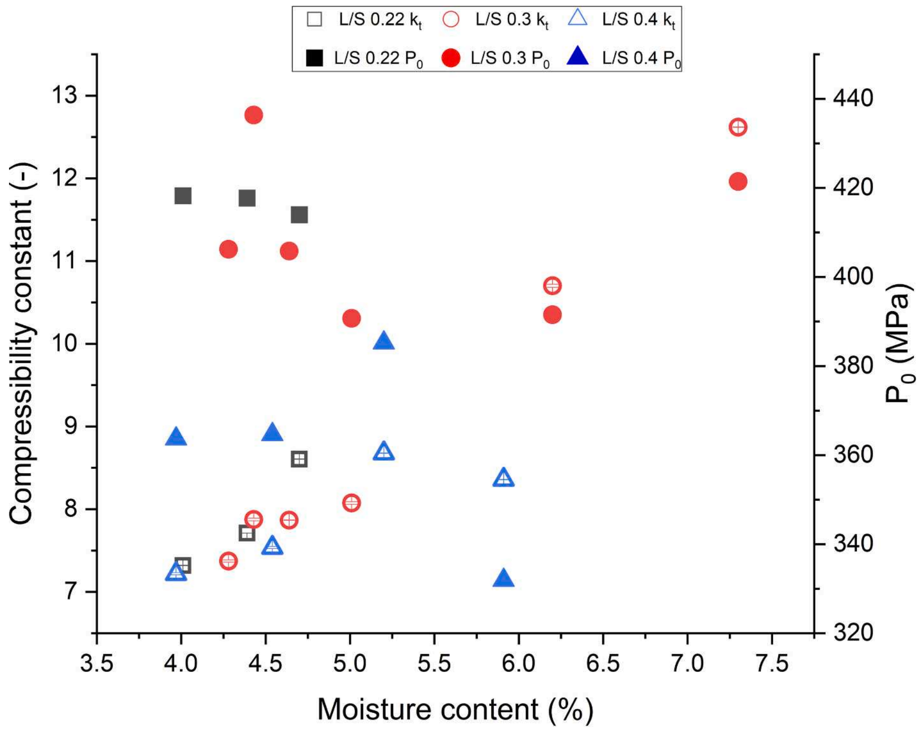

Fig. 8. Compressibility and pressure at 0 porosity value at different moisture content and L/S (filled symbols for pressure at 0 porosity and non-filled for compressibility constant).

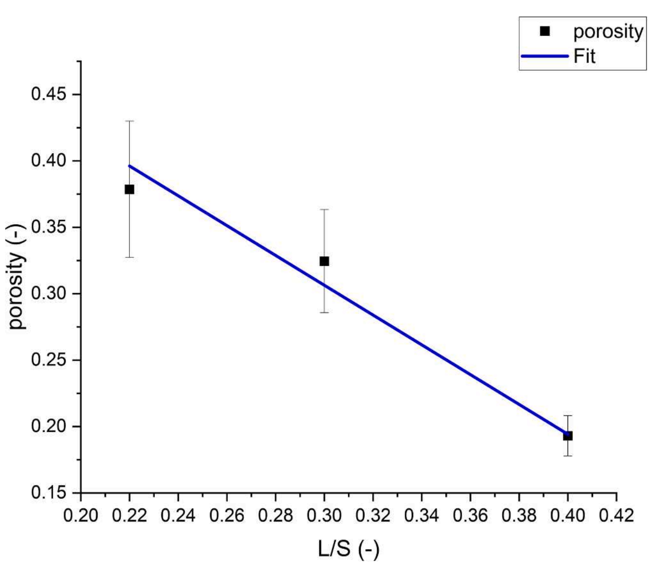

Fig. 9. Relationship between L/S and granule porosity.

allowing it to predict the granule porosity over a range of L/S ratios.

To further generalise the model and allow it to predict the tablet tensile strength for a range of moisture contents and granule porosities, a plane ($k_t = z_0 + a$*Moisture content + b*granule porosity) was fitted to the moisture content (x), granule porosity (y) and the compressibility constant (z) (fit parameters z_0 = -0.44, a = 1.56, b = 3.92, R^2 = 0.95). This is shown in Fig. 10 as a 3d view of the fit with lines indicating the distance between the point and the fitted plane. The biggest deviation of the fit is observed at the highest L/S ratio range extremities but overall, the plane fits most conditions well. A linear fit (P_0 = c + m*granule porosity) was also used to relate P_0 to the granule porosity (c = 303.05Mpa m = 307.82Mpa) allowing the model to be generalised for any moisture content and granule porosity in the tested range.

The parity between the prediction from the model and the experimental results are shown in Fig. 11. Overall, the model tended to underpredict values especially at higher compaction forces and mostly performed well (R^2 = 0.93). This was found to be related to the fitting process as when the parameters were directly used to simulate the results no obvious tendency to either over or under predict was present. This level error was considered acceptable for the model as the ability to cover a wide range of conditions makes the model suitable for application especially in the control of the equipment.

Precision was found to be improved at the cost of flexibility by fitting a moisture content to compressibility constant relationship for each L/S ratio using a linear fit producing 3 linear equations with the coefficient presented in Table 4.

This approach produced smaller deviation from the experimental data with the maximum delta never exceeding 0.25 MPa providing more accurate prediction if no change in L/S ratio is present.

Simulations were also run with the obtained fitting values and the root mean squared error (RMSE) for each set of L/S and moisture content is shown in Fig. 12 for the 3 approaches. Overall, the variation increases as the model is made more and more general as expected with the largest variation tending to be towards the limits of the tested range.

On average the most model produced a RMSE of 0.17 MPa which although larger than the one obtained via the other methods allows more flexibility in the model as any L/S in the tested range can be simulated. The generalisation of the model allows it to be used to predict the tablet properties across different L/S ratios and moisture content inside the tested range. This is particularly important in the usability of the flowsheet model as a tool to develop and test control models by enabling it to simulate the effect of varying conditions without having to use additional material and equipment time.

5. Conclusion

Overall, both the moisture content and L/S ratio affect the final tablet tensile strength of the produced tablets with the moisture having a larger effect on the final tablet tensile strength. This increase in tensile

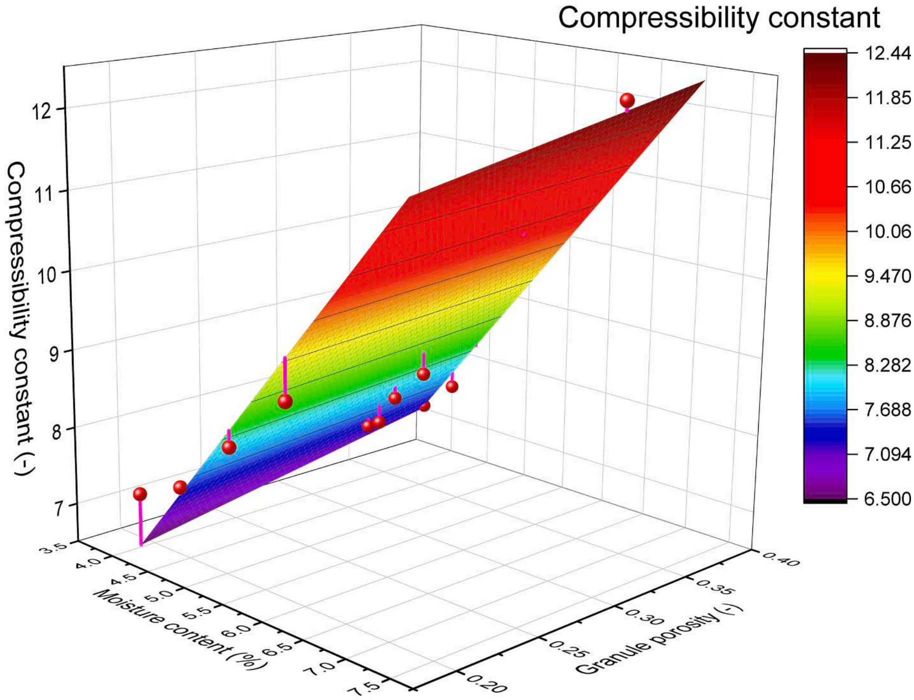

Fig. 10. 3d plane fitting of the compressibility constant in relation to the L/S ratio and granule porosity. Purple drop lines indicating the position of the points in relation to the plane.

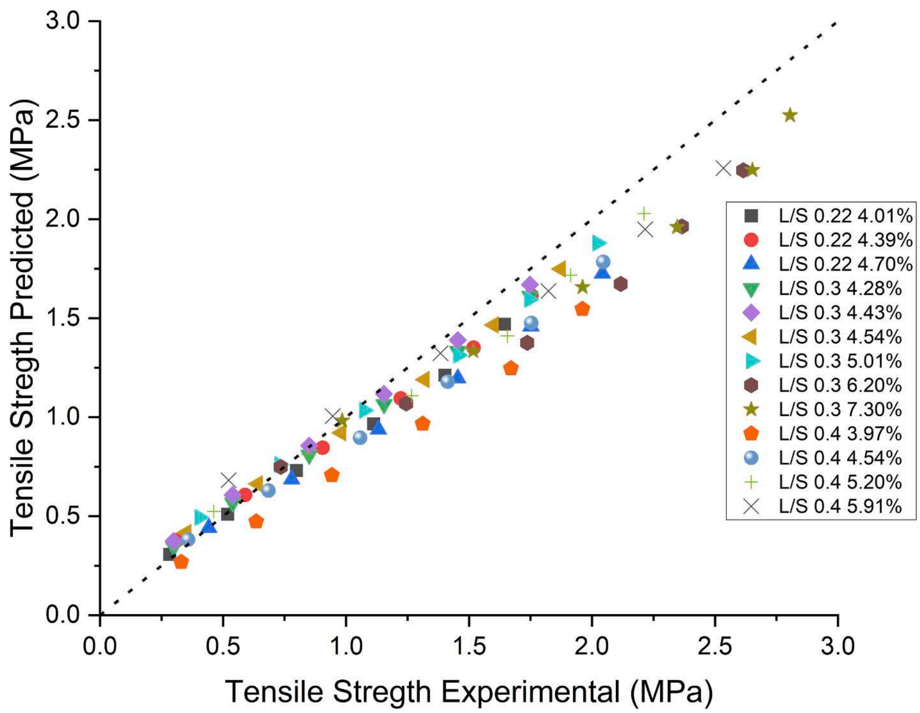

Fig. 11. Effect of compaction force on the tensile strength prediction error for different experiments.

Table 4
Linear coefficients to describe the effect of moisture content on the compressibility constant to generalise the model.

L/S ratio	m	c
0.22	1.923	−0.510
0.3	1.733	−0.103
0.4	0.971	3.212

strength can be linked to a decrease in the final tablet porosity due to the increase of the granule moisture content. The L/S ratio was also found to affect the porosity of the granules with an increase in L/S ratio leading to denser granules.

The compactability of the granules was not majorly affected by the change in moisture content or L/S ratio, therefore a single fit was used in this study allowing for a more general model to be used.

The compressibility parameters were affected by both the L/S ratio

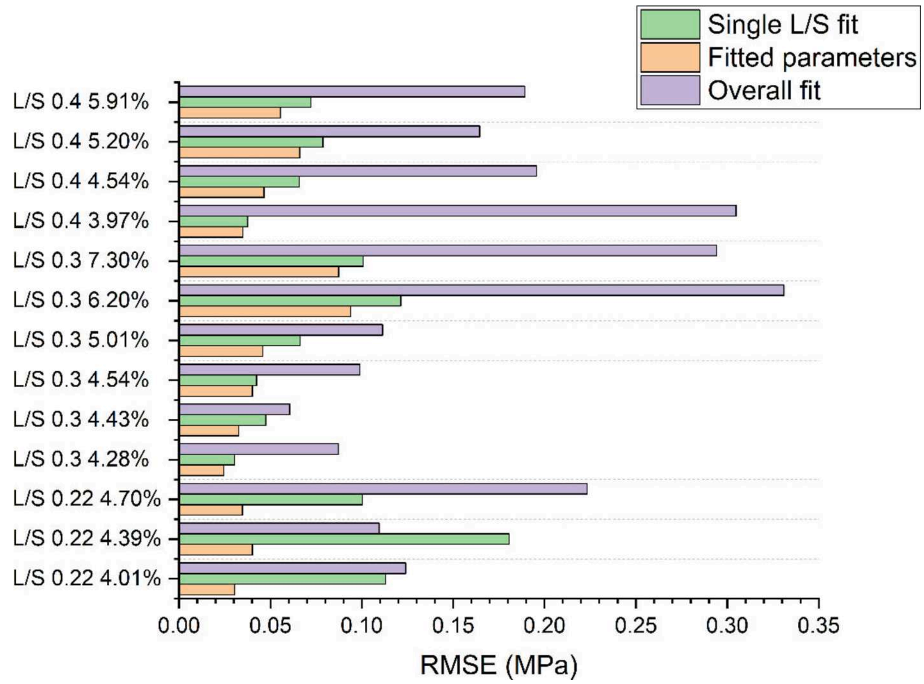

Fig. 12. Comparison of RMSE between using the fitted parameters, linear fits for each L/S and an overall fit.

and moisture content of the granules. The pressure at zero porosity decreased when the L/S ratio was increased while it did not show a relationship with the moisture content of the granules. The compressibility constant on the other hand was affected by the moisture content of the granule with an increase in its value as the moisture increases showing a linear relationship across the tested range. The relationship was also affected by the L/S ratio with an increase in the liquid used during granulation decreasing the effect of the moisture content on the compressibility constant.

The granule porosity was used instead of the L/S ratio to allow the model to rely on a physical property of the granules. A linear relationship between the L/S ratio and porosity was added to allow the model to predict over the tested range. The relationships between the compressibility constant, moisture and granule porosity in the compaction model was described using a plane. Overall, the performance remained good across the different conditions and the model managed to capture the effect to of the moisture content and L/S ratio over the tensile strength well. Lesser general models were also tested, and the performance compared between them. The model performance decreased as the deviation from the experimental results increased due to the generalisation of the model but allowed the model to predict tablet tensile strength over a wide range of conditions. The flexibility of the general model can be particularly useful during the development and testing of control strategies to minimise the amount of time and material required for testing and tuning control loops as it allows to simulate over a wider range of conditions.

CRediT authorship contribution statement

Daniele Monaco: Conceptualization, Methodology, Software, Investigation, Formal analysis, Writing – original draft, Visualization. **Gavin K. Reynolds:** Writing – review & editing, Resources, Supervision. **Pirjo Tajarobi:** Writing – review & editing, Resources, Supervision. **James D. Litster:** Writing – review & editing, Supervision. **Agba D. Salman:** Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2023.122624.

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