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Elaboration of microparticles by the complex coacervation: Electro-kinetic study of associative mixtures and application to the encapsulation of an antalgic active ingredient

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The main objective of this work is devoted to the microencapsulation process by the complex coacervation using two types of natural polymer namely sodium alginate and gelatin to encapsulate a pharmaceutical active ingredient of the "Diclofenac" family of analgesics and to prolong its release in vivo. In a first step, the influence of physicochemical parameters on the existing interactions between both polymers has been studied. The effects of pH, Pr:Ps (Protein: polysaccharide) ratio and the addition of salt concentration through the particle size and Zetametry by the dynamic light scattering technique, make it possible to experimentally limit the optimal domain of coacervate formation; which is used to formulate the Diclofenac-based microparticles. The results revealed a great influence of pH on the formation of the Pr:Ps complex with an impact on the mean diameter (D42). The latter recorded a clear increase, with a decrease in the electro-kinetic potential reflecting the neutralization of the charges at pH 3.5-4. The results also showed a better coacervation (interaction between the polymers) for ratios of alginate / gelatin equal to 4/1 and 3/1. The formulation of microparticles based on Diclofenac by coacervation was subsequently characterized on the technical (size and texture) and biopharmaceutical levels, which revealed a prolonged type release of 8 h.

Keywords: Coacervation interaction, Complex coacervation, Diclofenac, Gelatine, Microencapsulation, Prolonged release, Sodium alginate

Introduction

Microencapsulation allows the formulation of microcapsules or microspheres and has applications in the sectors of medical, pharmaceutical, cosmetic, chemical, agricultural and food[1]. The interest is to give the properties of encapsulated species that it does not have in a free state, such as masking unpleasant odors[2], increasing the stability of active ingredients sensitive to external aggressions (oxidation, pH, humidity), control the release of the active ingredient and separate incompatible products. The final characteristics of the formulated micro-particles (morphology, size, active ingredient content, release profile, etc.) depend on the choice of the methodology. Different encapsulation processes exist; such as mechanical technique (nebulization, drying and fluidized bed coating), chemical processes (interfacial polymerization and interfacial polycondensation) and physico-chemical processes (evaporation, solvent extraction, thermal gelation, iontropic gelation and simple or complex coacervation)[3].

The term "complex coacervation" was introduced in 1949 by Bungenberg de Jongen for the phase separation of the gum acacia/gelatin, which consists of the separation of a solution with a polysaccharide and a protein, into two liquid phases. The most concentrated phase is the coacerbated phase, the other being the equilibrium solution[4]. The principle is based on the partial desolvation of two colloids and their aggregation at low pH. The complex coacervation seems to be an interesting microencapsulation technique to achieve high encapsulation rates[5]. The physical parameters influence the complex coacervation through the protein/ polysaccharide ratio, pH, ionic strength (salt concentration), total polymer concentration as well as the molecular weight of the polysaccharides and proteins[6].

The optimal ratio and pH were found to be 3.5:1 and 3.5-3.8, respectively, to form the maximum

coacervate complex gelatin A/Na-alginate[7]. The complex coacervation of gelatin A/Na-alginate (4:1) was investigated[8] and the optimal coacervation occurs at pH 3.5. The formation of fish gelatin (FG)/alginate (AL) complexes was significantly influenced by the FG/AL ratio, pH, total biopolymer concentration (TB) and salinity. The complex formation and aggregation are facilitated at high TB amounts or addition of small amounts of NaCl, and are suppressed at high NaCl concentrations. The complexes are formed in a pH-dependent reversible manner. The inter-polymer complexation between Pectin (P) and Gelatin A (GA) was studied over a wide pH range (3 - 9) and ionic strength (I = 0 - 0.1 M NaCl). It has been reported that addition of NaCl resulted in a Surface Patch Binding (SPB) at high pH and GA concentration[10]. The complexation of fish gelatin with carboxylated chitosan occurred preferentially at pH 5 where their electrostatic interaction leads to a new lamellar porous structure that could be used in the future in the design of new food matrices[11].

The molecular weight of the biopolymer used to form the microparticles has also an effect on the coaservation. For a low molecular weight, the interaction occurs by simple ionic bridging rather than by formation of intermolecular electrostatic complexes. On the contrary, the interaction favours rather the formation of precipitates for high molecular weight[12]. The microparticles based on polysaccharides and proteins has attracted a great interest in recent decades because of their wide applications in various sectors such as pharmaceutical, cosmetic and food. Due to the difficult acidic conditions in the stomach, some APs cannot be administered as is (e.g. Diclofenac). Therefore, the microencapsulation is an excellent approach, not only to solve the problem of compatibility with stomach acidity, but also to formulate drugs with additional characteristics. It allows masking unpleasant flavours and odours of microencapsulated compounds, to protect them from oxidation and other unfavourable reactions and to prolong the release of the AP[13].

Saravanan and Rao[14] studied the Diclofenac encapsulated in alginate/gelatin microparticles and found that the release was prolonged up to 16 h. Encapsulation of a new antifungal drug (luliconazole) in microparticles obtained by spray-drying a complex mixture of alginate and polyelectrolyte gelatin was investigated by Szekalska *et al.*[15]. The addition of gelatin was found to modify the particle size, improve the encapsulation efficiency and mucoadhesiveness, and prolong the drug release. The complex coacervates based on natural biopolymers (GA and sodium alginate: SA) were investigated as a protein delivery system to allow controlled liberation of loaded proteins and bypass proteolytic degradation in chronic wounds[16]. The terpenes present in the essential oil (EO) of black pepper are volatile and their properties can be reduced under specific conditions. To solve this problem, Bastos *et al.*[17] have encapsulated EO with gelatin and SA by complex coacervation. A ratio of 6:1 (gelatin/SA) at pH 4.0 was ideal for the EO encapsulation.

This work focuses on the development of microparticles based on alginate and gelatin through complex coacervation, with the aim of encapsulating sodium diclofenac and prolonging its release. The study sought to determine the optimal conditions for coacervate formation by examining the combined effects of the polymer ratio, pH, and NaCl concentration, with particular attention to the 3:1 and 4:1 ratios. The originality of the approach lies in the simultaneous optimization of these physicochemical parameters, which are rarely investigated together, as well as in the direct application to the controlled release of a nonsteroidal anti-inflammatory drug. Coacervate formation was assessed through macroscopic observation and UV–visible spectrophotometry, and the optimized systems were subsequently used for active ingredient encapsulation and release kinetics analysis, demonstrating the potential of these biopolymers as pharmaceutical delivery vehicles

Experimental Section

Materials

Distilled water used in this work has a resistivity of 8 MΩ-cm and all reagents were of analytical grade supplied by Sigma Aldrich. Sodium alginate, extracted from brown algae and supplied by Sigma-Aldrich, is in the form of a fine, off-white to yellowish-brown powder with a medium viscosity grade. It typically exhibits a viscosity range of 20 to 200 mPa·s at 1% concentration and 20°C. The molecular weight of this product is approximately 30,000 Da. This molecular weight contributes to its physicochemical properties and applicability in various industrial and research contexts. This sodium alginate is known for its solubility in water, forming a colloidal solution.

Type B gelatin used in this study is supplied as a coarse yellow powder with the ability to swell in cold water. Upon heating, it forms a colloidal solution that undergoes gelation during cooling, developing variable firmness depending on conditions. It is water-soluble and has an isoelectric point of approximately 5. In a 1% (w/v) solution at 55°C, its pH ranges from 3.8 to 7.6. The material has a density of 1.32 g/cm³, and its molecular weight distribution lies predominantly between 50 and 300 kDa. Sodium azide, is a white odourless crystalline powder of crude molecular formula NaN3 (65.01 g/mol) and highly soluble in water. The Active Principle (AP: Diclofenac sodium: $C_{14}H_{10}Cl_2NNaO_2$, 318.13 g/mol) is a nonsteroidal anti-inflammatory drug supplied by the Algerian pharmaceutical company (SAIDAL Company).

Method

The method followed in this study has two parts; the first one was the development of microcapsules by varying the ratio: gelatin/alginate (R:GE/ALG), pH and salt concentration. The second part consisted in monitoring the release rate of Diclofenac after its addition to the coacervates obtained (biopolymers).

Preparation of the microcapsules

For the development of the microcapsules, we opted for a total concentration of Gelatin/ Alginate biopolymers) of 0.1%, the ratio was varied according to the matrix grouped in Table 1. Alginate and gelatin solutions were prepared separately by dispersing the appropriate quantities in distilled water under moderate stirring (100 rpm) at a temperature not exceeding 50°C. Both solutions were mixed by adding 0.1 g of sodium azide as preservative and homogenized for few minutes.

pH adjustment

The microencapsulation method was essentially based on the procedure described elsewhere[18,19]. The simultaneous desolvation of two water-soluble polyelectrolyte-type polymers of opposite charge (GE and AG) occurred, by the modification of pH, thus inducing electrostatic attraction of the two polymers. The pH is adjusted by adding a few drops of acetic acid (0.1N) to 20 mL of polymers solution under stirring (Table 2).

Brine preparation

The influence of NaCl on the interactions between biopolymers (Gelatin/Alginate) was studied at different NaCl different concentrations (0.05, 0.1, 0.5 and 1 M). The salt was added to the microparticles only for the optimum ratios R3/1 and R 4/1.

Characterizations of microcapsules

To characterize the interactions between the microcapsules, it was imperative to specify the pH of the reaction medium and the optimum ratio corresponding to the maximum interaction and to see the effect of adding salt on the development of the microcapsules. The morphology of the microcapsules was visualized by optical microscopy (Optika). The absorbance was measured with an UV-visible spectrophotometer (UV-1700 pharma Spec Shimadzu), The spectral measurements were taken in transmittance mode at 500 nm. The average diameter was measured with a laser particle sizer (Mastersizer, Malvern). The stability of the coacervates, evolution of coacervate size as a function of pH and zeta potential were determined by measuring the zeta potential (Nano Zeta Sizer, brand MALVERN).

In-vitro anti-inflammatory release studies

The kinetic of the release of Diclofenac sodium *in vitro* has been studied with the optimum ratios R3/1 and R4/1 at a pH of 3.5. The dissolution medium used is a simulated gastric medium at (0.1 M pH 1.2). The latter was encapsulated in the formulated microparticles. Four formulas (F1-F4) have been developed by addition of AP to the coservates according to the matrix (Table 3). The solutions were vigourously centrifuged (8000 rpm,

Table 1 — Quantitative matrix of the two biopolymers

Ratio	Gelatin (g)	Alginate(g)
R1/1	0.100	0.100
R2/1	0.133	0.066
R3/1	0.150	0.050
R4/1	0.160	0.040

Table 2 — Results of pH adjustment of ratios studied

Ratio	Initial pH	pH 5	pH 4.5	pH 4	pH 3.5	pH 3	pH 2
R 1/1	6.38	5.02	4.52	4.02	3.51	2.98	2.01
R 2/1	6.75	4.99	4.52	4.02	3.49	3.02	2.01
R 3/1	6.46	4.99	4.52	4.02	3.51	3.00	1.98
R 4/1	6.27	5.00	4.51	4.01	3.51	3.02	2.02

Table 3 — Quantitative matrix of the encapsulation of Diclofenac sodium

Polymer ratio	Ratio (polymer/PA)	Biopolymers Alg/Gel (g)	PA Diclofenac sodium (g)
$R_{3/1}$	F_1^*	0.10	0.10
	F_2^*	0.10	0.20
$R_{4/1}$	F_3^*	0.10	0.10
	F_4^*	0.10	0.20

*F_1 and F_3 the quantity of biopolymer is equal to the quantity of PA (for R3/1 and R4/1)

*F_2 and F_4 the quantity of PA is double that of the biopolymer (for R3/1 and R4/1)

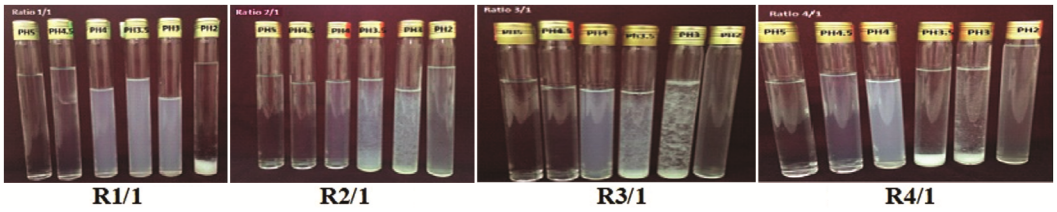

Fig. 1 — Effect of pH on the macroscopic aspect of biopolymers at t=0 day

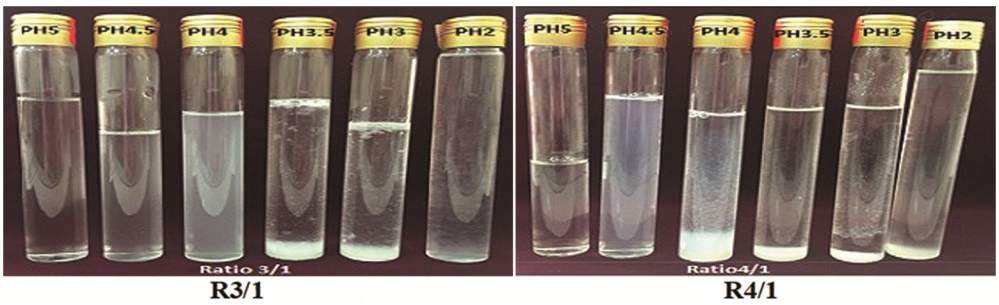

Fig. 2 — Effect of pH on the macroscopic aspect of biopolymers ($R_{3/1}$ and $R_{4/1}$) at t=10 days

10 min) to recover the microcapsules; a dissolution test was carried out and AP was analyzed by UV spectrophotometry (λ_{max}= 276 nm).

Results and Discussion

Characterization of the coacervates

Effect of pH on Gelatin/Alginate complex

pH plays a key role in the protein-polysaccharide interactions, by affecting the degree of ionization of functional groups (i.e. amino and carboxylic) present in the biopolymers. The turbidity, which results mainly from the size of complex particles in the solution, is a crucial indicator that can reflect the interaction between Gelatin/Alginate and the complexes formation. Visual examination at t = 0 day of the 24 formulae (4 ratios and for each pH) of biopolymers is illustrated in Fig. 1.

pH 5 and 4.5 produce solutions with an optical transparency while the opalescence below a threshold pH (4, 3.5, 3 and 2) reflects the interaction with formation of coacervate for ratios 1/1 and 2.1. For ratios 3/1 and 4.1, the precipitation of the coacervate at pH 3.5 and an opalescent aspect at pH 4 were observed. After 10 days (Fig. 2), the maximum precipitation was observed at pH 3.5 and 3 for ratios 3/1 and 4/1, respectively.

When the electrostatic interaction is weak, the phase separation is of liquid-liquid type, and turns to the liquid-solid type for strong interactions[20]. Xia and Dubin[21] have shown that the mass ratio proteins /polysaccharides (Pr/Ps) has a great influence on the

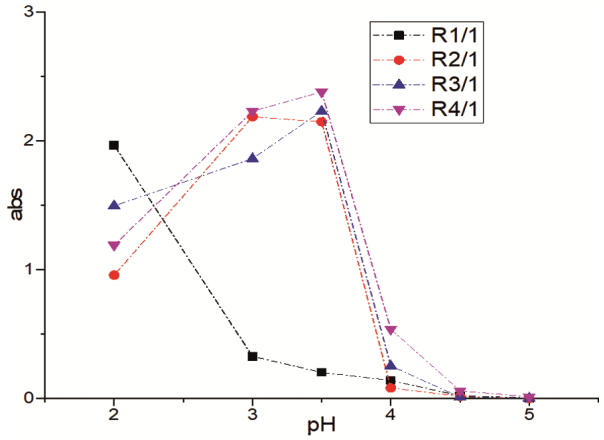

Fig. 3 — Evolution of the absorbance according to the different pH for the different ratios

phase separation by complex coacervation. The coacervation of the (alginate-gelatin) mixture is maximal in the pH range (4–5). Below pH 4, coacervation decreases due to excessive gelatin gelation, while above pH 5, the coacervation decreases because of the increased solubility of alginate. The turbidity, used to study the coacervation of the complexes, is known to be proportional to the number of particles present in solution and their conformation[22], it peaks at pH (3–4) for all samples except the 1/1 ratio where the maximum is obtained at pH 2 (Fig. 3).

The increase of pH for the ratio GE/ALG (1/1) makes the net charges of both polymers close to each other; thus preventing any interaction or complex formation[23]. For the other ratios (4/1, 3/1 and 2/1), the turbidity increases, and reaches a maximum between pH

3 and 4, as a result of electrostatic interactions between the negatively charged carboxylic acid groups of ALG and the amino groups of GEL positively charged[24]. Above pH 4, the carboxyl groups of the alginates are protonated, which reduces the electrostatic repulsion between the chains; and decreases turbidity, because the chains are less likely to clump together. In order to better understand the electrostatic interactions that occur between gelatin and alginate at different pH. Fig. 4 shows the variation of the zeta potential of both coaservate ratios (R3/1 and R4/1) as a function of pH (Table 4).

The more the cationic charges H^+ are present, the more the zeta potential tends towards negative values,

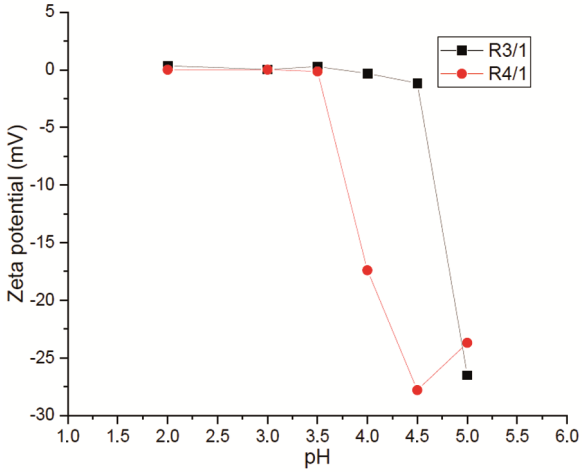

Fig. 4 — Variation of zeta potential of coaservates (R3/1 and R4/1) as a function of pH

the latter being neutralized in the pH ranges (4-3.5) and (3.5-3) for the ratios 3/1 and 4 /1 respectively. More interestingly, the maximum interaction occurs in the pH range (3-4) with charge neutralization. The latter occurring by electrostatic interaction contributes to the modification of solubility, desolvation and precipitation and gives information on the formation of coaservates. The neutralization pHs are between (3.5-4) and (3-3.5) for the ratios 3/1 and 4/1, respectively.

The granulometric analysis shows a gradual increase in the particle size of the alginate-gelatin mixture when the pH decreases from 5 to 3 for a fixed ratio. The size of the coaservates is ~ 5 nm for at pH 5 (Fig. 5a) for the ratio 3/1 and increases up to 150 µm at pH 3.5 (Fig. 5b)

For the ratio 4/1, the size averages 20 and 100 nm, respectively, at pH 5 (Fig. 6a) and pH 4.5 (Fig. 6b).

For both ratios the particle size increases from nm to µm when the pH decreases. Such an increase in the size indicates the formation of aggregates due the gelatin and alginate complex.

Effect of salinity on Gelatin/ Alginate complex

Figs 7 and 8 show the effect of the salt on the coaservate formulation for the optimum ratios

Table 4 — Variation of the zeta potential as a function of pH for the ratios R4/1 and R3/1

Ratio	Zeta potential (mV)					
	pH 2	pH 3	pH 3.5	pH 4	pH 4.5	pH 5
R3/1	0.3420	0.0407	0.2780	-0.3080	-1.160	-26.500
R4/1	0.8790	0.0209	-0.1380	-17.400	-27.800	-23.700

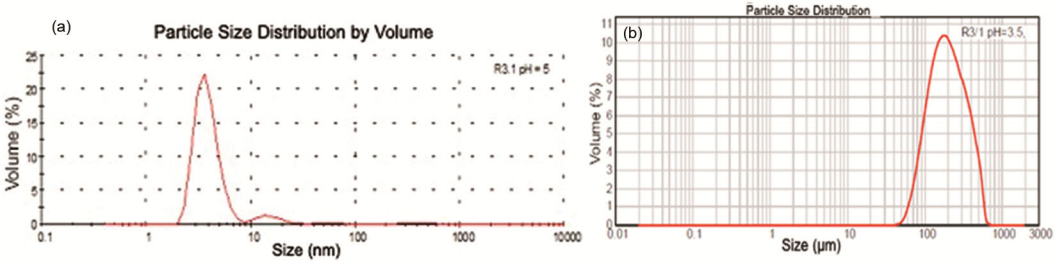

Fig. 5 — Size distribution of coaservates R3/1 at pH5 and 3.5

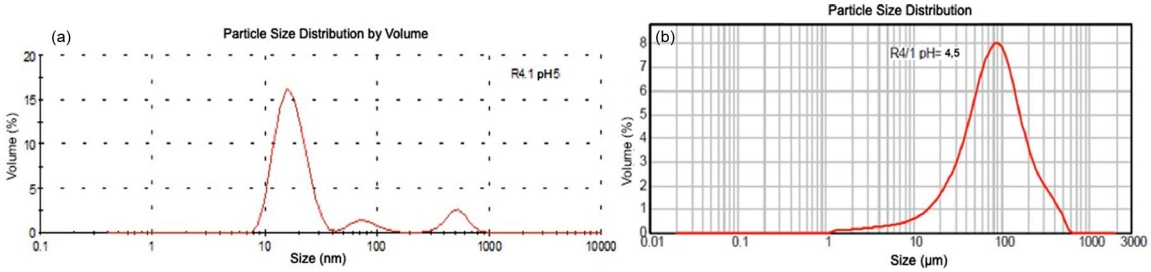

Fig. 6 — Size distribution of R4/1 pH5 and pH4.5 coaservates

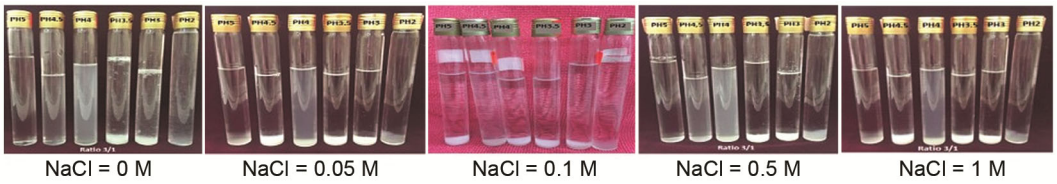

Fig. 7 — Effect of salinity on the macroscopic appearance of biopolymers (Ratio R3/1)

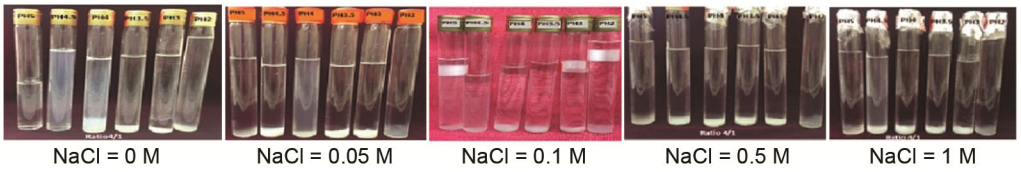

Fig. 8 — Effect of salinity on the macroscopic appearance of biopolymers for a ratio R4/1

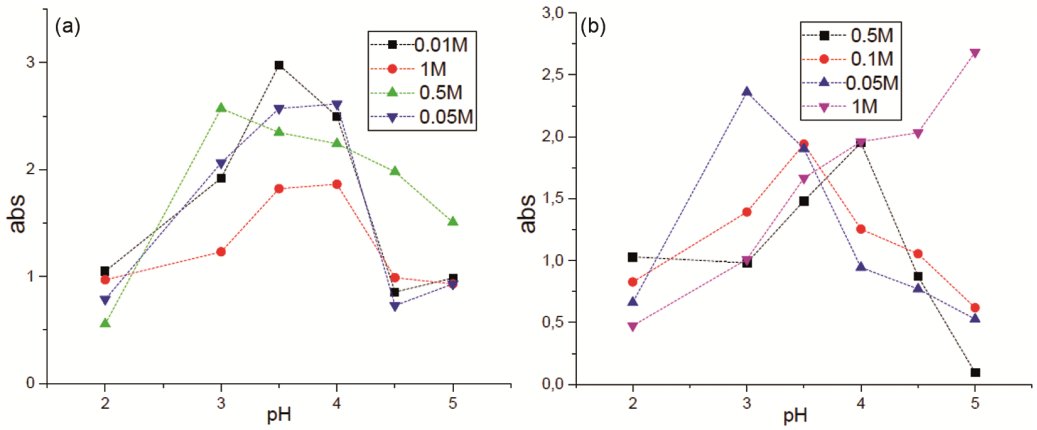

Fig. 9 — Evolution of the absorbance at different concentrations of salt i.e., (a) Ratio $R_{4/1}$, (b) Ratio $R_{3/1}$ as a function of pH

RGE/ALG (R3/1 and R4/1). The NaCl concentration (0.05, 0.1, 0.5 and 1 M) has an effect on the appearance of biopolymers whose precipitation is observed below pH 3.5 for the 3/1 ratios and from pH 3.5-4 for the 4/1 ratio for the NaCl concentrations 0.05 and 0.1 M. An opalescent appearance is observed at pH 4 and 4.5 for the ratio 3/1and pH 4.5 for the ratio 4/1.

The presence of salt favours the appearance of the coacervate and the explanation is due to the saturation of the anionic and cationic sites Na^+ and Cl^-. This means that in solution, the charges of the biopolymers are reduced by interactions with these ions, thus neutralizing the biopolymers, which end up precipitating. Indeed, the mineral ions in solution, amplifies the charges carried by the biopolymers through the interactions with these ions, this would promote the electrostatic attractions between the protein and polysaccharide molecules followed by formation of coacervates. The effect of the salt on the optical density for the ratios 3/1 and 4/1 at different concentrations is illustrated in Fig. 9.

For the ratio 4/1, the absorbance increases and reaches its maximum in the pH range (2 - 3.5). Then, it decreases above pH 3.5 irrespective of the salt concentration. Nevertheless, the maximal absorbance is affected by the amount of NaCl. At pH of 3.5, the maximum turbidity of the gelatin/alginate complex (ratio 4/1) decreases with increasing the NaCl concentration. The turbidity increases from 2.39 in the absence of NaCl (Fig. 3), to 2.98 for a concentration of 0.01 M NaCl and 2.56 for 0.05 M.

NaCl increases the ionic strength of the complex and reduces the electrostatic repulsion with the complex, which decreases the probability of separation of the mixture (alginate/gelatin) during the formation of coacervates.

When the NaCl concentration is increased by a factor of 10 (for example from 0.05 to 0.5 M or from 0.1 to 1 M), the maximal turbidity decreases from 2.34. At high NaCl concentrations, the ionic strength destabilizes the gelatin/alginate complex and a decrease of its turbidity. Indeed, the high salt concentration can disrupts the electrostatic attractions and maintains the

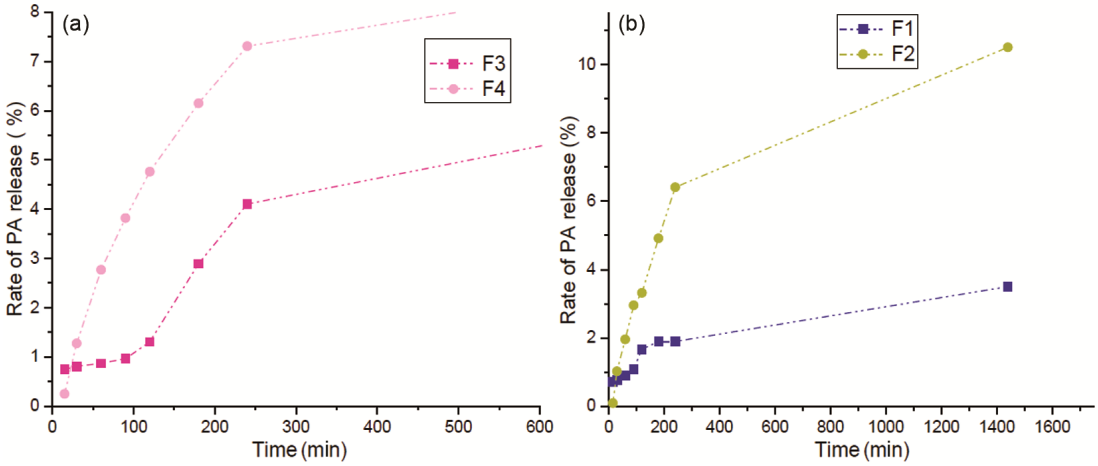

Fig. 10 — Cumulative release of Diclofenac sodium as a function of time for (a) R4/1 and (b) R3/1

components of the complex together, leading to their separation with the formation of precipitates. This was predicted by Veis and Aranyi[25], who studied the complex coacervation between myoglobin and anionic polysaccharides. Imeson *et al.*[26], showed that increasing the ionic strength resulted in a loss of the protective action of the polysaccharide for the protein, which is denatured after heat treatment.

For 3:1 ratio, it was observed that the maximum turbidity of the complex (alginate/gelatin/salt) varies with both the NaCl concentration and pH. For a concentration of 0.05 M NaCl, the maximum turbidity is reached at pH 3 (0.05 M) and 3.5 (1 M). When the concentration increases to 0.5 and 1 M, the maximum turbidity is observed at pHs 4 and 5, respectively. From this part of the study, it can be concluded that the optimal ratios are R3/1 and R4/1 with a pH adjustment between 3 and 4.

Application of the formulated coacervate in the pharmaceutical field

The second part of this work is dedicated to the encapsulation of a non-steroidal anti-inflammatory (Diclofenac sodium: PA) in the previously formulated microparticles and to study the kinetics of release of PA in order to prolong its liberation in-vivo. The study was carried out with the optimal ratios R3/1 and R4/1 at pH 3.5. Four formulations were prepared by addition of active ingredients to the coacervates according to the matrix mentioned. (Table 3). The cumulative drug release profiles of Diclofenac sodium are presented in Fig. 10, showing the evolution of the cumulative percentage of PA released as a function of time for all four formulations. The results confirm a prolonged release of the drug, with 8–10% of Diclofenac released after 10 h for the ratio R4/1 and after 25 h for the ratio R3/1.

It is observed that the release rate is lower when the quantities of PA and coacervate are equal (formulations F1 and F3). Conversely, doubling the amount of PA (formulations F2 and F4) leads to a faster release. For R3/1, 1.87% of the AP was released after 3 h 20 min, while doubling the PA quantity increased the release to 5.36%, corresponding to a 2.87-fold acceleration. For R4/1, 3.29% was released under the same conditions when PA and coacervate were equal, whereas doubling the PA increased the release to 6.56% (a twofold increase).These findings indicate that the PA/coacervate ratio strongly influences the release kinetics. To achieve a slower and more controlled release, a 1:1 PA-to-coacervate ratio using R3/1 is recommended. In contrast, to slightly accelerate the release, a 2:1 PA-to-coacervate ratio using R4/1 can be employed.

Conclusion

This study demonstrated successful development of biopolymer microparticles of gelatin and alginate through complex coacervation, optimized for encapsulation and prolonged release of sodium diclofenac. The optimal biopolymer ratios were identified as 3/1 and 4/1. The pH range allowing maximal coacervate formation was narrowed to 3.5–4 for the 3/1 ratio and 3–3.5 for the 4/1 ratio. NaCl concentration significantly influenced polymer interactions and coacervate formation, with best coacervation observed at low salt levels; higher NaCl concentrations destabilized the complex. Granulometric analysis revealed a significant increase in coacervate particle size from nanometers (5–20 nm at pH 5) to

micrometers (up to 150 µm at acidic pH 3–3.5), indicating aggregation behaviour. The encapsulated Diclofenac sodium exhibited a prolonged release profile, with approximately 8–10% released over 10 h for the 4/1 ratio and over 25 h for the 3/1 ratio. Doubling the active ingredient increased the release rate by factors of 2 and 2.87 for ratios 4/1 and 3/1, respectively. These findings enable tailored control of drug release kinetics by adjusting the polymer ratio, pH conditions, and drug-to-coacervate amounts. Specifically, a 1:1 drug-to-coacervate ratio at 3/1 provides slower release, while a 2:1 ratio at 4/1 accelerates drug liberation. This work firmly establishes gelatin/alginate complex coacervation as a promising technique for pharmaceutical micro-encapsulation and sustained drug delivery applications.

Conflict of interest

The authors declare no conflict of interest.

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