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Research Article

DEVELOPMENT OF CO-PROCESSED MICRO GRANULES FOR DIRECT COMPRESSION

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ABSTRACT

The objective of the study was to develop directly compressible co-processed micro-granules by increasing the flow property of granules, decreasing the disintegration time and increasing the binding properties of the dosage form. **Method:** The development and production of tablets dosage form has been a complex technological challenge. In the present study micro granules comprising of Lactose Monohydrate (L), Microcrystalline Cellulose (MCC) and Corn Starch (CS), were fabricated by conventional method and used as a directly compressible excipients. Different combinations of composite particles were evaluated for powder and compression properties. **Results:** The co-processing is the most widely explored method for the preparation of directly compressible adjuvant because it is cost effective as compared to spray dried technique and can be prepared in-house based on the functionality required. In present study the spherical particles obtained were of uniform size resulting in an increase in the degree of flowability. However, granules in the ratio of 7:2:1 (LMC-7:2:1) were found with excellent flow properties, high compressibility, low disintegration time to tablets and have better binding properties. Tablets of (LMC-7:2:1) exhibited low friability and good self-disintegrating property. **Conclusion:** It was concluded that said composite particles could be used as a new co-processed direct compression excipients.

Keywords: Direct compression, Micro granules, Binders or filler, Co-processed granules, Granules formation.

INTRODUCTION

The development in the field of APIs, excipients and tableting machines during the past decades has made tablet manufacturing a science and the tablets the most commonly used dosage form [1,2]. The ease of manufacturing, convenience in administration, accurate dosing, and stability compared to oral liquids, tamper-proofness compared to capsules, safe compared to parental dosage forms make it a popular and versatile dosage form. The art of tableting is performed by the three well-known methods i.e. wet granulation, roller compaction and direct compression.

Direct compression is the simplest and most economical method for the manufacturing of tablets because it requires less processing steps than other techniques. In early 1960's, the introduction of spray dried lactose (1960) and Avicel (1964) had changed the tablet manufacturing process and opened avenues of direct compression tableting.

The simplicity of the direct compression process is apparent from a comparison of the steps involved in the manufacture of tablets by wet granulation, roller compaction and direct compression techniques [3]. It has been estimated that less than 20 percent of pharmaceutical materials can be compressed directly into tablets [3] due to lack of flow, cohesion properties and lubrication. Therefore, they must be blended with other directly compressible ingredients to manufacture satisfactory tablets. In the development of directly compressible granules by the modification of a single substance, co-processing of two or more components was applied to produce composite particles or co-processed excipients. The composite particles or co-processed multi-component-based excipients are introduced to achieve better powder characteristics and tableting properties than a single substance or the physical mixture.

The directly compressible adjuvant should be free flowing. Flowability is required in case of high-speed rotary tablet machines, in order to ensure homogenous and rapid flow of powder for uniform die filling. During the short dwell-time (milliseconds), the required amount of powder blend should be transferred into the die cavities with reproducibility of + 5% [4].

Compressibility is required for satisfactory tableting, i.e., the mass must remain in the compact form once the compression force is removed. Few excipients can be compressed directly without elastic recovery. Hence, the directly compressible diluents should have good compressibility, i.e. relation between compaction pressure and volume [3,5].

Lactose is the most widely used filler-diluent in tablets. The general properties of lactose are its cost effectiveness, easy in the availability, bland taste, less hygroscopicity, excellent physical and chemical stability and water solubility [6]. Lactose based tablets exhibit better stability than mannitol and cellulose containing tablets at 40°C and 90% RH over a 10 week period [7]. The amorphous lactose yields tablets of higher tensile strength than crystalline lactose.

Starches are used in tablet formulations as a diluent, binder, and disintegrant, depending on the method of incorporation and the quantity used. The starch of United States Pharmacopeia (USP) grade has been used to obtain identical properties in tablets formulations. Mullick et al. (1992) reported that dextrinized rice, corn, wheat and tapioca starches prepared by dextrinization exhibited very good flow, compression and disintegration properties for direct compression tableting. Dextrinized tapioca starch was found to be the best [8].

Microcrystalline cellulose (MCC) is purified partially depolymerized cellulose, prepared by treating α-cellulose with mineral acids. Apart from its use in direct compression, microcrystalline cellulose is used as a diluent in tablets prepared by wet granulation, as filler in capsules and for the production of spheres. Lahdenpaa et al. (1997) demonstrated that the tablets containing higher percentage of Avicel pH101 exhibited higher crushing strength and lower disintegration time, while the tablets containing Avicel pH102 and pH 200 showed lower crushing strength, shorter disintegration time and small weight variation [9]. Hardness of MCC tablets was decreased with an increase in the percentage of magnesium stearate while the disintegration time was unaffected by addition of lubricant [10]. Paronen (1986) reported that Avicel pH-101 undergoes plastic deformation [11]. Among directly compressible fillers, microcrystalline cellulose is the most compressible and has the highest dilution potential.

There is a lack of awareness in some situations that the excipients behave differently, depending upon the vendor so much so that substitution from one source to that of another is not possible [12]. Hence, there is a need for greater quality control in purchasing of raw material to assure batch uniformity.

It was interesting to develop co-processed particles of Lactose monohydrate, CS grains and microcrystalline cellulose. The prime objective of the study was to develop the composite particles between these materials, having the RS as the main component as it was plentiful and inexpensive. Reviews of the literature [3,13,14,15,16,17,18] yield had no report on the combination of lactose monohydrate, corn

starch and microcrystalline cellulose used to form co-processed excipients.

It has been reported in a survey conducted in 1992 that direct compression is the preferred method of compression used by majority of the manufacturers [19]. A single drug or excipients do not possess all the desired physico-mechanical properties required for the development of robust directly compressed product, which can be scaled up smoothly [20]. Hence, there is a need to have excipients with multiple characteristics built into them such as better flow, low/no moisture sensitivity, superior compressibility and rapid disintegration ability [21]. New combinations of existing excipients are an interesting option for improving the overall characteristics of the material, which is to be compressed. Excipient mixtures prepared by co-processing have improved functionality as compared to simple physical blends [22].

The development of these single bodied excipients known as co-processed excipients has gained importance in the last decade [23]. The compaction properties of mixtures had been reviewed by Fell (1996) [24], who concluded that the relationship between the tableting properties of a mixture could only rarely be predicted from knowledge of the same properties of the individual components [25]. Directly compressible adjuvant can be prepared by various methods.

Summary of various methods used to prepare directly compressible adjuvant[14, 36, 16]

Methods	Advantages and limitation	Examples
Chemical Modification	Relatively expensive Requires toxicological data, Time consuming	Ethyl cellulose, methyl cellulose, hydroxypropyl methylcellulose and sodium carboxymethyl cellulose from cellulose[14], Cyclodextrin from starch[14], Lactitol
Physical modification	Relatively simple and economical	Dextrates and compressible sugar, sorbitol
Grinding and/or sieving	Compressibility may also alter because of change in particle properties such as surface area and surface activation[16]	α-lactose monohydrate (100 #), dibasic dicalcium phosphate
Crystallization	Impart flowability to excipients but not necessarily self-binding properties. Require stringent control on possible polymorphic conversions and processing conditions[16]	β-lactose, dipac
Spray drying	Spherical shape and uniform size give spray-dried material good flowability, poor re-workability[16]	Spray dried Lactose, Emdex, Fast Flo Lactose, Avicel Ph, Karion instant, TRI-CAFOS S, Advantose 100
Granulation/ Agglomeration	Transformation of small, cohesive, poorly flowable powders into flowable and	

The present investigation was aimed at evaluating and characterizing co-processed micro granules comprising of lactose monohydrate, corn starch and microcrystalline cellulose. This co-processed blend consists of individual materials having filler, binder and disintegrant characteristics. Use of such a product also reduces the cost of final formulation.

MATERIALS AND METHODS

Materials

Lactose Monohydrate was obtained as gift sample from DMV-Fonterra New Zealand. Corn Starch was obtained from the Roquette France. Micro-crystalline cellulose was also obtained from a commercial source Mingtai Chem Taiwan.

Equipments

Friabilator (Erweka, Offenbach, F.R.G.), Retsch sieve shaker type AS200 (F. Kurt Retsch GmbH, Germany) fitted with US standard sieves (Dual Mfg. Co., Chicago, IL), Tablet Hardness Tester (TBH30, Erweka, Heusenstamm, Germany), disintegration test apparatus (ZT31, Erweka, Heusenstamm, Germany).

Method

Preparation of Composite Particles

Physical mixture for wet granulation was prepared having different ratios of lactose monohydrate, microcrystalline cellulose and corn starch such as 4:3:3, 5:3:2 & 7:2:1. Each was first sieved through 100-mesh screen and after mixing blend was again passed through sieve # 100-mesh.

1 Kg of blend was prepared for each combination. Physical mixture was wet granulated with purified water and wet mass was then dried and passed through oscillating granulator to obtain micro granules.

Physical properties of powder

Co-processed micro granules were evaluated for their flow properties, like angle of repose, angle of spatula, friability, bulk density, tapped density, Carr's compressibility index and Hausner's ratio[26-28].

Granules friability

Five grams of the granules of the 250-400 µm size fractions were placed in friabilator and tumbled for 5 minutes at 25 rpm. The percentage of loss, after sieving by 400µ sieve size was recorded.

Powder morphology

Shape and surface topography of micro granules were observed by scanning electron microscopy.

Angle of repose[29]

The angle of repose was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation [30]:

$$\text{Tan } \theta = h/r$$

Where h = height of the powder cone; r = radius of the powder cone.

Angle of spatula

A steel spatula with a 5 x 7/8 inches blade was inserted to the bottom of the heap and withdrawn vertically. The angle of the heap formed on the spatula was measured as the angle of spatula.

Bulk density and tapped density[31]

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10-mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in the volume was noted. LBD and TBD were calculated using the following formulas[6]

LBD = weight of the powder/volume of the packing

TBD = weight of the powder/tapped volume of the packing

Compressibility index[32]

The compressibility index of the granules was determined by Carr's compressibility index[33]:

Carr's index (%) = [(TBD – LBD) × 100]/TBD

Uniformity coefficient

The uniformity coefficient was obtained by sieve analysis of 10 g of the powdered material using a RETSCH sieve shaker type AS200 fitted with US standard sieves ranging in size from 0.149 to 0.40 mm.

Flowability index

The flowability index was calculated with the point scores, ranging from 0 to 100, in a scale described by Carr to evaluate the flow and the arching properties of powders.

Total porosity[34]

Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V_{bulk}) and the true volume of granules (V)[35]:

Porosity (%) = $V_{bulk} - V/V_{bulk} \times 100$

Particle size distribution

Particle size distribution was done by sieve analysis using standard sieves i.e. # 40, # 60, # 80 and #100.

Physical properties of tableting

Compressibility of the composite particles was assessed by direct compression of powder sample (~500 ± 5mg), with no additive, on a hydraulic press, using round, flat-faced punch and die assembly (15.0mm in diameter). All powders were compressed at the force of 8.8 KN. The produced tablets were evaluated as follows.

Hardness, thickness, and diameter

Hardness, thickness, and diameter of prepared tablets were determined by using Tablet Hardness Tester. The average results were determined by 10 tablets.

Friability

The friability of the compacts was measured using the Roche friabilitor set at a rotation speed of 25 rpm. Five grams of tablets were rotated for 4 min (100 rotations). At the end of the run the tablets were weighed accurately, and the percentage friability was computed from the weight of tablets before and after the test.

Disintegration time

The disintegration time of tablet was determined in de-ionized water at 37°C ± 0.5°C using USP disintegration test apparatus. The disintegration test was performed without disc. The data given are at the average of 6 tablets.

RESULTS AND DISCUSSION

The present study investigated the basic physico-chemical property and binding functionality of new developed co-processed micro granules prepared by conventional method for direct compression.

Co-processing is the way through which new excipients come to market without undergoing the rigorous safety testing of a completely new chemical[17]. It can be defined as combination of two or more established excipients by an appropriate process[14].

Co-processing is one of the most widely explored and commercially utilized methods for the preparation of directly compressible adjuvant. It was demonstrated that the composite particles between Lactose Monohydrate, Corn Starch and Microcrystalline Cellulose could be formed via conventional method (Table: 1). The photomicrographs revealed the composite particle consisting of cellulose fibers and starch grains were embedded in aggregate of the lactose forming a one-body particle (Figure 1a, 1b, 1c &2a,2b,2c).

Table 1: Preparation of co-processed micro-granules

Method	Co-processing Adjuvant	Formulation of compressible adjuvant	Result based on different parameters
Conventional	Lactose, MicrocrytallineCellulose Corn starch	LMC-4:3:3	Fair
Conventional	Lactose, MicrocrytallineCellulose Corn starch	LMC-5:3:2	Good
Conventional	Lactose, MicrocrytallineCellulose Corn starch	LMC-7:2:1	Excellent

Particle size of starting material had a pronounced effect on the shape of composite particles produced. An increase in the quantity of microcrystalline cellulose in composite particles not only provided the larger size of the particles but also produced more shape irregularity of the composite particles (Figure 2a). The formation of oval-shaped particles was probably the result of the greater size of the cellulose fiber in comparison with the starch grain resulting in the deposition of smaller starch grains along the cellulose fiber to form the aforementioned particle shape. When the amount of microcrystalline cellulose in formulations was greater than 30%, the shape of composite particles became more irregular (Figures 2a and 2b).

Excipient mixtures in co-processing were produced to make use of the advantages of each component and to overcome specific disadvantages, of individuals. Most important characteristics are the binding and blending properties of the co-processed excipients. In present study this property was also investigated, found better than those of a physical mixture of the starting materials. Cost is another factor to be considered in the selection of present co-processed excipients.

Good flowability is an important requirement for direct compressible ingredients. A material developed for direct compression process should possess an adequate level of flowability when blending with other ingredients in formulation to ensure a uniform die filling of a powder blend during tableting. Several problems can be developed as material flows through the equipments. If the powder has cohesive strength, an arch or rat hole may form. Material if left stranded in stagnant zones that usually remain in place until an external force is applied to dislodge it.

There are several bulk powder characteristics that can be used for indirect estimation of the degree of powder flow. To evaluate the flow properties of prepared composite particles in comparison with the starting materials, the powder behaviors were examined that are angle of repose, angle of spatula, compressibility, and cohesion (Table 2 and 3).

LMC 4:3:3 had the highest angle of repose and angle of spatula, which indicated poor flowability as compared to LMC 7:2:1. Powder characterizations of starting material could not be done as electrostatic charges induced during size reduction caused the powder to be very cohesive, and it stuck to all surfaces contacted. Angle of repose values tended to increase when the cellulose components in composite particles were increased. However, when starch proportions were increased, only LMC 4:3:3 showed increased angle of repose values. The increase in angle of spatula

values seemed to fluctuate when the starch proportions were increased. However, it seemed that high cellulose content in composite particles resulted in an increase of angle of repose and spatula, which were indicative of less flowability. When using the percentage compressibility to assess the flowability of a bulk powder, a lower value indicates a better flow. Percentage compressibility was calculated from aerated bulk density and packed bulk density.

Fig.1 & 2: Particle Size & Shape Of Starting Material 2) Particle size & shape of composite particles produced

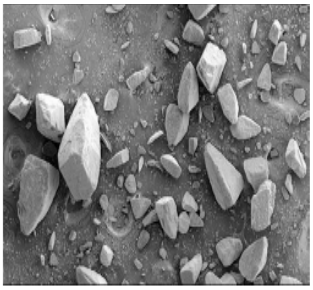


Fig 1a: lactose monohydrate magnification: 50 xs

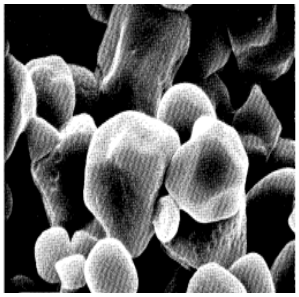


Fig 1b: Maize Starch Magnification: 2400x

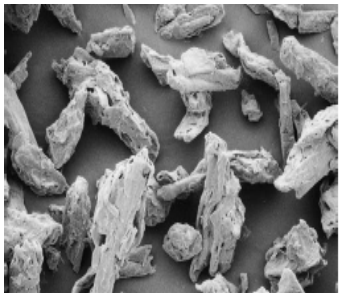


Fig 1c: Microcrystalline cellulose Magnification: 100x

Fig 2a: LMC-433 Magnification: 40x

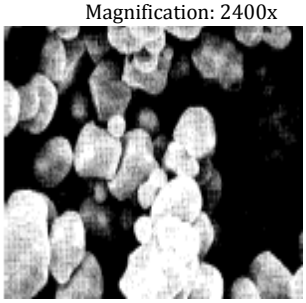


Fig 2b: LMC-532 Magnification: 40x

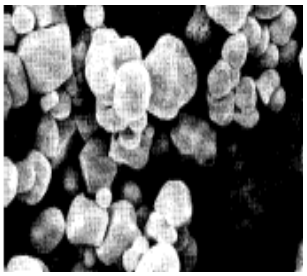


Fig 2c: LMC-721 Magnification: 40x

Table 2: Co-Processed micro granules characteristics

Materials	Angle of repose *	Angle of spatula	Bulk density	Tapped density	Compressibility
LMC-433	32.74	48.81	0.373	0.439	15.034
LMC-532	29.50	43.60	0.430	0.488	11.885
LMC-721	29.72	43.60	0.437	0.491	10.997

* Mean based on 3-5 results

Table 3: Co-processed micro granules characteristics

Materials	Flowability index mean (SD)	Porosity (%) mean (SD)	Granules friability mean (SD)	Cohesion (%) mean (SD)
LMC-433	50	40	20%	8.2
LMC-532	59	32	14%	5.5
LMC-721	65	26	10%	4.8

Sieving is one of the fundamental methods for the classification of powders and it is the method of choice for determining the size distribution of coarse powders. The two most important analytical performance parameters were determined during the sieving procedure that are the precision and the accuracy associated with the analysis. To evaluate precision, procedure was repeated for the particle-size determination of a properly subdivided sample three to five times and compares the percentages associated with each size fraction (Table 4a, 4b, and 4c).

Table 4a: Analytical sieving results (Sample Lmc-4:3:3)

Sieve mesh number	Sieve size opening (µm)	Mass sample retained on each sieve	% Sample retained on each sieve	Cumulative % sample retained	Cumulative % sample passing through Sieve
40	400	1.035	10.35	10.35	89.65
60	250	4.655	46.55	56.90	43.10
80	177	2.256	22.56	79.46	20.54
100	149	1.180	11.80	91.26	8.74
Pan	-	0.874	8.74	100.00	0.00
Total		10.00	100.00		

Table 4b: Analytical sieving results (Sample Lmc-5:3:2)

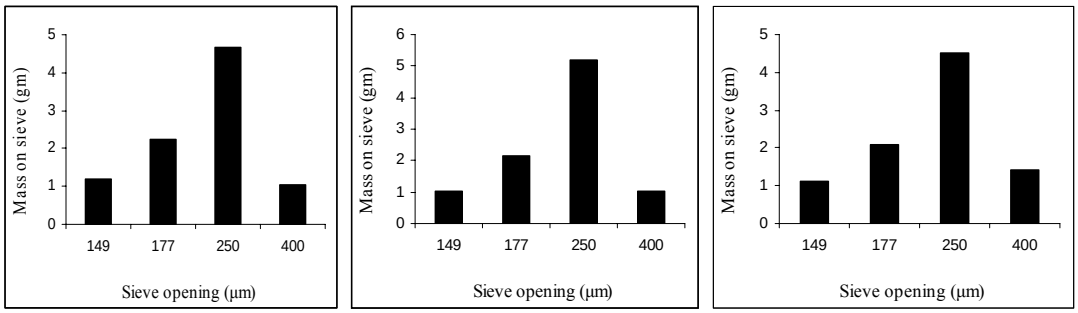
Sieve mesh no	Sieve Size (µm)	Mass sample retained on each sieve	% Sample retained	Cumulative % sample retained on sieve	Cumulative % sample passing through sieve
40	400	1.050	10.50	10.50	89.50
60	250	5.205	52.05	62.55	37.45
80	177	2.148	21.48	84.03	15.97
100	149	1.025	10.25	94.28	5.72
Pan	-	0.572	5.72	100	0.00
Total		10.00	100		

Table 4c: Analytical sieving results (Sample Lmc-7:2:1)

Sieve mesh no	Sieve size (µm)	Mass sample retained on sieve	% Sample retained on sieve	Cumulative % sample retained	Cumulative % sample passing through sieve
40	400	1.400	14.00	14.00	86.00
60	250	4.500	45.00	59.00	41.00
80	177	2.100	21.00	80.00	20.00
100	149	1.128	11.28	91.28	8.72
Pan	-	0.872	8.72	100.00	0.00
Total		10.00	100.00		

The raw data was converted into a cumulative weight distribution. The particle-size distribution of a sample was represented by a log-normal distribution. Distribution was specified by the geometric median particle size (*dg*) and the geometric mean standard deviation (σ*g*). It was concluded that two samples with identical *dg* and σ*g* values were drawn from the same total population. The value of *dg* is equal to the 50% value of the cumulative distribution, and the value of σ*g* is obtained by dividing the 84.1% value of the distribution by the 50% value.

Table 4a, 4b and 4c show the sieving results obtained from a powdered sample exhibiting a classic log-normal distribution. The data are typically presented by listing them as a function of both the sieve mesh number and associated sieve size opening (in microns). For each sieve in the nested series, the mass of sample retained on each sieve, the percentage of sample retained on each sieve, and the cumulative percentage of sample retained on each sieve were calculated. The cumulative percentage of sample passing through each sieve was also summarized (Fig. 3a, b, & c).



a) Sample LMC-4:3:3 **b) Sample LMC-5:3:2** **c) Sample LMC-7:2:1**

Fig. 3: percentage of sample retained on sieve

The composite particles of all mixing ratios between Lactose, Corn Starch and microcrystalline cellulose were evaluated for their compressibility by compressing the powders at the force of 8.8 kN. Physical properties of tablets prepared from composite particles are in Table 5.

When the quantity of corn starch was decreased, the hardness of the resultant tablets increased. Tablets with high hardness values resulted low percentage friability (less than 1%) and good self-disintegration could be obtained at all proportions of these three components. The results described that the process of conventional method improved the compact ability of these systems as the concentration of Lactose monohydrate was increased.

CONCLUSION

Normally the Pharmaceutical industries don't accept the combination of filler and binder until it exhibits significant advantages in the tablet compaction when compared to the physical mixture of the excipients.

Co-processing is an interesting method to produce physical modification in product in a special way without altering the chemical structure. A fixed and homogenous distribution for the components is achieved by embedding them within mini-granules.

The present study investigated the basic physico-chemical property and binding functionality of new developed co-processed micro-granules prepared by conventional method for direct compression. The compressibility of these materials was analyzed by using compression parameters. Three classes of excipients were evaluated, including Lactose Monohydrate, Maize Starch and Microcrystalline Cellulose (MCC).

This study confirmed the binding mechanism as it has shown that all three diluents investigated are capable of improving the compressibility and low disintegration time to tablets.

The compaction properties were also investigated. Results indicated that the ratio of 7:2:1 (LMC-7:2:1) was found with excellent flow properties It was concluded that said composite particles could be

used as a new co-processed directly compressible excipient and to enhance compressibility.

Although it is probably the oldest excipient used in solid dosage form formulations, lactose is still one of the most important, particularly as diluents in tableting. However, the inadequate compactability of [alpha]-lactose monohydrate at particle sizes that provides good flow properties of the powder mixture limits the use of crystalline [alpha]-lactose monohydrate as a filler-binder for direct tableting[37].

Because of the need for direct compression excipients, to accompany the progress being made on high speed rotary tablet presses, many researchers and excipient manufacturers modified crystalline [alpha]-lactose monohydrate to achieve a product exhibiting good compactability, reduced capping tendency and good flow properties.

Table 5: Physical properties of tablets made from micro granules

Sample #	Hardness (KP) mean (SD)	Diameter (mm) mean (SD)	Thickness (mm) mean (SD)	Friability (%)	DT (seconds) mean (SD)
LMC-433	4.6	14.99	3.92	0.80%	30
LMC-532	8.24	14.98	3.97	0.65%	60
LMC-721	13.46	14.99	3.95	0.20%	90

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