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Research Article

O/W Pickering emulsion stabilized by magnesium carbonate particles for drug delivery systems

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Abstract

This study investigates the formulation of surfactant-free Pickering emulsions that release a drug at a specific pH to improve its oral bioavailability. The stabilizing particles composed of magnesium carbonate particles. Pickering oil-in-water emulsions stabilized with magnesium carbonate particles and encapsulating a hydrophobic drug model (ibuprofen) were formulated using a high-energy process with rotor-stator turbo mixer (IKA® T25 digital ultra-Turrax). The experimental approach explored the impact of all formulation parameters, dispersed phase and amount of magnesium carbonate particles on the physicochemical properties of Pickering emulsions. The O/W Pickering emulsion was characterized by a methylene blue test, pH and conductivity measurements, and droplet size determination. In addition, Pickering emulsions stabilized by magnesium carbonate particles have the advantage of being destabilized in acidic medium leading to the release of the active principle via the droplets. The acidic medium release study (pH equal to 1.2) showed ibuprofen release as a function of initial droplet loading and saturation concentration. In the simulated intestinal medium at pH equal to 6.8, we found a better release of ibuprofen from emulsions that already had saturation in an acid medium. Thus, the interest of these Pickering emulsions lies on the fact that their non-toxicity and magnesium carbonate particles allow destabilization of the emulsions and release of the drug. These emulsions not only protect patients from the side effects of acid-based drugs, but also contribute to increase the bioavailability of these acidic drugs.

Keywords: emulsion -Pickering-magnesium carbonate- ibuprofen-oral bioavailability

INTRODUCTION

In many industrial sectors such as pharmacy [1], cosmetics [2], agri-food [3] and chemistry [4], emulsions are formulations used to obtain useful properties or suitable compositions. These emulsions are metastable dispersed systems consisting of least two immiscible liquids and an amphiphilic agent. One of the liquids is dispersed in the other in form of small spherical droplets whose size varies according to the conditions from 0.1 to a few tens of micrometers [5–7]. The system thus created does not correspond to a thermodynamically stable state; the most stable state would consist in the macroscopic separation of the two fluids. These metastable dispersed systems are conventionally stabilized by surfactant molecules. However, the demand for surfactants in the global economy is exponential growing [8,9]. Thus, it is necessary to reduce the use of surfactant in all these applications. On the one hand for the sake of environmental respect and on the other hand for the safety of consumers, surfactants can be toxic and harmful to the environment but also harmful to consumers [10,11].

Ramsden and Pickering [12,13] demonstrated at the beginning of the last century the feasibility of surfactant-free emulsions in presence of solid particles. These emulsions are called "Pickering Emulsions". This concept of emulsions stabilized by solid particles is gaining renewed interest today because of the many advantages. It offers good stability, environmental protection, user safety, variety of particles, etc. In addition, one of the main advantages of Pickering emulsions is that they are more stable than other types of emulsions [12,14,15]. The adsorption of solid particles at the oil-water interface is almost irreversible and strong (unlike surfactants which are in thermodynamic equilibrium at the interface), leading to the formation of a dense film, creating a barrier around the droplets and thus making the droplets very resistant to coalescence. Recently, the applications of emulsions stabilized by solid particles are reconsidered in biopharmaceutics. This type of formulation are potential system of encapsulation of drugs, allowing the controlled and targeted release of the asset from the internal phase [5,6,16–18].

An interesting approach would therefore be the formulation of a surfactant-free Pickering emulsion encapsulating drugs and then using a stimulus such as pH to establish controlled release systems. The formulation of pH-dependent Pickering

emulsions for controlled release of active substances to improve their oral bioavailability is precisely the general objective of this work. Thus, the interest of these Pickering emulsions lies on the fact that their non-toxicity and magnesium carbonate particles allow destabilization of the emulsions and release of the drug. These emulsions not only protect patients from the side effects of acid-based drugs, but also contribute to increase the bioavailability of these acidic drugs. In fact, magnesium carbonate particles once in the stomach can increase the pH and promote the release of active ingredients such as ibuprofen whose solubility is strongly influenced by pH.

1. MATERIALS AND METHODS

1.1. Materials

Magnesium carbonate particles, Potassium chloride, Methylene blue, sodium hydroxide, hydrochloric acid, potassium phosphate monobasic and potassium phosphate dibasic were purchased from Sigma-Aldrich. The oily phase used throughout the study is a peanut oil Niani® from the market (mainly composed of mono-unsaturated, polyunsaturated fatty acid and saturated fatty acid). The aqueous phase used is distilled water. Ibuprofen was purchased from FAGRON S.A (Saint-Denis, France). Acrodisc Syringe Filters with Nylon Membrane and dialysis membrane tubing (Spectra/Por molecular porous membrane tubing MWCO 12–14 kDa) were purchased respectively from PALL life sciences and Spectrum laboratories (USA). All the chemicals were analytical grade and used as received.

1.2. Methods

1.2.1. Formulation of Pickering Emulsions

During the formulation, the type of emulsions formed is one of the most important properties and characteristics. The Bancroft rule, which states that the type of emulsion depends on the medium in which the particles are introduced initially, served as a model for the preparation of the formulations.

1.2.1.1. Preparation of the dispersed oil phase

The amount of ibuprofen to be incorporated is dissolved in the peanut oil. The mixture is homogenized with a magnetic stirrer at 1000 rpm for one minute.

Preparation of the dispersing aqueous phase:

In distilled water, the magnesium carbonate particles were progressively added by stirring at 1680 rpm.

1.2.1.2. Emulsification

In the suspension previously prepared, the oily phase is gradually added followed by the fragmentation of the drops of oil with the mixer. Subsequently, the final mixture is homogenized vigorously for one minute at 5000 rpm. The total time of preparation of the emulsion is five minutes. The preparation of all the emulsions of this work was carried out under the same operating conditions (stirring speed, stirring time, type of stirrer, temperature). Thus, O / W emulsion containing ibuprofen in the internal phase was realised. We prepared the Pickering emulsions in the following proportions (Table 1):

Table 1 : Proportions of formulations

Tubes	TA (TA')	TB (TB')	TC (TC')	TD (TD')	TE (TE')	TF (TF')	TG (TG')	T1 (T1')	T2 (T2')	T3 (T3')	T4 (T4')	T5 (T5')	T6 (T6')	T7 (T7')	T8 (T8')
Oil (ml)	**15**	**15**	**15**	**15**	**15**	**15**	**15**	8	9	10	11	12	13	14	15
Water (ml)	**15**	**15**	**15**	**15**	**15**	**15**	**15**	22	21	20	19	18	17	16	15
Magnesium carbonate (g)	**0,2**	**0,4**	**0,6**	**0,8**	**1**	**1,50**	**2,00**	1	1	1	1	1	1	1	1

The notation prime is used when the emulsions contain additionally NaCl at a concentration of 5 mg / mL (TA', TB', TC', TD', TE', TF', TG', T1', T2', T3', T4', T5', T6', T7' and T8').

After preparation, each formulation was distributed into two tubes and stored at room temperature, protected from light for 28 days. The first tube is reserved for macroscopic examination and the second for the study of physicochemical characteristics. We first looked for the quantity of particles to be used with the tubes TA, TB, TC, TE, TF, TG, TA', TB', TC', TD', TE', TF', TG', which guided us to choose 1g of magnesium carbonate in the tubes where we varied the volume fraction of dispersed phase (T1, T2, T3, T4, T5, T6, T7, T8, T1', T2', T3', T4', T5', T6', T7' and T8').

The incorporation of ibuprofen in the dispersed oily phase was carried out using the proportions of the tubes having a better stability after 28 days of follow-up (T3, T4, T5, T6, T3', T4', T5' and T6'). The formulation method remains the same except that here ibuprofen is dissolved in the oily phase before emulsification. The solubilization of ibuprofen in the oil was carried out using a magnetic stirrer (Table S1).

1.2.2. Pickering emulsion stability study

1.2.2.1. Bottle test

The emulsions are conserved in the absence of light and an ambient temperature in 50 ml conical bottle. This visual inspection makes it possible to demonstrate certain phenomena of instability such as sedimentation, flocculation, and coalescence.

1.2.2.2. Direction of the emulsions

We used the dye test based on the determination of the solubility of the methylene blue in the emulsion obtained. Two milliliters of the emulsion were placed on a blade and mixed with a few milligrams of methylene blue. After assembly with a slide, observation will be done under optical microscope Axio Zeiss imager A1 coupled to a computer containing the Axio Vision release software Version 4.5 (Zeiss optical microscope).

1.2.2.3. Droplet size measurements

The technique used is based on the estimation of the mean diameter of the droplets by individual counting. The optical

microscope Axio Zeiss imager A1 coupled to a computer containing the Axio Vision release software Version 4.5 (Zeiss optical microscope) was used for measurements (Figure S1).

1.2.2.4. pH of the emulsions

The measuring cell is introduced into a 50 ml conical bottle containing the emulsion. Be sure to place the electrode at the emulsified phase for the sediment tubes. The reading time is set to three minutes after insertion of the electrode.

1.2.3. Encapsulation efficiency (E.E)

The concentration of ibuprofen in each sample is determined following the measurement of the absorbance of ibuprofen in water at 222 nm by UV-visible spectrophotometry (Evolution 300 UV-visible). The equation of the following line (Eq.1) made it possible to determine the concentrations of ibuprofen in the external phase:

$$Abs. = 115{,}4\ C + 0{,}1675 \text{ with } R^2 = 0{,}9938 \qquad Eq.\ (1)$$

The encapsulation efficiency was calculated according to the following relation:

$$\%E.E = \frac{[ibuprofen\ total] - [ibuprofen\ externe]}{[ibuprofen\ Total]} \times 100 \quad Eq.(2)$$

1.2.4. In vitro release study using pH

In vitro dissolution profiles of Pickering emulsions encapsulating ibuprofen were obtained using a dialysis membrane (12,000-14,000 Da). The dialysis tube containing 5 ml of ibuprofen-loaded Pickering emulsions and 5 ml of the dissolution medium was introduced into the *in vitro* release medium containing 250 ml of the dissolving dissolution medium at 100 rpm. This dissolution medium consists of an acidic buffer solution simulating the gastric fluid at pH = 1.2 and a phosphate buffer solution simulating the intestinal fluid at pH = 6.8. Whole assemblies were maintained at a temperature of 37 ± 1 ° C. At 15 minutes intervals, 5 ml samples of the dissolution medium were removed and analysed by UV-visible spectrophotometry. Sink conditions were maintained by replacing 5 mL of the release medium with 5 mL of fresh media at each sampling point. The percentage released in ibuprofen was obtained from the amount of ibuprofen initially present in the emulsions, compared to that measured in the release medium. For each point, three determinations were made.

2. RESULTS AND DISCUSSION

2.1. Stability of Pickering emulsions

The study of the physicochemical and analytical parameters of the various emulsions formulated and stored in the absence of light at room temperature for 28 days, allowed us to follow the evolution of the formulations as a function of time.

2.1.1. Bottle test and emulsion direction

The main results obtained with regard to visual inspection showed macroscopically homogeneous and stable emulsions for the majority of tubes with percentages of emulsified phases of 100% for tubes T3, T4, T5, T6, T7, T8, TA, TB, TC, TD, TE; emulsions exhibiting a creaming phenomenon with respective percentages of 52.63 and 68.42% for the T1 and T2 tubes.

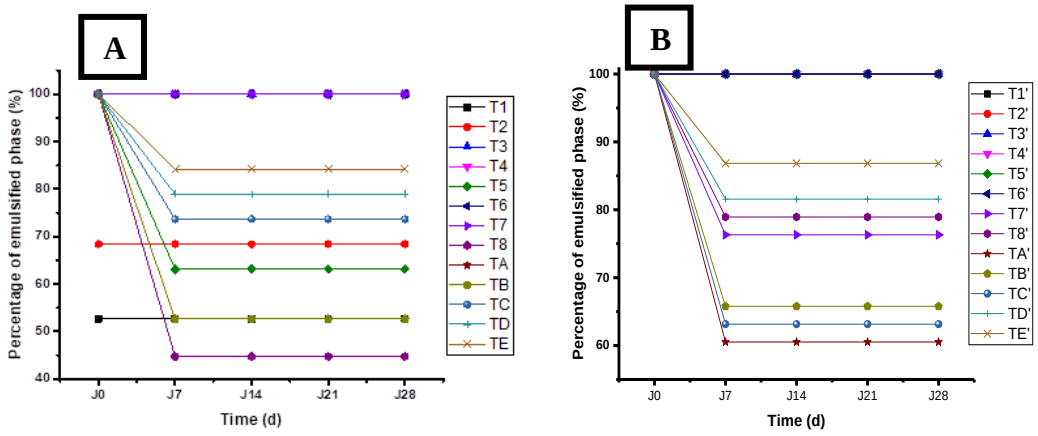

Figure 1: Percentage of emulsifying phase during the storage: (A) emulsion without NaCl, (B) emulsion with NaCl

An oily supernatant was observed at day 7 (J7) due to a coalescence phenomenon with percentages of emulsified phases ranging from 44 to 84% for the tubes T5, T8, TA, TB, TC, TD, TE. On the other hand, the tubes with NaCl were all homogeneous and stable after formulation with percentages of emulsified phases of 100%. At day 7 (J7), these tubes with NaCl exhibited coalescence with higher percentages of emulsified phases (60 to 86% against 44 to 84% for the tubes without NaCl). However, it should be borne in mind that macroscopic observation alone does not prejudge the stability of the emulsion. In fact, macroscopic observation does not allow us to see oily droplets the size of which is on the order of a micrometer.

The type of the emulsions was established by means of the methylene blue test and the measurement of the conductivity. The methylene blue test carried out under an optical microscope showed heterogeneous droplets dispersed in an external phase coloured blue, thus indicating the O/W nature of the emulsions (Figure 2).

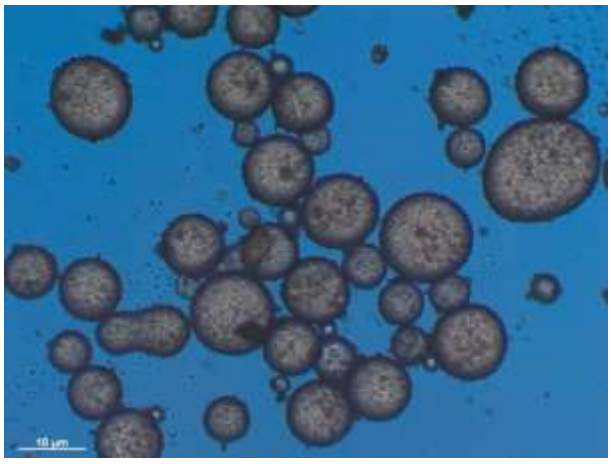

Figure 2: Aspect of the tube T3 after 28 days of storage Pickering emulsion (1g of magnesium carbonate particles) coloured by a hydrophilic dye (Methylene blue)

About the values of the conductivity, for all the formulations, we have obtained values near to water's conductivities values. Indeed, the values of the conductivity of an emulsion depends on its external phase [20] and the presence of electrolytes in this phase. The results thus obtained throughout the storage period show that the emulsions have not undergone any phase inversion phenomenon. In addition, the conductivity values of the external phase of the emulsion are lower than the normal value of the conductivity of water with or without NaCl. Indeed, the oil being apolar, the oily droplets having a heterogeneous distribution in the dispersing phase will reduce the conductive role of the electrolytes of water and NaCl. Similar results have been observed by ROJAS [21]. However, regarding our study, the increase in the volume fraction of dispersed phase as well as the magnesium carbonate / dispersed phase ratio did not influence the values of the conductivity. Furthermore, the conductivity values of emulsions containing NaCl (T') are much higher than those of emulsions without NaCl (T).

2.1.2. Size of droplets

Figure 3 shows the size of the droplets according to the amount of magnesium carbonate particles used. We found that the size of droplets not varied when we change the ratio magnesium carbonate particles/dispersed phase (emulsion with 1 g of magnesium carbonate particles).

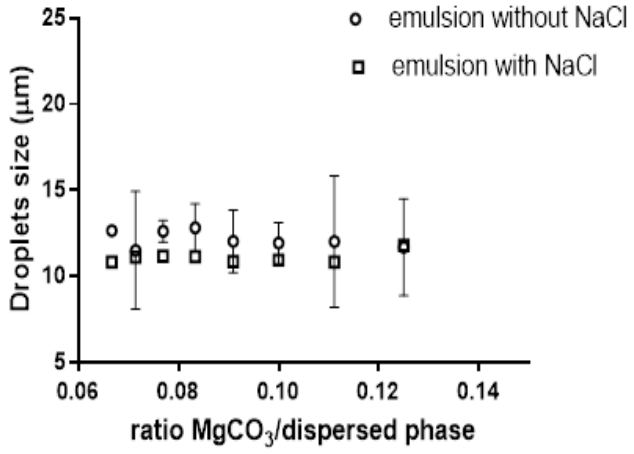

Figure 3: Evolution of the size of the droplets of emulsions depending on the ratio magnesium carbonate particles/dispersed phase (1g)

The size of the droplets plays an important role in the stability of the emulsions. It is one of the variables that most influences the rate of sedimentation described by Stokes' law [22,23]. Thus, first, we studied the evolution of droplet size as a function of the $MgCO_3$ / dispersed phase ratio. This ratio was obtained by varying the volume fraction of dispersed phase relative to a fixed quantity of particles. We observed for the emulsions without NaCl a slight increase in the size of the droplets when the volume fraction of the dispersed phase is increased [6,7,24]:

This phenomenon can be explained by the fact that when the volume phase fraction increases, new interfaces are created while the quantity of particles does not vary. Thus, the droplets formed are not entirely covered with particles. This is the cause of a limited coalescence of the droplets leading to an increase in their diameters. Adding NaCl to the dispersing phase before formulation can cause partial flocculation of the particles, thus limiting this phenomenon of limited coalescence. This is probably the cause of the slight decrease in droplet size when the $MgCO_3$ / dispersed phase ratio increased. In a second step, we studied the impact of the increase in the quantity of particles on the evolution of the size of the droplets compared to a fixed volume of dispersed phase. We did not find any significant variation in droplet size. However, the relation which links the diameter of the droplets (D), the dispersed phase and the amount of particles is the following [6,7,24]:

$$D = \frac{6}{\rho_{oil}.A}\frac{m_{oil}}{m_{particles}}$$

ρ_{oil} = density of oil; A= interfacial area covered by particles; m_{oil}= masse of oil; $m_{particles}$= masse of particles.

From this relationship, we can say that the interfacial area covered by the particles was not sufficient to cause a decrease in the size of the droplets even if we increased the mass of the particles. This probably explains the fact that we did not observe a decrease in the size of the droplets when the quantity of particles was increased. We have also observed that emulsions containing NaCl had much finer droplets than emulsions without NaCl. This reduction in size is simply due to the fact that the NaCl changes the zeta potential of the particles resulting in partial flocculation. This partial flocculation reduces the mobility of the particles at the interface. This leads to a decrease in the coalescence of the droplets[17].

2.1.3. pH of the Emulsions

Figure 4 shows the effect of the variation of the magnesium carbonate particles/dispersed phase on the pH values. We can find that the increase of the ratio magnesium carbonate particles/dispersed phase did not change the pH values. All emulsions exhibited basic pH.

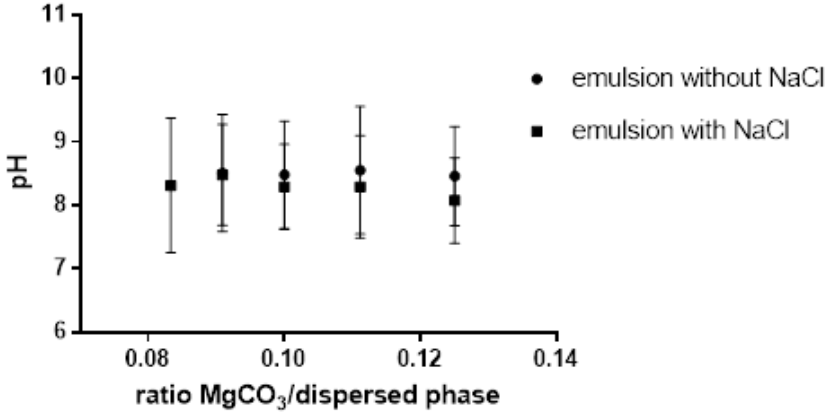

Figure 4: Evolution of the pH of emulsions depending on the ratio magnesium carbonate particles/dispersed phase (1g)

We performed it according to two parameters: the volume fraction of dispersed phase and the particle / dispersed phase ratio. Thus, we noticed that the increase in the volume fraction of dispersed phase as well as the $MgCO_3$ / dispersed phase ratio did not lead to significant changes in the pH values of the emulsions. We also noticed a basic character for all the emulsions. Yang and al. had worked with LDH particles and had found that adjusting the pH to high values allowed good stabilization of the emulsion by promoting better adsorption of particles at the interfaces [25]. However, we noted a decrease in pH values for emulsions containing ibuprofen. This decrease in pH is no doubt due to the acidic nature of ibuprofen which has a very low solubility in water [26,27].

2.2. Encapsulation efficiency of ibuprofen

The evaluation of the encapsulation efficiency (E.E) showed good encapsulation rates. Better rates were obtained in the most stable emulsions without NaCl (Figure 5).

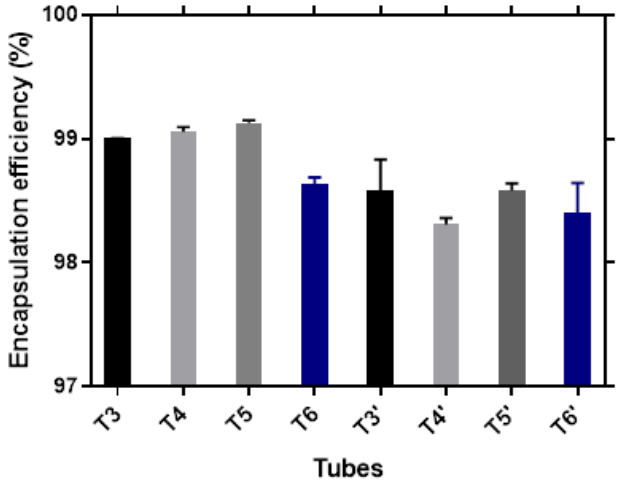

Figure 5: Encapsulation efficiency of emulsions

About the study of encapsulation efficiency, the first remark is that we had obtained good encapsulation rates (Figure 4). These rates being higher in the tubes T3, T4 and T5 not containing NaCl. These tubes are among the most stable tubes. Indeed, the stability of the emulsions guarantees good protection of the droplets against coalescence. In addition, the low solubility of ibuprofen in water (0.02 mg / mL) means that it remains in the internal phase. Similar results were obtained by frélishowska and al. [6] with caffeine.

2.3. In vitro release study using pH

The choice of magnesium carbonate particles was done because of their no toxicity and their capacity to be solubilized in the gastric medium (pH equal to 1.2). The idea is to induce a specific destabilization of the droplets on function of pH, leading to the emulsion destabilization and to the release of encapsulated ibuprofen. As can be seen from the Figure 6, the percentages of ibuprofen released were strongly dependent on the saturation concentration of the medium.

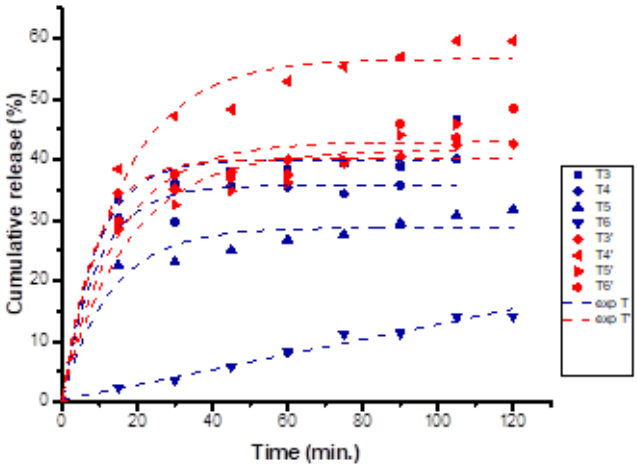

Figure 6: Ibuprofen dissolution profiles in an acid medium (pH = 1.2) as a function of time, modelled according to first order kinetics.

The modelling parameters are available in the supplementary information (Table S2).

For most tubes, the percentages released in ibuprofen were less than 60% of the initial load. Indeed, ibuprofen has a very low solubility in an acid medium (0.06 mg / mL) [26,27]. As a result, the saturation concentration in the dissolution medium is quickly reached. Thus, several release profiles as a function of time were obtained. These profiles were modelled according to kinetics of the first order of equation $\boldsymbol{P_t = P_0 + A.exp^{Kt}}$ with determination coefficients close to 1 [19,28,29].

The release of ibuprofen was also studied in phosphate buffer at pH = 6.8 simulating the intestinal fluid. This study was carried out after 120 minutes of residence in an acid medium corresponding to the residence time of the emulsion in the stomach (Figure 7). There was a significant release of ibuprofen from the emulsion that already had saturation in an acid medium. The greater release in this medium is strongly favored by a prior destabilization of the emulsions in an acid medium. Thus, the interest of these Pickering emulsions is that they are able to increase the bioavailability ibuprofen. In fact, magnesium carbonate particles once in the stomach can increase the pH and promote the release of active ingredients such as ibuprofen whose solubility is strongly influenced by the pH [26,27].

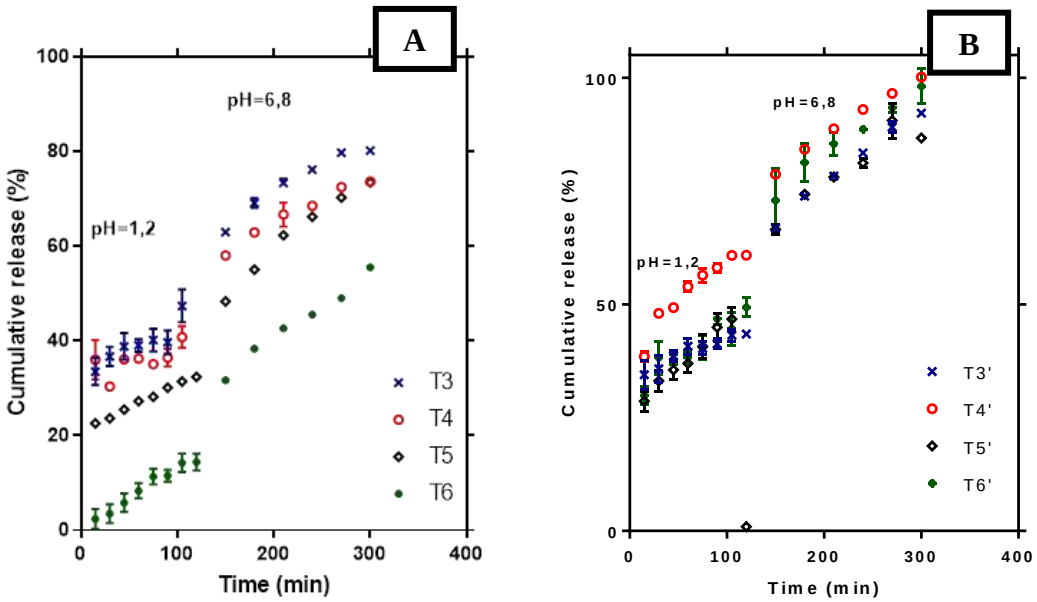

Figure 7: Dissolution profiles of ibuprofen in acid buffer at pH = 1.2 followed by a study in phosphate buffer at pH = 6.8 for Pickering emulsion: (A) emulsion without NaCl, (B) emulsion with NaCl

CONCLUSION

In this study, the general objective was to make a formulation of pH-dependent Pickering emulsions for controlled release of active substances to improve their oral bioavailability. We stabilized oil-in-water type Pickering emulsions with magnesium carbonate particles. A model of lipophilic drug, ibuprofen, was incorporated into the oily phase. The solubilization of the magnesium carbonate particles in an acidic medium was used as an external stimulus for the destabilization of the emulsions. Thus, the interest of these Pickering emulsions lies on the fact that their non-toxicity and magnesium carbonate particles allow destabilization of the emulsions and release of the drug. These emulsions not only protect patients from the side effects of acid-based drugs, but also contribute to increase the bioavailability of these acidic drugs. In fact, magnesium carbonate particles once in the stomach can increase the pH and promote the release of active ingredients such as ibuprofen whose solubility is strongly influenced by pH.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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SUPPLEMENTARY INFORMATIONS

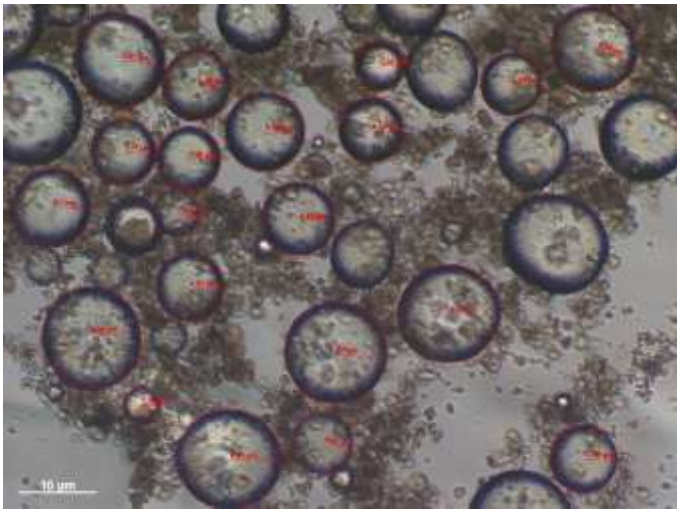

Figure S1: Determination of the size of droplets

Table S1: Proportions of formulations containing ibuprofen.

Tubes	T3	T4	T5	T6	T'3	T'4	T'5	T'6
Water (ml)	20	19	18	17	20	19	18	17
Oil (mL)	10	11	12	13	10	11	12	13
Concentrations of ibuprofène (mg/mL)	1,80	1,98	2,16	2,34	1,80	1,98	2,16	2,34
$MgCO_3$ (g)	1	1	1	1	1	1	1	1

Table S2: Parameters for modelling release profiles according to first order kinetics

	P_0		A		K		R^2
	Value	Ecartype	Value	Ecartype	Value	Ecartype	
T3	40,0412	1,52141	-39,9138	3,71307	-0,10931	0,03157	0,942
T4	35,7512	1,35355	-35,5569	3,2817	-0,10566	0,02957	0,943
T5	28,7661	1,15816	-28,2568	2,81115	-0,07632	0,01944	0,925
T6	-6323,6469	1,1547E6	6323,9806	1,1547E6	1,97379E-5	0,0036	0,971
T3’	40,1322	0,93071	-39,9874	2,47126	-0,11424	0,02253	0,97
T4’	56,6764	1,55863	-55,7780	3,51103	-0,06267	0,00964	0,969
T5’	41,6168	2,26305	-40,4413	4,33196	-0,05636	0,01501	0,924
T6’	42,9480	1,80202	-42,3440	4,18547	-0,06739	0,0165	0,926