Tabletability, compactibility and compressibility: a complex relationship easily displayed with JMP.

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Summary

- Tablets and powder compression
- Compaction studies
- Data modelling
- Data visualization
- Real case studies

Tablets are the most popular drug delivery dosage form

Compression

Applied Force (kN)

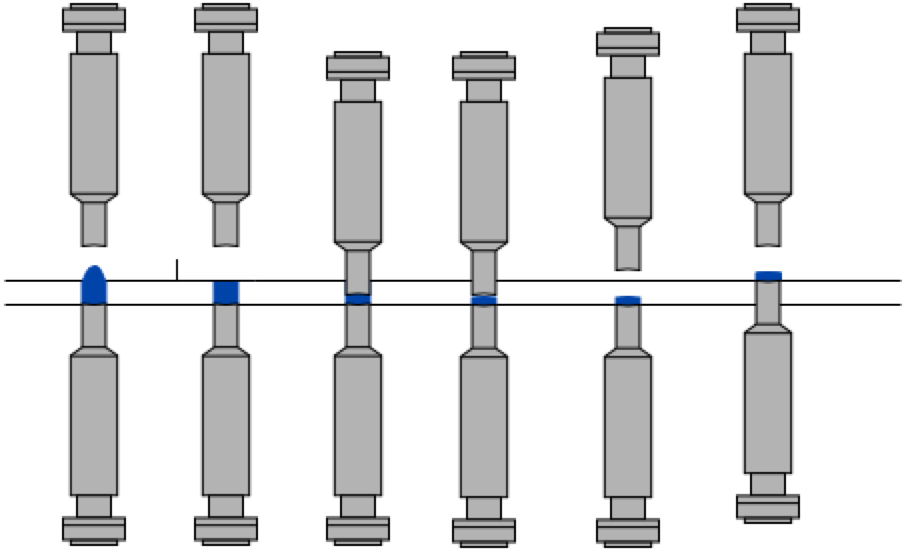
Powder

Density

Particle Size

Particle Shape

Flowability



Applied Force (kN)

Tablets

Shape → area

Thickness

Volume

Weight

Hardness

Compaction Pressure

$$Pressure = \frac{Applied\ Force}{Area}$$

Tensile Strength

$$Ts = \frac{2 \cdot F}{\pi DT}$$

True Density

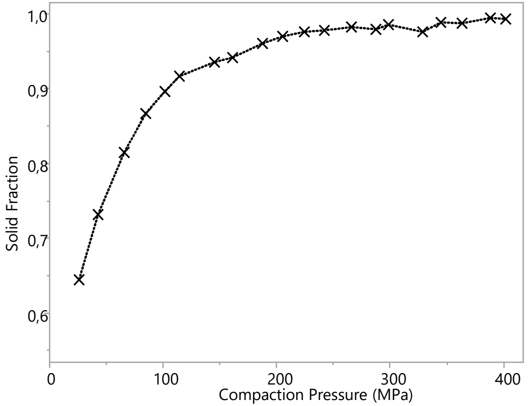
The powder density once all voids are removed.

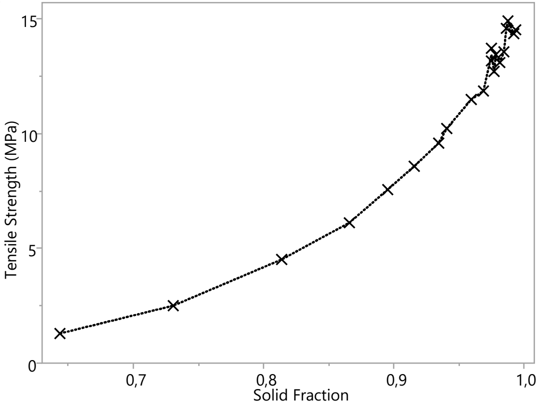
Solid Fraction

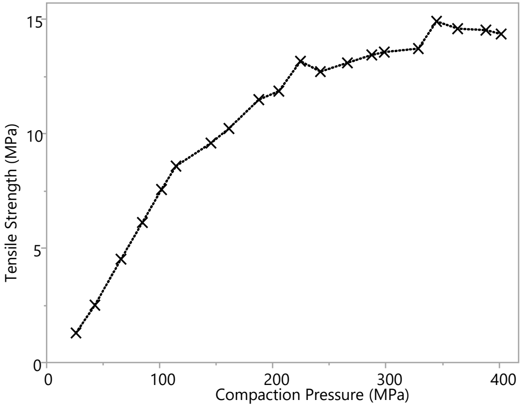
$$Solid\ Fraction = \frac{Tablet\ Density}{True\ Density}$$

$$Porosity = 1 - Solid\ Fraction$$

Compaction Studies







Compressibility profile

Solid fraction
by
Compaction pressure

Compactibility profile

Tensile strength
by
Solid fraction

Tabletability profile

Tensile strength
by
Compaction pressure

Avicel_102 - JMP EA

File Edit Tables Rows Cols DOE Analyze Graph Tools Add-Ins View Window Help

Avicel_102
- Distribution of Weight (mg)
- Distribution of...ensity (g/cm3)
- True Density b...eckel equation
- Solid Fraction ...akita equation
- Compactibility_Rysh
- Plot (7/0)
  - Compressibility Plot
  - Compactibility Plot
  - Tabletability Plot
  - Scatterplot 3D
  - Scatterplot 3D f(x)
  - Dashboard 2D
  - Dashboard 3D

Columns (18/0)
- Tablet ID
- Filling depth (mm)
- Compaction Force (kN)
- Ejection (kN)

Rows

All rows	20
Selected	0
Excluded	0
Hidden	0
Labeled	0

	Tablet ID	Filling depth (mm)	Compaction Force (kN)	Ejection (kN)	Compaction Pressure (MPa)	Weight (mg)	Thickness (mm)	Crushing strength (N)	Tensile Strength (MPa)	Tablet v (cm
1	1	8,005	2,63	0,16	26,3	250	2,610	59	1,2746697674	
2	2	8,007	4,30	0,16	43	249	2,290	101	2,4869787387	
3	3	8,006	6,61	0,16	66,1	249	2,056	164	4,4978702042	
4	4	8,015	8,50	0,16	85	243	1,886	204	6,0992250747	
5	5	8,013	10,19	0,16	101,9	245	1,839	246	7,5429209949	
6	6	8,014	11,47	0,15	114,7	245	1,798	273	8,5616829376	
7	7	8,014	14,56	0,14	145,6	245	1,762	299	9,5686675369	
8	8	8,014	16,15	0,18	161,5	256	1,829	331	10,204705348	
9	9	8,013	18,79	0,18	187,9	245	1,716	349	11,468175343	
10	10	8,014	20,57	0,16	205,7	252	1,748	367	11,83888541	
11	11	8,013	22,48	0,16	224,8	252	1,737	405	13,1474457	
12	12	8,014	24,24	0,17	242,4	248	1,706	384	12,692243008	
13	13	8,013	26,63	0,16	266,3	250	1,712	397	13,075940251	
14	14	8,015	28,78	0,15	287,8	252	1,731	412	13,421044897	
15	15	8,014	29,89	0,18	298,9	247	1,686	405	13,545144235	
16	16	8,014	32,90	0,18	329	252	1,737	422	13,699313791	
17	17	8,013	34,51	0,18	345,1	251	1,708	451	14,889319751	
18	18	8,014	36,37	0,18	363,7	246	1,676	433	14,568004371	
19	19	8,015	38,87	0,17	388,7	250	1,691	435	14,505470842	
20	20	8,014	40,22	0,18	402,2	252	1,707	434	14,336475255	

evaluations done

Flat-face punch ∅11,89 mm – Area 1 cm^2

True Density Estimation

C. Sun, A Novel Method for Deriving True Density of Pharmaceutical Solids Including Hydrates and Water-Containing Powders, (2013)

$$P = \frac{1}{C}\left[(1-\varepsilon_c) - \frac{\rho_{tablet}}{\rho_{true}} - \varepsilon_c \ln\left(\frac{1-\frac{\rho_{tablet}}{\rho_{true}}}{\varepsilon_c}\right)\right]$$

Heckel equation

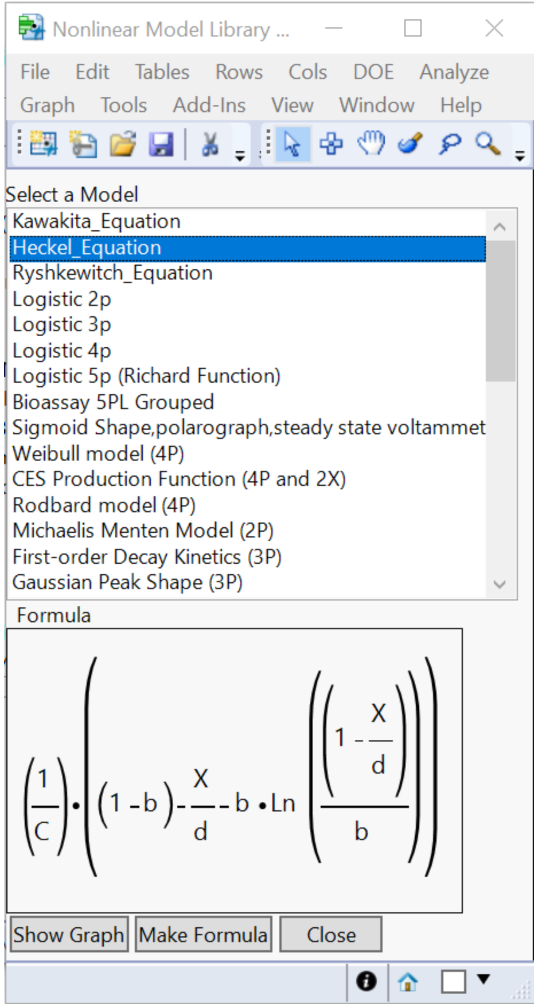
Analyze>Specialized Modeling>Nonlinear

Non linear model library

where: **C**, **b** and **d** are parameters

ρ_{tablet} is the variable **X**

ρ_{true} is the parameter **d**



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Heckel equation

Analyze>Specialized Modeling>Nonlinear

Non linear model library


NonlinLib.jsl

where: **C**, **b** and **d** are parameters

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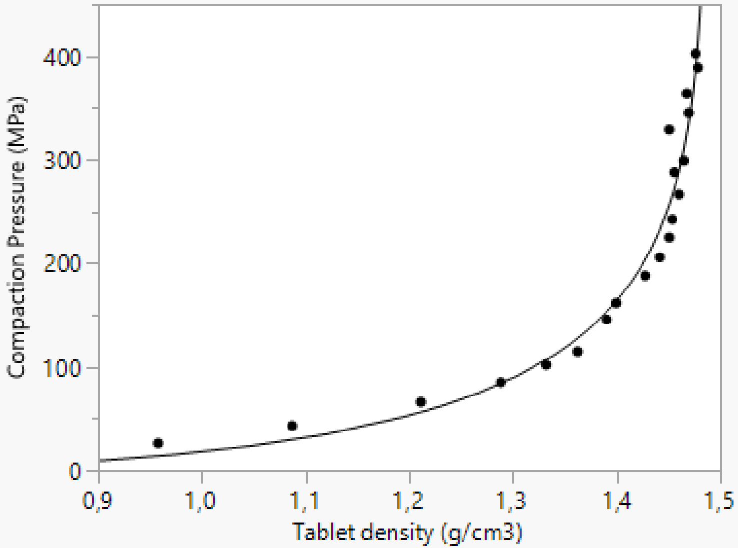
Nonlinear Fit

Response: Compaction Pressure (MPa), Predictor: Heckel_Equation

Plot



Solution

SSE	DFE	MSE	RMSE
11654,77982	17	685,57528	26,183493

Parameter	Estimate	ApproxStdErr
C	0,0053449496	0,0020575
b	0,6088675793	0,14207259
d	1,4874877423	659

Solved By: Analytic Gauss-Newton

Compressibility

Kawakita, Tsutsumi, A Comparison of Equations for Powder Compression, (1966)
Physical Properties and Compact Analysis of Commonly Used Yeli Zhang, Yuet Law, and Sibu Chakrabarti, Direct Compression Binders, 2003

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab}$$

$$C = \frac{V_0 - V}{V_0} \quad \textit{or} \quad C = \frac{SF_0 - SF}{SF_0}$$

V_0 starting vol.
V vol. at applied pressure

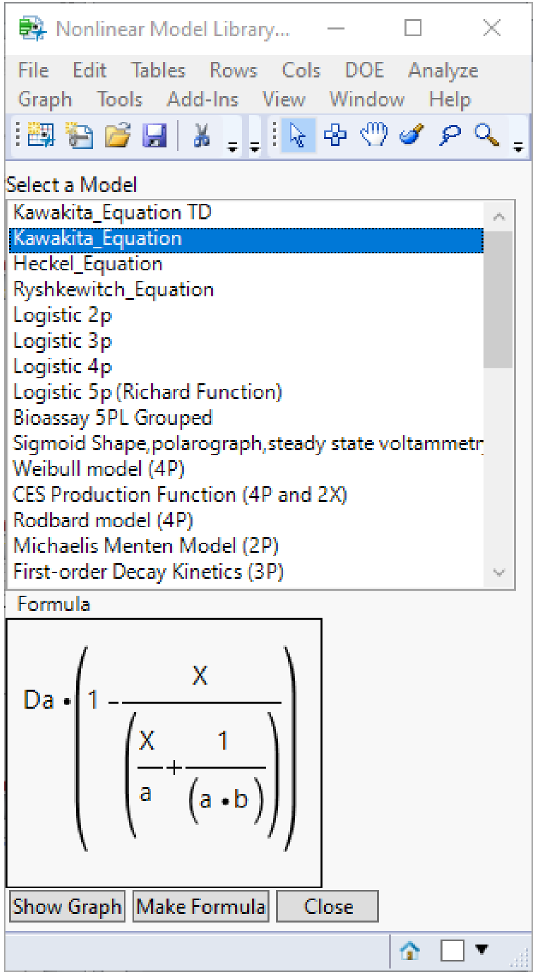
SF_0 starting solid fraction
V solid fraction at applied pressure

Kawakita equation

Analyze>Specialized Modeling>Nonlinear

Non linear model library

where: **a** and **b** are parameters
P is the variable **X**
SF is the variable **Y**



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V vol. at applied pressure

or

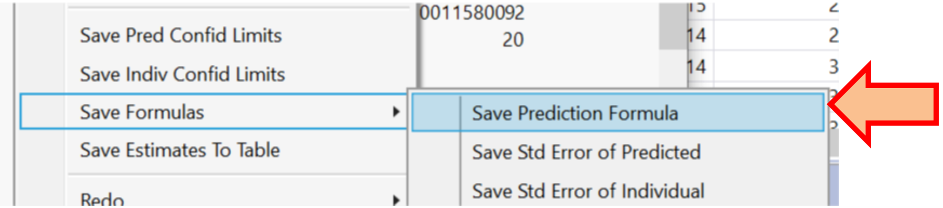
$$C = \frac{SF_0 - SF}{SF_0}$$

SF_0 starting solid fraction
V solid fraction at applied pressure

Kawakita equation

Analyze>Specialized Modeling>Nonlinear

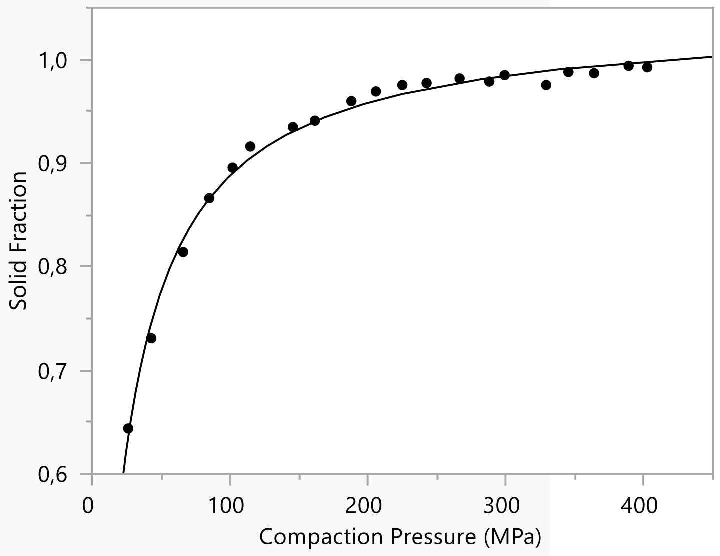
Non linear model library



Nonlinear Fit

Response: Solid Fraction, Predictor: Kawakita_Equation

Plot



Solution

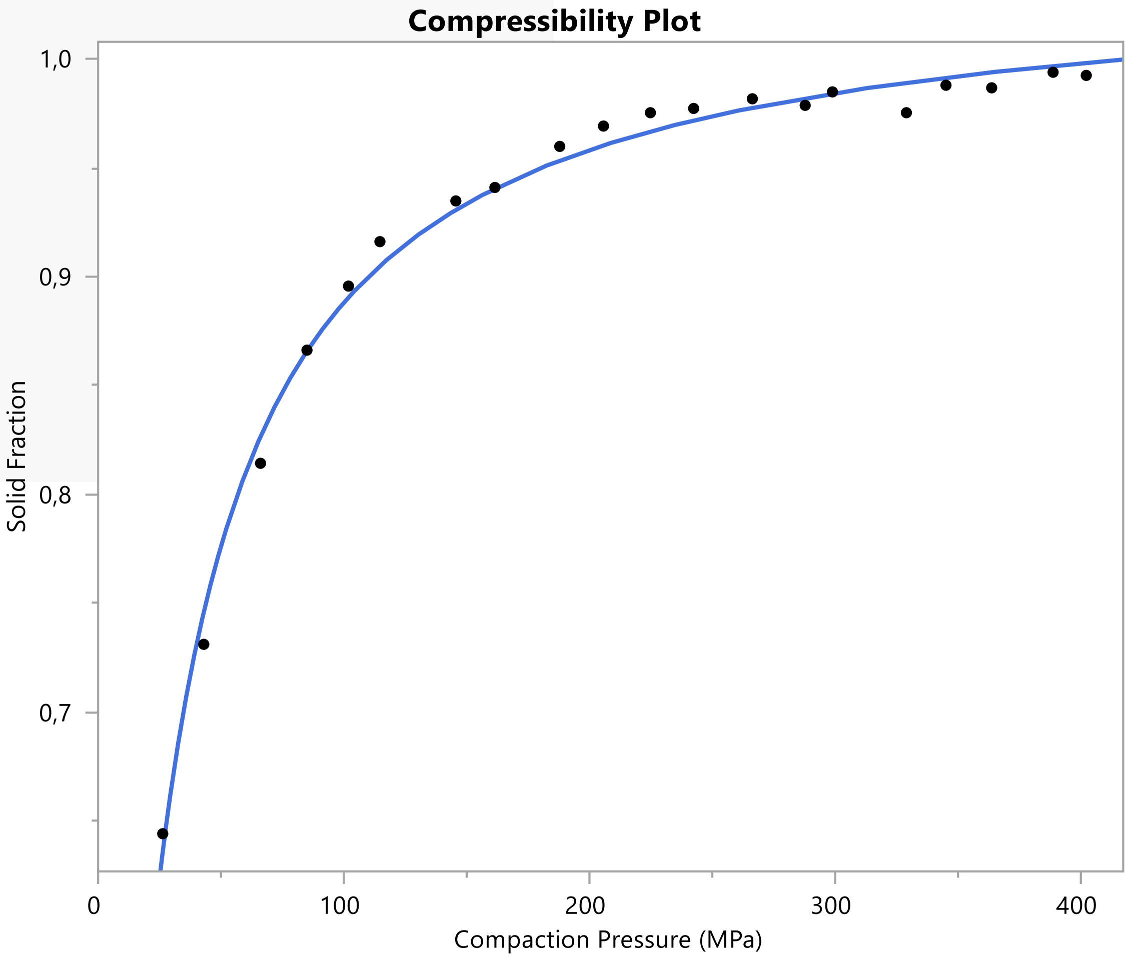
SSE	DFE	MSE	RMSE
0,0011580092	17	6,8118e-5	0,0082534

Parameter	Estimate	ApproxStdErr
Da	0,0605603482	0,1112878
a	-16,19845696	31,5351507
b	0,0538835229	0,00980698

Solved By: Analytic Gauss-Newton

Compressibility

The ability of a material to reduce in volume as results of an applied pressure



Compactibility

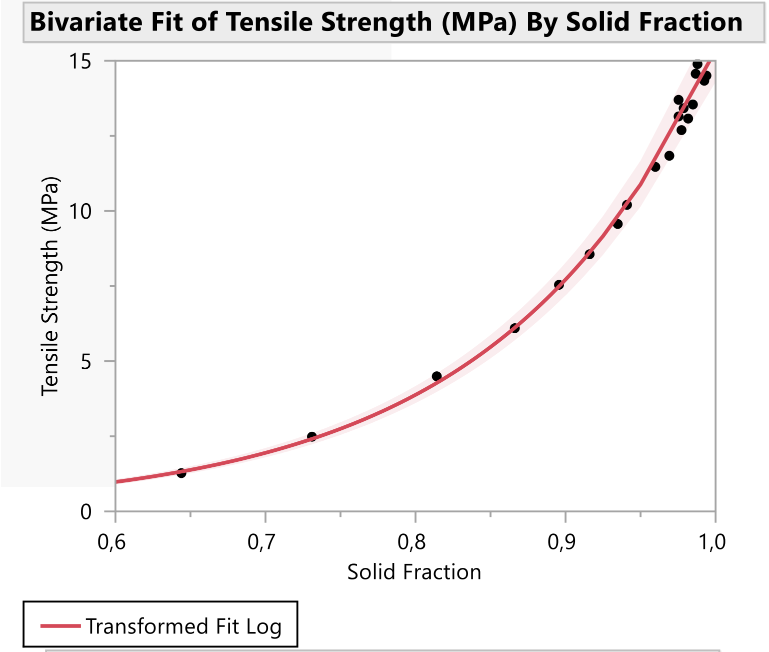
C. K. Tye, C. Sun, G. E. Amidon, Evaluation of the Effects of Tableting Speed on the Relationships between Compaction Pressure, Tablet Tensile Strength, and Tablet Solid Fraction, (2005)

$$TensileStrength = \sigma_0 e^{-b(1-SolidFraction)}$$

Ryshkewitch equation

Fit Y by X platform

Simply doing a “Fit special” with Y transformed as logarithm



Transformed Fit Log

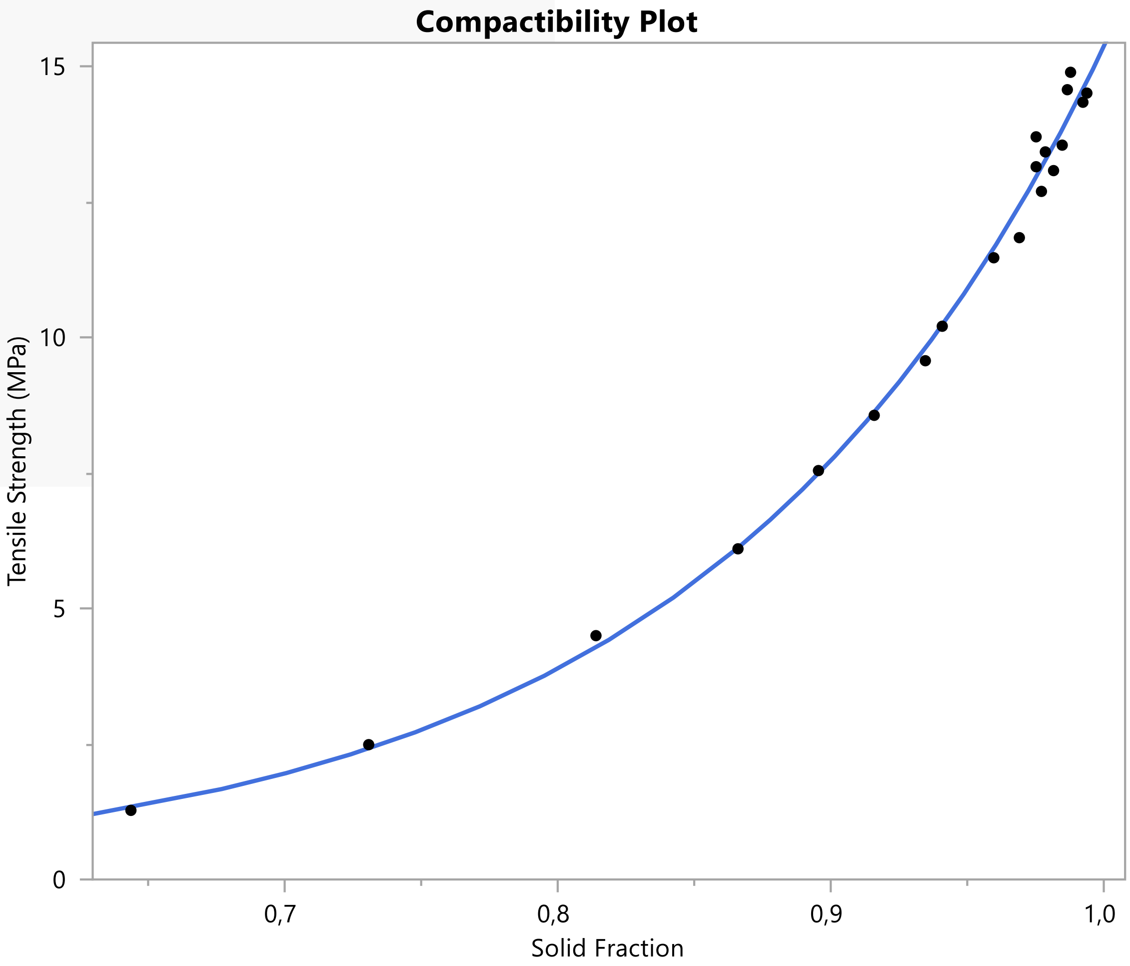
Log(Tensile Strength (MPa)) = -4,144067 + 6,8751709*Solid Fraction

Summary of Fit

RSquare	0,997629
RSquare Adj	0,997498
Root Mean Square Error	0,032703
Mean of Response	2,217537
Observations (or Sum Wgts)	20

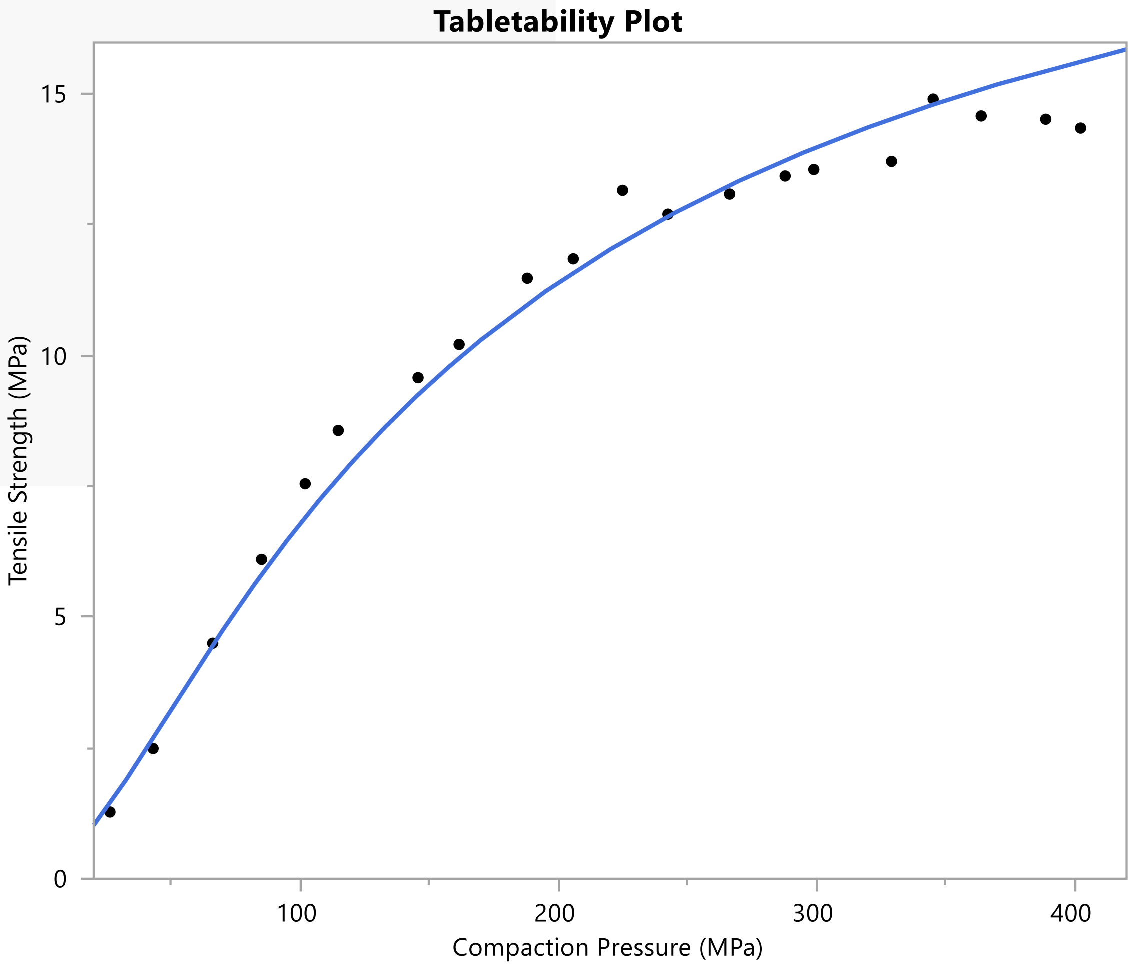
Compactibility

The ability to produce tablets with sufficient strength, under the effect of densification

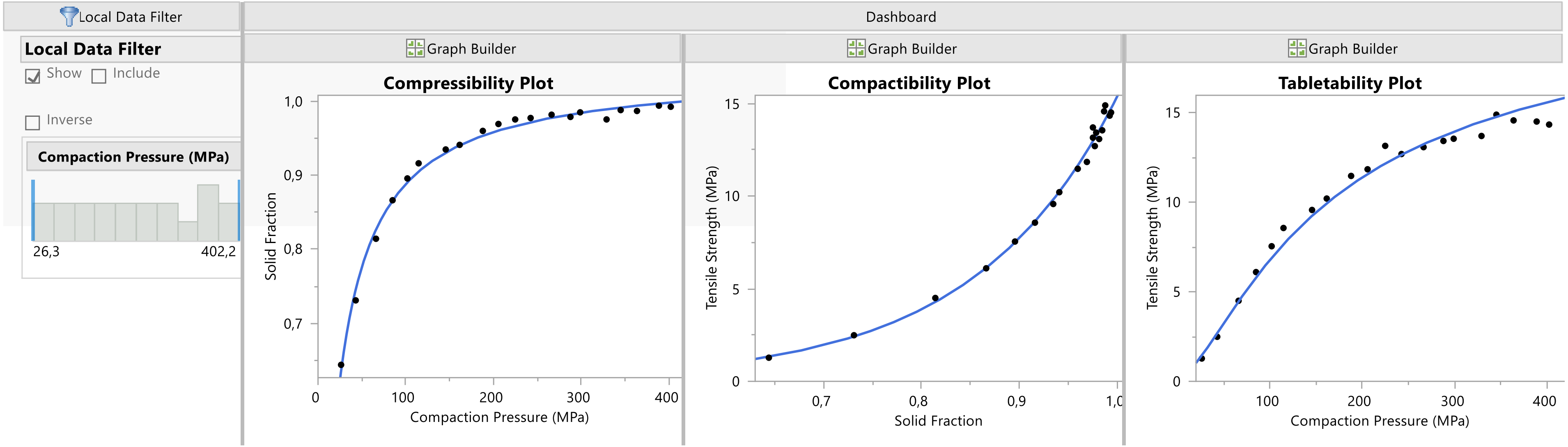


Tabletability

The capacity of a powder to be transformed into a tablet of specified strength under the effect of compaction pressure

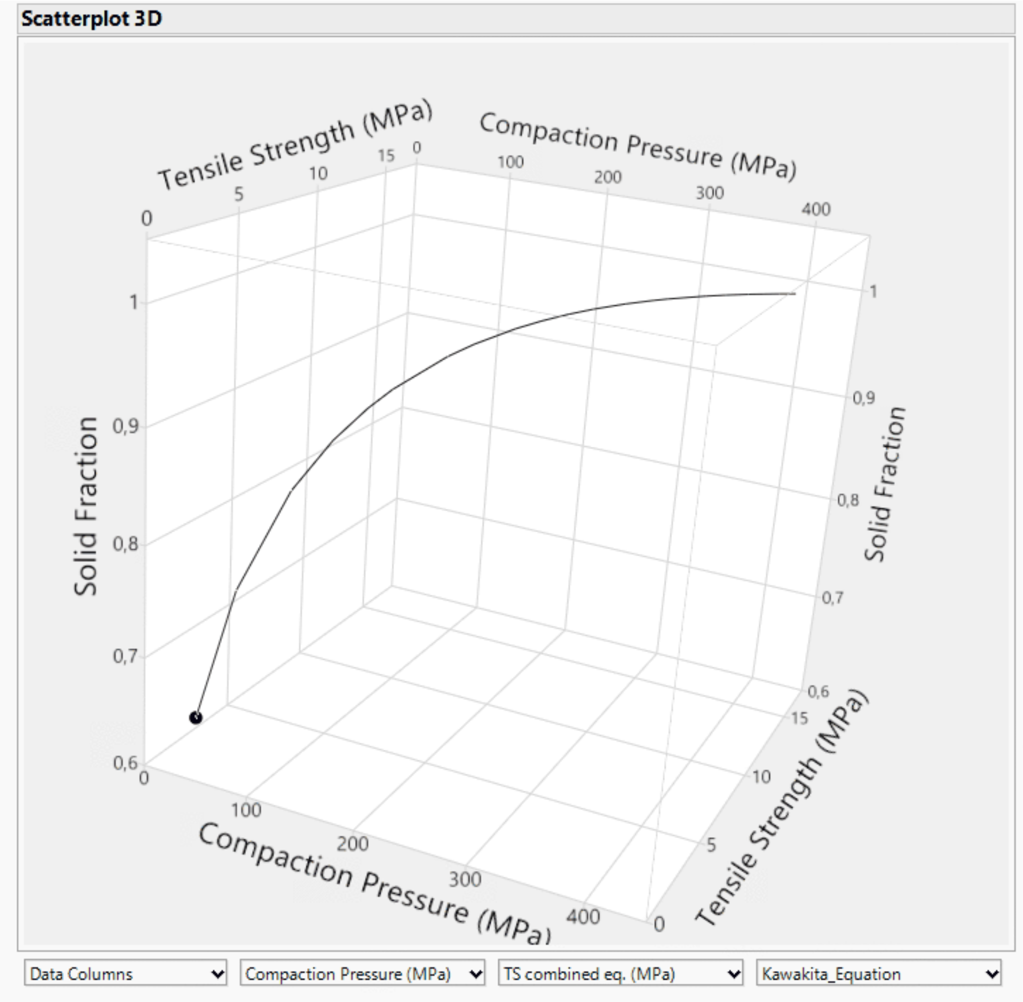


Dashboard

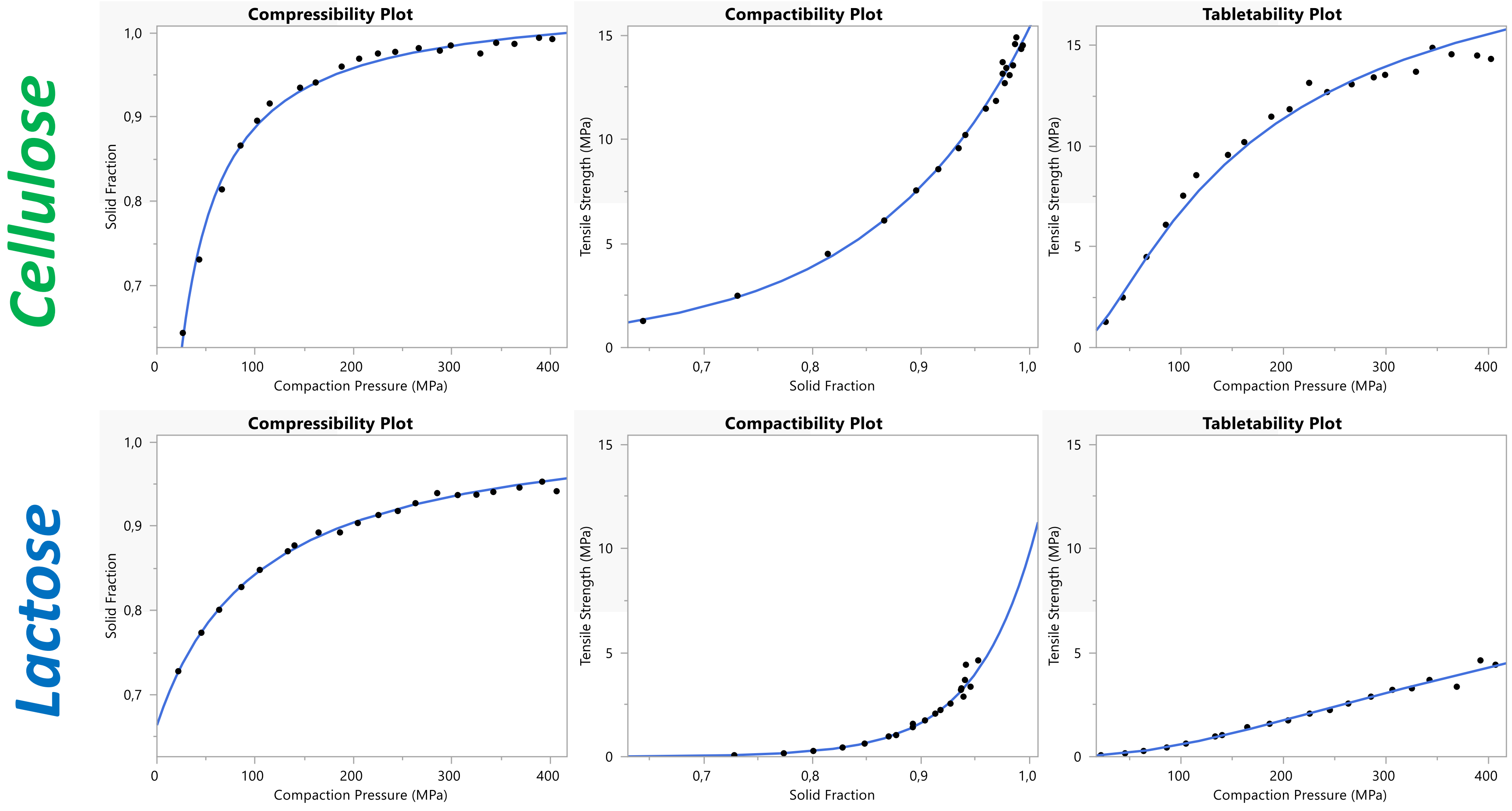


Local Data Filter
Dashboard
Local Data Filter
Show
Include
Inverse
Compaction Pressure (MPa)
26,3
402,2
Graph Builder
Compressibility Plot
Solid Fraction
Compaction Pressure (MPa)
Graph Builder
Compactibility Plot
Tensile Strength (MPa)
Solid Fraction
Graph Builder
Tabletability Plot
Tensile Strength (MPa)
Compaction Pressure (MPa)

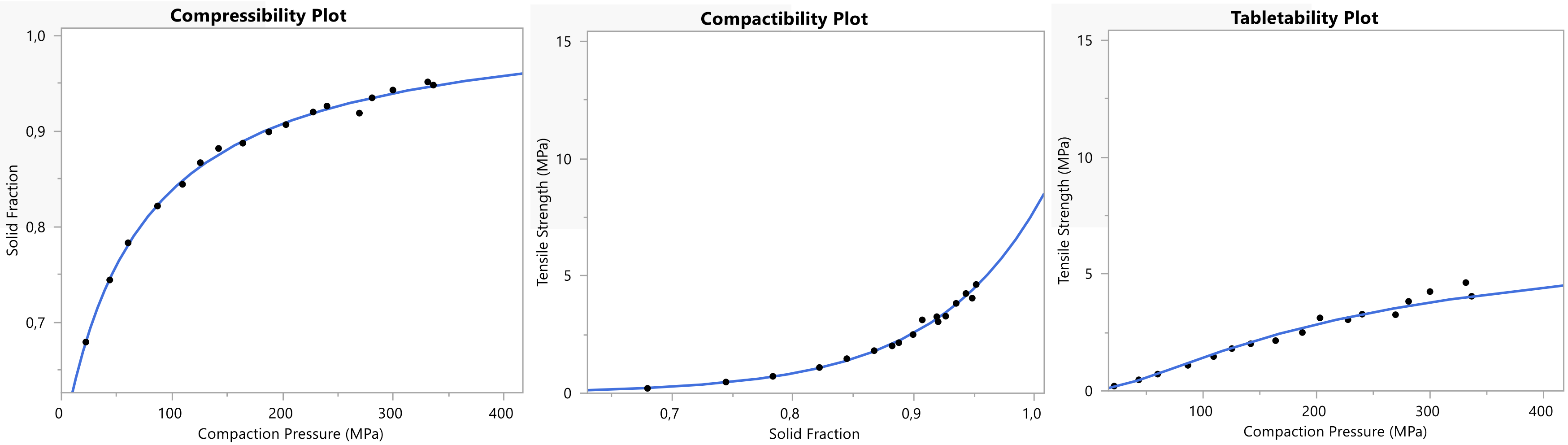
3D Scatterplot



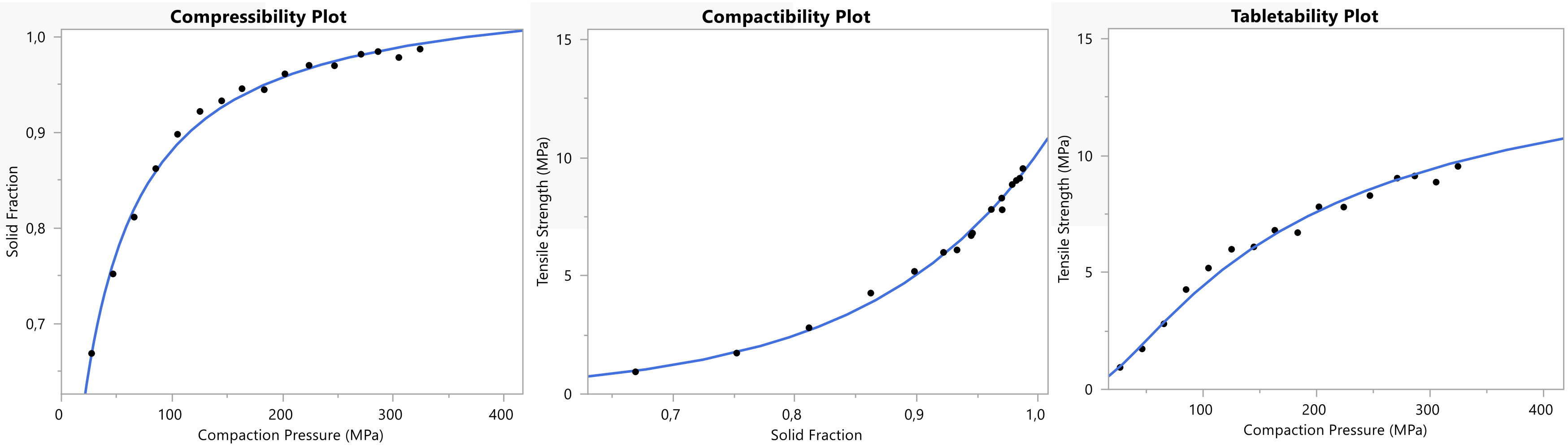
Compaction studies on cellulose, lactose and placebo formulations


Cellulose
Lactose
Compressibility Plot
Compactibility Plot
Tabletability Plot
Solid Fraction
Tensile Strength (MPa)
Compaction Pressure (MPa)
1,0
0,9
0,8
0,7
0
100
200
300
400
5
10
15

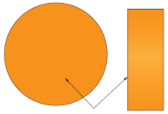
Cellulose 25% *Lactose 75%*



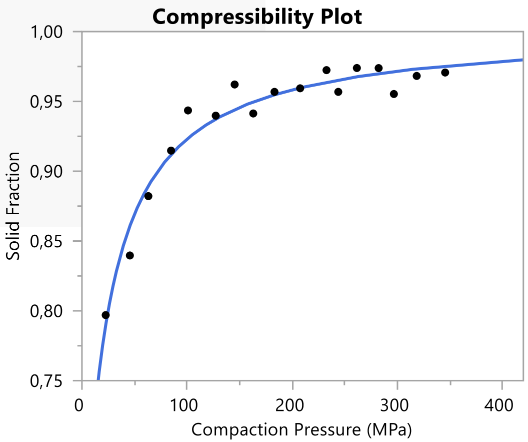
Cellulose 75% *Lactose 25%*

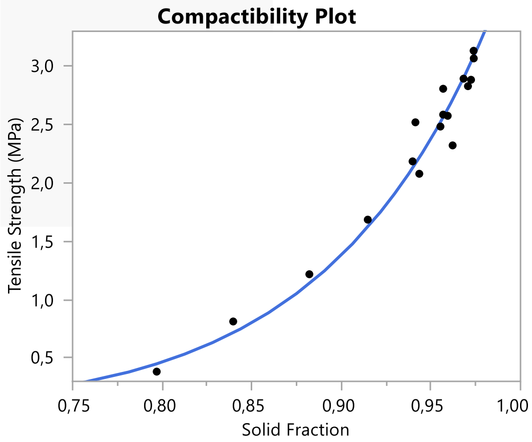


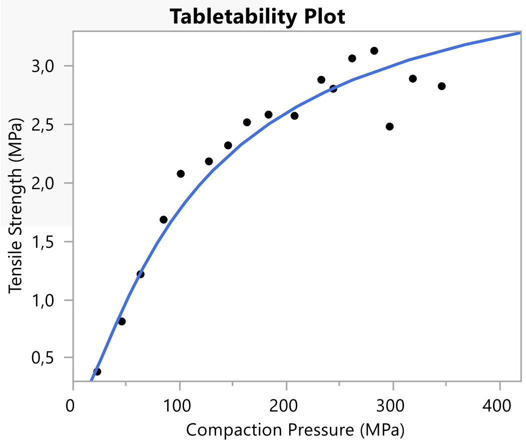
Compaction studies on real tablets formulation, using manufacturing punches (EU standard tooling)

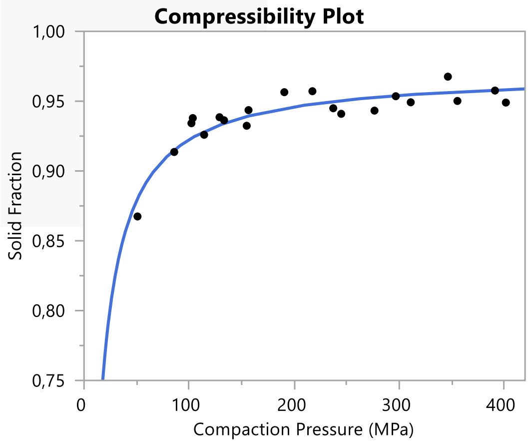


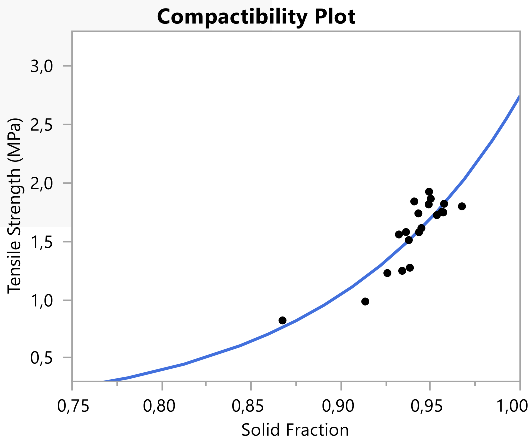
FLAT-FACE PLAIN

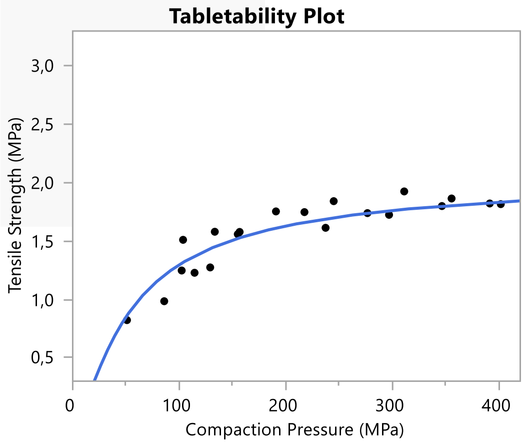


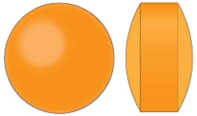








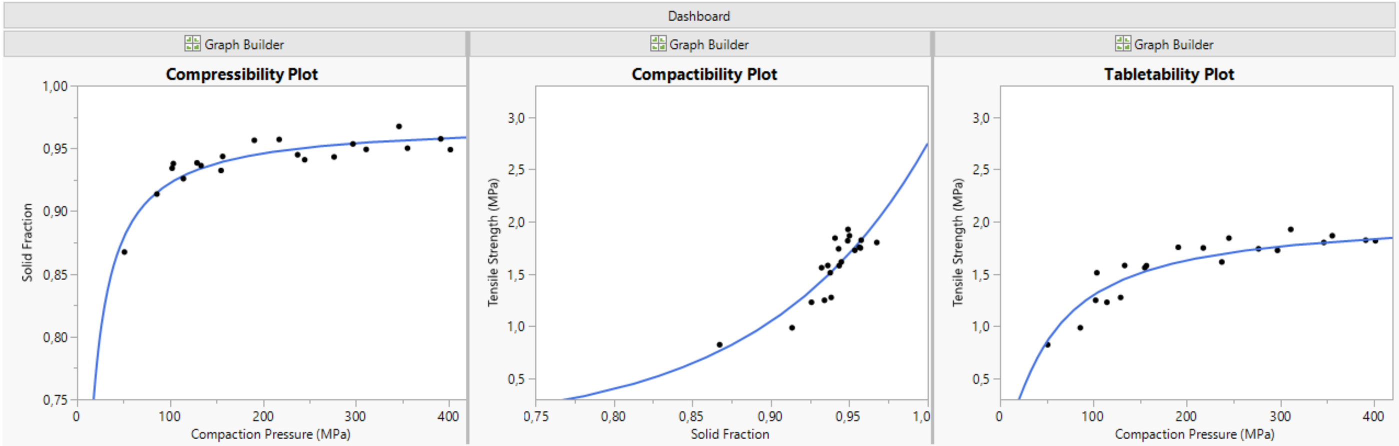




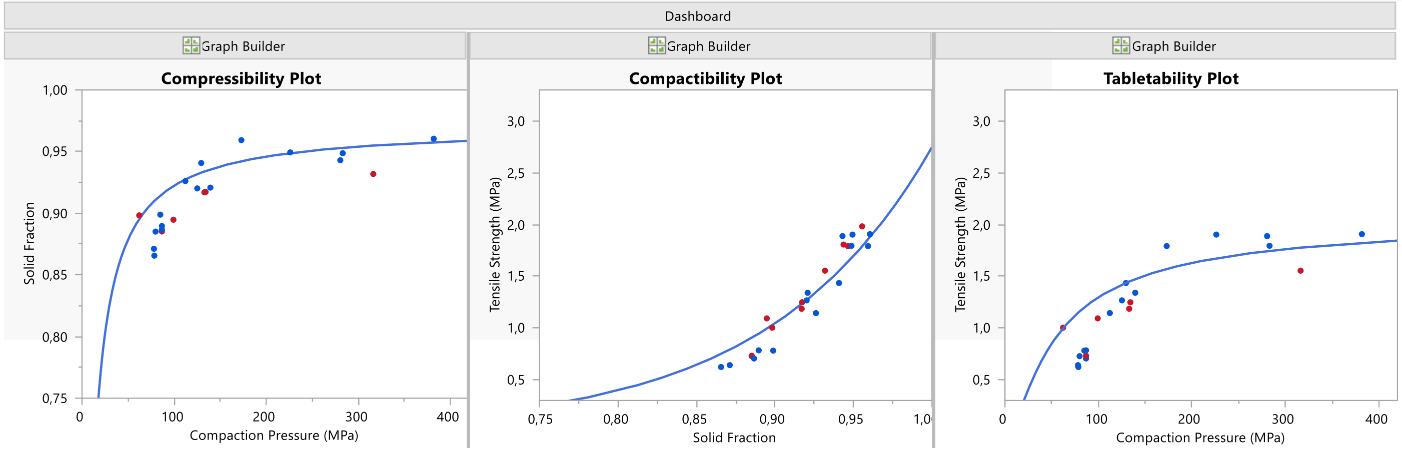
STANDARD CONVEX

Single punch press Vs Rotary press

Natoli NP-RD10A
Single punch
Alternative



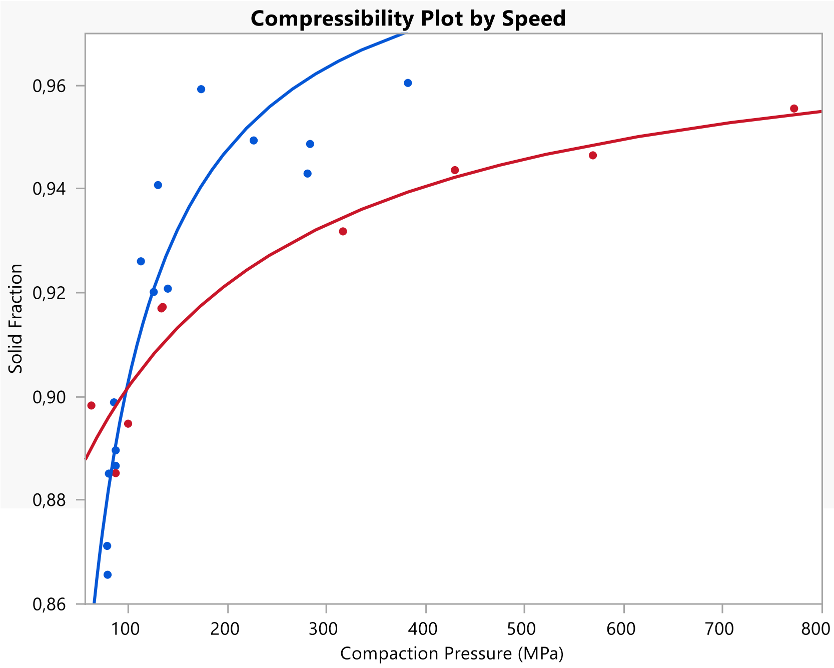
Korsch PH103
Rotary press

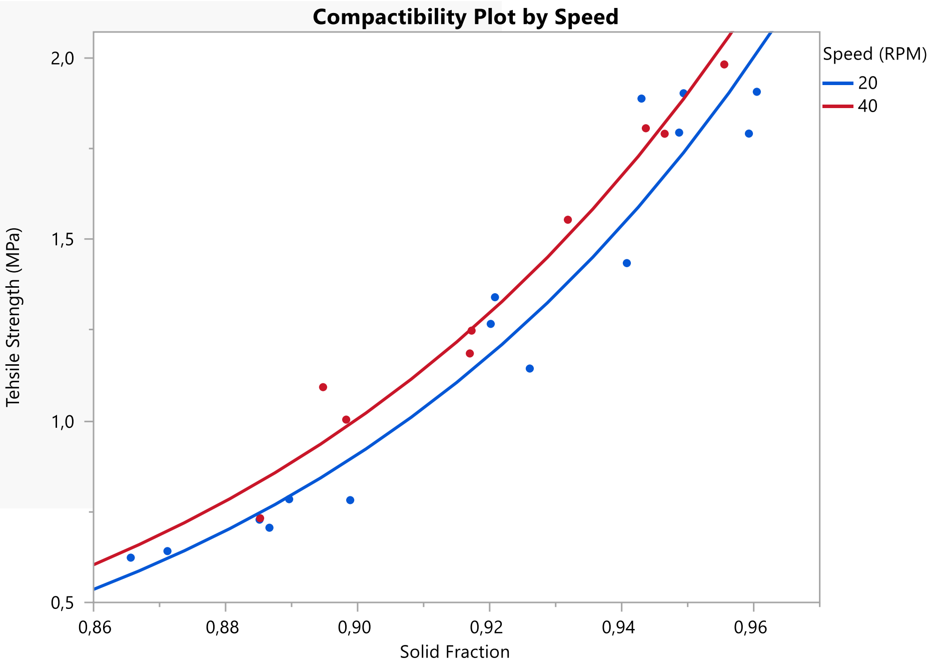


***Dwell time** is defined as the amount of time that the compression force applied when forming the tablet is above 90% of its peak value.*

Higher speed, shorter dwell time

Lower speed, longer dwell time





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Thank you

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- Y. Zhang, Y. Law, S. Chakrabarti, Physical Properties and Compact Analysis of Commonly Used Direct Compression Binders, AAPS PharmSciTech, (2003)
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- C. Sun, Decoding Powder Tabletability: Roles of Particle Adhesion and Plasticity, Journal of Adhesion Sicence and Technology, (2011)
- Natoli engineering, Tabletability, Compactibility, and Compressibility: What's the Difference? , (2017)