Development of a modified-release hydrophilic matrix system of a plant extract based on co-spray-dried powders

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ABSTRACT

The aim of this paper was to develop a modified-release solid dosage form containing a plant extract, namely *Hamamelis virginiana* extract. To this purpose, a co-spray-dried powder consisting of *H. virginiana* extract, sodium carboxymethylcellulose (Na-CMC) and colloidal silicon dioxide (SiO_2) was formulated, which showed good flow properties for direct compression and was useful as a modified-release hydrophilic matrix system. *H. virginiana* extract was selected as a model plant extract due to its extensive use in treatments for chronic varicose veins. Different ternary co-processed powders were obtained by modifying the viscosity grade and concentration of Na-CMC. For a given set of spray-drying operating conditions, the use of medium viscosity (MV) Na-CMC in the formula led to high process yields and satisfactory product moisture contents. Compacted powders were able to modulate the extract release in different media, being the polymer concentration the fundamental factor affecting the rate of drug release. The co-spray-dried powder with a plant extract solid residue:SiO_2:Na-CMC MV ratio of 1:1:0.075 was the best formulation because of its good flowability, compactability, stability and release properties. It was found that the release mechanism was a combination of extract diffusion and matrix erosion. The results indicated that the co-spray-drying of adequately designed formulations is a good strategy to improve the functionality of medicinal plant extract powders.

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1. Introduction

Modified-release drug delivery systems (MRSs) have been widely studied to improve drug efficiency and patient compliance, as well as to reduce drug toxicity. These systems are particularly useful in the treatment of chronic pathologies because they provide effective plasma drug concentration–time profiles, keeping constant plasma drug concentration in the therapeutic range over a prolonged period of time [1].

Hydrophilic polymers play an important role in the design of MRSs [2]. Matrices containing these substances are one of the most popular controlled-release dosage forms [3]. These matrices consist of a compact containing a mixture of one or more active ingredients with one or more hydrophilic polymers (gel-forming agents), which retard the drug release. Hydrophilic matrices are currently widely used as MRSs because they are simple to formulate, inexpensive and easy to produce, and have a good *in vitro–in vivo* correlation [4]. When a hydrophilic matrix containing a swellable glassy polymer comes into contact with a solvent, there is a progressive change from the glassy to the rubbery state, which leads to the swelling process and the formation of a thick gel layer on the matrix surface [4,5]. This gel layer is responsible for the control of the drug release rate. The rapid formation of the viscous gel layer upon hydration is crucial to attain the modified drug release from matrix tablets [3]. Various transport phenomena take place through this layer: the solvent diffusion towards the tablet core, the outward transport of the drug to the solvent medium, and matrix erosion. The thickness of the gel layer increases as more solvent penetrates into the system, and the surface (previously hydrated) gradually relaxes until it loses consistency and erosion begins. Consequently, penetration of the medium into the matrix is accompanied by the formation of a series of fronts (swelling, diffusion and erosion or dissolution fronts), which move constantly during the tablet dissolution process [6].

Modified release concepts applied to medicinal plant extracts are still in an exploratory stage. However, some plant drugs have been formulated as MRS, providing significant performance enhancements compared to conventional phytomedicines. Considerable improvements in solubility, bioavailability, pharmacological activity, stability, toxicity reduction, sustained delivery, and protection from physical and chemical degradation have been demonstrated [7,8].

There are few reports on matricial systems containing plant extracts [9,10]. Therefore, there is yet a great potential for the development of novel herbal MRS in solid dosage forms (such as tablets or multiparticulate systems) and for the study of the variables and mechanisms that modulate the release rate of plant extracts.

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In addition, it is important to highlight the growing popularity of natural products. In 2006, the global medicine market based on plant extracts amounted to € 19 billion, and was forecasted to exceed € 26 billion by 2011 [11].

Dried plant extracts offer many advantages over conventional liquid forms, such as lower storage costs, higher concentration and stability of active substances. However, these attributes are dependent on the processing steps throughout manufacture. Several drying techniques (including freeze, spray and spouted bed drying) have been proposed in the literature to produce high-quality solid products. Among these, spray-drying is the method most commonly used in the herbal processing industry, giving plant extracts with precise quality properties (moisture content, solubility, bulk density and hygroscopicity) in continuous operation [12]. Moreover, the co-spray-drying of herbal drugs with other materials allows improving the physico-mechanical properties of the powders making them appropriate for direct compression [13].

Considering that the herbal medicine market is forecasted to increase, the possibility to treat chronic pathologies using plant extracts, the attributes of hydrophilic matrices to modulate drugs release, and the capability of the spray-drying technology to produce co-processed powders with desired properties, in this work *Hamamelis virginiana* was selected as a model plant to test the applicability of spray-dried powders to produce modern drug delivery systems. Particularly, *H. virginiana* is widely used for the treatment of chronic varicose veins [14], which affects one out of two people age 50 and older [15]. The tannins of the dried leaves have venotonic properties [16]. Therefore, *H. virginiana* could be a potential herbal medicine to be administered as a MRS. As advantages, the use of matricial systems can reduce the dose frequency in long-term treatments and consequently improve treatments compliance, reduce fluctuation in drug blood levels and adverse side effects, and decrease the overall health care costs.

In this context, the goal of the present work was to develop a novel controlled-release co-processed powder based on a medicinal plant extract with good properties for the production of tablets by direct compression, aiming to better identify the variables and mechanisms that modulate *H. virginiana* extract release and to demonstrate the suitability of producing MRSs based on herbal medicines. Particularly, the effects of the hydrophilic polymer viscosity and concentration and of the dissolution medium pH and agitation speed on the extract release rate were comprehensively investigated to understand the *in-vitro* release properties of herbal medicine matrices.

2. Materials and methods

2.1. Materials

H. virginiana is a tall, highly branched deciduous shrub or small tree. Indigenous to the Atlantic coast of North America, it is found in damp woods ranging from Nova Scotia to Florida and as far west as Texas [14]. Dried leaves of *H. virginiana* were used as received from the supplier (Droguería Argentina, Argentina). The leaves were green or greenish-brown (often broken), crumpled and compressed into more or less compact masses. The lamina of the leaves, generally 5–12 cm long and 3–8 cm wide, was ovate. The base of the leaves was oblique and asymmetric, and the apex was acute. The margins were roughly dentate and the venation was pinnate and prominent on the abaxial surface. The physical appearance of the dried leaves was in agreement with the description of various pharmacopoeias and specific literature [14,17].

Colloidal silicon dioxide (SiO_2) (Aerosil 200, Degussa AG, Germany) and sodium carboxymethylcellulose (Na-CMC) of ultra high (UHV), high (HV) and medium (MV) viscosity grade (Fluka Analytical, Sigma-Aldrich, Argentina) were used as received from the suppliers. Distilled water was used for the preparation of the fluid plant extract and aqueous dispersions to be spray-dried.

Simulated gastric fluid (SGF, pH 1.2) was prepared by using sodium chloride anhydrous and hydrochloric acid 37% (v/v). Monobasic potassium phosphate and sodium hydroxide (0.2 N) were used as simulated intestinal fluid (SIF, pH 6.8) without enzymes according to the USP 30-NF 25 [18]. All reagents were of analytical grade.

2.2. Fluid plant extract (FPE) preparation

The fluid plant extract (FPE) of *H. virginiana* was prepared by decoction of 160 g of dried leaves in 4000 ml of boiling water for 160 min, according to EMA [16]. The FPE was separated from the leaves by filtration through a cellulose-based filter paper (Whatman no. 1), therefore it can be assumed that the FPE did not contain fine insoluble particles. The final volume was about 3500 ml due to leaf water absorption and water evaporation.

2.3. Solid residue (SR) assay

The solid residue (SR) content of the FPE was determined by solvent evaporation under reduced pressure, followed by drying in an oven at 80 °C to constant weight. The SR was 0.8 g per 100 ml of FPE. Therefore, 28 g of SR was obtained from 160 g of dried processed leaves, being the solid residue yield 18 wt.%.

2.4. Spray-drying: sample preparation and operating conditions

The components used to prepare the dispersions to be spray-dried were a hydrophilic polymer (Na-CMC), a drying adjuvant (SiO_2) and the FPE. The polymer and the drying adjuvant were added to the FPE with different purposes. The polymer was introduced to modulate the drug release, and its selection was based on a screening of different common natural polymers (guar gum, xanthan gum, sodium alginate and chitosan) and semi-synthetic polymers (polyacrylic acid, hydroxyethylcellulose, hydroxypropyl methylcellulose and Na-CMC). The screening studies indicated that Na-CMC properly modified the release of the *H. virginiana* extract and gave the highest process yield. This polymer is widely used in oral and topical pharmaceutical formulations, being one of the dominant hydrophilic carriers used in hydrophilic matrices due to its gel-forming capacity [19].

The drying adjuvant is usually added to improve the powder flowability, compressibility and compactability [12,13]. SiO_2 demonstrated to be a very effective excipient to obtain powders from fluid plant extracts with good flow and stability properties [13], and to reduce the adhesion of the product on the spray-dryer chamber wall [20].

Aqueous dispersions of different compositions were prepared by mixing the FPE with both excipients, until the Na-CMC was totally dissolved. The dispersions were mixed for 60 min before atomization and during the spray-drying process using a magnetic stirrer bar rotating at 1000 rpm to keep them homogenized. Three Na-CMC molecular weights (ultra high, high and medium viscosity) and four polymer concentrations (SR:SiO_2:Na-CMC ratio: 1:1:0.3, 1:1:0.15, 1:1:0.075 and 1:1:0.0375) were tested. The total solid concentrations for the different formulations ranged from 1.63–1.84 g per 100 ml of FPE. The 1:1 SR:SiO_2 ratio was selected based on previous studies of other co-processed dry plant extract powders [12,13].

The aqueous dispersions were spray-dried in a Mini Spray-Dryer Büchi B-290 (Büchi Labortechnik AG). A two-fluid nozzle with a cap-orifice diameter of 0.5 mm was used. The atomizing air pressure was kept constant at 6 bars for all the experiments. The other experimental conditions were: drying air inlet temperature 150 °C, atomization air volumetric flow rate 400 l/h, feed volumetric flow rate 10% (2 ml/min) and drying air volumetric flow rate 100% (about 35–38 m³/h).

In addition, the FPE without additives, the 1:1 SR:SiO_2 sample and pure Na-CMC MV were spray-dried under the same operating conditions for comparative purposes. The corresponding total solids concentrations were 0.8, 1.6 and 0.24 g per 100 ml, respectively.

2.5. Viscosity of mixtures

The viscosities of the aqueous dispersions without SiO_2 were determined. This compound was not incorporated because it settled during the assay. Measurements were taken in triplicate, using a capillary Cannon–Fenske Routine-type viscometer (Tube size 100, IVA) immersed in a constant temperature bath at 20 °C.

2.6. Process yield

The process yield was calculated as the ratio of the weight of powder collected after every spray-drying experiment to the initial amount of solids contained in the spray dispersion.

2.7. Moisture content

Moisture content of the powders was measured by using a halogen moisture analyzer (model M45, OHAUS). The moisture content of the samples was determined immediately after the spray-drying step.

2.8. Angle of repose (α)

The angle of repose was determined by pouring around 7 g of spray-dried powder through a funnel located at a fixed height above a graph paper placed on a flat horizontal surface and measuring the height (h) and radius (r) of the conical pile formed. The tangent of the angle of repose is given by the h/r ratio [21].

2.9. Bulk and tap densities

In order to determine the density of the spray-dried samples, the powder was gently poured into a 10 cm^3 graduated cylinder. Bulk density (D_B) was calculated as the ratio of the weight (g) of the sample contained in the cylinder to the volume occupied (10 cm^3). Tap density (D_T) was estimated by tapping the cylinder until no measurable change in volume was noticed. Powder compressibility was evaluated using the Carr Index (CI) [22] defined by Eq. (1).

$$CI = \frac{(D_T - D_B)}{D_T} 100 \tag{1}$$

2.10. Hygroscopicity

Hygroscopicity was determined by adapting the method proposed by Tonon et al. [23]. Spray-dried samples (approximately 0.2 g) were stored in containers at 25 °C and 75.3%RH (given by a saturated aqueous solution of NaCl). After 7 days, the samples were reweighed. The hygroscopicity was expressed as grams of adsorbed moisture per 100 g of dry solids.

2.11. Particle morphology and size distribution

Some selected spray-dried samples were dried under air flow on a porthole. Afterwards, the samples were metalized with gold in a PELCO 91000 sputter coater. Particle morphology was assessed using an EVO 40-XVP, LEO scanning electron microscope (SEM).

Particle size distribution was measured using a laser light diffraction instrument (Horiba LA-950V2). Average particle size was expressed as D [4,3], i.e. mean volume diameter.

2.12. X-ray diffraction (XRD)

XRD patterns were recorded using a Rigaku Geigerflek (DMAX 3 C) X-ray diffraction system. The anode X-ray tube was operated at 35 kV and 15 mA. Measurements were taken from 2° to 60° on the 2θ scale at a step size of 4°/min.

2.13. Thermal analysis. Glass transition temperature (T_g) determination

The glass transition temperature (T_g) of the powders was measured by differential scanning calorimetry (Pyris 1, Perkin Elmer). Selected samples of 10 mg were placed in aluminum pans and scanned from 30 to 150 °C at a heating rate of 10 °C/min. The purpose of this first thermal scan was to remove the residual moisture that could affect the determination of T_g. Then, the samples were cooled from 150 to 30 °C at a cooling rate of 10 °C/min, and re-heated from 30 to 150 °C at the same rate. T_g was calculated from thermograms as the temperature at which one-half of the change in heat capacity, ΔCp, occurred (i.e., the half ΔCp method) [24].

2.14. Preparation of matrices and compactability curve

According to Alonso [25], the recommended dose for adults of H. virginiana dry extract is 500 mg per day divided in three intakes if a yield (dry plant extract/leaf mass ratio) of 20 wt.% is obtained. As described in Section 2.3, the extraction yield was approximately 18 wt.%; therefore, a daily dose of 550 mg would be appropriate. For the modified release system, two intakes are proposed. The efficacy of this dosing frequency was not verified because the aim of the present work was to study the release modulation of plant extracts from hydrophilic matrixes containing a swellable polymer, and not to demonstrate the particular efficacy of modified H. virginiana extract release on the treatment of varicose veins.

In order to study the compactability of the selected co-spray-dried powders, the solid formulations were compressed in a hydraulic press (Delfabro) at different forces (4.9, 7.3 and 9.8 kN) for 5 s. Flat punches of 14 mm diameter were used. The hardness of each compact was determined as the average of 6 measurements using a hardness tester (Scout).

2.15. Evaluation of matrices

2.15.1. Water uptake

Sorption of water by the matrices was determined using a device similar to that described by Nogami et al. [26]. The apparatus consisted of a U-shaped tube that presents at one extreme a matrix holder with a porous glass base, and at the other end it is connected to a graduated pipette horizontally oriented and calibrated at the same level of the holder base. First, the system was filled with water up to 0 ml (starting position). Then the matrix was placed in the holder (time zero). The matrix began capturing water by capillarity; the volume of water sorbed by the sample was recorded at given time intervals. All the assays were performed in triplicate at room temperature (between 20 and 25 °C).

2.15.2. Radial front movement

Swelling studies of the matrices were performed by clamping each matrix between two transparent glasses and introducing them into a vessel with distilled water at 37 °C without agitation, as reported by Colombo et al. [6]. The experiment was carried out in triplicate. At specific time intervals, the matrices between the two transparent glasses were photographed, keeping the focal distance of the camera constant during all the measurements.

The H. virginiana extract is light orange; this characteristic color enables direct visualization of the different fronts. As shown in Fig. 1, three fronts were identified as described by Siepmann and Siepmann [27]: the swelling front (at radius r_s) separating the swollen from non-swollen matrix, the diffusion front (at radius r_d) constituting the boundary between the swollen matrix containing both dissolved and non-dissolved drug (strongly colored) and the swollen matrix containing only dissolved drug (pale colored), and the erosion front (at radius r_e) indicating the limit between the matrix and the dissolution medium. The position of each front (swelling, diffusion
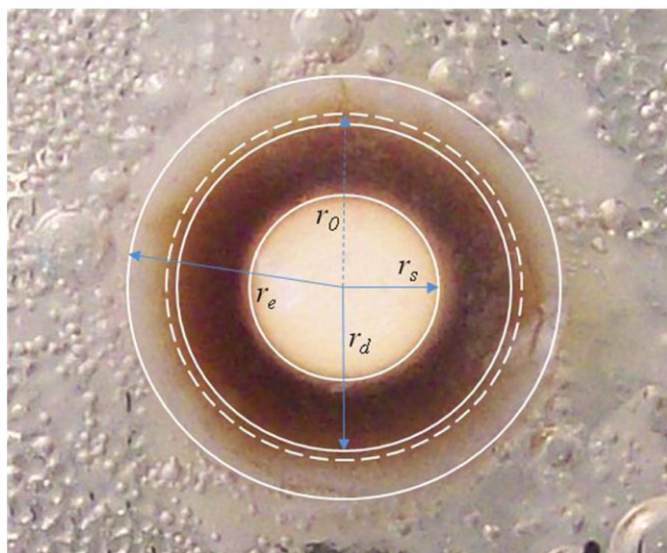
Fig. 1. Fronts position of 1:1:0.075 SR:SiO$_2$:Na-CMC MV matrices at 180 min.

and erosion) was determined from the distance between the corresponding moving boundary (r_s, r_d and r_e) and the radius of the tablet at time 0 (r_0), i.e. $r_s - r_0$, $r_d - r_0$ and $r_e - r_0$ for the swelling, diffusion and erosion front, respectively.

2.15.3. Matrix erosion

Matrix erosion studies were performed according to a method similar to those reported by Bhise et al. [28] and Rao and Devi [29] using the standard USP/NF dissolution Apparatus II (Erweka). Pre-weighed matrices were placed in the dissolution test apparatus and subjected to dissolution in 900 ml of SIF (pH 6.8) maintained at 37 ± 0.5 °C using a paddle rotation of 50 rpm. The matrix systems were removed at regular intervals from the dissolution vessels and dried to constant weight in a hot-air oven at 60 °C. The percentage of matrix erosion at a given time t was estimated by Eq. (2):

$$\text{Matrix erosion}(\%) = \frac{W_i - W_t}{W_i} \times 100 \tag{2}$$

where W_i is the initial weight of the matrix and W_t is the weight of the matrix subjected to erosion for a given time t. The reported matrix erosion data correspond to an arithmetic mean of three determinations.

2.15.4. Drug release

Extract release experiments were carried out in an Apparatus II (Erweka) with a paddle rotation speed of 50 and 100 rpm, using 900 ml of different media (distilled water, SGF pH 1.2, and SIF pH 6.8) maintained at 37 ± 0.5 °C. At predetermined time intervals, samples were withdrawn and total tannins (hydrolysable and condensed) were determined spectrophotometrically at 280 nm [30]. All the experiments were conducted in triplicate and mean values are reported. Finally, the release profiles were compared using the similarity factor, f_2, calculated by Eq. (3):

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{q}\right) \sum_{t=1}^{q} (R_t - T_t)^2 \right]^{-0.5} 100 \right\} \tag{3}$$

where q is the number of dissolution time points, R_t and T_t are the percentages of drug released at each time. An f_2 value between 50 and 100 indicates similarity between the two compared release profiles [31].

2.15.5. Drug release kinetic models

Drug release data were analyzed by means of the kinetics models proposed by Korsmeyer et al. [32] (Eq. (4)) and Peppas and Sahlin [33] (Eq. (5)).

$$\frac{M_t}{M_\infty} = k't^n \tag{4}$$

$$\frac{M_t}{M_\infty} = k_d t^m + k_r t^{2m} \tag{5}$$

where M_t/M_∞ is the drug released fraction at time t (being $M_t/M_\infty \leq 0.6$, and the drug loading was considered as M_∞) [31], and k and k' are release rate constants characteristic of the drug/polymer system.

In Eq. (4) n is a release exponent that characterizes the drug release mechanism, which is also dependent on the shape of the tested matrix. The matrices under study were cylinders with an aspect ratio (diameter/thickness) around 2. For this geometry, a release exponent $n = 0.45$ indicates that the drug release is controlled by Fickian diffusion. Values of n between 0.45 and 0.89 imply non-Fickian or anomalous phenomena involving first-order kinetics, in which diffusion and relaxation-erosion of the polymer contribute to the overall release. Finally, $n = 0.89$ corresponds to the lack of dependence on time in the release kinetics (i.e., zero-order kinetics), being drug release controlled by the relaxation–erosion of the polymer [27].

In Eq. (5), k_d and k_r are the diffusion and relaxation rate constants, respectively, and m is the purely Fickian diffusion exponent, which is around 0.43 for the studied geometry [33]. According to Peppas and Sahlin [33], the following equation can be used to estimate the drug release ratio of relaxational over Fickian contributions:

$$\frac{R}{F} = \frac{k_r'}{k_d} t^m \tag{6}$$

The kinetic parameters involved in the considered models were fitted by minimizing the sum of squared errors between the experimental and the calculated drug released fractions.

3. Results and discussion

3.1. Effect of the Na-CMC viscosity

The influence of polymer viscosity on the powder flow properties, moisture content, process yield, and extract release from compacted powders was studied aiming to find the best formulation to produce modified-release tablets by direct compression efficiently. The composition of the tested sprayed aqueous dispersions selected was SR:SiO$_2$:Na-CMC = 1:1:0.3.

All the powders obtained by spray-drying presented a light orange color and the typical extract smell.

The flow properties of the spray-dried powders have a direct relation with their behavior during storage, manipulation and technological processing. Good flow properties of dried plant products are particularly necessary for direct compression [21]. According to the USP 30-NF 25 [18], repose angles between 25 and 30° represent an excellent powder flow, between 31 and 35° the flow can be considered good, and within the 36–40° range the flow is fair. For values higher than 41°, the powder has bad flow properties. The obtained angles of repose were 26 ± 3°, 23 ± 2° and 20 ± 4° for the powders containing Na-CMC of ultra high, high and medium viscosity, respectively (Table 1). Thus, for all the polymers tested, the powder flow was excellent.

Regarding Carr Index (CI), values of 10% indicate an excellent flow, between 11 and 15% denote good flowability, between 16 and 20% reveal fair flow, between 21 and 25% indicate acceptable flow, and

Table 1
Process yields, flow properties and moisture content of co-spray-dried powders.

Sample	Angle of repose (°)	Carr's Index (%)	Moisture content (%)	Process yield (%)
SR: SiO_2:Na-CMC UAV (1:1:0.3)	26 ± 3	15 ± 2	2.05 ± 0.57	34.10 ± 3.90
SR: SiO_2: Na-CMC AV (1:1:0.3)	23 ± 2	15 ± 1	2.06 ± 0.33	60.50 ± 1.80
SR: SiO_2: Na-CMC MV (1:1:0.3)	20 ± 4	13 ± 2	2.55 ± 0.17	76.36 ± 0.93
SR: SiO_2: Na-CMC MV (1:1:0.15)	17 ± 3	13 ± 2	2.76 ± 0.24	81.80 ± 0.72
SR: SiO_2: Na-CMC MV (1:1:0.075)	25 ± 5	15 ± 2	2.56 ± 0.13	83.57 ± 0.90
SR: SiO_2: Na-CMC MV (1:1:0.0375)	25 ± 3	16 ± 1	2.62 ± 0.11	83.43 ± 0.98

between 26 and 31% are an indication of poor flow [18]. The CI of the three tested powders were in the range 13 ± 2% to 15 ± 2%, indicating good flowability (Table 1). The relative good agreement found between the Carr Index and the angle of repose measurements demonstrates that all the produced co-spray-dried powders had appropriate properties for direct compression. Therefore, the flow properties were almost not affected by the polymer viscosity.

The mean moisture contents of the powders were between 2.05 and 2.55%. According to the open literature, these values are relatively low for spray-dried plant extracts. Among other authors, Tonon et al. [23] reported moisture contents between 4 and 15% for different spray-dried plant extracts with drying adjuvants (such as maltodextrin and SiO_2). In previous studies, the use of SiO_2 in a SR:SiO_2 ratio of 1:1 was found to be effective in lowering the moisture content of Cáscara sagrada spray-dried powders [13]. This effect was also observed for the *H. virginiana* extract. In fact, the moisture content of spray-dried FPE and SR:SiO_2 1:1 was about 3.2 ± 0.42% and 2.4 ± 0.23%, respectively.

The achieved process yields were 34.10, 60.50 and 76.36% for the powders containing Na-CMC of ultra high, high and medium viscosity, respectively. As all the spray-drying experiments were run under the same operating conditions, the different process yield values could be explained in terms of the Na-CMC molecular weight [19]. As reported by Tonon et al. [23], the increase in feed viscosity can increase the adhesion of the solids on the spray-dryer wall, reducing the process yield.

In a first stage, preliminary *in vitro* extract release experiments of compacted powders with Na-CMC of different viscosities were carried out for 4 h in distilled water (Fig. 2). The release profiles were similar; the f_2 factor value was higher than 76. The similarity among the release profiles could be attributed to the relatively high percentage of polymer used (13 wt.%). Some authors, such as Escudero et al. [34] and Maderuelo et al. [4], highlighted that when percentages of a hydrophilic polymer (Hydroxypropyl methylcellulose) were around 20 wt.%, the variation in the viscosity grade did not cause important changes in the drug release behavior.

Taking into account this similarity among release profiles in distilled water for the three Na-CMC viscosities, the matrix containing medium-viscosity Na-CMC (SR:SiO_2:Na-CMC MV = 1:1:0.3) was selected to further study the release behavior of the extract in biorrelevant media (pH 1.2 followed by pH 6.8). Na-CMC MV enabled the production of a powder with good flow properties for direct compression and satisfactory moisture content with the highest process yield.

3.2. Effect of Na-CMC MV concentration

The influence of Na-CMC MV concentration on powder flow properties, moisture content, process yield and extract release from compacted powders was evaluated.
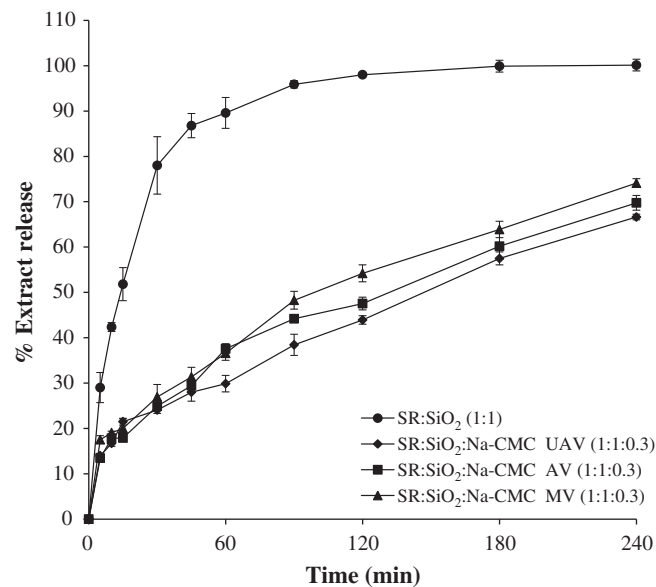

Fig. 2. Extract release from SR:SiO_2 compacts and matrix systems with different Na-CMC viscosity grades in distilled water.

As it can be observed in Fig. 3, the 1:1:0.3 SR:SiO_2:Na-CMC MV matrix did not enable a complete extract release when it was immersed in SGF for 2 h followed by 6 h in SIF (simulating physiological conditions). For this reason, new co-processed powders containing decreasing proportions of Na-CMC MV (SR:SiO_2:Na-CMC MV ratio: 1:1:0.15, 1:1:0.075 and 1:1:0.0375) were obtained under the same spray-drying operating conditions previously described. The comparison of the extract release profiles between the 1:1:0.3 and 1:1:0.15 SR:SiO_2:Na-CMC matrices gave an f_2 value of 28, therefore the profiles were not similar. For the 1:1:0.15 and 1:1:0.075 ratios, the f_2 value was 53, indicating similarity between these two release profiles. On the other hand, the 1:1:0.0375 SR:SiO_2:Na-CMC rapidly liberated the extract, because the polymer concentration was insufficient to modify the extract release. As expected, the extract release rate decreased as the polymer concentration increased, basically due to the higher gel viscosity [35–37].

All the tested formulations containing Na-CMC MV exhibited good flow properties (see Table 1). Moreover, the corresponding process
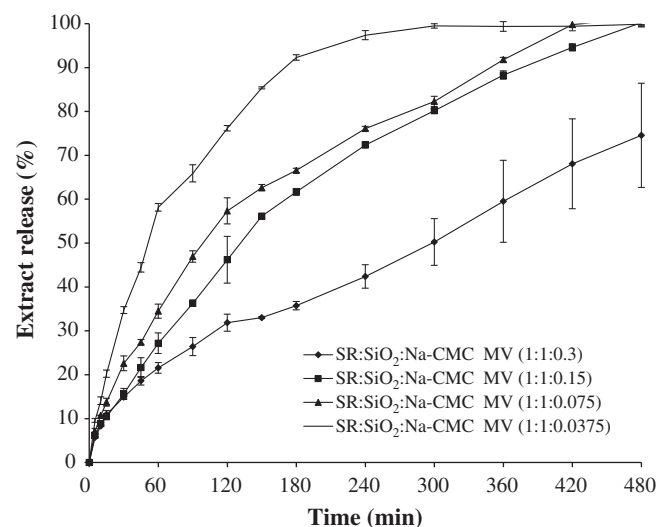

Fig. 3. Extract release from matrix systems with different Na-CMC MV concentrations in SGF (the first 2 h) and SIF (the remaining 6 h).

yields can be considered excellent (76.36, 81.80, 83.57 and 83.43% for SR:SiO$_2$:Na-CMC equal to 1:1:0.3, 1:1:0.15, 1:1:0.075 and 1:1:0.0375, respectively) taking into account that the powders were obtained in a lab-scale spray dryer. The process yield increase could be attributed to the decrease in the Na-CMC content, which results in liquid dispersions with lower viscosity (4.81 ± 0.02, 2.86 ± 0.01, 1.88 ± 0.02 and 1.71 ± 0.12 cSt for SR:SiO$_2$:Na-CMC equal to 1:1:0.3, 1:1:0.15, 1:1:0.075 and 1:1:0.0375, respectively) and, thus, with lower adhesion to the spray-dryer chamber walls [23]. Regarding the moisture content, all the SiO$_2$:Na-CMC MV samples presented values lower than 2.80% (see Table 1).

Based on the experimental results previously analyzed it can be concluded that both compacts, 1:1:0.075 and 1:1:0.15 SR:SiO$_2$:Na-CMC, were good from a pharmaceutical point of view (high process yield, good flow properties, relatively low moisture content and adequate drug release profile). Due to its lower Na-CMC MV content, the 1:1:0.075 SR:SiO$_2$:Na-CMC powder was selected for further characterization studies and analysis of the extract release mechanism.

3.3. Material characterization

3.3.1. Particle morphology and size distribution

The 1:1:0.075 SR:SiO$_2$:Na-CMC powder exhibited an unimodal and non-Gaussian particle size distribution, and a mean volume particle diameter of 10.67 ± 0.03 μm (Fig. 4).

The initial raw material and process conditions play an important role in particle formation [38]. In this study, the operating conditions were the same for all the experiments; therefore, the differences in particle morphology could be attributed to the qualitative and quantitative composition used for preparing each sample. The pure extract particles (*i.e.* without additives) were either smooth or slightly shriveled and spherical (Fig. 5 a). In the case of the co-processed 1:1 SR:SiO$_2$ powder, the particles were mostly of spherical shape with a rough surface (Fig. 5 b). This type of surface is characteristic of particles containing SiO$_2$ [39]. As suggested by Gradon et al. [40] and Nandiyanto et al. [41], among others, the rough surface could be ascribed to the migration of small suspended SiO$_2$ particles to the surface of the droplet during drying. The spray-dried particles of Na-CMC MV were smooth and corrugated, as observed in Fig. 5 c. This morphology was also reported for other spray-dried products containing polymers [42,43].
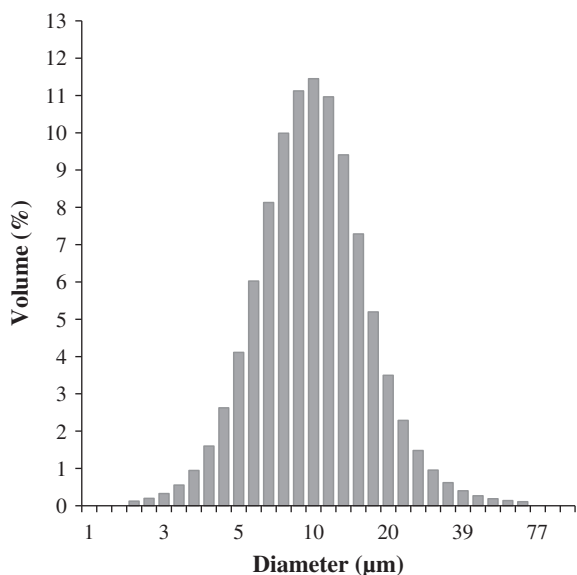

Fig. 4. Particle size distribution for the 1:1:0.075 SR:SiO$_2$:Na-CMC MV sample.

Ternary co-processed particles exhibited a rough surface associated with the presence of SiO$_2$ (Fig. 5 d). Some particles were corrugated, and the degree of this surface corrugation was related to the Na-CMC MV concentration (Fig. 5 e and f). Corrugated shapes are generally associated with less cohesive and more dispersible particles [44]. This feature and the possible presence of SiO$_2$ on the particles surface could be responsible for the good flow found for co-processed powders.

3.3.2. Powder X-ray diffraction (PXRD)

The 1:0:0, 1:1:0, 0:1:0 and 1:1:0.075 SR:SiO$_2$:Na-CMC MV samples were subjected to XRD measurements. All the tested samples exhibited a completely amorphous state, confirmed by the presence of broad non-defined peaks with abundant noises (Fig. 6). Therefore, the spray-drying process did not affect the structure of the original components of the co-processed powders.

3.3.3. Hygroscopicity

The hygroscopicity measurements carried out for the extract without additives and pure Na-CMC MV indicated that both were very hygroscopic materials. The moisture uptake for these samples, stored for 7 days at RH = 75.3%, was 26.6 ± 0.1 and 25.7 ± 0.9 g per 100 g of dry solids, respectively. On the other hand, the hygroscopicity values obtained for the 1:1:0.3, 1:1:0.15 and 1:1:0.075 SR:SiO$_2$:Na-CMC MV samples were 17.26 ± 0.32, 16.29 ± 0.19 and 16.53 ± 0.16 g per 100 g of dry solids, respectively. The moisture uptaken by the ternary co-processed powders was lower than those corresponding to the pure SR and Na-CMC MV. Finally, the hygroscopicity value of 1:1 SR:SiO$_2$ was 12.7 ± 0.5 g per 100 g of dry solids. These results suggest the importance of using SiO$_2$ as drying adjuvant to produce powders less sensitive to relative humidity changes. Similar results were found for plant extracts of Cáscara sagrada and *Bauhinia forficata* [12,13].

3.3.4. Glass transition temperature

Glass transition is a well-known phase transformation of amorphous materials from a glassy to rubber-like state [45]. The temperature at which this transition occurs is called glass transition temperature (T_g). The powder stability is closely associated with the T_g values, which depend on storage conditions such as humidity and temperature. For constant RH conditions, amorphous materials with T_g values above storage temperature can be considered stable [46]. The glass transition temperatures were 73.9, 118.8, and 138.1 °C for the 1:0:0, 1:1:0 and 1:1:0.075 SR:SiO$_2$:Na-CMC MV samples, respectively. These results indicated that the selected additives increased the T_g of the powders, enhancing product shelf life. Even in a low proportion, the addition of Na-CMC MV increased the T_g significantly (approximately 20 °C compared to that of the 1:1:0 SR:SiO$_2$:Na-CMC MV samples). The stability provided by the selected additives was also evident when the samples were conditioned at 75% RH. The extract without additives changed into a rubbery state, whereas the extract with additives (with and without the polymer) remained as a powder.

Several authors have found that the stickiness phenomenon is closely related to T_g. The stickiness on the spray-dryer walls usually occurs at operating temperatures above the product glass transition temperature [46], leading to low process yields and operational problems. Considering the estimated T_g values, and the fact that for all the spray-drying experiments the outlet air temperature was about 92–95 °C, the worst process yield would be expected for the FPE without additives. In fact, the process yield for this sample was 68%, while the yields for the ternary co-processed powders containing Na-CMC MV were above 76%.

3.3.5. Compactability

Fig. 7 presents, for the 1:1:0.075 SR:SiO$_2$:Na-CMC MV compacts, hardness as a function of compression force. For all the tested compression forces, compact hardness was above 5 kg$_f$, indicating that the co-processed material was suitable for direct compression [47].
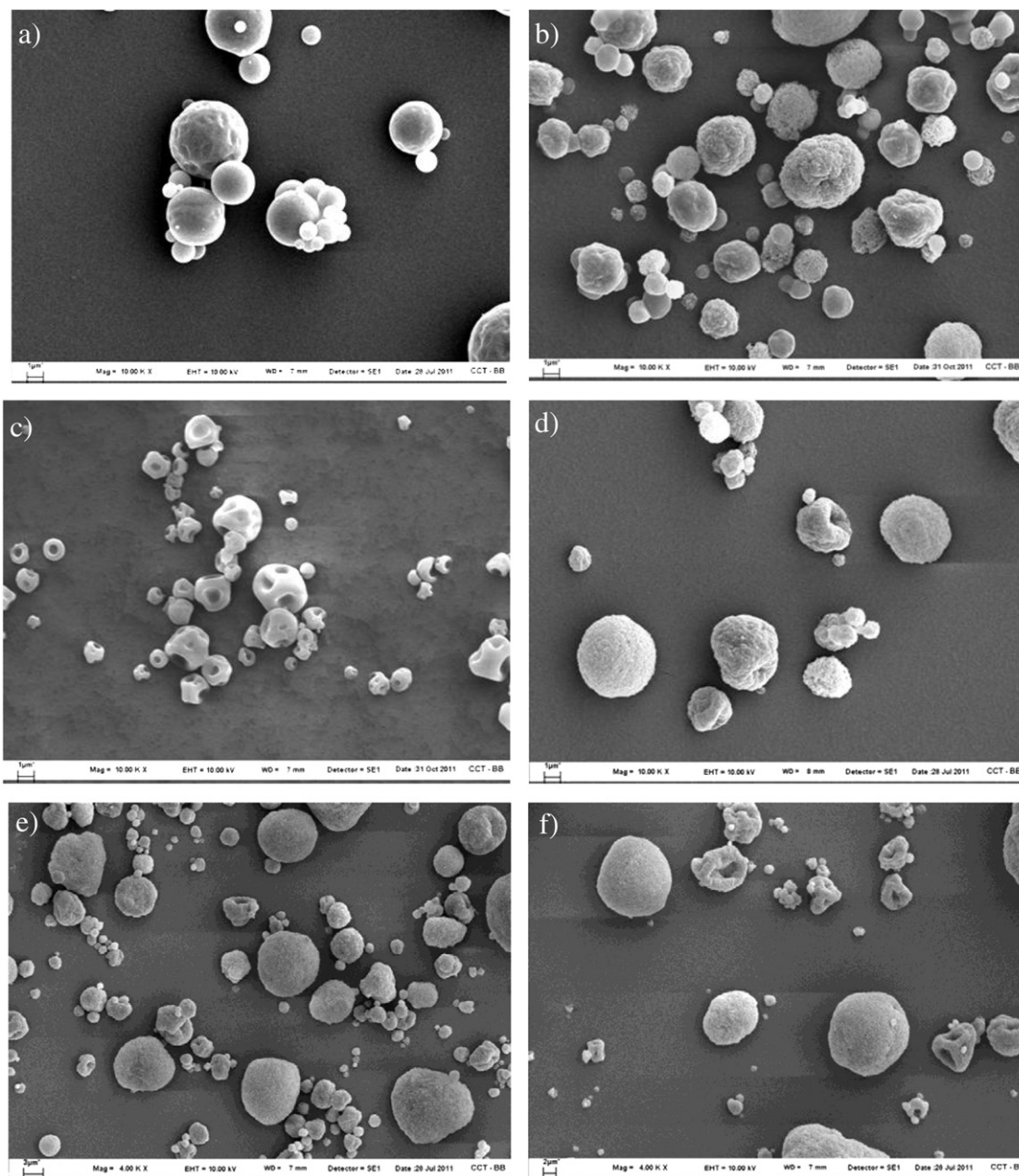
Fig. 5. SEM microphotographs. a) Extract without excipients 10,000×, b) SR:SiO$_2$ 1:1 10,000×, c) spray dried Na-CMC MV 10,000×, d) SR:SiO$_2$:Na-CMC MV 1:1:0.075 10,000×, e) SR:SiO$_2$:Na-CMC MV 1:1:0.075 4000×, f) SR:SiO$_2$:Na-CMC MV 1:1:0.3 4000×.

Therefore, the powders exhibited not only appropriate flow properties, but also good compactability.

3.4. Plant extract release mechanism

In order to elucidate the extract release mechanism, the following studies were performed: water uptake, swelling dynamics, release kinetics in media with different pH, and matrix erosion.

3.4.1. Water uptake

Swelling of a polymer matrix depends on the rate of water penetration into the system [48]. As shown in Fig. 8, the 1:1:0.075 SR:SiO$_2$:Na-CMC MV matrix incorporated more than 40% of its weight in water after 30 min of the test. This fast water uptake could be explained in terms of the hydrophilic characteristics of the particle

constituents (water-soluble extract, hydrophilic polymer and colloidal silicon dioxide) [49]. Good wetting properties are desired to facilitate the formation of the gel layer around the matrix when it is in contact with the fluid. The gel layer modulates the penetration of water into the dry core, reducing the water uptake over time.

3.4.2. Radial front movement

Front movement kinetics was evaluated for the 1:1:0.075 SR:SiO$_2$: Na-CMC MV sample. As previously described in Section 2.15.2 and shown in Fig. 1, which presents a photograph of the matrix at 180 min after the start of the test, the 1:1:0.075 SR:SiO$_2$:Na-CMC MV compact behaved as a swellable matrix, presenting swelling, diffusion and erosion fronts.

Colombo et al. [6] defined the gel layer thickness as the difference between the positions of the erosion and swelling fronts. As shown in
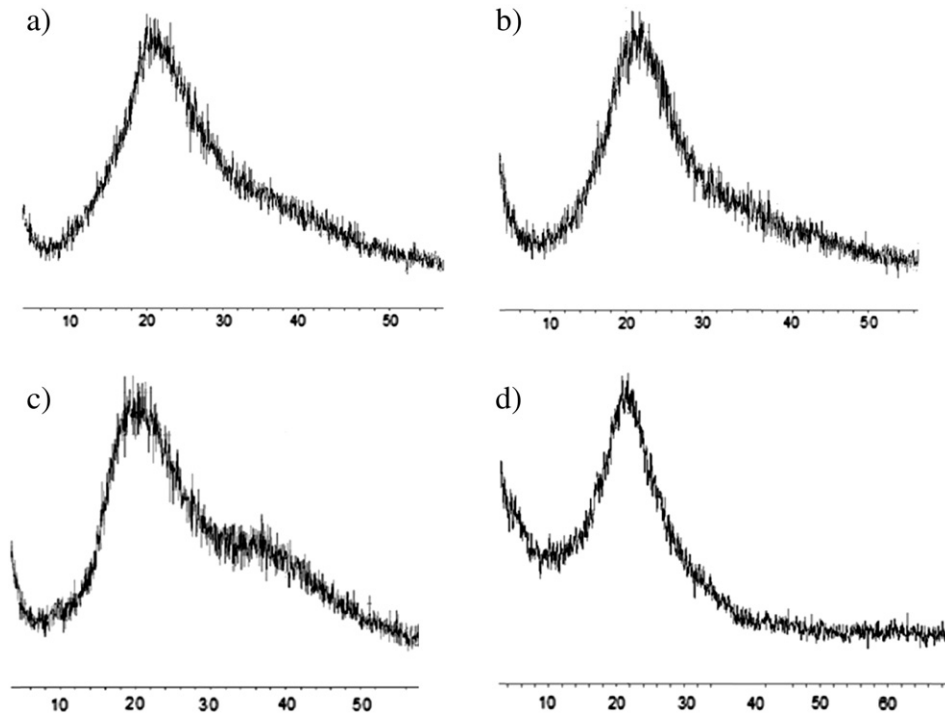
Fig. 6. X-ray diffraction (XRD) patterns. a) Extract without excipients, b) extract SR:SiO₂:Na-CMC MV (1:1:0.075), c) Na-CMC MV and d) SiO₂.

Fig. 9, the gel layer thickness, which has to be crossed by the extract, varied with time.

The rate of outward movement of the erosion front was relatively rapid during the first stage due to the swelling process (Fig. 9); then a balance between expansion and erosion of the gel layer took place slowing down the erosion front movement [50]. As presented in Fig. 1, the matrix surface showed signs of erosion, a typical characteristic of Na-CMC earlier noticed in different dissolution profiles [51,52].

In addition, the changes in extract color intensity in Fig. 1 reflected the diffusion of the plant extract through the gel layer. As expected for matrices containing soluble drugs [5], an inward movement of the diffusion front was observed. Simultaneously, the absolute value of the distance between the swelling front and the initial position increased substantially as expected for hydrophilic matrices.
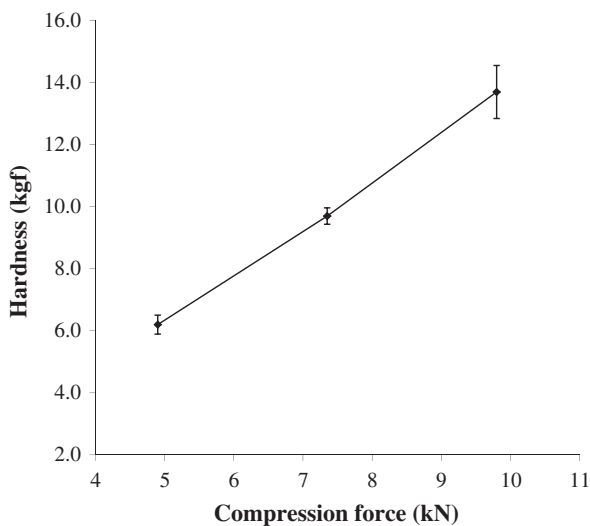
3.4.3. Drug release studies in different media

For some hydrophilic matrices, drug release is affected by the changes in gel layer properties due to gastrointestinal tract pH variations [3]. Na-CMC is an anionic polymer, prone to erosion and sensitive to the dissolution fluid pH [51]. For this reason and with the purpose of understanding the extract release mechanism, dissolutions test in media with different pH (1.2 and 6.8) were performed.

As shown in Fig. 10, at pH 1.2 the 1:1:0.075 SR:SiO₂:Na-CMC MV matrices did not release the extract completely by the end of the testing period (8 h). According to a visual inspection of the dissolution test, the matrices initially swelled, the extract diffused through the gel layer and erosion took place during the first 3 h. From this time onwards, the reached volume remained constant and no erosion was observed. At the end of the dissolution test, residual matrices containing the remaining extract were found. The Na-CMC present
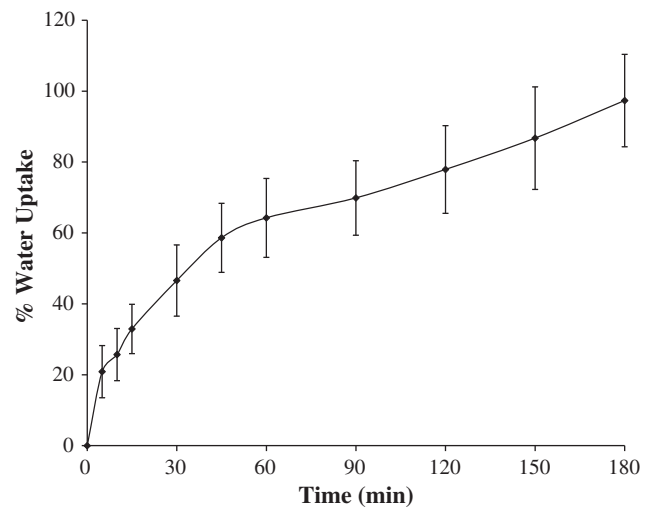

Fig. 7. Compactability curve for 1:1:0.075 SR:SiO₂:Na-CMC MV matrices.
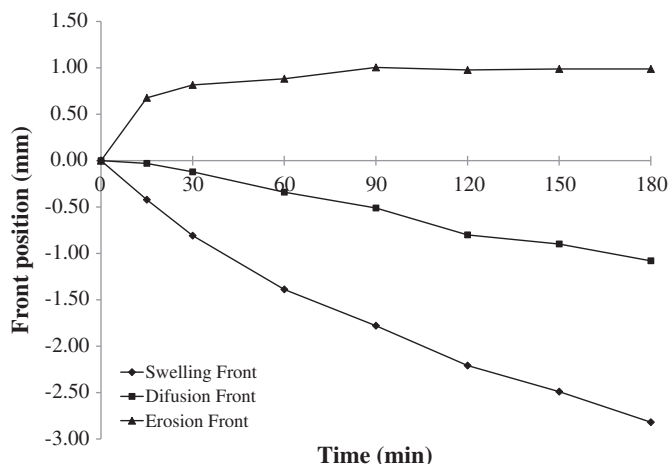

Fig. 8. Water uptake percentage by 1:1:0.075 SR:SiO₂:Na-CMC MV matrices.

Fig. 9. Fronts movement of 1:1:0.075 SR:SiO$_2$:Na-CMC MV matrices.

Table 2
H. virginiana release kinetics parameters according to the Korsmeyer et al. [32] and Peppas and Sahlin (1989) equations.

	Korsmeyer equation			Peppas and Sahlin equation		
	n	k' (min^{-n})	r^2	k_d $(min^{-0.43})$	k_r $(min^{-0.86})$	r^2
SR: SiO$_2$:Na-CMC MV (1:1:0.075) at pH 1.2 (2 h)	0.70	0.020	0.9978	0.020	0.0068	0.9985
SR: SiO$_2$:Na-CMC MV (1:1:0.075) at pH 6.8 (8 h)	0.67	0.020	0.9892	0.022	0.0052	0.9929

in the matrices at pH 1.2 probably reverted to its acidic form, which is an insoluble substance in water and acidic medium [53]. Therefore, the possible consolidation of an insoluble external layer limited the extract release and matrix erosion. On the other hand, at pH 6.8 the matrices provided a complete extract release in 8 h (Fig. 10). The matrices swelled and, during the dissolution test, their dimensions decreased drastically as a result of polymer erosion. This behavior was confirmed by the erosion study, which is discussed in the following section. The complete extract release could be attributed to the high solubility of Na-CMC at this pH, which is related to the presence of ionized carboxylic acid groups [3,52,54]. Similar behaviors were found by Conti et al. [3,54] for matrices of Diltiazem HCl and Na-CMC. As presented in Fig. 3 and included in Fig. 10 (dashed lines), the 1:1:0.075 SR:SiO$_2$:Na-CMC MV matrices exposed to pH 1.2 for 2 h and then to pH 6.8 for 6 h also released the extract completely by the end of the experiment. Due to the change in the medium, the release profile between 2 and 4 h became slower than that measured at pH 1.2 for 8 h. This behavior could be explained in terms of the CMC insoluble acidic form that previously appeared on the external layer at pH 1.2, which needs some time at pH 6.8 to revert from the high resistance layer (CMC acidic form) to an erodible layer (CMC salt).
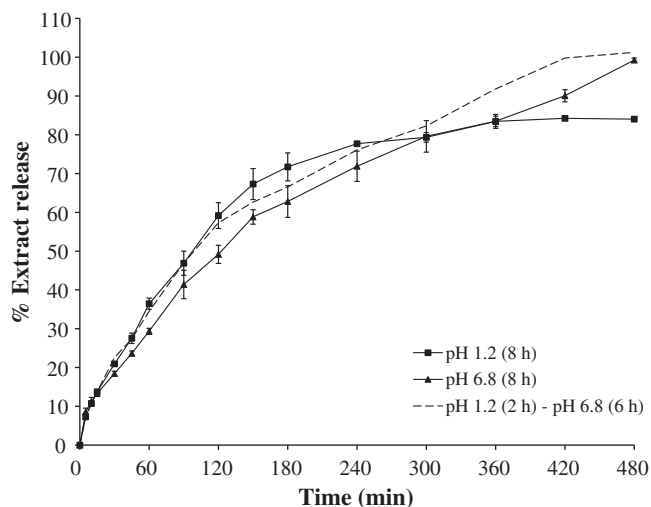
The parameters for each tested kinetics equation together with the determination coefficient (r^2) used to evaluate the goodness of the release models are listed in Table 2. The release profiles for the matrices exposed to pH 1.2 for 2 h and then to pH 6.8 for 6 h and to pH 1.2 for 8 h were almost the same up to 120 min, time at which the drug release percentages were lower than 60%, the maximum release value required to apply the Korsmeyer [33] and Peppas and Sahlin [33] equations. In agreement with the visual observations, the fitted n value corresponding to the Korsmeyer equation was 0.7 and 0.67 for pH 1.2 and 6.8, respectively (Table 2). These values implied that, for both media, the release was not a Fickian diffusional transport involving diffusion and polymer relaxation–erosion as part of the initial drug release mechanism.

According to Peppas and Sahlin [33] parameters given in Table 2, for the 120 min assay time, the ratios of relaxational over Fickian contributions (Eq. (6)) were 2.66 and 1.85 at pH 1.2 and 6.8, respectively. These results indicated that at pH 1.2 and 6.8 polymer relaxation was responsible for 73% and 65% of the total drug release at that time, respectively. Consequently, the drug release by erosion seems to be more important than the drug transport by diffusion.

3.4.4. Erosion studies

The matrix weight loss and extract release in the dissolution medium for the 1:1:0.075 SR:SiO$_2$:Na-CMC MV sample at pH 6.8 is shown in Fig. 11. For the dissolution tests, tablets of 570 mg (containing 275 mg of SR, 275 mg of SiO$_2$ and 20 mg of Na-CMC MV) were used. Considering the initial matrix weight and composition, Fig. 11 shows that the matrix weight loss was always higher
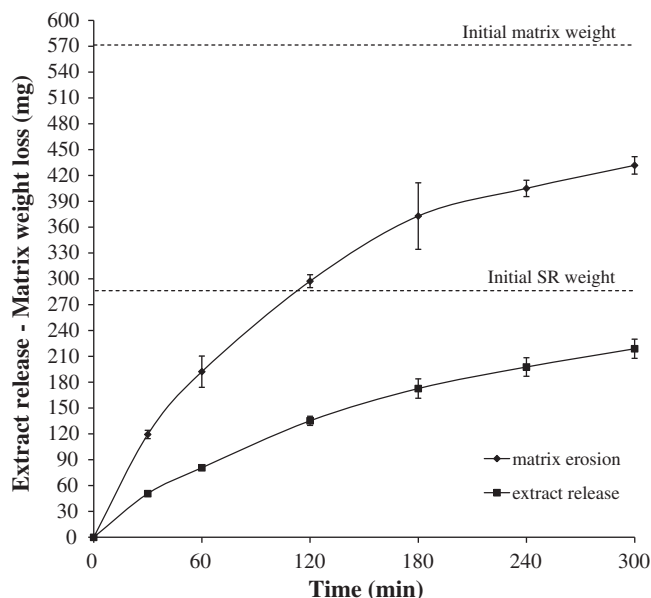

Fig. 10. Extract release from 1:1:0.075 SR:SiO$_2$:Na-CMC MV matrices at different pH media.

Fig. 11. Erosion and release profiles for the 1:1:0.075 SR:SiO$_2$:Na-CMC MV matrices: matrix weight loss and extract release.
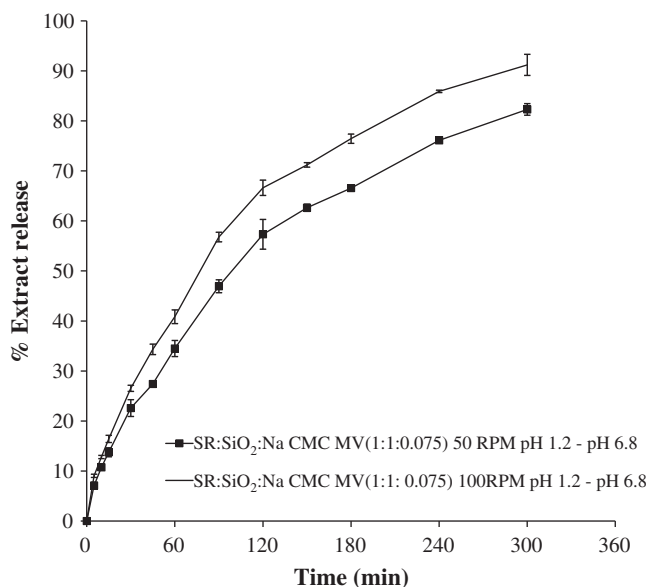
Fig. 12. Extract release profiles for the 1:1:0.075 SR:SiO₂:Na-CMC MV matrices at different RPM, in SGF (the first 2 h) and SIF (the remaining 6 h).

than the released extract weight and after 120 min even higher than the initial SR weight. Therefore, the results indicate that the gel layer erosion mechanism takes place [52].

According to the extract release profiles shown in Fig. 12, and in agreement with the expected behavior for erodible matrix systems [55], the higher the dissolution medium agitation speed, the higher the rate of extract release. This result together with those of the radial front movement studies and the release mechanism suggested by the analyzed kinetic models confirmed that the extract release is given by a combination of drug diffusion and matrix erosion.

4. Conclusions

The scalable spray-drying technology together with the proposed co-processed formulation (regardless of polymer viscosity) gave powders with good flow properties for direct compression and low moisture contents. However, the use of medium viscosity Na-CMC led to the highest process yields. Polymer concentration was the main factor in the extract release modulation. The results indicated that the 1:1:0.075 SR:SiO₂:Na-CMC MV ternary co-processed powder exhibited very attractive properties such as good flowability, low moisture content, low hygroscopicity, high T_g value, good compactability and adequate drug release profiles. Drug transport to the dissolution medium took place by combined mechanisms of extract diffusion and matrix erosion. Moreover, the polymer relaxational contribution appeared to be the main mechanism for the drug release.

This work allowed the development of novel modified-release materials based on a medicinal plant extract with improved powder functionality *via* spray-drying. Through the use of specific methodologies, the variables and mechanisms that modulate *H. virginiana* extract release were identified.

The efficacy of modified *H. virginiana* extract release on the treatment of varicose veins should be verified by further studies. That analysis was beyond the scope of the present work, which aimed at evaluating the potential of MRS based on a hydrophilic matrix to modulate the release rate of model plant extracts.

Acknowledgements

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