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High-amylose sodium carboxymethyl starch matrices for oral, sustained drug-release: Formulation aspects and *in vitro* drug-release evaluation

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Abstract

High-amylose sodium carboxymethyl starch (HASCA), produced by spray-drying (SD), was previously shown to have interesting properties as a promising pharmaceutical sustained drug-release tablet excipient for direct compression, including ease of manufacture and high crushing strength.

This study describes the effects of some important formulation parameters, such as compression force (CF), tablet weight (TW), drug-loading and electrolyte particle size, on acetaminophen-release performances from sustained drug-release matrix tablets based on HASCA. An interesting linear relationship between TW and release time was observed for a typical formulation of the system consisting of 40% (w/w) acetaminophen as model drug and 27.5% NaCl as model electrolyte dry-mixed with HASCA. Application of the Peppas and Sahlin model gave a better understanding of the mechanisms involved in drug-release from the HASCA matrix system, which is mainly controlled by surface gel layer formation. Indeed, augmenting TW increased the contribution of the diffusion mechanism. CFs ranging from 1 to 2.5 tonnes/cm^2 had no significant influence on the release properties of tablets weighing 400 or 600 mg. NaCl particle size did not affect the acetaminophen-release profile.

Finally, these results prove that the new SD process developed for HASCA manufacture is suitable for obtaining similar-quality HASCA in terms of release and compression performances.

Keywords: Drug delivery; Sustained release; Excipient; Polymer; Tablet; Matrix; Starch; Amylose; *In vitro*

1. Introduction

The widespread success of hydrophilic polymers in matrix tablets as systems for oral, controlled drug-release can be attributed to their ease of manufacture, relatively low cost, biocompatibility, favourable *in vivo* performance and versatility in controlling the release of drugs with a wide range of physicochemical properties.

Starch is composed of amylose and amylopectin, essentially a linear polymer of glucopyranose units and a branched polymer (Bilariedis, 1991). It is possible to chemically modify their hydroxyl groups by an etherification process resulting in substituted amylose (SA) (Cartilier et al., 1999). These polymers are referred to as SA,R-*n*, where R defines the substituent, typically 1,2-epoxypropanol (or glycidol = G), and *n* represents the degree of substitution (DS) expressed as the ratio mole of substituent/kg of amylose. High-amylose cornstarch, which contains 70% of amylose chains and 30% of amylopectin, has been instrumental in producing SA polymers.

Tablets have been prepared by direct compression, i.e. dry-mixing of drug and SA,G-*n*, followed by compression, which is the easiest way to manufacture an oral dosage form. SA,G-2.7 polymeric matrices allowed nearly constant *in vitro* drug-release (Cartilier et al., 1999; Chebli et al., 1999; Chebli and Cartilier, 2000). Compression forces (CFs) ranging from 0.5 to 5.0 tonnes/cm^2 had no significant effect on the release properties

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of SA,G-*n* polymers with a DS greater than 1.5. Release time was directly proportional to tablet weight (TW) for tablets containing 10% of acetaminophen. Sustained drug-release matrix systems based on SA,G technology have large ranges of use for drug-loading, drug-solubility and TW (Cartilier et al., 1999; Chebli and Cartilier, 2000). Another striking feature of this drug delivery system is that the high crushing strength values of these tablets (Cartilier et al., 1999) are due to an unusual sintering process occurring during tableting, with only the tablet's external layer going through densification, deformation and partial melting (Moghadam et al., 2007).

High-amylose sodium carboxymethyl starch (HASCA), obtained at a lab-scale, has been proposed recently as suitable material for oral matrix tablets (Cartilier et al., 2005; Ungur et al., 2005). These tablets can be improved by the addition of electrolytes as the polymer is ionic. Such addition permits the integrity of 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 remarkable, close-to-linear release profile (Cartilier et al., 2005). Adding the right amount of electrolytes maintains equilibrium between (a) the hydrogen bonds created through –COOH and –OH associations, which enhance gel strength and maintain matrix structure, and (b) swelling of the polymer chains, increased by their repulsion of $–COO^-$ groups, which gives the matrix its necessary elasticity. Other factors also need to be considered: the effect of porosity after dissolution of the drug and electrolyte on gel structure; the effect of NaCl on gel viscosity and, therefore, on drug diffusion; the effect of creating an intramatrix buffer system on gel structure and all other factors affecting it, such as the nature and concentration of the drug, electrolytes and other excipients as well as pH conditions of the external medium (Domingues Nabais et al., 2007). Further, the combined presence of NaCl and polymer carboxylic groups creates a buffered matrix, which renders the matrix insensitive to pH changes of the surrounding medium (Domingues Nabais et al., 2007).

Because of industrial constraints, HASCA was prepared on a pilot-scale in totally amorphous form, but appeared to be unsuitable for tableting and sustained drug-release. An original process was designed to transform it by spray-drying (SD) HASCA into a suitable sustained drug-release excipient for matrix tablets while decreasing ethanol quantities and to prepare a scale-up for easier and economical industrial HASCA production. This process set a final ethanol/HASCA ratio w/w of 3.2, which is an advantage for economical, environmental and safety reasons (Brouillet et al., 2007).

The effects of formulation parameters on drug-release from HASCA-based matrix systems were investigated to further assess the utility of spray-dried HASCA as a directly compressible excipient for controlled drug-release. The present paper describes the impacts of CF, TW, drug-loading and electrolyte particle size on drug-release profiles, providing a better understanding of the mechanistic aspects of controlled drug-release from HASCA-based matrix systems.

2. Materials and methods

2.1. Materials

Spray-dried HASCA, prepared from amorphous HASCA supplied by Roquette Frères (Lestrem, France), was obtained from Amylose Project Inc. (Beaconsfield, Quebec, Canada). The DS was equal to 0.045 (number of moles of substituent/number of moles of anhydroglucose). Only spray-dried HASCA was tested in the present study. Anhydrous ethyl alcohol was purchased from Commercial Alcohol Inc. (Brampton, Ontario, Canada). Acetaminophen was procured from Laboratoires Denis Giroux Inc. (Ste-Hyacinthe, Quebec, Canada), and sodium chloride (NaCl) (crystals, lab grade) was from Anachemia Ltd. (Montreal, Quebec, Canada). All chemicals were of reagent grade and were used without further purification.

2.2. HASCA-manufacturing process

First, 10 g of amorphous HASCA were dispersed under stirring in 80 g of a hydro-alcoholic solution (16.66%, w/w ethanol) at 70 °C. The solution was kept at this temperature for 1 h under stirring. It was then cooled to 35 °C under stirring. A volume of 23.5 ml of pure ethanol was added "slowly and gradually" to the solution. Note that the final alcohol to starch ratio w/w was 3.2 (or 4 ml/g). The final solution was passed through a Büchi B-290 Mini Spray-Dryer at 140 °C to obtain HASCA in dry powder form (Brouillet et al., 2007). Spray-dryer airflow was 601 NormLitre/hour and liquid flow was 0.32 l/h. The DS of HASCA was 0.045 (number of moles of substituent/number of moles of anhydroglucose).

2.3. Tablet preparation

Tablets with a diameter of 1.26 cm were prepared by direct compression, i.e. manual dry-mixing of acetaminophen, HASCA, and sodium chloride (NaCl) in a mortar, followed by compression in a 30-tonnes manual pneumatic press (C-30 Research & Industrial Instruments Company, London, U.K.). Despite poor powder flow properties, no lubricant was added to the formulation because it was unnecessary, considering the peculiar tableting process involved here. Furthermore, 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 (Cartilier et al., 2005). Tablets containing 40% of acetaminophen as model drug, 27.5% of NaCl and 32.5% of HASCA were prepared to study the effects of CF on the dissolution rate. They weighed 400 or 600 mg each and were subjected to various CFs: 1, 1.5 and 2.5 tonnes/cm^2 for 30 s. Tablets containing 40% of acetaminophen, 27.5% of NaCl and 32.5% of HASCA were also produced to investigate the influence of TW on the dissolution rate. They weighed 300, 400 or 600 mg and were all compressed at 2.5 tonnes/cm^2 for 30 s. Finally, 600-mg HASCA tablets containing 40% of drug and 27.5% of NaCl were prepared in the same conditions to examine the impact of NaCl particle size on the drug-dissolution rate.

2.4. Tablet hardness testing

Tablet hardness was quantified in a PHARMATEST type PTB301 hardness tester. These tests were performed on 200-mg HASCA tablets obtained under a CF of 2.5 tonnes/cm^2. Typical tablets containing acetaminophen and NaCl were also analysed. The results are expressed in Strong-Cobs (SC).

2.5. Drug-release evaluation

The drug-release properties of some typical HASCA matrix tablets were assessed by an *in vitro* dissolution test. Since HASCA is an ionic polymer used for oral, sustained drug-release, *in vitro* release experiments were conducted in a pH gradient simulating pH evolution in the gastrointestinal tract, taking into account the pH-dependency of the drug-release mechanism. The tablets were individually placed in 900 ml of a hydrochloric acid medium (pH 1.2) simulating gastric pH, at 37 °C, in U.S.P. 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, then 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. pH gradient conditions were: pH 1.2 for 1 h, pH 6.8 for 3 h, and pH 7.4 until the end of the dissolution test. To prevent the tablets from sticking to the glassware, a small, curved grid was placed at the bottom of the recipient so that drug-release could occur from all sides of the matrix. 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 % in function of time (h). Drug-release profile reproducibility was excellent as the standard-deviation values observed for the % of drug released versus time were generally lower than 1%, ranging from 0.2 to 2.4%. Standard-deviation bars were omitted in the figures for clarity.

2.6. Evaluation of swollen tablet integrity

It has been reported previously that HASCA matrix tablets crack and separate into two parts loosely attached at their centre, or even split into several parts when swollen in aqueous solution, particularly when going through a pH gradient. The addition of an electrolyte provided complete stabilization of the swollen matrix structure or at least significantly delayed the appearance of the above-mentioned problems and/or decreased their intensity (Cartilier et al., 2005). Thus, a standardized method was designed to describe the modifications occurring during tablet immersion in aqueous solutions.

Matrix tablets, similar to the ones tested for drug-release, were placed individually in 900 ml of a hydrochloric acid solution (pH 1.2), at 37 °C, in the U.S.P. XXIII Dissolution Apparatus No. 2 with rotating paddle (50 rpm). After remaining in the acidic solution for 1 h, the tablets were transferred for 3 h to a phosphate-buffered solution (pH 6.8), at 37 °C, in the same U.S.P. XXIII Dissolution Apparatus No. 2 equipped with rotating paddle, then to a phosphate-buffered solution (pH 7.4) under similar conditions until the end of the test. To prevent the tablets from sticking to the glassware, a small, curved grid was placed at the bottom of the recipient so that drug-release could occur from all sides of the matrix. All formulations were tested in triplicate.

The observation of macroscopic transformations was standardized in a table with specific qualitative terms describing them and recording the moment at which they appear (h). A sequence of two events was noted. Crack(s) in the tablets were often followed by more drastic modification of matrix structure, bursting being partial or total. The following terms have been employed: C1 = crack type 1; nC1 = multiple cracks type 1; C2 = cracks type 2. C1 represents a single crack appearing along the radial surface of the cylinder. nC1 denotes multiple cracks appearing along the radial surface of the tablet. C2 means that one or more cracks appear on one or both facial surfaces of the tablet. The erosion process is not linked to the appearance of cracks. This allows the consideration of a rather semi-quantitative approach, keeping in mind that the more the tablets fully split apart, the higher are the risks of undesired burst release *in vivo*.

3. Results and discussion

3.1. Tablet hardness control

The goal of tablet hardness testing was more tablet quality control than the performance of a fundamental study on the mechanical characteristics of the polymer. A mean hardness value of 27.0 ± 1.5 SC (equivalent to 189N) was determined from 10 pure 200-mg HASCA tablets. For a formulation containing 40% acetaminophen, 27.5% NaCl and 32.5% HASCA, the hardness value for 400-mg tablets was 16.9 SC, and for 600-mg tablets, it was 39.7 SC. Considering that HASCA represents only 32.5% of the total powder and that NaCl is known to have poor compaction properties, these results prove the potential of HASCA for industrial tableting applications. Another advantage of such good compaction properties is that no binder is required, which simplifies formulation optimization.

The relationship between TW and CF versus tablet thickness (TT) was investigated to understand the good binding properties of HASCA. During tablet preparation, diameter remained the same for each TW, and thus, the only geometric variable, which had to be considered here was TT. These results are presented in Table 1 and Fig. 1, which reveal a perfect linear relationship between TW and TT. The slope remains almost identical, even for the lowest CF, i.e. 1 tonnes/cm^2. Thus, densification was the same for all CFs, meaning that particle re-arrangement was optimal and that some peculiar phenomenon took place, even at low CFs, leading to an intense densification process. This phenomenon was already reported in the case of SA,G-2.7, where a sintering by total or partial melting process was seen, which also confirmed the excellent binding properties recorded previously for SA,G-*n* tablets (Cartilier et al., 1999; Moghadam et al., 2007). On the other hand, Table 1 indicates that, practically, CF does not influence TT. A very slight effect of CF on TT was

Table 1
Influence of compression force (CF) on tablet thickness (TT)

Formulation (% w/w)			TW (mg)	CF (tonnes/cm^2)	TT (mm)
Drug	HASCA	NaCl			
40	32.5	27.5	600	2.5	3.12[a]
40	32.5	27.5	600	1.5	3.23 ± 0.03
40	32.5	27.5	600	1.0	3.36 ± 0.01
40	32.5	27.5	400	2.5	2.09[a]
40	32.5	27.5	400	1.5	2.18 ± 0.01
40	32.5	27.5	400	1.0	2.16 ± 0.02
40	32.5	27.5	300	2.5	1.57 ± 0.01

TW, tablet weight.
[a] Tests performed on two samples only.

apparent only in the case of 600-mg tablets, i.e. a 7% decrease in TT corresponded to a CF increase from 1 to 2.5 tonnes. Note that the tablets did not contain any lubricant. In these conditions, CF was probably not sufficient to allow maximal densification. Indeed, it has already been observed that the addition of a lubricant to SA,G-2.7 fully removes the slight influence of CF on TT, even for larger TWs (Wang, 2006).

3.2. Effect of TW on acetaminophen-release from HASCA tablet matrices

The influence of TW on the drug-release profile from HASCA matrices is depicted in Fig. 2. Total drug-release time increased as TW rose. Once-a-day, sustained drug-release dosage forms were easily obtained with HASCA technology. Fig. 3 reports the drug-release rate in function of release time for the same matrix tablets. The drug profile can be divided into two stages. First, a burst effect occurs corresponding to the drug being rapidly dissolved and released from the tablet surface before the gel membrane is fully formed at the surface. Second, the release rate decreases continuously until the end of the process. This is particularly obvious in Fig. 3. The phenomenon, which could be explained by an increase in the drug molecule diffusion pathway, is typical of a diffusion-controlled mechanism.

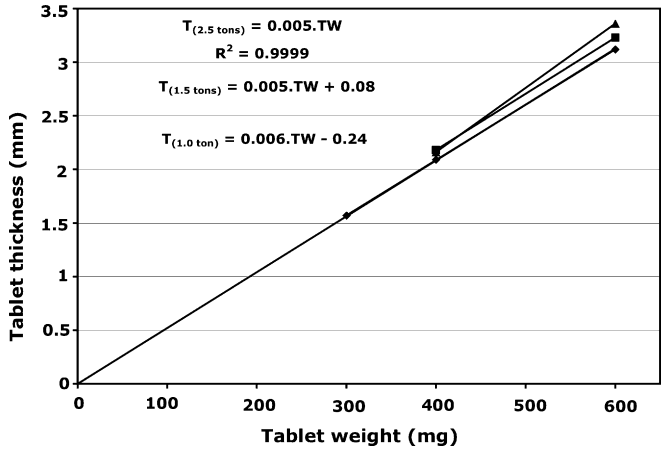

Fig. 1. Influence of tablet weight (TW) on tablet thickness (TT) of HASCA matrix tablets containing 40% acetaminophen and 27.5% NaCl under different CFs (▲: 1 tonnes/cm^2, ■: 1.5 tonnes/cm^2, ♦: 2.5 tonnes/cm^2).

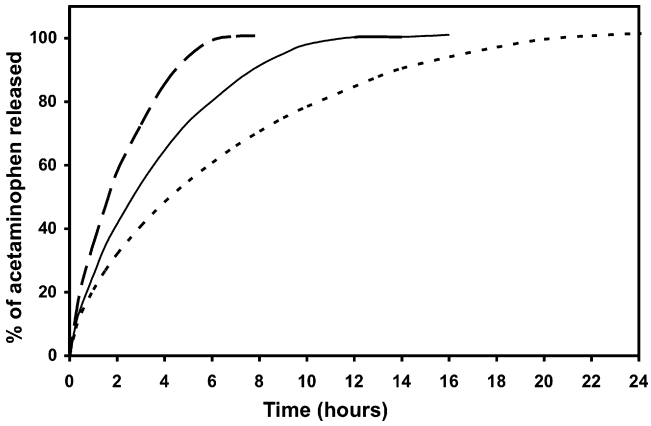

Fig. 2. Effect of TW on % acetaminophen release from 300-mg (dashed line), 400-mg (continuous line) and 600-mg (dotted line) HASCA matrix tablets containing 40% acetaminophen and 27.5% NaCl.

After gel formation, drug-release is controlled by drug diffusion across the gel layer after its dissolution. Fig. 4 reports M_t/M_∞ in function of the square root of time where M_t and M_∞ are the amounts of drug released at time t and the overall amount released, respectively. Hydrophilic matrices manifest a linear relationship between M_t/M_∞ and the square root of time when the transport phenomenon is governed only by Fickian diffusion, i.e. when drug-release is purely controlled by drug diffusion through the gel layer. No linear relationship was evident, and, thus, release from HASCA matrices was not controlled solely by Fickian diffusion, but also by a more complex mechanism.

To understand the drug-release results, they can be expressed according to the equation proposed by Peppas (1985):

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

where M_t is the amount of drug released at time t, M_∞ is the total amount of drug released, k is a kinetic constant, and n is the diffusional exponent for drug-release. Practically, one has to use the first 60% of a release curve to determine the slope obtained from Eq. (1) regardless of the geometric shape of the delivery device. Two competing release mechanisms, Fickian

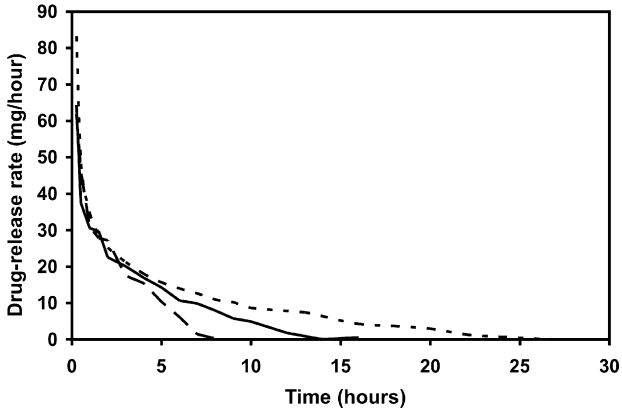

Fig. 3. Influence of TW on the acetaminophen-release rate from 300-mg (dashed line), 400-mg (continuous line) and 600-mg (dotted line) HASCA matrix tablets containing 40% acetaminophen and 27.5% NaCl.

Table 2
Determination of the ratio of relaxational over Fickian kinetic constants (k_2/k_1) for acetaminophen-release from 600-, 400- and 300-mg HASCA tablets

Formulation (% w/w)			TW (mg)	TT (mm)	Aspect ratio (2a/l)	m	k_2/k_1
Drug	HASCA	NaCl					
40	32.5	27.5	600	3.12	4.04	0.450	0.32
40	32.5	27.5	400	2.09	6.03	0.466	0.74
40	32.5	27.5	300	1.57	8.02	0.472	1.04

TW, tablet weight; TT, tablet thickness.

diffusional release and Case-II relaxational release, are the limits of this phenomenon (Sinclair and Peppas, 1984). Fickian diffusional release occurs by molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water.

The two phenomena controlling release are considered to be additive. Therefore, one may write (Peppas and Sahlin, 1989):

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \tag{2}$$

where the first term is the Fickian contribution and the second term is the Case-II relaxational contribution. Eq. (2) can be rewritten as:

$$\frac{M_t}{M_\infty} = k_1 t^m \left[1 + \left(\frac{k_2}{k_1}\right) t^m\right] \tag{3}$$

By comparing Eqs. (1) and (3), it is concluded that $m = n$ when the relaxational mechanism is negligible. The percentage of drug-release due to the Fickian mechanism, F, is clearly calculated as:

$$F = \left[1 + \left(\frac{k_2}{k_1}\right) t^m\right]^{-1} \tag{4}$$

which leads to the ratio of relaxational over Fickian contributions as:

$$\frac{R}{F} = \left(\frac{k_2}{k_1}\right) t^m \tag{5}$$

Consequently, k_1 and k_2 were calculated from Fig. 5, and the k_2/k_1 ratio served to analyze the release behaviour of acetaminophen from 300-, 400- and 600-mg HASCA matrices (Table 2). Increasing TW decreases the k_2/k_1 ratio value. In other words, augmenting TW heightens the contribution of the diffusion mechanism. In fact, at low TWs, the tablets are very thin, and the matrix is totally hydrated quickly and gelified. In that case, drug-release is principally controlled by simple relaxation of the polymer chains. With an increase in TW, drug diffusion through the gel layer becomes the predominant transport phenomenon after the initial burst effect. However, the controlled release mechanism is neither pure diffusion nor pure polymer relaxation, but rather a combination of both. Chebli et al. reported similar results and conclusions in the case of acetaminophen-transport from non-ionic SA matrices (Chebli et al., 1999; Chebli and Cartilier, 2000). Furthermore, it has been shown that the water uptake of SA,G-2.7 tablets is very different from that of HPMC (hydroxypropyl methylcellulose) tablets (Moghadam et al., 2007). First, SA,G-2.7 tablets absorb much less water, but their % water uptake depends heavily on TW, unlike HPMC tablets. The retrogradation process specifically shown by amylose chains, i.e. their association in water to form a tight gel network explains this. Indeed, the external polymer layer must go through the steps of water penetration, polymer relaxation and amylose chain retrogradation before the external gel layer is able to control water and drug diffusion. That process takes some time to be completed. Thus, TT will affect the respective contributions of relaxation and diffusion because, before the diffusion control mechanism starts to be effective,

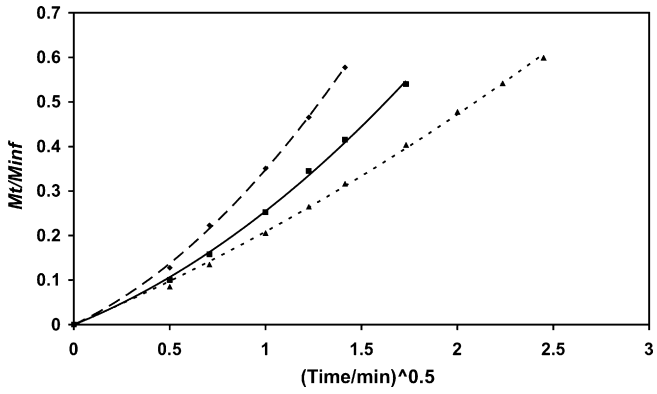

Fig. 4. Presentation of 60% acetaminophen release versus square root of time from 300-mg (♦), 400-mg (■) and 600-mg (▲) HASCA tablets containing 40% acetaminophen and 27.5% NaCl.

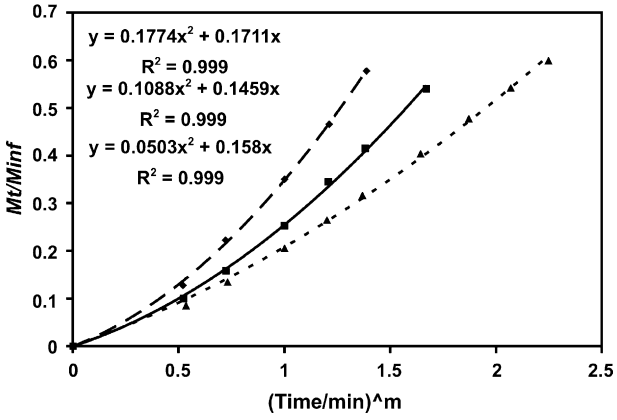

Fig. 5. Presentation of 60% acetaminophen release versus $(\text{time})^m$ from 300-mg (♦), 400-mg (■) and 600-mg (▲) HASCA tablets containing 40% acetaminophen and 27.5% NaCl.

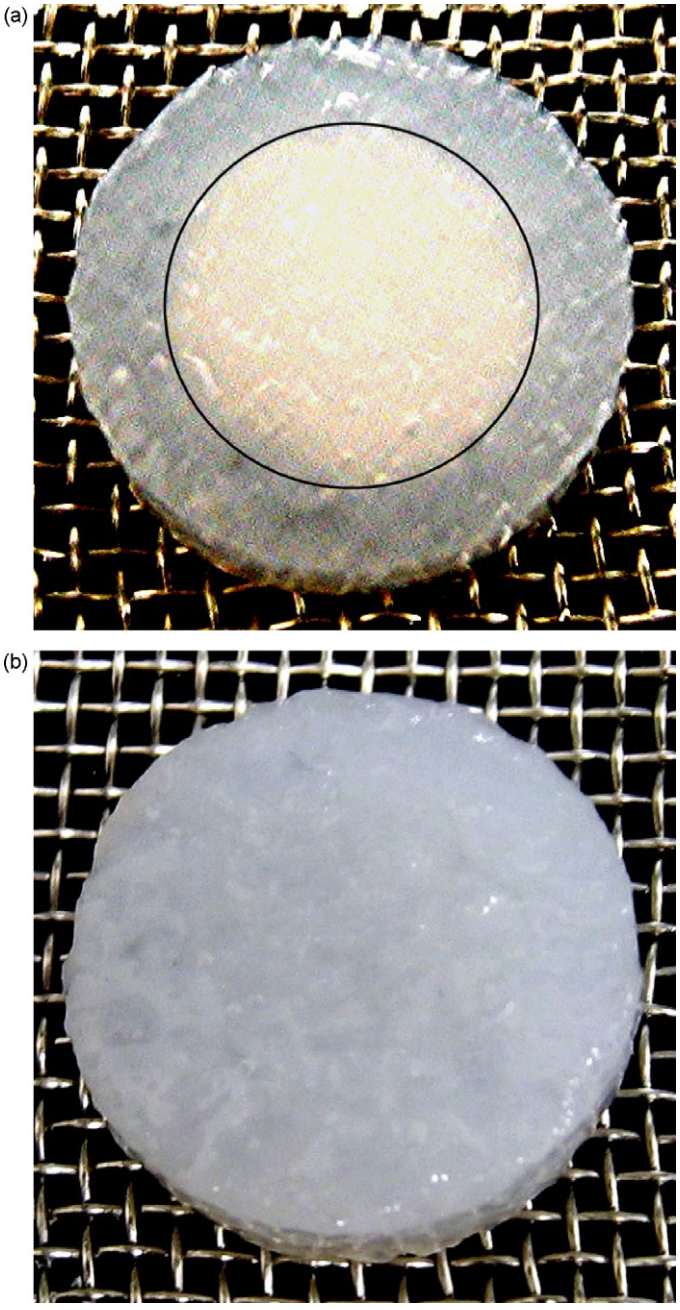

Fig. 6. Pictures of typical 600-mg HASCA tablet matrices (40% acetaminophen, 27.5% NaCl, 32.5% HASCA) after immersion in a pH gradient simulating the pH evolution of the gastrointestinal tract (pH 1.2 for 1 h, pH 6.8 for 3 h, and pH 7.4 until the end of the dissolution test): (a) 16 h of immersion, and (b) 22 h of immersion.

water will diffuse in a larger percentage of the tablet in the case of a thinner tablet.

Hydrated HASCA matrices manifest rather moderate swelling and do not show erosion (Fig. 6a and b), especially when compared to other typical hydrophilic matrices. This is most probably the reason for the differences in release profiles demonstrated by HASCA tablets in comparison to other typical hydrophilic matrices.

The strong dependence of drug-release on TW is further confirmed in Fig. 7. The time for 25% of drug-release (T25%) is considerably less affected by TW variation than the time for 95% of drug-release. This T25% time value relates to the burst effect, and thus, depends on the amount of drug at the tablet surface available for immediate dissolution and release in the medium. Further, in theory, when doubling TW, one doubles tablet height and drug content, with the % drug being kept constant, but increases the total surface by only 25%; in practice, the increase in surface was around 20% in the present case (for example, the external surface of a 600-mg tablet was only 1.2 times the surface of a 300-mg tablet, 3.72 and 3.11 cm^2, respectively). However, the time for 95% of release increases 3.4 times, showing that a non-linear relationship exists between surface and release time. In contrast, it is striking that a linear relationship has been observed between TW and release time. After the burst period, a gel layer is formed around the dry core, hindering inward water penetration and outward drug diffusion. Consequently, drug-release is controlled by its diffusion through the gel layer. One may consider that the surface, thickness and structure of the gel layer are nearly the same for each TW, as the eluting medium penetrates at the same rate to a certain depth of the tablet, regardless of its size, where hydration, polymer relaxation, and molecular rearrangement occur, allowing gel-formation (Varma et al., 2004). However, the dry and/or partially hydrated core increases in function of TW. This core may be viewed as a drug reservoir. Thus, more time will be required to empty it, and it will be proportional to the concentration of the internal reservoir, and, hence, proportional to TW, which is reflected by the linear relationship exhibited by T95%, T50% and T25%.

3.3. Influence of CF on acetaminophen-release from HASCA matrices

Fig. 8 charts the effect of CF on the acetaminophen-release profile of 600- and 400-mg HASCA matrix tablets. Between 1 and 2.5 tonnes/cm^2, CF does not significantly influence drug-release from HASCA matrices. This range of CFs has been selected because it covers the normal range of compaction forces employed at the industrial level. The slight increase in the drug-release rate for 400-mg tablets at low CFs, i.e. 1 and

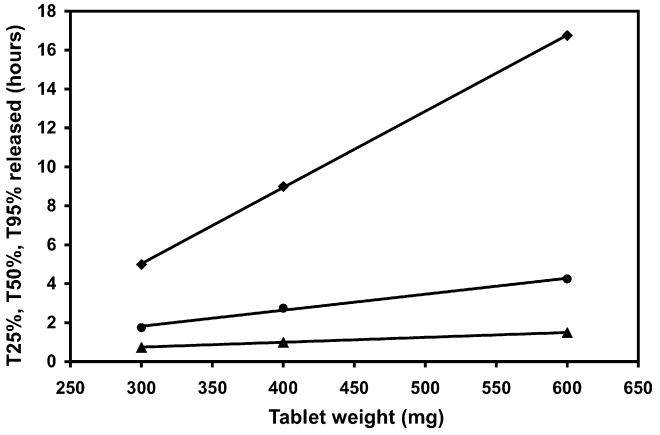

Fig. 7. Effect of TW on acetaminophen T25% (▲), T50% (●) and T95% (♦) release from HASCA tablets containing 40% acetaminophen and 27.5% NaCl.

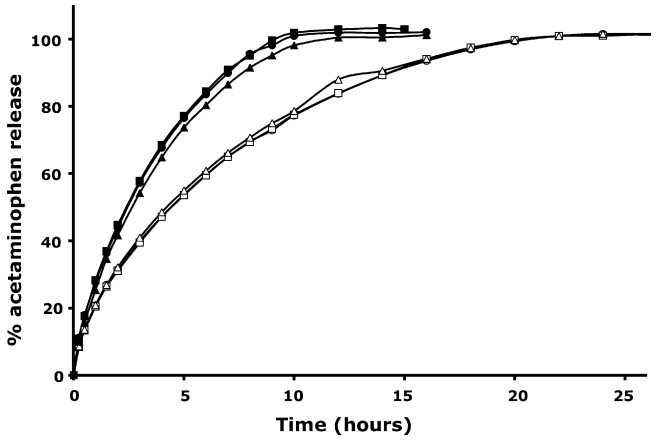

Fig. 8. Effect of compression force (CF) on acetaminophen release from HASCA tablets containing 40% acetaminophen and 27.5% NaCl (600-mg tablets, CF 1 tonnes/cm^2: (◯) 600-mg tablets, CF 1.5 tonnes/cm^2: (□) 600-mg tablets, CF 2.5 tonnes/cm^2: (△) 400-mg tablets, CF 1 tonnes/cm^2: (●) 400-mg tablets, CF 1.5 tonnes/cm^2: (■) 400-mg tablets, CF 2.5 tonnes/cm^2: (▲)).

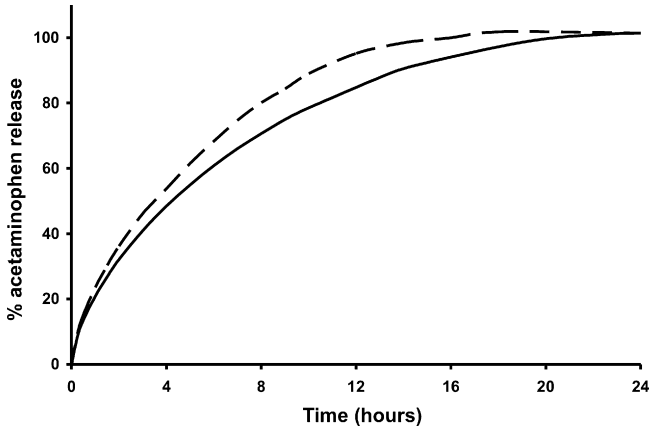

Fig. 9. Influence of drug-loading on acetaminophen release from 600-mg HASCA tablets compressed at 2.5 tonnes/cm^2 containing 10% acetaminophen (dashed line) or 40% acetaminophen (continuous line).

1.5 tonnes/cm^2, could be explained by the fact that 400-mg swollen matrices are very thin and subject to slight erosion due to tablet movement on the grid in the dissolution tester. Erosion was not apparent for 600-mg tablets.

Table 1 reports that TT decreased very slightly with increased CF, i.e. about 4% for 400-mg tablets and 8% for 600-mg tablets for CFs ranging from 1.0 to 2.5 tonnes/cm^2. Nevertheless, this moderate effect did not reflect on the drug-release rate from pilot-scale spray-dried HASCA matrices. Ungur et al. (2005) have already noted that in the case of lab-scale HASCA, CF influenced microporosity, but did not alter the drug-release rate. Moghadam et al. (2007) pointed out that in the case of SA,G-2.7 matrices, CF did not influence water uptake and the drug-release rate (except moderately for the first 60-min burst release) for CFs ranging from 1.5 to 5.0 tonnes/cm^2. However, SA,G-2.7 TT was not affected by CFs ranging from 2.5 to 5.0 tonnes/cm^2, but a very slight impact was noted for lower CFs. The peculiar mechanism of densification, i.e. sintering by viscous flow and melting under compression, has been demonstrated by scanning electron microscopy and porosimetry for these matrices. Thus, such very low porosity might also explain why CF does not impact the drug-release rate.

Thus, SA matrices have some specific features regarding the influence of CF on water and drug-transport mechanisms. Spray-dried HASCA matrices do not show any importance of CF on the amplitude of the burst effect, on the time-lag, or on the drug-release rate. On the other hand, the gelation properties and drug-release rate of some typical hydrophilic matrices, such as higher plant hydrocolloidal matrices, are drastically affected by changes in compression (Kuhrts, 1992; Ingani and Moës, 1986). Furthermore, it has been reported that in a number of cases, CF had no or very little influence on the drug-release rate from HPMC hydrophilic matrix tablets, at least beyond a certain CF level (Varma et al., 2004; Ford et al., 1987; Velasco et al., 1999), whereas in other cases, CF had an effect on this parameter (Levina, 2004) or only on the time-lag before the establishment of quasi-stationary diffusion (Salomon et al., 1979).

The independence of the drug-release profile from CF is a very interesting feature of spray-dried HASCA as it facilitates its industrial applications, and one does not need to pay attention to the usual slight variations in CF that occur during industrial manufacturing.

3.4. Effect of drug-loading on drug-release from HASCA matrices

Fig. 9 reports on the influence of drug-loading, i.e. 10 and 40% of acetaminophen, on the drug-release profile. An increase in drug-loading corresponded to an increase in total release time (17 h for 10% loading compared to 23 h for 40% loading). Usually, the opposite observation is made with hydrophilic matrices. It should be noted that despite small cracks appearing gradually on the tablet surface since the 7th hour (Table 3), no burst could be detected on the drug-release profile of tablet formulations containing 10% of acetaminophen (Fig. 9). We hypothesize that HASCA matrix tablets, after crack formation and exposure of new surfaces to the external medium, will rapidly form a tight cohesive gel able to maintain control on drug-release. In a certain way, it is as if the gel layer controlling drug-release is able to "heal", thus, protecting the internal drug reservoir, though the dosage form manufacturing process generates a matrix without

Table 3
Influence of drug-loading and NaCl content on the integrity of HASCA swollen matrix tablets

Formulation (% w/w)			Cracks		Erosion
Drug	HASCA	NaCl	Time	Type	
10	75	15	5.0/6.5	C1/C2	No
10	62.5	27.5	7.0	C2	No
10	55	35	5.0	C2	No
10	45	45	5.0/8.0	C1/C2	+
10	40	50	6.5/8.0	C2/C1	++
20	52.5	27.5	10.5	C2	No
20	45	35	6.0	C2/C1	No
40	32.5	27.5	No	No	No

any doubt. Also, if we suppose that a peculiar gel layer forms around a dry and partially gelified core, we may consider that increasing matrix drug-loading raises the drug concentration in a core of approximately the same size, and that longer time will be needed to drain this higher drug quantity out of the swollen matrix.

Table 3 shows that for an identical amount of electrolyte like NaCl, increasing non-electrolyte concentration improved the mechanical qualities of the swollen matrix. Indeed, for tablets containing 27.5% NaCl, cracks appeared after 7 h of immersion for 10% acetaminophen concentration compared to 10 h for 20% acetaminophen. Finally, they did not appear at all when acetaminophen concentration was elevated to 40% (see Fig. 6a and b). While these aspects are still under investigation, one can already say that the effects of electrolytes and non-electrolytes, drug(s) or excipient(s) need to be balanced to maintain swollen tablet integrity. Thus, the nature, solubility and respective concentrations of both types of ingredients must be taken into account when formulating HASCA matrices. We can say further that, regarding their mechanical properties, HASCA matrices perform better in general when they contain high amounts of soluble materials until, of course, a certain level where erosion occurs. We have already demonstrated the direct influence of electrolyte and drug quantity in lab-scale HASCA matrix tablets on the integrity of swollen matrices, confirming that for moderate cracks in the surface, as in our case, there is no significant effect on drug-release control (Cartilier et al., 2005).

Nevertheless, the present work confirms that spray-dried HASCA matrices have a good capacity to control drug-release for 10 and 40% of a soluble drug like acetaminophen.

3.5. Effect of NaCl particle size distribution on acetaminophen-release

NaCl, a model electrolyte, was added to the tablet formulation to maintain the integrity of HASCA swollen matrices (Cartilier et al., 2005). NaCl being an important component in the formulation of HASCA matrix tablets, it is interesting to evaluate the role of NaCl particle size in the release rate of a typical formulation. The various granulometric fractions tested in these experiments were: 600–125 μm (the usual particle size distribution used for all other experiments in the present work), 600–425 microns, and 300–250 microns. A modification in NaCl particle size did not lead to a significant difference in TT (Table 4). Second, Fig. 10 displays the absence of effect of NaCl particle size on the acetaminophen-release profile from 600-mg tablets containing 40% acetaminophen and 27.5% NaCl. When the surface of particles is increased, one often observes an increase in the dissolution rate. However, it must be remembered that NaCl is freely soluble in water and thus, dissolves quickly in it, which could explain why the dissolution surface does not influence matrix performances.

Table 4
Influence of NaCl particle size on 600-mg tablet thickness (TT)

Formulation (% w/w)			TW (mg)	NaCl granulometric fraction (μm)	TT (mm)
Drug	HASCA	NaCl			
40	32.5	27.5	600	600–125	3.12[a]
40	32.5	27.5	600	600–425	3.15 ± 0.00
40	32.5	27.5	600	300–250	3.09 ± 0.02

TW, tablet weight.
[a] Tests performed on two samples only.

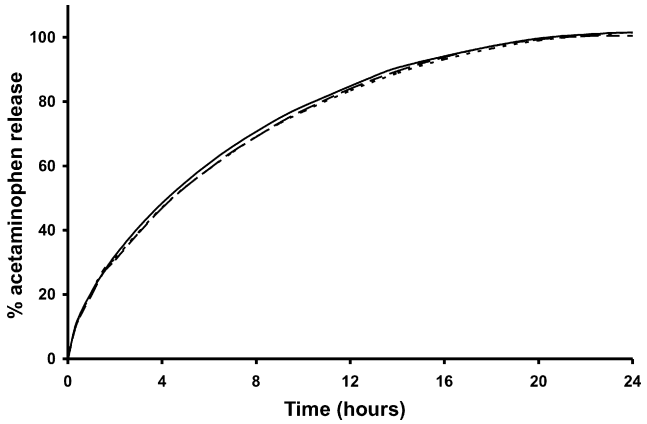

Fig. 10. Effect of NaCl particle size distribution on acetaminophen release from 600-mg HASCA tablets compressed at 2.5 tonnes/cm^2 containing 40% acetaminophen and 27.5% NaCl (300–250-μm fraction: dotted line, 600–425-μm fraction: dashed line and 600–125-μm fraction: continuous line).

4. Conclusion

The present study confirms that the drug-release rate and mechanisms from spray-dried HASCA matrices are mainly controlled by the formation of a surface gel layer, which limits diffusion of the drug through the matrix. Augmenting TW increases the contribution of the diffusion mechanism. It may be considered that the surface, thickness and structure of the gel layer are nearly the same for each TW, as the eluting medium penetrates at the same rate to a certain depth of the tablet, regardless of its size, where hydration, polymer relaxation and molecular rearrangement occur, allowing the formation of gel. However, the dry and/or partially hydrated core increases in function of TW. This core may be viewed as a drug reservoir. Thus, the time required to empty it will be proportional to the concentration of the internal reservoir, hence proportional to TW. This is reflected by the linear relationship exhibited by T95%. The absence of influence of CF on the drug-release rate shows that porosity does not play a major role in the control of drug-release. HASCA matrices generally perform better when they contain high amounts of soluble materials until, of course, a certain level where erosion occurs. Furthermore, moderate cracks in the surface, if any, have no significant influence on drug-release. NaCl particle size does not impact the acetaminophen-release profile. Finally, these results prove that the new SD process developed for HASCA manufacture is suitable for producing similar-quality HASCA in terms of release and compression performances.

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