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Physical chemistry behavior of enteric polymer in drug release systems

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ABSTRACT

We report an analysis based on the electrical impedance (EI) spectrum of the samples of enteric random copolymer poly-methacrylic acid-co-methyl methacrylate as a function of pH of media. Important aspects of the charge transport and conformational processes in enteric polymer can be identified by mapping the complex impedance as a function of the frequency, which allows that some parallelism between titration and EI measurements can be obtained. However, the latter technique reveals details of this complex equilibrium that not appear using common titration methods. The relaxation frequency observed in the impedance spectrum act as a probe for the detection of phase transitions and conformational changes of the polymeric chains, once the distribution of size of particles can be related with this parameter. The progressive introduction of the alkali and the variation of pH between 4 and 10 are associated with a three steps process, related to the equilibrium shift from a precipitated solid or suspension, to a colloidal-like dispersion and to a complete solubilization of the copolymer. All those experimental features were reflected simultaneously as a turning point in plots of impedance, relaxation frequency and visible absorption with alkali addition giving a better and detailed insight to these processes.

1. Introduction

Great attention has been devoted to the use of oral-delivery systems containing acrylic polymer matrices of the so-called "enteric polymers" type, since these polymers are essentially insoluble in the gastric juice and may be used to impart enteric solubility to the encapsulated drug serving as a drug target device (Vachon and Nairn, 1995; Morishita et al., 1993; Moustafine et al., 2005a,b; Raffin et al., 2007; Oosegi et al., 2008).

It is known mainly by titration methods that these polymers are sensitive to pH changes and are able to protect the drug from the degradation action of the enzymes and gastric fluid, which is very acid (pH = 1–2) (Moustafine et al., 2006; Haznedar and Dortunc, 2004; Hori et al., 2005; Cui et al., 2007), and also to avoid side effects such as gastritis for example in patients who consume aspirin daily (Vachon and Nairn, 1995). Thus, these materials should be very useful for the transportation to the intestine, protection of drugs of proteinic nature (Rao et al., 2003; Dupeyron et al., 2005; Amorim and Ferreira, 2001; Shen, 2003; Allémann et al., 1998), and as cation-exchange membrane dependent of pH of media (Raffin et al., 1995).

A series of enteric copolymers named Eudragit were developed by Röhm GmbH & Co. KG that could be widely used for controlled drug delivery (Moustafine et al., 2006; Siepmann et al., 2008; Lau and Gleason, 2008; Quinteros et al., 2008; Bando and McGinity, 2006). As indicated in literature, the Eudragit is a reversibly soluble polymer depending on pH (Dourado et al., 2002) (generally applied as a coating) and is useful to improve the stability of microspheres of drugs during storage (under ambient conditions) and to promote the controlled delivery of drug in specific diseases (Cui et al., 2007; Maestrelli et al., 2008; Krishnamachari et al., 2007).

The chemical structures of these polymers are shown in Fig. 1. In the case of Eudragit L-100, we have that $R_1 = R_3 = R_4 = CH_3$, $R_2 = H$, is a random copolymer (50/50). This poly-methacrylic acid-co-methyl methacrylate was used in the present study.

In fact an enteric copolymer should have in its structure a hydrophilic monomeric unit, such as that of the methacrylic acid one, and another hydrophobic one, such as the methyl methacrylate. The behavior of this material is dependent on protonation state: at higher pH, the carboxylic groups became ionized, changing their conformations and expanding them due to the repulsion between the negative charges of the carboxylates. At lower pH the carboxylic groups are not ionized. The conformations are them so closed allowing that the copolymer can precipitate.

This process is mimicking the pH change that accounts in the gastro-intestinal tract (GIT) from the stomach to the intestine. The GIT is specifically designed to degrade dietary proteins and facilitate absorption of amino acids and oligopeptides (Allémann et al., 1998). The recovering of therapeutic compounds with this polymer

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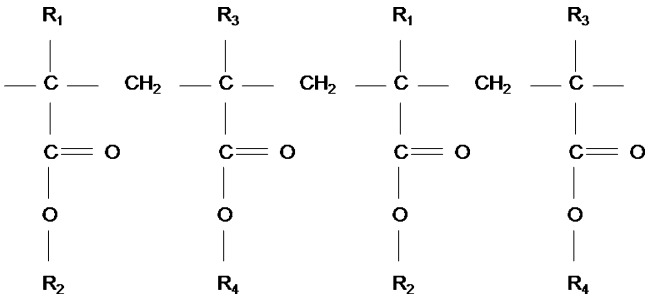

Fig. 1. Schematic view of enteric polymer structure.

allows that the molecules remain intact when they reach the systemic circulation.

The processes of drug-polymer interaction, drug stability, pH and time dependence of enteric polymers are characterized by conventional techniques as dynamic light scattering (particle size) (Krishnamachari et al., 2007; Mastiholimath et al., 2007), Differential Scanning Calorimetry (DSC), thermogravimetry, X-ray diffractometry, FTIR spectroscopy (Maestrelli et al., 2008), turbidimetry, viscosity (Moustafine et al., 2006), and UV–vis absorption (Dourado et al., 2002), while to characterize the entrapment efficiency is used the high-performance liquid chromatography (HPLC) (Krishnamachari et al., 2007).

On the other hand, the electrical impedance (EI) spectroscopy is a technique that has been used with success to detect conformational changes in proteins and interactions of surfactants with other molecules as dyes (de Oliveira et al., 2006; de Oliveira, 2008; de Oliveira et al., 2005; Tenorio et al., 2002; Cortina et al., 2006; de Oliveira et al., 2003; de Oliveira et al., 2008; de Oliveira and de Melo, 2006; Anand et al., 2001). Furthermore, the process of electrical relaxation of the species involved gives valuable information about conformational changes and so phase transitions.

The aim of the present paper is to analyze in details the conformational and phase transitions that occur to this enteric copolymer during pH changes using mainly the technique of impedance spectroscopy that gives additionally information respect to other techniques about the charge carriers and derivative parameters, establishing this technique as a convenient tool to analyze the physical chemistry processes of the enteric polymer during drug release.

2. Materials and methods

2.1. Materials

The enteric polymer (Eudragit L-100) was purchased from Röhm Pharma (Germany) and an amount of 100 mg was dispersed into 50 ml of distilled water. After 1 h under intense stirring in order to generate complete dispersion of this material, the measurements of electrical and optical properties were carried out, by progressive insertion of small aliquots of 60 μl of NaOH from a 0.164 M mother solution. This concentration of alkali was used to avoid a significant variation of the initial volume.

2.2. Apparatus

For the analysis of electrical response as a function of frequency, the applied voltage of signal was fixed to 100 mV (with no external polarization) and the frequency was swept in the range from 1 Hz to 10 MHz by the use of a Solartron 1260 impedance analyzer (Solartron, UK) with the corresponding data of impedance acquired by the software Smart (Solartron, UK). In each experiment, two ($20 \times 5\ mm^2$) stainless steel plates were dipped parallelly at a fixed distance (17 mm) within a 50-ml glass beaker containing 20 ml of interest solution (de Oliveira et al., 2006; de Oliveira, 2008; de Oliveira et al., 2005; Tenorio et al., 2002).

The measurements of absorption in the visible region were carried on by Femto Spectrophotometer 800XI (Femto, Brazil) as a function of alkali addition. The pH of the solution was measured using a pHmeter Digimed (Digimed, Brazil).

3. Results

The real part of impedance (by scanning the frequency) was measured at different NaOH additions (see Fig. 2), after continuously stirring of solution. As we can see, the spectrum is well defined in terms of two regions of frequencies:

i) The low frequency side in the Z' response (interval in which the impedance is independent of frequency) represents the range of frequencies in which the ions can move over long distances, performing successful hopping from one site to the neighboring site;
ii) The high frequency side of the Z' (interval in which the impedance is dependent of frequency) represents the range of frequencies in which the ions are strictly confined to their potential wells and the ions can make only localized motion within the wells (Rambabu et al., 2008).

From the Kramers–Kronig relations (Macdonald, 1987; Daniel, 1967; Anderson, 1964) the real and imaginary parts of impedance are related and the transition between two regions (as described above) is obtained in the imaginary part of impedance as a critical frequency named relaxation frequency. The value of this frequency can be obtained directly from the peak in the spectrum of Z'' or similarly from the frequency of extreme in the characteristic semicircle of RX diagram.

Note that from results of Fig. 2, the progressive introduction of NaOH allows that the impedance can be reduced, which is associated with a shift in the value of relaxation frequency deviated to higher values.

As indicated above, through the representation of RX diagrams (Rambabu et al., 2008; Macdonald, 1987; Ram, 2008; Feliciangeli et al., 2007; Dutta et al., 2008; Rao et al., 2008) for this system (as indicated in Fig. 3) the formation of characteristic semicircles is verified. The reduction of the characteristic radius is monotonic, allowing the impedance to be reduced with alkali addition.

Associated with this behavior it was observed that from NaOH concentration, between 2.46 mM and 7.38 mM, the pH attained a plateau (see Fig. 4).

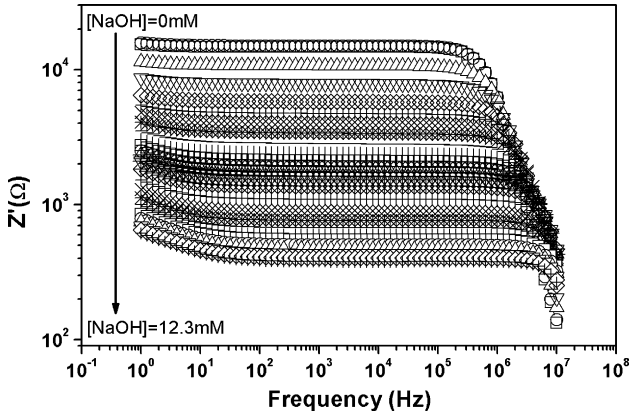

Fig. 2. Real part of impedance for the aqueous solution of enteric polymer as a function of frequency and NaOH concentration.

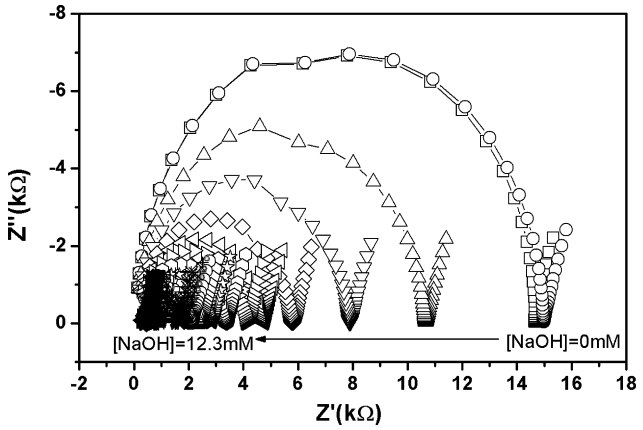

Fig. 3. RX diagram of aqueous solutions of enteric polymer as a function of NaOH concentration.

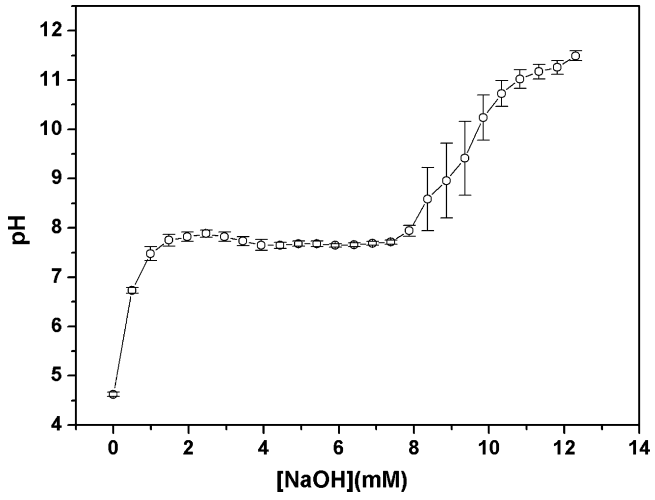

Fig. 4. Variation of pH of aqueous solution of enteric polymer as a function of NaOH concentration.

The plot of the value of impedance at right side of the semicircle in RX diagram versus NaOH addition, as indicated in Fig. 5 reveals the existence of two regions with different slopes (shown by auxiliary lines) that are connected by points with minimized variation of impedance.

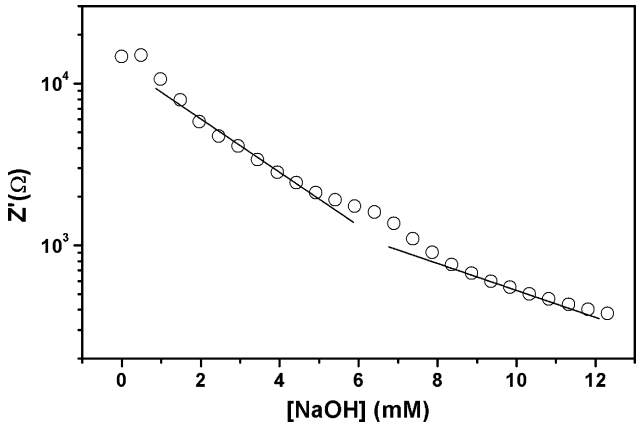

Fig. 5. Real part of impedance measured in the right side of characteristic semicircles for the aqueous solution of enteric polymer as a function of NaOH concentration.

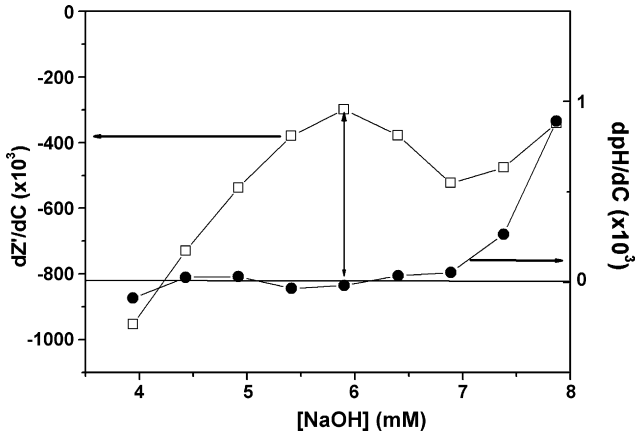

Fig. 6. Comparison of the first derivative of the real part of impedance measured in the right side of characteristic semicircle with the first derivative of the pH as a function of NaOH concentration.

Surprisingly, the differentiation of data in Figs. 4 and 5 leads to an analogy between the two techniques (see Fig. 6), corresponding exactly to the turning point, as is indicated by the arrow.

In Fig. 7 we can observe that the relaxation frequency varies directly with the increase in NaOH concentration. From an alkali critical concentration of 7.38 mM, the saturation of the relaxation frequency is observed attaining their maximal value.

To compare the results obtained with the electrical impedance spectroscopy with a conventional technique we measure the absorption of light of samples in the visible region (Dourado et al., 2002), associating the zero absorbance with the spectrum of specific sample in which occur the maximal solubility of system, considered to be a solution at molecular level, as shown in Fig. 8. In the condition of minimal solubility we can see the precipitated particles from an optical microscope as shown in Fig. 9.

From the calculus of the area under the spectrum of absorbance versus the wavelength (as indicated in Fig. 10) it is possible to observe that at the concentration of NaOH above 5 mM, the area under spectrum tends to be zero. This value is the same in which the transition in impedance spectrum is observed (as indicated by the first auxiliary line in Fig. 5), characterizing the minimal concentration of solubilization (or absence of scattering light centers to the optical response of the sample).

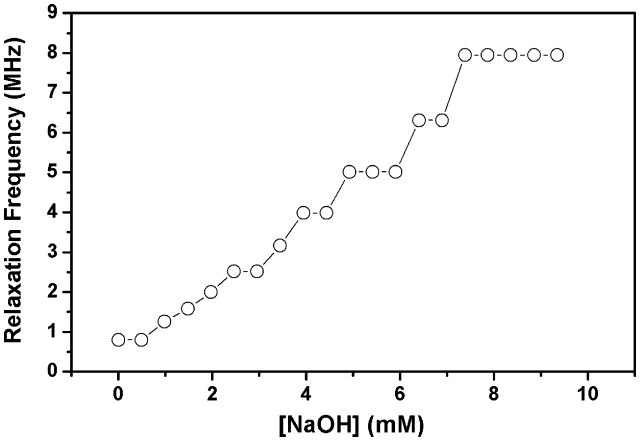

Fig. 7. Dependence of relaxation frequency as a function of NaOH concentration.

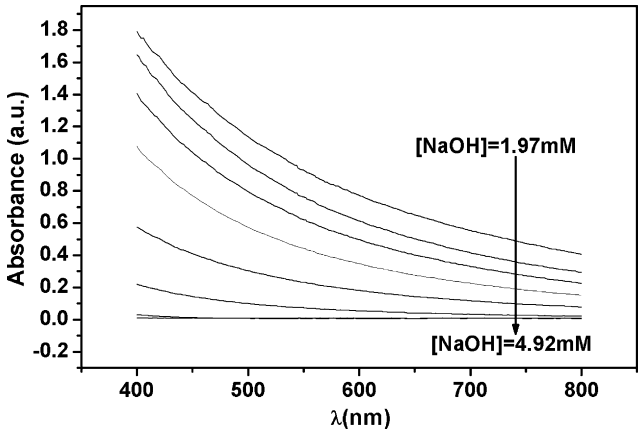

Fig. 8. Absorbance spectrum of the enteric polymer as a function of NaOH concentration.

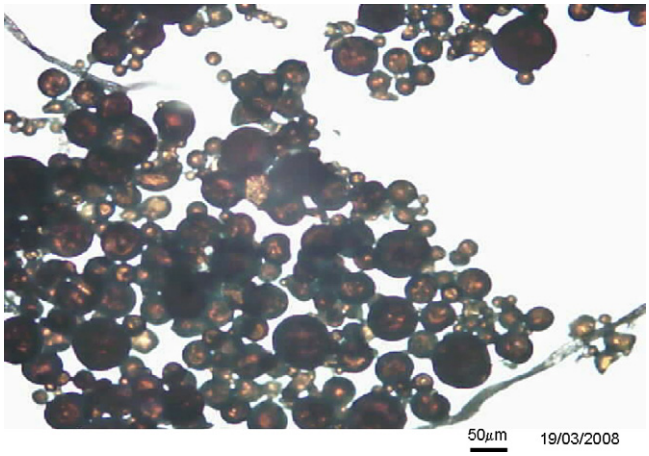

Fig. 9. Image of aggregates of the enteric polymer precipitated from the solution.

4. Discussion

A stirred aqueous suspension of the random copolymer polymethacrylic acid-co-methyl methacrylate behaves, by adding small amounts of NaOH solution, as indicated in Fig. 4. Three well defined regions are observed. The middle one resembles a buffer (Flora et al., 2008). No appreciable pH change is observed in this part due to the consumption of the alkali added by the presence of chains with carboxylic groups which are restored by the precipitated copolymer. Thus, this equilibrium acts as a buffer and no free alkali remains up to pH 7–8. The trend observed in this curve is due to the presence of several species in this multiple equilibrium, insoluble polymer and non-ionized, partially ionized and fully ionized chains. At pH higher than 7 the system becomes soluble which can be attributed to the fully ionized species probably with highly stretched conformations adopted by the chains during ionization. At pH between 6 and 7 the clear solution turns into a fine stable colloidal dispersion which resembles a micelle dispersion. To our knowledge this observation was not found in the literature. Further decrease in pH produces a precipitation, as the polymer–polymer interactions for non-ionized macromolecules predominate over the polymer–solvent ones.

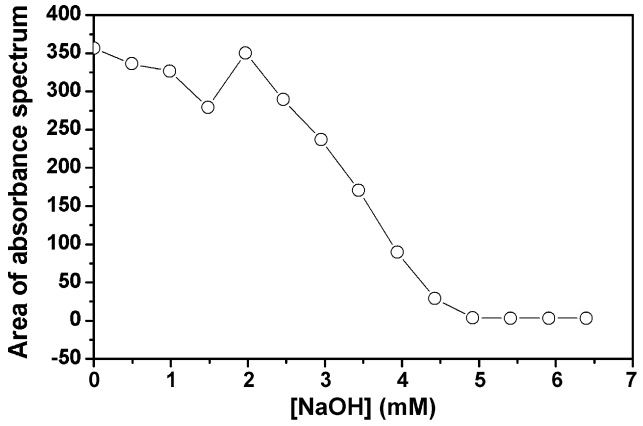

Fig. 10. Area under the absorbance spectrum versus wavelength as a function of NaOH concentration.

From concentration of NaOH of 8–10 mM those entities are the same and are the only species in the system in correspondence with the complete dissolution of the copolymer as sodium carboxylate species. The size of such entities is the smallest of all of them probably related to the hydrodynamic volume of the expanded random coils of the fully ionized species and the absent of colloidal or even greater particles in suspension. This hypothesis is confirmed by the trend observed in the impedance relaxation frequency as indicated in Fig. 7, where the dissolution process begins in the horizontal line of the graph at about 7 mM and pH around 7. Then, the graph steadily falls at lowers than 7 mM. Those features are clearly revealed by the EIS technique because other species should be greater in size because of they form part of the dispersion or the solid suspension. The process can be described as follows: the region from 5 mM to 7 mM should be related partially to ionized species that begin to form another phase with nano–micro dimensions forming a stable dispersion. Finally, the non-ionized species precipitate into bigger particles that cannot be maintained in suspension. However, these particles are perfect spheres in the range of several microns according to the optical micrograph shown in Fig. 9, suggesting that partially ionized species impart to the solution surfactant characteristics because behave as an anionic surfactant.

The presence of two regions seems to differentiate the process of ionization from the process of solubilization. Furthermore, the coincidence of turning point for impedance and pH measurements with the fall in the area of the absorbance spectra, are evidences of the displacement of the equilibrium between the species involved due to their different chemical structure. Another piece of information is the increase observed for the relaxation frequency in Fig. 7, as an indication that species with different sizes are present and these species become smaller with pH increasing reaching the least size when they are soluble (horizontal value of frequency). Thus, confirming all the above discussed and that complete solubilization begins at a concentration of NaOH about 7 mM.

We can correlate this relaxation frequency with the distribution of size of particles because of inertia of such molecular aggregates as has been pointed out in the literature (de Oliveira et al., 2006; de Oliveira, 2008; de Oliveira et al., 2005; Tenorio et al., 2002; Rambabu et al., 2008). The increase in the dimension of aggregates can be associated with the delocalization of ions in the wells, allowing that the characteristic time to the motion of ions and consequently the relaxation frequency can be affected.

From this analysis, we can see that the increase in the concentration of NaOH promotes the reduction in the size of macromolecular aggregates, as the relaxation frequency tends to grow steadily in this range and later presents a discontinuity indicating a sudden transition.

Thus, from the discussion above it can be inferred that the electrical impedance spectroscopy was able to describe completely the complex behavior of such enteric polymer, obtaining a better insight about the behavior of equilibrium when compared with a conventional technique, as the absorption of light. In this case, we

can see that the absorbance falls as a consequence of the decreasing in the amount of insoluble particles that disperse light, because solution of dissolved chains is transparent.

5. Conclusions

The enteric random copolymer (poly-methacrylic acid-co-methyl methacrylate) with the pH decrease transit from a completely solubilization (at pH > 7), to a colloidal dispersion at pH between 6 and 7 and finally to a suspension of the precipitated polymer.

The electrical impedance spectroscopy was able to demonstrate that the behavior of this copolymer and all these changes are typical transitions associated with conformational processes of polymeric chains, characterized through the relaxation frequency. The increase in pH solution is associated with the shift of relaxation frequency to more elevated values due to the successive decrease in the size of the aggregates. Considering these aspects we can conclude that the EI technique is a convenient tool to characterize the drug release processes, once more details about the conformational processes of enteric polymer were revealed if compared with the results to titration and absorption spectra.

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