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# Catalyst-free synthesis of 5-hydroxymethylfurfural from fructose by extractive reaction in supercritical CO<sub>2</sub> – subcritical H<sub>2</sub>O two-phase system

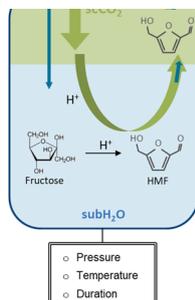
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An extractive reaction configuration using supercritical carbon dioxide (scCO<sub>2</sub>) as the extracting solvent was tested for the production of 5-hydroxymethyl furfural (HMF) from a 5 wt% fructose aqueous feed. In this configuration, extraction of HMF by scCO<sub>2</sub> prevents HMF degradation in the aqueous phase. Because of water co-extraction by scCO<sub>2</sub>, the volume of the reactional mixture was maintained by continuous injection of water. Reaction was operated in a 90 mL high pressure reactor, where an HMF maximum yield of 62.4 % was achieved at 160 °C and 25 MPa, with a CO<sub>2</sub> flow rate of 20 g.min<sup>-1</sup> for 420 min. This is the first time that HMF is reportedly produced with such a yield by a catalyst-and organic solvent-free process. Besides, the separation efficiency reached 97.3 % and the relative purity of HMF in the extract was 95.8 wt%. Therefore, this configuration avoids post reactional purification which is needed in conventional batch processes or in extractive

reaction processes using organic solvents. Based on kinetic and thermodynamic studies, modeling of the extractive reaction process was developed to perform a sensitivity analysis for CO<sub>2</sub> flow rate and extraction efficiency, upon the HMF yield. As an example, it was shown that for 800 min reaction duration, a CO<sub>2</sub> flow rate of 100 g.min<sup>-1</sup> or an extraction efficiency increase by a 10-fold factor could theoretically led to HMF yields of 73.0 % and 73.7 %, respectively.

## Nomenclature

C	concentration, mol.L <sup>-1</sup> .
E	extraction coefficient.
m	mass, g.
KK	partition coefficient.
K'	thermodynamic equilibrium constant.
M	molar mass, g.mol <sup>-1</sup> .
m	mass, g.
n	number of moles, mol.
ṅ	molar flow rate, mol.min <sup>-1</sup> .
P	pressure, MPa.
Q	volumetric flow rate, L.min <sup>-1</sup> .
R	rate of reaction or extraction, mol.L <sup>-1</sup> .min <sup>-1</sup> .
S	selectivity.
T	temperature, °C.
t	reaction duration, min.
V	volume, L.
X	conversion rate.
x	mole fraction.

Y	yield.
scCO <sub>2</sub>	supercritical carbon dioxide.
subH <sub>2</sub> O	subcritical water.

### Greek symbols

α	mass transfer efficiency coefficient.
ρ	density, g.L <sup>-1</sup> .

### Subscripts

CO <sub>2</sub>	carbon dioxide.
H <sub>2</sub> O	water.
F	fructose.
FA	formic acid.
HMF	5-hydroxymethylfurfural.
LA	levulinic acid.

### Superscripts

<sup>0</sup>	initial.
<sup>L</sup>	liquid phase (bottom phase in the reactor).
<sup>V</sup>	vapor phase (upper phase in the reactor).

## 1. Introduction

Because of the anticipated depletion of fossil hydrocarbons together with the environmental impact of their use, lignocellulosic biomass appears to be the major renewable option to produce fuels, materials and chemicals. Among the various chemical building blocks that can be synthesized from renewable C6 sugars, 5-hydroxymethylfurfural (HMF) is a highly versatile and valuable platform chemical [1]. For instance, its oxidation can produce furan-2,5-dicarboxylic acid (FDCA) that can be further transformed into polyethylene furanoate (PEF), a potential substitute to oil based polyethylene terephthalate (PET) [2,3]. Another example of HMF application is its hydrogenation into 2,5-bishydroxy-methylfuran (BHMF) that can be used to produce polyester polymers by enzymatic catalysis without any toxic residuals, an interesting property for tissue engineering applications [2,4].

The main pathway for the production of HMF from cellulose (Fig. 1), which represents about 50 % of the lignocellulosic biomass, implies the hydrolysis of the β-1, 4-glycosidic bond in order to release glucose, then the isomerization of glucose into fructose, and finally the dehydration of fructose into HMF [5,6]. The dehydration of fructose into HMF in aqueous medium requires an acid catalyst and temperatures in the range of 120–180 °C [7–10]. In these conditions, HMF is further degraded into formic acid and levulinic acid by rehydration, and to humins by cross-polymerization with fructose, leading to a maximum yield of about

50 % in a classic batch process [11,12]. Its purification is then usually carried out using a liquid-liquid (L–L) separation step. A recent industrial development regarding HMF production relied on the conversion of fructose in an aqueous media at 200 °C and 2 MPa, using a strong acid catalyst, and in a second step on the use of an organic solvent for the L–L extraction of the produced HMF [13]. To boost the HMF selectivity and yield, the combination of reaction and separation in a single step has been suggested [11,14–16]. This process intensification strategy relies on biphasic systems where HMF is synthesized in the aqueous phase, using a strong acid catalyst, *e.g.*, mineral acid or zeolite, and continuously extracted in the organic phase, *e.g.*, methyl isobutyl ketone (MIBK), to avoid its degradation. The production of HMF from fructose by extractive reaction with hydrochloric acid as the acid catalyst and MIBK as the extracting solvent in an RTL (Graesser raining-bucket) contactor has been modeled and optimized, and a minimal cost of production of 1.90 \$/kg of HMF has been evaluated [17]. Continuous extractive reaction using the same chemicals was also studied in a biphasic microreactor, and an organic-to-aqueous volume ratio of 2 using MIBK at 200 °C with a residence time of 2 s was found to give the highest HMF yield (93 %) and a productivity of 60 kg.L<sup>-1</sup>.h<sup>-1</sup> [18]. More generally, the HMF yield from glucose or fructose using extractive reaction in biphasic microreactors with an organic solvent reached values higher than 80 % [15]. However, the use of MIBK or other organic solvents leads to separation issues, with some of the HMF remaining in the recycled solvent and some solvent contaminating the HMF fraction

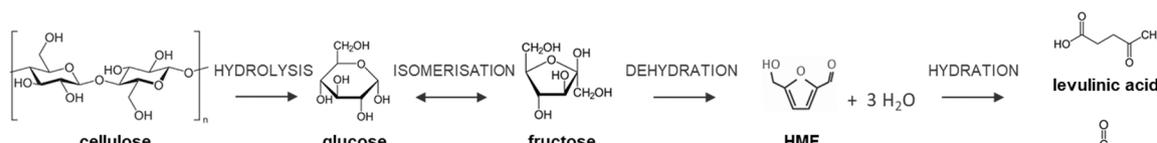


Fig. 1. Reaction pathway for the synthesis of 5-hydroxymethylfurfural from cellulose.

after distillation [14]. A study based on COnductor-like Screening MOdel for Realistic Solvents (COSMO-RS), has shown that ten organic solvents with better environmental, health and safety (EHS) impacts than MIBK (e.g., ethyl acetate and methyl propionate), exhibit partition coefficients sometimes higher than MIBK ( $K = 3.1$ ) for the system water-HMF-solvent with values comprised between 1.9 and 3.8 [10]. However, because of a lack of thermodynamic data, supercritical CO<sub>2</sub> (scCO<sub>2</sub>), a solvent with very low EHS impacts, was not assessed in this latter work.

The use of scCO<sub>2</sub> as a solvent for the purification of platform molecules by a reactive extraction processes, where a reaction, e.g., complexation, helps the extraction, has already been studied. For instance, acetic acid [19] or citric acid [20] have been extracted from water by scCO<sub>2</sub>, using tri-*n*-octylamine to complex with the carboxylic acids and help their extraction. Likewise, scCO<sub>2</sub> has been used as the extractive solvent in an extractive reaction process applied to the production of furfural from xylose, with the use of a solid acid catalyst in the aqueous phase [21]. The maximum furfural yield (52.3 %) was achieved at 150 °C and 20 MPa, with a CO<sub>2</sub> flow rate of 3.77 g.min<sup>-1</sup> and an initial load of 0.4 g of xylose. In this scCO<sub>2</sub> – subcritical H<sub>2</sub>O (subH<sub>2</sub>O) system, furfural presents a partition coefficient equal to 0.959 at 150 °C and 20 MPa [21]. In a recent study, extractive reaction of HMF from glucose was performed in a two-phase scCO<sub>2</sub> – subH<sub>2</sub>O system [22]. The experimental maximum HMF yield (32.6 %) obtained at 200 °C and 20 MPa, with a CO<sub>2</sub> flow rate of 1.9 g.min<sup>-1</sup> and an initial load of 0.3 g of glucose, was lower than the maximum yield that can be obtained from fructose (48 %) in a similar biphasic system in batch mode [12] and the separation efficiency (ratio of extracted HMF to total produced HMF) was only 12.7 % [22]. Some studies [10,23] have proposed the addition of salts (e.g., NaCl) in the aqueous phase or the use of ethanol as co-solvent in scCO<sub>2</sub> to improve the partition coefficient of HMF.

Moreover, when contacted with high pressure CO<sub>2</sub>, the pH of water decreases to a value close to 3.2 at 150 °C and 15 MPa [24] due to carbonic acid formation, providing an acidic media that can promote the acid-catalyzed dehydration of sugars into furans (e.g., fructose into HMF and xylose into furfural) which constitutes another advantage of using scCO<sub>2</sub> as the solvent in this system. This was evidenced by Labauze et al. [12] who studied the kinetics of dehydration of fructose into HMF, in a biphasic scCO<sub>2</sub> – subH<sub>2</sub>O system, without any added catalyst, at 120 – 160 °C and 10 – 25 MPa. Actually, a moderate acid catalytic action of CO<sub>2</sub> was experimentally observed due to the autocatalytic character of the reaction and a specific kinetic model (HMF production from fructose and its degradation) was developed, considering the influence of pressure and temperature and thus the CO<sub>2</sub> concentration in the aqueous phase.

In the present study, the possibility to continuously extract HMF with scCO<sub>2</sub>, during HMF synthesis from fructose without any added catalyst, was investigated. For that purpose, batch mode reactions as well as semi-continuous extractive reactions were experimentally operated. Our study focused on the assessment and improvement of the configuration using only carbon dioxide and water as catalysts and solvents, to estimate the performance (HMF yield, HMF separation efficiency, HMF purity in the extract) of this environmental-friendly extractive reaction system. Aside from the green chemistry aspect of our system – no harmful chemicals and solvents involved – compare to other processes using acid catalysts and/or organic solvents, and distillation for the separation of HMF and the organic solvent, our system also benefits from no cross contamination of solvent by HMF, and reciprocally, since a simple decrease of pressure is used to fully separate HMF and CO<sub>2</sub>. To our knowledge, this is the first reported study about the production of a furan compound from a sugar by a catalyst-and organic solvent-free process in semi-continuous extractive reaction mode with continuous injection of water. Moreover, based on kinetic and thermodynamic studies obtained in semi-continuous mode, modeling of the extractive reaction process was developed to perform a sensitivity analysis in respect to CO<sub>2</sub> flow rate and extraction efficiency, upon the global HMF

yield.

## 2. Material and method

### 2.1. Chemicals

For the experiments, D-(–)-fructose (Sigma-Aldrich, >99 % purity) was purchased from Sigma Aldrich and carbon dioxide was supplied by Air Liquide (99.98 % purity). For the analyses by high-performance liquid chromatography (HPLC), the following standards have been used: HMF (Acros Organics, 98 %), formic acid (Acros Organics, 99 %), levulinic acid (Sigma-Aldrich, 99 %) and furfural (Acros Organics, 99 %).

### 2.2. Experimental set-up

A solution of 5 wt% fructose in distilled water (about 3.7 g of fructose in 70 g of water) was charged into a 90 mL high pressure reactor (Top Industrie, France) (Fig. 2). The solution was heated to the desired temperature (120–160 °C) using electric heating collars. The temperature was reached after 15–20 min, and the reactor was charged with CO<sub>2</sub> using a piston pump with three heads (Dose HPP400-C, SFE Process), cooled with a refrigerating fluid at 3 °C. All the concentrations of re-agents were known when high pressure CO<sub>2</sub> was fed into the reactor (time zero). The CO<sub>2</sub> flow rate was measured with a mass flow meter (Bronkhorst). The extractive reaction was carried out under magnetic stirring at 500 rpm. The pressure inside the reactor was set with a heated back-pressure regulator (TESCOM - S/N 87122M). The extract, containing water, HMF and other solubilized compounds in scCO<sub>2</sub>, was collected in a heavy-walled borosilicate glass tube contained in an iced water bath with an outlet pipe connected to the vent of the installation (1 atm) to release CO<sub>2</sub>. To compensate the amount of water extracted by the CO<sub>2</sub> stream, experiments at constant liquid volume in the reactor were operated with a continuous injection of water in the reactor using a syringe pump (Model 100DX, Teledyne Isco). The inlet water flow rate was first theoretically determined based on the value of the solubility of water in scCO<sub>2</sub> calculated using the Chrastil model [25], and further adapted during the experiments based on the actual extracted water flow rate, measured at the outlet of the reactor by collecting and weighing the extract over a given time period.

At the end of the reaction, the reactor was cooled down to room temperature overnight, then the pressure was slowly released. The borosilicate tube collecting the extract and the outlet pipe plunging in this tube were rinsed with ethanol, and the rinsing solution was added to the collected extract for analysis. The final mixture in the reactor and the collected extract were weighed and filtered through a 0.45 µm filter (Millipore) before HPLC analysis.

### 2.3. Analytical methods

The liquid samples were analysed by HPLC following the NREL protocol [26], with a Dionex Ultimate 3000 system equipped with a Shodex RI-101 refractive index detector and an Agilent Hi-Plex H column. Sulfuric acid at 0.005 mol.L<sup>-1</sup> was used as the mobile phase at a flow rate of 0.6 mL.min<sup>-1</sup>. The column temperature was kept at 60 °C. Concentrations for the calibration curves were comprised between 0.2 and 5 wt% for fructose, 0.1 and 2 wt% for HMF, 0.05–1 wt% for formic acid and levulinic acid, 0.01 and 0.2 wt% for furfural.

### 2.4. Determination of conversion rate, yield, selectivity, separation efficiency and relative purity

Fructose conversion rate ( $X_F$ ), global HMF yield ( $Y_{HMF}$ ), and HMF selectivity ( $S_{HMF}$ ) were calculated from the following equations (Eqs. 1, 2 and 3).

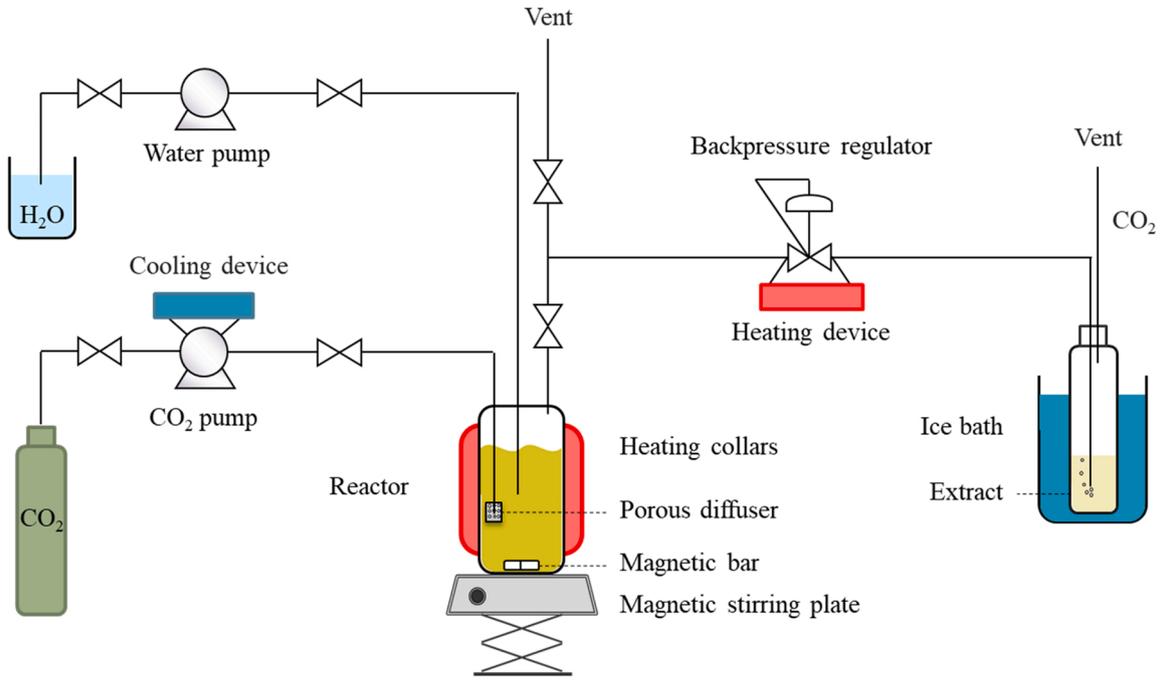


Fig. 2. Experimental set-up for the production of 5-hydroxymethylfurfural from fructose by semi-continuous extractive reaction in a supercritical CO<sub>2</sub> – subcritical H<sub>2</sub>O two-phase system.

$$X_F = \frac{n_F^0 - n_F}{n_F^0} \quad (1)$$

$$Y_{HMF} = \frac{n_{HMF,extract} + n_{HMF,reactor}}{n_F^0} \quad (2)$$

$$S_{HMF} = \frac{n_{HMF,extract} + n_{HMF,reactor}}{n_F^0 - n_F} \quad (3)$$

With  $n_i$  the mole amount of compound  $i$  and  $n_F^0$  the mole amount of fructose at initial time. In extractive reaction mode, the global HMF yield corresponds to the sum of the HMF yield in the extract ( $Y_{HMF,extract}$ ) and its yield in the remaining mixture in the reactor ( $Y_{HMF,reactor}$ ).

The separation efficiency was defined as the ratio of the molar quantity of the extracted HMF ( $n_{HMF,extract}$ ) to the global amount of the produced HMF ( $n_{HMF,extract} + n_{HMF,reactor}$ ) (Eq.4).

$$\text{Separation efficiency} = \frac{n_{HMF,extract}}{n_{HMF,extract} + n_{HMF,reactor}} \quad (4)$$

These parameters were assessed at the end of the reaction and not over time, because of the formation of humins, a sticky solid that plugged the pipe of the sampling device plunging in the liquid phase of the reactor, as explained in the Supplementary Data.

Since not all compounds in the extract were identified by HPLC, only a relative mass purity of HMF compared to formic acid, levulinic acid and furfural was determined in the extract following Eq. 5.

$$\text{Purity}_{HMF,extract} = \frac{m_{HMF,extract}}{m_{HMF,extract} + m_{FA,extract} + m_{LA,extract} + m_{furfural,extract}} \quad (5)$$

Where  $m_{i,extract}$  is the mass of compound  $i$  in the extract (in g).

## 2.5. Extractive reaction model

One of the objectives of modeling the extractive reaction process was to run a sensitivity analysis on parameters such as the CO<sub>2</sub> flow rate or the extraction efficiency in order to theoretically determine the most favourable conditions for HMF production. Indeed, such a study could not be experimentally done due to experimental set-up limitations.

The extractive reaction pathway for HMF production by extractive reaction is shown in Fig. 3. It is based on the conventional reaction pathway for fructose transformation into HMF, where an equation describing the HMF extraction by scCO<sub>2</sub> has been added. Maintaining a constant liquid volume allowed using the conventional equations of a batch system, where the evolution of the molar concentrations is only related to the reaction advancement and not to the removal of water by scCO<sub>2</sub>.

The reactional pathway is thus composed of five parallel and consecutive reactions ( $R_{1F}$ ,  $R_{2F}$ ,  $R_{3F}$ ,  $R_{1H}$ , and  $R_{2H}$ ) and a specific term ( $R_{ex}$ ) describing the HMF extraction from the aqueous phase (subH<sub>2</sub>O) where it is produced, into the scCO<sub>2</sub> phase.

Based on the kinetic model developed by Labauze et al. [12] for HMF synthesis in a two-phase scCO<sub>2</sub> – subH<sub>2</sub>O system, a set of differential equations to be solved was proposed. In the present work, only the rate of extraction of HMF,  $R_{ex}$ , was added in the set of differential equations to calculate the variation of HMF concentration over reaction time in the

aqueous phase ( $\frac{dC_{HMF}^L}{dt}$ ), that is expressed as follows (Eq. 6).

$$\frac{dC_{HMF}^L}{dt} = R_{1F} - R_{1H} - R_{2H} - R_{ex} \quad (6)$$

where  $R_{ex}$  is the rate of extraction of HMF (in mol.L<sup>-1</sup>.min<sup>-1</sup>).  $R_{ex}$  can be expressed as a function of  $Q_{CO_2}$ , the volumetric flow rate of CO<sub>2</sub> (in L.min<sup>-1</sup>),  $V$ , the volume of the liquid phase where the reactions take place

$$\text{(in L) and } C_{HMF}^V \text{ the concentration of HMF in the scCO}_2 \text{ phase (in mol. L}^{-1}\text{). } R_{ex} \text{, the rate of extraction of HMF, is expressed as follows (Eq. 7).}$$

$$R_{ex} = \frac{Q_{CO_2} \cdot C_{HMF}^V}{V} = \frac{Q_{CO_2} \cdot E \cdot C_{HMF}^L}{V} \quad (7)$$

where  $E$  is an extraction coefficient which will be detailed further and  $C_{HMF}^L$ , the concentration of HMF in the aqueous phase (in mol.L<sup>-1</sup>).

The experimental set-up was designed to attempt minimizing mass transfer limitation by using a porous diffuser for the generation of small bubbles of scCO<sub>2</sub> into the subH<sub>2</sub>O phase, in order to ensure a large interfacial supercritical fluid-liquid area and a magnetic stirring in the reactor for longer residence time of the bubbles (Fig. 2). However, to

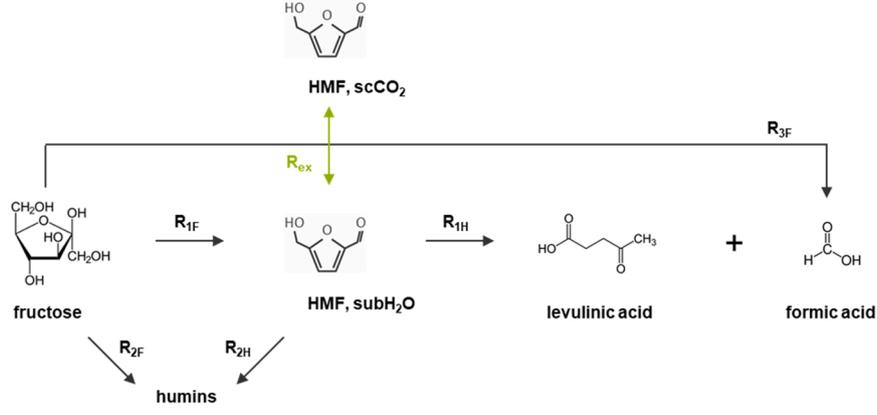


Fig. 3. Extractive reaction scheme for 5-hydroxymethylfurfural production as considered in this study.

consider possible mass transfer limitation, we used an extraction coefficient ( $E$ ) defined as follows (Eq. 8).

$$E = K'_{HMF} \cdot \alpha \quad (8)$$

where  $K'_{HMF}$  is the thermodynamic equilibrium constant and  $\alpha$  is a global mass transfer efficiency coefficient. Therefore, if the mass transfer efficiency is optimal ( $\alpha = 1$ ), the extraction coefficient is equivalent to the thermodynamic equilibrium constant.

$K'_{HMF}$  is defined as the ratio of  $C_{HMF}^V$ , the concentration of HMF in the scCO<sub>2</sub> phase (in mol.L<sup>-1</sup>), and  $C_{HMF}^L$ , the concentration of HMF in the subH<sub>2</sub>O phase (in mol.L<sup>-1</sup>) at equilibrium (Eq. 9).

$$K'_{HMF} = \frac{C_{HMF}^V}{C_{HMF}^L} \quad (9)$$

It is not used in our predictive model but as a reminder, the thermodynamic equilibrium constant,  $K'_{HMF}$ , can be expressed as a function of  $K_{HMF}$ , the partition coefficient of HMF (Eq. 10).

$$K'_{HMF} = K_{HMF} \cdot \frac{\rho_{V(T,P,x_{H_2O})} \cdot M_V}{\rho_{L(T,P,x_{CO_2})} \cdot M_L} \quad (10)$$

where  $\rho_V$  and  $\rho_L$  are the densities of the vapor and liquid phases (in g.L<sup>-1</sup>),  $M_V$  and  $M_L$  are the molar mass of the vapor and liquid phases (in g.mol<sup>-1</sup>), respectively.

The value of the concentration of dissolved carbon dioxide in water,  $C_{CO_2}^L$  (in mol.L<sup>-1</sup>), was necessary for the kinetic model used in this work, as described in Labauze et al. (2019) [12]. This value was considered as constant during a given experiment at constant pressure and temperature. It is thus estimated based on Eq. 11.

$$C_{CO_2}^L = \frac{\rho_{L(T,P,x_{CO_2})}}{\frac{1-x_{CO_2}}{x_{CO_2}} \cdot M_{H_2O} + M_{CO_2}} \quad (11)$$

where  $x_{CO_2}$  is the mole fraction of CO<sub>2</sub> in the liquid phase at (T, P). This latter was determined following the method explained in Deleau et al. [27] based on the work of Enick and Klara (1990) [28], and using the Span and Wagner (1996) equation of state [29]. The density of the

H<sub>2</sub>O-rich liquid phase,  $\rho_{L(T,P,x_{CO_2})}$  was also determined following the method explained in Deleau et al. [27] which is based on the correlation of Batzel and Wang [30].

The flow rate of co-extracted water by the CO<sub>2</sub> stream,  $\dot{n}_{H_2O}$  (in mol.min<sup>-1</sup>), has been estimated using Eq. (12).

$$\dot{n}_{H_2O} = \frac{\dot{n}_{CO_2} \cdot C_{H_2O}^v \cdot M_{CO_2}}{d} \quad (12)$$

where  $\dot{n}_{CO_2}$  is the flow rate of CO<sub>2</sub> (in mol.min<sup>-1</sup>),  $M_{CO_2}$  is the molar mass of CO<sub>2</sub> (in g.mol<sup>-1</sup>),  $d$  is the density of scCO<sub>2</sub> (in g.L<sup>-1</sup>) and  $C_{H_2O}^v$  is the

concentration of H<sub>2</sub>O in the scCO<sub>2</sub> phase (in mol.L<sup>-1</sup>), which is estimated assuming phase equilibrium and using Eq. (13) proposed by Chrastil [25].

$$C_{H_2O}^v = \frac{d^k \exp\left(\frac{a}{T} + b\right)}{M_{CO_2}} \quad (13)$$

where,  $T$  is the temperature (in K),  $k$ ,  $a$  and  $b$  are solubility constants determined as explained in Chrastil [25]. For instance, at 150 °C and 25 MPa, the density of scCO<sub>2</sub> equals 415.50 g.L<sup>-1</sup> (based on NIST website),  $k = 1.549$ ,  $a = -2826.4$  and  $b = -0.807$ , so the concentration of H<sub>2</sub>O in scCO<sub>2</sub> equals  $1.45 \times 10^{-1}$  mol.L<sup>-1</sup>.

The concentrations of fructose, HMF, formic acid and levulinic acid vs. reaction time were computed by solving the system of differential equations using the ode23s solver available in the MATLAB R2021a software. From the concentrations of fructose and HMF, the fructose conversion rate and HMF yield were calculated following Eqs. (1) and (2).

The extraction coefficient,  $E$ , was determined for given process conditions by fitting the calculated fructose conversion rate, global HMF yield, HMF yield in the extract and HMF yield in the reactor to their respective experimental values, by using the least square method (lsqnonlin MATLAB function). In order to assess the performance of this fitting, average absolute relative deviation (AARD) was determined.

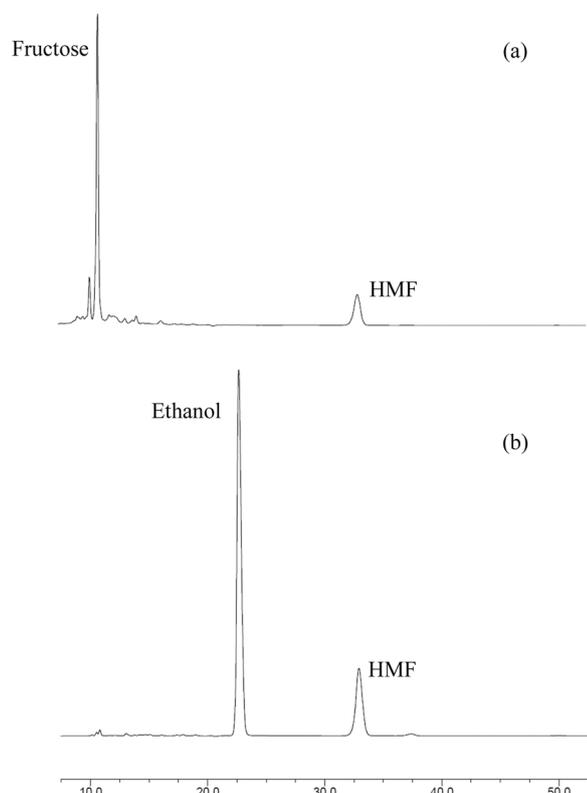
### 3. Results and discussion

#### 3.1. Experimental results

In all the collected extracts, the absence of fructose, which is totally insoluble in scCO<sub>2</sub>, guaranteed that no liquid from the reactor was mechanically sucked up in the extract tube. Besides, extracts were all translucent suggesting that humins were not co-extracted neither. Thus, only the actual solubilization of solutes in scCO<sub>2</sub> was responsible for the presence of compounds in the extract. Examples of chromatograms of the remaining liquid in the reactor and extract samples are shown in Fig. 4. Note that, expressing relative purity of HMF in the extract (Eq.5) in respect to the by-products that we were able to detect by HPLC analysis, (*i.e.*, formic acid, levulinic acid and furfural) was relevant, since no other major pics were visible on the chromatograms of the extract (Fig. 4b).

##### 3.1.1. Extractive reaction without injection of water

The experimental set-up was first used with continuous injection of CO<sub>2</sub> only. Corresponding experimental results in terms of fructose conversion rate, global HMF yield, HMF selectivity and separation efficiency are presented in Table 1. In that configuration, the reaction time was limited due to the co-extraction of water by scCO<sub>2</sub>. Indeed, based on



**Fig. 4.** HPLC chromatograms of the remaining liquid in the reactor (a) and the extract (b). Extractive reaction conditions: 160 °C, 25 MPa, 420 min, CO<sub>2</sub> flow rate of 20 g.min<sup>-1</sup>, H<sub>2</sub>O flow rate of 0.300 g.min<sup>-1</sup> (Entry 6 from Table 2). Analytical conditions: Shodex RI-101 refractive index detector, Agilent Hi-Plex H column, H<sub>2</sub>SO<sub>4</sub> solution (0.005 mol.L<sup>-1</sup>) as eluent at 0.6 mL.min<sup>-1</sup>, column temperature kept at 60 °C. Retention times: fructose 10.8 min, formic acid 14.7 min, levulinic acid 17.4 min, ethanol 22.7 min, 5-hydroxymethylfurfural (HMF) 32.9 min, furfural 50.1 min.

Eq. 13, at 150 °C and 25 MPa, the solubility of water in scCO<sub>2</sub> was estimated at 6.38 g.L<sup>-1</sup>, leading to a theoretical water extraction flow rate of 0.154 g.min<sup>-1</sup> for a CO<sub>2</sub> flow rate of 10 g.min<sup>-1</sup>. Under these experimental conditions (triplicate), the actual water extraction flow rate was 0.133 ± 0.006 g.min<sup>-1</sup>, which is slightly less than the theoretical value based on Chrastil model [25].

Increasing the CO<sub>2</sub> flow rate from 5 to 10 g.min<sup>-1</sup> had no impact on the conversion rate of fructose and the global HMF yield after 120 min of experiment, but showed a positive impact on the separation efficiency with an increase of 8 % (Table 1). In the case of an extractive reaction time of 180 min, the HMF yield increased to only 23.8 %, which is close to the value obtained in the batch process (26.2 %) [12].

When no water injection was operated, at 150 °C and 25 MPa with a CO<sub>2</sub> flow rate of 10 g.min<sup>-1</sup> the reaction time was limited to 180 min because of a drastic reduction in the volume of the aqueous phase (from 70.9 mL to 32.0 mL) and a low volume of liquid in the reactor could not ensure efficient bubbling of scCO<sub>2</sub>. In the conventional batch process,

**Table 1**

Production of 5-hydroxymethylfurfural from fructose at 5 wt% in a two-phase scCO<sub>2</sub>–subH<sub>2</sub>O system by extractive reaction with continuous injection of CO<sub>2</sub> at 150 °C and 25 MPa, and without injection of H<sub>2</sub>O.

	$\dot{m}_{CO_2}$ (g.min <sup>-1</sup> )	t (min)	X <sub>F</sub> (%)	Y <sub>HMF</sub> (%)	S <sub>HMF</sub> (%)	S <sub>FA</sub> (%)	S <sub>LA</sub> (%)	S <sub>furfural</sub> (%)	Separation efficiency (%)
Entry 1	5.0 <sup>(**)</sup>	120	29.4 ± 0.5	17.3 ± 0.1	58.9 ± 1.3	2.8 ± 0.6	0.9 ± 0.6	0.3 ± 0.1	6.3 ± 3.1
Entry 2	10.0 <sup>(**)</sup>	120	28.8 ± 0.6	17.5 ± 0.3	60.8 ± 0.2	2.8 ± 0.7	0.4 ± 0.0	0.3 ± 0.0	14.2 ± 0.1
Entry 3	10.0 <sup>(*)</sup>	180	54.5	28.4	62.3	5.2	0.7	0.4	23.8

(\*) Single experiment.

(\*\*) Experiments run in duplicate.

the HMF yield vs. reaction time exhibits a typical bell-shape curve corresponding to an intermediate chemical of consecutive reactions [9,12]. In order to observe a positive effect on the HMF yield obtained by extractive reaction compared to a batch process, experiments should be carried out for a longer reaction time to exceed the reaction time corresponding to the maximum yield of HMF in a batch process. In that case, water co-injection was necessary to allow compensating the co-extraction of water by scCO<sub>2</sub>, which is a specificity of this solvent compared to other hydrophobic solvents used for extractive reaction such as MIBK for example [15,21].

### 3.1.2. Extractive reaction with continuous injection of water

As explained above, in order to avoid the volume reduction of the aqueous reactional medium, water was continuously injected in the reactor to compensate the flow rate of water extracted by scCO<sub>2</sub>. Besides, the reaction time for the extractive reaction experiments with continuous injection of water was set to exceed  $t_{max}$  (450 min at 150 °C and 25 MPa, 250 min at 160 °C and 25 MPa), the reaction time at which the maximum HMF yield was obtained in batch conditions in the work of Labauze et al. [12]. Several conditions of CO<sub>2</sub> flow rate, pressure, temperature and reaction time have been tested and experimental results are presented in Table 2. By comparing Entry 1 of Table 2 with Entry 3 of Table 1, it can be observed that for similar operating conditions (CO<sub>2</sub> flow rate, pressure, temperature), the HMF yield is higher (+ 7 %) without water addition in the reactor for about the same reaction time. This is due to the volume reduction of reactional aqueous phase leading to a higher concentration of fructose and thus faster kinetics of HMF formation. With a CO<sub>2</sub> flow rate equal to 10 g.min<sup>-1</sup> and an H<sub>2</sub>O flow rate equal to 0.105 ± 0.032 g.min<sup>-1</sup>, at 25 MPa and 150 °C, for 600 min, an HMF yield of 39.0 ± 1.9 % was reached (Entry 2, Table 2), while when the temperature was increased to 160 °C (Entry 3, Table 2), the HMF yield reached 48.5 % after 360 min of experiment. Under the same conditions, a slight increase in pressure to 27 MPa (Entry 4, Table 2) did not significantly affect the HMF yield (48.3 ± 2.2 %). In these cases, reaction performances were comparable to results obtained in batch mode [12], indicating that in these conditions, the CO<sub>2</sub> flow rate was too low to allow a significant extraction of HMF and prevent its degradation.

When the flow rate of CO<sub>2</sub> was increased to 20 g.min<sup>-1</sup>, a global HMF yield of 60.6 ± 2.2 % was obtained (Entry 5, Table 2), which is beyond the maximum value of the HMF yield for a batch system. The fructose conversion rate reached 97.0 ± 2.3 % so the selectivity was 62.5 ± 2.2 %, and the separation efficiency reached 96.7 ± 0.5 %, meaning that almost all the HMF produced was extracted by scCO<sub>2</sub>. The observed increase in the global HMF yield and separation efficiency could then be attributed to a better mass transfer induced by the higher CO<sub>2</sub> flow rate through more favorable hydrodynamics around the droplets and higher interfacial area. A longer reaction time (420 min) improved slightly the conversion rate of fructose with a value of 98.0 % and the HMF yield to a value of 62.4 % (Entry 6, Table 2). During this experiment the yield of HMF in the extract was followed over time as presented in the Supplementary Data. To compare these results with the literature data regarding the influence of the CO<sub>2</sub> flow rate, this latter was normalized in respect to the initial mole number of reactants. In our

**Table 2**

Fructose conversion rate ( $X_F$ ), HMF yield ( $Y_{HMF}$ ), HMF selectivity ( $S_{HMF}$ ) and separation efficiency obtained from a 5 wt% fructose solution under different conditions in a  $\text{scCO}_2$  –  $\text{subH}_2\text{O}$  biphasic system with continuous injection of  $\text{CO}_2$  and  $\text{H}_2\text{O}$ .

	$\dot{m}_{\text{CO}_2}$ (g. min <sup>-1</sup> )	$\dot{m}_{\text{H}_2\text{O}}$ (g. min <sup>-1</sup> )	P (MPa)	T (°C)	t (min)	$X_F$ (%)	$Y_{HMF}$ (%)	$S_{HMF}$ (%)	$S_{FA}$ (%)	$S_{LA}$ (%)	$S_{\text{furfural}}$ (%)	Separation efficiency (%)
Entry 1 <sup>(*)</sup>	10.0	0.110	25	150	205	43.6	21.4	48.6	3.2	0.7	0.4	18.7
Entry 2 <sup>(***)</sup>	10.0	0.105 ± 0.032	25	150	600	87.0 ± 1.3	39.0 ± 1.9	44.3 ± 2.3	4.9 ± 1.3	2.3 ± 1.6	0.4 ± 0.1	65.3 ± 5.2
Entry 3 <sup>(*)</sup>	10.0	0.130	25	160	360	94.5	48.5	51.3	12.7	5.1	0.4	53.6
Entry 4 <sup>(**)</sup>	10.0	0.113 ± 0.020	27	160	360	93.5 ± 8.9	48.3 ± 2.2	51.7 ± 2.6	5.8 ± 1.6	1.6 ± 1.6	0.4 ± 0.1	65.6 <sup>(****)</sup>
Entry 5 <sup>(***)</sup>	20.0	0.293 ± 0.028	25	160	360	97.0 ± 2.3	60.6 ± 2.2	62.5 ± 2.2	5.3 ± 0.4	1.1 ± 0.3	0.5 ± 0.0	96.7 ± 0.5
Entry 6 <sup>(*)</sup>	20.0	0.300	25	160	420	98.0	62.4	63.7	5.4	1.0	0.4	97.3

(\*) Single experiment.

(\*\*) Experiments run in duplicate.

(\*\*\*) Experiments run in triplicate.

(\*\*\*\*) Standard deviation could not be calculated since for one experiment the reactor was empty at the end of the experiment, the water injected in the reactor did not compensate the water extracted by  $\text{scCO}_2$ .

case, a  $\text{CO}_2$  flow rate of  $20 \text{ g}\cdot\text{min}^{-1}$  was equivalent to a normalized flow rate of  $974 \text{ g}\cdot\text{min}^{-1}$  of  $\text{CO}_2$  per initial mole of fructose. Computing normalized values from recent studies regarding the production of furans from sugars by extractive reaction in  $\text{scCO}_2$  –  $\text{subH}_2\text{O}$  biphasic system, gave higher values, with 1415 and 1141  $\text{g}\cdot\text{min}^{-1}$  of  $\text{CO}_2$  per initial mole of xylose [21] and glucose [22], respectively. With lower normalized  $\text{CO}_2$  flow rate values, better results in terms of furan com-pound yield were obtained in the present work, with at most 62.4 %, against 52.3 % and 32.6 %, for furfural production from xylose catalysed by a solid acid [21] and HMF production from glucose without catalyst [22], respectively. This better yield in our work is certainly resulting from two factors. First, the reaction chemistry is more favorable for the conversion of fructose into HMF, where only dehydration, catalysed by Brønsted acids, is required, whereas xylose and glucose conversions into furans require isomerisation and dehydration, catalysed by Lewis and Brønsted acids, respectively [31,32]. Second, the thermodynamic conditions we used (higher pressure and lower temperature) likely resulted in a higher value of HMF partition coefficient for the  $\text{scCO}_2$  –  $\text{subH}_2\text{O}$  system, compared to the other studies mentioned previously, where 150 °C and 20 MPa [21] and 200 °C and 20 MPa [22] were used, respectively.

The global selectivity of HMF (Eq. 3) was about 63 % at 160 °C, 25 MPa with a  $\text{CO}_2$  flow rate of  $20 \text{ g}\cdot\text{min}^{-1}$  (Entries 5 & 6, Table 2). The remaining fructose has been either unreacted (2–3 %), or converted into humins as it could be noticed in the reactor at the end of the experiment, or converted into formic acid ( $S_{FA} = 5.3$  %), levulinic acid ( $S_{LA} = 1.1$  %) and furfural ( $S_{\text{furfural}} = 0.5$  %), that are partly extracted by  $\text{scCO}_2$ . In these conditions, the HMF relative purity (Eq. 5) in the extract compared to formic acid, levulinic acid and furfural reached 95.8 wt%. This high HMF purity prevents the need for extensive purification after this extractive reaction process and consequently it should minimize the global production cost of HMF using the proposed process.

### 3.2. Determination of the extractive coefficient ( $E$ )

After having experimentally evidenced the benefits of the proposed semi-continuous extractive reaction process compared to a conventional batch process, we used the previously presented model describing the complete extractive reaction process with the objective to predict the operating conditions that should maximize the HMF yield. To do so, the extractive coefficient,  $E$ , as defined in Eq.8, was first determined for each thermodynamic conditions tested (All entries of Table 2, except entry 4), by fitting the calculated fructose conversion rate, global HMF yield, HMF yield in the extract and HMF yield in the reactor to their respective experimental values (Fig. 5). At 160 °C and a  $\text{CO}_2$  flow rate of  $10 \text{ g}\cdot\text{min}^{-1}$ ,  $E$  was found to be equal to 0.0029 with an AARD of 0.6 %, and at

160 °C and a  $\text{CO}_2$  flow rate of  $20 \text{ g}\cdot\text{min}^{-1}$ ,  $E$  was found to be equal to 0.0093 with an AARD of 30.5 %. This latter value is negatively impacted by the absolute relative deviation (ARD) of HMF yield in the reactor. The low values of HMF yields in the reactor amplifies differences between calculated and experimental values leading to high ARD, 150,3 % and 80.1 % at 360 and 420 min, respectively. If these ARD values are not considered, then the AARD value at 160 °C and a  $\text{CO}_2$  flow rate of  $20 \text{ g}\cdot\text{min}^{-1}$  is 2.3 %. Therefore, we considered good adequation between the model curves and the experimental points, leading to reliable values for the extraction coefficient,  $E$ .

With a  $\text{CO}_2$  flow rate equal to  $10 \text{ g}\cdot\text{min}^{-1}$  and 25 MPa (Fig. 5a and b), it can be observed that the values of  $E$  varied from 0 to 0.0029 when the temperature was increased from 150° to 160°C, meaning that at 160 °C extraction of HMF actually occurred, allowing an improvement in HMF yield. However, in these conditions,  $E$  was found to be low and even based on a small number of experimental points, this suggests that despite the use of a porous diffuser for the bubbling of  $\text{scCO}_2$  into the  $\text{subH}_2\text{O}$  phase and the magnetic stirring, mass transfer limitations were significant in our experimental set-up. Since the partition coefficient of HMF,  $K_{HMF}$ , in this biphasic system at 25 MPa and 160 °C is expected to be low, i.e., in the range of 0.05 – 0.5, it means that the mass transfer efficiency,  $\alpha$ , could be in the range of 0.006 – 0.06. This hypothesis was confirmed by the fact that when the  $\text{CO}_2$  flow rate was increased to  $20 \text{ g}\cdot\text{min}^{-1}$ , at the same temperature and pressure (Fig. 5c), the value of  $E$  was increased to 0.0093. The observed increase in the value of  $E$  could then be attributed to a better mass transfer (increased  $\alpha$ ) induced by the higher  $\text{CO}_2$  flow rate.

Interestingly, these results showed that, despite a very low extraction coefficient,  $E$ , the proposed extractive reaction process enabled to go beyond the limited yield (48 %) obtained in the case of a batch process [12], where HMF degradation occurs. However, the experimental HMF yield obtained in this work was lower than values evidenced in other intensified processes using organic solvents such as MIBK for example [15,18]. The main advantage of the process presented here lies in the exclusive use of environmental-friendly compounds as reaction and separation media:  $\text{H}_2\text{O}$  and  $\text{CO}_2$ .

### 3.3. Sensitivity analysis

Increasing the  $\text{CO}_2$  flow rate value would certainly enhance the global HMF yield by increasing its extraction rate in the  $\text{scCO}_2$  phase. Although our high-pressure  $\text{CO}_2$  pump was limited to  $20 \text{ g}\cdot\text{min}^{-1}$ , by using the predictive model, it was possible to theoretically explore the influence of high  $\text{CO}_2$  flow rates. For that purpose, the most favorable extraction coefficient,  $E = 0.0093$ , obtained at 160 °C, 25 MPa and  $20 \text{ g}\cdot\text{min}^{-1}$  of  $\text{CO}_2$ , was kept unchanged and assumed independent of the  $\text{CO}_2$

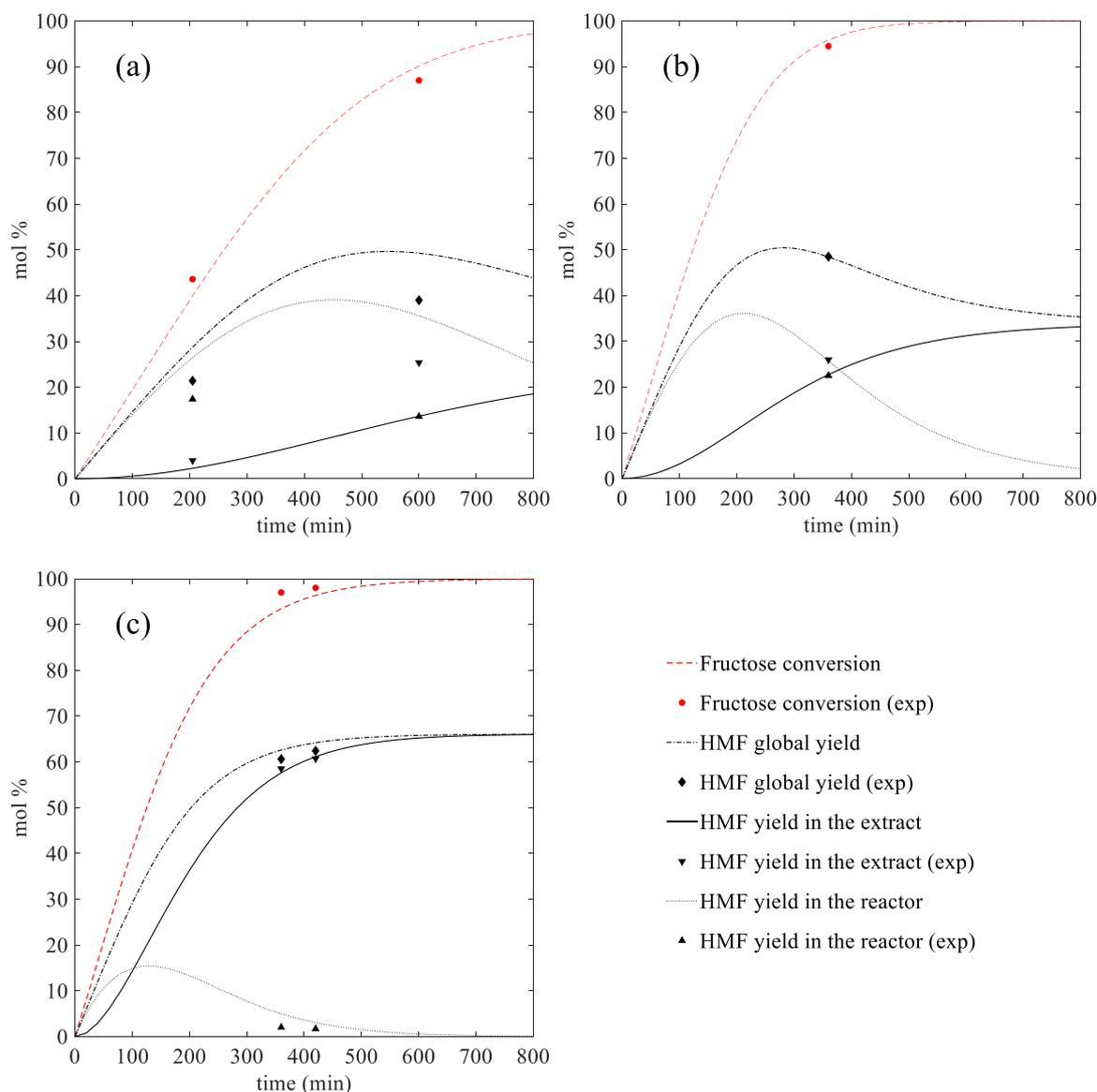


Fig. 5. Determination of the extraction coefficient ( $E$ ) based on model fitting to experimental data obtained by extractive reaction at 25 MPa. (a)  $T = 150\text{ }^{\circ}\text{C}$ ,  $\dot{m}_{\text{CO}_2} = 10\text{ g}\cdot\text{min}^{-1}$ ,  $E = 0$ , (b)  $T = 160\text{ }^{\circ}\text{C}$ ,  $\dot{m}_{\text{CO}_2} = 10\text{ g}\cdot\text{min}^{-1}$ ,  $E = 0.0029$ , (c)  $T = 160\text{ }^{\circ}\text{C}$ ,  $\dot{m}_{\text{CO}_2} = 20\text{ g}\cdot\text{min}^{-1}$ ,  $E = 0.0093$ .

flow rate in the range  $0\text{--}100\text{ g}\cdot\text{min}^{-1}$  to run simulation of the extractive reaction process. Such simulations showed that at  $100\text{ g}\cdot\text{min}^{-1}$ , the estimated HMF maximum yield could reach  $73.0\%$  after  $800\text{ min}$  (Fig. 6). Besides, this value is likely to be underestimated as we can expect an improvement in mass transfer efficiency,  $\alpha$ , as experimentally previously observed when the  $\text{CO}_2$  flow rate was increased from  $10$  to  $20\text{ g}\cdot\text{min}^{-1}$ .

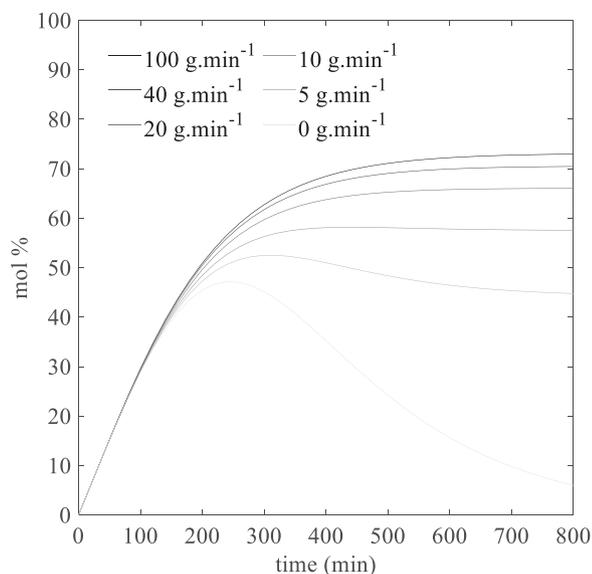
As mentioned above, the extraction efficiency,  $E$ , was low because of mass transfer limitation,  $\alpha < 1$ , combined with unfavourable thermo-dynamic conditions, *i.e.*, low  $K_{\text{HMF}}$  values. By implementing higher values for  $E$  in the model, the influence of the extraction efficiency could be theoretically explored, either related to a better  $\text{scCO}_2$  –  $\text{subH}_2\text{O}$  contacting system (higher  $\alpha$ ) and/or better thermodynamic conditions (higher partition coefficient is expected with higher pressure). On Fig. 7, it can be observed that simulating an increase of  $E$  from  $0.0093$  to  $0.093$  with a  $\text{CO}_2$  flow rate equal to  $20\text{ g}\cdot\text{min}^{-1}$ , led to an increase in HMF yield from  $63.2\%$  to  $67.0\%$  and from  $66.0\%$  to  $73.7\%$  after  $360$  and  $800\text{ min}$ , respectively. Note that a significantly higher value of  $E$  ( $0.93$ , close to the partition coefficient of furfural in the biphasic  $\text{scCO}_2$  –  $\text{subH}_2\text{O}$  system [21]), showed barely no enhancement of HMF maximum yield

with a value of  $74.4\%$  after  $800\text{ min}$ .

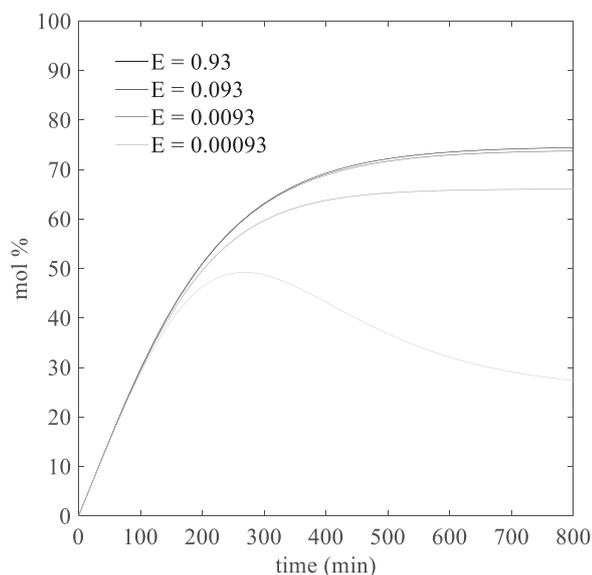
Another simulation of the combination of a favourable extraction coefficient,  $E = 0.93$ , and a high  $\text{CO}_2$  flow rate,  $\dot{m}_{\text{CO}_2} = 100\text{ g}\cdot\text{min}^{-1}$ , led to barely no improvement on the HMF yield with values of  $67.4\%$  and  $74.5\%$ , after  $360$  and  $800\text{ min}$ , respectively. Therefore, based on our experimental system,  $75\%$  appeared to be the HMF theoretical maximum yield at  $160\text{ }^{\circ}\text{C}$ . This is most probably due to the hydro-dynamics of our system that generated mass transfer limitations and to the direct decomposition of fructose into formic acid and humins. This hypothesis was confirmed by obtaining higher HMF yields when the kinetics constants of these direct decomposition reactions (R2F and R3F, Fig. 3) were artificially set to zero in the model. Whatever its efficiency, the proposed extractive reaction process cannot alleviate this limitation in HMF yield at this temperature.

#### 4. Conclusion

Extractive reaction process applied to the production of HMF from fructose in a biphasic  $\text{scCO}_2$  –  $\text{subH}_2\text{O}$  system allowed the exploitation of some advantages of  $\text{CO}_2$ , on one side as a reversible acid catalyst when



**Fig. 6.** Sensitivity analysis of the  $\text{CO}_2$  flow rate,  $\dot{m}_{\text{CO}_2}$ , on the HMF yield (%) obtained by simulation of its production from fructose at 5 wt% in a biphasic  $\text{scCO}_2$  –  $\text{subH}_2\text{O}$  system by extractive reaction at 160 °C, 25 MPa and with an extraction coefficient;  $E = 0.0093$ .



**Fig. 7.** Sensitivity analysis of the extraction coefficient,  $E$ , on the HMF yield (%) obtained by simulation of its production from fructose at 5 wt% in a biphasic  $\text{scCO}_2$  –  $\text{subH}_2\text{O}$  system by extractive reaction at 160 °C, 25 MPa and  $\dot{m}_{\text{CO}_2} = 20 \text{ g}\cdot\text{min}^{-1}$ .

solubilized in water, and particularly, on another side as a green extracting solvent. The HMF maximum yield (48 %) obtained in batch mode in a biphasic  $\text{scCO}_2$  –  $\text{subH}_2\text{O}$  system was exceeded with the one pot extractive reaction process with continuous injection of  $\text{CO}_2$  and  $\text{H}_2\text{O}$  presented in this work with an experimental value of 62.4 %, thus validating the proof of concept of the studied process. Besides, the very high HMF separation efficiency (97.3 %) prevents the need to recover HMF in the reactor. The high HMF relative purity in the extract (95.8 wt %) prevent the use of extensive purification techniques as it is the case in conventional batch processes and enable to consider further chemical transformation into high value-added chemicals directly in line under pressure (e.g., hydrogenation or oxidation).

Sensitivity analysis was performed using an adapted model and

showed that the HMF yield in the present system could theoretically reach 75 % by increasing the flow rate of  $\text{CO}_2$  and improving the extraction efficiency. Nevertheless, this value could not be exceeded due to direct decomposition reactions of fructose into formic acid and humins.

Finally, two main intensified processes implying extractive reaction for the production of HMF from C6 sugars with high yields have emerged: one implies the use of biphasic microreactors with HCl as catalyst and MIBK as extracting solvent where yields can exceed 90 % [15], and the other one, presented in this work, which is catalyst-and organic solvent-free with the use of  $\text{H}_2\text{O}$  and  $\text{CO}_2$ , and with an HMF theoretical maximum yield of 75 %.

The under-progress experimental measurement of HMF partition coefficient between water and carbon dioxide could lead to model improvements by expressing extraction rate uncoupling thermodynamics and mass transfer phenomena.

#### CRediT authorship contribution statement

**Vincent Oriez:** Data curation, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. **Hélène Labauze:** Writing – review & editing. **Bouchra Benjelloun-Mlayah:** Funding acquisition, Project administration, Validation, Writing – review & editing. **Yuya Hiraga:** Writing – review & editing. **Masaru Watanabe:** Writing – review & editing. **Jean-Stéphane Condoret:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **Séverine Camy:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **Thomas Deleau:** Software.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Data availability

Data will be made available on request.

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