Research Article

การพัฒนาสารตอกอัดโดยตรงร่วมกระบวนการจากแมนนิทอลและแป้งข้าวโพด โดยใช้แลคติทอลเป็นสารยึดเกาะ

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บทคัดย่อ

การพัฒนาสารตอกอัดโดยตรงร่วมกระบวนการจากแมนนิทอลและแป้งข้าวโพดโดยใช้แลคติทอลเป็นสารยึดเกาะ
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การตอกอัดโดยตรงเป็นวิธีที่ง่ายและประหยัดที่สุดในการผลิตยาเม็ด โดยนำส่วนประกอบต่างๆ ผสมให้เข้ากันดีแล้วตอกให้เป็นเม็ดยา สิ่งสำคัญในการผลิตด้วยวิธีนี้คือสารช่วยตอกอัดโดยตรงที่ดีและมีประสิทธิภาพ **วัตถุประสงค์:** เพื่อพัฒนาสารช่วยตอกอัดโดยตรงร่วมกระบวนการชนิดใหม่ จากแมนนิทอลและแป้งข้าวโพดโดยวิธีแกรนูลเปียก **วิธีดำเนินการวิจัย:** สารช่วยตอกอัดโดยตรงร่วมกระบวนการ เตรียมจากส่วนผสม 2:1 ของแมนนิทอลและแป้งข้าวโพด โดยใช้แลคติทอลเป็นสารยึดเกาะ (ในปริมาณร้อยละ 0 –15 ของน้ำหนักแห้ง) นำแกรนูลที่เตรียมได้มาศึกษาสมบัติทางฟิสิกส์และเตรียมเป็นยาเม็ดเปล่าเพื่อศึกษาความสามารถในการตอกเป็นยาเม็ด (tabletabiliy) เวลาการแตกกระจายตัว อัตราส่วนความไวต่อสารช่วยลื่น สารช่วยตอกอัดโดยตรงที่เตรียมได้ นำมาเตรียมยาเม็ดไฮโดรคลอโรไทอาไซด์ เพื่อศึกษากราฟการละลายโดยเทียบกับตำรับยาต้นแบบ โดยใช้ค่า similarity factor (f_2) **ผลการวิจัย:** แกรนูลร่วมกระบวนการของแมนนิทอลและแป้งข้าวโพดสัดส่วนสองต่อหนึ่งที่ใช้แลคติทอลเป็นสารยึดเกาะ (0%, 10% และ 15% ใช้ชื่อว่า MCL00, MCL10 และ MCL15 ตามลำดับ) มีการไหลที่ดีถึงดีเยี่ยม มีความชื้นต่ำ (ร้อยละ 1.60 ± 0.17 ถึงร้อยละ 1.63 ± 0.06) มีเส้นผ่านศูนย์กลางมัธยฐานเท่ากับ 445, 610 และ 595 ไมโครเมตร ตามลำดับ ค่าความต้านแรงดึงของยาเม็ดเปล่าของสารช่วยตอก MCL มีค่าเพิ่มขึ้นตามปริมาณที่เพิ่มขึ้นของแลคติทอล (ANOVA, Tukey post-hoc, p<0.01) มีอัตราส่วนความไวต่อสารช่วยลื่นอยู่ในช่วง 0.29 - 0.53 ยาเม็ดเปล่าที่ผลิตได้จากสารช่วย MCL10 และ MCL15 ผ่านการประเมินตามข้อกำหนดต่างๆ ที่เภสัชตำรับระบุ ยาเม็ดไฮโดรคลอโรไทอาไซด์ความแรง 50 มิลลิกรัม ที่ผลิตจาก MCL10 ทั้งที่ไม่ใส่และใส่สารช่วยแตกกระจายตัวในปริมาณร้อยละ 2 - 4 ให้ยาเม็ดที่มีลักษณะทางกายภาพที่ดีและผ่านเกณฑ์การทดสอบการปลดปล่อยตัวยา ค่า similarity factor ที่คำนวณจากค่าการละลายเทียบกับยาต้นแบบมีค่าตั้งแต่ 51-60 **สรุปผลการวิจัย:** แลคติทอลเป็นสารยึดเกาะที่มีประสิทธิภาพในการเตรียมแกรนูลร่วมกระบวนการแมนนิทอลและแป้งข้าวโพด ทั้ง MCL10 และ MCL15 มีสมบัติด้านการไหลและความสามารถในการตอกเป็นยาเม็ดที่ดี เหมาะสมในการใช้เป็นสารช่วยตอกอัดโดยตรง ในการศึกษานี้ MCL10 มีความเหมาะสมที่สุดในการใช้ผลิตยาที่มีค่าการละลายน้ำยากมากอย่างเช่นไฮโดรคลอโรไทอาไซด์ การเติมสารช่วยแตกกระจายตัวยิ่งยวด จึงอาจมีความจำเป็นเพื่อบังคับให้เวลาในการแตกกระจายตัวของยาเม็ดและการปลดปล่อยตัวยาเร็วตามต้องการ

คำสำคัญ: สารตอกอัดโดยตรง, แมนนิทอล, แป้งข้าวโพด, แลคติทอล, ไฮโดรคลอโรไทอาไซด์

Development of Mannitol-Corn Starch Co-processed Direct Compression Excipient Using Lactitol as Binder

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Abstract

Development of Mannitol-Corn Starch Co-processed Direct Compression Excipient Using Lactitol as Binder

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Direct compression is the simplest and most economic method to produce tablets that ingredients are thoroughly mixed and then compressed into tablets. The important role of this process is the good and effective direct compression excipient. **Objective:** The aim of this study was to develop a new co-processed direct compression excipient from mannitol and corn starch using wet granulation method. **Methods:** The direct compression excipients were prepared by co-processing mannitol with corn starch in a ratio of 2:1 using lactitol (0 - 15% on dry basis) as a binder. The resulted granules were evaluated for physical properties. These excipients were used to prepared placebo tablets to characterize tabletability, disintegration time and lubricant sensitivity ratio. All excipients were used to formulate hydrochlorothiazide (HCTZ) tablets. Dissolution profiles of the HCTZ tablets were compared to the original product using similarity factor (f_2). **Results:** The 2:1 mannitol-corn starch co-processed granules containing lactitol as binder (0%, 10% and 15% named as MCL00, MCL10 and MCL15, respectively) performed good to excellent flowability with relatively low %moisture contents (1.60 ± 0.17-1.63 ± 0.06). The median diameter ($d_{0.5}$) of MCL00, MCL10 and MCL15 were 445, 610 and 595 μm, respectively. Tensile strength of placebo tablets from MCL excipients increased with the increase amount of lactitol (ANOVA, Tukey post-hoc, p<0.01). Lubricant sensitivity ratios were between 0.29-0.53. Placebo tablets from MCL10 and MCL15 met the acceptance criteria according to pharmaceutical compendia. HCTZ tablets (50 mg/tab) produced from MCL10 without or with superdisintegrant at 2-4% offered good physical characteristics and complied with the dissolution test. The similarity factors calculated from dissolution profiles and compared to that of the original product were 51-60. **Conclusion:** Lactitol was an effective binder for co-processed mannitol-corn starch granules. Both MCL10 and MCL15 exhibited good flowability and high tabletability and suited for direct compression excipient. In the present study, MCL10 was the most suitable excipient to deal with such a very slightly soluble drug like HCTZ. The adding of superdisintegrant might need to attain the desired disintegration time and drug release.

Keywords: Direct compression excipient, mannitol, corn starchm, lactitol, hydrochlorothiazide

Introduction

Direct compression provided a short process of tablet production. However, neither all active pharmaceutical ingredients (APIs) nor small doses of APIs can be applicable. The right flow and compression characteristics are the most important factors to compensate the poorly compactable APIs (Bolhuis and Armstrong, 2006; Saha and Shahiwala, 2009). The direct compression (DC) excipients are normally more expensive than basic excipients. Most commercial available direct compression excipients also do not provide multifunction properties. To develop a good and cheap DC excipient by co-processing is therefore interesting and challenging. Co-processed excipient is a mixture of two or more excipients interacting at sub-particle level to obtain the product with added value related to the ratio of its functionality. Co-processing is very cost effective method for providing new excipient with multifunction such as excellent flowability, tabletability and self disintegrating (Mirani *et al*., 2011).

Mannitol or D-mannitol is isomeric with sorbitol. It is commonly used as an excipient in chewable tablet formulations because of its negative heat of solution, sweetness, and very good mouth feel. It is usually used as a diluent in rapidly dispersing oral dosage forms (Rowe *et al*., 2012). Nowadays, mannitol is widely used as direct compression excipient because it is safe to APIs, non-hygroscopic and good in compaction into tablets (Ohrem *et al*., 2014). Non-hygroscopicity of mannitol is excellent for APIs stability. Commercial DC excipients from mannitol are available under the brand names Mannogem® and Pearitol®. Mannogem® (SPI Pharma, 2016) and Pearlitol® (Roquette, 2012) are produced by wet granulation or spray drying to provide various functional grades to meet the specific application needs of the formulator. Pearlitol®Flash is a commercial instance of mannitol-corn starch agglomerates, developed by Roquette. It is claimed to disintegrate very quickly in the mouth. For co-processing, mannitol has been used by several researchers to fabricate direct compression excipients for orodispersible tablets because of the sweet and cooling taste. Jacob *et al*. formulated mannitol with microcrystalline cellulose (MCC) by spray drying in various ratios. They found that co-processed mannitol and MCC provided good tablet characteristics. However, to pass the orodispersible tablet disintegration time the disintegrant had to be added up to 5% (Jacob *et al*., 2007). Daraghmeh *et al.* prepared and characterized a novel excipient from chitin and mannitol (2:8 by weight) produced by roll compaction. The results showed that the multifunctional excipient was successfully used in formulation of orodispersible and fast immediate release tablets (Daraghmeh *et al*., 2015). Gonnissen *et al*. prepared compressible paracetamol by co-spray drying with various carbohydrates (lactose, lactitol, sorbitol, mannitol, erythritol, maltodextrin, xylitol and maltitol) at 1:1 ratio. They found that only paracetamol-mannitol had good tablet tensile strength. Additionally, the replacing part of the mannitol fraction by erythritol or maltodextrin as binder in amounts of 10% and 30% improved powder flowability and tablet tensile strength. Maltodextrin had a positive effect on tablet tensile strength while erythritol mainly improved powder flowability (Gonnissen *et al*., 2007).

Corn starch is generally used as filler, glidant and disintegrant in tablet manufacturing (Ochubiojo and Rodrigues, 2012; Builders and Arhewoh, 2016). Under compaction, corn starch undergoes plastic deformation (Paronen and Juslin, 1983; Alebiowu and Itiola, 2002). Lactitol is a synthetic polyol derived from lactose. It does not cause Maillard reaction and has low hygroscopicity (Rowe *et al.*, 2012; Zacharis, 2012). However, the use of lactitol as binder in wet granulation is less studied.

Hydrochlorothiazide (HCTZ) is a thiazide diuretic used for arterial hypertension (Carter and Emst, 2017). HCTZ is a Class III drug with poor water solubility (722 mg/L) (Lindenberg *et al.,* 2004). Its melting point is 265-270^{O}C with decomposition. Under stress condition, HCTZ

undergoes hydrolysis to yield formaldehyde and 4-amino-6-chloro-m-benzenedisulfonamide (Connors *et al*., 1986). In combination with other hypertensive drugs, HCTZ degraded under stress tests (Lusina *et al.,* 2005; Wadher *et al*., 2016). HCTZ tablets are available in 12.5, 25 and 50 mg doses. In the present study, HCTZ dose of 50 mg was used as a model drug to challenge the formulation work due to the problem related to dissolution.

SuperTab®11SD, a commercial available spray-dried lactose (SDL) was used as a benchmark for tabletability study only because lactose is a sugar alcohol and performs brittle fracture under compression like mannitol. SDL is manufactured by spray-drying crystalline lactose monohydrate to give spherical agglomerates in a matrix of amorphous lactose thus it holds high tabletability and free flowing. However, compaction property of SDL is influenced by the particle size of the primary crystals and amorphous portion in the particles (Lerk, 1993; Russu *et al*., 2006). The objective of this study was to develop a new multifunctional excipient from mannitol and corn starch using lactitol as a binder. Wet granulation was used for the co-processing because this method is simple and cheap. Most pharmaceutical manufacturers already have equipments to prepare this DC excipient for in-house uses. The co-processing of these components was supposed to offer a cost effective excipient with good characteristics for self disintegrating, free flowing and good tabletability.

Methods

1. Chemicals

Mannitol monohydrate was purchased from Maxway, Thailand. Corn starch was purchased from National starch and chemical, Thailand. Hydrochlorothiazide was purchased from Pharmasant laboratory, Co., Ltd, Thailand. SuperTab®11 SD was purchased from DFE Pharma, New Zealand. Talcum, magnesium stearate, calcium stearate were purchased from IL Shinindustrial (Korea), Union Derivan S.A. (Germany) and Fluka Chemical (UK), respectively. Sodium fumaryl stearate (Lubripharm®) was a gift from SPI Pharma. Lactitol monohydrate was purchased from Danisco, USA. Croscarmellose sodium (Ac-di-sol®) was purchased from FMC Biopolymer, USA.

2. Preparation of mannitol-corn starch granules and tablets

Co-processed granules composing of mannitol and corn starch in the ratio of 2:1 were prepared by wet granulation method. Deionized water and 60% lactitol stock solution were used as binders. Lactitol was varied from 0 - 15% on dry basis of the blend. Wet mass was performed in a planetary mixer and then passed through a 12 mesh sieve. The granules were dried at 55°C for three hours and then passed through a 20 mesh sieve. The resulted granules were screened with a sieve number 60 to discard the fine particles. Each batch of the granules was blended with magnesium stearate (1%w/w) for three minutes using a lab scale V-shape mixer. Placebo tablets (200 mg) were compressed using a 8-mm diameter flat face punch and die using a hydraulic hand press (Carver, USA) with pressures of 10, 20 and 30 kN for tabletability study.

In order to examine the uniform flow of the granules into the tablet dies, the blends were also compressed using a rotary tabletting machine (Charatchai Machinery CMRT-8, Thailand) because the interruption of flow to the tabletting dies is a main problem in direct compression tabletting. The resulted tablets were used for stability study.

3. Evaluation of granules and tablets

3.1 Flowability

The granules were evaluated for bulk density, tapped density using a tapped volumeter (Erweka SVM 12, Germany). Carr's index and Hausner ratio were calculated as per the official procedure (USP29/ NF24, 2005). These Carr's index and Hausner ratio were calculated using bulk density and tapped density as follows:

Carr's index = [(tapped density – bulk density) / tapped density] x 100

Hausner ratio = tapped density / bulk density

The acceptable scale of flow ability should be equivalent to "fair" or better flow scale.

Angle of repose (α) was determined on a fixed base method using powder flow meter (Electrolab EFT-01, India). An average of three determinations was calculated from the following equation. The angle of repose equals to 40^{o} and lesser is acceptable.

tan α = height of the pile of powder / 0.5 base diameter

3.2 % Moisture content

Three different samples were determined using a moisture balance (Chyo IB-30, Japan) at 105^{o}C for 5 min.

3.3 Particle size distribution

Particle size distribution was performed using a sieve shaker (Retsch AS 200, Germany). A stack of standard sieves (no. 35, 40, 60, 80, 100, 120, 140 and 170) was used. The sieves were agitated for 5 min. The weight retained on each sieve was determined. The particle size distribution was reported in terms of $d_{0.1}$, $d_{0.5}$, and $d_{0.9}$ which give an indication of size of the fine ($d_{0.1}$) and coarse ($d_{0.9}$) fractions, and of the median particle size ($d_{0.5}$) (USP29/NF24, 2005).

3.4 Tablets weight variation

Tablets weight variation was carried out according to USP29/NF24. Ten tablets were weighed individually. The results were expressed as mean ± SD.

3.5 Crushing strength and tensile strength

The tablet crushing strength (F) was determined after 24 h of compression using a hardness tester (Erweka TBH10, Germany). The tablet diameter (d) and thickness (h) were measured using a micrometer. The tablet tensile strength (TS) was calculated using the equation as follows (USP35/NF30, 2012).

Tensile strength (MPa) = 2F / πdh

3.6 Friability

Tablets were randomly selected and weighed with total weight close to 6.5 g. Friability was performed using Roche type friabilator (Brother Join, Thailand) rotated at 25 rpm for 4 min. The tablets then were dedusted and reweighed. The loss in weight was recorded as percentage friability that should be less than 1.0%.

% Friability = [1 – (weight of tablets after friability/ weight of tablets before friability)] x 100

3.7 Disintegration time

The test was performed on six tablets at 37 ± 0.5^{o}C in deionized water in accordance with USP35/NF30 using disintegration apparatus (Labindia DT100, India). The tablet disintegration time was achieved at a time (min) when no residue remained on the screen of the apparatus.

3.8 Lubricant sensitivity ratio (LSR)

Placebo tablets (200 mg/tab) with 1%w/w of lubricant were produced using a hydraulic press at 15 kN pressure. Four lubricants (talcum, magnesium stearate, calcium stearate and sodium fumaryl stearate) were investigated. The duration of mixing time (5 min and 20 min) of each lubricant was compared for LSR which was calculated from the formula:

$$LSR = \frac{\text{(tablet hardness without lubricant – tablet hardness with lubricant)}}{\text{(tablet hardness without lubricant)}}$$

4. Accelerated stability study

In this study, placebo tablets (200 mg/tab) from each DC excipients (MCL00, MCL10, MCL15 and SDL with 1%w/w of magnesium stearate) were produced using a rotary tableting machine. The compaction force was optimized to result in the tablet crushing strength of 6-10 kP and the tablet thickness in between 2.8-3.0 mm. The resulted tablets were kept in well-closed containers for 6 months at room temperature (RT), 45^{o}C/75%RH and 45^{o}C/75%RH in opened containers. The tablets were evaluated for the average weight, hardness, friability and disintegration time.

5. Formulation of hydrochlorothiazide (HCTZ) tablets

5.1 Hydrochlorothiazide tablets (50 mg/tab) preparation

The first series of formulations, HCTZ tablets were formulated using MCL00, MCL10 and MCL15. A 200 mg of tablet weight was designed to follow the previous study of placebo tablets. HCTZ and each co-processed excipient were mixed thoroughly. The blend was then lubricated by mixing with 1%w/w of magnesium stearate. To expand the process to the ideal size for the manufacturing-scale, the powder blends were compressed into tablets using a rotary tabletting machine. The tablets were evaluated for physical properties and dissolution for screening the optimal excipient.

The second series of formulations was done using MCL10 to optimize the most acceptable HCTZ tablets. A 180 mg of tablet weight was considered because the weight of the first series of formulations was too high to promote the adequate drug release. HCTZ was initially mixed with MCL10 and Ac-di-sol® (0%, 2% and 4%w/w) for 5 min then 1%w/w magnesium stearate was added and mixed for 3 min using a lab scale V-shape mixer. Tablets were produced using Carver hydraulic hand press at compression force of 20 kN. The tablets were stored for 24 h to allow the elastic recovery and hardening. Then, the tablets were determined for the tablet hardness, %friability, disintegration time and dissolution.

5.2 Dissolution test

The basket dissolution apparatus was used. The dissolution medium was 900 ml of 0.1 N HCl maintained at 37.0 ± 0.5°C and the rotation rate was 100 rpm (USP35/NF30, 2012). The absorbance of the withdraw solutions at various time intervals was determined at 272 nm using a UV-visible spectrophotometer (Shimazu UV-1800, Japan) and was transformed to concentration by reference to a standard curve obtained experimentally (r^2 = 0.9999). The dissolution profile comparison was characterized in term of similarity factor (f_2) calculated according to the method proposed by Moore and Flanner (FDA, 1997).

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t) \right]^{-0.5} \times 100 \right\}$$

The term n was number of time points at which %dissolved was determined. R_t was %dissolved of original product at a given time point. T_t was %dissolved of formulation to be compared at the same time point. The f_2 value above 50 indicates the two profiles are similar.

6. Statistical analysis

All data obtained were expressed as mean ± SD. For statistical comparison of the results, a one-factor ANOVA test was used. If the significant differences existed (p<0.01), Tukey post-hoc test was used to specify those excipients having significant each other. The analysis was done using Microsoft Excel 2007.

Results and Discussion

Characteristics of co-processed excipients

Table 1 shows the characteristics of the three formulated co-processed excipients (MCLs) and a SDL (SuperTab®11 SD). In terms of angle of repose, value close to 25° means excellent flowability while the value close to 40° means fair flowability. Carr's index of less than 10% and Hausner ratio of between 1.00-1.10 indicate the excellent flowability according to the official criteria (USP29/NF24, 2005).

Angle of repose of MCL00, MCL10 and MCL15 was 32.2 ± 0.5°, 30.5 ± 0.6° and 30.2 ± 0.4°, respectively. The observed angle of repose indicated that the 2:1 mannitol-corn starch co-processed granules performed good to excellent flowability. The moisture contents of all co-processed excipients were between 1.60 ± 0.17% to 1.63 ± 0.01%. Carr's index and Hausner ratio were in the range of 7.33 ± 0.70 to 9.24 ± 1.39 and 1.08 ± 0.01 to 1.10 ± 0.02 indicating all formulations had good compressibility index.

Table 1. Characteristics of direct compression excipients

DC excipients	Angle of repose (α) (n = 3)	Bulk/Tapped density (g/ml)	Carr's Index (%)	Hausner ratio	% Moisture content	Particle size distribution (μm) ($D_{0.1}$,$D_{0.5}$,$D_{0.9}$
MCL00	32.2 ± 0.5	0.55 ± 0.01/ 0.59 ± 0.01	7.33 ± 0.70	1.08 ± 0.01	1.60 ± 0.20	200, 445, 760
MCL10	30.5 ± 0.6	0.59 ± 0.01/ 0.64 ± 0.0	7.98 ± 1.10	1.09 ± 0.01	1.60 ± 0.17	365, 610, 800
MCL15	30.2 ± 0.4	0.59 ± 0.01/ 0.65 ± 0.01	9.24 ± 1.39	1.10 ± 0.02	1.63 ± 0.06	315, 595, 795
SDL	Not flow	0.65 ± 0.0/ 0.73 ± 0.01	10.82 ± 0.75	1.12 ± 0.01	0.10 ± 0.00	n/a*, 130, 210

* n/a = not available.

Physical properties of placebo tablets

Table 2 demonstrates the characteristics of placebo tablets made from different DC excipients using a hydraulic hand press at various compression pressures. All the tablets complied the current USP friability tolerance limit, except those of SDL contained tablets at 10 kN pressure had the friability higher than 1.0%. Tablet thickness from MCLs excipients resulted in the range of 2.83 ± 0.02 mm to 2.94 ± 0.03 mm.

Table 2. Physical properties of placebo tablets.

DC excipients	Compression pressure (kN)	Crushing strength (kP)	Tensile strength (MPa)	Thickness (mm)	%Friability
MCL00	10	7.06 ± 0.67	1.91 ± 0.19	2.87 ± 0.03	0.82
	20	8.50 ± 0.99	2.33 ± 0.26	2.83 ± 0.04	0.65
	30	8.39 ± 0.72	2.30 ± 0.20	2.83 ± 0.02	0.51
MCL10	10	10.00 ± 0.76	2.61 ± 0.20	2.94 ± 0.03	0.56
	20	10.35 ± 0.64	2.77 ± 0.17	2.88 ± 0.03	0.08
	30	11.05 ± 0.44	2.96 ± 0.14	2.87 ± 0.03	0.02
MCL15	10	15.08 ± 1.06	3.94 ± 0.27	2.93 ± 0.02	0.36
	20	14.91 ± 0.88	3.92 ± 0.21	2.92 ± 0.02	0.13
	30	14.47 ± 0.93	3.77 ± 0.24	2.94 ± 0.01	0.38
SDL	10	5.16 ± 0.84	1.38 ± 0.22	2.90 ± 0.03	1.11
	20	11.19 ± 0.67	3.14 ± 0.18	2.76 ± 0.02	0.51
	30	14.81 ± 0.67	4.21 ± 0.16	2.73 ± 0.03	0.44

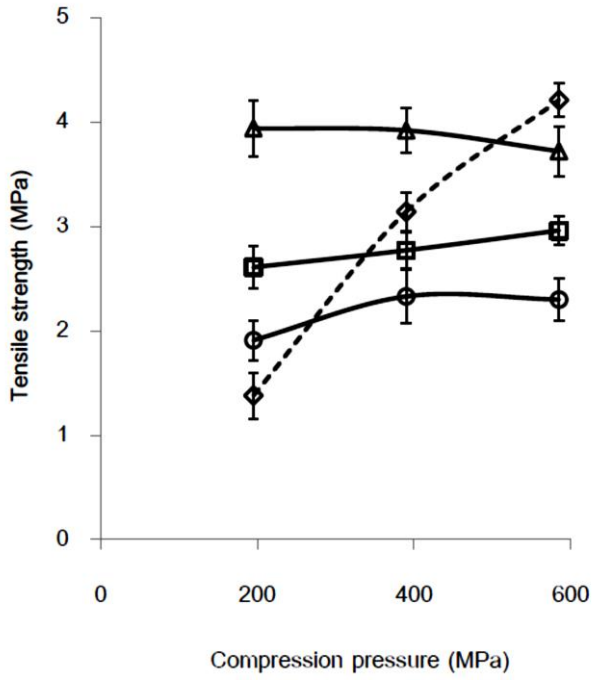

Figure 1. Tabletability profiles of placebo tablets consisting MCL00 (O), MCL10 (□), MCL15 (△), and SDL (◊).

Figure 1 demonstrates tabletability profiles conducted from the relationship between compression pressures and tablet tensile strength. Tabletability means the ability of the powder compaction into tablets with adequate mechanical strength (Amidon *et al*., 2017). Tablet tensile strength contributes from compression bonding. Theoretically, when granules undergo compression, both elastic and plastic deformation can occur simultaneously but one usually predominates. Plastic deformation creates a large number of contact points between particles where bonding occurs. Particle fragmentation happens next at higher compression pressure and creates new clean surface sites where particle bonding occurs (Miller, 1999).

Tablets consisting SDL showed the different profile from those consisting MCLs. By its nature, SDL performs predominantly brittle fracture. The existing amorphous lactose in SDL also performs plastic deformation (Munoz-Ruiz *et al*, 1993; Gharraibeh and Aburub, 2013). Higher amorphous contents provide superior tabletability (Russu *et al*., 2006; Ruangchayajatuporn *et al*, 2011). At low pressure (195 MPa) tablet tensile strength was low because it might not reach the critical compaction. At higher pressure the plastic deforming amorphous lactose and crystalline lactose worked together and the tablet tensile strength increased significantly (ANOVA, Tukey post-hoc test, p <0.01). Tablet tensile strength of MCL00, MCL10 and MCL15 did not increase proportionally with the increasing compression pressure (ANOVA, p>0.01). This indicated that the maximum of plastic deformation almost reached at 10 – 20 kN pressures. At higher compaction, brittle fracture deformation of mannitol did not freely take place.

The main purpose of binder is to enlarge size of agglomerates and thus improve flowability of the granules. The successive binder should also improve tablet tensile strength and tablet friability. Lactitol itself cannot be compressed into tablets of sufficient hardness (Bolhuis *et al*., 2009). It has not been considered to be used as a binder thus there is not much information available about this use. However, Olinger *et al*. fabricated direct compression lactitol granules conducting with various binders including lactitol solution (2-30% dry weight). They found that lactitol surprisingly worked very well (Olinger and Pearson, 1998). As shown in Figure 1, tensile strength of tablets from MCLs granules increase with the increase amount of lactitol. The tensile strength of MCL10 and MCL15 was higher than MCL00 (ANOVA, Tukey post-hoc test, p <0.01). This was expected to happen because the higher amount of lactitol could cause more plastic deformation and increased stronger bonding between adjacent particles. By the fact that amorphous lactose in SDL is responsible for the better binding and plastic deformation whereas it still undergoes fragmentation under compaction (Bolhuis *et al*., 2004; Gohel and Jogani, 2005). It is noteworthy to point out that SDL needed more compaction to yield the equal tablet tensile strength. Therefore MCLs consumed less energy in tabletting and reduced the machine deterioration. However, theirs exact behaviors under compaction are complicate and need to further investigate using more proper instruments.

Lubricant sensititvity ratio (LSR)

Most lubricants are hydrophobic and provide lubricant film on the surface of particles. Lubricants reduce die wall friction during tablet compression and ejection and also prevent the formation of compaction. This effect is more sensitive in high plastically materials (Almaya and Aburup, 2008). The effect of lubricant on tablets hardness depends on many factors such as its nature, concentration, mixing time (Shah and Mlodozeniec, 1977) and specific surface area (Obe and Otsuka, 2012). However, other properties of excipients such as particle size, flowability and deformation mechanism also influence on the lubricant sensitivity (Almaya and Aburub, 2008).

Table 3 shows the LSRs of four lubricants. All tablets hardness was weakened by lubricants, except those of tablets contained talc resulted in the lowest LSRs in MCLs. Talc is less efficient in lubrication than magnesium stearate since it has less hydrophobicity and has weakly-bonded sheet structure which allows them to slip past one another (Fiume, 2012; Li and Wu, 2014). Talc is usually replaced when formulation with magnesium stearate exhibited in excessive problems.

Other three lubricants (magnesium stearate, calcium stearate and sodium fumaryl stearate) are metallic salts of fatty acid. They differ in melting point, hydrophobicity and impurity but their lubricant efficiency is similar. Among these lubricants, sodium fumaryl stearate is usually used because it is less hydrophobic than magnesium stearate and calcium stearate whereas prolonged mixing time improves its lubricated effect and has no effect on disintegration time (Li and Wu, 2014).

Considering each lubricant, LSRs of MCLs significantly higher than SDL (ANOVA, Tukey post-hoc test, p <0.01). These results due to the larger in median particle size of MCLs (455 – 610 μm) compared to that of SDL (130 μm). Hence, the lower amount of lubricant is needed for effective coverage. In accordance with aforementioned tabletabity results that MCLs underwent plastic deformation rather than brittle fracture. Corn starch in MCLs protected the fragmentation of mannitol thus new clean surface was less fractured under compaction.

Prolonging the mixing time decreased the hardness of tablets made from both MCLs and SDL but there was no statistically significant difference between 5 min and 20 min of mixing time (ANOVA, p>0.01). _However, the overcoating of lubricant may affect the wettability of the particles and prolongs dissolution time (Obe and Otsuka, 2012).

Table 3. Lubricant sensitivity ratio of placebo tablets.

DC excipients	Mixing Time (min)	Lubricant sensitivity ratio (LSR)			
		Talc	Mag. stearate	Cal. stearate	Sod. fumaryl stearate
MCL00	5	0.00	0.34	0.32	0.35
	20	0.00	0.40	0.40	0.33
MCL10	5	0.28	0.41	0.42	0.29
	20	0.33	0.37	0.42	0.33
MCL15	5	0.28	0.41	0.50	0.53
	20	0.38	0.48	0.59	0.48
SDL	5	0.10	0.10	0.10	0.05
	20	0.15	0.20	0.15	0.19

Stability data

Table 4 presents the stability data of placebo tablets after storing for 6 months in well closed container and opened container to exacerbate high humidity. Among three MCL excipients, tablets made from MCL00 did not successfully comply the friability test. At 45°C/75%RH, all batches in well-closed containers or opened containers exhibited the minor reduction of tablet hardness. Disintegration time of all formulas increased from the initial time except for MCL00. The mean weight of tablets, disintegration time and %friability were not likely to change. The results showed that placebo tablets itself could persevere the physical appearance, tablet hardness, disintegration time and friability within the specified limits throughout the storage period.

Table 4. Stability data of placebo tablets prepared by using a rotary tableting machine at speed of 25 rpm.

DC fillers	Storage conditions	Tablet weight (mg) (n=20)	Crushing strength (kP)	Tensile strength (MPa)	Disintegration time (min)	%Friability
MCL00	Initial time	201.3 ± 1.9	4.29 ± 0.22	1.10 ± 0.3	0.5 ± 0.0	1.25
	RT	201.0 ± 2.0	6.10 ± 0.30	1.60 ± 0.1	0.6 ± 0.1	1.45
	45°C/75%RH	200.4 ± 2.2	5.88 ± 0.00	1.57 ± 0.1	0.5 ± 0.1	1.35
	45°C/75%RH*	200.6 ± 2.2	5.84 ± 0.29	1.50 ± 0.1	0.5 ± 0.0	1.09
MCL10	Initial time	202.0 ± 2.1	8.35 ± 0.54	2.16 ± 0.3	2.3 ± 0.1	0.34
	RT	202.0 ± 1.6	9.56 ± 0.63	2.52 ± 0.2	4.0 ± 0.1	0.38
	45°C/75%RH	200.3 ± 1.9	8.60 ± 0.41	2.25 ± 0.1	4.2 ± 0.5	0.49
	45°C/75%RH*	203.7 ± 2.1	6.85 ± 0.44	1.74 ± 0.1	4.9 ± 0.1	0.61
MCL15	Initial time	201.7 ± 2.5	11.12 ± 0.86	2.96 ± 0.1	2.9 ± 0.2	0.28
	RT	201.5 ± 2.9	13.10 ± 0.87	3.49 ± 0.2	4.4 ± 0.6	0.34
	45°C/75%RH	199.4 ± 3.4	11.58 ± 0.77	3.05 ± 0.2	5.6 ± 0.5	0.45
	45°C/75%RH*	201.6 ± 3.0	9.94 ± 0.89	2.59 ± 0.2	5.9 ± 0.6	0.46
SDL	Initial time	200.0 ± 1.3	4.31 ± 0.52	1.16 ± 0.2	5.4 ± 0.1	1.25
	RT	200.1 ± 1.6	6.72 ± 0.44	1.85 ± 0.1	19.6 ± 0.5	0.77
	45°C/75%RH	200.1 ± 1.9	7.77 ± 0.67	2.14 ± 0.2	19.6 ± 0.4	0.71
	45°C/75%RH*	200.0 ± 0.9	7.63 ± 0.89	2.10 ± 0.2	17.6 ± 0.6	0.59

* The tablets were packed in opened containers.

HCTZ tablets properties and drug release

Table 5 demonstrates the physical properties of HCTZ tablets. In preliminary study, three formulations were developed in a 200 mg/tab to go along with the placebo tablet. Tablets were compressed using a rotary tabletting machine to expand the process to the ideal size of manufacturing-scale. The tablets were produced by controlling the compression pressure and optimized the crushing strength close to those from hydraulic hand press. The rotating speed was set at 25 rpm. The data showed that all the physical properties were acceptable except for the friability of the tablets consisting MCL00 thus the drug dissolution was not tested. The percentage drug dissolved of HCTZ-MCL10 acceptably passed the dissolution test but that from MCL15 was less than 60%(Q) in 60 min. HCTZ-MCL15 exhibited significantly higher tablet crushing strength

when compared to MCL00 and MCL10 (ANOVA, Tukey post-hoc test, $p<0.01$). Without the adding of superdisintegrant, HCTZ-MCLs disintegrated within 0.4 ± 0.0 to 10.2 ± 1.3 min. In this series, the increase in tablets tensile strength and the tablet weight conversely influenced the water penetration into the tablet core and prolonged the disintegration time. Thus, HCTZ tablets in weight of 180 mg/tab were subsequently formulated with the adding of 2-4%w/w of superdisintegrant. MCL10 was selected for this aspect. Croscarmellose sodium (Ac-di-sol®) was used because it was well documented for the mechanism of swelling, wicking and strain recovery (Desai *et al*., 2016).

Table 5. Physical properties and similarity factors of hydrochlorothiazide tablets.

Tablet excipients	Tablet weight (mg) (n=20)	Crushing strength (kP) (n=10)	Thickness (mm) (n=10)	% Friability	DT (min) (n=6)	f_2 (n =12)
MCL00	203.7 ± 2.3	3.59 ± 0.33	2.89 ± 0.04	1.85	0.4 ± 0.0	-
MCL10	200.7 ± 3.3	4.90 ± 0.33	2.84 ± 0.05	0.47	7.9 ± 1.2	-
MCL15	200.3 ± 3.6	7.26 ± 0.63	2.83 ± 0.01	0.42	10.2 ± 1.3	-
MCL10 + 0%*	179.3 ± 2.7	4.06 ± 0.41	2.50 ± 0.04	0.67	3.5 ± 0.4	51
MCL10 + 2%*	180.7 ± 2.2	4.24 ± 0.39	2.52 ± 0.03	0.55	1.1 ± 0.2	60
MCL10 + 4%*	180.3 ± 2.6	5.25 ± 0.51	2.51 ± 0.05	0.56	1.3 ± 0.3	54

* HCTZ tablets containing croscarmellose sodium (Ac-di-sol®).

To control equal pressure applied to each formula, hydraulic hand press was used. In this series, the tablet crushing strength was found to be 4.06 ± 0.41 kP to 5.25 ± 0.51 kP and the friability was within the official limit. Disintegration time of the HCTZ-MCL10 tablets containing 2%w/w and 4%w/w croscarmellose sodium was reduced significantly in comparison to that without the adding (ANOVA, Tukey post-hoc test, p <0.01). As a result, disintegrating time reduced from 3.5 ± 0.4 min to 1.1 ± 0.2 min and 1.3 ± 0.3 min, respectively. There was no statistically significant difference between the disintegration time of the formulas adding croscarmellose sodium of 2% and 4% (ANOVA, p >0.01).

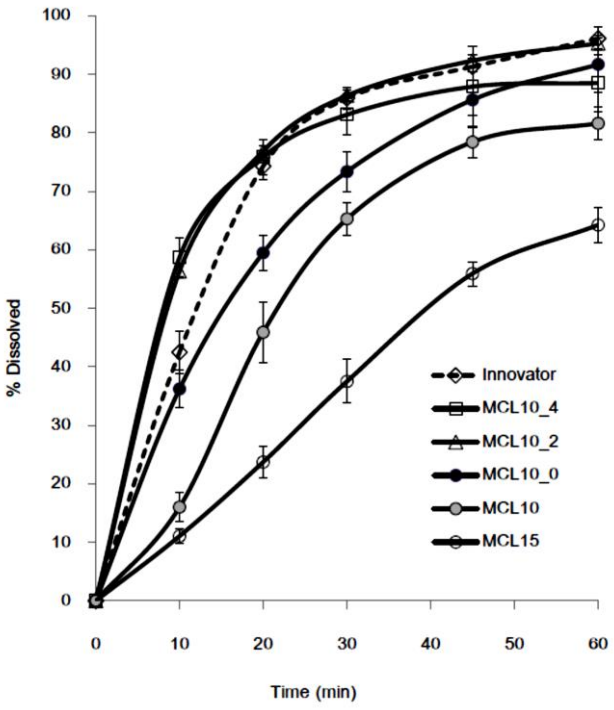

Figure 2. Comparative *in vitro* drug release profiles of hydrochlorothiazide tablets.

Figure 2 presents the dissolution data of all HCTZ formulations. To anticipate bioequivalence of the developed formulations, similarity factor (f_2) was calculated from HCTZ tablets dissolution data (n=12) compared to the original product. The similar factor was 51, 60 and 54 for HCTZ tablets from MCL10 with 0%, 2% and 4% w/w of croscarmellose sodium, respectively. The results indicated that formulation of a very slightly soluble drug like HCTZ, the addition of the optimal amount of superdisintegrant to promote the rapid disintegration should be considered.

Conclusion

Lactitol was proved to be an effective binder for the co-processed granules. MCL excipients consisting lactitol exhibited good flow properties and suited for direct compression excipient. MCL10 and MCL15 excipients were capable to produce tablets with satisfactory mechanical strength and good stability. Placebo tablets from MCL10 and MCL15 complied with the acceptance criteria according to pharmaceutical compendia. HCTZ-MCL10 showed the good physical characteristics and passed the dissolution test without adding external superdisintegrant. In case of the high binding ability of MCL15 and the nature of HCTZ caused long disintegration time and insufficient of drug dissolving within 60 min. The addition of superdisintegrant should be needed to improve this adequacy.

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