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Research paper

High-amylose carboxymethyl starch matrices for oral sustained drug-release: *In vitro* and *in vivo* evaluation

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Abstract

High-amylose corn starch, that contains 70% of amylose chains and 30% of amylopectin, has been used to obtain substituted amylose (SA) polymers. Tablets have been prepared by direct compression, i.e. dry mixing of drug and SA, followed by compression, which is the easiest way to manufacture an oral dosage form. Until now, their controlled-release properties have been assessed only by an *in vitro* dissolution test. Amylose-based polymers are normally subject to biodegradation by α-amylase enzymes present in the gastrointestinal tract, but matrix systems show no significant degradation of tablets by α-amylase *in vitro*.

High-amylose sodium carboxymethyl starch (HASCA) is an interesting excipient for sustained drug-release in solid oral dosage forms. In addition to the easy manufacture of tablets by direct compression, the results show that *in vitro* drug-release from an optimized HASCA formulation is not affected by either acidic pH value or acidic medium residence time. In addition, a compressed blend of HASCA with an optimized quantity of sodium chloride provides a pharmaceutical sustained-release tablet with improved integrity for oral administration. *In vivo* studies demonstrate extended drug absorption, showing that the matrix tablets do not disintegrate immediately. Nevertheless, acetaminophen does not seem to be the most appropriate drug for this type of formulation.

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

1. Introduction

It is possible to chemically modify the hydroxyl groups of amylose by an etherification process, resulting in substituted amylose (SA) [1,2]. These polymers are referred to as SA,R-*n*, where R defines the substituent used, typically 1,2-epoxypropanol (or glycidol = G), and *n* represents the degree of substitution (DS) expressed as the mole ratio of substituent/kg of amylose. High-amylose corn starch, that contains 70% of amylose chains and 30% of amylopectin (Hylon VII®, Eurylon), has been employed to obtain SA polymers. SA matrix 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. Their controlled-release properties have been assessed by an *in vitro* dissolution test. Release times of 95% of the drug ranged from 9 to 20 h for all DSs studied for 400-mg matrices containing 10% of a soluble drug [2].

Drug transport analysis has revealed that diffusion, relaxation, molecular rearrangement and, in some cases, physical erosion, are simultaneously involved in the control of drug release. SA,G-2.7 matrices allow nearly constant drug-release [2–4]. Such a release profile is unusual for an hydrophilic matrix system where fickian release, i.e.

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first-order kinetics, is expected. SA hydrophilic matrix tablets sequentially present a burst effect, typical of hydrophilic matrices, and near-constant release, typical of reservoir systems. After the burst effect, the surface pores disappear progressively by the molecular association of amylose chains; this allows the creation of a polymer layer acting as a diffusion barrier and explains the peculiar behaviour of SA polymers [5].

When testing their *in vitro* resistance to α-amylase enzymatic degradation, SA,G-2.7 matrix systems and dry-coated tablets maintain their structure, and control the release of [^{186}Re], showing no significant degradation of tablets by α-amylase [6].

High-amylose sodium carboxymethyl starch (HASCA) has been recently proposed as a suitable material for oral matrix tablets [7,8]. These tablets can be advantageously improved by the addition of electrolytes. 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 remarkable close-to-linear release profile [8].

Establishing a meaningful relationship between *in vitro* drug-release and *in vivo* absorption from an extended-release dosage form is an important part of the dosage form development process, the ultimate goal of *in vitro–in vivo* correlation (IVIVC) ideally being the application of *in vitro* data as a surrogate for *in vivo* evaluation [9]. However, it must be understood that ''IVIVC is not only a drug-dependent characteristic; it is also a product-dependent characteristic'' [9]. Therefore, the Food and Drug Administration has strictly limited IVIVC conditions of use, thereby avoiding overenthusiastic applications [10].

The purpose of this study was (1) to optimize the concentration of sodium chloride in a formulation that maintains the integrity of swollen HASCA matrix tablets; (2) to evaluate the *in vitro* drug-release characteristics of an optimized sustained-release formulation containing HASCA, sodium chloride and acetaminophen, employing a pH gradient to simulate various pH conditions found in the gastrointestinal tract; (3) to demonstrate the extended-release properties of this new drug delivery system *in vivo* by comparing the pharmacokinetic parameters of a SA formulation and a commercially available, immediate-release tablet in healthy volunteers under fasting conditions; and (4) to elaborate the relationship between *in vitro* release and *in vivo* absorption, if any, for this specific sustained-release acetaminophen formulation among healthy volunteers under fasting conditions.

2. Materials and methods

2.1. Materials

HASCA, where ''HAS'' means high-amylose substituted starch and ''CA'' defines the substituent used, herein chloroacetate, was obtained from Amylose Project Inc. (Beaconsfield, Que., Canada). Acetaminophen was purchased from Laboratoires Denis Giroux inc. (Ste-Hyacinthe, Que., Canada), and sodium chloride (crystals, lab grade) from Anachemia Ltd. (Montreal, Que., Canada). Commercially available, immediate-release Tylenol® regular-strength tablets containing 325 mg of acetaminophen, from McNeil (Guelph, Ont., Canada), were chosen as the reference formulation. All chemicals were of reagent grade and were tested without further purification.

2.2. Preparation of HASCA tablets

Tablets were prepared by direct compression, i.e. dry mixing of acetaminophen, HASCA, and NaCl, followed by compression. HASCA, acetaminophen and NaCl were mixed manually in a mortar. No lubricant was added to the formulation. Indeed, it has been demonstrated earlier that magnesium stearate, at standard levels, does not influence the *in vitro* release profile from HASCA matrix tablets containing NaCl as well as their integrity [8]. Tablets were prepared on an IR 30-ton press (C-30 Research & Industrial Instruments Company, London, UK). To evaluate the NaCl percentage in the formulation that maintains the integrity of the swollen matrix, tablets of 600 mg containing 40% of acetaminophen as a model drug and 17.5%, 22.5% or 27.5% of NaCl, were prepared. On the other hand, 600-mg tablets containing 40% of drug and 27.5% of NaCl were produced to investigate the influence of acidic pH value and residence time in the acidic medium on the release characteristics of HASCA tablets as well as to perform *in vivo* studies. All tablets were compressed at 2.5 tons/cm^2 for 20 s. The diameter of the tablets was 1.26 cm.

2.3. Drug-release studies

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, the *in vitro* release experiments were conducted in a pH gradient simulating the pH evolution of the gastrointestinal tract to examine the pH-dependency of drug-release properties. The tablets were placed individually 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 buffer medium (pH 6.8) simulating jejunum pH, then finally transferred to another phosphate buffer 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 standard pH gradient conditions (A) were: pH 1.2 for 1 h, pH 6.8 for 3 h, and pH 7.4 until the end of the dissolution test (24 h). The influence of NaCl percentage in the formulation on swollen matrix tablet integrity and

drug-release was studied under standard conditions. To investigate the influence of pH of the acidic medium and residence time in the acidic medium on drug-release from HASCA matrices, different dissolution tests were performed, in which both pH of the acidic medium and residence time in the acidic medium were varied, as shown in Table 1.

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 (hours).

2.4. Pharmacokinetics in healthy human volunteers

The pharmacokinetic study, carried out at Notre-Dame de Secours Hospital, Byblos, Lebanon, was conducted in 5 healthy volunteers (3 males and 2 females) of mean age 22.6 ± 1.8 years and mean weight 82.4 ± 24.4 kg. All subjects had a normal medical history, medication history, physical examination, and biochemical screening (hematology, blood urea nitrogen, serum creatinine, alkaline phosphatase, liver enzymes, and glucose). None of them had taken any enzyme-inducing agents for at least 30 days prior to the initiation of this study. They were also instructed to abstain from medications and alcohol for at least 1 week prior to and during the study period. Informed consent was obtained from all subjects after the nature and purpose of the study were explained to them, along with a brief description of the drug effect. The protocol complied with the particular recommendation of Notre-Dame de Secours Hospital and was approved by its Ethics Committee.

A single-dose, non-blinded, balanced, 2-way crossover design was adopted using 2 acetaminophen dosing arms: a commercially available, immediate-release (IR) dosage form (Tylenol® containing 325 mg of acetaminophen per tablet) and a sustained-release (SR) formulation comprising 240 mg of acetaminophen per tablet (Amylose Project Inc.). All subjects were fasted overnight, and in the morning, each of them was given a single oral dose of either a SR acetaminophen tablet or an IR Tylenol® tablet, as a reference, with 240 ml of water. A standardized lunch or snack was served 4 h after drug administration. A 1-week washout period was allowed before the next treatment to avoid potential carry-over effects. Blood samples (9 ml) were collected, in heparinized plastic tubes, at different time intervals for each of the 2 products: at 0 (blank), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h post-dosing for Tylenol®, and at 0 (blank), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 17, 24 and 36 h post-dosing for the SR dosage form. The blood samples were then centrifuged for 5 min at 10,000 rpm, and plasma samples stored in a freezer (−70 °C) until analysis.

Table 1
pH gradient conditions used to simulate various possibilities of gastric pHs and residence times encountered by HASCA matrices during their gastrointestinal transit

pH value	1.2	3.5	4.5	6.8	7.4
Conditions A (standard)	1 h	–	–	3 h	Until 24 h
Conditions B	10 min	–	–	3 h	Until 24 h
Conditions C	–	3 h	–	3 h	Until 24 h
Conditions D	–	–	6 h	3 h	Until 24 h
Conditions E	–	–	–	3 h	Until 24 h

2.5. High-performance liquid chromatography (HPLC) analysis of plasma samples

Acetaminophen plasma concentrations were analyzed by HPLC. The HPLC system consisted of a pump (LC-10AD, Shimadzu), a UV–Vis spectrophotometric detector (SPD-10AVP, Shimadzu) operating at a wavelength of 254 nm, a Rheodyne injector, a reverse-phase column (C18, 15 cm × 4.6 mm) and an integrator (C-R 8A Chromatopac, Shimadzu). The mobile phase, a mixture of water and acetonitrile (94:6 v/v%), was pumped at a flow rate of 1.2 ml/min. The lower detection limit of the assay was 0.01 μg/ml of acetaminophen in plasma.

Frozen plasma samples were allowed to reach room temperature. A 200-μl aliquot of plasma was placed into a test tube (Eppendorf), to which 70 μl of internal standard (theophylline aqueous solution 50 μg/ml for high concentrations [>0.35 μg/ml] and 5 μg/ml for low concentrations [⩽0.35 μg/ml]) and 430 μl of 10% perchloric acid were added. The mixture was vigorously shaken for 5 min, then centrifuged for another 5 min at 10,000 rpm. The supernatant was finally collected, and 50 μl of the filtrate was injected into the HPLC system to record either peak areas or heights.

2.6. Pharmacokinetic data analysis

Since the two formulations presented different doses of acetaminophen, the drug plasma concentrations obtained after Tylenol administration were dose-adjusted, i.e. divided by the acetaminophen dose in the Tylenol formulation (325 mg) and multiplied by the acetaminophen dose in the sustained-release formulation (240 mg), before calculation of the pharmacokinetic parameters. Further weight adjustment was performed before plotting the drug concentration–time curves to take into account the high weight variation of the volunteers enrolled in the study.

Maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) after oral administration were directly determined from the plasma concentration values. The measured plasma concentrations served to calculate the area under the plasma concentration–time curve from time zero to the last concentration time point (AUC_{0-t}) and the area under the plasma concentration–time curve from time zero to infinity ($AUC_{0-\infty}$). AUC_{0-t} was calculated according to the trapezoidal rule, and $AUC_{0-\infty}$ was calculated by the sum of AUC_{0-t} and the last measured concentration divided by the elimination constant (C_t/k_e).

The Wagner–Nelson method [11] was adopted to calculate the percentages of acetaminophen absorbed in function of time for each volunteer enrolled in the study. The absorbed percentages were calculated by the following equation:

$$\%\ \text{Absorbed} = [(C_t + k_e \times\ \text{AUC}_{0\text{–}t})/(k_e \times\ \text{AUC}_{0\text{–}\infty})] \times 100$$

where C_t is the plasma concentration at time t; k_e is the elimination rate constant; $\text{AUC}_{0\text{–}t}$ is the area under the plasma concentration–time curve from time zero to time t, and $\text{AUC}_{0\text{–}\infty}$ is the area under the plasma concentration–time curve from time zero to infinity.

All the pharmacokinetic parameters were determined for each volunteer, and the averages, standard deviations and coefficients of variation calculated.

2.7. IVIVC

An IVIVC for this specific acetaminophen SR formulation, if any, was explored by plotting the point-to-point relationship of the percentage of drug absorbed *in vivo vs.* the percentage of drug released *in vitro* at the same time, up to the maximum amount of drug absorbed *in vivo*.

3. Results and discussion

3.1. In vitro drug-release characteristics from HASCA matrix tablets

Fig. 1 shows the *in vitro* release profile of acetaminophen from HASCA SR matrix tablets containing NaCl in concentrations ranging from 17.5% to 27.5% w/w. Remarkably, all total release times were close to 24 h for 600-mg tablets containing such large amounts of soluble materials, i.e. around two-thirds w/w of each tablet were composed of acetaminophen and NaCl. Further, an increase in NaCl tablet content did not lead to an increment in the burst-effect. Only after 2 h of dissolution could a slight rise in the drug-release rate be observed with escalating NaCl concentrations. However, 9–12 h after the beginning of the dissolution process, some cracks appeared on the surface of the tablets containing 17.5% or 22.5% NaCl, leading, at the same time, to an increase in the drug-release rate. This can be explained by an augmentation in the tablet diffusion surface as well as by new drug particles being directly exposed to the medium for free dissolution, creating a kind of reduced-scale burst-effect. Even if these cracks did not lead to a dramatic change in the drug-release rate (Fig. 1), good mechanical resistance to stress is essential for normal therapeutic use. Indeed, when the stomach churns, thereby exerting significant physical force on the formulation, there is a strong risk of the tablet breaking apart, which could elicit a burst of drug-release. The optimal amount of NaCl found to maintain the integrity of the swollen tablets during the totality of the dissolution test was 27.5% for tablets containing 40% of acetaminophen. It has been previously reported that adding an optimal percentage of electrolyte to the formulation could maintain the integrity of swollen hydrophilic matrix tablets while allowing controlled and sustained drug-release [8].

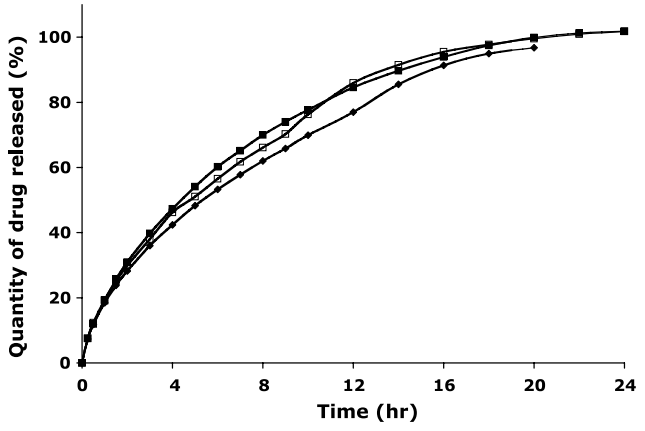

Fig. 1. Cumulative percent of acetaminophen released *in vitro* from HASCA matrices containing 40% of drug and increasing concentrations of NaCl (◆, 17.5% of NaCl; □, 22.5% of NaCl; ■, 27.5% of NaCl).

The swelling of SA tablets can be described as moderate when compared to the usual hydrophilic matrices such as hydroxypropylmethylcellulose [5]. This is particularly true for HASCA tablets, which form a very rigid gel with surprisingly high mechanical strength in the swollen state [7,8]. As a consequence, it is possible to create tablets that do not show any disintegration, even if mechanical stresses occur, for example, after administration in the gastrointestinal tract. However, in the absence of an electrolyte, such swollen HASCA tablets show cracks and/or partial or complete separation of the tablet parts, which forbid their normal and safe therapeutic use. One possible explanation for the appearance of cracks on the surface of the tablets may be that the rigidity of the gel and its tight network hinder water penetration into the tablets but, more importantly, strongly decrease diffusion of the dissolved drug out of the matrix tablets, thereby tremendously increasing internal osmotic pressure, which in the end produces cracks and/or partial or complete separation of the tablet parts to relieve the tablets' internal stress. Fig. 1 shows that the addition of an electrolyte like NaCl to the HASCA formulation can provide complete stabilization of the swollen matrix structure or at least significantly delay apparition of the above-mentioned problems and/or decrease their intensity. These results were the opposite of what were expected as, indeed, adding an electrolyte to the formulation should pump more water and faster inside the tablet, thereby increasing internal osmotic pressure and making the tablet present cracks. It is believed that adding an appropriate amount of electrolytes maintains a delicate equilibrium between (a) hydrogen bonds created, among others, through –COOH associations, which enhance gel strength and maintain matrix structure, and (b) swelling

of the polymer chains, increased by their repulsion due to the $-COO^-$ groups, which gives the matrix its necessary elasticity.

The picture is further complicated by other factors, which combine their effects to produce complex behaviour: the effect of porosity after dissolution of the drug and the electrolyte on gel structure; the effect of NaCl on gel viscosity and, therefore, on drug diffusion; the effect of 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, and the pH conditions of the external medium.

Since HASCA is an ionic polymer used for oral, sustained drug-release, the *in vitro* release experiments were conducted in a pH gradient simulating the pH evolution of the gastrointestinal tract to study the pH-dependency of the release properties. Because of the ionic nature of the HASCA polymer, one would expect immersion in changing pH environments to result in differences in the behaviour of the formulation when in contact with the various pH media, which could lead to a pH-dependent release rate. Fig. 2 shows the release profiles from HASCA SR matrix tablets containing 27.5% of NaCl in pH gradients where both acidic pH value and residence time in the acidic medium varied according to Table 1. No significant differences in the drug-release profiles were observed. The drug-release profile from such SR matrix tablets appears to be independent of both the acidic pH value and residence time in the acidic medium. Most probably, the combined presence of NaCl and the carboxylic groups of the polymer creates a buffered environment in the matrix, allowing it to be insensitive to pH changes of the surrounding medium. This is important considering that materials that possess pH-independent release properties are preferable for oral extended-release formulations, since they are not affected by intra- and inter-subject variations of both gastric pH and gastrointestinal transit time [12]. It is expected that this observation will remain true as long as the ionization and solubility of other ingredients in the formulation are not significantly affected by pH changes in the gastrointestinal tract, as is the case with acetaminophen (pK_a 9.5) [13].

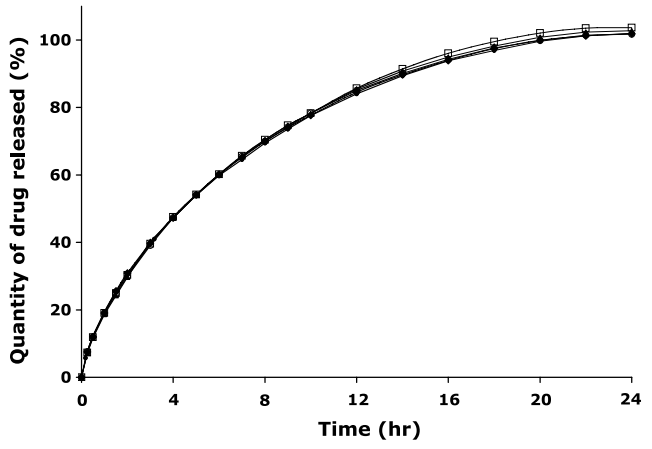

Fig. 2. Cumulative percentage of acetaminophen released *in vitro* from optimized HASCA matrices (32.5% of HASCA, 40% of acetaminophen, and 27.5% of NaCl) in pH gradients with different acidic pH conditions (●, 10 min at pH 1.2; ◆, 1 h at pH 1.2; □, 3 h at pH 3.5; ▲, 6 h at pH 4.5; ○, no acidic medium).

3.2. Pharmacokinetics in healthy human volunteers

The model drug chosen was acetaminophen, a commonly-used analgesic and antipyretic, which is well absorbed orally by passive diffusion with high permeability throughout the intestinal tract [14]. According to the Biopharmaceutics Classification System [15], acetaminophen is classified as a "class I" drug. Its solubility in water varies from sparingly soluble to soluble at 37 °C, with pH-independent solubility at physiological values (from 1 to 8.5). Hence, this drug is not considered to ionize in the physiological pH range (pK_a 9.5) [13]. The plasma elimination half-life ($t_{1/2}$) of acetaminophen ranges from 1 to 4 h [16]. Moreover, the drug is safe and non-toxic when doses ranging from 200 to 400 mg are administered. Therefore, the chosen dose, i.e. 240 mg, did not represent any risk of toxicity to the subjects. In addition, acetaminophen is not subject to any significant enzymatic degradation or gastrointestinal bacterial degradation. Food reduces the rate of acetaminophen absorption but not its extent [17]. Finally, acetaminophen is easily detected, quantified and relatively inexpensive. Considering that this was an exploratory *in vivo* study to evaluate a new drug-delivery system, it was important to avoid the usual contraindications of a SR dosage form, i.e., the risk of dose dumping, as a consequence of tablet rupture or erosion, and accumulation in the body. Acetaminophen, at that dosage strength, was thus a safe choice as a model drug. Because of the above-mentioned characteristics, the controlled release of acetaminophen from numerous formulations has been widely investigated [18–20].

The mean drug plasma concentration–time profiles following oral administration of the HASCA SR formulation and the commercial IR tablet are illustrated in Fig. 3. The absence of a burst-effect during the time range between 5 min and 2 h after administration of the HASCA SR matrix tablets to fasted, healthy volunteers, which coincides with normal gastric residence times for a dosage form given in a fasted state [21], suggests that the gel was strong enough to resist the powerful peristaltic contractions normally occurring in the fasted state and which open the pylorus and clear the stomach of any residual material (sometimes called housekeeper waves). Therefore, the *in vivo* concentration–time profiles show that the tablets maintain their integrity while traversing the stomach. No burst-effect was also detected during the first 3–5 h after administration of the formulation. Considering that residence time in the small intestine is about 3 h [21], this was the period of time where the HASCA polymer was under attack by α-amylase. This absence of burst-effect whilst the dosage form traverses the small intestine indicates that the HASCA polymer resisted α-amylase biodegradation.

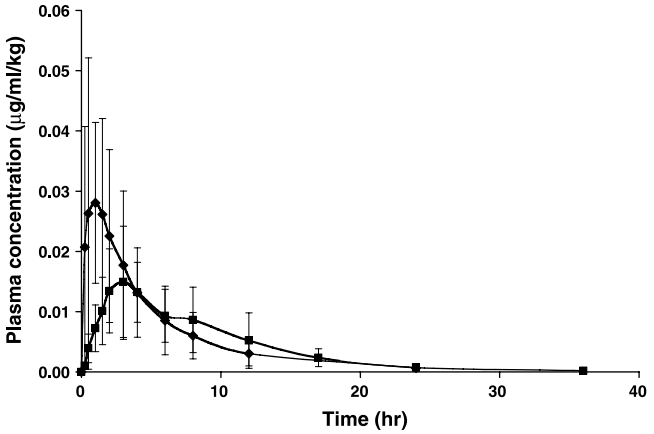

Fig. 3. Acetaminophen plasma concentration (expressed in µg/ml/kg) *vs.* time profiles (mean ± SD) following oral administration of the HASCA SR formulation (■) and the commercial IR tablet (◆).

There were large differences in plasma concentrations between the IR and the SR dosage forms. Differences in the curves reflected different release rates of the 2 formulations. The first portion of the plasma concentration–time curves (Fig. 3) showed large differences, demonstrating IR for the Tylenol® formulation and a SR profile for the HASCA formulation. The mean (±standard deviation) pharmacokinetic parameters and their respective coefficients of variation (%CV) are listed in Table 2. C_{max} for IR and SR formulations were significantly different from each other ($P = 0.008$); T_{max} for IR and SR formulations were significantly different from each other ($P = 0.028$). The AUCs for IR and SR formulations were not significantly different ($P = 0.76$). The data were analyzed at 95% CI using 2-Tailed *t*-test (paired values). However, this exploratory study was conducted on a very small number of volunteers to evaluate the *in vitro* and *in vivo* potential of a new SR matrix formulation. Accordingly, these results have to be considered cautiously.

The very rapid drug absorption from the IR tablets was confirmed by the C_{max} and T_{max} values, i.e. 2.90 µg/ml and 45 min, respectively. The AUCs calculated for HASCA tablets and for Tylenol after dose-adjustment were similar, which suggests that the total amount of drug absorbed by the body after administration of the same dose was the same for both formulations, irrespective of the absorption rate.

There was relatively high inter-subject variability of the estimated pharmacokinetic parameters, particularly for T_{max}. A possible explanation for the relatively high inter-subject variation of the estimated pharmacokinetic parameters is given by the large differences in anatomic characteristics of the volunteers, like their weight, especially for such a small number of subjects.

Fig. 4 shows the average cumulative percentage of drug absorbed in function of time (hours), calculated by the Wagner–Nelson method. Since the k_e value in the Wagner–Nelson calculation has to be obtained after bolus intravenous administration of the drug, we used a value from the literature, i.e. 2.52 h^{-1} [22]. *In vivo* absorption appeared to be continuous, although its rate decreased strongly after 4 h and became marginal after 12 h. After 4–6 h, the drug-release rate might well not be able to compensate for the fast elimination of acetaminophen, which could explain the decrease in drug plasma concentration for the SR curve in Fig. 3. The high variations observed in Fig. 4 might be explained, among others, by the same factors.

As suggested by the *in vitro* release profiles, the results of the *in vivo* study indicate that the HASCA formulation slowed acetaminophen absorption compared to the IR formulation, with significant drug-release for up to 12 h. However, therapeutic blood levels were not maintained over a more extended time period due to the high k_e of

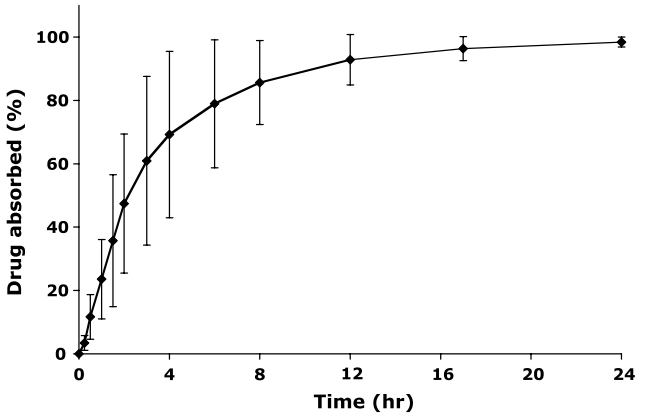

Fig. 4. Cumulative percentage (mean ± SD) of acetaminophen absorbed following the oral administration of HASCA SR matrix tablets to 5 healthy volunteers.

Table 2
Pharmacokinetic parameters of acetaminophen (mean ± SD and %CV) following oral administration of the HASCA sustained-release formulation and the IR tablet

	$AUC_{0-24\ h}$ (µg × h/ml)	$AUC_{0-\infty}$ (µg × h/ml)	C_{max} (µg/ml)	t_{max} (h)
Tylenol®				
Mean ± SD	11.59 ± 3.13	11.76 ± 3.20	2.90 ± 0.97	0.75 ± 0.50
%CV	27.01	27.24	33.37	66.67
HASCA matrix tablet				
Mean ± SD	11.14 ± 3.45	11.24 ± 3.46	1.32 ± 0.46	4.40 ± 2.51
%CV	30.96	30.82	34.95	57.05

acetaminophen. Other limitations of this *in vivo* study include the small number of volunteers and, as mentioned above, the high inter-subject anatomic variability. However, our pilot study has clearly demonstrated the difference between the IR tablet and the HASCA SR tablet with respect to their release mechanisms. Further, the absence of immediate and fast disintegration of the HASCA tablets proves the potential of this new excipient as an efficient drug-delivery system. However, it must be remembered that ours was a non-blinded study where volunteers were not randomized, as the protocol was specific to each drug formulation.

3.3. IVIVC

To assess the relationship between *in vivo* acetaminophen absorption and *in vitro* acetaminophen release from the HASCA matrix tablet formulation, percent drug-release *in vitro* was compared to percent *in vivo* absorption at given time points. Fig. 5 presents the results for the 5 volunteers and the average mean. Certain deviations from the ideal 1:1 relationship, which is represented by the straight line with slope = 1 [23], were observed. While a linear relationship between the percentage released *in vitro* and the average percentage absorbed *in vivo* seems to be present for a portion of the curve, it appears that the release rate is faster *in vivo*. At this stage, we do not know if this is due to really faster release *in vivo* or to the fast elimination of acetaminophen, which renders application of the Wagner–Nelson method difficult and lacking in precision. Moreover, the intercept value should approximate zero for a "perfect" IVIVC, i.e. when the percentage absorbed varies in direct proportion to the percentage released *in vitro*. It is possible that *in vivo*, the matrix system takes a little more time to be hydrated enough to trigger burst-release. Finally, the variations seen from volunteer to volunteer are large, and volunteers seem to divide into 2 groups, but with such a small number of subjects, it is impossible to be sure. It is noteworthy that a poor IVIVC has already been reported for a SR matrix tablet containing similar doses of acetaminophen, although these results look more erratic and their dosage forms are more subject to pH variations than the present ones [23].

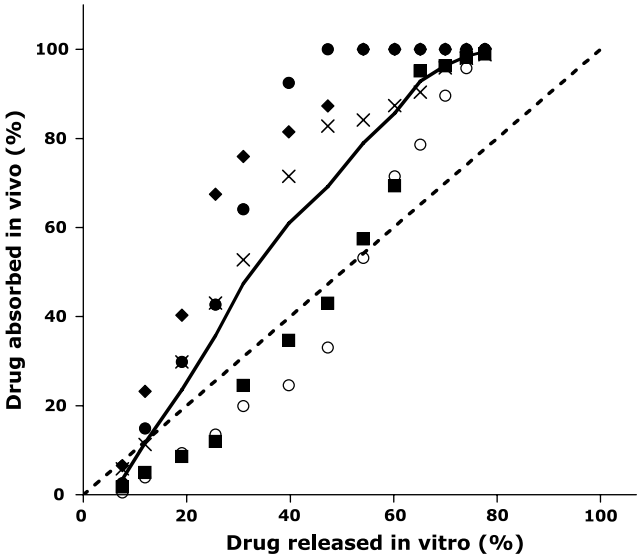

Fig. 5. IVIVC plot for HASCA SR matrix tablets administered to 5 healthy volunteers (◆, volunteer 1; ○, volunteer 2; ×, volunteer 3; ●, volunteer 4; ■, volunteer 5; —, average; - - - -, linear).

However, it must be reiterated that the drug and the strength chosen, i.e. acetaminophen and 240 mg, were not the most appropriate for evaluating HASCA SR matrix tablets, since the drug's short half-life would require excessively large amounts of drug in each dosage unit to maintain sustained effects, forcing the dosage form itself to become unreasonably large. In addition, the elimination rate of this drug from the body was too high compared to the release rate from the proposed formulation, not allowing therapeutic blood levels to be maintained over an extended time period. Again, it must be emphasized that, as this was the first time that the new drug-delivery system was administered to human volunteers, their safety was the main concern when choosing the drug and its strength. Therefore, further investigations like increasing dosage strength and the release rate are required to obtain a meaningful IVIVC for acetaminophen associated with this formulation.

4. Conclusion

HASCA is an interesting excipient for sustained drug-release in solid oral dosage forms. In addition to the easy manufacture of tablets by direct compression, the results show that *in vitro* drug-release from an optimized HASCA formulation is not affected by either acidic pH value or acidic medium residence time. In addition, a compressed blend of HASCA with an optimized quantity of NaCl provides improved integrity to a pharmaceutical SR tablet for oral administration. The *in vivo* study demonstrates extended drug absorption, showing that the matrix tablets do not disintegrate immediately. Nevertheless, acetaminophen does not seem to be the most appropriate drug for this type of formulation.

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