Faculty of Pharmacy[1], Applied Science University, Amman; Faculty of Pharmaceutical Sciences[2], Hashemite University, Zarga, Jordan

Sustained release matrix tablets prepared from cospray dried mixtures with starch hydrophobic esters

N. Sakhnini[1], N. Al-Zoubi[2], G. H. Al-Obaidi[1], A. Ardakani[1]

Received June 10, 2014, accepted September 14, 2014

Dr. Adel Ardakani, Faculty of Pharmacy, Applied Science University, Al-Arab Street, Amman, Jordan
ardakani@asu.edu.jo

Pharmazie 70: 177–182 (2015) *doi: 10.1691/ph.2015.4093*

In this work, starch acetate and propanoate derivatives with moderate degree of substitution were synthesized and characterized for employment as matrix formers for sustained release from tablets. Matrix tablets were prepared from cospray-dried and simple physical mixtures of starch/starch derivatives and theophylline as a model drug. The release was rapid for matrix tablets prepared from simple physical mixtures. On the other hand, tablets prepared from cospray-dried mixtures with starch acetate and starch propanoate showed much slower and extended release. Scanning electron micrographs of tablet surfaces revealed enhanced inter-particulate bonding and plastification for cospray-dried agglomerates in comparison with physical mixtures.

1. Introduction

Over the past few decades, a large number of polymers prepared by chemical modification of native biopolymers have been investigated as pharmaceutical excipients. Starch is an interesting native biopolymer for this objective because of its safety, availability and low cost. Chemically modified starches include sodium starch glycolate used as superdisintegrant, hydroxypropyl starch and hydroxyethyl starch used as thickeners, emulsifying agents and binders (Häusler 2009). Native starch has been used in tablets as filler, binder and disintegrant. The direct use of native starch has not shown great potential in controlled-release drug delivery due to a substantial swelling followed by tablet disintegration and rapid enzymatic degradation. Therefore, chemically modified starch has been investigated for this purpose (Ameye et al. 2001; Wöhl-Bruhn et al. 2012; Singh and Nath 2012a, 2013a, b)

In particular the preparation of hydrophobic starch esters is promising to enhance the starch properties for controlled drug release application by increasing hydrophobicity, minimizing both swelling and enzymatic degradation. This has been emphasized in literature for starch acetate as a matrix former (Korhonen et al. 2000; Pohja et al. 2004; Van Veen et al. 2005; Mäki et al. 2006; Singh and Nath 2012b, 2013c), membrane former (Tarvainen et al. 2004; Chen et al. 2007; Nutan et al. 2007) and in microencapsulation (Tuovinen et al. 2004). Similarly to starch acetate, other more hydrophobic ester derivatives of starch may have a high potential for application in controlled release drug delivery but there is very limited information regarding their use in this field.

Spray-drying is a widely used technique for the preparation of microparticles with enhanced flow and compression properties (Broadhead et al. 1992). Matrices prepared using spray-dried mixtures may show different release profiles from their equivalents prepared using physical mixtures as reported previously (Takeuchi et al. 1998; Pringles et al. 2005; Al-Zoubi et al. 2011). This research aimed to evaluate spray drying with hydrophobic starch derivatives (acetate and propanoate) followed by compaction into matrix tablets as a method of controlling drug release in comparison with simple physical mixing. Theophylline was used as a model drug.

2. Investigations and results

2.1. Modification of the starch

Acylation of the starch was carried out by pre-activating the starch with pyridine to open out the crystalline zone to improve the accessibility of esterifing reagent (Santayanon et al. 2003). After that the appropriate anhydride was added to complete the acylation (Fig. 1). The propionyl or the acetyl contents were highly affected by reaction parameters such as pyridine concentration, pre-activation temperature, pre-activation time, acid anhydride concentration, and the acylation temperature and acylation time. Several preliminary experiments were performed with the objective to optimize the conditions and prepare the two modified starch derivatives with relatively high and similar DS values. The optimum conditions per 5 g of dried unmodified starch were found to be: pyridine amount of 24 ml (divided into two portions, 16 ml for the pre-activation and 8 ml added during the acylation reaction), pre-activation temperature 90 °C and pre-activation time 19 h. Under these conditions, almost similar degree of substitution was obtained (DS = 1.8 and 1.7 for starch acetate and propanoate, respectively).

2.2. Characterization of starch esters

2.2.1. FT-IR spectroscopy

Comparing the IR spectra of starch acetate, starch propanoate and unmodified starch (Fig. 2), the unmodified starch the most important bands are: broad peak between 3000-3700 cm^{-1} corresponds to the OH stretching, the peak at 2935 cm^{-1} to CH stretching while the peak at 1655 corresponds to δ(OH) bending and the bands at 1155, 1086, 1022 cm^{-1} corresponding to C-O bond stretching (Goheen and Wool 1991; Mano et al. 2003; Zhi-

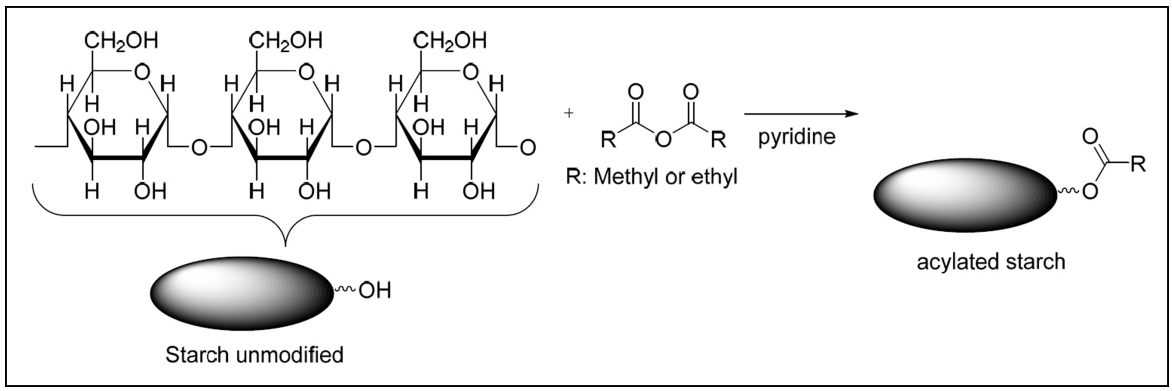

Fig. 1: Esterfication reaction of starch with the appropriate anhydride.

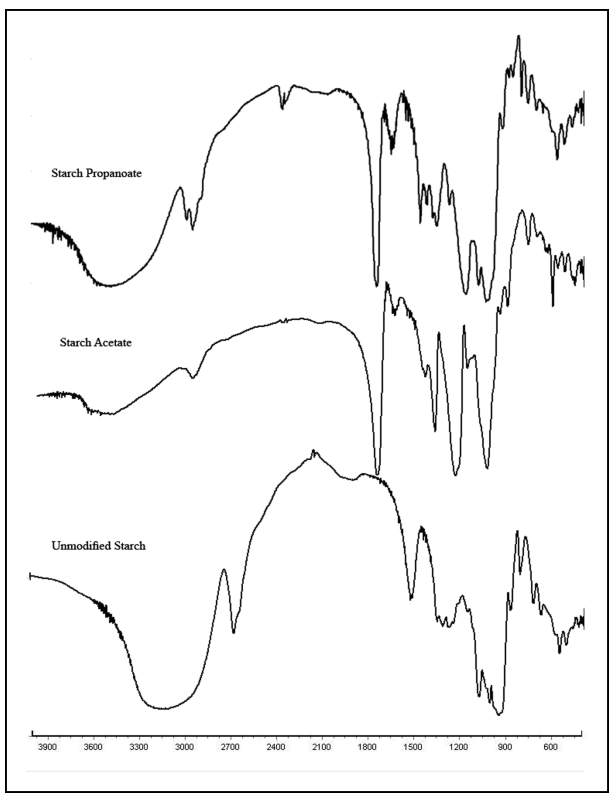

Fig. 2: Transmission FTIR spectra of starch propanoate, starch acetate and unmodified starch.

gang and Zidan 2012). The absorption bands at 935, 855, 767, 577 cm^{-1} are due to the entire anhydroglucose ring stretching vibrations. In comparison with unmodified starch, the two acylated starch derivates spectra showed new absorption peaks at 1760 cm^{-1} which corresponds to carbonyl C = O stretching vibration and 1240 cm^{-1} corresponds to carbonyl C-O stretching vibration. The acetylated starch derivative spectrum showed an extra band at 1380 cm^{-1} corresponding to methyl CH_3 vibration, while the propanoate starch derivative showed absorption peaks at 1471 and 1360 cm^{-1} corresponding to methylene $\delta(CH_2)$ and methyl CH_3, respectively (Silverstein 2005). The intensities of the peaks at 3488 and 1655 cm^{-1} were weakened for the acylated starch derivatives due to the replacement of some of the hydroxyl group -OH in the native starch molecule indicating that the acylated starch derivatives were found during esterification process.

2.2.2. *Solid-state ^{13}C NMR spectroscopy*

Comparing the ^{13}C NMR spectra of starch acetate, starch propanoate and the unmodified starch (Fig. 3), showed that the

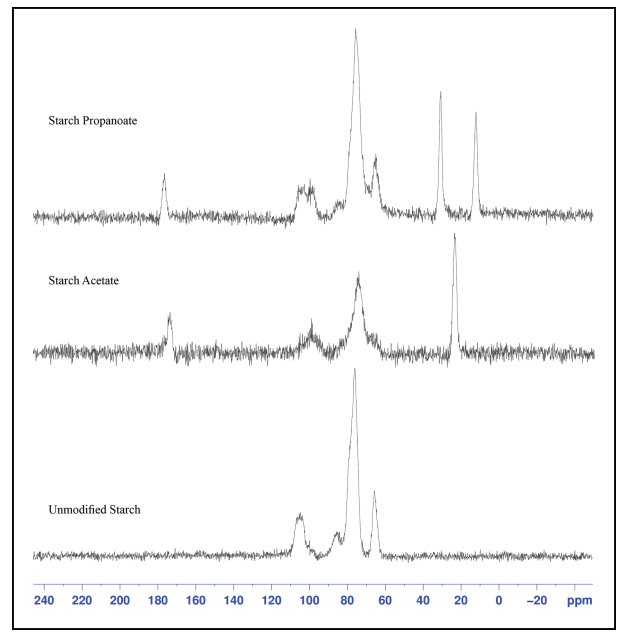

Fig. 3: Solid-state 13C NMR spectra of starch propanoate, starch acetate and unmodified starch.

starch back-bone signals are at 65.8-104.6 ppm (Liebert et al. 2008). The methyl C of the acetate signal appears at 24.5 ppm while its corresponding carbonyl C peak at 174.6 ppm. For the propanoate, the methyl C peak was observed at 31.1 ppm, and the methylene peak at 12.5 ppm, while its corresponding carbonyl C peak at 174.9 ppm. From the data shown, one clear methyl peak and another clear carbonyl peak were both observed for the acetylated starch. Both mentioned peaks were absent in the unmodified starch spectrum. As for the propanoated starch again two clear peaks for the ethyl carbons and one for carbonyl C were observed, showing the difference between the unmodified starch and the two acylated starch polymers.

2.3. *Characterization of spray dried powder*

The results of production yield and encapsulation efficiency for agglomerates prepared by spray drying theophylline with starch and its chemically modified derivatives (starch acetate and starch propanoate) are given in the Table. It can be seen that the production yield, which is expressed as the mass percentage of the harvested agglomerates to the initial mass of drug and polymer(s), was 56.7, 60.1 and 25.3% for spray-dried agglomerates based on starch, starch acetate and starch propanoate respectively. The encapsulation efficiency was 99.0, 100.1 and 115.1 % for spray-dried agglomerates based on starch, starch acetate

Table 1: Production yield and encapsulation efficiency (mean ± S.D., n = 3) for agglomerates prepared by spray drying with starch and its derivatives at 1:2 drug:polymer (D:P) ratio

Polymer	Production yield (%)	Encapsulation efficiency (%) (mean ± S.D.)
Starch	56.7	99.0 ± 0.4
Starch acetate	60.1	100.1 ± 1.6
Starch propanoate	25.3	115.1 ± 2.7

and starch propanoate respectively. The lower yield values and higher drug content (encapsulation efficiency) in the case of starch propanoate might be presumably explained by the formation of coarser dispersion of polymer in the ethanol/water solvent mixture (due to higher lipophilicity and expected lower solubility and dispersibility) leading to formation of larger droplets containing high content of dispersed polymer with the subsequent higher adhesion of such droplets to the internal surfaces of drying chamber and cyclone before they dry and reach the product vessel.

Scanning electron micrographs for the spray-dried agglomerates are presented in Fig. 4. They show that the size of agglomerates was larger in the cases of starch acetate and starch propanoate (Fig. 4A and 4B, respectively) than in the case of unmodified starch (Fig. 4C). This might be explained by the lower solubility and dispersibility of starch acetate and propanoate than starch in the solvent mixture used for spray drying. The agglomerates were composed of isodiametric (spherical or nearly-spherical) particles and needle-shaped (acicular) particles. The needle shaped particles are mainly seen in starch acetate and starch propanoate agglomerates but are also present to a less extent in starch agglomerates. The X-ray microanalysis was used to determine if these two different shapes of particles differ in composition and it was found that the acicular particles have high nitrogen content, while the isodiametric particles have much lower nitrogen content, indicating that the acicular particles are theophylline crystals.

2.4. In vitro drug release

Figure 5 shows the release profiles for theophylline from matrix tablets prepared by compressing spray dried agglomerates and equivalent physical mixtures. It can be seen that starch acetate and propanoate were able to effectively sustain the release of theophylline from matrix tablets prepared from cospray dried mixtures in comparison with their equivalent matrix tablets prepared from physical mixtures that showed very rapid release, which has been seen also for both types of matrix tablets based on unmodified starch.

Starch is commonly known by its disintegration properties and therefore, it is not suitable as a sustained release matrix former. Chemical modification to make the starch more hydrophobic and less swellable is necessary for such application. The previously published work on chemical modification of starch for sustaining drug release was mainly through formation of acetate derivative with high DS values. Paronen et al. (1997) and Korhonen et al. (2000) reported that increasing DS of starch acetate led to higher disintegration time of its compacts and slower release from its matrix tablets. This has been explained by the increase in hydrophobicity, thus masking the native swelling and disintegrating properties of starch, and decreased surface porosity due to enhanced deformation and fragmentation. Starch propanoate is more hydrophobic and thus is expected to produce better sus-

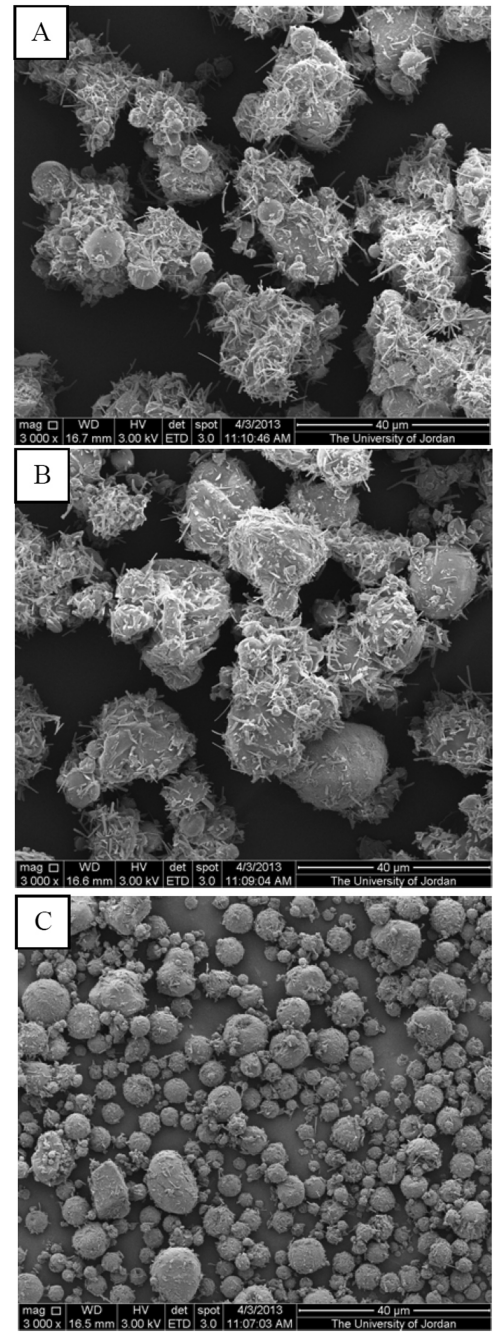

Fig. 4: SEM pictures for agglomerates prepared by cospray drying theophylline with starch acetate (A) starch propanoate (B) and starch (C) at 1:2 drug:polymer ratio.

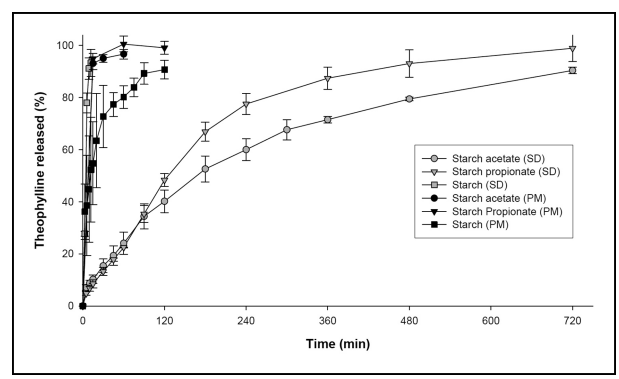

Fig. 5: Release profiles of theophylline from matrix tablets prepared using spray-dried agglomerates (SD) and physical mixtures (PM).

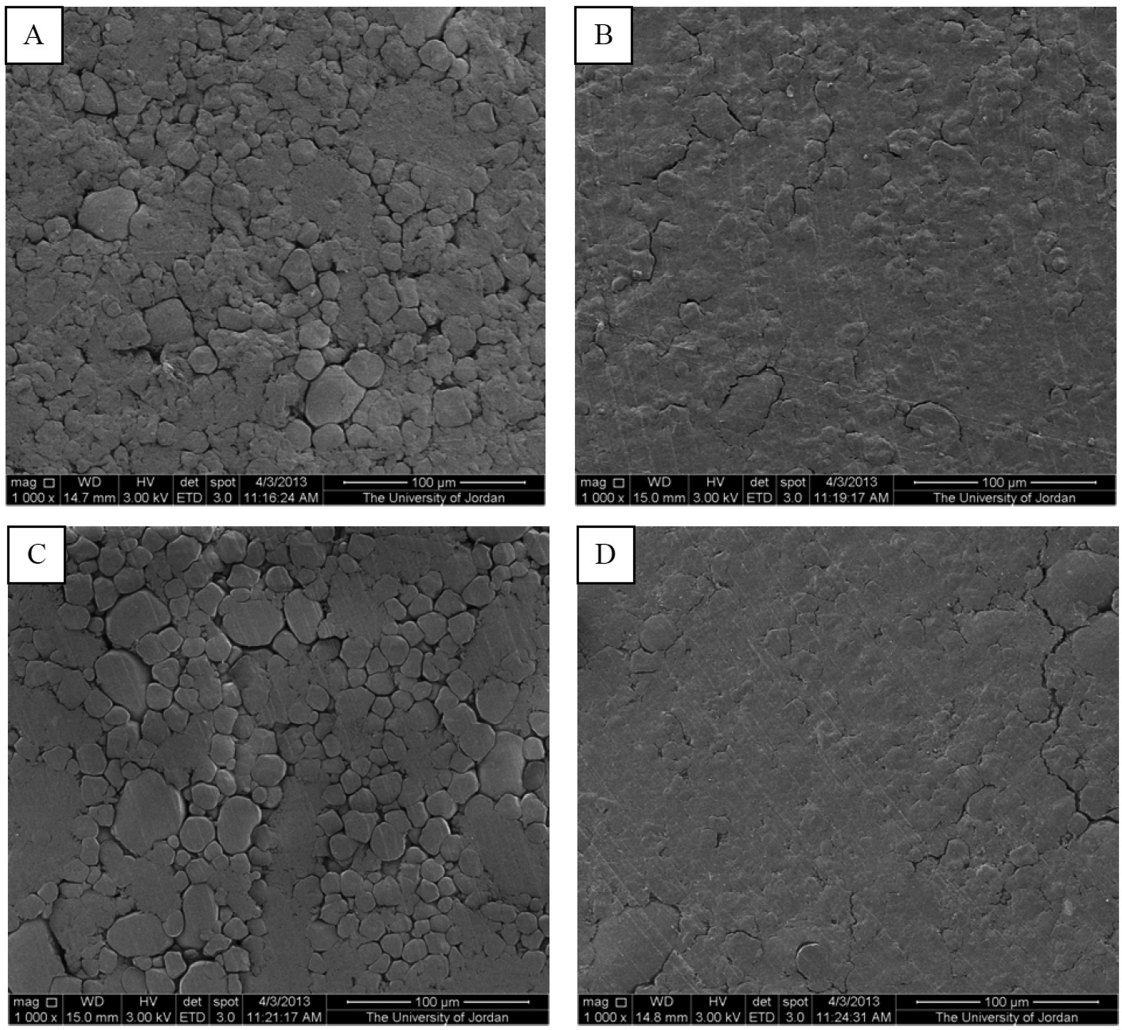

Fig. 6: SEM micrographs of surfaces of matrix tablets of theophylline with starch acetate (A and B) and starch propanoate (C and D) prepared from simple and spray dried physical mixtures, respectively.

tained release properties than starch acetate. However, Paronen et al. (1997) reported that starch propanoate and starch hexanoate derivatives produced weak tablets that disintegrated rapidly and were not able to produce efficient sustained drug release. This points out the importance of mechanical strength and surface porosity related to particles deformation and fragmentation behaviors. In view of that, the effective sustained release from spray-dried matrix tablets is most probably attributed to enhanced compression behavior leading to stronger and less porous matrix tablets. This has been demonstrated by the SEM micrographs of tablet surface shown in Fig. 6. It can be seen that for the surface of starch acetate and starch propanoate tablets from physical mixtures, borders of the deformed particles were still visible after compression (Fig. 6A and C, respectively). On the other hand for starch acetate and starch propanoate tablets prepared from spray-dried mixtures (Fig. 6B and D, respectively), the matrix was firmer having a smoother surface, while the borders of deformed particles can hardly be seen indicating interparticular plastification under compression (Korhonen et al. 2000; Raatikainen et al. 2002).

2.5. Conclusions

The results show that cospray drying with starch acetate and propanoate followed by compression into matrix tablets enables the release control of theophylline from the moderately substituted starch derivatives through the improvement of matrix integrity, whereas corresponding matrices prepared from simple physical mixtures disintegrated rapidly and failed to control the release.

3. Experimental

3.1. Materials

Commercially available analytical grade reagents were used without further purification. Chemicals were purchased from appropriate commercial sources: Maize starch and methanol were purchased from GCC Gainland chemical company (UK); hydrochloric acid from GFS (Europe); acetic anhydride from Tedia (USA); theophylline anhydrous and propanoic anhydride from Sigma-Aldrich (Canada/USA); isopropyl alcohol from S.D. Fine Chemicals Limited (India); pyridine from Xilong Chemical Industry Incorporated (China); potassium hydroxide from Qualigens (India); absolute ethanol from S&C Chemicals (UK).

3.2. Synthesis of starch acetate and propanoate

To a round bottomed flask 5 g of dried starch was added followed by 16 ml of pyridine. The two materials were mixed using a magnetic stirrer and heated to 90 °C for 19 h to pre-activate the starch, under nitrogen flushing. A reflux condenser was used to prevent the loss of the organic liquid. After the pre-activation for 19 h, the temperature was decreased to 75 °C and 60 ml of acetic or propionic anhydride were added slowly followed by a further 8 ml of pyridine. Heating was continued for a further 3.5 h, after which the content of the reaction flask was coagulated by the addition of 200 ml of isopropanol with stirring. The solid product was filtered off and washed

with 100 ml methanol and dried in an oven at 40 °C until no more change in weight was observed (Santayanon et al. 2003).

3.3. Characterization of starch esters

3.3.1. Degree of substitution

The degree of substitution was determined following a previously reported method (Ogawa et al. 1999; Ayucitra 2012). One gram of the modified starch ester was added to 50 ml of 75% ethanol, the solution was heated in a water bath for 30 min to 50 °C. After cooling to room temperature, 40 ml of 0.5 M of potassium hydroxide was added, the mixture was stirred for 72 h at room temperature and the excess KOH was then titrated with 0.5 N HCl. The same procedure was applied for unmodified starch, which was used as a blank. The acyl content (A%) was calculate according to the following equation:

$$A\% = \frac{(Vo - Vn) \times Y \times 10^{-3}}{M} \times 100\% \quad (1)$$

Where V_o (ml) is the volume of 0.5 N HCl used to titrate the blank, V_n (ml) the volume of 0.5 N HCl used to titrate the sample, N the normality of the HCl used, M (g) the amount of dry starch ester sample, Y is the formula weight of the acyl group. The acyl content (A%) was used to calculate the DS, according to the following Eq. (2)

$$DS = \frac{162 \times A\%}{Y - 100 - (Y - 1) \times A\%} \quad (2)$$

Where 162 is the molecular weight of the anhydroglucose unit, Y is the formula weight of the acyl group, and the number 1 represents the atomic weight of hydrogen (Zhigang and Zidan 2012).

3.3.2. FTIR spectroscopy

FTIR spectra of starch and starch ester derivatives were recorded on a Rayleigh WQF-520 FTIR BRAIC spectrophotometer (Beijing–China). The data region was 4000–500 cm^{-1}. The dried polymers were finely milled with an agate pestle and mortar and KBr discs (1% w/w) were prepared from the resulting fine powder by applying 10 tons pressure for 2 min.

3.3.3. Solid-state ^{13}C NMR spectroscopy

The ^{13}C NMR spectra of starch and starch ester derivatives were recorded on a Bruker Avance III 500 MHz, 4 mm MAS Probe BB/1H/19F K3167/0212. Samples were packed in 4 mm zirconia rotors of magic angle spinning (54.74°) at 303.0 K. CP-MAS ^{13}C was carried out at 125.771 MHz. The pulse delay value (d1) was 5 s and contact time (p15) was 2 ms.

3.4. Spray drying

Agglomerates of theophylline with starch derivatives were prepared at 1:2 drug:polymer ratio by spray drying in a Pulvis mini-spray GA 32 (Yamato Scientific, Japan) equipped with a standard 406 μm spray nozzle. Preliminary experiments showed poor solubility of starch acetate and propanoate in water and in other solvents suitable for spray drying. Therefore, it was sought to cospray-dry theophylline with a fine slurry of these polymers. After preliminary experiments, good dispersion of these polymers was found by sonication in 60% ethanol/water solvent mixture at 40 °C. For preparation of dispersion, theophylline (2 g) was dissolved in 40 ml 60% (v/v) ethanol/water solvent mixture. The mixture was heated to 40 °C and 4 g of the polymer was dispersed in the mixture by sonication in a thermostated sonicator (FS 100B, Decon Laboratories, Sussex, UK) for 20 min. The volume was completed to 60 ml so that the total solid concentration in the slurry was 10%. The dispersions were then spray dried while being under sonication. The operation conditions were fixed as follows: inlet air temperature 110 °C, outlet air temperature 60 °C, spray air pressure 1 kg/cm^2, spray feed rate 6 ml/min. Spray-dried agglomerates based on unmodified starch were prepared in a similar procedure but using 30% ethanol/water at 40 °C as a solvent mixture.

3.5. Drug content determination

Accurately weighed samples (about 25 mg) of each spray-dried batch were dissolved in 100 mL phosphate buffer (pH = 6.8) with the aid of sonication. Theophylline content was determined, after appropriate dilution, using UV spectrophotometer (Spectronic 601; Milton Roy, Ivyland, PA, USA) at a wavelength corresponding to maximum absorbance (λ_{max} = 272 nm). The encapsulation efficiency was expressed as percentage of the actual amount of theophylline to the theoretical (initially added) amount. The procedure was carried out in triplicate and the average and standard deviation was determined.

3.6. Preparation of matrix tablets

For comparison, matrix-tablets were prepared from spray-dried agglomerates and physical mixtures of similar composition. 120 mg of spray-dried particles, containing theoretically 40 mg of theophylline, was directly compacted in a 7-mm diameter round flat-faced punch and die set using manual hydraulic press (Riken Seiki, Japan) at pressure 222 MPa (8.5 kN) for 60 s. Equivalent matrix-tablets from physical mixtures were prepared by mixing theophylline and matrix former using a spatula for 15 min and then, 120 mg of the powder mixture was compressed as described for the spray-dried agglomerates.

3.7. In vitro release experiments

Release study was performed in a USP Apparatus II paddle system (Pharma Test PTW 2, Hainburg, Germany) at 100 rpm using 900 ml of phosphate buffer (pH = 6.8) at a temperature of 37 ± 0.5 °C as a dissolution medium. At predetermined time intervals, samples were taken and filtered through 5 μm cellulose acetate syringe filters and the concentration of drug dissolved was determined by UV spectroscopy at wavelength corresponding to maximum absorbance (λ_{max} = 272). All tests were performed in triplicates.

3.8. Field Emission Gun Scanning Electron Microscopy (FEG-SEM)

The spray-dried agglomerates and surface of matrix tablets were evaluated by scanning electron microscopy (FEI Company – Inspect F50 / FEG, Eindhoven, Netherlands). Samples were mounted on aluminum stubs with double-sided sticky discs of conductive carbon and then coated with ~15 nm of platinum in a sputter coater (Emitech K550X, Ashford, Kent, UK).

Acknowledgment: The authors are grateful to the Applied Science University, Amman, Jordan, for the full financial support granted to this research project (Grant No. DRGS/2010-2)

References

Al-Zoubi N, AlKhatib H, Obeidat W (2011) Evaluation of hydrophilic matrix tablets based on Carbopol® 971P and low-viscosity sodium alginate for pH-independent controlled drug release. Drug Dev Ind Pharm 37: 798–808.

Ameye D, Voorspoels J, Foreman P, Tsai J, Richardson P, Geresh S, Remon JP (2001) Trypsin inhibition, calcium and zinc ion binding of starch-g-poly (acrylic acid) copolymers and starch/poly (acrylic acid) mixtures for peroral peptide drug delivery. J. Control. Rel 75: 357–364.

Ayucitra A (2012) Preparation and characterization of acetylated corn starch. Int J Chem Eng. Appl 3: 156–159.

Broadhead J, Edmond Rouan SK, Rhodes CT (1992) The spray drying of pharmaceuticals. Drug Dev Ind Pharm 18: 1169–1206.

Chen L, Li X, Li L, Guo S (2007) Acetylated starch-based biodegradable materials with potential biomedical applications as drug delivery systems. Curr Appl Phys 7: 90–93.

Goheen S, Wool R (1991) Degradation of polyethylene starch blends in soil. J Appl Polym Sci 42: 2691–2701.

Häusler O (2009) Handbook of Pharmaceutical Excipients, 6th ed., Pharmaceutical Press, p. 685–691.

Korhonen O, Raatikainen P, Harjunen P, Nakari J, Suihko E, Peltonen S, Paronen P (2000) Starch acetates—multifunctional direct compression excipients. Pharm Res 17: 1138–1143.

Liebert T, Kulicke W M, Heinze T (2008) Novel approach towards hydrolytically stable starch acetates for physiological applications. React Funct Polym 68: 1–11.

Mäki R, Suihko E, Korhonen O, Pitkänen H, Niemi R, Lehtonen M, Ketolainen J, (2006) Controlled release of saccharides from matrix tablets. Eur J Pharm Biopharm. 62: 163–170.

Mano J, Koniarova D, Reis L (2003) Thermal properties of thermoplastic starch/synthetic polymer blends with potential biomedical applicability. J Mater Sci Mater Med 14: 127–135.

Nutan MT, Vaithiyalingam SR, Khan MA (2007) Controlled release multiparticulate beads coated with starch acetate: Material characterization, and identification of critical formulation and process variables. Pharm Dev Technol 12: 307–320.

Ogawa K, Hirai I, Shimasaki C, Yoshimura T, Ono S, Rengakuji S, Nakamura Y, Yamazaki I (1999) Simple determination method of degree of substitution for starch acetate. Bull Chem Soc Jpn 72: 2785–2790.

Paronen P, Peltonen S, Urtti A, Nakari J (1997) Starch acetate composition with modifiable properties, method for preparation and usage thereof. US patent 5667803.

Pohja S, Suihko E, Vidgren M, Paronen P, Ketolainen J (2004) Starch acetate as a tablet matrix for sustained drug release. J Control Release 94: 293–302.

Pringels E, Ameye D, Vervaet C, Foreman P, Remon JP (2005) Starch/Carbopol® spray-dried mixtures as excipients for oral sustained drug delivery. J Control Release 103: 635–641.

Raatikainen P, Korhonen O, Peltonen S, Paronen P (2002) Acetylation enhances the tabletting properties of starch. Drug Dev Ind Pharm 28: 165–175.

Santayanon R, Wootthikanokkhan J (2003) Modification of cassava starch by using propionic anhydride and properties of the starch-blended polyester polyurethane. Carbohydr Polym 51: 17–24.

Silverstein RM, Webster FX, Kiemle DJ (2005) Spectrometric Identification of Organic Compounds. 7th ed., John Wiley & Sons, Infrared Spectroscopy, p. 80–106.

Singh AV, Nath LK (2012a) Evaluation of acrylamide grafted moth bean starch as controlled release excipient. Carbohydr Polym 87: 2677–2682.

Singh AV, Nath LK (2012b) Evaluation of acetylated moth bean starch as a carrier for controlled drug delivery. Int J Biol Macromol 50: 362–368.

Singh AV, Nath, LK (2013a) Formulation development and evaluation of lamivudine controlled release tablets using cross-linked sago starch. Expert Opin Drug Deliv 10: 173–182.

Singh AV, Nath LK (2013b) Evaluation of microwave assisted grafted sago starch as controlled release polymeric carrier. Int J Biol Macromol 60: 62–68.

Singh AV, Nath LK (2013c) Evaluation of chemically modified hydrophobic sago starch as a carrier for controlled drug delivery. Saudi Pharm J 21: 193–200.

Takeuchi H, Yasuji T, Hino T, Yamamoto H, Kawashima Y (1998) Spray-dried composite particles of lactose and sodium alginate for direct tabletting and controlled releasing. Int J Pharm 174: 91–100.

Tarvainen M, Peltonen S, Mikkonen H, Elovaara M, Tuunainen M, Paronen P, Sutinen R (2004) Aqueous starch acetate dispersion as a novel coating material for controlled release products. J Control Release 96: 179–191.

Tuovinen L, Peltonen S, Liikola M, Hotakainen M, Lahtela-Kakkonen M, Poso A, Järvinen, K (2004) Drug release from starch-acetate microparticles and films with and without incorporated α-amylase. Biomaterials 25: 4355–4362.

Van Veen B, Pajander J, Zuurman K, Lappalainen R, Poso A, Frijlink HW, Ketolainen J (2005) The effect of powder blend and tablet structure on drug release mechanisms of hydrophobic starch acetate matrix tablets. Eur J Pharm Biopharm 61: 149–157.

Wöhl-Bruhn S, Bertz A, Harling S, Menzel H, Bunjes H (2012) Hydroxyethyl starch-based polymers for the controlled release of biomacromolecules from hydrogel microspheres. Eur J Pharm Biopharm 81: 573–581.

Zhigang L, Zidan Z (2012) Homogeneous synthesis and characterization of starch acetate in ionic liquid without catalysts. Starch 64: 37–44.