Powder Technology 336 (2018) 360–374

Contents lists available at ScienceDirect

Powder Technology

journal homepage: www.elsevier.com/locate/powtec

Quantification of lubrication and particle size distribution effects on tensile strength and stiffness of tablets

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ARTICLE INFO

Article history:
Received 11 January 2018
Received in revised form 4 May 2018
Accepted 2 June 2018
Available online 06 June 2018

Keywords:
Tensile strength
Elastic modulus
Tablet compaction
Particle size distribution
Lubricant sensitivity

ABSTRACT

We adopt a Quality by Design (QbD) paradigm to better control the mechanical properties of tablets. To this end, the effect of particle size distribution, lubricant concentration, and mixing time on the tensile strength and elastic modulus of tablets is studied. Two grades of lactose, monohydrate and spray-dried, are selected. Tablets are compressed to different relative densities ranging from 0.8 to 0.94 using an instrumented compaction simulator. We propose a general model, which predicts the elastic modulus and tensile strength envelope that a specific powder can obtain based on its lubrication sensitivity for different particle size distributions. This is possible by introducing a new dimensionless parameter in the existing tensile strength and elastic modulus relationships with relative density. A wide range of lubrication conditions is explored and a predictable model is calibrated. The mechanical properties of lactose monohydrate tablets are noticeably dependent on particle size, unlike spray-dried lactose where little to almost no sensitivity to particle size is observed. The model is designed in a general fashion that can capture mechanical quality attributes in response to different lubrication conditions and particle size, and it can be extended to powders than undergo different deformation mechanisms, complex mixtures, and doubly convex tablets. Therefore, the model can be used to map the achievable design space of any given formulation.

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1. Introduction

Lubricants are one of the key ingredients in the pharmaceutical formulations to improve flowability, increase bulk powder density, and reduce die wall friction and ejection forces [9, 14, 21, 29, 35, 38, 46, 55]. Magnesium stearate (MgSt) is the most frequently used lubricant [54]; typically added to the formulation in small amounts (0.25%–1.0% (w/w)) [30, 35]. It has been shown that MgSt can adversely affect the physical and chemical properties of tablets [24, 60]. Hypothetically, MgSt forms a layer on the host particles weakening the interparticle bonding [5, 10, 22]. The lubricant type and concentration, type of mixer and its operation method, and mixing time are all important processing variables that affect the powder compactibility, interparticle bonding and thus, final mechanical properties of tablets [4, 7, 9, 26, 43, 44, 53]. However, the deformation mechanism of host particles also play a role [5]. For example, brittle materials that undergo fragmentation are said to be unaffected by MgSt due to the creation of unexposed surfaces during compression [10, 23]. In contrast, plastically deformable powders are significantly impacted by lubricant mixing [6, 12, 36]. Mollan and Çelik [37] ascribed the reduction in the total work of compaction by increasing the lubricant concentration to decreased particle cohesiveness. Zuurman et al. [64] argued that the decrease in tablet strength of pharmaceutical powders such as microcrystalline cellulose mixed with MgSt is caused by a more extensive relaxation of the lubricated tablets corresponding to a weaker interparticle bonding.

Over the past decade there has been growing interest in quantifying what the powder experiences in mixing with lubricant to enable a more robust prediction of tablet quality attributes. The blender parameters were translated to a more relevant and fundamental variables, strain and shear rate, using a modified Couette shear cell to better quantify lubrication effect [31, 34]. Shear rate is proportional to the energy input rate per unit mass and total strain is proportional

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https://doi.org/10.1016/j.powtec.2018.06.001
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to the total energy input per unit mass. Narang et al. [39] derived a dimensionless equation to quantify total shear imparted by the force feeder on the granulation in terms of a shear number, which provides guidance to the scale-up and interchangeability of tablet presses. Kushner and Moore [28] proposed an empirical model, which can describe the impact of both formulation and process parameters on the extent of lubrication in a pharmaceutical powder blend.

Particle size distribution (PSD) also plays an important role on the compaction and tablet properties [51]. A decrease in particle size of the powdered material has been shown to increase tablet porosity [11, 33]. Smaller particles are inclined to be more cohesive since the interparticle cohesive forces are comparable to the weight of the particles making them more compressible [8, 13]. Reduction in particle size typically results in an increase in the mechanical strength of tablets [20, 33, 47, 56]. This is attributed to a greater packing density after the particle rearrangement and an increase in the surface area available for interparticulate attractions [11, 50, 59]. Attempts were made to correlate specific surface area to the mechanical strength of tablets and a linear relationship was found for different types of lactose [11, 59]. However, Nyström et al. [40] suggested that the intermolecular forces are the dominating mechanism in the compactibility of powders and only in some cases the available surface area could be used to establish a model to correlate with mechanical strength of tablets. On the contrary, sodium chloride tablets have been reported to become stronger as their particle size increased associated to more bonding between particles through solid bridges [2].

Katikaneni et al. [25] investigated the tableting properties and predominant consolidation mechanism of ethylcellulose as lubricant concentration and particle size varied individually. The concurrent effect of lubrication and particle size on mechanical properties of pharmaceutical tablets during and after compaction has also been explored. Van der Watt [57] was the first to show that tablet properties change after the same MgSt mixing time for different particle sizes of Avicel PH 102. In more recent years, Almaya and Aburub [3] examined the effect of particle size on lubricant sensitivity for different types of materials. They concluded that for MCC (a plastically deforming material) particle size impacts tablet strength only in the presence of lubricant. For starch (a viscoelastic material) tablet strength is affected by the particle size with or without added lubricant. Finally, for dibasic calcium phosphate dihydrate (a brittle material) particle size has no effect on tablet strength with or without the lubricant. Nevertheless, there is no previous work that goes beyond the qualitative predictions.

The primary goal of the present study is to adopt a Quality by Design (QbD) paradigm to better control the mechanical properties of tablets. We aim to quantify the lubrication effect combined with the particle size on the tensile strength and elastic modulus of tablets. To this end, the envelope of mechanical quality attributes of two grades of lactose, namely lactose α-monohydrate (LM) and spray-dried lactose (SDL), caused by different PSD and lubrication conditions was explored. Tablets were compressed to different relative densities ranging from 0.8 to 0.94 using an instrumented compaction simulator. We propose a general model for predicting the elastic modulus and tensile strength spectrum that a specific powder can obtain based on its lubrication sensitivity for different PSDs. This was possible by introducing a new dimensionless parameter in the existing tensile strength and elastic modulus relationships that is a non-linear function of the PSD, lubricant concentration and its mixing time with the host particles. A wide range of lubrication conditions was explored and the model exhibited a good predictability. The mechanical properties of LM tablets were noticeably dependent on particle size, unlike SDL where little to almost no sensitivity to initial particle size was observed. The model is designed in a general fashion that can capture mechanical quality attributes in response to different lubrication conditions and initial particle size.

2. Material and methods

2.1. Materials

The materials used in this study include α-lactose monohydrate (Foremost Farms, Wisconsin, USA), Spray-dried Fast-Flo lactose monohydrate N.F. (Foremost Farms, Wisconsin, USA) and magnesium stearate N.F. non-Bovine (Mallinckrodt, Missouri, USA) as lubricant.

The true density of lactose monohydrate (LM), spray-dried lactose (SDL), and magnesium stearate (MgSt) powders was measured using an AccuPyc Pycnometer (Accupyc II 1340, Micromeritics) with helium as density medium. The powders were dried at 50 °C for 24 h before the test.

2.2. Powder preparation

Each powder was sieved through a vibrational sieve shaker (Octagon 2000, Endecotts Ltd., England) into different particle

Table 1
Mean (μ) and standard deviation (σ) for each particle size distribution, MgSt concentration (C_l), and the mixing time (t_m) for all the cases studied.

Powder	Cases	PSD (μm)	μ (μm)	σ (μm)	c_l (%)	t_m (s)
Lactose monohydrate	1	0–75	62.83	22.87	0.5	30
	2	0–75	62.83	22.87	0.25	120
	3	0–75	62.83	22.87	0.5	120
	4	0–75	62.83	22.87	1	120
	5	0–75	62.83	22.87	2	120
	6	0–75	62.83	22.87	2	300
	7	0–75	62.83	22.87	0.25	1200
	8	0–75	62.83	22.87	0.25	2400
	9	0–75	62.83	22.87	2	1200
	10	75–106	114	26.89	0.25	120
	11	75–106	114	26.89	0.25	1200
	12	75–106	114	26.89	2	1200
	13	106–150	149.3	25.6	0.25	120
	14	106–150	149.3	25.6	0.5	120
	15	106–150	149.3	25.6	0.25	1200
	16	106–150	149.3	25.6	2	1200
	17	as-received	77.72	31.85	0.25	120
	18	as-received	77.72	31.85	0.25	1200
	19	as-received	77.72	31.85	2	1200
Spray-dried lactose	20	0–75	65.14	17.15	0.5	30
	21	0–75	65.14	17.15	2	30
	22	0–75	65.14	17.15	1	120
	23	0–75	65.14	17.15	0.5	600
	24	0–75	65.14	17.15	2	600
	25	0–75	65.14	17.15	2	1200
	26	75–106	89.39	17.74	1	30
	27	75–106	89.39	17.74	0.5	120
	28	75–106	89.39	17.74	2	120
	29	75–106	89.39	17.74	1	600
	30	106–150	120.9	27.04	0.5	30
	31	106–150	120.9	27.04	2	30
	32	106–150	120.9	27.04	1	120
	33	106–150	120.9	27.04	0.5	600
	34	106–150	120.9	27.04	2	600
	35	106–150	120.9	27.04	2	1200
	36	150–212	171.9	33.91	0.5	30
	37	150–212	171.9	33.91	2	30
	38	150–212	171.9	33.91	1	120
	39	150–212	171.9	33.91	0.5	600
	40	150–212	171.9	33.91	2	600
	41	as-received	128.3	39.5	0.25	120
	42	as-received	128.3	39.5	2	1200

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