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DESCRIPTION

[0001] The present invention relates to compositions, particularly agglomerates, comprising at least one lactose component, at least one cellulose component and at least one starch component, its preparation and its use, particularly as a direct tableting excipient.

[0002] Tablets are defined from a technological perspective as solid single dosage forms of pharmaceuticals, which are produced by compressing powders and granulates in various forms. The composition of tablets can be extremely diverse and has to be developed individually for each active agent, each intended use and each manufacturing technology.

[0003] Typical tablet formulations contain, in addition to the pharmaceutically active component, so-called tableting excipients, such as fillers (e.g. lactose, cellulose powder and calcium diphosphate), sugar alcohols (e.g. mannitol, sorbitol, Xylitol and malitol), disintegrants (e.g. croscarmellose, crosslinked PVPP, starch and sodium-carboxymethyl cellulose), lubricants (e.g. stearic acid, magnesium stearate), glidants (e.g. silicon dioxide (Aerosil®)) or mixtures thereof. Tableting excipients are additives that make a practical manufacturing of tablets possible and have an essential influence on the processability of the tablet formulation and on the properties of the finished tablet. The tableting excipients are selected depending on the pharmacokinetic requirements and the respective active agent.

[0004] Usually, the pharmaceutically active agents together with the respective tableting excipients are manufactured into a granulate with the aid of a solvent (e.g. via wet granulation). Subsequently, the obtained granulate is pressed to form a tablet. However, the simplest and most economical way of manufacturing tablets is direct tableting, i.e. tableting without previous granulation of active component(s) and tableting excipients. Tablet formulations which are suitable for direct tableting have to have a sufficient plastic deformability and good flow properties and must not exhibit any separation tendencies. Due to these complex requirements, direct tableting has only rarely been carried out so far (K. Bauer, "Pharmazeutische Technologie", 1993, publisher Georg Thieme, Stuttgart).

[0005] Besides cost effectiveness, a further advantage of direct tableting is that no granulation of the pharmaceutically active component is necessary and therefore solvent-sensitive components can readily be processed to form tablets.

[0006] Hence, there is a great demand for tableting excipients which can simply be mixed with the pharmaceutically active agent and optionally with further tableting excipients and subsequently be compressed directly (direct tableting excipient). The property profile of directly compressible tablet formulations described above is in most cases not achieved by simply (physically) mixing the commercially available individual components of a tablet formulation. Therefore, mixed granulates comprising different tableting excipients are often used.

[0007] Such mixed granulates are suitable for the conventional production of tablets and other dosage forms, but may also be advantageous as direct tableting excipient.

[0008] US 6,770,368 describes a granulate consisting of starch and lactose used as excipients for direct tableting. The granulate is prepared by spray drying a solution or suspension of both components.

[0009] US 4,693,750 describes an excipient for direct tableting, which essentially consists of lactose and cellulose. For this purpose, cellulose powder and lactose are mixed in hot water and subsequently spray dried.

[0010] EP 0 948 321 discloses the production of a lactose/ethyl cellulose preparation, wherein both components are dispersed in water by means of a stirrer and subsequently spray dried.

[0011] US 6,770,368 concerns granules consisting of lactose and starch. As particularly preferred embodiment, a granulate containing 85% by weight of α -lactose monohydrate and 15% by weight of native maize starch is described. The latter product is commercially available under the tradename StarLac® (Meggler Group, Wasserburg). The granulate is used for direct compression tablet manufacture and is particularly characterized by its rapid disintegration profile. However, the tablet hardness achieved with the StarLac® product might be improved.

[0012] Granules made of α -lactose monohydrate (75 wt.-%) and a microcrystalline cellulose (25 wt.-%) are commercially available under the tradename MicroceLac® 100 (Meggler Group, Wasserburg). The granulate is primarily used for direct compression (DC) tablet manufacture and is suitable for providing improved hardness, which can be yielded in the tablets produced therewith. Although MicroceLac® provides excellent tablet hardness, the disintegration times are to be improved.

[0013] WO 2011/074961 deals with co-processed excipient compositions comprising granules, said granules comprising at least one filler-binder and at least one lubricant which have been subjected to granulation together, said granules being coated with lactose. It was found that flowability can be increased without sacrificing disintegration. The developed excipient is said to have overcome the obligatory final coating of excipients with lubricants which complicates tablet manufacture and loss of compactability.

[0014] There was a long-lasting need of direct tableting excipients that exhibit a good flowability while simultaneously having a high hardness yield and fast disintegration times. Such a performance is requested for a variety of drug containing tablets e.g. for analgetics.

[0015] Thus, in one aspect, the present invention provides a composition comprising at least one lactose component, at least one cellulose component and at least one starch component, according to claim 1.

[0016] Lactose belongs to the group of disaccharides and consists of the two molecules β -D-

galactose and α/β -D-glucose, which are linked together by a β -1,4 glycosidic bond. According to the invention, the lactose component is anhydrous lactose or a lactose monohydrate. Lactose monohydrate is preferred, since it is less hygroscopic compared to anhydrous lactose and is thus more suitable in compositions containing water-sensitive pharmaceutically active components.

[0017] Cellulose is a polysaccharide composed of a large number of β -D-glucose molecules, which are linked by a 1,4- β glycosidic bond. The hydroxyl groups present in the polysaccharide can be chemically modified in a variety of ways. The hydroxyl groups of cellulose can, independently of each other, be at least partially alkylated, hydroxy alkylated, sulfonated, nitrated, carboxy alkylated or/and xanthogenated under certain reaction conditions. The modified celluloses obtained are defined as "*cellulose derivatives*", whose profile of properties, e.g. with regard to water-solubility and active substance compatibility, can be tailored for the respective applications. According to the invention, the cellulose component may be selected from celluloses such as microcrystalline cellulose (MCC) and powder cellulose and cellulose derivatives such as hypromellose (hydroxypropyl methyl cellulose (HPMC)), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), carboxymethyl cellulose (CMC), carboxyethyl cellulose (CEC), ethyl cellulose (EC), hypromellose phthalate, and salts thereof. In preferred embodiments, the cellulose component is a microcrystalline cellulose (MCC), preferably having a molecular weight of 20.000 to 50.000 Da, more preferably of 32.000 to 39.000 Da.

[0018] Starch is a carbohydrate consisting of a large number of glucose units joined by glycosidic bonds. The polysaccharide is contained in large amounts in e.g. potatoes, sweet maize (corn) and rice and may be derived therefrom. Modified starches (starch derivatives) have been chemically modified to allow the starch to function properly under conditions frequently encountered during processing or storage, such as high heat, high shear, low pH, etc. Modified starches are e.g. E-coded according to the international number system for food additives (INS(EG) 1400-1405, 1410, 1412-1414, 1420, 1422, 1440, 1442, 1443, 1450, 1451).

[0019] According to the invention, the starch component is native starch, such as corn (maize) starch.

[0020] The composition according to the invention preferably comprises the lactose component in an amount of 55-90% by weight, more preferably 60-90% by weight, more preferably 65-85% by weight, more preferably 65-75% by weight and even more preferably 68-72 % by weight or 72-75% by weight, based on the total mass of the composition. The lactose component is preferably present in an amount of 68-72% by weight based on the total mass of the composition.

[0021] The cellulose component is preferably present in an amount of 5-30% by weight, more preferably 10-30% by weight, more preferably 15-25% by weight and even more preferably 19-22% by weight or 15-19% by weight, based on the total mass of the composition. The cellulose component is preferably present in an amount of 19-22% by weight based on the total mass of the composition.

[0022] The starch component may be comprised in the composition in an amount of 5-25% by weight, preferably 5-20% by weight, more preferably 8-13% by weight and even more preferably 8-12% by weight or 11-13% by weight, based on the total mass of the composition. The starch component may be comprised in the composition in an amount of preferably 8-12% by weight based on the total mass of the composition.

[0023] According to the present invention, addition of a lubricant is surprisingly not necessary to support the tableting process. Thus, in a preferred embodiment, the present composition is substantially free of a lubricant.

[0024] In a preferred embodiment, the composition of the invention consists of at least one lactose component, at least one cellulose component and at least one starch component. More preferably, the composition consists of lactose monohydrate, microcrystalline cellulose and native starch, such as corn (maize) starch.

[0025] The compositions of the invention preferably have a total amount of water of less than 9% by weight, preferably 0.001-8% by weight, more preferably 0.001-7% by weight, more preferably 0.001-6.5% by weight and even more preferably 0.001-5.5% by weight, based on the total amount of the composition. The term "*total amount of water*" means the sum of molecularly complexed water (crystal water) plus free water.

[0026] In a preferred embodiment of the invention, the total amount of free water is less than 8% by weight, preferably 0.001-5% by weight and more preferably 0.001-3% by weight, based on the total amount of the composition, the amount of which is determined by the weight loss of the composition at a temperature of between 80°C and 130 °C.

[0027] The composition is preferably present in the form of agglomerates, such as granules, spheres, flakes or pellets, more preferably granules. The agglomerates of the present invention particularly have a spherical morphology or a spheroidal morphology. The agglomerates may have a mean particle size d_{50} of 5-500 μm , preferably 50-250 μm . The composition and particularly the agglomerate of the present invention is substantially homogeneous, i.e. a substantially homogeneous mixture of the components of the composition. "Homogeneous mixture" or "homogeneous" as used herein means that the composition of the components is essentially constant over the whole agglomerate, i.e. the agglomerates of the invention do not exhibit any domains enriched by one of the components, e.g. a coating of a certain component.

[0028] During the tableting process, the composition of the invention may be mixed with at least one pharmaceutically active component and optionally further excipients. Thus, in one aspect, the present invention provides a composition further comprising at least one pharmaceutically active component and optionally further excipients. Suitable pharmaceutically active components are particularly present in solid form and may be paracetamol, acetyl salicylic acid, ibuprofen, ketoprofen, diclofenac salts.

[0029] In another aspect, the composition, preferably the agglomerate, is free of a pharmaceutically active component.

[0030] Further excipients may be glidants, such as talcum; fillers, such as titanium dioxide and calcium diphosphate; binders, such as glucose, starch, gelatin, PVP; antistatic agents, such as aluminum oxide; surfactants, such as saponins; humectants, such as glycerol or PEG; glidants, such as silicon dioxide; and lubricants, such as magnesium stearate. More preferably, the excipients are selected from the group consisting of glidants, fillers, binders, antistatic agents, surfactants, and humectants as described above.

[0031] In a further aspect of the invention, a method for manufacturing a composition as described above is provided. The method of the invention comprises the steps of

1. (i) providing a solution or suspension comprising at least one lactose component, at least one cellulose component and/or at least one starch component in a liquid medium, and
2. (ii) spraying the solution or suspension obtained in step (i) in an environment at an increased temperature, optionally at reduced pressure, thereby removing the liquid medium at least partially.

[0032] In step (i), the at least one lactose component, the at least one cellulose component and the at least one starch component are preferably at least partially solved in a liquid medium, such as water, or an organic solvent, such as ethanol, acetic acid and acetone, and mixtures thereof.

[0033] The solution or suspension obtained in step (i) preferably has a total amount of lactose component, cellulose component and/or starch component in the range of between 5 and 60% by weight, more preferably 30-50% by weight, based on the total amount of solution or suspension.

[0034] The obtained solution or suspension is configured such that it may be pumped through spray nozzles having a diameter of 1.0 to 3.0 μm at a pressure of 0.5-100 bar and at a temperature of 20°C at a rate of 10-3000 kg/h.

[0035] In step (ii), the solution or suspension obtained in step (i) is sprayed in an environment at an increased temperature of preferably 30-300 °C, even more preferably 50-250 °C. The pressure in the environment may be reduced to about 0-1.0 bar, preferably 0.003-0.4 bar. The spraying apparatus is configured such that in step (ii), the liquid medium is at least partially removed. The solution or suspension is preferably sprayed via nozzles, in particular one-substance or two-substance nozzles. In a preferred embodiment, the solution or suspension is pressed through a one-substance nozzle at a pressure of 10-100 bar, more preferably 30-60 bar, or pressed through a two-substance nozzle at a pressure of 0.5-5 bar, more preferably

1.5-3.5 bar.

[0036] In a preferred embodiment, the method according to the invention is conducted in a spray dryer, which is known in the field (e.g. type tall spray dryer).

[0037] In another embodiment, step (ii) may be conducted in the presence of particles of at least one of the cellulose component, the starch component or the lactose component, e.g. in a fluid bed granulator.

[0038] In a preferred embodiment, however, a process in a spray drier is performed, since this process is very cost-effective and the products obtained thereby result in the desired properties as described above.

[0039] In another aspect, the present invention relates to a product as obtained by the above described process.

[0040] In a further aspect, the present invention is directed to the use of a composition as described above as an excipient in making oral dosage forms, particularly as a tableting excipient, more particularly as a direct tableting excipient. Thus, in a further aspect, the present invention also provides an oral dosage form comprising a composition as described above and at least one pharmaceutically active component and optionally further excipients as described above. The oral dosage form of the invention may be configured for immediate release or for sustained release, particularly for immediate release. The oral dosage form of the invention may be in the form of a tablet, a capsule, a sachet, a granulate, preferably in the form of a tablet.

[0041] The composition of the invention may also be used in cosmetics, cleaning applications or engineering applications.

[0042] It has turned out that the use of the composition according to the invention as a (direct) tableting excipient in standard tablet formulations results in a significant improvement of the tablet hardness and abrasion resistance compared to tablets in which the components of the composition according to the invention have been formulated as individual components, i.e. in a physical mixture. Simultaneously, the disintegration times have not been affected adversely in view of the increased hardness of the directly tableted dosage forms. The invention is further illustrated by the following figures and examples.

Figures

[0043]

Figure 1:

Tablet hardness vs. compaction pressure: composition of the invention, MicroceLac and

StarLac

Figure 2:

Disintegration time vs. tablet hardness: composition of the invention, MicroceLac and StarLac

Figure 3:

Disintegration time vs. compaction pressure: composition of the invention and physical mixtures

Figure 4:

Hardness vs. compaction pressure in paracetamol-containing tablet: composition of the invention, MicroceLac and StarLac

Figure 5:

Friability vs. compaction pressure in paracetamol-containing tablet: composition of the invention, MicroceLac and StarLac

Figure 6:

Disintegration time vs. tablet hardness in paracetamol-containing tablet: composition of the invention, MicroceLac and StarLac

Figure 7:

Paracetamol release vs. time: composition of the invention, MicroceLac and StarLac

Figure 8:

SEM-image of agglomerates of the invention

Figure 9A + B:

SEM-image of agglomerates according to Example 5

Figure 9C:

SEM-image of a physical mixture according to Example 5

Figure 10:

Tensile strength vs. compaction pressure at different mixing times

Figure 11:

Hardness vs. compaction force for composition 9 and PM9

Examples

Methods

[0044] Release times are determined using apparatus II (Erweka, Germany DT 808 LH). The tests take place in 1000 ml 0.01 HCl, 0.05 M phosphate buffer (pH 6.8) [produced according to the United States Pharmacopeial Convention (USP)] or acetate buffer (pH 4.5) [USP] at a rotation speed of 50 rpm. The quantitative measurement of the released active substance is carried out by means of UV spectroscopy.

[0045] Tablets were pressed on a Korsch apparatus EK 0 using punches having 7 mm (round),

8 mm (round) and 11 mm (round), providing tablets having a tablet weight of 150 mg, 240 mg or 500 mg, respectively.

[0046] Friability was tested according to Ph. Eur method on a Erweka friability tester.

[0047] Tablet hardness was tested with a Erweka TBH 425 tablet hardness tester.

Example 1 Tablets of the invention

[0048] Composition 1 according to the invention was manufactured by spray-drying an aqueous suspension/solution (solid content: 40 wt.-%) containing lactose monohydrate, microcrystalline cellulose and native maize starch (see Table 1) in a spray-drying apparatus under the following conditions: water evaporation 1500 kg/h, inlet air temperature 165°C and 40 bar dispersion pressure with one component nozzles. The obtained aggregates of the invention were mixed with magnesium stearate and tablets (8 mm, round, 240 mg) were pressed on a Korsch EK 0 apparatus. The composition of the tablets is indicated in Table 1.

[0049] For comparison, tablets were prepared from MicroceLac® and StarLac® using magnesium stearate as additional lubricant in the same manner as described above.

[0050] The tablet hardness was determined in relation to the respective compaction pressure used during tablet preparation. From Figure 1, it can clearly be observed that the tablet hardness of the composition of the invention is comparable to the tablet hardness of MicroceLac®. MicroceLac® is known to provide excellent compactability and hardness. On the other hand, the tablets were subjected to a disintegration test. Figure 2 shows the results of the disintegration time versus tablet hardness. It can be seen that despite the high tablet hardness of the tablets of the invention (>175N), the disintegration time is still below 200 seconds and thus comparable to the StarLac tablets. StarLac® is known as an excipient for short tablet disintegration times. From the results above, it can be seen that the tablets of the present invention synergistically combine the desirous characteristics of StarLac® and MicroceLac®, resulting in tablets having ideal hardness at excellent short disintegration times.

Table 1: Composition of tablets according to Example 1

tablet	Composition 1	MicroceLac 1	StarLac 1
Composition of invention [wt-%]: 70% lactose monohydrate, 20 % microcrystalline cellulose, 10% native maize starch	99.5	-	-
MicroceLac® 100 [wt-%]: 75% α -lactose monohydrate 25% microcrystalline cellulose	-	99.5	-
StarLac® [wt-%]: 85% α -lactose monohydrate 15% native maize starch	-	-	99.5
magnesium stearate	0.5	0.5	0.5

[0051] Further compositions (compositions 2-4) were made under the conditions as described above. Tablets were pressed in the same manner as described above. The compositions and test results of the tablets are shown in Table 2.

Table 2: Compositions 2-3

		Composition 2	Composition 3
80% lactose monohydrate 12.5% microcrystalline cellulose 7.5% native maize starch [wt-%]		99.5	-
60% lactose monohydrate 25.5% microcrystalline cellulose 12.5% native maize starch [wt-%]		-	99.5
magnesium stearate [wt.-%]		0.5	0.5
Tablet hardness [N] at compaction force	6 kN	70	170
	9 kN	93	249
	13kN	122	311
disintegration time (s) at compaction force	6 kN	26	48
	9 kN	22	178
	13kN	15	315

[0052] All tablets shown in Table 2 have good hardness at acceptable disintegration times.

[0053] Figure 8 shows a representative SEM-image of an agglomerate of the compositions according to the invention. Also from the SEM image of complete and broken agglomerates it can be derived that the agglomerates represent a homogeneous mixture.

Example 2 Physical mixtures

[0054] In order to compare the tablets according to the invention with tablets produced from physical mixtures, tablets (7 mm, round, 150 mg) were pressed on a Korsch EK0 apparatus. The physical mixtures were homogeneously mixed on a turbula blender, Willy A. Bachofen Maschinenfabrik, Muttenz, Swiss before tableting. The composition of the tablets is shown in Table 3.

Table 3: Comparison of composition of the invention and physical mixtures

	Composition 5	Composition 6	PM 5	PM 6
composition of the invention: 70% lactose monohydrate 20% microcrystalline cellulose 10% native maize starch [wt-%]	99.5	96.5	-	-

	Composition 5	Composition 6	PM 5	PM 6
lactose monohydrate [wt-%]	-	-	69.65	67.55
microcrystalline cellulose [wt-%]	-	-	19.9	19.3
native maize starch [wt-%]	-	-	9.95	9.65
magnesium stearate [wt-%]	0.5	0.5	0.5	0.5
sodium croscarmellose [wt-%]	-	3	-	3

[0055] The disintegration times in water at 37°C of the obtained tablets were determined. The data are illustrated in Figure 3. Figure 3 shows that the tablets of the present invention (compositions 5 and 6) in each case have significantly reduced disintegration time as compared to the tablets prepared from the physical mixture (PM).

Example 3 Drug-containing tablets

[0056] Paracetamol-containing tablets (11 mm, round, 500 mg) were prepared on a Korsch EK 0. The composition of the tablets is indicated in Table 4.

Table 4: Composition of drug-containing tablets

	Composition 7	MicroceLac 7	StarLac 7
composition of the invention: 70% lactose monohydrate 20% microcrystalline cellulose 10% native maize starch [wt-%]	88	-	-
StarLac® [wt-%]	-	-	88
MicroceLac® [wt-%]	-	88	-
magnesium stearate [wt-%]	1	1	1
Aerosil [wt-%]	1	1	1
paracetamol [wt-%]	10	10	10

[0057] The results in Example 1 also apply to the tablets of the invention containing an active ingredient such as paracetamol. As can be seen from Figures 4-7, the tablet hardness and friability of the tablets according to the invention are comparable to those of the MicroceLac tablet (which is known to have excellent hardness and friability characteristics) (Figures 4 and 5). On the other hand, however, the disintegration time of the tablets according to the invention is comparable to the disintegration rate of the StarLac tablet (which is known to have excellent disintegration characteristics) (Figure 6). The release of paracetamol over time is indicated in Figure 7. The graph shows the fastest release time for the tablets of the invention (composition 7) as compared to the reference tablets (MicroceLac 7 and StarLac 7). This release profile

makes the compositions of the invention ideally suitable for immediate release applications.

Example 4 Tablets with higher amounts of active agent

[0058] Tablets (11 mm, round, 500 mg) containing paracetamol (30%) as a pharmaceutically active component were prepared on a Korsch EK0 apparatus. The composition of the tablets is indicated in Table 5.

Table 5: Tablets containing 30% of paracetamol

		Composition 8	MicroceLac 8	StarLac 8
composition of the invention: 70% lactose monohydrate 20% microcrystalline cellulose 10% native maize starch [wt-%]		68.5	-	-
StarLac® [wt-%]		-	-	68.5
MicroceLac® [wt-%]		-	68.5	-
magnesium stearate		1	1	1
Aerosil [wt-%]		0.5	0.5	0.5
paracetamol [wt-%]		30	30	30
tablet hardness (N) at compaction force [kN]	7 kN	52	51	-
	13 kN	90	104	-
	19 kN	115	133	-
Friability (%) at compaction force [kN]	7 kN	2.5	1.8	-
	13 kN	0.5	0.2	-
	19 kN	5.4	2.4	-
disintegration time [min] at compaction force [kN]	7 kN	0:44	2:04	-
	13 kN	0:44	25:32	-
	19 kN	1:25	>60	-

[0059] While the StarLac 8 tablets have high and thus unacceptable friability at any compaction force, the results in Table 5 clearly show that the tablets according to the invention have an acceptable hardness (>90 N), acceptable friability (<1%) and acceptable short disintegration times (<1 min) at a compaction force of 13 kN. The tablets containing MicroceLac (MicroceLac 8) have an acceptable hardness (104 N). However, these tablets provide long and unacceptable disintegration times (>25 min).

Example 5 Morphological observations

[0060] In order to investigate the morphological properties, agglomerates according to the invention were made of 70% lactose monohydrate, 20% microcrystalline cellulose and 10% native maize starch. The agglomerate according to the invention was manufactured by spray-drying an aqueous suspension/solution (solid content 40 wt.-%) in a spray-drying apparatus under the following conditions: water evaporation 1,500 kg/h, inlet air temperature 165 °C and 40 bar dispersion pressure with one component nozzles (composition 9). For comparison, a physical mixture made of 70% spray-dried lactose monohydrate, 20% microcrystalline cellulose and 10% native maize starch was compounded in a turbula blender, Willy A. Bachofen Maschinenfabrik, Muttensz, Switzerland (PM9). The SEM-micrographs of the agglomerate according to the invention (Figure 9A and B) and the physical mixture (Figure 9C) are illustrated in the Figures. In the agglomerate according to the invention, all compounds together form homogeneous sphericals and cannot be separated by physical processes. Therefore, the predetermined concentration of the components in the composition can be ensured at any time during delivery. In the physical mixture, the components lactose, cellulose and starch are separated from each other (Figure 9C). Due to the different sizes and characteristics of the compounds, at least a partial segregation of the components might occur, which makes it impossible to deliver several portions having the same composition.

Example 6

[0061] In a further step, 0.5 wt.-% magnesium stearate were added to composition 9 and the physical mixture PM9 prepared in Example 5. Composition 9 and PM9, respectively, were mixed with magnesium stearate at different mixing times (0.5, 2.0 and 5.0 minutes). From the magnesium stearate containing compound 9 and the magnesium stearate containing physical mixture PM9, tablets were pressed on a Korsch EK0 apparatus (8 mm, round, 240 mg). The tablets were compacted at different compaction pressures. In Figure 10, the tensile strength is shown over the compaction pressure. The data show that the agglomerates according to the invention (composition 9) are far less sensitive to the mixing procedure than the physical mixture.

[0062] In Figure 11, the tablet hardness is shown over the compaction force. The results evidence that the compressibility of tablets containing composition 9 is improved over tablets containing a physical mixture.

[0063] The following items are also described:

1. 1. Composition comprising at least one lactose component, at least one cellulose component and at least one starch component.
2. 2. Composition according to item 1, wherein the lactose component is selected from anhydrous lactose and lactose monohydrate.
3. 3. Composition according to item 1 or 2, wherein the cellulose component is selected from cellulose, such as microcrystalline cellulose (MCC), and powder cellulose; and cellulose derivatives, such as hypromellose (hydroxypropylmethylcellulose (HPMC)),

hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), carboxymethylcellulose (CMC), carboxyethylcellulose (CEC), ethylcellulose (EC), hypromellosephthalate, and salts thereof.

4. 4. Composition according to any of items 1-3, wherein the starch component is selected from starch, such as native starch, pregelatinized starch and starch derivatives, particularly native starch.
5. 5. Composition according to any of items 1-4, wherein the lactose component is present in an amount of 55-90% by weight, more preferably 60-90% by weight, more preferably 65-85% by weight, more preferably 65-75% by weight and even more preferably 68-72% by weight or 72-75% by weight, based on the total mass of the composition.
6. 6. Composition according to any of items 1-5, wherein the cellulose component is present in an amount of 5-30% by weight, preferably 10-30% by weight, more preferably 15-25% by weight and even more preferably 19-22% by weight or 15-19% by weight, based on the total mass of the composition.
7. 7. Composition according to any of items 1-6, wherein the starch component is present in an amount of 5-25% by weight, preferably 5-20% by weight, more preferably 8-13% by weight, and even more preferably 8-12% by weight or 11-13% by weight, based on the total mass of the composition.
8. 8. Composition according to any of items 1-7, wherein the composition consists of at least one lactose component, at least one cellulose component and at least one starch component.
9. 9. Composition according to any of items 1-8, wherein the composition consists of lactose monohydrate, microcrystalline cellulose and native starch.
10. 10. Composition according to any of items 1-9, wherein the composition is substantially free of a lubricant.
11. 11. Composition according to any of items 1-10 having a total amount of water of less than 9% by weight, preferably 0.001-8% by weight, more preferably 0.001-7% by weight, more preferably 0.001-6.5% by weight and even more preferably 0.001-5.5% by weight, based on the total amount of the composition.
12. 12. Composition according to any of items 1-11 having a total amount of free water of less than 8 % by weight, preferably 0.001-5 % by weight, more preferably 0.001-3 % by weight, based on the total amount of the composition.
13. 13. Composition according to any of items 1-12, wherein the composition is in the form of agglomerates, such as granules, particularly having a mean particle size d_{50} of 5-500 μm , preferably 50-250 μm .
14. 14. Composition according to item 13, wherein the agglomerate represents an homogeneous mixture of the components of the composition.
15. 15. Composition according to any of items 13 or 14, wherein the agglomerate has a spherical morphology or a spheroidal morphology.
16. 16. Composition according to any of items 1-15 further comprising at least one pharmaceutically active component and optionally further excipients.
17. 17. Composition according to item 16, wherein the excipients are selected from the group consisting of glidants, fillers, binders, antistatic agents, surfactants, humectants and lubricants.

18. 18. Method for manufacturing a composition according to any of items 1-17 comprising the steps of
 1. (i) providing a solution or suspension comprising at least one lactose component, at least one cellulose component and/or at least one starch component in a liquid medium, and
 2. (ii) spraying the solution or suspension obtained in step (i) in an environment at an increased temperature, optionally at reduced pressure, thereby removing the liquid medium at least partially.
19. 19. Method according to item 18, wherein the liquid medium is selected from water, organic solvents such as ethanol, acetic acid and acetone, and mixtures thereof.
20. 20. Method according to any of items 18 or 19, wherein the total amount of lactose component, cellulose component and/or starch component is in the range of between 5 and 60% by weight, preferably 30-50% by weight, based on the total amount of the solution or suspension.
21. 21. Method according to any of items 18-20, wherein the temperature in step (ii) is in the range of 30-300°C, preferably about 50-250°C.
22. 22. Method according to any of items 18-21, wherein spraying in step (ii) is performed through nozzles, particularly one-substance or two-substance nozzles.
23. 23. Method according to any of items 18-22, wherein the pressure in step (ii) is in the range of 0 to 1.0 bar, preferably 0 to 0.5 bar, more preferably 0.003 to 0.4 bar.
24. 24. Method according to any of items 18-23 which is conducted in a spray dryer.
25. 25. Method according to any of items 18-24, wherein step (ii) is conducted in the presence of particles of at least one of the cellulose component, the starch component or the lactose component.
26. 26. Method according to item 25 which is conducted in a fluid bed granulator.
27. 27. Use of a composition according to any of claims 1-17 as an excipient in making oral dosage forms, particularly as a tableting excipient, more particularly as a direct tableting excipient.
28. 28. Use of the composition according to any of claims 1-17 in cosmetics, cleaning applications or engineering.
29. 29. Oral dosage form comprising a composition according to any of claims 1-17, at least one pharmaceutically active component, and optionally further excipients.
30. 30. Oral dosage form according to claim 29 for immediate release.
31. 31. Oral dosage form according to any of claims 29 or 30, which is a tablet, a capsule, a sachet or a granulate.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

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P a t e n t k r a v

- 5 **1.** Agglomerat bestående af mindst en lactosebestanddel, mindst en cellulosebestanddel, mindst en stivelsesbestanddel og en samlet mængde af vand på mindre end 9 vægt-%, beregnet på basis af agglomeratets samlede mængde,
hvor lactosebestanddelen er udvalgt blandt vandfri lactose og lactosemonohydrat og foreligger i en mængde på 55-90 vægt-% beregnet på basis af agglomeratets samlede mængde,
10 hvor stivelsesbestanddelen er udvalgt blandt nativ stivelse og foreligger i en mængde på 5-25 vægt-% beregnet på basis af agglomeratets samlede mængde,
og hvor cellulosebestanddelen foreligger i en mængde på 5-30 vægt-% beregnet på basis af agglomeratets samlede mængde.
15
- 2.** Agglomerat ifølge krav 1, hvor cellulosebestanddelen er udvalgt blandt cellulose, såsom mikrokrySTALLinsk cellulose (MCC) og pulvercellulose; og cellulosederivater, såsom hypromellose (hydroxypropylmethylcellulose (HPMC)), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), carboxymethylcellulose (CMC), carboxyethylcellulose (CEC), ethylcellulose (EC), hypromellosephthalat og salte deraf.
20
- 3.** Agglomerat ifølge et af kravene 1 eller 2, hvilket har en samlet mængde af vand på 0,001-8 vægt-%, mere foretrukket 0,001-7 vægt-%, mere foretrukket 0,001-6,5 vægt-% og endnu mere foretrukket 0,001-5,5 vægt-%, beregnet på basis af agglomeratets samlede mængde.
25
- 4.** Agglomerat ifølge et af kravene 1-3, hvor agglomeratet foreligger i form af granulater, især med en gennemsnitlig partikelstørrelse d_{50} på 5-500 μm , fortrinsvis 50-250 μm .
30
- 5.** Agglomerat ifølge krav 4, hvilket danner en homogen blanding af alle bestanddele.

- 6.** Fremgangsmåde til fremstilling af et agglomerat ifølge et af kravene 1-5 omfattende de følgende trin
- 5 (i) at tilvejebringe en opløsning eller suspension bestående af mindst en lactosebestanddel, mindst en cellulosebestanddel og mindst en stivelsesbestanddel i et flydende medium, og
- (ii) at sprøjte opløsningen eller suspensionen opnået i trin (i) i et miljø ved en øget temperatur på 30 - 300°C, eventuelt ved reduceret tryk på 0 - 1,0 bar, hvorved det flydende medium fjernes i det mindste delvist.
- 10 **7.** Fremgangsmåde ifølge krav 6, hvor det flydende medium er udvalgt blandt vand, organiske opløsningsmidler, såsom ethanol, eddikesyre og acetone, og blandinger deraf.
- 15 **8.** Fremgangsmåde ifølge et af kravene 6-7, hvilken udføres i en spraytørrer.
- 9.** Anvendelse af et agglomerat ifølge et af kravene 1-5 som et hjælpestof til fremstilling af orale doseringsformer, især som et tableteringshjælpestof, mere især som et direkte tableteringshjælpestof.
- 20 **10.** Oral doseringsform omfattende et agglomerat ifølge et af kravene 1-5, i det mindste en farmaceutisk aktiv bestanddel og eventuelt yderligere hjælpestoffer.

DRAWINGS

Figure 1

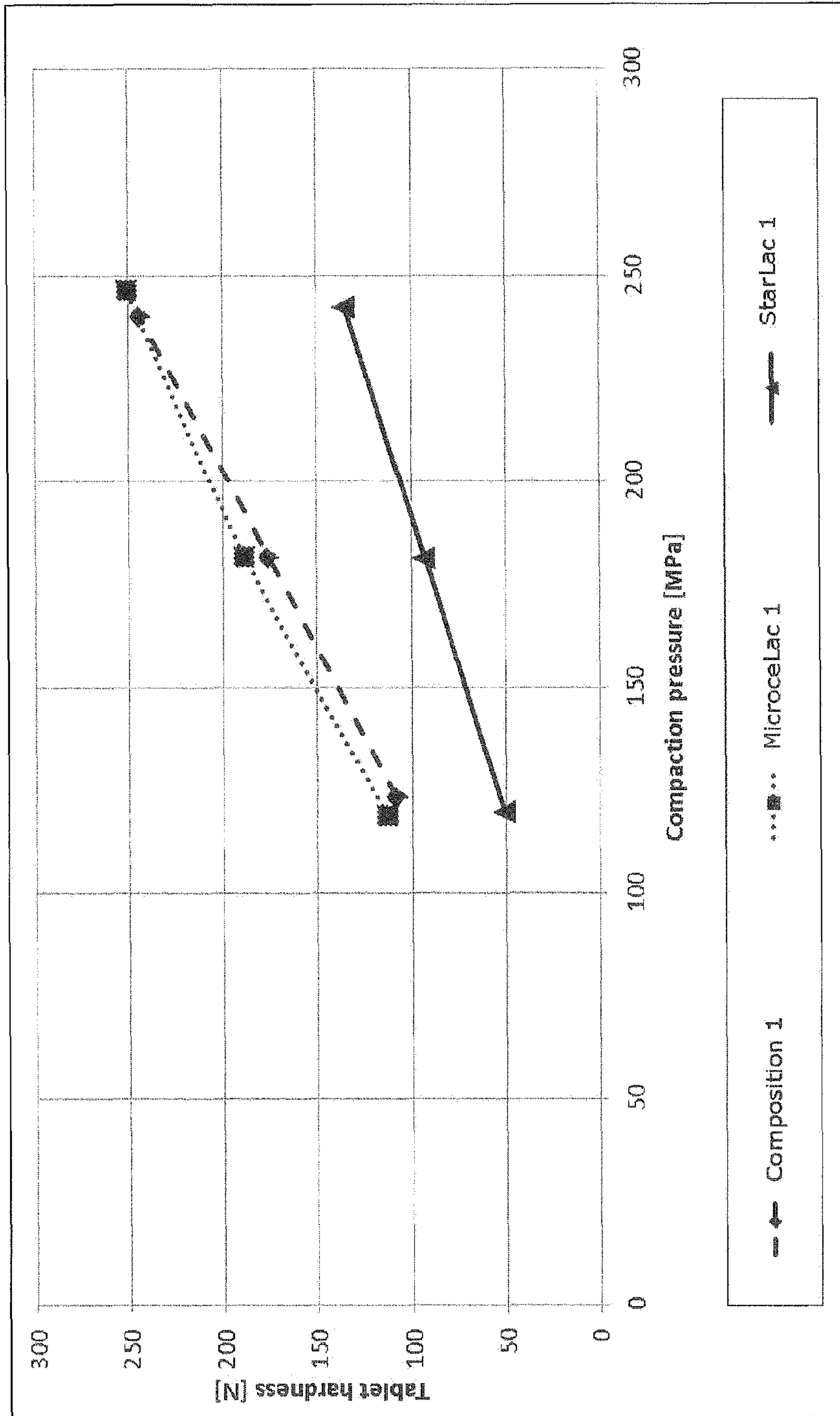


Figure 2

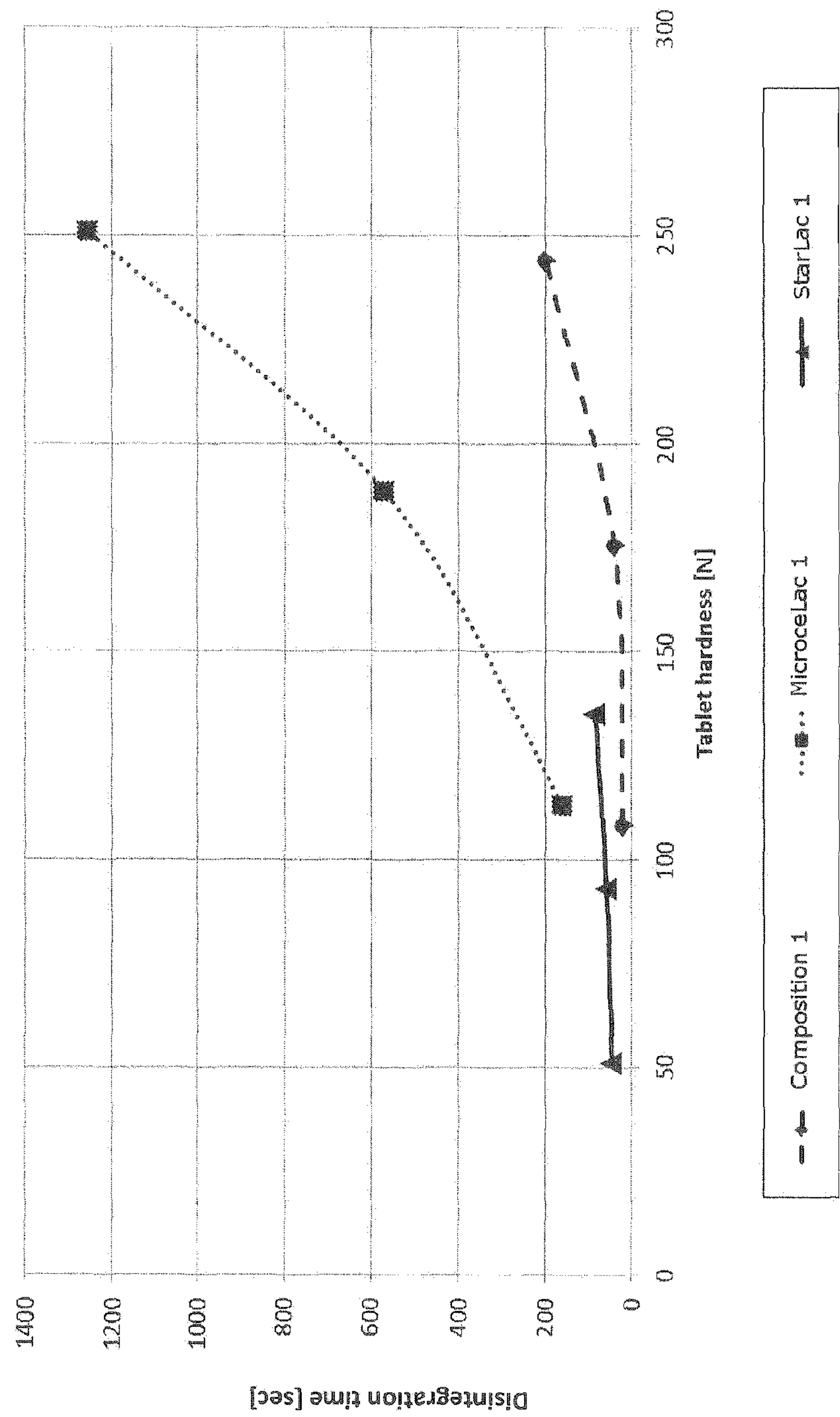


Figure 3

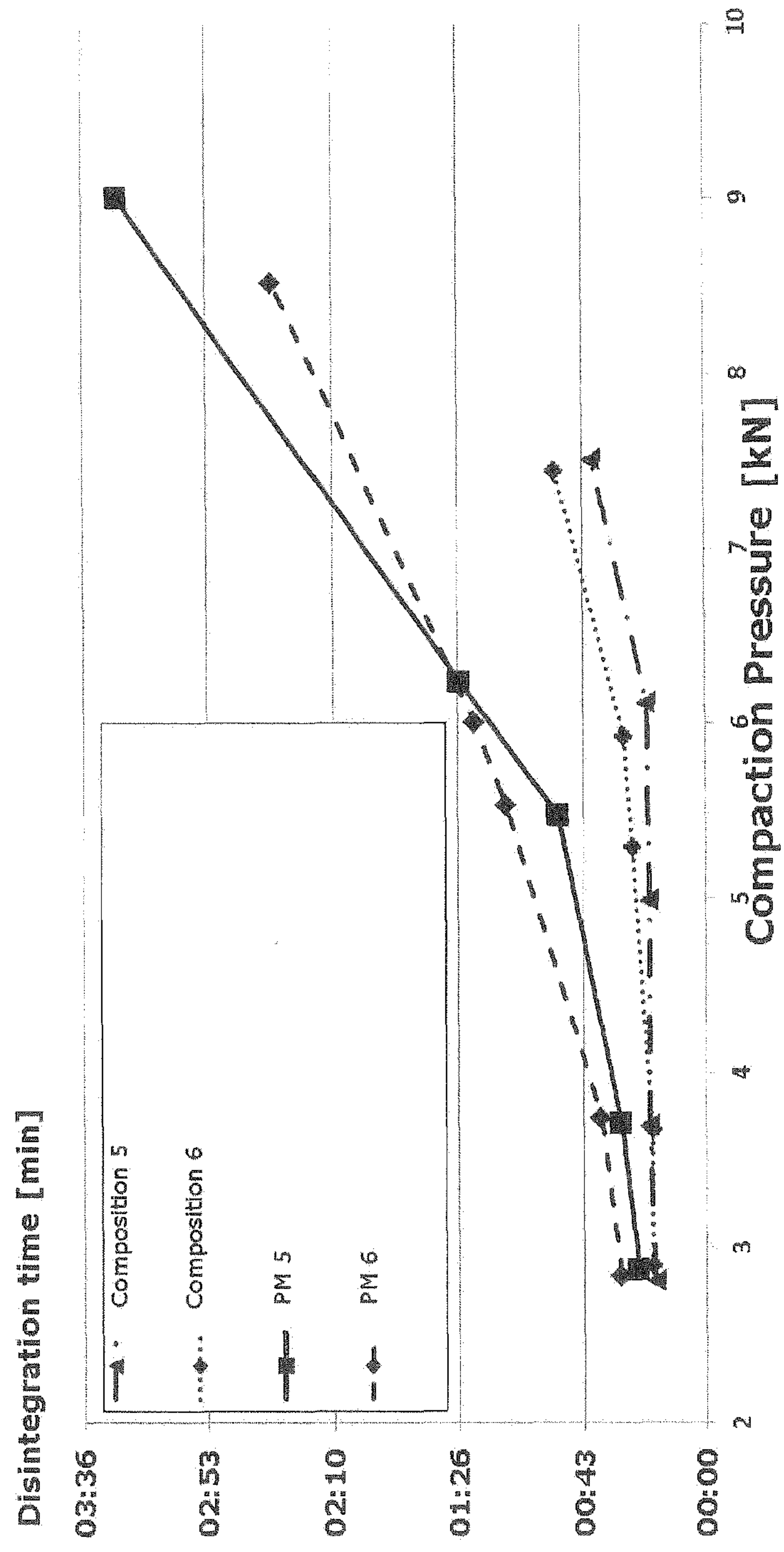


Figure 4

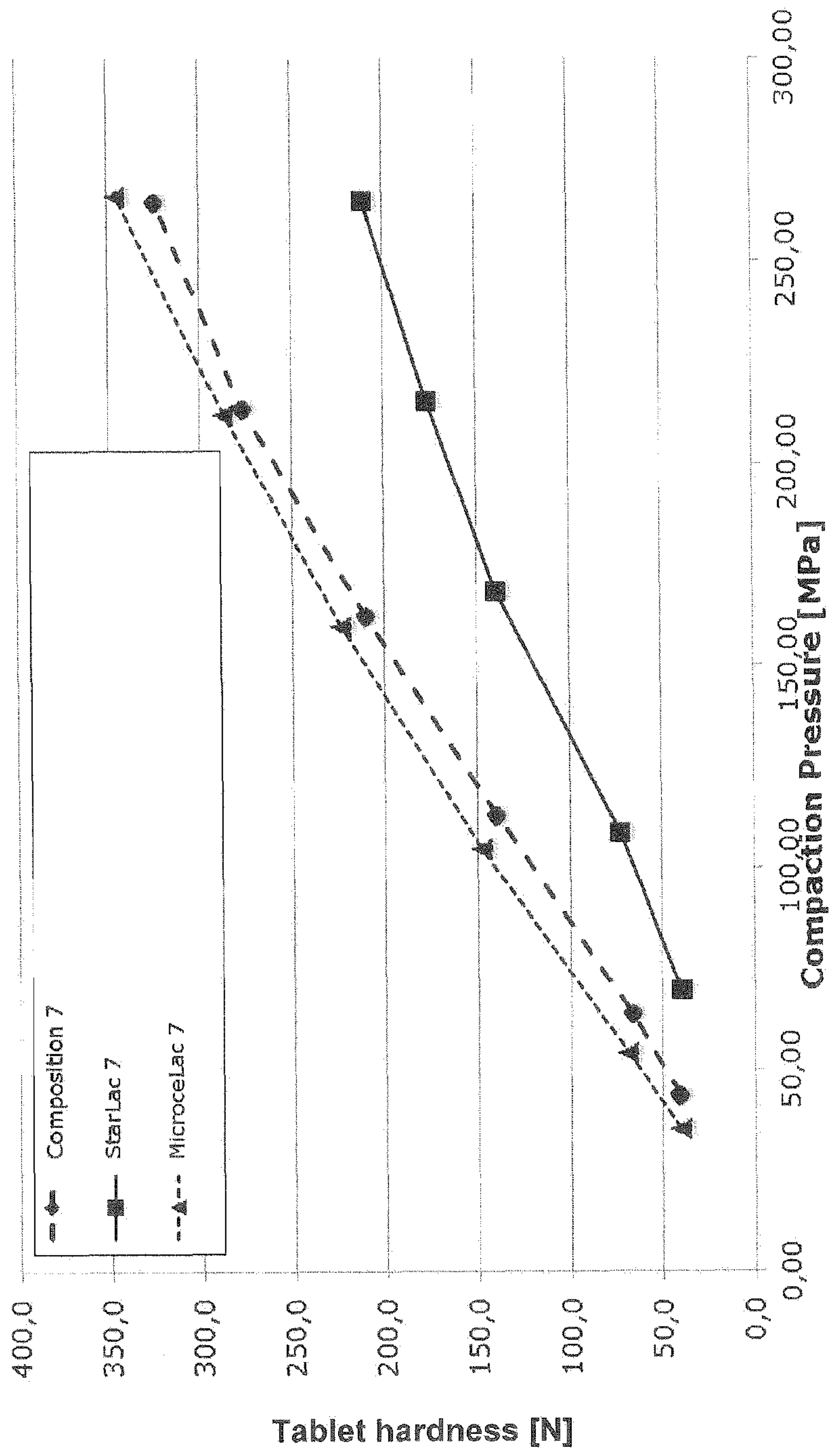


Figure 5

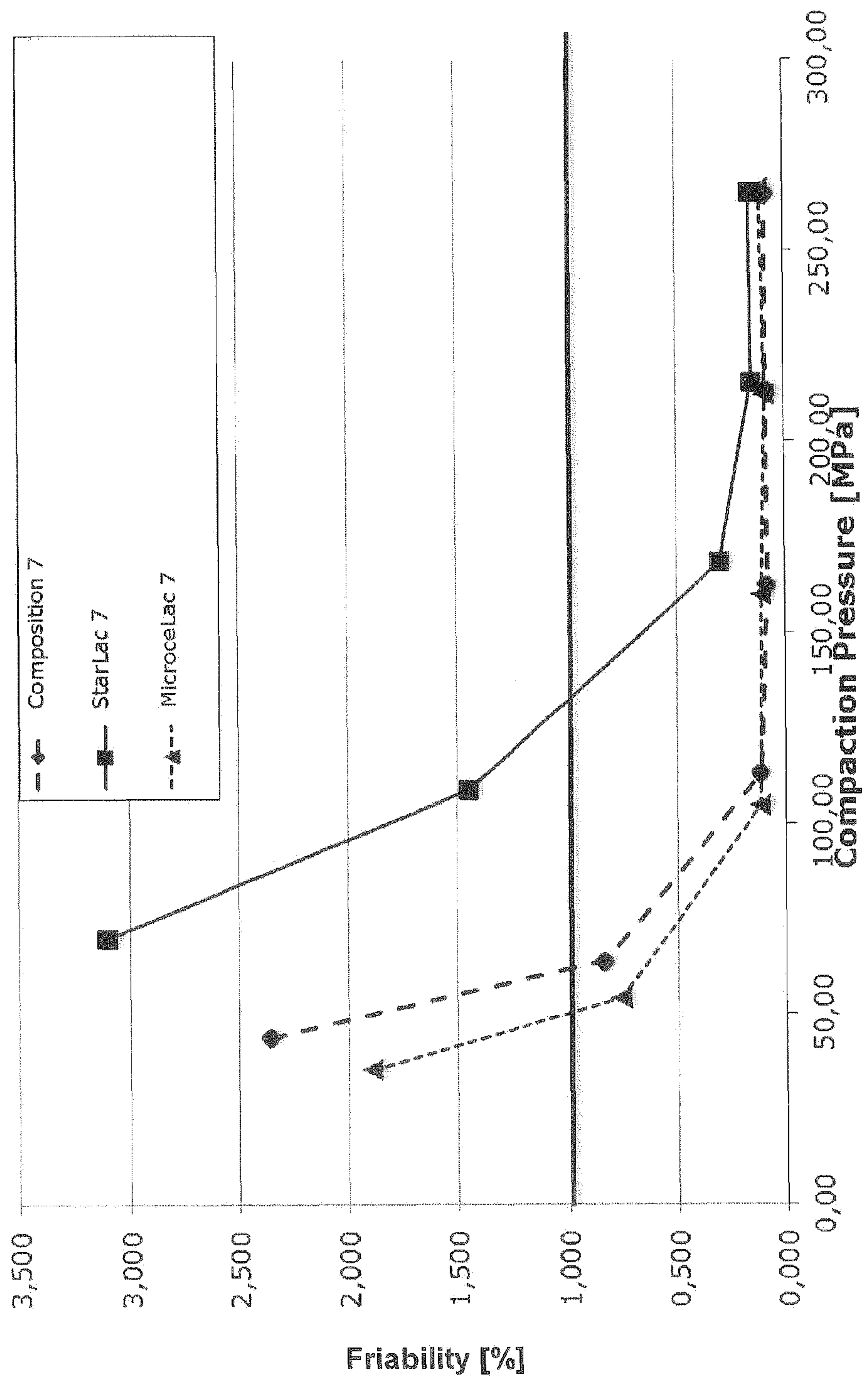


Figure 6

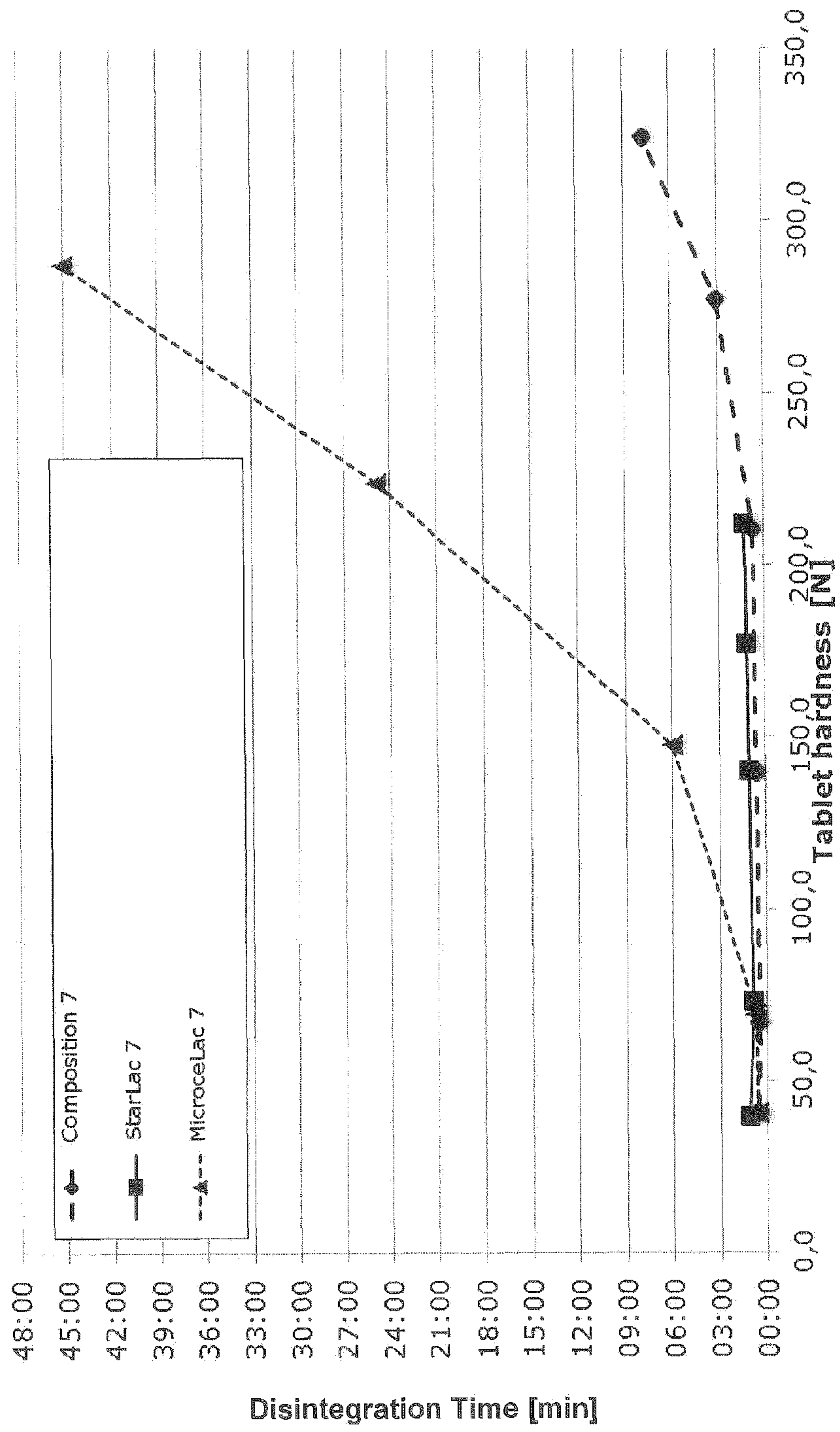


Figure 7

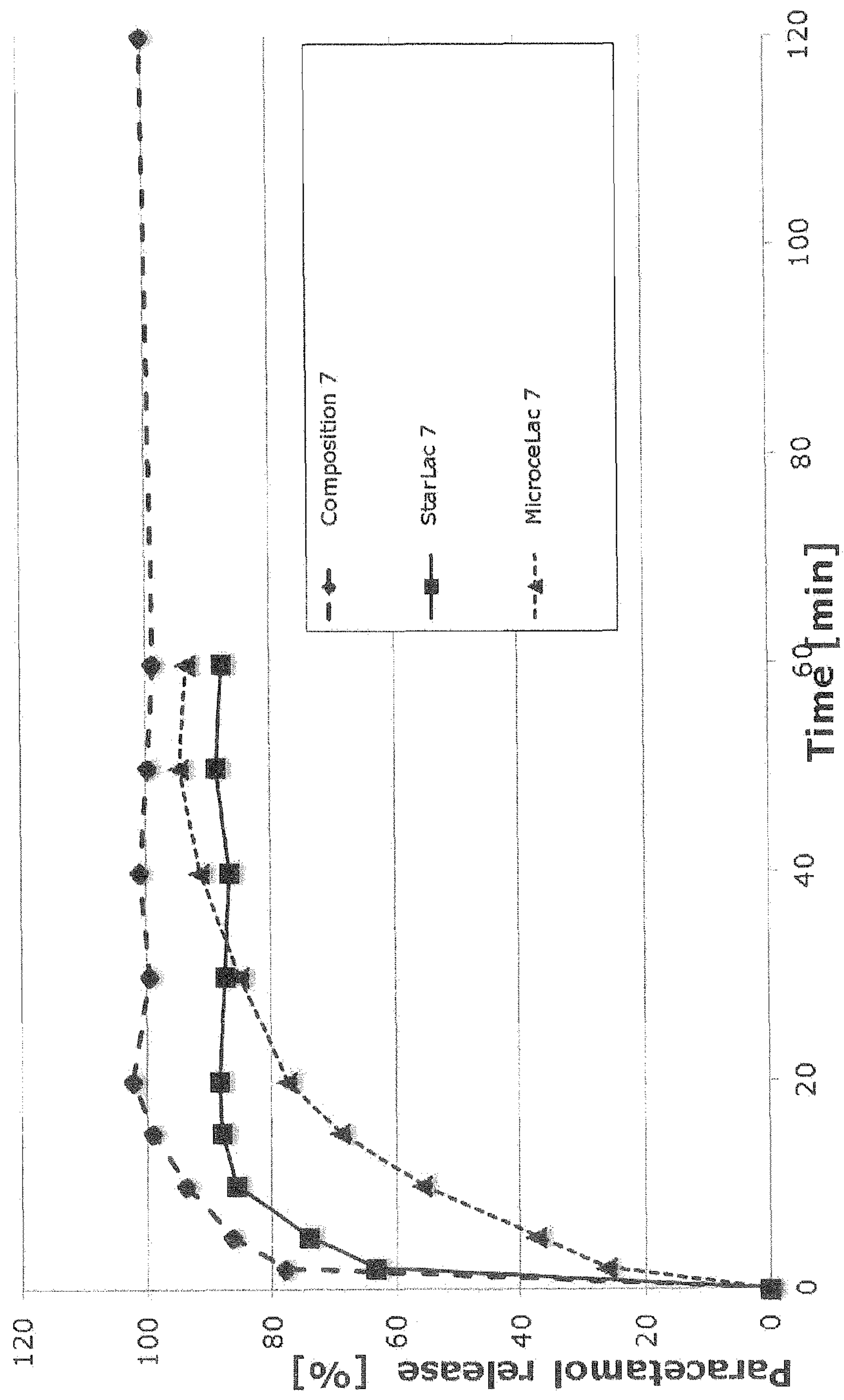


Figure 8

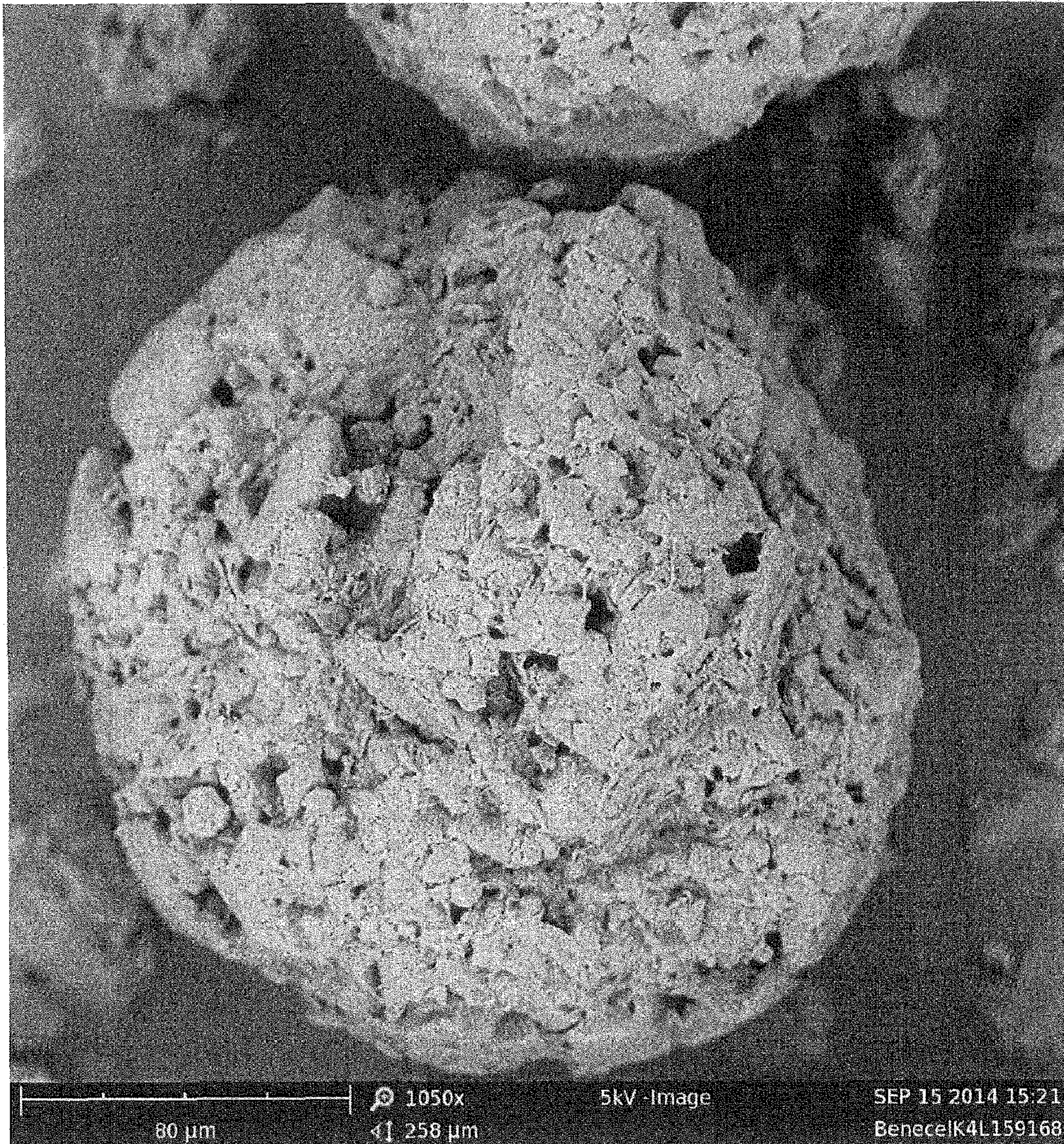


Figure 9A

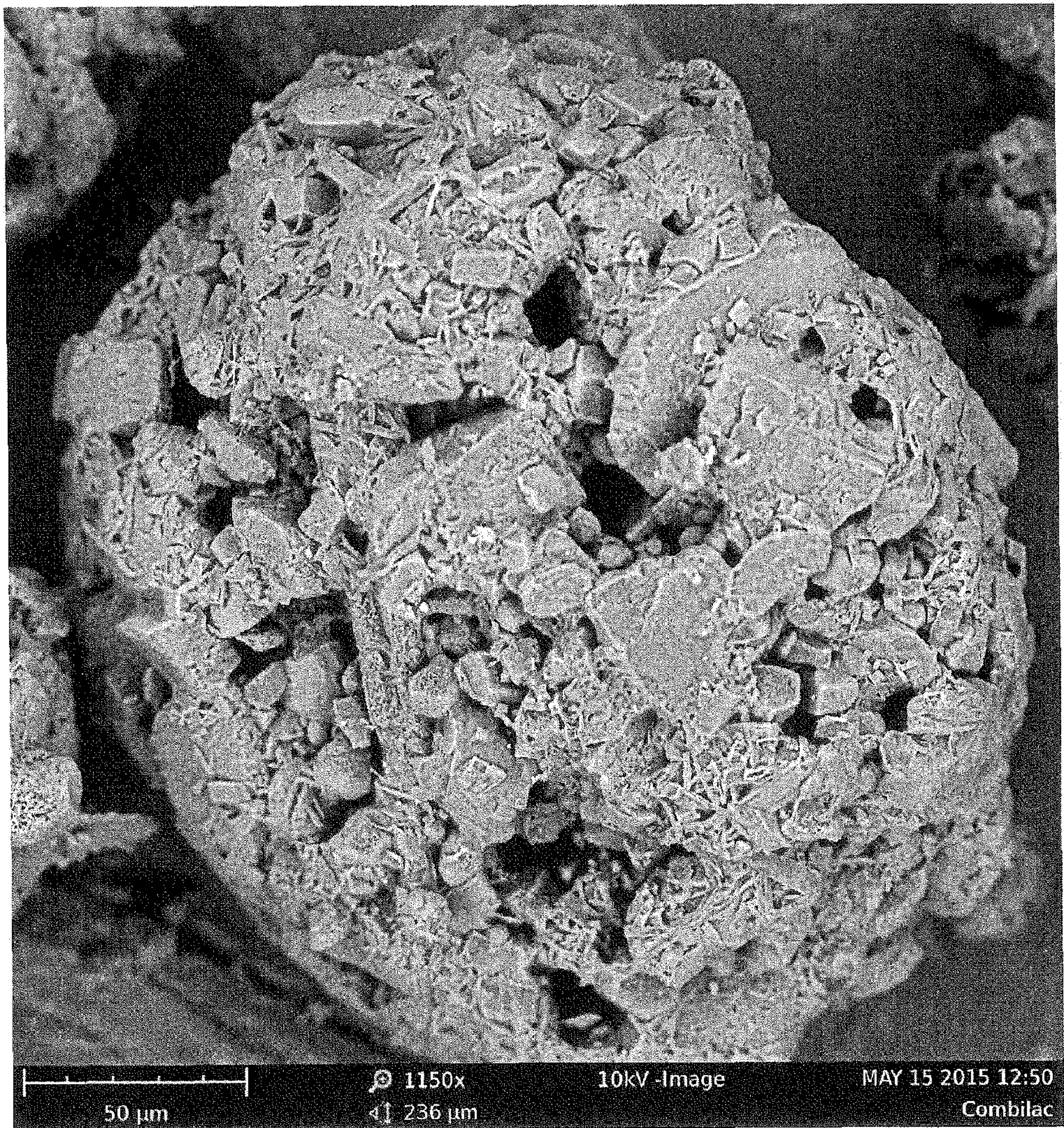


Figure 9B

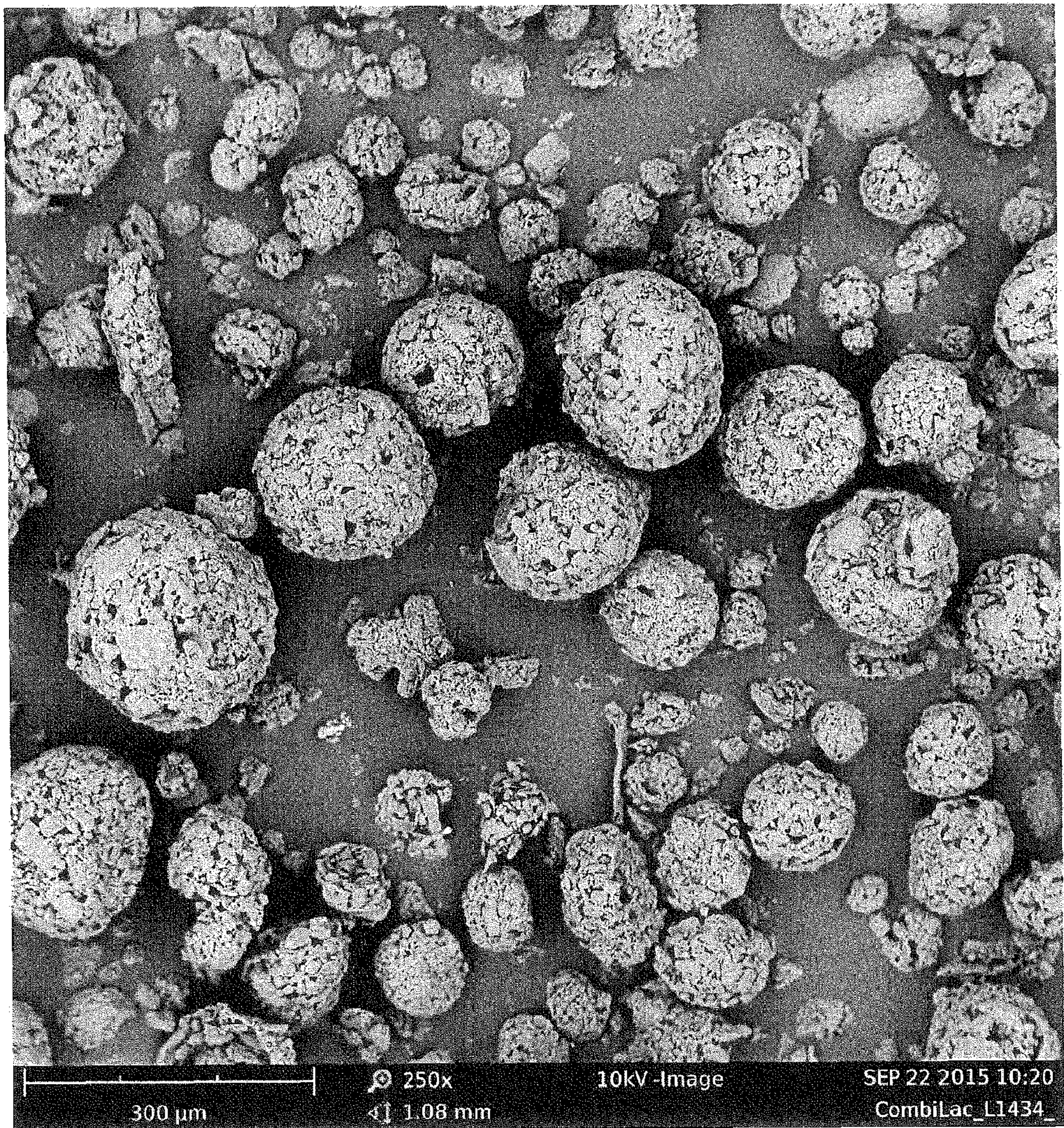


Figure 9C

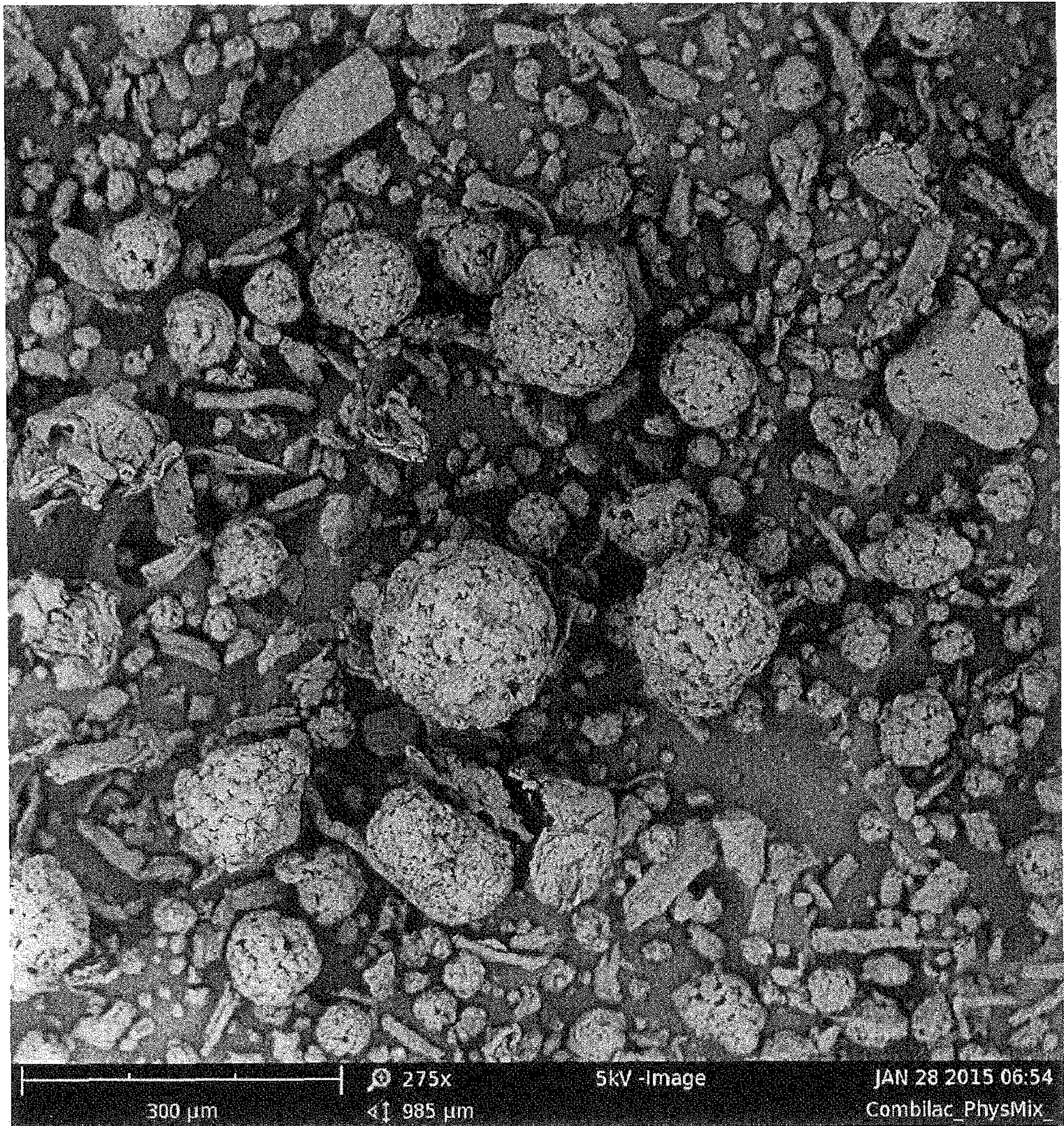


Figure 10

Tensile strength vs. compaction pressure
at different mixing times

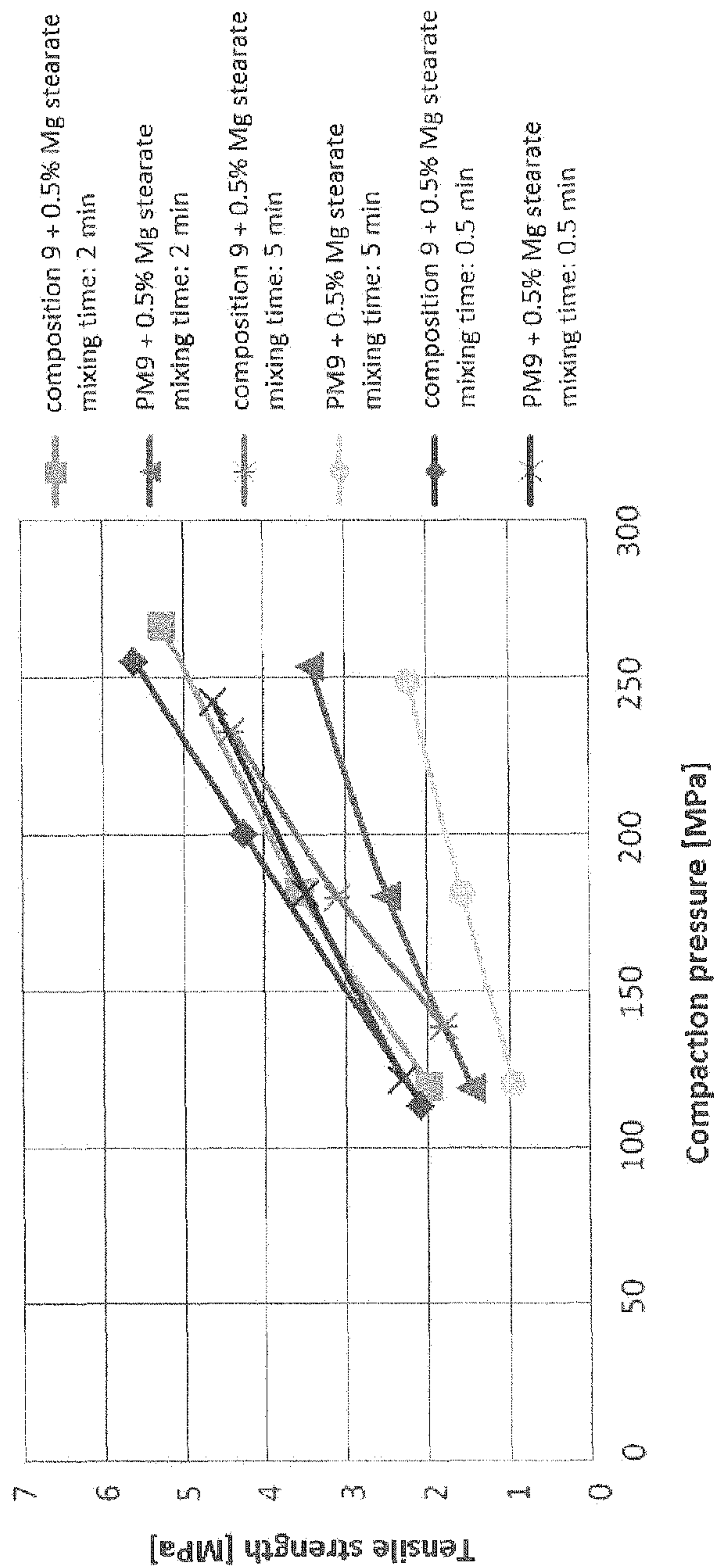


Figure 11

