

# Modification of flow and compressibility of corn starch using quasi-emulsion solvent diffusion method

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## ABSTRACT

**Objective(s):** The aim of this study was to improve flowability and compressibility characteristics of starch to use as a suitable excipient in direct compression tableting. Quasi-emulsion solvent diffusion was used as a crystal modification method.

**Materials and Methods:** Corn starch was dissolved in hydrochloric acid at 80°C and then ethanol as a non-solvent was added with lowering temperature until the formation of a precipitate of modified starch. Flow parameters, particle size and thermal behavior of the treated powders were compared with the native starch. Finally, the 1:1 mixture of naproxen and each excipient was tableted, and hardness and friability of different tablets were evaluated.

**Results:** Larger and well shaped agglomerates were formed which showed different thermal behavior. Treated starch exhibited suitable flow properties and tablets made by the treated powder had relatively high hardness.

**Conclusion:** It was found that recrystallization of corn starch by quasi emulsion solvent diffusion method could improve its flowability and compressibility characteristics.

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## Introduction

The tablet is the most popular mode of dosage forms in pharmaceuticals intended for oral administration, which has more stability, uniformity of the dosage and facility in use compared with the other dosage forms.

Moreover, from the manufacturing point of view, tablets can be produced at the much higher rate than the other pharmaceutical forms. Direct compression is one of the most advanced technologies used in the tablets manufacturing process with the advantages include fewer processing stages, reduction of the final cost of the product, elimination of heat and moisture effects, more appropriate process for thermo-sensitive and hygroscopic substances and the increase in stability of the products (1). Meanwhile, flowability and compressibility of excipients used in tablets manufacturing process are a serious limitation for direct compression and a few numbers of excipients have suitable characteristics for this process. Also, the production of high-dose formulations is difficult by using direct compression (2).

There are some methods to modify the physico-chemical characteristics of excipients. Quasi-emulsion solvent diffusion (QESD) method of

spherical crystallization technique has been successfully accepted as an efficient method for performing crystallization and particles size enlargement (2-4). This approach transforms a microcrystalline drug into an agglomerated form during the crystallization process, and the resultant agglomerated crystals assume a spherical form (5, 6).

Different types of natural starch are readily available and have been widely used in tablet production due to their inertness, low cost and utilization as fillers, binders, disintegrants and glidants (7, 8). However, poor compressibility and flowability of this polysaccharide have limited its use in direct compression. The characteristics of compressibility and flowability of starch have been improved by the manufacturers over the years by means of a series of modifications of the natural product such as pre-gelatinization and reticulation (9, 10). Nevertheless, the manufacturing procedure and the resultant materials are not cheap compared to native starch (11). Moreover, high lubricant sensitivity (12) and problems in flow characteristics (13) make them less suitable for use in direct compression.

Therefore, this study aimed to evaluate the effect of crystallization using QESD method on the

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compressibility and flow characteristics of starch in order to assess the excipient modification, as well as to examine the treated excipient for tableting by direct compression.

## Materials and Methods

### Materials

Corn starch (Hakim Pharmaceutical Company, Iran), naproxen (Merck, Germany), ethanol (Simintak, Iran), and hydrochloric acid (HCl) (Merck, Germany) were prepared from indicated sources. Spray dried lactose (Darusazi Aburayhan, Iran) and sorbitol (Merck, Germany) were used as direct compression excipients to compare with the modified excipient. Naproxen was used as a model drug for tablet preparation because of its poor compressibility (14).

### Crystal modification of starch using QESD method

Firstly, 5 g starch was dissolved in 200 ml HCl 0.1 M at 80°C. The solution was kept at 40°C, and then 200 ml ethanol was gradually added. Consequently, the solution was stirred for 15 min and left to cool down at to the room temperature. The precipitated crystals were collected by vacuum filtration and dried in an oven at 40°C for 24 hr. Finally, the dried crystals were stored in a desiccator at room temperature. The process was repeated several times until the necessary starch value for different tests is obtained.

### Powder flow measurement

The flowability of untreated and modified powders was measured using an automated powder flow ability analyzer (Erweka TBH 28, Frankfurt, Germany) with the 15 mm *nozzle* tip (n=6).

An appropriate amount of the sample was poured in a 100 ml measuring cylinder to determine the bulk and tapped densities. The bulk density ( $\rho_{\text{bulk}}$ ) was obtained by reading the volume directly from the cylinder and calculating the mass/volume ratio. The tapped density ( $\rho_{\text{tap}}$ ) was determined by tapping the samples into the 100 ml measuring cylinder using a tapping machine (n=6). The Carr's Index (CI) was calculated using the equation (15):

$$CI = [(\rho_{\text{tapped}} - \rho_{\text{bulk}}) / \rho_{\text{tapped}}] \times 100$$

### Particle size analysis

Sieving method was used for determination of particle size. A total of 15 g of powder was sieved using an Erweka vibration sieve (Erweka, Germany) through a nest of sieves. The vibration rate was set at 300 strokes/min and the sieving time was 10 min. The powder fractions retained by the individual sieve were weighed and expressed as mass percentage. Then the geometric mean and diameter standard deviation were determined by plotting

cumulative mass percentage versus particle size. The experiments were carried out in triplicate.

### Scanning electron microscopy (SEM)

The surface characteristics of samples of the powders were observed using a scanning electron microscopy (SEM) (LEO 1450 VP, UK). The samples were sputter coated with silver for 1 min in a sputter coater (Polaron E5400, UK).

### Differential scanning calorimetry (DSC)

Sample of the powders (5 mg) were heated ranging from 25-200°C at 10°C. min<sup>-1</sup>, in a sealed aluminum pans on nitrogen atmosphere and the thermograms were obtained using the instrumental software (Mettler, Switzerland). Calibration was performed using indium standard.

### X-ray diffraction of powder (XRD)

The X-ray diffraction patterns of samples were collected using an X-ray diffractometer (Philips Pw, 1830, Netherland) operated at 40 kV, 30 mA and a scanning rate of 0.06°min<sup>-1</sup> over the range 10-50 2 $\theta$ , using Cu K $\alpha$ 1 radiation of wavelength 1.5405 Å.

### Tablet preparation and characterization

Two hundred mg of each powder (untreated or modified) was thoroughly mixed with 200 mg naproxen and the resulted powder was directly compressed using 8 mm flat-faced punches in a single punch tableting machine (Korsch, Germany) under the same pressure. The hardness of tablets was measured using Erweka hardness tester (n=10). Also the friability of tablets was determined using a friabilator (Erweka, GmbH, Germany).

### Data analysis test

One-way ANOVA was used to assess the significance of the differences of the groups. The Tukey-Kramer post test was used to compare the means of different treatment groups. Results with  $P < 0.05$  were considered statistically significant.

## Results

In this study hydrochloric acid (HCl) was used as good solvent for recrystallization of starch. Hot water was not applied as solvent for starch, because after dissolution of starch and lowering the solution temperature it swelled at 60-70°C before settling by non-solvent. Ethanol was also examined as non-solvent.

Regarding the effect of temperature on starch solubility, HCl with high temperature (80°C) was used in which optimum solubility of starch was observed. To evaluate the effect of HCl on characteristics of starch, solution was cooled until spontaneous sedimentation of starch. To evaluate the effect of temperature on settling, addition of

**Table 1.** Micromeritics properties of untreated and treated powders

Excipients	Geometric mean diameter $\pm \delta$ ( $\mu\text{m}$ )	Flow rate (g/sec) (Mean $\pm$ SD) (n=6)	Bulk density(g/cm <sup>3</sup> ) (Mean $\pm$ SD)( n=6 )	Tapped density (g/cm <sup>3</sup> ) (Mean $\pm$ SD) (n=6 )	Carr's index (%) (Mean $\pm$ SD) (n=6)
Untreated starch	75.01 $\pm$ 1.63	*	0.49 $\pm$ 0.02	0.61 $\pm$ 0.03	20 $\pm$ 1
Treated starch	253.50 $\pm$ 1.78	37.78 $\pm$ 3.44	0.71 $\pm$ 0.01	0.85 $\pm$ 0.00	17 $\pm$ 1
Sorbitol	200.03 $\pm$ 1.06	16.87 $\pm$ 0.65	0.46 $\pm$ 0.01	0.54 $\pm$ 0.01	14 $\pm$ 1
Flowlack	138.04 $\pm$ 1.17	26.55 $\pm$ 1.96	0.62 $\pm$ 0.01	0.71 $\pm$ 0.01	13 $\pm$ 1

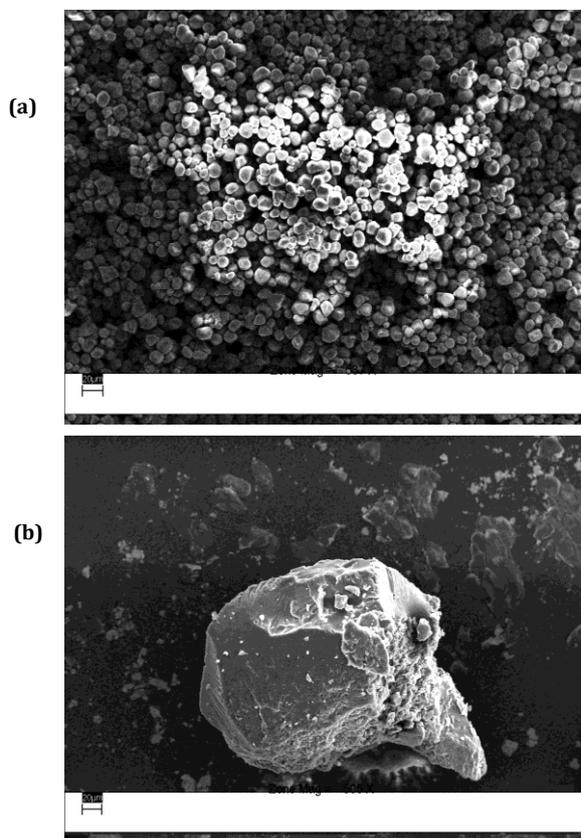
\* flow was not measur

non-solvent to the starch solution was carried out at different temperatures (30, 40, 50 and 60°C) to aid the settling of crystals. Quantity of sediments was the highest level at 40°C. Furthermore, by addition of different amounts (100, 150, 200, 250 and 300 ml) of ethanol to the primary solution it was shown that the quantity of 200 ml of non-solvent could be most effective in complete sedimentation. Stirring time was the other important factor. The optimum stirring time was 10 min for starch recrystallization. In the lower periods formation of settled particles was incomplete and in the longer times agglomerated particles were broken. This result was in accordance with another study in which the optimized stirring time was 10 min for the suitable formation of agglomerates of naproxen (14). Drying conditions of sediments identified that the most effective temperature is 40°C with keeping in oven duration of 24 hr. The resulted powder had poor flow characteristics at higher drying temperatures. This finding was similar with the other study in which increase in drying temperature minimized flow properties of modified wet-milled corn starch (16).

Table 1 depicts the micromeritics properties of untreated and treated starch. In the present study, the micromeritics characteristics of two commercially available direct compression excipients, sorbitol and spray dried lactose, have been determined for comparison with the data related to untreated and treated starch. Untreated starch did not show flowability by the flow meter apparatus (Table 1). On the other hand, the flow rate of treated starch was very high (37.78 g/sec) and larger than both spray dried lactose and sorbitol ( $P < 0.05$ ) (Table 1). Also, bulk and tapped densities of starch were increased by QESD method and both were higher than untreated starch and the other two excipients ( $P < 0.05$ ). However, Carr's index of treated starch was only less than untreated powder, and it was higher than the index of sorbitol and spray dried lactose ( $P < 0.05$ ).

The SEM of untreated and treated starch particles were depicted in Figure 1. According to Figure 1 treated powder had markedly larger particle size compared with untreated sample.

The X-ray diffraction patterns of untreated starch showed two peaks at  $2\theta$  about 15 and 23° and a wide doublet at 17 and 18° (Figure 2) which was similar to the findings of the other investigations (17-20). Two other peaks at  $2\theta$  of 38 and 45° also appeared at X-ray diffraction pattern of untreated starch, which could be



**Figure 1.** Micrographs of starch samples: (a) untreated; (b) treated (magnification 250 $\times$ )

due to some impurities in powder and were removed after recrystallization. However, X-ray diffraction of treated starch showed a different pattern with one peak at  $2\theta$  at 13° and another strong peak at 20°, whilst peaks at 15 and 23° and doublet peak was removed (Figure 2).

The thermograms of two types of starch revealed that for untreated starch there are two endothermic peaks appeared at 135°C and 150°C (Figure 3). Liu and coworkers reported peaks at about 120°C and 140°C for corn starch. These peaks were attributed to the melting of amylose-pectin complexes and non-complex amylose crystalline, respectively (21). Also, in another study a broad peak was shown at about 100-150°C (22). However, thermogram of treated starch indicated that the second endothermic peak has been shifted to 175°C. properties elastic deformation of powder (12), while prepared tablets containing treated starch exhibited relatively high hardness (7.70 $\pm$ 0.63 kg). The hardness of the latter tablets was larger than tablets

made by spray dried lactose with the hardness of 4.32 kg and lower than sorbitol tablets with the hardness of 9.8 kg ( $P < 0.05$ ). Besides, tablets of treated starch had low friability (data not shown).

## Discussion

Optimization of quantity of non-solvent, stirring time, and drying condition was needed to get more spherical and larger particles of treated starch. Low amounts of densities and high Carr's index of untreated starch confirmed its low flow characteristics. The results of densities and Carr's index of starch was close to the findings of another investigation, which reported that maize starch did not flow through the funnel of flow meter and the low bulk and tapped densities represented poor flow of the excipient (23). In our study, despite the similarity between bulk density of untreated starch and sorbitol ( $P > 0.05$ ), Carr's index of starch was higher than sorbitol. Besides, mean diameter of starch particles was 75 microns, which was smaller in comparison to the two other excipients ( $P < 0.05$ ).

Therefore, low particle size of untreated starch could be the reason for its poor flowability. In agreement with the present study, Odeku and coworkers (2008) claimed that particle size and shape were responsible for poor flowability of starch (10).

Modifying starch by QESD method changed this powder from a material with a poor flow to a free flowing excipient. Also, bulk and tapped densities of starch were increased by QESD method and both were higher than untreated starch and the other two excipients ( $P < 0.05$ ). However, Carr's index of treated starch was only less than untreated powder, while it was higher than the index of sorbitol and spray dried lactose ( $P < 0.05$ ). This result demonstrated that compressibility of starch was modified after recrystallization, but the QESD was more effective on flowability of starch than its compressibility.

The technology of particle design of excipients has emerged as one of the areas of research in tablets manufacturing process. Among the particle modifying methods to improve the physical characteristics of a crystalline material quasi

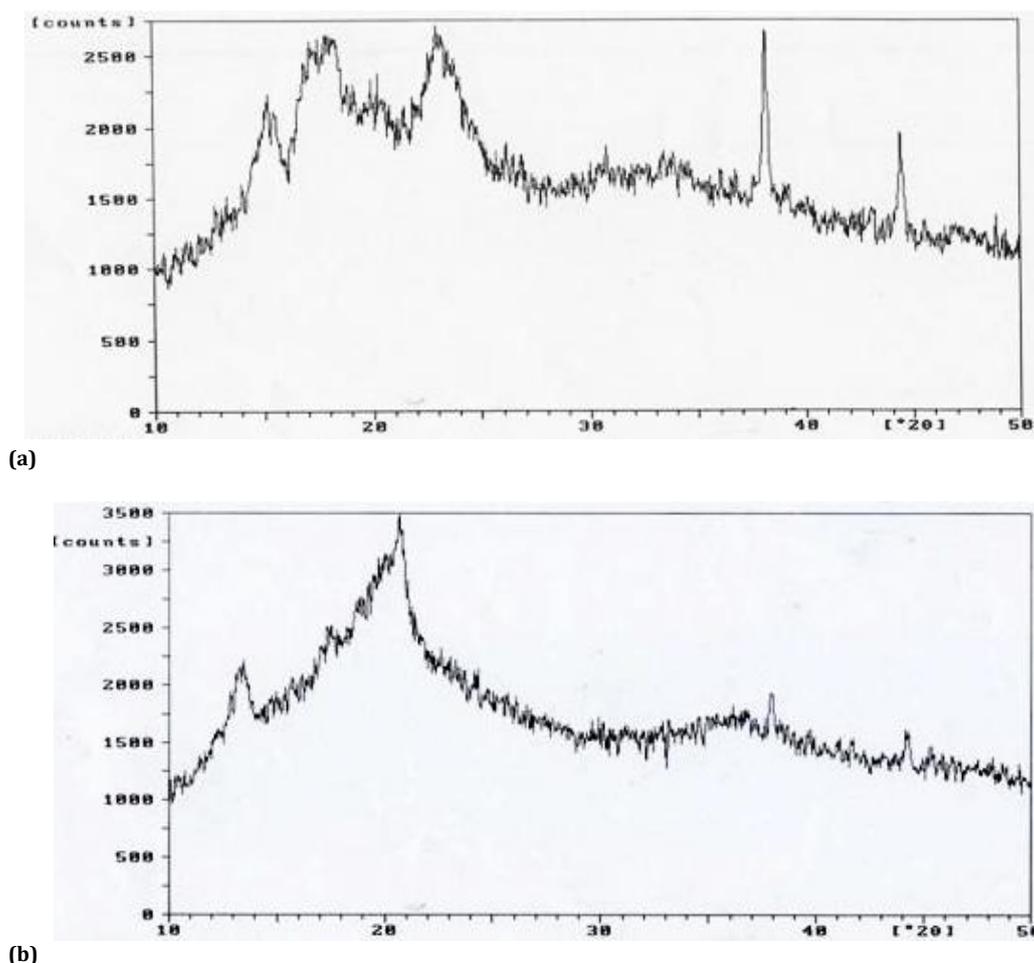
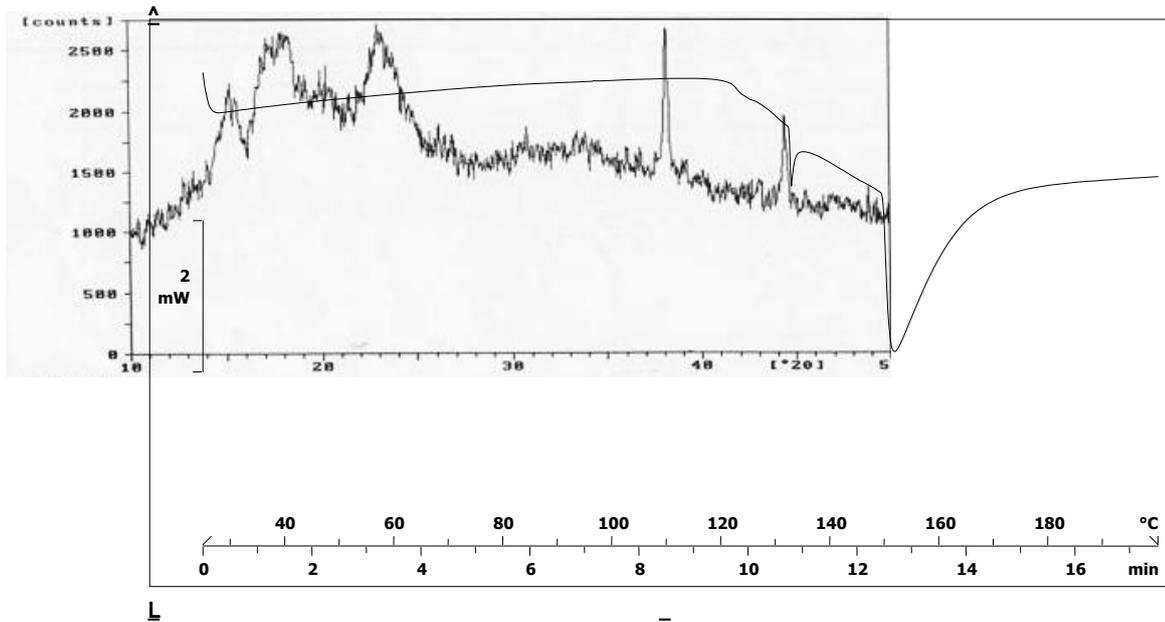
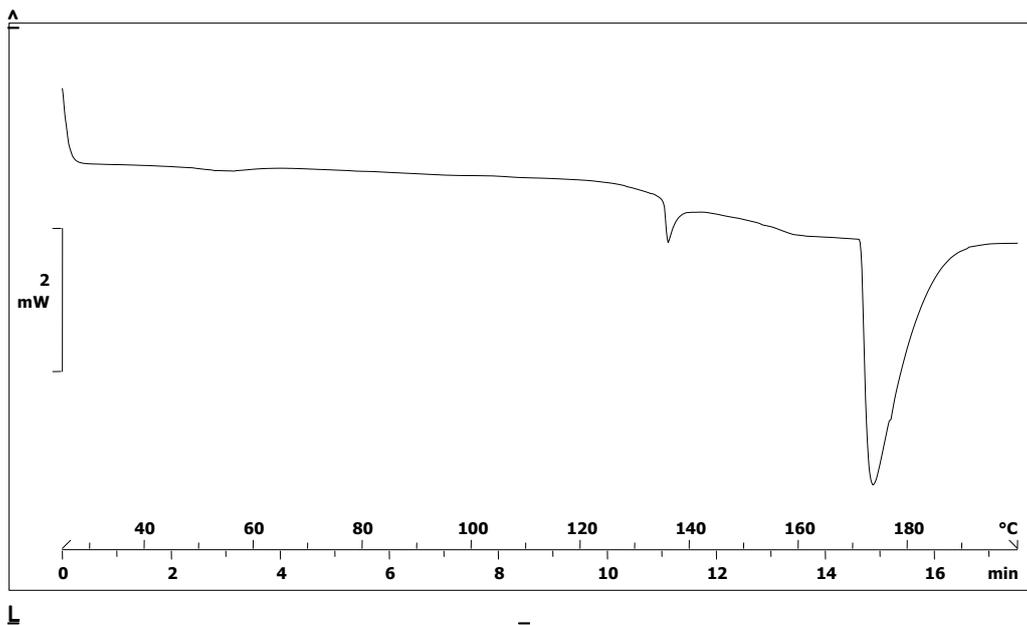


Figure 2. The X-ray diffraction spectra of starch samples: (a) untreated; (b) treated



(a)



(b)

**Figure 3.** The thermograms of starch samples: (a) untreated; (b) treated

emulsion solvent diffusion is one of the most effective processes in which changes in particle size, shape and surface area are occurred via recrystallization (3, 24). Evaluation of the effect of spherical crystallization on particle design of different powders such as lobenzarit (25), metformin (26), benzoic acid (27), ascorbic acid (2) and naproxen (14) showed that size enlargement and high sphericity of particles are responsible for improving flow. On the other hand, taking into the

consideration the small size and cohesiveness of particles of untreated corn starch, it has been proven that particle size enlargement can modify flow of the powder (28). In our study, modification of corn starch by QESD method significantly increased average particle size, so that the mean diameter of modified starch was 253.5 microns, which even was larger than sorbitol and spray dried lactose ( $P < 0.05$ ) (Table 1).

**Table 1.** Micromeritics properties of untreated and treated powders

Excipients	Geometric mean diameter $\pm \delta$ ( $\mu\text{m}$ )	Flow Rate (g/sec) (Mean $\pm$ SD) (n=6)	Bulk density(g/cm <sup>3</sup> ) (Mean $\pm$ SD) (n=6)	Tapped density(g/cm <sup>3</sup> ) (Mean $\pm$ SD) (n=6)	Carr's index (%) (Mean $\pm$ SD) (n=6)
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\* flow was not measurable

The SEM of untreated and treated starch particles showed that particle size of powder has been significantly increased due to crystallization of particles out of quasi emulsion droplets of drug solution (Figure 1). Therefore, enlargement of recrystallized particles was the main parameter responsible for improving flow of corn starch. Furthermore, smoothness of particle surface could help free flowing of modified powder (Figure 1).

XRD results revealed that the native corn starch is presented in the form of the cereal or A type polymorph (17-20). In addition, higher intensity of XRD peaks demonstrated that powder crystallinity has been increased due to the effect of modifying method.

DSC results showed two peaks for corn starch which could possibly attributed to amylose-pectin complex and amylose crystalline. Difference between peaks in the present investigation and the other studies could be due to different levels of amylose/amylopectin ratios in the investigated corn starch. After recrystallization the second peak shifted to higher temperature which could confirm recrystallization effect. Therefore, DSC results showed change in crystallinity of starch after modifying by QESD and regeneration of a new crystal form of material. The same finding was obtained by another investigation in which two sharp peaks appeared in the same regions of thermogram of corn starch (29). Change in thermograms of starch after modification was also demonstrated in the other study, in which endothermic peaks appeared at a higher temperature suggesting that the size and perfection of the crystallites were greater than the primary starch (30).

Increase in compressibility of treated starch might be due to enhanced fragmentation of new crystallites and therefore, more binding of the particles (2). Also, reduced thickness of tablets made by treated starch could assert particle rearrangement and plastic deformation of the excipient.

## Conclusion

The results of this study confirmed that recrystallization of corn starch by quasi emulsion

solvent diffusion method could improve the flow and compressibility of the starch. The modified powder had free flow properties even that it was comparable with the other excipients. The suitable flow plus improved compressibility of modified starch could candidate this material as an appropriate excipient utilizable in tablet manufacture by direct compression.

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## References

- Gonnissen Y, Remon JP, Vervaet C. Development of directly compressible powders via co-spray drying. *Eur J Pharm Biopharm* 2007; 67:220-226.
- Kawashima Y, Imai M, Takeuchi H, Yamamoto H, Kamiya H, Hino T. Improved flowability and compactibility of spherically agglomerated crystals of ascorbic acid for direct tableting designed by spherical crystallization process. *Powder Technol* 2003; 130:283-289.
- Teychenne S, Sicre N, Biscans B. Is spherical crystallization without additives possible? *Chem Eng Res Des* 2010; 88:1631-1638.
- Krishna EH, Gupta VRM, Krishna M, Jyothi S, Dasari R. Preparation and evaluation of sodium CMC zaltoprofen spherical agglomerates for direct compression. *J Pharm Res* 2013; 6:61-67.
- Kawashima Y, Handa T, Takeuchi H, Okumura M, Katou H, Nagata O. Crystal modification of phenytoin with polyethylene glycol for improving mechanical strength, dissolution rate and bioavailability by a spherical crystallization technique. *Chem Pharm Bull* 1986; 34:3376-3383.
- Kaul D, Nguyen NT, Venkataram S. Crystal habit modifications and altered tableting characteristics. *Int J Pharm* 1992; 88:345-350.
- Alebiowu G, Itiola OA. Compressional characteristics of native and pregelatinized forms of sorghum,

- plantain, and corn starches and the mechanical properties of their tablets. *Drug Dev Ind Pharm* 2002; 28:663-672.
8. Ahmad MZ, Akhtar S, Anwar M, Rahman M, Siddiqui MA, Ahmad FJ. Compactibility and compressibility studies of Assam Bora rice starch. *Powder Technol* 2012; 224:281-286.
9. Pifferi G, Santoro P, Pedrani M. Quality and functionality of excipients. *Farmaco* 1999; 54:1-14.
10. Odeku OA, Schmid W, Picker-Freyer KM. Material and tablet properties of pregelatinized (thermally modified) Dioscorea starches. *Eur J Pharm Biopharm* 2008; 70:357-371.
11. Gohil UC, Podczeczek F, Turnbull N. Investigations into the use of pregelatinised starch to develop powder-filled hard capsules. *Int J Pharm* 2004; 285:51-63.
12. Jivraj II, Martini LG, Thomson CM. An overview of the different excipients useful for the direct compression of tablets. *PSTT* 2000; 3:58-63.
13. Schussele A, Bauer-Brandl A. Note on the measurement of flowability according to European pharmacopoeia. *Int J Pharm* 2003; 257:301-304.
14. Maghsoodi M, Taghizadeh O, Martin GP, Nokhodchi A. Particle design of naproxen-disintegrant agglomerates for direct compression by a crystallo-co-agglomeration technique. *Int J Pharm* 2008; 351:45-54.
15. Carr RL. Evaluating flow properties of solids *Chem Eng* 1965; 72:163-168.
16. Malumba P, Massaux C, Deroanne C, Masimango T, Bera F. Influence of drying temperature on functional properties of wet-milled starch granules. *Carbohydr Polym* 2009; 75:299-306.
17. Veregin RP, Fyfe CA, Marchessault RH, Taylor MG. Characterization of the crystalline A and B starch polymorphs and investigation of starch crystallization by high-resolution <sup>13</sup>C CP/MAS NMR. *Macromolecules* 1986; 19:1030-1034.
18. Atichokudomchai N, Varavinit S. Characterization and utilization of acid-modified cross-linked Tapioca starch in pharmaceutical tablets. *Carbohydr Polym* 2003; 53:263-270.
19. Wang YJ, Truong VD, Wang L. Structures and rheological properties of corn starch as affected by acid hydrolysis. *Carbohydr Polym* 2003; 52:327-333.
20. Lacerda LG, da Silva Carvalho Filho MA, Demiate IM, Bannach G, Ionashiro M, Schnitzler E. Thermal behaviour of corn starch granules under action of fungal  $\alpha$ -amylase. *J Therm Anal Calorim* 2008; 93:445-449.
21. Liu H, Yu L, Simon G, Dean K, Chen L. Effects of annealing on gelatinization and microstructures of corn starches with different amylose/amylopectin ratios. *Carbohydr Polym* 2009; 77:662-669.
22. Simoes RD, Rodriguez-Perez MA, de Saja JA, Constantino CJL. Thermomechanical characterization of PVDF and P (VDF-TrFE) blends containing corn starch and natural rubber. *J Therm Anal Calorim* 2010; 99:621-629.
23. Hauschild K, Picker KM. Evaluation of a new coprocessed compound based on lactose and maize starch for tablet formulation. *AAPS Pharm Sci* 2004; 6:27-38.
24. Nokhodchi A, Maghsoodi M, Hassan-Zadeh D, Barzegar-Jalali M. Preparation of agglomerated crystals for improving flowability and compactibility of poorly flowable and compactible drugs and excipients. *Powder Technol* 2007; 175:73-81.
25. Amaro-Gonzalez D, Biscans B. Spherical agglomeration during crystallization of an active pharmaceutical ingredient. *Powder Technol* 2002; 128:188-194.
26. Barot BS, Parejiya PB, Patel TM, Parikh RK, Gohel MC. Compactibility improvement of metformin hydrochloride by crystallization technique. *Adv Powder Technol* 2012; 23:814-823.
27. Katta J, Rasmuson AC. Spherical crystallization of benzoic acid. *Int J Pharm* 2008; 348:61-69.
28. Yang J, Sliva A, Banerjee A, Dave RN, Pfeffer R. Dry particle coating for improving the flowability of cohesive powders. *Powder Technol* 2005; 158:21-33.
29. Shogren RL. Effect of moisture content on the melting and subsequent physical aging of cornstarch. *Carbohydr Polym* 1992; 19:83-90.
30. Le Bail P, Morin FG, Marchessault RH. Characterization of a crosslinked high amylose starch excipient. *Int J Biol Macromol* 1999; 26:193-200.