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High-amylose sodium carboxymethyl starch matrices for oral, sustained drug release: development of a spray-drying manufacturing process

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Abstract

Context: High-amylose sodium carboxymethyl starch (HASCA) was recently proposed as a material for oral, sustained drug-release tablets prepared by direct compression. It was produced on a pilot scale, but appeared to be unsuitable for tableting and sustained drug release. Pilot-scale dry powder HASCA was dispersed in hot water and then precipitated with ethanol to give a dry powder presenting the required properties, but very high volumes of ethanol were used to recover the product. *Objective*: A process was therefore designed to transform totally amorphous pregelatinized HASCA by spray-drying into a suitable sustained drug-release excipient for matrix tablets while decreasing ethanol quantities. *Results and discussion*: During the first manufacturing step, that is, heating of the initial hydro-alcoholic suspension, powder and water concentrations are key parameters for the acquisition of excellent binding properties. Hence, a variable ratio of amylose Vh, a crystalline polymorph of amylose, to the amorphous form, is observed depending on the key parameter values. As the most crystalline samples give the weakest tablets, binding properties do not appear to be linked to the presence of a Vh form of amylose. On the other hand, a high water concentration results in excessive tablet strength, that is, inverse conditions leading to the appearance of a Vh form of amylose. Finally, variations in hydro-alcoholic composition appear to affect only tableting properties and do not influence the drug-release rate. *Conclusion*: A process designed to transform totally amorphous pregelatinized HASCA by spray-drying is proposed for easier, economical industrial HASCA production.

Key words: *Amylose; drug delivery; excipient; matrix; polymer; spray-drying; starch; sustained release; tablet*

Introduction

Starches and modified starches are used currently and safely in the food and pharmaceutical industries. Various starch-modification methods, chemical, physical, enzymatic, or a combination thereof, are employed to create new starch products with specific or improved properties. Unmodified and physically modified starches like totally pregelatinized starch (e.g., Lycatab®PGS) or partially pregelatinized starch (e.g., Starch 1500®) have been widely used as binders, disintegrants, or fillers in tablets[1]. Starch is considered a good candidate for chemical reaction/transformation because of its composition, that is, mixture of amylose and amylopectin,

two glucose polymers presenting three hydroxyl groups available as chemically active, functional entities. Oxidation, ethoxylation, and carboxymethylation are some of the modifications commonly deployed to prepare starch derivatives. Sodium starch glycolate, a low amylose content sodium carboxymethyl starch (e.g., Explotab® or Glycolys®), is a well-known tablet disintegrant[2,3]. More recently, Contramid®, a specific type of high-amylose cross-linked starch, has been used in tablets for drug-controlled release[4].

Substituted amylose (SA) has been introduced as a promising pharmaceutical excipient for sustained drug release. SA matrix tablets have been prepared by direct compression, that is, dry mixing of drug and SA polymers,

followed by compression, which is the easiest way to manufacture an oral dosage form[5,6]. High-amylose corn starch, containing 70% of amylose chains and 30% of amylopectin, has been tested for the production of SA polymers by an etherification process. These polymers are referred to as SA,R-n, where R defines the substituent and n represents the degree of substitution (DS) expressed as the ratio of mole of substituent per kilogram of amylose[5,6]. First, a range of substituents, such as 1,2-epoxypropanol (or glycidol=G), 1,2-epoxybutane, 1,2-epoxydodecane, and 1-chlorobutane, were investigated[6]. SA,G polymers and especially SA,G-2.7 demonstrated interesting properties as excipients for controlled drug-release systems. SA,G-2.7 matrices allowed nearly constant drug release. In vitro dissolution release times of 95% of the drug ranged from 9 to 20 hours for all DSs studied for 400 mg matrices containing 10% of a soluble drug[5,6]. Moreover, sustained drug-release matrix systems based on SA,G technology presented large ranges for drug-loading, drug solubility, and tablet weight[5,7]. Another advantage of this excipient is that there is no significant influence of compression forces, ranging from 49 to 490 MPa, on the release properties of SA,G-n polymers with a DS greater than 1.5[7]. In contrast to pregelatinized starches known for their poor binding properties[8,9], SA,G polymers have shown good compression behavior, which results in unusually high crushing strength values comparable to those of microcrystalline cellulose tablets, a reference among binders/fillers[5,10]. Another striking feature is that, unlike amylose-based polymers, which are usually subject to biodegradation by α-amylase enzymes present in the gastrointestinal tract, SA,G matrix systems and dry-coated tablets maintain their structure and control [^{186}Re] release, with no significant degradation by α-amylase[11].

Reacting high-amylose starch with sodium chloroacetate/chloroacetic acid in place of nonionic substituents has been proposed for excipients more readily acceptable by regulatory agencies[12,13]. Indeed, as mentioned above, carboxymethyl starch containing low amounts of amylose already serves as a disintegrating agent in immediate release tablets. In contrast, high-amylose sodium carboxymethyl starch (HASCA) has been recently suggested as a suitable material for oral matrix tablets[12,13]. These tablets can be advantageously improved by the addition of electrolytes as the polymer is ionic. Such addition permits the integrity of the swollen matrix tablets to be maintained when they are immersed in a medium undergoing pH changes simulating the pH evolution of the environment surrounding an oral pharmaceutical dosage form transiting along the gastrointestinal tract while allowing controlled and sustained drug release with a remarkably close-to-linear release profile[12,13].

The first laboratory-scale batches of nonionic SA polymers were prepared by reacting the substituent and high-amylose starch in a heated, alkaline medium. After neutralization of the suspension, the resultant gel was filtered and washed with water and acetone. The powder product was exposed overnight to air, allowing to collect the excipient in a readily compressible powder form[5,12]. HASCA was then produced according to a similar laboratory-scale process[12,13]. HASCA was obtained on a pilot scale using a drying method without organic solvents. However, the HASCA appeared to be unsuitable for tableting and sustained drug release. To obtain a dry powder presenting the required binding and sustained drug-release properties[12,13], the dry powder of pilot-scale HASCA was thus dispersed in hot water and then precipitated with ethanol using the laboratory process, as previously described, though the original process used acetone to precipitate SA polymers[5,6]. However, the main drawback of the above method, that is, precipitation by a nonsolvent, is that very high volumes of organic solvent are needed to recover the product, yielding 1 part of solid recovered for up to 30 parts or more of ethanol.

The purpose of our study is to design an original process transforming totally amorphous HASCA by spray-drying (SD) into a suitable sustained drug-release excipient for matrix tablets while decreasing ethanol quantities and to prepare the scale up for easier and economical industrial production of HASCA.

Materials and methods

Materials

Amorphous pregelatinized HASCA (batch 3285, ref. 729094) was obtained in powder form from Roquette Frères (Lestrem, France) and contained approximately 70% of amylose chains and 30% of amylopectin. The DS was equal to 0.045 (number of moles of substituent/number of moles of anhydroglucose). Anhydrous ethanol was purchased from Commercial Alcohol Inc. (Brampton, ON, Canada). SA,G-2.7 was obtained exactly like described in US patent no. 5,879,707. Acetaminophen was procured from Laboratoires Denis Giroux Inc. (Ste-Hyacinthe, QC, Canada) and sodium chloride (NaCl) (crystals, laboratory grade) from Anachemia Ltd. (Montreal, QC, Canada). All chemicals were of reagent grade and were used without further purification.

SD HASCA manufacturing process

Suspensions consisting of amorphous HASCA of various weights and 80 g of a hydro-alcoholic solution [containing various % (w/w), water/ethanol] were heated at 70°C. The solutions were kept at this temperature

for 1 hour under stirring. The solution was then cooled down to 35°C with stirring. A volume of pure ethanol, corresponding to a final alcohol to starch ratio of 4 mL:1 g, was added 'slowly and gradually' to the solution. The final suspension was passed through a Büchi B-190 Mini Spray Dryer™ (Büchi, Flawill, Switzerland) at 140°C to obtain SD HASCA in the form of a fine, dry powder. The spray-dryer airflow rate was 601 NormLiter/h. The normalized pump conditions were set at level 4 = 20%, corresponding to a distilled water flow of 0.35 L/h.

Table 1a and b describes the composition of the HASCA suspensions during the two operational steps, that is, heating of the initial hydro-alcoholic suspensions and SD of the final suspensions: where % (w/w) WATER = the percent of water by weight in the starting hydro-alcoholic solution in which the powder is dispersed at the beginning of the process. Eighty grams of this solution serves to disperse each HASCA powder sample.

SOLUTION weight (g) = weight of the hydro-alcoholic solution employed to disperse each HASCA powder sample.

HASCA weight (g) = weight of the HASCA powder added to the hydro-alcoholic solution.

% (w/w) HASCA-I = [HASCA weight/(HASCA weight + SOLUTION weight)] × 100.

% (w/w) water-I = [(water weight)/(HASCA weight + SOLUTION weight)] × 100.

% (w/w) EtOH-I = [(ethanol weight)/(HASCA weight + SOLUTION weight)] × 100.

EtOH added (g) = quantity (g) of ethanol added to the hydro-alcoholic suspension to obtain a SD suspension having EtOH/HASCA-II ratio of 3.2.

EtOH/HASCA-II = 3.2 = ratio of the total weight of ethanol on the weight of HASCA in the suspension to be spray-dried.

% (w/w) HASCA-II = [HASCA weight/(HASCA weight + SOLUTION weight + EtOH added)] × 100.

% (w/w) water-II = [water weight/(HASCA weight + SOLUTION weight + EtOH added)] × 100.

% (w/w) EtOH-II = [EtOH total weight/(HASCA weight + SOLUTION weight + EtOH added)] × 100.

X-ray diffraction

X-ray diffraction (XRD) was performed to characterize the crystalline or amorphous state of SD HASCA powder samples. Powder XRD patterns were obtained with an automatic Philips Diffractometer controlled by an IBM PC (50 acquisitions, 3–25°θ, 1100 points; acquisition delay 500 ms), using a Cu anticathode ($K_{\alpha 1}$ 1.5405Å) with a nickel filter. A smoothing function was applied on the spectra for better reading of the peaks. SA,G-2.7 powder XRD pattern was obtained with an automatic Inel Diffractometer (Counter CPS120°, 35 kV, 35 mA, Cobalt wavelength $K_{\alpha 1}$ = 1.7890Å).

Scanning electron microscopy

The morphology of the samples prepared according to the manufacturing process described in section 'SD HASCA manufacturing process' was studied by scanning electron microscopy (SEM, Hitachi S 4000, Hitachi, Tokyo, Japan). Before investigation, the samples were mounted on double adhesive tape and sputtered with a thin gold palladium coat.

Table 1. Compositions of (a) HASCA initial hydro-alcoholic suspensions (heating step) and (b) spray-drying suspensions (drying step).

(a) Initial hydro-alcoholic suspensions

Batch	% (w/w) WATER	SOLUTION weight (g)	HASCA weight (g)	% (w/w) HASCA-I	% (w/w) water-I	% (w/w) EtOH-I
A	65.22	80	16	16.67	54.35	28.99
B	65.22	80	12	13.04	56.71	30.25
C	65.22	80	10	11.11	57.97	30.92
D	74.47	80	12	13.04	64.75	22.20
E	74.47	80	10	11.11	66.19	22.70
F	83.33	80	10	11.11	74.07	14.81
G	100.00	80	10	11.11	88.89	0.00

(b) Spray-drying suspensions

Batch	EtOH added (g)	% (w/w) HASCA-II	% (w/w) water-II	% (w/w) EtOH-II	EtOH/ HASCA-II
A	23.36	13.40	43.71	42.88	3.2
B	10.56	11.70	50.87	37.43	3.2
C	4.16	10.62	55.41	33.97	3.2
D	18.00	10.91	54.12	34.97	3.2
E	11.60	9.84	58.60	31.56	3.2
F	18.64	9.21	61.36	29.43	3.2
G	32.00	8.20	65.57	26.23	3.2

Apparent particle density

Helium pycnometry (Multivolume pycnometer 1305™, Micromeritics, Norcross, GA, USA) was undertaken. Powder samples were dried at 100°C in an oven overnight. The samples were then taken out of the oven and cooled at ambient temperature in a desiccator and weighed before measurement. Sample holder volume was 5 mL, and HASCA sample weight was between 0.5 and 1.5 g. The results are expressed in g/cm^3.

Surface area

Krypton adsorption/desorption isotherms were measured with a Micromeritics ASAP 2010™ instrument (Micromeritics). HASCA samples were outgassed overnight at 200°C. Specific surface area was calculated from adsorption data in the relative pressure range of 0.10–0.28, included in the validity domain of the Brunauer–Emmett–Teller (BET) equation[14]. BET-specific surface area was calculated from the cross-sectional area of 0.218 nm^2 per krypton molecule, following IUPAC recommendations.

Tablet crushing force

SD HASCA tablets weighing 200 mg were prepared by direct compression. The excipient was compressed in a hydraulic press (Workshop Press PRM 8 type, Rassant Industries, Chartres, France) at a compaction load of 245 MPa with a dwell time of 30 seconds (flat-faced punch die set). The diameter of all the tablets was 12.6 mm. Tablet crushing force (Newtons or N) was quantified with a hardness tester (ERWEKA® Type TBH 200, Erweka Gmbh, Heusenstamm, Germany). The data presented here are the mean values of three measurements.

Drug-release evaluation

Matrix tablets were prepared by direct compression. SD HASCA, acetaminophen, and NaCl were dry-mixed manually in a mortar. No lubricant was added to the formulation. Indeed, it was demonstrated earlier that magnesium stearate, at standard levels, did not influence the in vitro release profile of HASCA matrix tablets containing NaCl as well as their integrity[12,13]. Six hundred milligram tablets, containing 40% of acetaminophen as a model drug, 27.5% of NaCl, and 32.5% of SD HASCA, were produced to investigate the influence of thermal treatment and SD on the release characteristics of SD HASCA tablets. They were prepared in a hydraulic press (Workshop Press PRM 8 type, Rassant Industries). All tablets were compressed at 245 MPa for 30 seconds. The diameter of the tablets was 1.26 cm.

The drug-release properties of some typical SD HASCA matrix tablets were assessed by an in vitro dissolution test. Because HASCA is an ionic polymer used for oral, sustained drug release, in vitro release experiments were conducted in a pH gradient simulating the pH evolution of the gastrointestinal tract. The tablets were placed individually in 900 mL of an hydrochloric acid medium (pH 1.2) simulating gastric pH, at 37°C, in USP XXIII Dissolution Apparatus No. 2 equipped with a rotating paddle (50 rpm). They were then transferred to a phosphate-buffered medium (pH 6.8) simulating jejunum pH, and finally, transferred to another phosphate-buffered medium (pH 7.4) simulating ileum pH, until the end of the test. The dissolution apparatus and all other experimental conditions remained the same. The pH gradient conditions were pH 1.2 for 1 hour, pH 6.8 for 3 hours, and pH 7.4 until the end of the dissolution test (24 hours). The amount of acetaminophen released at predetermined time intervals was followed spectrophotometrically (244 nm). All formulations were tested in triplicate. The drug-release results are expressed as cumulative percentage in function of time (hours).

Results and discussion

Process design

Both SA,G-2.7 and HASCA produced at the laboratory scale demonstrated excellent binding and sustained drug-release properties[5,6,12,13]. However, HASCA produced at the pilot scale did not generate tablets suitable for sustained drug release.

From the presence of large peaks at 15° and 23.2° (2θ) corresponding to $d = 6.5$ and 4.4 (Å), it was concluded that SA,G-2.7 had an essentially amorphous character with a minor crystalline fraction (Figure 1). The same was true with laboratory-scale HASCA (data not shown). The crystalline part of SA,G-2.7 was considered
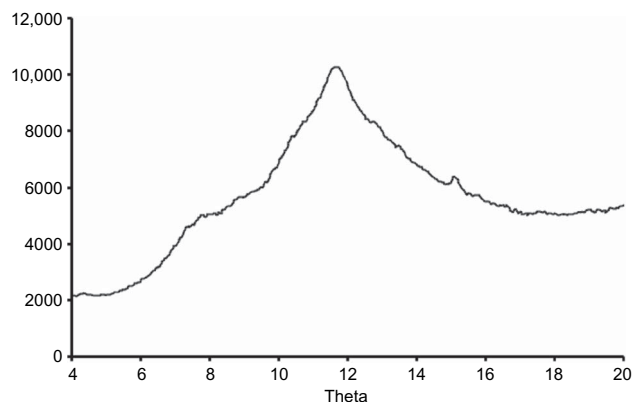

Figure 1. Powder X-ray diffraction pattern of SA,G-2.7 sample produced at the laboratory scale.

as being essentially a V polymorph of amylose. This polymorph did not occur frequently in cereal starch compared to other crystalline forms of starch, that is, A and B polymorphs[15]. V-amylose, a generic term for crystalline amylose obtained as single helices, co-crystallizes with compounds such as iodine, fatty acids, and alcohols[16–19]. Especially for alcohols, these types of complexes mainly occur by precipitation of amylose with alcohols (methanol, ethanol, and *n*-propanol) in heated, aqueous solution[20–23] or from amylose solubilized in dimethyl sulfoxide[24]. This might explain the presence of amylose–acetone or amylose–ethanol complexes in SA,G-2.7 or HASCA produced according to the original laboratory-scale process.

On the other hand, pilot-scale HASCA displays the characteristic pattern of a totally amorphous powder (data not shown) and is industrially produced as such for economical and technical reasons. In light of the laboratory process[5,6], pilot-scale HASCA was dispersed in hot water and then precipitated with ethanol to finally collect a dry powder possessing the required binding and sustained drug-release properties[12,13]. The main drawback of this method is that very high volumes of organic solvent are needed to recover the product, with yields going to 1 part of solid recovered for up to 30 parts or more of ethanol.

Two main functions of the nonsolvent may be distinguished: first, precipitation and crystallization of HASCA, if any, and, second, the removal of residual water to give a suitable dry powder. The first step is to dissolve the macromolecules. In the case of amylose, the macromolecules can be dispersed at a very low concentration in hot water[25–27]. Then, the polymer is precipitated by a nonsolvent addition. The problem with highly diluted solutions is that they require very high quantities of nonsolvent to precipitate and collect a dry powder. Increasing the starch concentration in the solution may solve the problem. However, because of the presence of its hydroxyl groups, amylose in aqueous solution forms a gel through hydrogen-bonding. Thus, raising the starch concentration in water heightens the apparent viscosity of the solution and the gel formation of starch[28]. A way to overcome this problem is to employ an organic solvent or water/organic solution as medium to limit the formation of a viscous starch paste[29–31]. Various organic liquids like ethyl alcohol[32,33] and isopropyl alcohol[29,30,31,34] have been tested. It has been proposed that alcohol disrupts the amylose gel structure by bonding to hydroxyl groups on starch molecules. Unlike water-bonding, this binding is terminal and produces no connectivity between amylose molecules, reducing the apparent viscosity of the solution and resulting in amylose precipitation at high alcohol concentrations[28].

Thus, keeping easier, more economical industrial production of HASCA in mind, an original process was designed to transform, by SD, amorphous pregelatinized HASCA into a suitable sustained drug-release excipient for matrix tablets, while drastically decreasing ethanol quantities.

It has been previously observed that (1) XRD results of laboratory-scale batches, which were used as sustained release matrices, showed the presence of a minor fraction of an SA V-form dispersed in a continuous amorphous phase and (2) pilot-scale HASCA obtained as a pregelatinized amorphous powder did not show any binding or sustained release properties. In view of these observations, it was first thought that the V-form was necessary to obtain a suitable, sustained drug-release excipient (see Figure 1). However, further results surprisingly showed that in fact this V-form was not necessary to obtain sustained drug-release properties but even decreased the binding properties of SD HASCA. Anyway, a delicate equilibrium had to be maintained between (a) adequately dispersing and/or dissolving HASCA to allow crystalline re-arrangement of a fraction of HASCA shifting from the amorphous state to a V-form, (b) avoiding a too high increase in viscosity to maintain acceptable SD conditions, and (c) avoiding unfavorable HASCA gel formation and/or crystallization occurring before the SD process as the presence of a carboxylic function on glucosidic units of HASCA dramatically influences the gel-forming process through strong hydrogen-bonding. Furthermore, even if SD appears, at first glance, to be a practical method to easily remove large quantities of water from a pharmaceutical product, it is not obvious that methods and results, if any, obtained for native starches and starch derivatives differing in the nature of their substituents and/or amylose concentration could be directly applied to the SD of HASCA. Experiments are thus necessary in case of processes implying a peculiar thermal treatment and fast rates of drying, particularly when the amorphous/crystalline state is of essence in achieving good tableting and sustained drug-release properties. In fact, the process described herein is not just a drying process but more a process to transform an unsuitable product into an efficient sustained drug-release matrix tablet excipient.

Thus, in a first step, hydro-alcoholic solutions with different water/ethanol ratios and HASCA powder concentrations were prepared. Water concentration had to remain as low as possible to limit dissolution of the starch, thus avoiding a too high viscosity hindering agitation and homogenization. Because, it was first thought that a crystalline re-arrangement, that is, the presence of a V-form fraction, was necessary (see Figure 1), a sufficient amount of ethanol was added to attain that goal. Then, a volume of ethanol was added after

heating the HASCA suspension. Note that the final EtOH/HASCA ratio of 3.2 was chosen to limit ethanol use as much as possible in the process for economical, environmental, and safety reasons, while still allowing easy SD. The second step of the process consisted of recovering the product in the form of a dry powder by SD. Traditional chemical dehydration by nonsolvent addition was discarded to avoid the necessity of large volumes of organic solvent. These working conditions facilitated the easy production of HASCA powder samples whose properties are described in subsequent sections.

X-ray diffraction study

The XRD results on typical SD HASCA samples appear in Figure 2. The presence of a V-type complex in HASCA spray-dried batches was verified by XRD. The XRD diagram of the SD-A sample reveals reflections at *Bragg* angles 2θ = 6.80°, 12.96°, 19.92°, and a less intense one at 2θ = 21.88°. This XRD pattern is close to those reported previously for pure amylose–ethanol complexes[21]. Table 2 reports that such peaks are, in fact, more characteristic of the Vh amylose polymorph although the diffraction peaks are broader[35]. A Vh amylose structure, often called a pseudo V-form, is
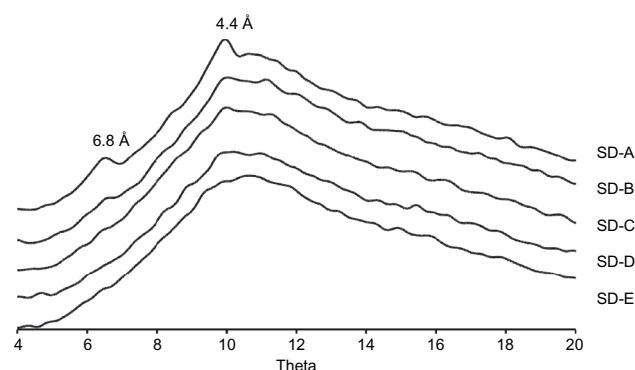

Figure 2. Powder X-ray diffraction patterns of different HASCA samples produced by spray-drying.

Table 2. Observed distances (Å) for HASCA and different types of V-amylose complexes reported in the literature.

Reference	Organic solvent	Observed *d*-spacings (Å)			
SD-HASCA This work	Ethanol	4	4.4	6.8	12.9
SA,G-2.7 This work	Acetone		4.4	6.5	
Pure V-amylose Bear[21]	Ethanol		4.5	7	
Pure Vh amylose Le Bail et al.[35]	Ethanol	3.93	4.47	6.84	11.87

indeed characterized by a larger structure. The V-type helix is a form of order existing in both crystalline and amorphous regions[36].

A progressive loss of the crystalline part is observed when decreasing % (w/w) HASCA-I and/or increasing % (w/w) water-I in the different spray-dried suspensions (Table 1 and Figure 2). In fact, usually higher volumes of ethanol are required to obtain highly crystalline complexes. Here, the crystalline part becomes more and more diluted compared to the amorphous part to a point that it is no longer detectable by XRD. Note that SD-F and SD-G are not differentiable from SD-E and are not presented in the figure for the purpose of clarity. SD samples generate the same type of patterns and thus the same type of structures, that is, a pseudo V-form dispersed in an amorphous matrix, although their respective proportions cannot be determined exactly here, until of course the pseudo V-form can no more be detected.

Scanning electron microscopy

An SEM picture of the starting material, that is, amorphous pregelatinized HASCA obtained at the pilot level, appears in Figure 3. The initial product consisted of large, flat, and splinter-shaped particles.

Products obtained by SD were also characterized by SEM (Figures 4 and 5). Samples from spray-dried suspensions were characterized by more or less collapsed spherical particles of various sizes (Figures 4 and 5). This typical shape appears when, under the drying action, the solid forms a crust around each droplet, raising vapor pressure inside. Collapsed particles are
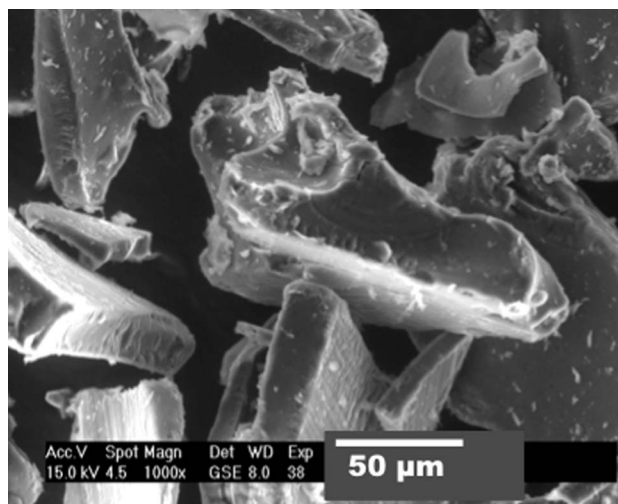

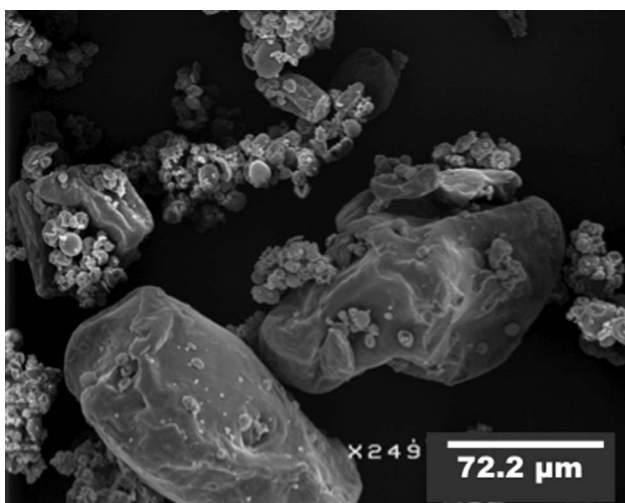**Figure 3.** Scanning electron microscope picture of amorphous HASCA particles.

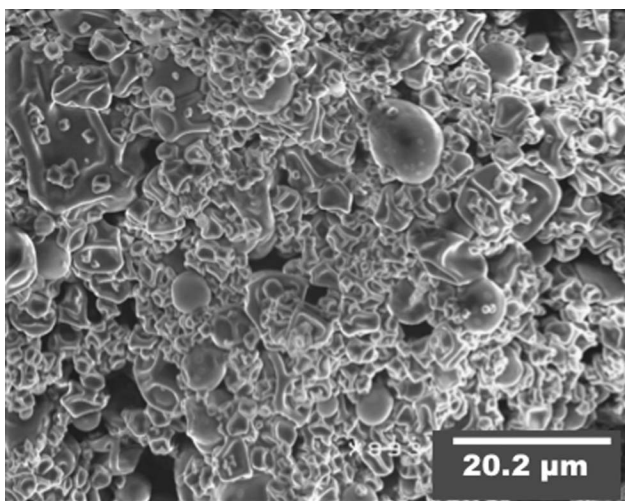**Figure 4.** Scanning electron microscope picture of SD-A HASCA particles.

Figure 5. Scanning electron microscope picture of SD-D HASCA particles.

created when the vapor is released[37]. SD-A (Figure 4) contains large, smooth, and polyhedral particles with small, more or less collapsed spherical particles often agglomerated on them. On the other hand, SD-D is composed of small collapsed spherical particles together forming larger agglomerates (Figure 5). The main preparation difference between these two samples is, on the one hand, the higher % (w/w) HASCA-I for SD-A, and, on the other hand, the lower % (w/w) water-I for SD-A compared to SD-D (Table 1). Both factors do not favor HASCA's complete dissolution for SD-A compared to SD-D. In fact, the water/ethanol (p/p) ratio is approximately equal to 1.9 for SD-A and 2.9 for SD-D. This could explain the presence of these large

particles in SD-A, most probably corresponding to the initial amorphous particles that are only partially dissolved. Thus, in the case of SD-D, a major part of the initial starch product is dissolved before being spray-dried, and the general appearance will be more typical of a spray-dried product. On the one hand, increasing water concentration helps to dissolve HASCA, which is a necessary condition for the formation of a pseudo-V-amylose complex, because amylose chains have to be free for that purpose. On the other hand, the SD process being developed to decrease ethanol concentration will not lead to amounts of pseudo-V-amylose detectable by XRD, even if large amounts of amylose are dissolved previously (Figure 2).

Apparent particle density

The apparent particle density values of samples SD-A and SD-D are enumerated in Table 3. Apparent particle density results may be interpreted in light of the information garnered by SEM. SD-D had a lower apparent particle density than SD-A. Indeed, SD-D was composed of small, more or less collapsed spherical particles resulting from the SD of HASCA, which had almost been fully dissolved (Figure 5). It has been mentioned earlier that, under the drying action, the solid in the solution formed a crust around each droplet, raising vapor pressure inside. Eventually, collapsed particles were formed when the vapor was released. Such structures were obviously less dense than plain particles. Indeed, SD-A contained large, smooth, and polyhedral particles with small, more or less collapsed spherical particles often agglomerated on them (Figure 4). These large particles appeared as plain particles and likely did not present porous structures, which resulted in increased global apparent particle density. Also, SD-A had a lower apparent particle density than amorphous particles. Again, this could have been related to the bulk aspect of small particles. Because of surface coagulation and vapor release, SD-A small particles may have become closed structures with internal porosity unlike that of amorphous particles. In fact, amorphous HASCA had a much higher apparent particle density than all spray-dried samples, which confirms our interpretation of the apparent particle density values based on the open or closed porosity of HASCA particles.

Table 3. Apparent particle density values of typical HASCA samples.

HASCA type	Apparent particle density (g/cm^3)
SD-A	1.26 ± 0.03
SD-D	1.04 ± 0.10
Amorphous starting material	1.48 ± 0.01

Surface area

The specific surface area value of a typical SD sample, that is, SD-D, has been obtained to gain supplementary information on the type of product obtained by SD ($S = 2.28$ m^2/g).

Tablet crushing force

It was not possible to obtain tablets with the initial amorphous pregelatinized HASCA pilot batch, even at very high compression forces (up to 490 MPa). Table 4 gives the crushing force values of compacts generated by SD HASCA. Clearly, the SD process produces tablets whose mechanical properties vary from adequate to excellent.

Some general trends can be underlined concerning the concentration of the different compounds in the initial hydro-alcoholic suspension and the SD suspension. Figures 6–8 depict the influence of various parameters of the initial hydro-alcoholic and SD suspensions on tablet crushing force. Figure 6 charts the influence of % (w/w) HASCA-I of the initial hydro-alcoholic HASCA suspensions on HASCA tablet crushing force for differ-

Table 4. Tablet crushing force determined for 200 mg tablets (Ø = 12.6 mm, F = 245 MPa) of pure SD HASCA.

SD HASCA type	Mean ± SD (N)
SD-A	60 ± 3
SD-B	107 ± 3
SD-C	142 ± 1
SD-D	143 ± 9
SD-E	170 ± 8
SD-F	182 ± 1
SD-G	186 ± 1

ent water concentrations. A quasi-linear relationship was observed between tablet crushing force and % (w/w) HASCA-I of the initial hydro-alcoholic solution for the 11–17% (w/w) range. Interestingly, lower water concentrations of the starting hydro-alcoholic solution followed the same trend in parallel but gave higher tablet crushing force values. We can assume that decreasing powder weight while keeping the same water concentration allowed better dissolution of the initial HASCA dispersion. Considering that the initial HASCA particles did not show any binding properties, we may emit the hypothesis that the newly formed small particles are responsible for the increased crushing force. Indeed, we can suppose that augmenting the number of smaller particles enlarged the surface area of the particulate product and, consequently, provided a higher number of binding points. The progressive disappearance of the large HASCA particles, because of their progressive dissolution induced by the rising water/HASCA ratio, thus elicited increased crushing force. Figure 7 profiles the influence of HASCA concentration in the SD dispersion [% (w/w) HASCA-II] on tablet crushing force. The final ethanol addition, which allowed apparent viscosity reduction of the suspension before SD, did not really change the earlier observations. Surprisingly, the relationship appeared to be sigmoid when values obtained for the different water concentrations were pooled, and a maximum crushing force value was obtained near 9.5% (p/p) with less HASCA. Figure 8 enunciates the influence of % (w/w) WATER of the starting hydro-alcoholic solution on tablet crushing force for different weights of HASCA powder dispersed in 80 g of the hydro-alcoholic solution. Clearly, increasing water concentration in the starting hydro-alcoholic solution for the same powder quantity enhanced tablet crushing force until a certain limit was reached.
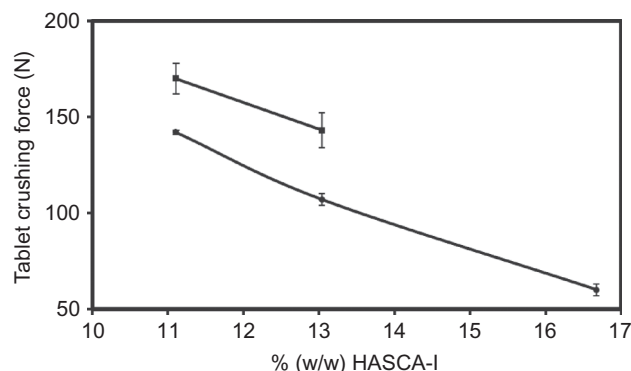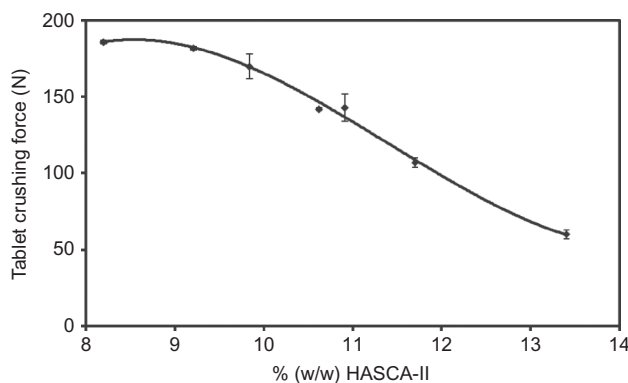

Figure 6. Influence of % (w/w) HASCA-I of initial hydro-alcoholic HASCA suspensions on HASCA tablet crushing force for different water concentrations of the starting hydro-alcoholic solution (●: 65.22%, w/w, WATER; ■: 74.47%, w/w, WATER).

Figure 7. Influence of HASCA concentration in spray-drying solution (%, w/w, HASCA-II) on HASCA tablet crushing force.
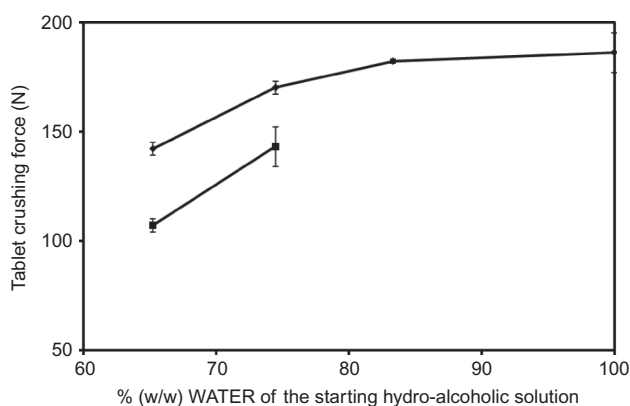
Figure 8. Influence of % (w/w) WATER of the starting hydro-alcoholic solution on HASCA tablet crushing force for different weights of HASCA powder dispersed in 80 g of hydro-alcoholic solution (■: 12 g HASCA; ♦: 10 g HASCA).
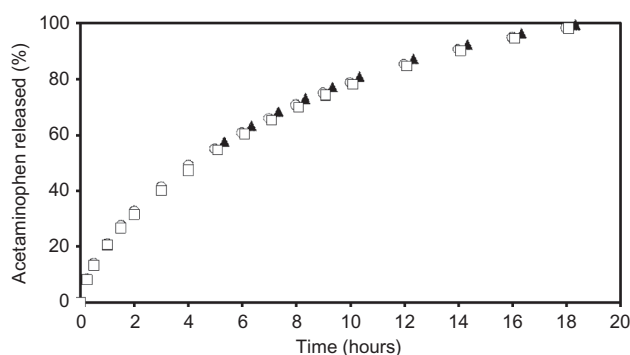

Figure 9. Cumulative percentage of acetaminophen released in vitro from optimized HASCA matrices (32.5% of HASCA, 40% of acetaminophen, and 27.5% of NaCl) in standard pH gradient conditions (▲: SD-A; ○: SD-D; □: SD-F).

Further, an aqueous HASCA solution was prepared under the same conditions as for SD-G, but no ethanol was added before SD. Not only was this solution difficult to manipulate because of its high viscosity, but also it was impossible to end the experiment with a laboratory-scale spray dryer. The high viscosity of this solution seemed to attract too many problems, confirming the necessity of the hydro-alcoholic solution in the case of industrial manufacturing.

Thus, the two key parameters for HASCA excellent binding properties are powder and water concentrations during the first manufacturing step, that is, heating of the initial hydro-alcoholic suspension. A compromise must be reached between targeting very high tablet crushing force through a high water concentration and limiting viscosity through higher alcohol concentration. In the second stage, the addition of ethanol is more concerned with decreasing viscosity to easily process the suspension through the spray dryer than having an effect on material properties.

Finally, binding properties do not appear to be linked to the presence of a Vh form of amylose, as the most crystalline samples are the ones giving the weakest tablets (Figure 2 and Table 4). On the other hand, tablet crushing force rose with water concentration, although these conditions did not lead to the appearance of a Vh form of amylose. It can be hypothesized that increasing tablet crushing force was obtained by first decreasing the particle size of amorphous pregelatinized HASCA through SD. Second, the combination of water and ethanol may have had a plasticizer effect, helping partial melting of the excipient and particle re-arrangement under compression. The peculiar melting process was demonstrated earlier by SEM and porosimetry in the case of SA,G-2.7, although no explanation was provided[5,10].

Drug-release evaluation

Typical drug-release profiles from matrix tablets made of spray-dried HASCA are shown in Figure 9. SD-A, SD-D, and SD-F were chosen because they present different crystalline levels and different binding properties. Acetaminophen release was found to be similar for the three samples. The time for 95% drug release was equal to 16:30 hours, and it could be said that SD HASCA matrix systems exhibited sustained drug-release properties. Thus, combined with the heating of HASCA hydro-alcoholic suspensions, the SD process was able to restore binding and sustained drug-release properties. Further, it appears that, within the limits of this protocol, variations in hydro-alcoholic composition only affected tableting properties and did not influence the drug-release rate. The presence of the Vh form of HASCA appears to be unnecessary to obtain sustained drug release (Figures 2 and 9), but also its concentration does not influence the drug-release process, provided it remains as a minor component in the amorphous matrix. This is certainly an advantage as it makes the method robust and allows us to focus on the experimental conditions of heating HASCA hydro-alcoholic suspensions to optimize tablet strength in the design of an industrial manufacturing process.

Conclusion

Pregelatinized amorphous HASCA produced on a pilot scale appeared to be unsuitable for tableting and sustained drug release. The main drawback of the laboratory process, precipitation by a nonsolvent, was that very high volumes of ethanol were used to recover the product with yields going to 1 part of solid recovered

for up to 30 parts and more of ethanol. An original process was designed to transform totally amorphous pregelatinized HASCA by SD into a suitable sustained drug-release excipient for matrix tablets while decreasing ethanol quantities and to prepare the scale up for easier and economical industrial production of HASCA. This process involves a final EtOH/HASCA ratio of 3.2, which is an advantage for economical, environmental, and safety reasons. The two key parameters for obtaining excellent SD HASCA-binding properties are powder and water concentrations during the first manufacturing step, that is, heating of the initial hydro-alcoholic suspension. A compromise must be reached between targeting very high tablet crushing force through high water concentration and limiting viscosity through higher alcohol concentration. In the second stage, the addition of ethanol before SD is more concerned with decreasing viscosity to easily process the suspension through the spray dryer than having an effect on material properties. Binding properties do not appear to be linked to the presence of a Vh form of amylose, as the most crystalline samples are the ones giving the weakest tablets. On the other hand, high water concentration leads to high tablet crushing force, that is, inverse conditions evoking the appearance of a Vh form of amylose. We hypothesize that increasing tablet crushing force is possible by first decreasing the particle size of amorphous HASCA through SD. Second, the combination of water and ethanol may have a plasticizer effect, helping partial melting of the excipient and particle re-arrangement under compression. Finally, it appears that variations in hydro-alcoholic composition affect only tableting properties and do not influence the drug-release rate. The presence of the Vh form of HASCA appears to be unnecessary to obtain sustained drug release, but also its concentration does not influence the drug-release process, provided it remains as a minor component in the amorphous matrix. This is certainly an advantage, making the method robust and focusing on the experimental conditions of heating HASCA hydro-alcoholic suspensions, to optimize tablet strength in the design of an industrial manufacturing process.

Declaration of interest

The authors are inventors of PCT patent application related to this work (PCT/CA2008/001089).

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