



Preparation and physicommechanical properties of co-precipitated rice starch-colloidal silicon dioxide

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ABSTRACT

A new directly-compressible co-precipitated powder composing of rice starch and colloidal silicon dioxide (CSD) was prepared. The ratio of starch:CSD was tested at 8:1, 4:1, 2:1, 4:3 and 1:1, with three concentrations of sodium hydroxide (NaOH) (0.5, 1.0, 2.0 M) employed in the dispersion of CSD. Co-precipitated powders exhibited improved flowability, compactibility, superior bulk and tapped densities compared to that of native starch and physical mixtures. Scanning electron microscopic images showed adsorption of CSD on the surface of starch granules, while X-ray diffraction indicated that the granules remained crystalline. The moisture contents of co-precipitated powders were similar to that of native starch, while the moisture sorption at high relative humidity was affected only when the preparation was carried out with the use of 2.0 M NaOH. The optimum ratio of starch:CSD to yield powder with good flow and compactibility was found to be 4:1, with the use of either 0.5 or 1.0 M NaOH to disperse CSD. The results suggested potential application of rice starch-CSD co-precipitate in direct compression of pharmaceutical tablet.

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1. Introduction

Starch has been one of the most commonly used excipients in manufacturing of pharmaceutical tablets due to its inertness and inexpensive price. However, its application in direct compression has been limited mainly because of the inherently poor flowability and compactibility. In case of rice starch, the flowability is particularly very poor because the size of starch grains is small (2–8 μm) and the shape is also polygonal. The addition of a glidant or a flow regulator, such as colloidal silicon dioxide (CSD, *aka* fumed silica), to the formulation improves flowability [1]. However, the fluffy CSD is somewhat difficult to handle due to its low bulk and tapped densities. Separation after simple mixing with other excipients can also occur as a result of differences in the density.

Many studies have highlighted the improvement of the functional characteristics of pharmaceutical excipients through 'co-processing' [2–4], including starch [5]. The term co-processed excipients are defined as combinations, using appropriate method, of two or more excipients that possess performance advantages that cannot be achieved using a physical admixture of the same combination of excipients [6]. A number of developed co-processed excipients are currently employed commercially. Examples include microcrystalline cellulose-silicon dioxide (Prosolv®), lactose-cellulose (Cellactose®), lactose-maize starch (Starlac®), and sucrose-dextrin (Di-pac®) [7].

Co-processed excipients containing silicon dioxide or its salts have been reported in chitosan, chitin and starch. Chitosan-silica and chitosan silicate prepared by co-precipitation have been shown to possess properties as superdisintegrant/filler with improved flow, compactibility and water uptake [8]. Co-precipitated chitin-metal silicates also showed binding and disintegrating properties and can potentially be used as multifunctional excipient in tablet formulation [9,10]. For starch, co-spray drying of starch and silicon dioxide yielded spherically agglomerated starches with improved flowability [11].

A survey of literature to date found no report on the preparation of co-processed rice starch-silicon dioxide by co-precipitation method. In this study, this simple and effective method is utilized and the physicommechanical properties of co-precipitated powders were studied in comparison with native rice starch and rice starch-CSD physical mixture. Based on the obtained results, the potential application of the co-precipitated powders as pharmaceutical excipient is assessed.

2. Experimentals

2.1. Materials

Rice starch (RS) was product of Cho Heng Co.Ltd. (Nakornprathom, Thailand). Colloidal silicon dioxide (CSD) (Aerosil 200 SP) was from JRP Pharma. Potassium carbonate, magnesium nitrate, sodium chloride, potassium chloride and potassium nitrate (Merck, Germany) were of analytical reagent grade and used as saturated salt solutions.

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2.2. Preparation of co-precipitated RS-CSD and physical mixtures

RS (100 g) was dispersed in 200 ml of 0.05 M NaOH solution. CSD was dispersed in 200 ml of 0.5, 1 or 2 M NaOH solution, to which 200 ml of deionized water was added under stirred mixing at room temperature for 10 min or until homogenization of the silica suspension was accomplished. The silica suspension was gradually added to the starch suspension under vigorous stirring. The amounts of CSD were 12.5, 25, 50, 75 or 100 g, corresponding to the starch: CSD ratios of 8:1, 4:1, 2:1, 4:3 and 1:1, respectively. After 1 h of mixing at room temperature, hydrochloric acid solution (2 M) was added dropwise at the rate of ~100 ml/min until the pH of the mixture was 6.5, at which the optimal precipitation was achieved. The co-precipitated product was collected by filtration through a Whatman no.4 filter paper, washed with 1 L of distilled water at least 20 times to remove the salts, then collected and tray-dried at 70 °C for 24 h in a hot air oven. Physical mixtures were prepared by thorough mixing of 100 g rice starch with 12.5, 25 or 50 g of colloidal silicon dioxide in a plastic bag for 5 min using tumbling technique. The starch: CSD ratios of physical mixtures were 8:1, 4:1, and 2:1, respectively.

2.3. Physico-mechanical properties of co-precipitated powders

2.3.1. FT-IR

FT-IR spectra were recorded on a Nicolet Nexus 470FT-IR equipped with a DTGS detector using an attenuated total reflectance (ATR) mode. For each spectrum, 64 scans were recorded at a resolution of 4 cm⁻¹. Spectra were baseline-corrected using Omnic ver.6.2 software.

2.3.2. SEM analysis

SEM experiments to analyze the granule surface, shape and size were conducted using a Phillip XL 30 ESEM (FEI company, Hillsboro, Oregon, USA) equipped with a large field detector. The acceleration voltage was 10–20 kV under low vacuum mode (0.7–0.8 torr).

2.3.3. X-ray Diffraction (XRD)

XRD patterns were recorded on a Siemens D-500 X-ray diffractometer. Diffractograms were registered at Bragg Angle (2θ) range of 5 to 40° at a scan rate of 2.5° per minute and step size of 0.02°.

2.3.4. Moisture content

Powder moisture content was determined using a Kett F-IA moisture content balance with halogen heating. The heating temperature was set at 105 °C. The sample (2 g) was placed on the pan and the exact weights of sample before and after being heated to a constant weight were recorded. The moisture content of the sample was then calculated.

2.3.5. Porosity, Hausner ratio and Carr's compressibility indices

The bulk and tapped densities were determined as the ratio of the powder weight to the powder volume before tapping and after tapping until no further changes in volume occur (Stampfvolumeter SVM, Erveka), respectively [12]. Porosity was calculated based on true density determined using a pycnometer. Hausner ratio was calculated as the ratio of the bulk density to the tapped density, while Carr's index was the percentage ratio of the difference between the value of the two densities to that of the tapped density. The Carr's index was used to designate the flowability of the sample.

2.3.6. Angle of repose

Sample (100 g) was poured through a glass funnel fixed at a height of 15 cm onto a level bench top. The height (h) and radius (r) of the conical pile formed were measured and the tangent of the angle of repose is calculated by the h/r ratio. The test was carried out in triplicate.

2.3.7. Moisture sorption capacity

The moisture sorption of co-precipitated samples was evaluated at various relative humidity (RH) at a period of 7 days. Sample (1 g), previously dried to a constant weight at 80 °C, was placed in a calibrated cup with an internal diameter of 2.5 cm. Samples were then placed in desiccators containing saturated salt solutions providing 51, 62, 75, 83 and 92% RH at 30 °C for 7 days. Moisture sorption of samples was determined as percentage of the weight gained [13].

2.3.8. Compactibility of co-precipitated powder

Powder sample (250 mg) was compressed in a hydraulic press at compression forces of 0.5, 1.0, 1.5, 2.0 and 3.0 Tons, using a 4.6 mm flat face punches. The hardness of each compact was measured in triplicate using a hardness tester (Erweka).

2.4. Statistical analysis

All tests were performed at least in triplicate. The statistical significant tests were performed using analysis of variance (ANOVA) at 95% confidence level ($p < 0.05$). Significant differences among mean values were determined by Duncan's multiple range test.

3. Results and discussion

RS-CSD co-processing was achieved via co-precipitation. Starch granules swelled mildly in dilute (0.05 M) alkaline NaOH solution [14] and formed slurry, while CSD was uniformly dispersed in a more concentrated (0.5, 1.0 or 2.0 M) NaOH solution before mixing. In most cases, the addition of CSD dispersion into pre-swelled starch slurry yielded milky formed a milky suspension. The addition of HCl into the mixture reversed the swelling of starch granules, resulting in the entrapment or precipitation of CSD on the surface of starch granules. Starch and CSD particles are associated at a higher degree compared to that of the physical RS-CSD mixtures. Therefore, particle separation is less likely to occur and less dust is being produced. The only exception was RSC-A-3, in which the addition of CSD dispersion (12.5 g in 2.0 M NaOH) caused a rapid swelling of starch to form non-reversible thick gel and the product could not be retrieved.

FT-IR spectra of rice starch, silicon dioxide, and co-precipitated excipients (Fig. 1) showed no variation and/or shift in the position of characteristic absorption bands in the IR spectra, suggesting that no chemical interaction between starch and silicon dioxide took place.

Fig. 2 illustrates the morphology of co-precipitated RS-CSD at 8:1 (RSC-A-1), 4:1 (RSC-A-4) and 2:1 (RSC-A-7) ratio in comparison with the corresponded physical mixtures, native RS and CSD under scanning electron microscope. Physical mixtures (Fig. 2C, E, G) showed some dispersion of the flaky CSD on the surface of aggregated,

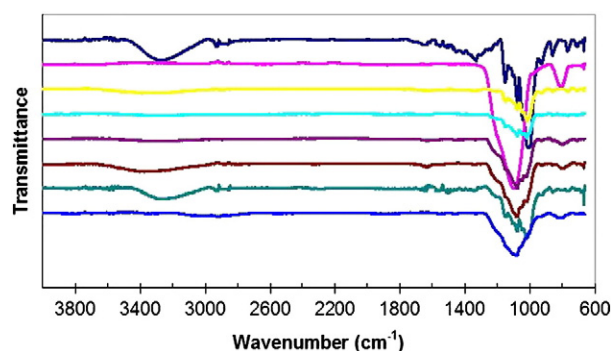


Fig. 1. FT-IR spectra of (from top to bottom) rice starch (RS), colloidal silicon dioxide (CSD), co-processed RS:CSD powders 8:1 (RSC-A-1), 4:1 (RSC-A-4), 2:1 (RSC-A-7), physical mixtures RSM-1 and RSM-3.

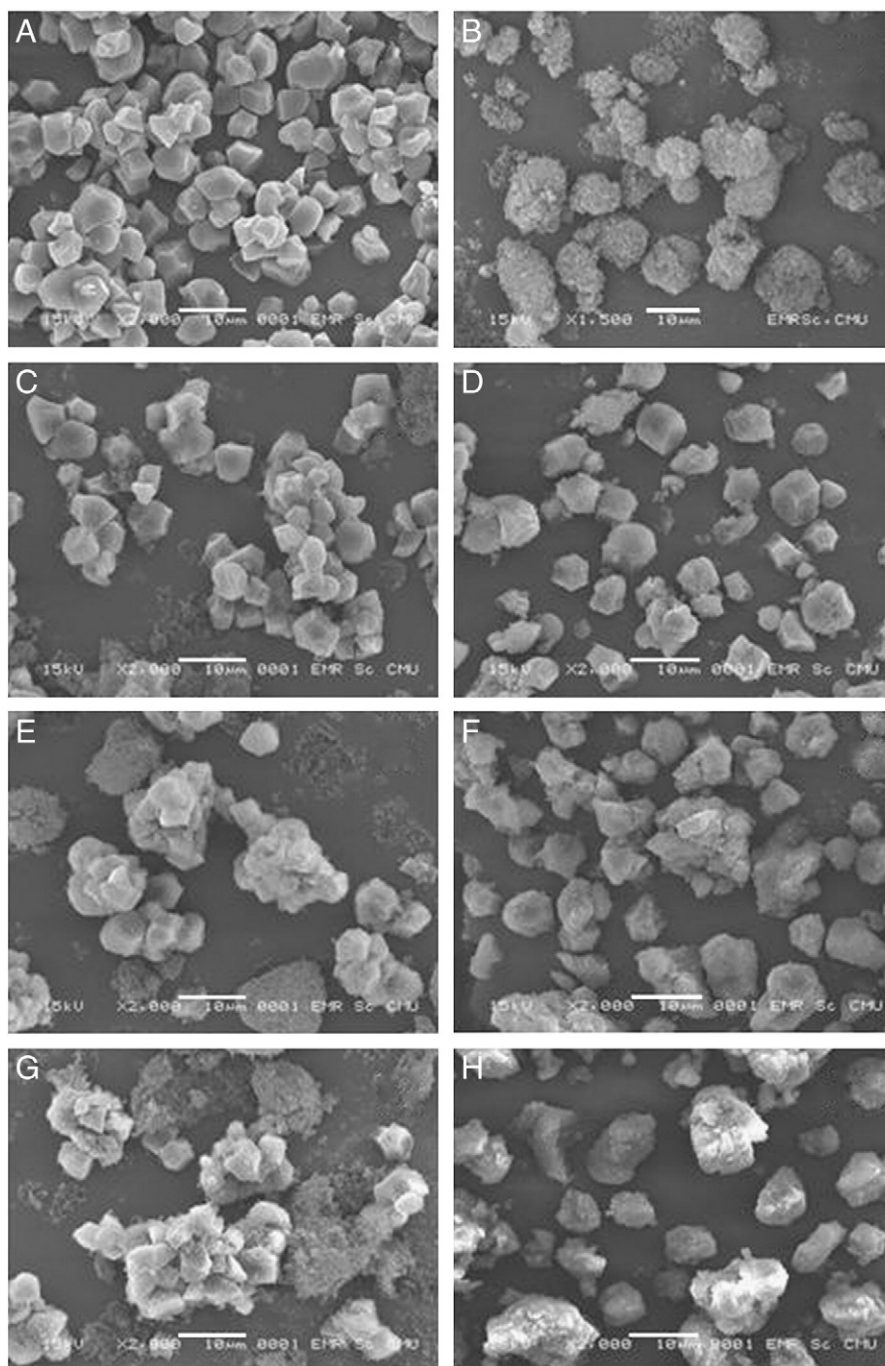


Fig. 2. SEM images of (A) native rice starch (RS), (B) colloidal silicon dioxide (CSD), (C) physically-mixed 8:1 RS-CSD (RSM-A), (D) co-processed 8:1 RS-CSD, (E) physically-mixed 4:1 RS-CSD (RSM-B), (F) co-processed 4:1 RS-CSD, (G) physically-mixed 2:1 RS-CSD (RSM-C), (H) co-processed 2:1 RS-CSD.

polygonal-shaped RS granules. Most of CSD particles, however, remained as isolated agglomerates. Co-precipitated powders (Fig. 2D, F, H), in contrast, exhibited more thorough and intimate deposition of CSD on the RS granule surface. This increased the roughness of the particles surface. At 2:1 ratio RS-CSD, the shape of the granules was significantly altered as CSD covered most of the surface. This is similar to a study on chitin-Mg silicate co-precipitate [9].

XRD pattern of RS exhibited strong diffraction peaks at Bragg angles 2θ of 15.1, 17.9 and 23.0 (Fig. 3), which was a typical A-type pattern. CSD showed a broad band between 16.0 and 23.0, with no distinctive peak, indicating the amorphous characteristic [8]. In both the physical mixture and the co-precipitated powders, the intensity

of RS diffraction peaks decreased as the CSD ratio in the mixture increased, with no loss of any specific peak. This is simply due to the dilution effect caused by CSD [9]. No new peak was observed, which suggested that no chemical interaction between RS and CSD occurred in both physical mixtures and co-precipitated powders.

Moisture contents of co-precipitated powders ranged between 9.6 and 12.2%, compared to 9.9% of native RS (Table 1). The tests were carried out under the same heating temperature (105 °C) but with slight differences in the time required to reach constant weight. Samples with higher moisture contents required longer time to reach constant weight than those with lower moisture contents. The variation of the moisture content values was due to the combined effects of

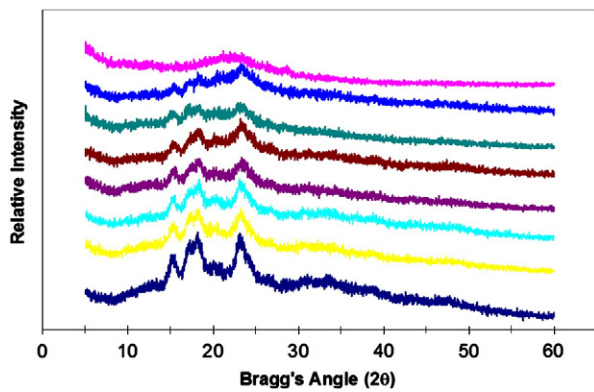


Fig. 3. XRD images of (from top to bottom) colloidal silicon dioxide (CSD), co-processed 2:1 RS:CSD (RSC-A-7), physically-mixed 2:1 RS:CSD (RSM-C), co-processed 4:1 RS:CSD (RSC-A-4), physically-mixed 4:1 RS:CSD (RSM-B), co-processed 8:1 RS:CSD (RSC-A-1), physically-mixed 8:1 RS:CSD (RSM-A), and rice starch (RS).

RS-CSD ratio and NaOH concentration used to disperse CSD. Higher amount of CSD corresponded with higher MC value, as was the higher concentration of NaOH within the same RS-CSD ratio.

The porosities of co-precipitated powders were in the range of 57–74% compared to 72 and 98% for native starch and CSD, respectively. At RS:CSD ratio of 8:1 and 4:1, % porosity was significantly lower than that of RS. This is possibly because the precipitation of CSD on the granules of native RS has eliminated some void space between starch granules or agglomerates [15], which accounted for about 20% of the total porosity [16]. As the CSD amount was increased in the powders of ratio 2:1 and less, increase in porosity were observed due to the effect of CSD. This is confirmed by significant increases in the porosity of RS-CSD physical mixtures as the amounts of CSD in the mixtures were increased (Table 1). Lower porosity percentages implied that the co-precipitated products could be handled or processed more easily than the more porous physical mixtures.

The improved flowability of co-precipitated powders, compared to the native RS, was evidenced by the values of compressibility index (CI), Hausner ratio, and the angle of repose (Table 1). CI values of co-precipitated starches were in the range of 10–15, corresponding to the “good” flow character. The closely related Hausner ratio were between 1.12 and 1.18, while the angle of repose were in the range

of 23–35, interpreted as good to excellent [12]. The CI, Hausner ratio, and angle of repose of native rice starch were 21.6, 1.28 and 40.5, respectively. The improved flowability was due to the adsorption of CSD at the surface of RS granules, thus increased the roughness of granules which, in turn, diminished the attractive forces between particles [17]. In RS-CSD physical mixtures, CSD particles covered the surface of starch granules, forming agglomerates with good flow. However, their bulk and tapped densities were significantly higher than those of co-precipitated powders.

Fig. 4A–C showed the moisture sorption profiles of co-precipitated RS-CSD, in comparison with physical mixtures and native RS (Fig. 4D). RS showed a typical starch monolayer adsorption pattern with a maximum of 12% sorption at 93%RH, while moisture sorption of co-precipitated starches ranged broadly from 10.9 to 27.8% at 93%RH. A closer look revealed that the moisture sorption of co-precipitated powders was mainly dependent of the NaOH concentration used to disperse CSD. When 2.0 M NaOH was used, the co-precipitated powders (RSC-A-6,-9,-12,-15) showed high moisture sorption (23.6–27.8% at 93%RH) (Fig. 4C), possibly due to the hydrophilic nature of highly-swelled starch granules caused by high concentration NaOH [13]. The use of 0.5 or 1.0 M NaOH yielded powders with moisture adsorption in the range of 10 to 15% at 93%RH, which were not significantly different from that of native starch (Fig. 4A–B). The amount of CSD in the co-precipitated powder showed no significant effect on the moisture sorption. This is in contrast with the moisture sorption data of physical mixtures, which showed a gradual decrease as the amount of CSD in the mixture was increased (Fig. 4D).

Compactibility of co-precipitated RS-CSD powders, physical mixtures and native rice starch are compared as slope of pressure-hardness profile (PHP) and hardness range of compacts (Table 1, Fig. 5A–D). Native rice starch showed appreciable compactibility as a result of its granule shape to form “interlock”. Rice starch was reported to be the most compressible starch [18] while our study showed that the hardness of RS compact was 3–7 times higher than that of corn, tapioca and mung bean starches. The PHP slope and the strength of co-precipitated compacts were significantly higher than those of rice starch and physical mixtures, suggesting that both the presence of CSD and the intimate interaction between CSD and starch granules as achieved in co-precipitated powders were vital to the improvement of powder compactibility.

Table 1
Physicomechanical properties of co-processed powders, physical mixtures, and native rice starch.

Sample	RS:CSD ratio	NaOH (M)	MC (%)	Porosity (%)	CI (%)	Hausner ratio	Angle of repose	PHP slope	Hardness range (kg)
RSC-A-1	8:1	0.5	9.6	60.25	12.22	1.14	25.5 ± 0.3	5.74	9.9–24.4
RSC-A-2	8:1	1.0	9.7	62.47	11.96	1.14	26.6 ± 1.5	9.15	8.6–32.6
RSC-A-3 ^a	8:1	2.0	ND	ND	ND	ND	ND	ND	ND
RSC-A-4	4:1	0.5	10.0	61.00	12.64	1.14	30.9 ± 2.2	8.29	7.2–28.5
RSC-A-5	4:1	1.0	10.1	59.84	11.61	1.13	26.6 ± 1.1	7.74	5.2–25.5
RSC-A-6	4:1	2.0	10.5	57.93	10.42	1.12	25.3 ± 0.9	7.06	8.7–27.2
RSC-A-7	2:1	0.5	10.2	69.22	13.59	1.16	34.3 ± 1.3	8.71	7.7–30.6
RSC-A-8	2:1	1.0	10.7	67.64	13.04	1.15	33.6 ± 1.7	8.75	6.3–28.9
RSC-A-9	2:1	2.0	11.2	67.12	11.70	1.13	29.8 ± 0.6	11.83	4.1–33.8
RSC-A-10	4:3	0.5	10.2	67.93	13.33	1.15	32.8 ± 1.9	9.79	4.0–28.8
RSC-A-11	4:3	1.0	10.5	69.40	13.04	1.15	33.0 ± 0.7	8.13	2.2–23.0
RSC-A-12	4:3	2.0	10.8	68.06	12.50	1.14	34.1 ± 0.7	8.49	5.8–27.0
RSC-A-13	1:1	0.5	10.4	68.66	13.54	1.16	34.0 ± 1.7	7.65	1.8–20.8
RSC-A-14	1:1	1.0	11.2	71.67	12.95	1.15	25.7 ± 0.3	9.20	4.7–28.3
RSC-A-15	1:1	2.0	12.2	70.19	12.77	1.15	27.2 ± 0.1	10.97	2.0–30.2
RSM-A	8:1	–	9.7	81.53	15.96	1.19	27.5 ± 1.2	5.61	6.7–21.2
RSM-B	4:1	–	9.8	88.76	14.89	1.18	26.6 ± 0.4	5.62	3.1–14.0
RSM-C	2:1	–	9.6	92.11	13.68	1.16	26.7 ± 2.7	4.52	1.2–5.7
RS	–	–	9.9	71.83	21.65	1.28	40.5 ± 1.4	3.68	1.6–10.8
CSD	–	–	ND	97.96	15.79	1.19	ND	ND	ND

RS – rice starch, CSD – colloidal silicon dioxide, MC – moisture content, CI – Carr’s compressibility index, PHP – pressure-hardness profile, ND – not determined.

^a Did not yield co-processed powder (see Results and discussion).

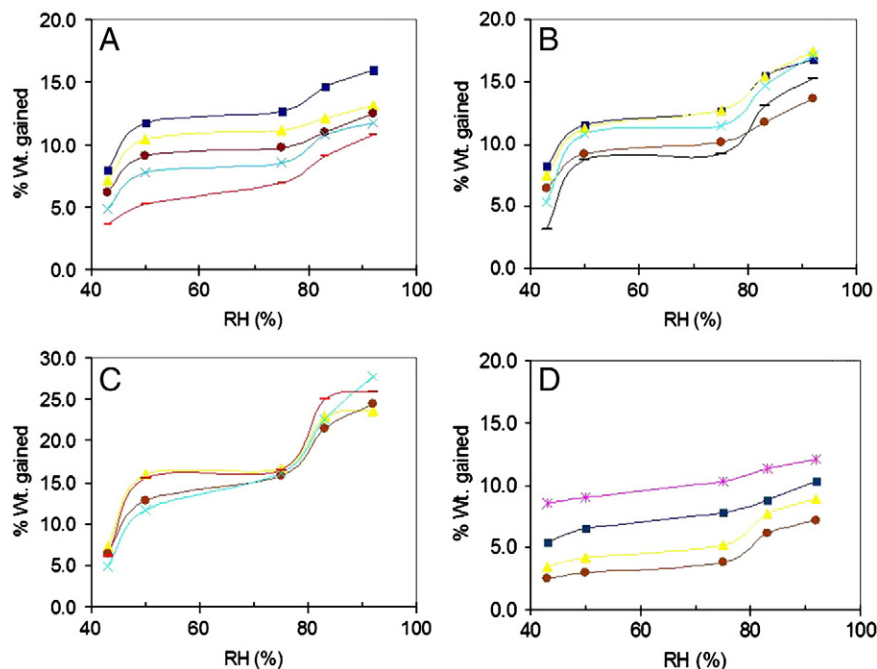


Fig. 4. Moisture sorption profiles of co-processed RS-CSD powders prepared using different concentrations of NaOH and ratios of RS:CSD. Values calculated as percentage of weight gained under 7-day storage at different relative humidity (%RH). (A) 0.5 M NaOH (B) 1.0 M NaOH (C) 2.0 M NaOH (D) physical mixtures. Ratio of RS:CSD were 8:1 (—■—), 4:1 (—△—), 2:1 (—●—), 4:3 (—×—), and 1:1 (—□—), compared to pure native rice starch (—). Pure CSD did not show moisture absorption.

4. Conclusions

Co-precipitation of colloidal silicon dioxide and rice starch resulted in a new co-processed powder with improved flow and compact properties over native rice starch, while retained superior bulk and tapped densities, and ease of handling over physical mixtures. FT-IR, SEM and XRD collectively confirmed the physical interaction between the two components with no chemical interaction taking place. The 4:1 ratio of starch and colloidal silicon dioxide was shown to be a proper

combination with respect to its physicochemical properties. The results suggested potential application of rice starch-colloidal silicon dioxide co-precipitate in direct compression of pharmaceutical tablet.

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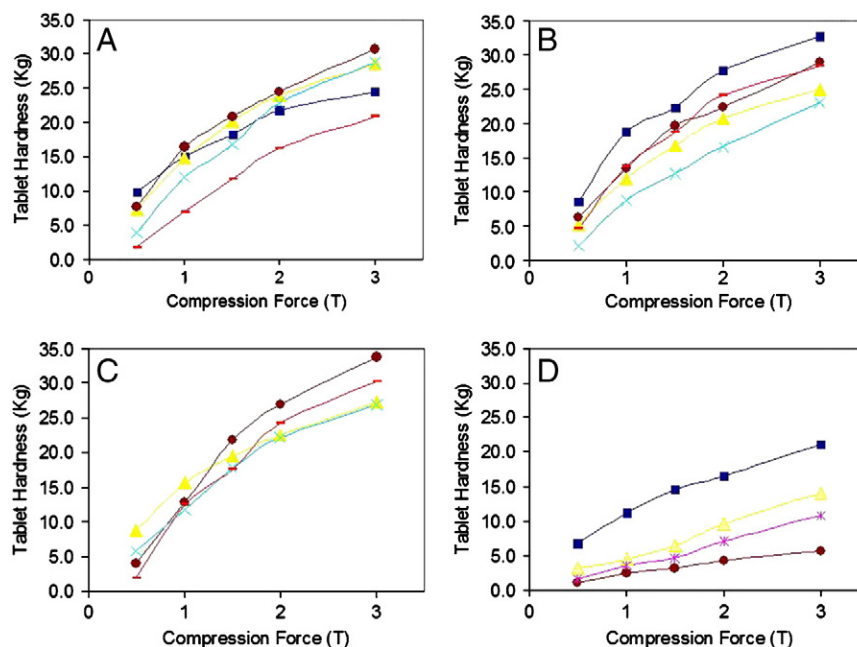


Fig. 5. Pressure-hardness profiles of co-processed RS-CSD powders prepared using different concentrations of NaOH and ratios of RS:CSD. (A) 0.5 M NaOH (B) 1.0 M NaOH (C) 2.0 M NaOH (D) physical mixtures. Ratio of RS:CSD were 8:1 (—■—), 4:1 (—△—), 2:1 (—●—), 4:3 (—×—), and 1:1 (—□—), compared to native rice starch (—).

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