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Research paper

Compaction properties of isomalt

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ABSTRACT

Although other polyols have been described extensively as filler-binders in direct compaction of tablets, the polyol isomalt is rather unknown as pharmaceutical excipient, in spite of its description in all the main pharmacopoeias. In this paper the compaction properties of different types of ispomalt were studied. The types used were the standard product sieved isomalt, milled isomalt and two types of agglomerated isomalt with a different ratio between 6-O-α-D-glucopyranosyl-D-sorbitol (GPS) and 1-O-α-D-glucopyranosyl-D-mannitol dihydrate (GPM). Powder flow properties, specific surface area and densities of the different types were investigated. Compactibility was investigated by compression of the tablets on a compaction simulator, simulating the compression on high-speed tabletting machines. Lubricant sensitivity was measured by compressing unlubricated tablets and tablets lubricated with 1% magnesium stearate on an instrumented hydraulic press. Sieved isomalt had excellent flow properties but the compactibility was found to be poor whereas the lubricant sensitivity was high. Milling resulted in both a strong increase in compactibility as an effect of the higher surface area for bonding and a decrease in lubricant sensitivity as an effect of the higher surface area to be coated with magnesium stearate. However, the flow properties of milled isomalt were too bad for use as filler-binder in direct compaction. Just as could be expected, agglomeration of milled isomalt by fluid bed agglomeration improved flowability. The good compaction properties and the low lubricant sensitivity were maintained. This effect is caused by an early fragmentation of the agglomerated material during the compaction process, producing clean, lubricant-free particles and a high surface for bonding. The different GPS/GPM ratios of the agglomerated isomalt types studied had no significant effect on the compaction properties.

1. Introduction

Nowadays there is an increasing interest in sugar substitutes such as mono- and disaccharide alcohols, also called polyols, in pharmaceutical tablet formulations. The reason for this interest is their taste, reduced calorie content and non-cariogenic characteristics. In addition, the majority of these polyols can be consumed by diabetics without any significant increase in body glucose, insulin or lactic acid concentration unlike the conventional saccharides such as sucrose, glucose and lactose. As polyols do not contain a carbonyl group, they are not subject to the Maillard reaction, and, hence are chemically more stable than related saccharides.

Another advantage of polyols is their non-animal source, so they can be used as a substitute for sugars such as lactose in tablets, prepared by direct compaction. Because of their low hygroscopicity, as compared with other polyols, special forms of both mannitol and isomalt are preferred as filler-binders for direct compaction of disintegrating tablets [1]. The compaction properties of mannitol have been described extensively [2,3]. On the other hand, isomalt is a very well known food ingredient but rather unknown as a pharmaceutical excipient, in spite of its description in both Ph.Eur. and USP/NF.

Isomalt is a mixture of two disaccharide alcohols, derived from the hydrogenation of isomaltulose. The principal components are the disaccharide alcohols 6-O-α-D-glucopyranosyl-D-sorbitol (GPS) and 1-O-α-D-glucopyranosyl-D-mannitol dihydrate (GPM). GPM crystallizes with 2 mol water whereas GPS crystallizes without water. For this reason isomalt contains about 5% water of crystallization. Isomalt is the only polyol produced from sucrose. Ndindayino et al. [4] evaluated four grades of sieved and ground isomalt for their physical characteristics. X-ray diffraction patterns confirmed the crystalline nature of the different types of isomalt and did not show any polymorphic behaviour. Water sorption isotherms showed that the different isomalt grades were not hygroscopic below a relative humidity of 85%. Only one fraction of sieved isomalt (Palatinit™C) exhibited potential characteristics for direct compaction. Evaluation by Heckel plot analysis showed that isomalt exhibits plastic behaviour and undergoes elastic recovery primarily in the die. The binding properties were acceptable after addition of 1% magnesium stearate, but there was a lack in the uptake capacity of active ingredients. Moreover, good flow could only

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be achieved after addition of colloidal silica. In order to improve its tabletting properties, isomalt was melt-extruded prior to compression [5]. After fusion, crystalline isomalt was transformed into an amorphous form. Although the tabletting properties of amorphous isomalt were dramatically improved, the extruded isomalt powder showed agglomeration problems due to recrystallization of the amorphous phase into a stable crystalline form in the presence of atmospheric moisture. Direct compaction of mixtures formulated with co-extruded isomalt/paracetamol powders yielded harder tablets compared with physical mixtures [6].

Recently, two good flowing, agglomerated forms of isomalt containing small primary particles, especially designed for direct compaction were marketed by BENEO-Palatinit. The agglomerates are prepared by milling the starting product sieved isomalt and by a subsequent agglomeration process in a fluid bed. The difference between agglomerated isomalt type 720 and type 721 is the ratio GPS:GPM. In type 720 the ratio GPS:GPM is 1:1 and in type 721 the ratio is 3:1. As the water solubility of GPS is higher than that of GPM, the products have different solubilities [7].

The aim of this study was to evaluate the compaction properties of the new, agglomerated types of isomalt. Their compaction properties and lubricant sensitivity will be compared with those of sieved and milled isomalt.

2. Materials and methods

2.1. Materials

Different types of isomalt were obtained from BENEO-Palatinit, Mannheim, Germany. Three types have a GPS/GPM ratio of 1:1. These are sieved isomalt (galenIQ™ 980), milled isomalt (galenIQ™ 800) and agglomerated isomalt (galenIQ™ 720). One agglomerated isomalt (galenIQ™ 721) has a GPS/GPM ratio of 3:1. Magnesium stearate Ph.Eur was obtained from Centrachemie, Etten Leur, The Netherlands.

2.2. Methods

The bulk density was determined by pouring 50 g of powder into a calibrated plastic cylinder and observing the volume taken up by the powder. Tap density was determined after 500 taps according to DIN 53194. The presented data are the mean value of six measurements.

Flow properties of the polyols were determined by measurement of the minimum aperture of the vessel through which the material was still flowing [8]. The Hausner ratio was calculated from bulk and tap densities [9].

The particle size distribution was measured using laser diffraction (Sympatec RODOS SR 480, Sympatec, Clausthal-Zellerfeld, Germany). Compressed air was used to disperse the powder. The data represent the mean of three measurements.

N_2 adsorption–desorption isotherms of the polyols were measured at 77.35 K using Micromeritics TriStar (Micromeritics, Norcross, USA) in order to determine the specific surface areas. Prior to measurement, the sample was outgassed with nitrogen for 18 hours (Micromeritics VacPrep 061, Micromeritics). The BET equation was used to calculate the specific surface areas, according to the N_2 adsorption isotherms at the relative pressures between 0.05 and 0.25. The data represent the mean of three measurements.

The morphology of the particles was investigated by Scanning Electron Microscopy (SEM) analysis (JEOL 6301F, Jeol Ltd., Tokyo, Japan).

In order to study the compaction properties, flat-faced tablets of 500 mg having a diameter of 13 mm were prepared on a programmable compaction simulator (ESH testing, Brierley Hill, UK) at different compression forces. Before compression, the excipients were mixed with 0.5% magnesium stearate in a Turbula mixer (model 2P, W.A. Bachofen, Basle, Switzerland) at 90 rpm. The speed of the upper punch was 300 mm/s. This speed simulates high-speed tabletting machines [10].

For the measurement of lubricant sensitivity tablets were prepared from both pure isomalt and blends of isomalt and 1% magnesium stearate. Mixing with the lubricant was performed for 2, 5, 10 or 30 min in the Turbula mixer. Before compressing the unlubricated material, the die was prelubricated with magnesium stearate. Flat-faced tablets of 500 mg having a diameter of 13 mm were compressed with a force increase of 2 kN s^{-1} at 20 kN on a mechanical hydraulic press (ESH testing, Brierley Hill, UK).

The tablet crushing strength ($n = 10$) was determined with a Schleuniger 6M tester (Dr. Schleuniger Productronic, Soloturn, Switzerland).

3. Results and discussion

3.1. Powder characteristics, particle structure and flow properties

Fig. 1 shows scanning electron micrographs of four different types of isomalt. A sieved fraction of the basic isomalt product with a GPS/GPM ratio of 1:1 is shown in Fig. 1a. It consists of almost spherical, crystalline particles with a mean particle size of 830 μm, which are commonly used as starter pellets in pharmaceutical isomalt products. Milling these spheres results in milled isomalt (Fig. 1b; attend the larger magnification) with a mean particle size of 22 μm. This type can be used for wet granulation and agglomeration. Agglomeration of milled isomalt results in agglomerated isomalt (Fig. 1c). This product, with the trade name galenIQ™ 720 has recently been introduced as filler-binder for direct compaction of tablets. A comparable product, produced from a basic isomalt product with a GPS/GPM ratio of 3:1 is galenIQ™ 721 (Fig. 1d). The main difference between the two agglomerated products is their water solubility (see Table 1).

In addition to water solubility, Table 1 lists out mean particle size, specific surface area, bulk density, tap density and flow properties expressed as Hausner ratio and flow through narrow orifices. Just as could be expected from particle size (d_{50} 830 μm) and spherical form, the sieved isomalt has excellent flow properties. On the other hand, the flow properties of the milled isomalt with a d_{50} of 22 μm are extremely poor. The agglomerated isomalt types with a mean particle size of about 240 μm have an excellent flowability, as reflected by the low Hausner ratio and free flow through the smallest orifice.

3.2. Compaction properties

Fig. 2 shows the compaction profiles of sieved isomalt, milled isomalt and the two agglomerated isomalt types, lubricated with 0.5% magnesium stearate. The compactibility of sieved isomalt is extremely poor. However, milling of this product results in an enormous increase in crushing strength. Agglomeration of the milled isomalt has only a small effect on the compactibility, although the compaction properties of galenIQ™ 720 are somewhat better than those of galenIQ™ 721. The difference in compaction behaviour of sieved isomalt on the one hand and of the other products on the other hand will be caused by the increased surface area. Fig. 3 shows the specific surface area of sieved isomalt, milled isomalt and agglomerated isomalt type 721 and of tablets, compressed from these isomalts at different loads. The figure shows that the small surface area of sieved isomalt indeed increases with an increasing compaction from 0.05 to 0.20 m^2 g^{-1}, but does not nearly reach the surface area of the milled product. The surface

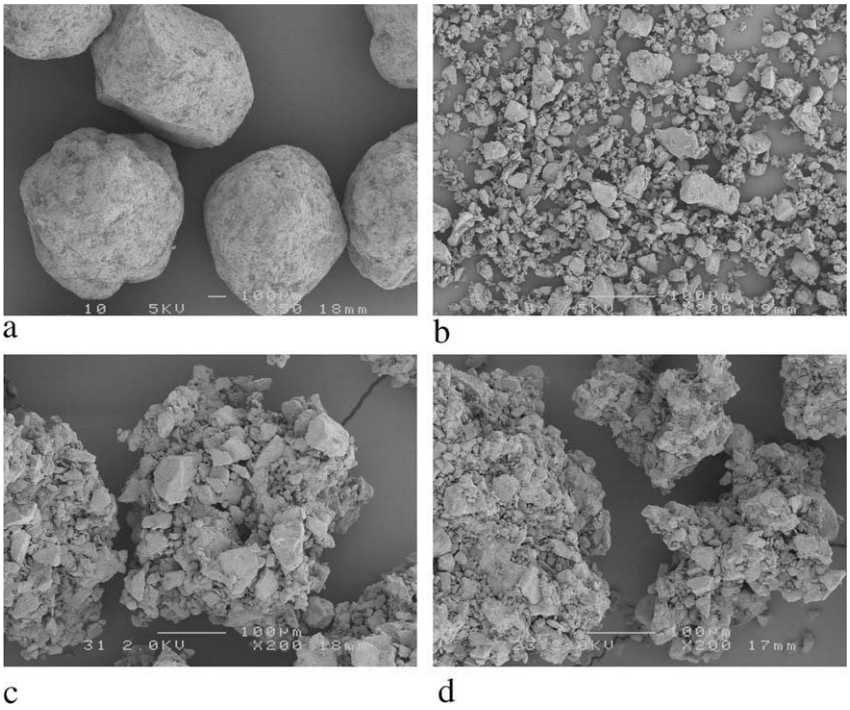

Fig. 1. Scanning electron micrographs of different types of isomalt: (a) sieved isomalt, (b) milled isomalt, (c) agglomerated isomalt, type 720, (d) agglomerated isomalt, type 721. Magnification (a) 50×, (b)–(d) 200×.

area of the milled isomalt hardly changes during compaction. This means that milled isomalt has a much higher surface for bonding, resulting in a higher crushing strength (Fig. 2). The agglomerated types of isomalt are produced by a fluid bed process using milled isomalt as the starting product. Just as could be expected, the agglomerates have a smaller surface area than milled isomalt (see Table 1). However, the surface area is higher than that of sieved isomalt. During compression, the surface area of agglomerated isomalt increases up to the same order of magnitude as found for milled isomalt. For agglomerated isomalt type 720 a similar increase in specific surface was found. This means that the granules of agglomerated isomalt fragment easily in primary particles and behave with respect to the compaction properties further just as milled isomalt. The deformation of particles during compaction is illustrated by scanning electron micrographs of the surface of fraction of tablets, compressed from the different types of isomalt. Fig. 4 shows tablets compressed at low- and high-compaction force, respectively. The original particles of sieved isomalt (Fig. 4a–b) are visible in the tablets, even if compressed at 20 kN. This means that particle fragmentation is limited and no high surface for bonding is created. This is consistent with the small increase in specific surface area (Fig. 3). The small particles of milled isomalt (Fig. 4c–d) are condensed to a solid mass in which the primary particles disappear with an increase in compaction force. This points to plastic deformation of isomalt, just has been found by Ndindayino et al. [4]. Just as could be expected, agglomerated isomalt (Fig. 4e–f) behaves just as milled isomalt: for tablets compressed at 20 kN, their pictures are rather similar.

As unlubricated tablets could not be compressed at high speed using the compaction simulator, for the evaluation of lubricant sensitivity both unlubricated and lubricated tablets were compressed at low speed on an instrumented hydraulic press. The dif-

Table 1
Physical properties of different types of isomalt.

	Sieved isomalt	Milled isomalt	Agglomerated isomalt type 720	Agglomerated isomalt type 721
Mean particle size (μm)	830 ± 22	22 ± 6	260 ± 24	220 ± 17
Specific surface area ($m^2\ g^{-1}$)	0.05 ± 0.00	0,84 ± 0.01	0.28 ± 0.00	0.32 ± 0.00
Bulk density ($g\ cm^{-3}$)	0.85 ± 0.01	0.46 ± 0.00	0.44 ± 0.01	0.46 ± 0.01
Tapped density ($g\ cm^{-3}$)	0.91 ± 0.01	0.65 ± 0.01	0.50 ± 0.01	0.52 ± 0.00
Hausner ratio	1.07 ± 0.01	1.40 ± 0.01	1.14 ± 0.02	1.14 ± 0.02
Flow through aperture (mm)	2.5	18	2.5	2.5
Water solubility at 20 °C (g/100 g)	25	25	25	42

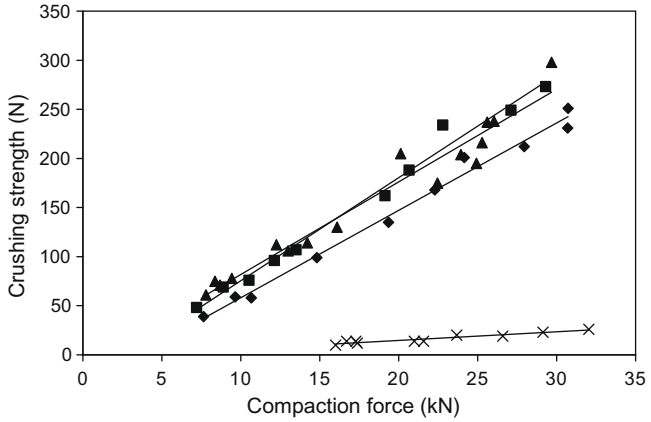

Fig. 2. Compaction profiles of sieved isomalt (×), milled isomalt (▲) and two types of agglomerated isomalt: type 720 (■) and type 721 (♦), respectively. All tablets were lubricated with 0.5% magnesium stearate and were compressed at 300 mm s^{-1}.

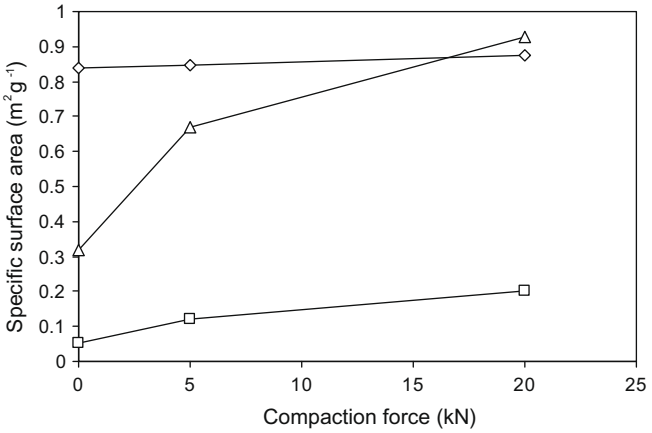

Fig. 3. Specific surface area (m^2) of (□) sieved isomalt (980), (◇) milled isomalt (800) and (Δ) agglomerated isomalt (721), as powder and after compaction at 5 kN and 20 kN, respectively.

ferent types of isomalt were mixed for 2, 5, 10 and 30 min with 1% magnesium stearate. Fig. 5 shows the crushing strength of both unlubricated tablets and lubricated tablets as a function of mixing time with lubricant. The figure shows that the lubricant sensitivity of sieved isomalt is very high. After 2 min, the crushing strength drops from about 60 N to almost zero. This is in contrast with the milled and agglomerated isomalt. Milled isomalt shows no significant change in crushing strength after mixing with magnesium stearate, not even after prolonged mixing. The both agglomerated isomalt types show a small, but significant decrease in crushing strength. The effect of an increasing concentration of magnesium stearate is shown in Fig. 6. A similar pattern can be seen: the lubricant sensitivity of sieved isomalt is high, even after addition of 0.5% magnesium stearate. The lubricant sensitivity of the milled and agglomerated types of isomalt is significant, but small. Mixing a material with lubricants such as magnesium stearate will cause a film to be formed around the particles of this material [11]. This film formation will occur for all the isomalt types investigated. The effect of this lubricant film on compactibility, however, is strongly dependent on both particle size distribution and fragmentation propensity of a material [12,13]. The big particles of sieved isomalt will be coated easily and fast by the lubricant film. As the particles hardly fragment during compression, this lubricant film has a strong negative effect on tablet crushing strength. On the other hand, it will be difficult to form a continuous lubricant film upon the small particles of milled isomalt, even after prolonged mixing [14]. For this reason, magnesium stearate has no significant effect on the crushing strength of tablets prepared from milled isomalt. The low lubricant sensitivity of the agglomerated isomalt types may be attributed to the granular structure of the products: a lubricant film, formed during the mixing process, will be destroyed by fragmentation of the brittle agglomerates during the early stages of compaction [13].

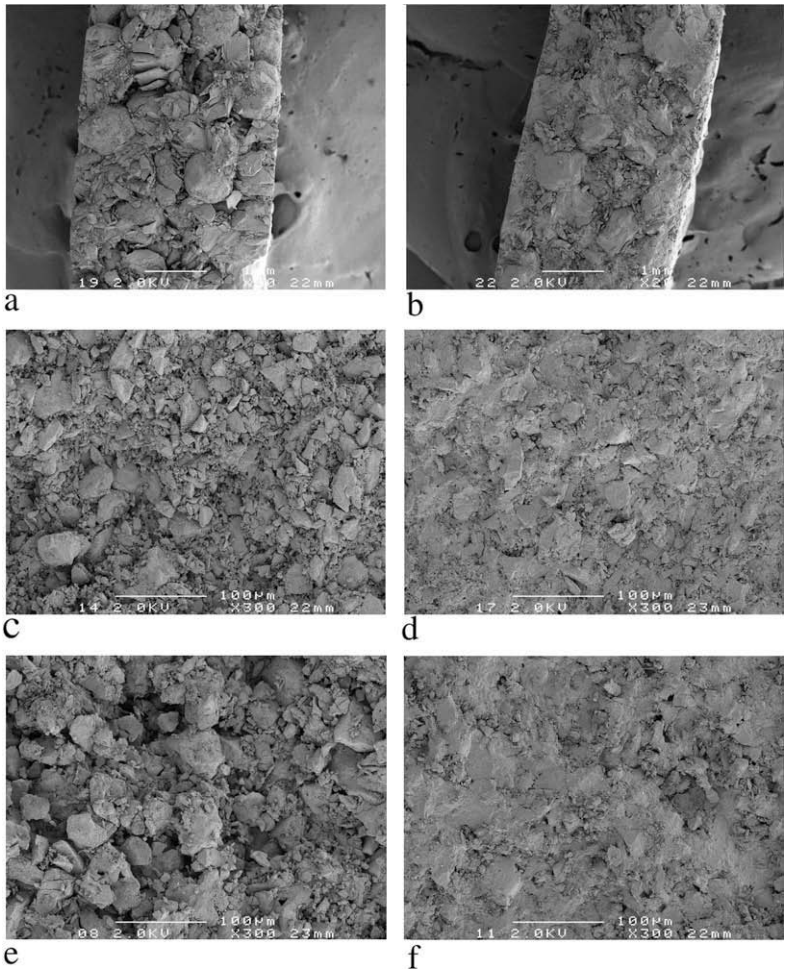

Fig. 4. Scanning electron micrographs of the surface of fraction of tablets, compressed from different types of isomalt. (a–b) sieved isomalt, (c–d) milled isomalt (e–f) agglomerated isomalt, type 721. Compression forces 2.5 kN (left Figs. 4c and e)or 5 kN (left Fig. 4a) and 20 kN (right figures). Magnification (a–b) 20×, (c–f) 300×.

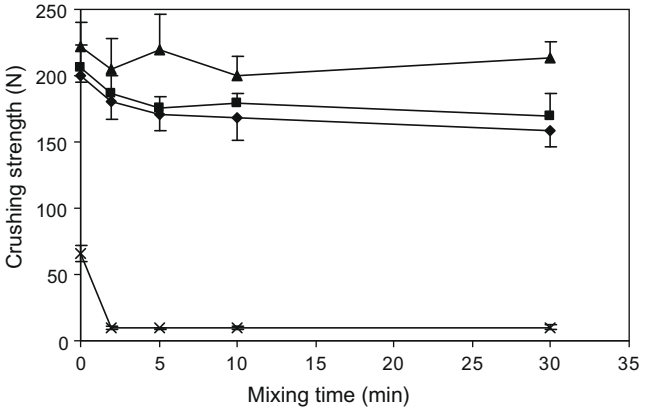

Fig. 5. Crushing strength versus mixing time with 1% magnesium stearate for tablets compressed from sieved isomalt (×), milled isomalt (▲) and two types of agglomerated isomalt: type 720 (■) and type 721 (♦), respectively. The tablets were compressed at 20 kN on an instrumented hydraulic press.

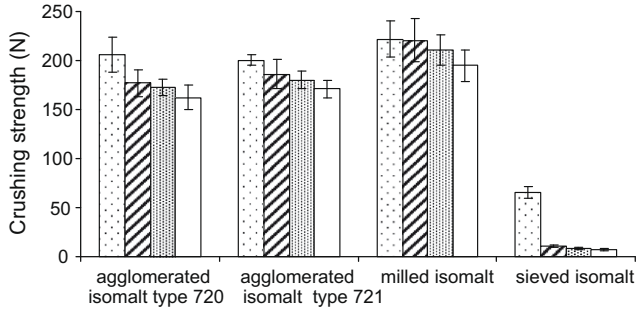

Fig. 6. Effect of concentration of magnesium stearate on crushing strength of tablets compressed from different types of isomalt. The tablets were compressed at 20 kN on an instrumented hydraulic press. Bars from left to right: 0%; 0.5%; 1% and 2% magnesium stearate.

4. Conclusion

Sieved isomalt has excellent flow properties but a small surface area and a limited particle fragmentation during compression, whose effect results in a too small surface area for bonding. Milling the sieved isomalt results in a product with an increased surface area, which leads to an enormous increase in compactability. The flow properties of the milled isomalt are too bad for use as filler-binder for direct compaction. Agglomeration of milled isomalt by fluid bed agglomeration improves both flowability and lubricant sensitivity whereas the good compaction properties are maintained. This effect is caused by an early fragmentation of the agglomerates during the compaction process, producing clean lubricant-free particles and a high surface area for bonding. The different GPM/GPS ratios of the agglomerated isomalt types had no significant effect on the compaction properties.

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