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APPLICATION OF CO-SPRAY DRIED NATIVE AND CARBOXYMETHYL YAM STARCH FOR HYDROCHLOROTHIAZIDE AND DIMENHYDRINATE DIRECT COMPRESSION TABLETS

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ABSTRACT

Co-spray-dried native and carboxymethyl yam starch (SDYS-CMS) exhibited suitable morphology, flowability, and dilution capacity, making it suitable for use as a direct compression filler. However, the evaluation of SDYS-CMS, a naturally derived co-processed excipient, as a direct compression filler for tablets containing drugs of contrasting aqueous solubility has not been clarified. The aim of this study was to prepare hydrochlorothiazide (HCTZ) and dimenhydrinate direct compression tablets using SDYS-CMS as a filler and to evaluate their physicochemical properties as a direct compression excipient. HCTZ, a poorly water-soluble drug, and dimenhydrinate, a water-soluble drug, were employed as model drugs to evaluate the effects of SDYS-CMS as a direct compression filler and direct compressed. Tablet properties, dissolution study, and lubricant sensitivity were determined. The results showed that SDYS-CMS tablets showed a disintegration time of less than 8 min and provided complete dissolution of both HCTZ and dimenhydrinate within 40 min. Moreover, increasing the compression pressure increased the crushing strength of the SDYS-CMS tablets more than SDYS tablets and Era-Tab® tablets, respectively, suggesting that SDYS-CMS improved the compactability of tablets. For lubricant sensitivity, SDYS-CMS tablets seemed to be indifferent to the addition of magnesium stearate. In conclusion, SDYS-CMS demonstrated suitable performance as a direct compression filler, providing complete drug dissolution of a poorly water-soluble drug, adequate mechanical strength, fast disintegration, and low lubricant sensitivity, supporting its potential as a multifunctional excipient for tablet manufacturing.

Keywords: co-spray dried native and carboxymethyl yam starch, direct compression tablets, tablet dissolution, lubricant sensitivity

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Introduction

Yam (*Dioscorea* spp.) is a widely cultivated tuber crop distributed across tropical and subtropical regions, including Nigeria, Jamaica, Brazil, China, and Thailand.[1,2,3] Owing to its high starch content, yam has attracted considerable attention as a potential alternative starch source for various food applications. Consequently, starch extracted from yam tubers has been extensively investigated for its physicochemical properties and industrial utilization in food products.[2,4,5] Among the yam species cultivated in Thailand, *Dioscorea esculenta* (Lour.) Burkill, commonly known as lesser yam, is one of the predominant species[6], which is widely used in both the food and pharmaceutical industries as a source of functional starch. The granules of yam starch are polygonal in shape with a size range of 2–20 µm, a morphology that plays a major role in increasing tablet hardness.[7]

Native yam starch and its carboxymethyl derivative (CMS) have been investigated as superdisintegrants for fast-disintegrating tablets, providing fast initial dissolution of hydrochlorothiazide (HCTZ) tablets. The highest swelling power of yam starch has a marked effect on tablet disintegration, and tablets containing yam starch showed the fastest disintegration time, particularly at low concentrations. CMS exhibited higher swelling power and formed a more viscous gel than native yam starch and could also function as a tablet disintegrant. However, at high concentrations, tablet disintegration and dissolution were retarded due to the formation of a gel mass. This concentration-dependent gelling behavior suggests that CMS has potential for use in controlled-release dosage forms.[7] In addition, pregelatinised *Dioscorea* starches prepared by oven drying or freeze drying have been evaluated for direct compression excipients.[8] Nevertheless, the application of native yam starch and CMS as a direct compression filler has not yet been fully clarified.

Direct compression fillers are common materials for the direct compression process of tablets. To develop a new direct compression diluent, excellent flowability, compressibility, and dilution potential of the excipient are required to carry poorly compactable drugs.[9] Starches from various natural origins and their common derivatives are well-known and safe for tablet formulations. Spray dried rice starches (Era-Tab® or Primotab®) were introduced as direct compressible fillers with excellent flow and binding properties.[10] In a previous study, the co-spray dried yam starch (SDYS) and CMS formed a co-processed directly compressible excipient. The material properties such as the spherically shaped particles, low particle size distribution, excellent flowability, and good compressibility indicated uniform die filling in the compression process. The high dilution capacity also demonstrated its ability to carry poorly compactable compounds in a satisfying tablet form.[11]

The purpose of this research was to prepare and determine HCTZ and dimenhydrinate direct compression tablets from SDYS-CMS. HCTZ, a poorly water-soluble drug, and dimenhydrinate, a water-soluble drug, were employed as model drugs to evaluate the effects of SDYS-CMS on drug dissolution. HCTZ and dimenhydrinate tablets were prepared using SDYS- CMS as a direct compression filler and were directly compressed. Tablet properties, dissolution study, and lubricant sensitivity were determined.

Materials and methods

Materials

Yam tuber was purchased from a local market in Nakhon Pathom, Thailand. HCTZ was obtained from China Chemical (China). Dimenhydrinate was obtained from Shanghai Pharmaceutical Co. Ltd

(China). Era-Tab® was purchased from Erawan Pharmaceutical Research and Laboratory (Thailand). Magnesium stearate was obtained from Faci Asia Pacific Pte Ltd. (China).

Preparation of SDYS-CMS fillers

Yam starches and CMS were prepared from yam tuber as previously described.[12] Briefly, yam starches were co-sprayed with 1.5% w/w CMS (SDYS-CMS). The starch slurry containing 30% w/w solid content was fed into the drying chamber via a two-fluid fountain nozzle (Mobile minor, S/N 2697, Niro, Denmark). The agglomerated particles were collected from the bottom of the product receiver. The losses on drying of all products were not more than 14.0%.

Preparation of tablets

As shown in Table 1, HCTZ or dimenhydrinate in SDYS, SDYS-CMS, or Era-Tab® tablets was directly compressed by a hydraulic press (P-16B-027, S/N 37876, Riken power, China). A dose of 15 mg was selected for both drugs to maintain a consistent filler-to-drug ratio across all formulations and to ensure sink conditions during dissolution testing. The drug and filler were homogeneously mixed for around 5 min before compression. For the lubricant sensitivity study, magnesium stearate was subsequently added to the drug-filler mixture and mixed for an additional 2 min before compression. For the dissolution study, tablets were compressed to a target hardness of 5–6 kg. For the compactability and lubricant sensitivity study, tablets were compressed at 30, 60, 90, and 120 MPa without hardness control by using a diametral Crushing Strength, Diameter and Thickness Tester (TBH 210TD, S/N 112367.0f3f, Erweka, Germany), and the resulting crushing strength was measured as an outcome variable. The constant tablet weight and diameter were 200 mg and 8 mm, respectively. After storage for 24 h, tablet properties were measured.

Dissolution study

The dissolution tests were performed following the United States Pharmacopeia dissolution test method.[13] For HCTZ tablets, the rotating basket apparatus (Dissolution Apparatus VK7000, S/N 1-6633-0403, Vankel, USA) was operated at a speed of 100 rpm, 37 ± 0.5°C and the amount of HCTZ in 900 mL of 0.1 N hydrochloric acid as the dissolution medium was determined using a UV-visible spectrophotometer at a wavelength of 272 nm. For dimenhydrinate tablets, the rotating paddle was operated at 50 rpm, 37 ± 0.5°C and the amount of dimenhydrinate in 900 mL of water as the dissolution medium was determined using a UV-visible spectrophotometer at a wavelength of 276 nm. Samples were withdrawn at 10, 20, 30, and 40 min and replaced with an equal volume of fresh medium to maintain sink conditions. The dissolution profile was obtained by plotting the average percentage of dissolved drug against time.

Effect of lubricant concentration

The mixture powder of drug and filler was mixed with 0.25-1.0%w/w of magnesium stearate, which was used as a lubricant before tablet compression. After storage for 24 h, the crushing strength was monitored using a multipurpose measuring device (Erweka, Germany); ten tablets were measured individually.

Table 1 Composition of HCTZ and dimenhydrinate direct compression tablets

Ingredient	SDYS tablet	SDYS- CMS tablet	Era-Tab® tablet
HCTZ or dimenhydrinate (mg)	15	15	15
SDYS (mg)	185	—	—
SDYS-CMS (mg)	—	185	—
Era-Tab® (mg)	—	—	185

Ingredient	SDYS tablet	SDYS- CMS tablet	Era-Tab® tablet
Total weight (mg)	200	200	200

The disintegration time was also evaluated using a disintegration apparatus (VK100, S/N 36-431-0403, Vankel, USA) following the United States Pharmacopeia test procedures for uncoated tablets.[13] One tablet was placed in each basket, and the apparatus was operated at 37 ± 2°C. The mean disintegration time of six tablets was measured.

Statistical analysis

Each value represents the mean ± standard deviation (SD). Data analysis was performed using one-way analysis of variance (ANOVA) with the least significant difference (LSD). A *p*-value below 0.05 indicates a significant difference (Table S1-6).

Results

Dissolution of HCTZ and dimenhydrinate tablets

HCTZ, a poorly water-soluble drug, and dimenhydrinate, a water-soluble drug, were employed as model drugs to evaluate the effects of SDYS-CMS on drug dissolution. Tablets with an average hardness of about 5–6 kg were selected. The physicochemical properties of HCTZ tablets and dimenhydrinate tablets, including tablet weight, thickness, diameter, hardness, disintegration time, dosage uniformity, and drug content, are shown in Table 2 and 3, respectively. For HCTZ tablets, the incorporation of SDYS-CMS resulted in a slightly greater tablet thickness and longer disintegration time than that of the SDYS and Era-Tab® tablets. For dimenhydrinate tablets, the SDYS and SDYS-CMS tablets also exhibited longer disintegration times than those of the SDYS and Era-Tab® tablets. Thus, the addition of SDYS-CMS increased the disintegration time of both HCTZ and dimenhydrinate tablets compared with the corresponding SDYS formulations, while the hardness remained within the targeted range of approximately 5–6 kg.

The drug content of all formulations was close to the labeled amount, with values of approximately 100%. The content uniformity acceptance values (AV) ranged from 0.77 to 1.19 for HCTZ tablets and from 0.80 to 0.96 for dimenhydrinate tablets. These results indicate that all tablet formulations exhibited consistent drug content and low variability in individual tablet drug content.

As shown in Figure 1, more than 90% of HCTZ and dimenhydrinate were released from all tablets within 30 min. At 40 min, the mean percentages dissolved were 94.03% for SDYS-CMS, 94.43% for SDYS, and 98.16% for Era-Tab® tablets for HCTZ, and 99.64% for SDYS- CMS, 99.08% for SDYS, and 97.9% for Era-Tab® tablets for dimenhydrinate (Figure 1). The release of the poorly water-soluble drug, HCTZ, from all tablets was similar; however, the SDYS-CMS tablet showed higher dimenhydrinate release than the solely SDYS tablet at all sampling times.

Table 2 Physical properties of HCTZ and dimenhydrinate tablets with various SDYSs as tablet base.

Drug	Filler	Weight, mg (SD)	Thickness, mm (SD)	Diameter, mm (SD)	Hardness, kg (SD)	Disintegration time, min (SD)
HCTZ	SDYS	205.12 (1.21)	3.20 (0.02)	8.01 (0.00)	5.60 (0.41)	2.39 (0.02)
	SDYS- CMS	203.89 (1.07)	3.51 (0.03)	8.05 (0.00)	5.65 (0.58)	3.53 (0.02)
	Era-Tab®	201.16 (0.56)	3.38 (0.02)	8.03 (0.00)	5.55 (0.20)	1.05 (0.02)
Dimenhydrinate	SDYS	205.06 (0.72)	3.29 (0.02)	8.05 (0.01)	5.57 (0.11)	2.45 (0.03)

Drug	Filler	Weight, mg (SD)	Thickness, mm (SD)	Diameter, mm (SD)	Hardness, kg (SD)	Disintegration time, min (SD)
	SDYS-CMS	204.45 (0.82)	3.23 (0.01)	8.07 (0.01)	5.32 (0.41)	3.77 (0.27)
	Era-Tab®	200.46 (0.71)	3.18 (0.02)	8.08 (0.01)	5.69 (0.33)	1.87 (0.25)

Table 3 Labeled amount and content uniformity of HCTZ and dimenhydrinate tablets.

Drug	Filler	Labeled amount (%) (SD)	Content uniformity (AV)
HCTZ	SDYS	98.84 (0.16)	1.13
	SDYS-CMS	99.93 (0.14)	1.19
	Era-Tab®	100.18 (0.23)	0.77
Dimenhydrinate	SDYS	100.92 (0.34)	0.94
	SDYS-CMS	100.22 (0.26)	0.80
	Era-Tab®	99.66 (0.19)	0.96

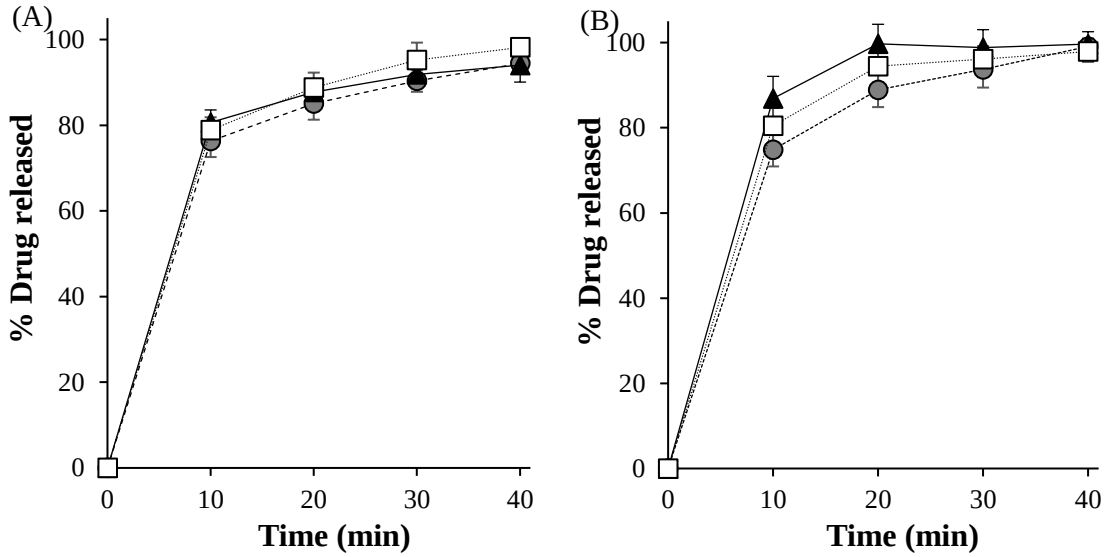


Figure 1 Dissolution profiles of (A) HCTZ and (B) dimenhydrinate tablets with various tablet bases, SDYS (●), SDYS-CMS (▲), and Era-Tab® (□). Each value represents the mean ± SD. (n = 6).

Lubricant sensitivity

In this study, tablet weight, thickness, and diameter remained constant. The effects of lubricant on the crushing strength and disintegration time of SDYS and Era-Tab® tablets were determined as shown in Figure 2. Although increasing the amount of lubricant from 0.25 to 1.00% w/w tended to decrease the crushing strength of all formulations (Table 4), adding 0.25% w/w of magnesium stearate did not affect the crushing strength of SDYS-CMS tablets, but decreased the crushing strength of SDYS alone and Era-Tab® tablets. In addition, increasing

compression pressure led to an increase in the crushing strength and disintegration time of all tablets. The crushing strength of the SDYS-CMS tablet was higher than that of SDYS alone and Era-Tab® tablets at the same compression pressure. This result was consistent with the lowest friability of SDYS-CMS (approximately 0.12 to 0.37%), indicating suitable friability (less than 1%).

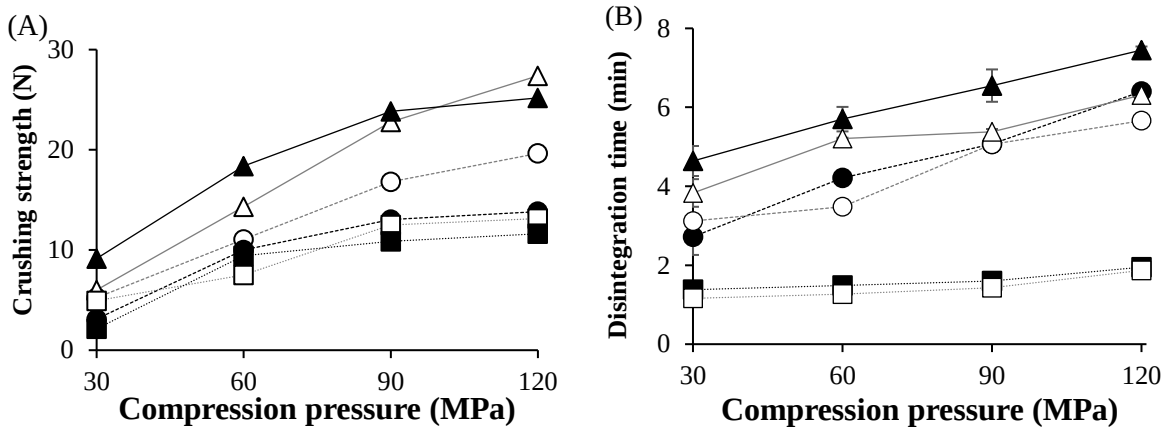


Figure 2 Effects of 0.25% w/w magnesium stearate on (A) crushing strength and (B) disintegration profile of SDYS (●), SDYS-CMS (▲), and Era-Tab® (■), compared with non-lubricated tablets (SDYS (○), SDYS-CMS (△), and Era-Tab® (□)). Each value represents the mean ± SD. (n = 10 for crushing strength and n = 6 for disintegration time).

Table 4 Effect of magnesium stearate concentration on the crushing strength of SDYS and SDYS co-sprayed with CMS tablets.

Product	Compression pressure (MPa)	Crushing strength (N), mean (SD)			
		Magnesium stearate (% w/w)			
		0.25	**0.50**	**0.75**	**1.00**
SDYS	30	3.12 (0.52)	2.49 (0.19)	2.18 (0.11)	2.03 (0.20)
	60	10.02 (0.14)	8.60 (0.74)	5.51 (0.36)	4.40 (0.42)
	90	13.03 (0.19)	11.53 (0.24)	8.20 (0.20)	5.71 (0.47)
	120	13.83 (0.58)	12.37 (0.92)	9.37 (0.49)	6.50 (0.28)
SDYS-CMS	30	9.15 (0.88)	5.97 (1.66)	3.97 (0.17)	3.61 (0.25)
	60	18.37 (1.06)	14.03 (0.88)	9.03 (0.27)	8.23 (0.35)
	90	23.84 (0.50)	17.46 (1.26)	11.70 (0.55)	11.07 (0.38)
	120	25.18 (0.79)	18.16 (1.63)	12.71 (0.27)	11.70 (0.28)
Era-Tab®	30	2.14 (0.15)	2.27 (0.11)	2.07 (0.33)	1.49 (0.28)
	60	9.44 (0.53)	5.62 (0.38)	4.72 (0.37)	3.89 (0.51)
	90	10.86 (0.46)	8.51 (0.34)	6.37 (0.53)	4.82 (0.41)
	120	11.62 (0.46)	9.36 (0.37)	6.68 (0.35)	5.44 (0.18)

As shown in Figure 2(B), tablets made from Era-Tab® disintegrated very fast, suggesting lower tablet bonding strength. SDYS tablets disintegrated more slowly than Era-Tab® tablets, while SDYS-CMS tablets exhibited longer disintegration times than other tablets. However, all formulations exhibited a disintegration time of less than 8 min.

Discussion

In the tableting process, the SDYS-CMS co-processed excipient was successfully applied as a direct compression filler without requiring a granulation step, demonstrating its suitability for simplified tablet manufacturing. The physical properties of both HCTZ and dimenhydrinate tablets complied with the desired pharmaceutical quality attributes, indicating that the co-processed excipient can accommodate drugs with different aqueous solubilities while maintaining acceptable tablet performance. In tablets without a disintegrating agent, the filler plays a major role in tablet disintegration. The native starch-based matrix readily allowed water penetration, swelling, and tablet breakup.[7] Era-Tab® tablets consistently showed the shortest disintegration time because it is a spray-dried rice starch that has been specifically engineered as a direct compression filler with a porous, spherical particle structure. This high porosity facilitates rapid water penetration into the tablet matrix upon immersion, promoting swift swelling and disintegration of the compact.[10]

The dissolution of drugs was therefore primarily governed by their intrinsic aqueous solubility rather than by differences in disintegration behavior. The release of the poorly water-soluble drug, HCTZ, from all tablets seemed to be similar. The similar dissolution profiles of HCTZ from SDYS, SDYS-CMS, and Era-Tab® tablets are consistent with the rapid disintegration of all three formulations (less than 8 min). Tablet disintegration was unlikely to be the rate-limiting factor for HCTZ dissolution. As HCTZ is a poorly water-soluble drug, its dissolution after tablet disintegration is more likely governed by its aqueous solubility and drug particle characteristics than by the type of filler. Similar findings have been reported for poorly soluble drugs, in which changes in the type or concentration of disintegrant did not substantially alter drug dissolution after rapid tablet disintegration.[14,15] Thus, the similar dissolution behavior observed among the three formulations suggests that the replacement of the conventional filler with SDYS or SDYS-CMS did not adversely affect HCTZ release under the conditions tested.

However, the SDYS-CMS tablet showed higher dimenhydrinate release than the solely SDYS tablet. This finding suggests that the incorporation of CMS modified the hydration behavior of the tablet matrix. Previous studies reported that, upon contact with the dissolution medium, the hydrophilic carboxymethyl groups facilitated water uptake and localized swelling, generating additional aqueous channels that promoted drug diffusion before complete matrix erosion. Such a mechanism is particularly advantageous for improving the release of highly soluble drugs while preserving the integrity of directly compressed tablets.[12,16]

An increase in alkali stearate lubricant has been reported to markedly reduce the hardness of plastic and elastic materials.[17] Therefore, it generally causes undesirable changes in the properties of tablets made from plastically deformable materials, such as lactose and starch. The bonding of the excipient powder is interfered with by the lubricant, leading to a reduction in the interparticular cohesive force.[18] Under the tested conditions, SDYS-CMS tablets maintained higher crushing strength after lubrication with 0.25% w/w magnesium stearate than the corresponding SDYS tablets, suggesting that the incorporation of CMS may reduce the apparent impact of magnesium stearate on tablet mechanical

strength. The carboxymethyl group might provide good cohesion properties of particles, resulting in enhanced interparticle bonding of the powder in the tablet.[19] In addition, the higher crushing strength of the SDYS-CMS tablet than SDYS alone and Era-Tab® tablets indicated the improvement of native yam starch compactability by encouraging starch granule consolidation under the compression process, providing suitable friability to be a potential direct compression filler.

The disintegration of tablets depended on the type of filler, the lubricant, the concentration and mixing time of lubricant, and the tablet strength. The addition of lubricant caused a reduction in crushing strength, leading to a reduced disintegration time. Generally, the disintegration time is inversely proportional to the tablet strength. An increase in compression pressure prolongs the disintegration time by reducing the porosity of compacts, leading to a decrease in water penetration into the tablet, thereby prolonging disintegration.[15] SDYS-CMS tablets in particular exhibited longer disintegration times than other tablets, because of slightly greater tablet thickness at equivalent crushing strength, suggesting higher compact density and reduced porosity. Without CMS, the tablet matrix probably fell apart easily when immersed in water. The carboxymethyl derivative of yam starch has been reported as an effective tablet disintegrant at low concentrations.[12] The effect of CMS concentration on tablet disintegration can be attributed to its hydration, swelling, and gel-forming properties. The introduction of carboxymethyl groups increases the hydrophilicity of starch, facilitating water uptake and swelling of the starch particles, which can promote tablet breakup at an appropriate concentration.[20] However, increasing the CMS content may result in greater hydration and swelling, potentially increasing the resistance to tablet breakup and prolonging disintegration. In the present study, the prolonged disintegration time of SDYS-CMS tablets may be attributed to the combined effects of increased swelling of CMS and the higher crushing strength of the tablets.

The markedly higher crushing strength of SDYS-CMS tablets compared with SDYS and Era-Tab® tablets across all compression pressures warrants consideration of the underlying deformation mechanism. Pharmaceutical powders generally undergo a combination of elastic deformation, plastic deformation, and brittle fracture during compression. Plastic deformation and fragmentation can increase the interparticulate contact area and facilitate the formation of interparticulate bonds, whereas elastic deformation is reversible and may contribute to stress relaxation and tablet recovery after compression.[21,22] The relative contribution of these mechanisms depends on the physicochemical and morphological properties of the constituent particles. Starch-based materials are generally capable of undergoing plastic deformation under compression, although their compaction behavior can vary depending on starch type, particle characteristics, moisture content, and formulation composition.[23] In the present study, the spherical morphology and relatively small particle size of the SDYS granules produced by spray drying may have facilitated particle rearrangement, close packing, and subsequent deformation during compression[11]. Nevertheless, because direct measurements of the deformation behavior or compaction parameters were not performed in the present study, the proposed mechanism should be considered a plausible explanation rather than a definitive mechanistic conclusion.

Conclusion

In this study, SDYS and its carboxymethyl derivative (CMS) formed a co-processed directly compressible excipient. SDYS-CMS tablets provided complete dissolution of both a poorly water-soluble drug, HCTZ, and a water-soluble drug, dimenhydrinate, in 40 min, consistent with the fast disintegration time of these tablets (less than 8 min). Moreover, the

crushing strength of SDYS-CMS tablets increased dramatically with an increase in compression pressure, demonstrating that CMS improved the compactability of the tablets. Less lubricant sensitivity was also found in the SDYS-CMS tablets. The multifunctional properties of SDYS-CMS indicate that it could be used as an efficient direct compression excipient.

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Supplementary

Table S1 Multiple comparison of concentration of CMS on tablet hardness data set of SDYSs with compression pressure 30-120MPa.

Dependent Variable	Conc (I)	Conc (J)	Mean Difference (I-J)	Std. Error	Sig.
SDCMS_30MPa	0	0.5	-.62900*	.18081	.001
	0	1	-.60400*	.18081	.002
	0	1.5	-1.85700*	.18081	.000
	0	2	.44100*	.18081	.019
	0.5	1	.02500	.18081	.891
	0.5	1.5	-1.22800*	.18081	.000
	0.5	2	1.07000*	.18081	.000
	1	1.5	-1.25300*	.18081	.000
	1	2	1.04500*	.18081	.000
	1.5	2	2.29800*	.18081	.000
SDCMS_60MPa	0	0.5	-2.07200*	.41755	.000
	0	1	-3.10600*	.41755	.000
	0	1.5	-4.34900*	.41755	.000
	0	2	3.80000*	.41755	.000
	0.5	1	-1.03400*	.41755	.017
	0.5	1.5	-2.27700*	.41755	.000
	0.5	2	5.87200*	.41755	.000
	1	1.5	-1.24300*	.41755	.005
	1	2	6.90600*	.41755	.000
	1.5	2	8.14900*	.41755	.000
SDCMS_90MPa	0	0.5	-1.86400*	.42812	.000
	0	1	-4.79400*	.42812	.000
	0	1.5	-5.97400*	.42812	.000
	0	2	4.30400*	.42812	.000
	0.5	1	-2.93000*	.42812	.000
	0.5	1.5	-4.11000*	.42812	.000
	0.5	2	6.16800*	.42812	.000
	1	1.5	-1.18000*	.42812	.008
	1	2	9.09800*	.42812	.000
	1.5	2	10.27800*	.42812	.000
SDCMS_120MPa	0	0.5	-.87100	.47833	.075
	0	1	-4.58600*	.47833	.000
	0	1.5	-5.12600*	.47833	.000
	0	2	4.24400*	.47833	.000

0.5	1	-3.71500*	.47833	.000
0.5	1.5	-4.25500*	.47833	.000
0.5	2	5.11500*	.47833	.000
1	1.5	-.54000	.47833	.265
1	2	8.83000*	.47833	.000
1.5	2	9.37000*	.47833	.000

*. The mean difference is significant at the 0.05 level.

Table S2 Multiple comparison of SDYS co-sprayed with various concentrations of CMS and Era-Tab® on tablet hardness data set that effected of 0%w/w Magnesium stearate.

Dependent Variable	Conc (I)	Conc (J)	Mean Difference (I-J)	Std. Error	Sig.
SDCMS_Mg0_30MPa	.00	.50	-.6290(*)	.18081	.001
	.00	1.00	-.6040(*)	.18081	.002
	.00	1.50	-1.8570(*)	.18081	.000
	.00	2.00	.4410(*)	.18081	.019
	.50	1.00	.0250	.18081	.891
	.50	1.50	-1.2280(*)	.18081	.000
	.50	2.00	1.0700(*)	.18081	.000
	1.00	1.50	-1.2530(*)	.18081	.000
	1.00	2.00	1.0450(*)	.18081	.000
	1.50	2.00	2.2980(*)	.18081	.000
SDCMS_Mg0_60MPa	.00	.50	-2.0720(*)	.41755	.000
	.00	1.00	-3.1060(*)	.41755	.000
	.00	1.50	-4.3490(*)	.41755	.000
	.00	2.00	3.8000(*)	.41755	.000
	.50	1.00	-1.0340(*)	.41755	.017
	.50	1.50	-2.2770(*)	.41755	.000
	.50	2.00	5.8720(*)	.41755	.000
	1.00	1.50	-1.2430(*)	.41755	.005
	1.00	2.00	6.9060(*)	.41755	.000
	1.50	2.00	8.1490(*)	.41755	.000
SDCMS_Mg0_90MPa	.00	.50	-1.8640(*)	.42812	.000
	.00	1.00	-4.7940(*)	.42812	.000
	.00	1.50	-5.9740(*)	.42812	.000
	.00	2.00	4.3040(*)	.42812	.000
	.50	1.00	-2.9300(*)	.42812	.000
	.50	1.50	-4.1100(*)	.42812	.000
	.50	2.00	6.1680(*)	.42812	.000
	1.00	1.50	-1.1800(*)	.42812	.008
	1.00	2.00	9.0980(*)	.42812	.000
	1.50	2.00	10.2780(*)	.42812	.000
SDCMS_Mg0_120MPa	.00	.50	-.8710	.47833	.075
	.00	1.00	-4.5860(*)	.47833	.000
	.00	1.50	-5.1260(*)	.47833	.000
	.00	2.00	4.2440(*)	.47833	.000
	.50	1.00	-3.7150(*)	.47833	.000
	.50	1.50	-4.2550(*)	.47833	.000
	.50	2.00	5.1150(*)	.47833	.000
	1.00	1.50	-.5400	.47833	.265
	1.00	2.00	8.8300(*)	.47833	.000
	1.50	2.00	9.3700(*)	.47833	.000

*. The mean difference is significant at the 0.05 level.

Table S3 Multiple comparison of SDYS co-sprayed with various concentrations of CMS and Era-Tab® on tablet hardness data set that effected of 0.25%w/w Magnesium stearate.

Dependent Variable	Conc (I)	Conc (J)	Mean Difference (I-J)	Std. Error	Sig.
SDCMS_Mg0.25_30MPa	.00	.50	-1.6590(*)	.23848	.000
	.00	1.00	-2.2840(*)	.23848	.000
	.00	1.50	-6.0310(*)	.23848	.000
	.00	2.00	.9740(*)	.23848	.000
	.50	1.00	-.6250(*)	.23848	.012
	.50	1.50	-4.3720(*)	.23848	.000
	.50	2.00	2.6330(*)	.23848	.000
	1.00	1.50	-3.7470(*)	.23848	.000
	1.00	2.00	3.2580(*)	.23848	.000
	1.50	2.00	7.0050(*)	.23848	.000
SDCMS_Mg0.25_60MPa	.00	.50	-.6180(*)	.27590	.030
	.00	1.00	-1.0830(*)	.27590	.000
	.00	1.50	-8.3500(*)	.27590	.000
	.00	2.00	.5800(*)	.27590	.041
	.50	1.00	-.4650	.27590	.099
	.50	1.50	-7.7320(*)	.27590	.000
	.50	2.00	1.1980(*)	.27590	.000
	1.00	1.50	-7.2670(*)	.27590	.000
	1.00	2.00	1.6630(*)	.27590	.000
	1.50	2.00	8.9300(*)	.27590	.000
SDCMS_Mg0.25_90MPa	.00	.50	-.2710	.22781	.240
	.00	1.00	-2.4740(*)	.22781	.000
	.00	1.50	-10.8050(*)	.22781	.000
	.00	2.00	2.1760(*)	.22781	.000
	.50	1.00	-2.2030(*)	.22781	.000
	.50	1.50	-10.5340(*)	.22781	.000
	.50	2.00	2.4470(*)	.22781	.000
	1.00	1.50	-8.3310(*)	.22781	.000
	1.00	2.00	4.6500(*)	.22781	.000
	1.50	2.00	12.9810(*)	.22781	.000
SDCMS_Mg0.25_120MPa	.00	.50	-1.2650(*)	.27045	.000
	.00	1.00	-2.3200(*)	.27045	.000
	.00	1.50	-11.3460(*)	.27045	.000
	.00	2.00	2.2130(*)	.27045	.000
	.50	1.00	-1.0550(*)	.27045	.000
	.50	1.50	-10.0810(*)	.27045	.000
	.50	2.00	3.4780(*)	.27045	.000
	1.00	1.50	-9.0260(*)	.27045	.000
	1.00	2.00	4.5330(*)	.27045	.000
	1.50	2.00	13.5590(*)	.27045	.000

*. The mean difference is significant at the 0.05 level.

Table S4 Multiple comparison of SDYS co-sprayed with various concentrations of CMS and Era-Tab® on tablet hardness data set that effected of 0.5%w/w Magnesium stearate.

Dependent Variable	Conc (I)	Conc (J)	Mean Difference (I-J)	Std. Error	Sig.
SDCMS_Mg0.5_30MPa	.00	.50	-1.5450(*)	.33823	.000
	.00	1.00	-2.8390(*)	.33823	.000
	.00	1.50	-3.4710(*)	.33823	.000
	.00	2.00	.2290	.33823	.502
	.50	1.00	-1.2940(*)	.33823	.000
	.50	1.50	-1.9260(*)	.33823	.000
	.50	2.00	1.7740(*)	.33823	.000
	1.00	1.50	-.6320	.33823	.068
	1.00	2.00	3.0680(*)	.33823	.000
	1.50	2.00	3.7000(*)	.33823	.000
SDCMS_Mg0.5_60MPa	.00	.50	-.4450	.26189	.096
	.00	1.00	-1.7740(*)	.26189	.000
	.00	1.50	-5.4320(*)	.26189	.000
	.00	2.00	2.9790(*)	.26189	.000
	50	1.00	-1.3290(*)	.26189	.000
	.50	1.50	-4.9870(*)	.26189	.000
	.50	2.00	3.4240(*)	.26189	.000
	1.00	1.50	-3.6580(*)	.26189	.000
	1.00	2.00	4.7530(*)	.26189	.000
	1.50	2.00	8.4110(*)	.26189	.000
SDCMS_Mg0.5_90MPa	.00	.50	-.8680(*)	.29708	.005
	.00	1.00	-3.4280(*)	.29708	.000
	.00	1.50	-5.9360(*)	.29708	.000
	.00	2.00	3.0140(*)	.29708	.000
	.50	1.00	-2.5600(*)	.29708	.000
	.50	1.50	-5.0680(*)	.29708	.000
	.50	2.00	3.8820(*)	.29708	.000
	1.00	1.50	-2.5080(*)	.29708	.000
	1.00	2.00	6.4420(*)	.29708	.000
	1.50	2.00	8.9500(*)	.29708	.000
SDCMS_Mg0.5_120MPa	.00	.50	-.7450	.39301	.064
	.00	1.00	-4.4780(*)	.39301	.000
	.00	1.50	-5.7860(*)	.39301	.000
	.00	2.00	3.0120(*)	.39301	.000
		.00	.7450	.39301	.064
	.50	1.00	-3.7330(*)	.39301	.000
	.50	1.50	-5.0410(*)	.39301	.000
	.50	2.00	3.7570(*)	.39301	.000
	1.00	1.50	-1.3080(*)	.39301	.002
	1.00	2.00	7.4900(*)	.39301	.000
	1.50	2.00	8.7980(*)	.39301	.000

*. The mean difference is significant at the 0.05 level.

Table S5 Multiple comparison of SDYS co-sprayed with various concentrations of CMS and Era-Tab® on tablet hardness data set that effected of 0.75%w/w Magnesium stearate.

Dependent Variable	Conc (I)	Conc (J)	Mean Difference (I-J)	Std. Error	Sig.
SDCMS_Mg0.75_30MPa	.00	.50	-.8140(*)	.13725	.000
	.00	1.00	-2.8210(*)	.13725	.000
	.00	1.50	-1.7820(*)	.13725	.000
	.00	2.00	.1120	.13725	.419
	.50	1.00	-2.0070(*)	.13725	.000
	.50	1.50	-.9680(*)	.13725	.000
	.50	2.00	.9260(*)	.13725	.000
	1.00	1.50	1.0390(*)	.13725	.000
	1.00	2.00	2.9330(*)	.13725	.000
	1.50	2.00	1.8940(*)	.13725	.000
SDCMS_Mg0.75_60MPa	.00	.50	-1.5190(*)	.22081	.000
	.00	1.00	-5.0000(*)	.22081	.000
	.00	1.50	-3.5180(*)	.22081	.000
	.00	2.00	.7910(*)	.22081	.001
	.50	1.00	-3.4810(*)	.22081	.000
	.50	1.50	-1.9990(*)	.22081	.000
	.50	2.00	2.3100(*)	.22081	.000
	1.00	1.50	1.4820(*)	.22081	.000
	1.00	2.00	5.7910(*)	.22081	.000
	1.50	2.00	4.3090(*)	.22081	.000
SDCMS_Mg0.75_90MPa	.00	.50	-2.1160(*)	.24668	.000
	.00	1.00	-4.4860(*)	.24668	.000
	.00	1.50	-3.5010(*)	.24668	.000
	.00	2.00	1.8260(*)	.24668	.000
	.50	1.00	-2.3700(*)	.24668	.000
	.50	1.50	-1.3850(*)	.24668	.000
	.50	2.00	3.9420(*)	.24668	.000
	1.00	1.50	.9850(*)	.24668	.000
	1.00	2.00	6.3120(*)	.24668	.000
	1.50	2.00	5.3270(*)	.24668	.000
SDCMS_Mg0.75_120MPa	.00	.50	-1.1040(*)	.31319	.001
	.00	1.00	-3.6000(*)	.31319	.000
	.00	1.50	-3.3390(*)	.31319	.000
	.00	2.00	2.6870(*)	.31319	.000
	.50	1.00	-2.4960(*)	.31319	.000
	.50	1.50	-2.2350(*)	.31319	.000
	.50	2.00	3.7910(*)	.31319	.000
	1.00	1.50	.2610	.31319	.409
	1.00	2.00	6.2870(*)	.31319	.000
	1.50	2.00	6.0260(*)	.31319	.000

*. The mean difference is significant at the 0.05 level.

Table S6 Multiple comparison of SDYS co-sprayed with various concentrations of CMS and Era-Tab® on tablet hardness data set that effected of 1.0%w/w Magnesium stearate.

Dependent Variable	Conc (I)	Conc (J)	Mean Difference (I-J)	Std. Error	Sig.
SD SDCMS_Mg1_30MPa	.00	.50	-.1730	.09451	.074
	.00	1.00	-.6100(*)	.09451	.000
	.00	1.50	-1.5750(*)	.09451	.000
	.00	2.00	.5370(*)	.09451	.000
	.50	1.00	-.4370(*)	.09451	.000
	.50	1.50	-1.4020(*)	.09451	.000
	.50	2.00	.7100(*)	.09451	.000
	1.00	1.50	-.9650(*)	.09451	.000
	1.00	2.00	1.1470(*)	.09451	.000
	1.50	2.00	2.1120(*)	.09451	.000
SDCMS_Mg1_60MPa	.00	.50	-2.0960(*)	.21314	.000
	.00	1.00	-3.0100(*)	.21314	.000
	.00	1.50	-3.8290(*)	.21314	.000
	.00	2.00	.5090(*)	.21314	.021
	.50	1.00	-.9140(*)	.21314	.000
	.50	1.50	-1.7330(*)	.21314	.000
	.50	2.00	2.6050(*)	.21314	.000
	1.00	1.50	-.8190(*)	.21314	.000
	1.00	2.00	3.5190(*)	.21314	.000
	1.50	2.00	4.3380(*)	.21314	.000
SDCMS_Mg1_90MPa	.00	.50	-3.1100(*)	.19680	.000
	.00	1.00	-3.3400(*)	.19680	.000
	.00	1.50	-5.3630(*)	.19680	.000
	.00	2.00	.8890(*)	.19680	.000
	.50	1.00	-.2300	.19680	.249
	.50	1.50	-2.2530(*)	.19680	.000
	.50	2.00	3.9990(*)	.19680	.000
	1.00	1.50	-2.0230(*)	.19680	.000
	1.00	2.00	4.2290(*)	.19680	.000
	1.50	2.00	6.2520(*)	.19680	.000
SDCMS_Mg1_120MPa	.00	.50	-2.8440(*)	.12752	.000
	.00	1.00	-2.7020(*)	.12752	.000
	.00	1.50	-5.1950(*)	.12752	.000
	.00	2.00	1.0660(*)	.12752	.000
	.50	1.00	.1420	.12752	.271
	.50	1.50	-2.3510(*)	.12752	.000
	.50	2.00	3.9100(*)	.12752	.000
	1.00	1.50	-2.4930(*)	.12752	.000
	1.00	2.00	3.7680(*)	.12752	.000
	1.50	2.00	6.2610(*)	.12752	.000

*. The mean difference is significant at the 0.05 level.