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Polyelectrolytes

Thermodynamics and Rheology

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Preface

The book on "Polyelectrolytes: Thermodynamics and Rheology" summarizes many of the recent research accomplishments in the area of polyelectrolytes such as state-of-art polyoxymethylene, structure and thermodynamics of polyelectrolyte complexes, polyelectrolytes: science and application, study on biological polyelectrolytes, polyelectrolyte hydrogels: thermodynamics of polyelectrolyte hydrogels rheologys, complexes formation between proteins and polyelectrolytes and its application in the downstream processes of enzyme purification, polyelectrolyte complexes: bridging the ensemble average—single-molecule strategies, stratified interpolyelectrolyte complexes: fabrication, structure, properties, and applications, Monte Carlo studies in polyelectrolyte solutions: structure and thermodynamics. As the title indicates, the book emphasizes on the various aspects of polyelectrolyte and their thermodynamics studies and rheological studies to scientific community. This book is intended to serve as a "one-stop" reference resource for important research accomplishments in this area. This book will be a very valuable reference source for university and college faculties, professionals, postdoctoral research fellows, senior graduate students, researchers from R&D laboratories working in the area of "Polyelectrolyte: Thermodynamics and Rheology." The various chapters in this book are contributed by prominent researchers from industry, academia, and government/private research laboratories across the globe. It covers an up-to-date record on the major findings and observations in the field of "Polyelectrolyte: Thermodynamics and Rheology."

The Chapter on "Polyelectrolyte: Thermodynamics and Rheology" give an overview of the area of state of art, new challenges and opportunities of polyelectrolyte-based studies and research. The following chapter provides an overview of structure and thermodynamics of polyelectrolyte complexes. This chapter explained with many subtopics, such as weak and strong electrostatic coupling, thermodynamics of polyelectrolytes and polyelectrolyte complexes, Flory-Huggins solution theory applied to polyelectrolyte solutions, enthalpy in polyelectrolyte solutions, polyelectrolyte gels, computer simulations and structure, Monte Carlo simulations and other simulation methods, molecular dynamics simulations, experimental characterization, polyelectrolyte complexes and gels, etc.

"Structure and Thermodynamics of Polyelectrolyte Complexes" is mainly concentrated on polyelectrolyte: science and application. The authors of this chapter discussed with recent research on polyelectrolyte, applications of polyelectrolyte, scaling theory, dynamic light scattering, neutron scattering, biopolymers and ionomers. In this section, authors are discussed with very nice subtopics, such as biopolymers, polynucleotides, polypeptides, ionomers, etc. Survey on applications of biological polyelectrolytes done in the "Biological Polyelectrolytes: Solutions, Gels, Intermolecular Complexes and Nanoparticles", the authors explained with many subtitles, such as introduction to biological polyelectrolytes, classification of biological polyelectrolytes, biological polyelectrolytes in solutions, intermolecular complexation and coacervation, biological nanoparticles, encapsulation, and drug release, also they explained about other topics, such as carbohydrate, protein, nucleic acids, protein-protein, protein-carbohydrates, protein–DNA, chitosan, gelatin, and pectin. "Polyelectrolyte Hydrogels: Themodynamics" discussed about the polyelectrolyte hydrogels: Thermodynamics, this chapter discussed about many interesting topics, such as classification of polyelectrolyte hydrogels, synthesis of polyelectrolyte hydrogels, polyelectrolyte hydrogels: thermodynamics, characterization of polyelectrolyte hydrogels, biomedical applications of polyelectrolyte hydrogels.

"Thermodynamic and Rheological Properties of Polyelectrolyte Systems" deals with the thermodynamic and rheological properties of polyelectrolyte systems. This chapter explained many properties, such as interactions, rheological properties, flow properties, etc. Authors of this chapter explained with different subjects such as interaction of polyelectrolytes with organic molecules, release of drugs from polyelectrolyte-drug dispersions, rheological properties of polyelectrolyte dispersions, flow properties of representative sodium salts of acid polyelectrolytes, flow properties of acid PE-drug dispersions, properties of carbomer-drug hydrogels, effect of the addition of other species on carbomer-drug dispersions, remarks on thermodynamic and rheological properties of polyelectrolytes, finally field of projections based on the properties of PE-drug complexes are also discussed. "Complexes Formation Between Proteins and Polyelectrolytes and Their Application in the Downstream Processes of Enzyme Purification" discussed about the complexes formation between proteins and polyelectrolytes and their application, from this chapter, we can see many different kinds of applications and use of polyelectrolyte and authors explained with many other topics including uses and applications of polyelectrolytes, aqueous solutions of polyelectrolytes, the formation of complexes between polyelectrolytes and proteins, the downstream processes of proteins and their scaling up process by PE-P formation, application of PE-P in downstream processes. Bridging the ensemble average-single-molecule strategies of polyelectrolyte complexes are discussed in "Polyelectrolyte Complexes", this chapter also explained about polyelectrolytes in biology, polyelectrolyte complexes in biology, man-made polyelectrolyte complexes, polyelectrolyte complex formation, nonideal thermodynamics, structure of the polyelectrolyte complexes, experimental observations at the individual complex level, correspondence to observations at the ensemble level and cooperative

effects in DNA condensation. The coming chapter on stratified interpolyelectrolyte complexes explained with fabrication, structure and properties and with several topics, such as fabrication of stratified interpolyelectrolyte complexes, controlling the fabrication of polyelectrolyte multilayers: effect of different physicochemical variables, structure: stratified and nonstratified systems, water content and hydration, rheological properties, permeability and porosity, response to osmotic stress, applications.

"Monte Carlo Studies in Polyelectrolyte Solutions: Structure and Thermodynamics" on Monte Carlo studies in polyelectrolyte solutions: structure and thermodynamics, this chapter discussing about, Monte Carlo studies of polyelectrolytes, theoretical approach of Monte Carlo studies, application level of Monte Carlo in polyelectrolyte, authors of this chapter are also trying to discuss more with many topics, such as coarse-grain model for polyelectrolyte and small ions, ideal gas and excess contribution to the partition function of the system, metropolis Monte Carlo method, Monte Carlo trial moves, conformational and persistence length of a single polyelectrolyte chain, counterions condensation and end-chain effects and morphology of polyelectrolyte complex.

Finally, the editors would like to express their sincere gratitude to all the contributors of this book, who made excellent support to the successful completion of this venture. We are grateful to them for the commitment and the sincerity they have shown toward their contribution in the book. Without their enthusiasm and support, the compilation of a book could have not been possible. We would like to thank all the reviewers who have taken their valuable time to make critical comments on each chapter. We also thank the publisher Springer for recognizing the demand for such a book, and for realizing the increasing importance of the area of "Polyelectrolyte: Thermodynamics and Rheology" and for starting such a new project, in which not many other publishers put their hands on.

Visakh P.M.
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Contents

Editor's Short Biodata

Visakh P.M. M.Sc., M.Phil. submitted his Ph.D. thesis to Mahatma Gandhi University, Kottayam, Kerala, India. He edited 9 books from Scrivener (Wiley) and Springer and more than 12 books in press, (from Wiley, Springer, Royal Society of Chemistry and Elsevier). He has been invited as a visiting researcher in Portugal (2013, 2014), Czech Republic (2012, 2013) Italy (2009, 2012), Argentina (2010) Sweden (2010, 2011, 2012), Switzerland (2010), Spain (2011, 2012), Slovenia (2011), France (2011), Belgium (2012) and Austria (2012) for his research work. He visited 15 universities in Europe. He published 5 publications, 3 reviews, and more than 13 book chapters. He has attended and presented more than 28 conferences, he has 68 citations and his h-index is 4. His research interests include polymer nanocomposites, bio-nanocomposites, and rubber-based nanocomposites, fire retardant polymers and liquid crystalline polymers and silicon sensors. Contact: visagam143@gmail.com

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Thermodynamic and Rheological Properties of Polyelectrolyte Systems

Ruben H. Manzo, Alvaro F. Jimenez-Kairuz, María E. Olivera, Fabiana Alovero and María V. Ramirez-Rigo

Abstract The chapter provides a treatment of the interaction between acidic or basic polyelctrolytes (PE) and ionizable organic molecules (selected model drugs) in aqueous environments, in terms of acid-base reactions. The electrostatic attraction between the ionized pending groups of the PE and the organic ions yields a high proportion of counterionic condensation with affinity constants in the range of 103 to 105. The high proportion of counterionic condensation in PE-drug aqueous dispersions determines many of the particular properties of these systems such as the effects of addition of electrolytes and non-electrolytes, the kinetic of drug release under different conditions, the raise of compatibility of low solubility drugs, the increase of chemical stability and the rheological behavior. The aqueous systems of acidic PE are characterized by their building viscosity capacity. Flow curves of PE-drug systems reflex the behavior of model PE-Na systems. However, complexes of a set of model drugs under similar conditions exhibit a wide range of viscosities. The determination of the kinetic of water sorption of PE-drug complexes in solid state provides valuable complementary information related to their swelling capacity. Rheology of PE-drug aqueous dispersions as well as their swelling capacity are relevant properties in the fields of mucoadhesivity and drug release.

Abbreviations

AA	Alginic acid
AA-Na	Sodium alginate
AH	Acidic organic molecule
AH_{st}	Stoichiometric concentration of an acidic organic molecule

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A^-	Dissociated species of an acidic organic molecule (*)
AH	Neutral species of an acidic organic molecule (*)
B_{st}	Stoichiometric concentration of a basic organic molecule
B	Neutral species of a basic organic molecule
BH^+	Protonated species of a basic organic molecule (*)
C	Carbomer
C934	Carbomer 934 P
C–Na	Sodium carbomer
CMC-Na	Sodium carboxymethylcellulose
CMC-Na (LV)	Low viscosity sodium carboxymethylcellulose
CMC-Na (MV)	Medium viscosity sodium carboxymethylcellulose
CMC-Na (HV)	High viscosity sodium carboxymethylcellulose
c*	Critical concentration
DC	Diffusion coefficient
DC_f	Fast mode of the diffusion coefficient
DC_s	Slow mode of the diffusion coefficient
EE	Eudragit E 100
EL	Eudragit L-100
ES	Eudragit S-100
HA	Hyaluronic acid/hyaluronan
HA-Na	Sodium hyaluronate
$[HCl]_{st}$	Stoichiometric concentration of hydrochloric acid
K_{cc}	Affinity constant for counterionic condensation
PE	Polyelectrolyte
RAH	Acidic pending groups of a polyelectrolyte
RAH	Undissociated fraction of the acidic pending groups of a polyelectrolyte (*)
RA^-	Dissociated fraction of the acidic pending groups of a polyelectrolyte (*)
$[RA^-BH^+]$	Counterionic condensed fraction between the dissociated acidic pending groups of a polyelectrolyte and a protonated basic organic molecule (*)
RNR_1R_2	Basic pending groups of a polyelectrolyte
RNR_1R_2	Non-protonated fraction of the amino pending groups of a basic polyelectrolyte (*)
$RNR_1R_2H^+$	Protonated fraction of the amino pending groups of a basic polyelectrolyte (*)
$[RNR_1R_2H^+A^-]$	Counterionic condensed fraction between the protonated basic pending groups of a polyelectrolyte and a dissociated acidic organic molecule (*)
(*)	italics denotate the dissociated or protonated species of a polyelectrolyte or a drug

Symbols

ζ	Electrokinetic potential
$\dot{\gamma}$	Shear rate
γ	Strain
τ	Shear stress
τ_0	Yield stress fluid
η	Dynamic viscosity
Tg δ	Loss tangent

1 Introduction

This chapter deals mainly with the thermodynamic and rheological properties of aqueous colloidal dispersions of complexes of polyelectrolytes (PE) with ionizable organic molecules, in particular model drugs. In addition, it follows with a description of a survey of several applications based on the unique properties of these systems.

PE can be defined as polymers carrying either positively or negatively charged ionizable groups [1].

The interaction of water soluble PE with inorganic or organic counterions generally generates stable colloidal dispersions also regarded as solutions when they are optically isotropic systems. These PE dispersions also exhibit electrokinetic potentials (ζ) which are negative or positive for acidic or basic PE respectively [2].

In most of acidic PE the ionizable moiety is the carboxylic group. Such is the case of carbomers (C, also known as carbopol or carboxyvinyl polymers), alginic acid (AA), hyaluronic acid (HA, also known as hyaluronan). Other acidic PE such as dextran sulfate, cellulose sulfate and nucleic acids are based on sulfate, or phosphoric ionizable groups.

Among basic PE, the nitrogen atom is the protonable center. There are also PE having a quaternary ammonium as a permanent cationic group. Chitosan, Eudragit E100 (EE) and trimethyl chitosan are representative members of this group. Figure 1 shows the chemical structure of some currently used acidic and basic PE.

There are several properties of the PE that are clearly different from that of uncharged polymers. The electrostatic interactions between the charges of PE lead to a rich behavior of their solutions, qualitatively different from those of uncharged polymers [3–5]. Thus, electrically charged PE chains follows unentangled dynamics in a much wider concentration range than solutions of uncharged polymers do.

Reports dealing with light scattering of flexible linear PE with acidic pending groups neutralized with monovalent inorganic cations (mainly Na^+) showed that such systems exhibit two clearly differentiated diffusion modes, one with diffusion coefficient (DC) ranging from 10^{-7} to 10^{-5} cm^2/s, and the other ranging from

10^{-9} to 10^{-8} cm^2/s, which are regarded as "fast" (DC_f) and "slow" (DC_s) modes, respectively [6–8].

The DC_s has been associated with the presence of multichain domains (clusters) with dimensions appreciably exceeding the size of single chains. Both, the origin of these domains as well as the mechanism by which macromolecules of the same charge interact themselves are not satisfactorily understood. The DC_s has been found in a wide variety of synthetic and biological polymers. Therefore, it appears that it is a universal property of charged macromolecules dispersed in polar solvents [7].

Another interesting property of PE is the osmotic pressure. The osmotic pressure of PE in salt-free solutions exceeds by several orders of magnitude that of neutral polymers at similar polymer concentrations. Besides, it increases almost linearly with polymer concentration and is independent of the chain molecular weight in a wide range of polymer concentrations. This almost linear concentration dependence of the osmotic pressure, together with its strong dependence on added salt, demonstrates that osmotic pressure is mainly due to the counterions contribution [1].

It is well known that the properties of the colloidal microenvironments that arise from the interaction of PE with small counterions largely determine their rheological behavior. For example, the viscosity of PE solutions is proportional to the square root of polymer concentration (Fuoss' law) [9], while for solutions of uncharged polymers, at the same concentration, the viscosity is proportional to polymer concentration.

Among acidic PE, C, different degrees of sodium carboxymethylcellulose (CMC-Na), HA and AA (Fig. 1) are currently used to build aqueous viscosity [10]. With such purpose they are generally presented salified with alkaline metals as Na^+ or K^+, so that their carboxylic groups are essentially dissociated. As shown in Fig. 1, C is a family of linear polyacrylic acid cross-linked with allyl sugars whose viscosifying properties are clearly associated to the crosslink density. Although, CMC, AA and HA are linear PE, their monomer unities are composed of highly hydrophilic carbohydrate structures.

Although basic PE have been used for a variety of purposes, they do not exhibit valuable viscosifying properties as the acidic ones [10].

2 Interaction of Polyelectrolytes with Organic Molecules

The interaction of acidic or basic PE with model organic molecules, as those shown in the Fig. 2 currently yields stable dispersions; however in some cases the complementary addition of an inorganic counterion contributes to the required compatibility [11–14].

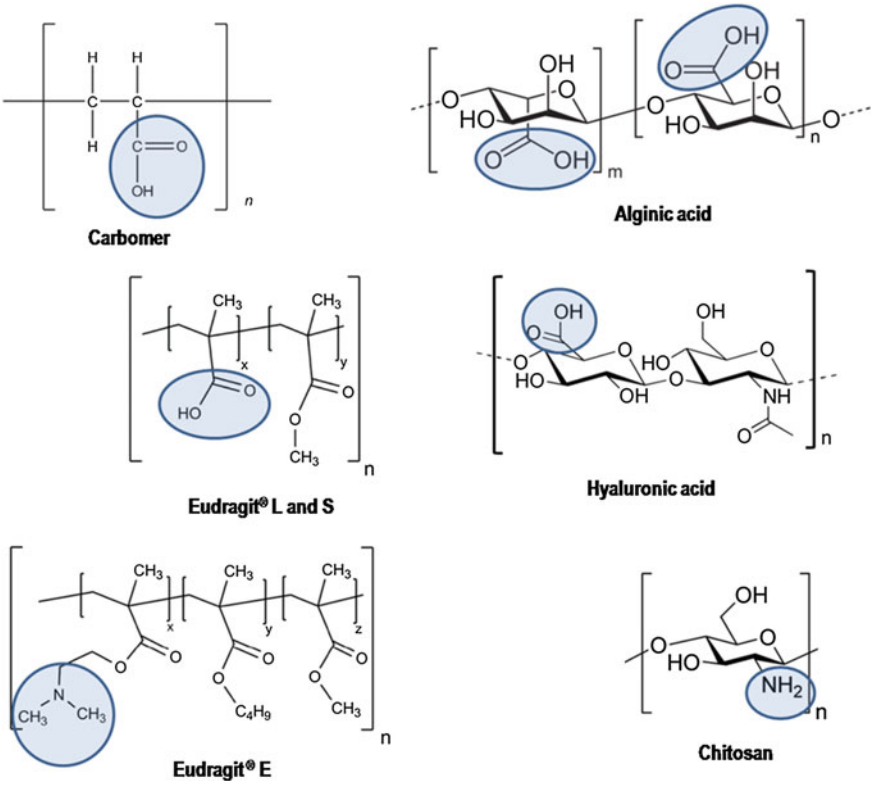

Fig. 1 Structural formula of some polyelectrolytes

2.1 Counterionic Condensation

The interaction of acidic or basic PE with model organic molecules having basic or acid groups respectively yields a high proportion of counterionic condensation [11–14].

Equation 1 depicts the reaction between acidic pending groups of a PE (RAH) with the basic groups of an organic molecule (B).

$$RAH + B \rightleftarrows RA^- + BH^+ \rightleftarrows [RA^-BH^+] \tag{1}$$

where B and BH^+ are the neutral and protonated species, RAH and RA^- represent the undissociated and dissociated fractions of the pending groups of the PE and $[RA^-BH^+]$ the counterionic condensed fraction.

In the same way, PE having protonable amino groups (RNR_1R_2) can react with the acidic groups of an organic molecule (AH) generating an analogue process of counterion condensation [12], in which AH and A^- are the neutral and anionic species, and RNR_1R_2, $RNR_1R_2H^+$ and $[RNR_1R_2H^+A^-]$ have the same meaning of Eq. 1.

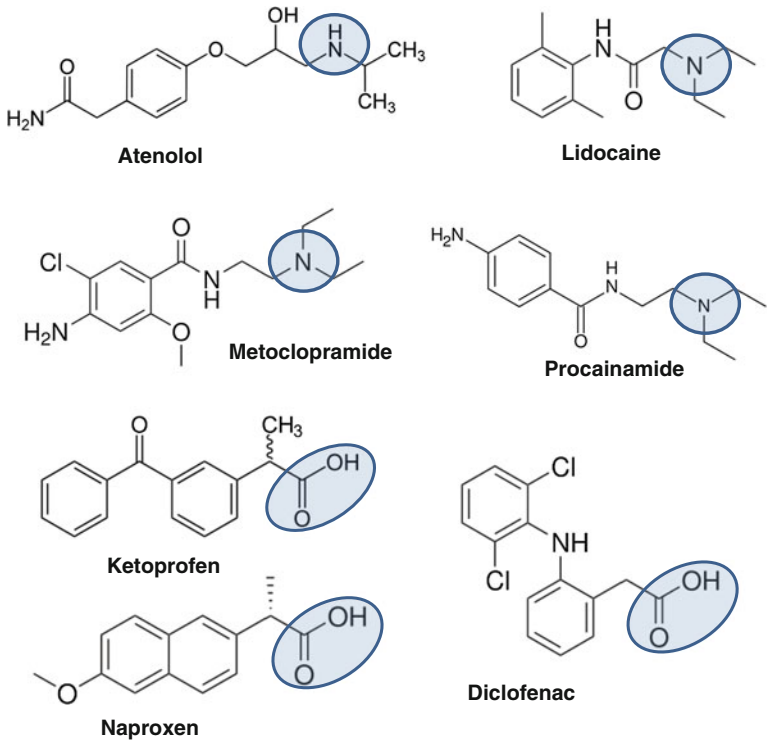

Fig. 2 Molecular structure of some of the model drugs used in several studies

$$RNR_1R_2 + AH \rightleftarrows RNR_1R_2H^+ + A^- \rightleftarrows [RNR_1R_2H^+A^-] \quad (2)$$

Equations 1 and 2 describe the main interaction between the ionized groups of the macromolecule and its opposite charged partners. However, owing to the structural complexity of such systems other kind of contributions such as hydrogen bonding and hydrophobic interactions, among others, would also play a role in the association process.

As happen with inorganic counterions, the acid-base interaction described by Eqs. 1 and 2 originates high ζ that contribute to the physical stability of the dispersions. Figure 3 shows the ζ of aqueous dispersions of acidic and basic PE loaded with ionizable model drugs. As expected, the dispersions obtained with acidic PE yield a negative ζ while those obtained with basic PE display a positive ζ.

The knowledge about the factors that determine the interaction between ionic or ionizable drugs and PE is relevant in several fields. At present, a detailed description about the factors governing such interaction is not fully available. The classical description of ion–ion interaction recognizes two relative stable regions: one referred to as a solvent separated ion pair, or as a loose ion pair and the other referred to as a contact ion pair, which is also known as a tight ion pair [20]. In the

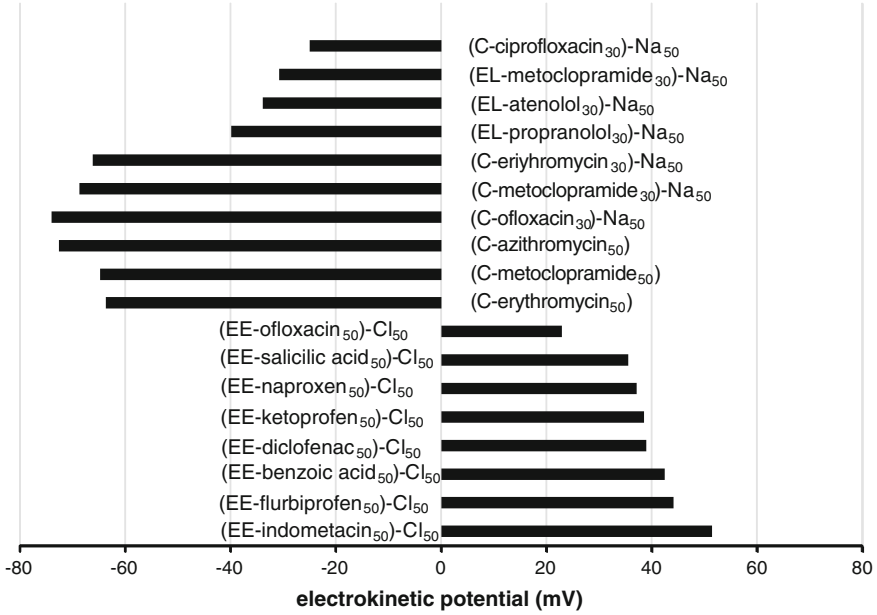

Fig. 3 Electrokinetic potentials (ζ) exhibited by aqueous dispersions of acidic and basic PE loaded with ionizable drugs. Carbomer data corresponds to C_{934}. The subscript numbers indicate the proportion of drug and inorganic counterion expressed in mol % which neutralizes the ionizable groups of each PE. (*Data adapted from references* [15–19])

same line, within the framework of the counterion condensation theory of PE, a common point in the theoretical treatments proposed is the recognition of two extreme modes of counterion association with the PE, currently referred to as loose and covalent bonding. The former is the delocalized confinement of the counterions within a condensation volume in the immediate vicinity of the PE, due only to long-range interactions, while the latter is a short range, site-specific interaction [21–23].

Theoretical treatments mainly address the interaction of acidic linear PE with inorganic cations. However, with organic counterions, although the main contribution to the overall interaction arises from the electrostatic attraction, non-electrostatic contributions would also play a role in the association process.

3 Species Distribution

Since drug speciation produces the free forms B and BH^+ or AH and A^- together with ion pairs with the ionizable groups of the PE, $[RA^-BH^+]$ or $[RNR_1R_2H^+AD^-]$, the stoichiometric concentration B_{st} or AH_{st} are distributed as:

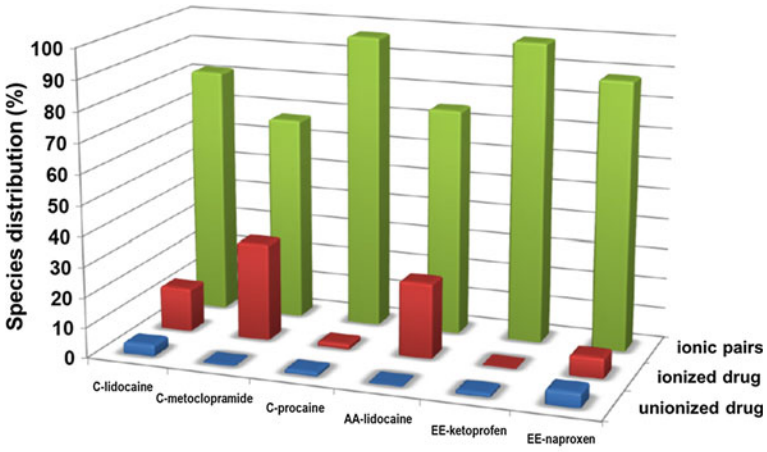

Fig. 4 Species distribution of model drugs from various hydrogels after partitioning in an organic solvent. C is Carbomer 934. (*Data adapted from references* [16] *and* [25])

$$B_{st} = (B) + (BH^+) + ([RA^-BH^+]) \tag{3}$$

$$AH_{st} = (AH) + (A^-) + ([RNR_1R_2H^+A^-]) \tag{4}$$

Species distribution in PE-drug dispersions has been determined through dialysis, selective solvent extraction of the neutral species od the drug, ultrafiltration and NMR spectroscopy. Typical results of species distribution of model organic molecules are shown in Fig. 4.

4 Affinity Constants for Counterionic Condensation

4.1 Acidic Polyelectrolytes

According with Eq. 1, the affinity constant for the counterionic condensation (K_{cc}) is expressed as:

$$K_{cc} = ([RA^-BH^+])/(RAH).(B) = ([RA^-BH^+])/(RA^-).(BH^+) \tag{5}$$

The following approach can be used to solve Eq. 5 in an aqueous dispersion:

$$(RA^-) + (HO^-) = (BH^+) + (H^+) \tag{6}$$

Then, under conditions in which $(RA^-) \gg (HO^-)$ and $(BH^+) \gg (H^+)$, Eq. 6 reduces to $(RA^-) = (BH^+)$.

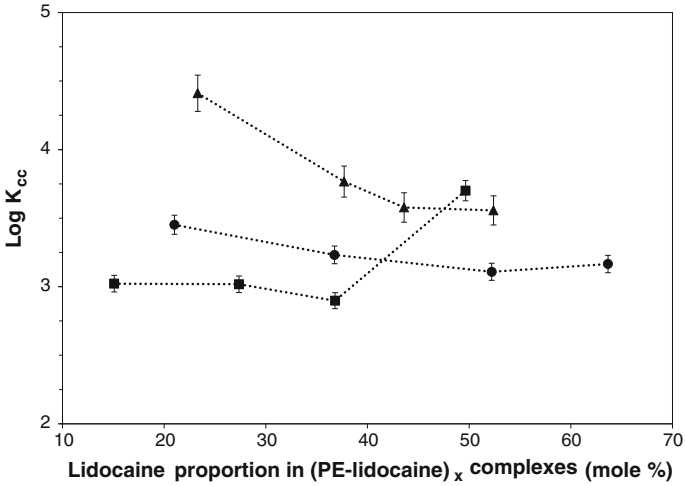

Fig. 5 Effect of the proportion of lidocaine loaded in some PE-drug complexes on the affinity constant K_{cc}. *Black triangle* Carbomer 934; *black circle* Eudragit L; *black rectangle* Eudragit S. (*Data adapted from references* [16] *and* [25])

The equilibrium properties of aqueous dispersions of complexes between model basic drugs lidocaine, atenolol and metoclopramide with three structurally related acidic PE was reported. Thus, K_{cc} of dispersions of polymetacrylates, EL, ES and C934 neutralized with increasing proportions of lidocaine and metoclopramide, were determined.

Figure 5 shows the K_{cc} of the three PE–drug systems loaded with increasing proportions of lidocaine.

It is worth emphasizing that, in these systems, the increase in the degree of neutralization of the acidic groups of the PE with model drugs produces an increase in their conductivity, viscosity and transparency [16, 24]. Also, the resulting dispersions exhibit high negative ζ. Such observations are consistent with the idea that a significant population of the condensed counterions keeps some degree of hydration and that charges are not fully neutralized. Therefore, the counterionic condensation generates the expansion of the PE chains, turning PE–drug complexes more hydrophilic than the PE alone.

With regard to PE–drug affinity, the branched PE C934 exhibited the highest K_{cc} at low lidocaine loading. This observation is consistent with its lower chain mobility, which correlates with its ability to build viscosity. However, the affinity decreases as the proportion of lidocaine was increased. This behavior would be primarily related to the close proximity between carboxylic groups, which would affect the ionic interaction through steric hindrance.

In spite, the linear PE EL exhibited a lower K_{cc} than C, which remains almost constant along a wide range of lidocaine loading. In addition, ES having the most

hydrophobic backbone exhibits the lowest K_{cc} at low lidocaine loading. However, at higher degrees of neutralization, K_{cc} is significantly raised. The long distance between ionizable groups, together with the expanding effect of the progressive ionization, seems to produce a positive effect to raise the ES–lidocaine affinity. Then, the distance between the acidic pending groups of the PE seems to play a significant role in K_{cc}. Thus, as lidocaine loading increases, C lowers K_{cc}, while ES raises it, and that of EL remains unchanged.

On the other hand, metoclopramide having an amino group of higher basic strength than lidocaine yields $(EL–metoclopramide)_{50}$ and $(ES–metoclopramide)_{50}$ with higher log K_{cc}, as it was also observed with$(C–metoclopramide)_{50}$ [25].

4.2 Basic PE

Several basic PE has been used for a variety of purposes. In all of them, basic nitrogen is the interacting atom susceptible of protonation in aqueous medium. Among them, chitosan and EE a polymethacrylate with diethylamino pending groups has been extensively studied.

The interaction of the linear polymetacrylate EE with organic acids yields stable aqueous dispersions when an inorganic anion (example Cl^-) is incorporated in the system.

The affinity constant K_{cc} for the complex $(EE\text{-}diclofenac_{50}Cl_{50})$ at 0.5 % of EE was determined for a model non-steroidal anti-inflammatory drug.

The constant was determined according with Eq. 2.

$$\begin{aligned} K_{cc} &= ([RNR_1R_2H^+A^-])/(RNR_1R_2)(AH) \\ &= ([RNR_1R_2H^+A^-])/(RNR_1R_2H^+)(A^-) \end{aligned} \tag{7}$$

To solve Eq. 7 the approach that equilibrium 8 was essentially shifted to the right was considered.

$$RNR_1R_2 + Cl^- + H^+ \rightleftarrows RNR_1R_2H^+ + RNR_1R_2 + Cl^- + H^+ \tag{8}$$

Therefore $[HCl]_{st} = (Cl^-)$ and the charge balance is

$$(RNR_1R_2H^+) + (H^+) = (HO^-) + (A^-) + (Cl^-) \tag{9}$$

Equation 9 under the experimental conditions used is reduced to $(RNR_1R_2H^+) = (A^-) + (Cl^-)$ or $(RNR_1R_2H^+) = (Cl^-)$ that let to solve Eq. 7.

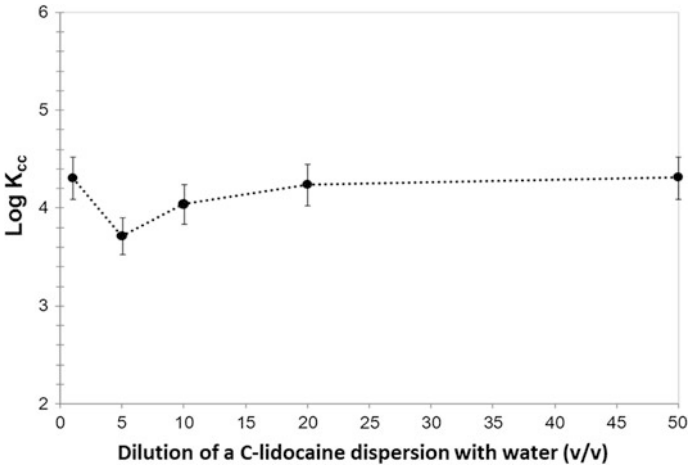

Fig. 6 Effect of the dilution of a dispersion C-lidocaine on the affinity constant K_{cc}. (*Data adapted from reference* [16])

4.3 Effects of Dilution

With regard to the effect of the PE-drug concentration on K_{cc}, available results indicate that the mass law exerts the control. In fact, Fig. 6 shows that in accordance with Eq. 1 log K_{cc} of the dispersion of $(C–lidocaine)_{75}$ [16] remained essentially constant over 50 times dilution (from 0.5 to 0.01 % C). A similar behavior was observed on a log K_{cc} of $(EL–lidocaine)_{50}$ which also remained constant over 10 times dilution [25].

5 Release of Drugs from Polyelectrolyte-Drug Dispersions

The reversibility of the PE-drug interactions described in the previous sections determines the rate and extent of the release of the loaded drugs from the complexes in aqueous dispersions [11–14, 26, 27]. In fact, experiments performed in bicompartimental cells limited by a semipermeable membrane that prevents the diffusion of the complex demonstrate that:

1. The release of drug towards water as receptor medium is mainly produced by the diffusion of the neutral species *B* or *AH* able to freely diffuse since the fraction of free charged species (A^- or BH^+) are compromised with the electrical gradient of the PE. Thus, the diffusion of the neutral species promotes the dissociation of ionic pairs according with the equilibria described in Eqs. 1 and 2 producing a feedback mechanism. In other words, the fraction of ionic pairs is a reservoir of drug and has been shown that the release rate is proportional to such fraction.

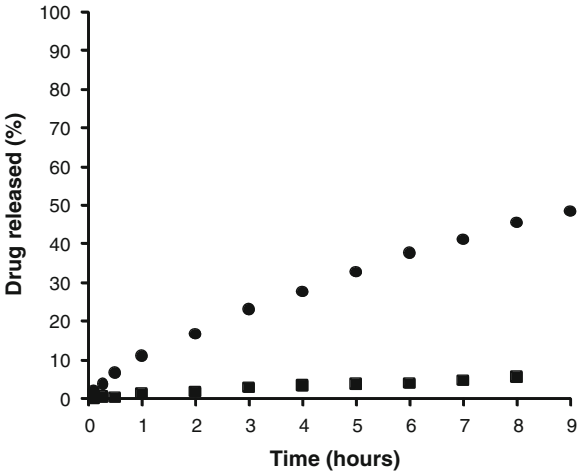

Fig. 7 Release profile of atenolol from the hydrogel C_{934}–atenolol in a Franz cell against water (*black square*) or NaCl solution (*black circle*) as receptor media. (*Data adapted from reference* [16])

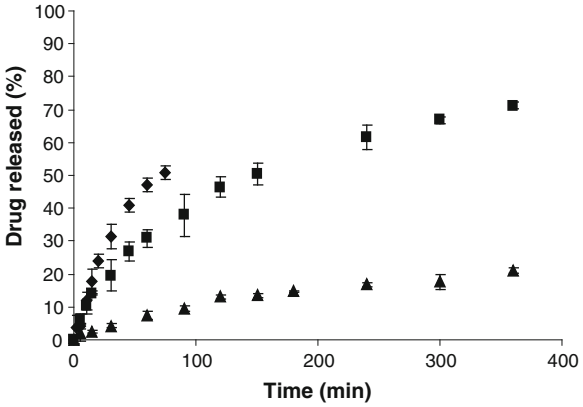

Fig. 8 Release profile of benzoic acid from drug solution (*black diamond*) and drug-containing EE aqueous dispersions against water (*black triangle*) or NaCl solution (*black square*) as receptor media. (*Data adapted from reference* [18])

2. As a saline solution (0.9 % NaCl) is placed as receptor medium in order to simulate a biological fluid, the diffusion of Na^+ and Cl^- into the donor compartment promotes an ionic exchange with the complex that raises the concentration of free species able to diffuse. As a consequence the release rate is increased as is shown in Figs. 7 and 8.

6 Rheological Properties of Polyelectrolyte Dispersions

6.1 Basic Concepts on Reology of PE

Rheology has been properly defined as the study of the flow and deformation of materials, with special emphasis being usually placed on the former [28]. There exist many fluids whose flow cannot be described by the linear response of the Newtonian flow equations. These materials are called as complex fluids, or non-Newtonian materials, since they display behaviors that range from that of viscous liquids to that of an elastic solid to some combination of the two. PE in aqueous dispersions exhibit behaviors of complex fluids [29].

Basically and considering the case of a slab of material sheared between two parallel plates (Fig. 9), there are two kinds of flows with relative movement of adjacent particles of liquid; they are called *shear* and *extensional* flows. The simple shear flow is the continual movement of particles of liquid *over* or *past* each other, by applying an external force to the top plate, while extensional (or *elongational*, or *stretching*) flows are where particles of liquid flow *towards* or *away from* each other. Then, from this deformation of material is possible calculate the resulting strain (γ). The *gradient* of the velocity in the direction at the right angles to the flow is called the *strain rate or shear rate* ($\dot{\gamma}$), and the force per unit area produced by the flow is called the *shear stress* (τ).

For a simple fluid, the dynamic viscosity (η) is simply the proportionality constant between stress and strain rates [28]:

$$\tau = \eta\dot{\gamma} \tag{10}$$

To thoroughly study the rheological behaviors observed in complex liquids it is necessary to perform a viscoelastic test by modifying the applied force both, by changing its magnitude and by adding a driving frequency. Dynamic oscillatory shear tests are performed by subjecting a material to a sinusoidal deformation and measuring the resulting mechanical response as a function of time.

Two principal models are used to describe much of the observed behavior seen in PE and other complex fluids; the Herschel-Bulkley and Maxwell models. The first is an empirical model that describes the flow of a yield stress fluid (τ_0) in response to varying shear rates, according to following equation [30]:

$$\tau = \tau_0 + k\dot{\gamma}^n \tag{11}$$

This model accounts for a yield stress combined with power law behavior in stress as a function of shear rate. Besides, this model predicts a viscosity that diverges continuously at low shear rates and is infinite below the yield stress. When $n = 1$, the Herschel-Bulkley model reduces to the Bingham fluid model where the flow above the yield stress would be purely Newtonian and the constant k would represent the viscosity [28].

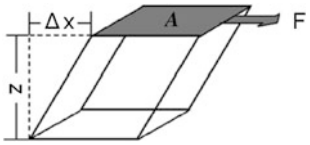

Fig. 9 Illustration of shear (a force "F" applied to a slab of height "z", over an area "A", results in a stress "$\sigma = F/A$", and get a deformation along the x-axis of "Δx", which results in a strain "$\gamma = \Delta x/z$")

On the other hand, the Maxwell fluid model explains the response of complex fluids to an oscillatory shear rate. The frequency-dependent behavior of this model, displayed into linear responses to applied shear rates has been found to be applicable to a variety of complex fluid systems. Although the linear viscoelasticity is useful for understanding the relationship between the microstructure and the rheological properties of complex fluids, it is important to bear in mind that the linear viscoelasticity theory is only valid when the total deformation is quite small. Therefore, its ability to distinguish complex fluids with similar micro- and nanostructure or molecular structures (e.g. linear or branched polymer topology) is limited. However, complex fluids with similar linear viscoelastic properties may show different non-linear viscoelastic properties [31].

7 Flow Properties of Representative Sodium Salts of Acid Polyelectrolytes

7.1 Carbomer

As early mentioned, C is a family of PE of very high molecular weight composed of linear poly(acrylic acid) cross-linked with allyl sugars. Both, the degree of crosslinking and the agent used for this purpose generate the different types and applications of C shown in Table 1.

In solid state, the molecules of C are basically folded. In contact with water C chains become rapidly hydrated and spread out generating an increase in viscosity. Due to the crosslinks they do not produce true hydrogels. However, neutralization with inorganic bases generates the dissociation of C carboxylic pending groups along the chains leading to their full deployment as a result of electrostatic repulsion between the generated charges [32].

The rheology of hydrogels of C was extensively studied since, after its synthesis in the 60th, its use became popular in pharmaceutical and cosmetic technology and also in other industries because of their excellent properties as a viscosifying agent and stabilizer in suspension and emulsions, even at concentrations below 0.5 % [32, 33]. At 0.25 % w/w aqueous concentration of C yield the viscosity described in Table 2.

Table 1 Pharmaceutical and cosmetic applications of different carbomers

Applications	Type of carbomer NF
Topical use (external use only)	907, 910, 934, 940, 941, 980, 1342, 5984EP, ETD2020, Ultrez 10
Oral and mucosal use (internal use)	934P, 971P, 974P, 71G

Table 2 Dynamic viscosity of different polyelectrolyte sodium salts in aqueous dispersions

PE-Na	PE dispersion (%)	Shear rate (r.p.m)	η (cps.)
C934-Na[a]	0.25	40	1,261
CMC-Na (LV)[d]	1.0	60	10–15
CMC-Na (MV)[d]	1.0	30	1,500–2,500
CMC-Na (HV)[d]	1.0	30	8,000–12,000
AA-Na[b]	1.0	55	46
HA-Na[c]	1.0	100	407

[a–d] Data extracted from references [10, 16, 41, 42] respectively

In cross-linked polymers as C, the crosslink keeps the strands of the polymer chains from displacing very far from the initial position during a disturbance and prevent the flow of the polymer strands relative to each other. Then, the macromolecule is able to recover its original structure. This behavior is described by the parameter known as elastic modulus and is proportional to the crosslink density [34].

Hydrogels of C are low concentrated dispersions neutralized by alkaline hydroxides and display a near Newtonian behavior. The appearance of the yield stress is observed at the critical concentration (c*), which marks the limit between the dilute and semi-dilute regime. The onset of this behavior occurs at around 0.5 % w/v depending on the type of C. These hydrogels show little to non-thixotropic behavior [1, 34].

7.2 Sodium Carboxymethylcellulose

This PE is described in the USP as the sodium salt of polycarboxymethyl ether of cellulose. Its typical molecular weight is 90.000–700.000. The rheological properties of CMC depend on the polymer concentration and on the degree of substitution (conversion of –OH into $–O–CH_2–COO^-$) which varies from 0.5 to 1.2 [35, 36]. Thus, various grades of CMC with different aqueous viscosities are available, currently regarded as low-, medium-, and high-viscosity (CMC-Na (LV), CMC-Na (MV) and CMC-Na (HV), respectively). At 1 % w/v aqueous concentration they yield the viscosities described in Table 2 [10].

The c* of CMC has been established at around 1 % w/v. Below the c* value CMC dispersions exhibit pseudoplastic flow without yield stress. However, at high concentrations, CMC dispersions exhibit thixotropic and viscoelastic behavior.

7.3 Alginic and Hyaluronic Acids

These PE are biopolymers. The first can be obtained from vegetal and the second from animal and microorganism sources [10].

AA swells but does not dissolves in water. However it is soluble in alkali hydroxides producing viscous dispersions. Various grades of sodium alginate (AA-Na) are available, yielding aqueous dispersions of varying viscosity within a range of 20–400 mPas in 1 % solution at 20 °C [10].

The precise composition of alginates varies markedly with the season and seaweed species, with the result that the rheological properties vary enormously from different suppliers, and even from different batches from the same supplier [37, 38].

The basic rheological properties of low concentration AA-Na dispersions have been extensively studied. They exhibit non-Newtonian pseudoplastic behavior (shear thinning) at concentrations between 0.125 and 1.5 % w/v, while at lower concentrations they behave as low viscosity Newtonian fluids [37].

In the presence of an electrolyte, e.g., increasing the concentration of NaCl up to 100 mM, a reduction in the viscosity of AA-Na dispersion was observed [10].

HA is currently presented as sodium hyaluronate (HA-Na). A number of rheological studies of HA-Na dispersions have been presented in the literature. These studies are difficult to compare when different sources of HA-Na are used. The rheology of HA-Na is extremely sensitive to protein contamination [39, 40]. Comparable results are obtained using protein free samples obtained from bacterial sources. Some of these studies were conducted in saline aqueous medium to reproduce physiological conditions in which dilute and semidilute HA-Na dispersions exhibit Newtonian behavior in a wide shear rate range. However, aqueous dispersions of 1 % w/v HA-Na exhibit shear thinning behavior without yield stress (Fig. 10). The viscosity of AA and HA dispersions is presented in Table 2.

8 Flow Properties of Acid PE-Drug Dispersions

Equilibrium and release properties of aqueous systems PE-drug dispersions can be reasonably predicted from the physicochemical properties of both partners. However such systems exhibit a wide variability in their rheological properties. Thus, Table 3 shows that C934 at 0.25 % w/v neutralized at 50 % with a set of representative basic D exhibits a wide range of apparent viscosities that in all cases are lower than that of C–Na. Table 3 also shows that the linear AA requires higher

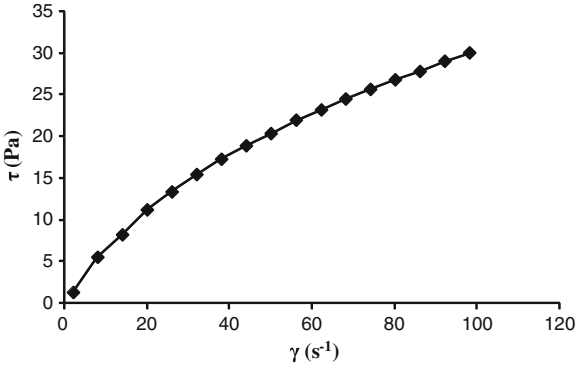

Fig. 10 Flow curve of HA-Na 1.0 % w/v aqueous dispersion. (*Data adapted from reference* [41])

Table 3 Apparent viscosity at 25 °C of a set of PE-drug aqueous dispersions in which the PE was 50 % neutralized by drugs. (*Data obtained from references* [16] *and* [42])

PE-drug	Viscosity (mPa.s)	% PE	Shear rate (s^{-1})
C-atenolol	666.9	0.25	100
C-procainamide	435.0	0.25	100
C-pilocarpine	438.7	0.25	100
C-lidocaine	199.6	0.20	100
C-metoclopramide	31.58	0.25	100
C-naphazoline	17.03	0.25	100
C-erythromycin	14.29	0.25	100
C-azithromycin	11.99	0.25	100
AA-lidocaine	229.0	5.00	50
AA-atenolol	80.00	5.00	50

concentrations to build viscosities of the same range. On the other hand, the acidic form of CMC, obtained from CMC yields CMC-drug complexes that are not dispersible in aqueous medium.

8.1 Carbomer as a Model of Cross-Linked Polyelectrolyte to Produce Polyelectrolyte-Drug Hydrogels

C934 is a hydrophilic mucoadhesive polymer suitable for internal use that was introduced in 1960. This acidic PE swells in contact with water. Upon neutralization with strong bases as NaOH or KOH, it forms hydrogels of high viscosity at very low concentrations (from 0.1 %) and in a wide pH range between 4.5 and 8. Rheological studies were conducted on C hydrogels partially or fully neutralized with inorganic bases or with simple organic molecules containing amino groups, for example triethanolamine [32].

8.2 Properties of Carbomer-Drug Hydrogels

In general C-drug dispersions are prepared starting from an aqueous dispersion of C, at concentrations of 0.1, 0.2, 0.25 or 0.5 % w/v that is neutralized with an appropriate proportion of the organic molecule. Compositions are identified as C-$drug_x$, where the subscript x is the proportion of drug expressed in mol % which neutralizes the carboxylic groups of C [11–13].

Dispersions of C in water have a pH between 3.0 and 3.4. Neutralization with basic molecules increases pH which generally ranges between 5.00 and 8.40 for the range between 25 and 100 % of neutralization of their carboxylic groups.

Neutralization of C934 with different basic drugs originates different kinds of dispersions. Some of them are presented as translucent hydrogels, for example those neutralized with lidocaine, atenolol, procaine, procainamide or pilocarpine. Others are presented as relatively opaque hydrogels as that obtained with metoclopramide. In other instances the neutralization products are low viscosity opaque dispersions that after a time generate a sediment easily redispersible by agitation. C-erythromycin and C-naphazoline are examples of that behavior. The physical stability of these products, as well as their viscosity and the transparency can be increased by adding Na^+ to the C-drug dispersion, obtaining systems C-$drug_xNa_y$. This strategy is useful in cases where the dispersion does not have the viscosity and/or physical stability required [13, 16].

Figure 11 shows the flow curves of dispersions of C neutralized at 50 % with a set of representative drugs, which are transparent - translucent hydrogels. They exhibit a behavior similar to that produced by (C–Na) since yield stress and shear thinning without thixotropy are also observed in all these systems.

Besides, the series of C-$lidocaine_x$ hydrogels prepared at 0.2 % C, with increasing proportions of lidocaine (25, 50, 75 and 100 mol %) exhibits a similar pattern along the full range of compositions (Fig. 12).

Figure 13 shows that the dynamic viscosity of the C-$drug_x$ hydrogels increases with the proportion of drug incorporated in the dispersion, between 0 and 75 %. However, at higher loading proportions it remains constant or even decreases, which is consistent with the behavior reported in literature for C–Na [32].

As early mentioned, the viscosity of PE dispersions is highly dependent on the concentration as it is shown in Fig. 14 for the system C-lidocaine. It was also observed that the elastic modulus of C varies from almost purely newtonian properties in diluted dispersion to the pseudoplastic behavior. At concentrations above 0.25 % C dispersion show a yield stress value with a plastic behavior which can be described by the Bingham fluid model [43, 44].

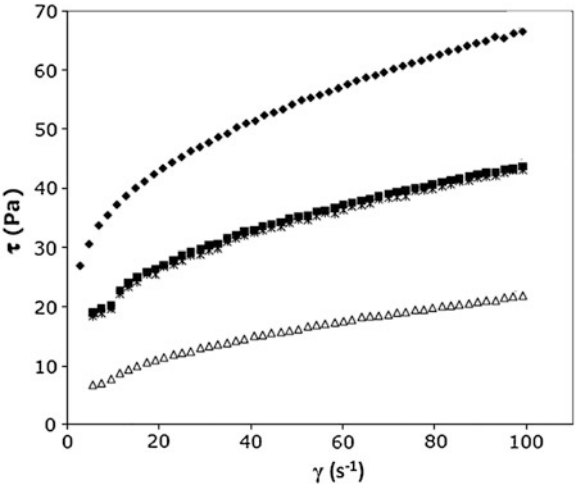

Fig. 11 Flow curves of 0.25 % Carbomer 934 P hydrogels loaded with different drugs. (*Black diamond*) atenolol; (*black square*) pilocarpine; (*asterisk*) procainamide; (*white triangle*) lidocaine. (*Data adapted from reference* [16])

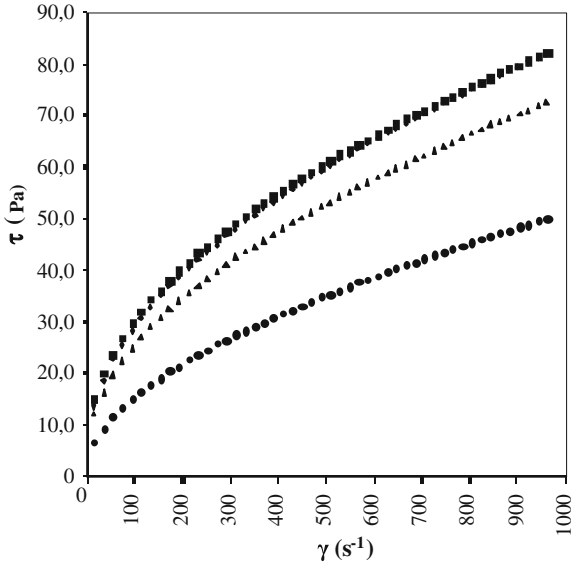

Fig. 12 Flow curves of 0.2 % carbomer hydrogels loaded with increasing proportions of lidocaine prepared in situ. (*Black diamond*) C-lidocaine$_{100}$; (*black square*) C-lidocaine$_{75}$; (*black triangle*); C-lidocaine$_{50}$; (*black circle*) C-lidocaine$_{25}$. (*Data adapted from reference* [16])

8.3 *Effect of the Addition of Other Species on Carbomer-Drug Dispersions*

The introduction of inorganic ions in aqueous dispersions of macromolecules generates a set of complex interactions such as changes in conformation, in the ζ and the hydration of their hydrophilic groups among others that affect their rheological behavior. In particular, the addition of salts to PE dispersions produces a

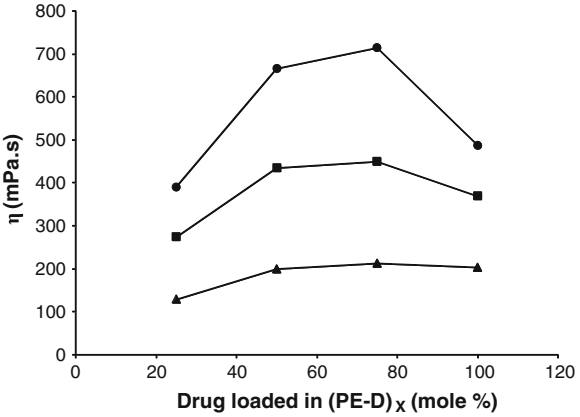

Fig. 13 Effect of drug proportion loaded in 0.25 % C dispersions on dynamic viscosity. (*Black circle*) atenolol; (*black square*) lidocaine; (*black triangle*) procainamide. Measurements were recorded at 25 °C and 100 s^{-1}. (*Data adapted from reference* [16])

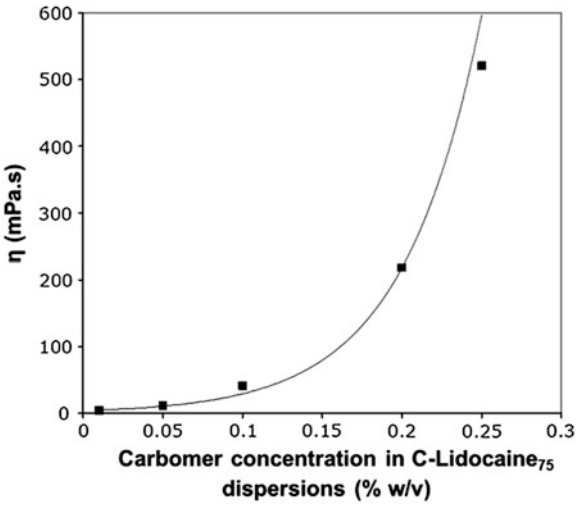

Fig. 14 Effect of concentration on viscosity of C-lidocaine$_{75}$ hydrogels prepared in situ. (*Data adapted from reference* [16])

significant lowering of viscosity that has been related to the reduction of the degree of swelling of the macromolecules [34].

In aqueous dispersions of cross-linked PE-drug the osmotic pressure generated by the accumulations of ions inside the microenvironment of the complex is one of the main factors that determine the high level of swelling. Therefore, the addition of inorganic ions decreases the osmotic difference between the macromolecular environment and the bulk medium with the consequent lowering of swelling that affect the rheology of the system [34].

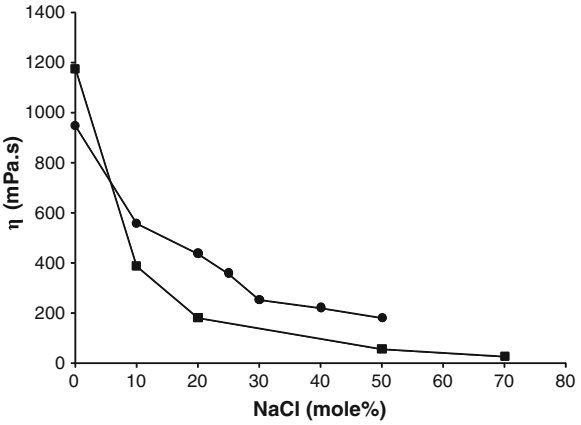

Fig. 15 Effect of addition of NaCl on the dynamic viscosity of 0.25 % C hydrogels loaded with lidocaine (*black square*) or atenolol (*black circle*). Measurements recorded at 25 °C and 100 s^{-1}. (*Data adapted from reference* [16])

Besides, the addition of inorganic salts (i.e. NaCl) to the PE-drug system also produces a displacement of organic ionic species from de PE environment as a consequence of the ionic exchange depicted in Eqs. 12 and 13:

$$[RA^{-}BH^{+}] + \mathrm{NaCl} \rightleftarrows RA^{-} + \mathrm{Na}^{+} + BH^{+} + \mathrm{Cl}^{-} \tag{12}$$

$$BH^{+} \rightleftarrows B + \mathrm{H}^{+} \tag{13}$$

The increase of the concentration of NaCl produces a decrease in the proportion of $[\mathrm{RA}^{-}BH^{+}]$ with the consequent increase of BH^{+} and Cl^{-} in the bulk phase. The incorporation of small ions (having higher mobility than the organic ones) in the PE environment would contribute to keep the level of hydration. However, a dramatic drop of viscosity is produced as depicted in Fig. 15. It should be noted that polymetacrylates, having a hydrophobic backbone without other hydrophylic moieties than carboxylic groups are particularly susceptive to the saline effect.

8.4 Properties of Alginic-Drug Dispersions

The rheological behavior of AA-drug dispersions is similar to that observed with AA-Na. In fact this linear PE requires higher concentrations than C to build comparable viscosities. Figure 16 shows the flow curve of a dispersion of AA-lidocaine$_{25}$ at a concentration of 5 % w/v which exhibits a modest shear thinning [42]. Since the concentration is clearly above c* the effect of the temperature on lowering the viscosity is important with an activation energy (Ea 1,770 kJ/mole) typical of entangled systems. A similar behavior was observed with other model drugs such as atenolol [42].

The viscosity of AA-lidocaine remains constant by increasing the proportion of lidocaine until 50 % but higher loading produces a dramatic drop of this property.

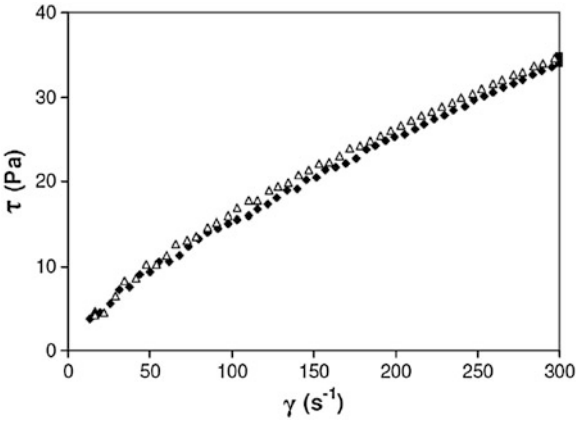

Fig. 16 Flow curve of AA-lidocaine$_{25}$ dispersion at 5.0 % w/v at 25 °C. (*Data adapted from reference* [42])

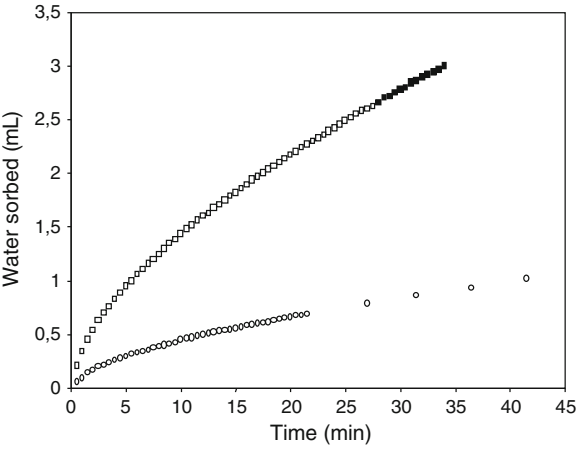

Fig. 17 Rate of water sorption (mL) by 0.100 g of C-lidocaine$_{75}$ (*white square*) and C 934P (*white circle*) as particulate solids. (*Data adapted from reference* [16])

8.5 Polyelectrolyte-Drug Complexes in Solid State

The PE-drug complexes are also obtained in solid state. They are presented as stable amorphous solids that in contact with water easily revert to the original dispersion [24, 45, 46]. Figure 17 shows that a C-lidocaine complex as particulate solid in contact with water swells quickly reversing the hydrogel state.

The same phenomenon is observed in complexes that have been compacted under the shape of circular matrices. In fact, it can be seen in Fig. 18 that water sorption rate is proportional to the viscosities reported in Table 3. Thus, the high swelling capacity exhibited by the complexes of atenolol and lidocaine in salt free medium makes them highly susceptible to the saline effect. Thus, the sorption rate decreases when a NaCl solution is used instead of water. On the other hand, the complex with metoclopramide has a very low rate of water sorption reveal a limited swelling capacity whose rate is barely affected in NaCl solution.

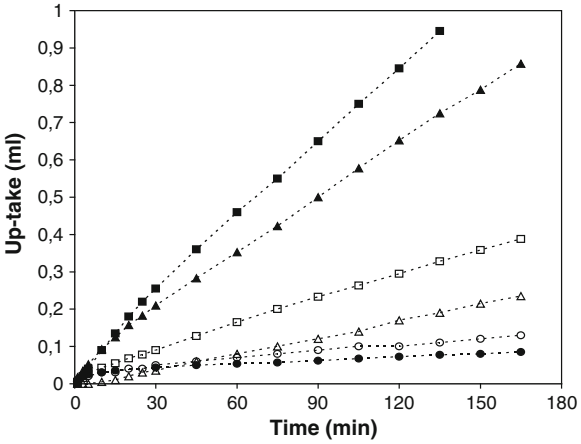

Fig. 18 Water sorption exhibited by discs 12 mm in diameter obtained by compaction of 200 mg PE-drug complexes in a hydraulic press. (*Black square*) C-atenolol$_{50}$; (*black square*) C-lidocaine$_{50}$; (*black circle*) C-metoclopramide$_{50}$. Filled and empty symbols are water and 0.9 % NaCl, respectively. (*Data adapted from reference* [16])

9 Remarks on Thermodynamic and Rheological Properties of Polyelectrolytes

The treatment of the interaction in aqueous environments between acidic or basic PE and ionizable organic molecules (selected model drugs) in terms of acid-base reactions provides solid basis to understand many of the properties of such systems.

The acid-base reaction renders organic ions that have lower ionic mobility than the small inorganic ions currently used as PE partners. Thus, the electrostatic attraction between the ionized pending groups of the PE and the organic ions yields a high proportion of counterionic condensation with K_{cc} in the range of 10^3–10^5. Available results have shown that the K_{cc} are not affected by the dilution of the dispersions.

The high proportion of counterionic condensation in PE-drug aqueous dispersions determines many of the particular properties of these systems such as the effects of addition of electrolytes and non-electrolytes, the kinetic of drug release under different conditions, the raise of compatibility of low solubility drugs, the improvement of chemical stability and the rheological behavior.

The available rheological studies performed with acidic PE characterized by their building viscosity capacity provide information on the basic rheological behavior of PE-drug systems. In a general way, the flow curves of acidic PE-drug systems reflex the behavior of model PE-Na systems. However, complexes of a set of model drugs under similar conditions exhibit a wide range of viscosities. At present, systematic studies that relate relevant structural properties of ionizable

organic molecules with the rheological behavior of their model PE complexes are not available.

The determination of the kinetic of water sorption of PE-drug complexes in solid state provides valuable complementary information related to their swelling capacity. At present, there are few reports addressing viscoelastic properties of these systems that would complement the present results. Then, it is an interesting field yet to be explored.

10 Field of Projections Based on the Properties of PE-Drug Complexes

The dynamic of sorption and swelling is an important property in the field of modified-release of drugs, in particular in the development of so-called hydrophilic matrices.

In fact, in experiments in which the matrices of the complexes are placed between 2 glass plates the dynamic of radial wetting may be registered (Fig. 19).

Penetration of water generates a dry core surrounded by a layer of gelled complex that modulates the rate of water penetration. The Figs. 20 and 21 show the development of the wetting and erosion fronts. Besides, inside the gel layer a diffusion front is also recognized in which the displacement of equilibria described in Eqs. 1 and 2 became evident by pH changes, detected by a pH-indicator.

The hydrogel layer generated by swelling modulates release of D as has been described in previous sections.

Complexes of C because of its branched structure generate a hydrogel layer resistant to erosion and the release mechanism of the drug is predominantly by diffusion of free species toward the bulk medium. However, complexes of the linear PE AA produce a gel layer of lower resistance to erosion and the main mechanism of the drug release is the diffusion to the bulk medium of AA-drug complex macromolecules.

Last, as expected, matrices of CMC-drug complexes in contact with water do not produce a gel layer [47].

Another application related to PE rheology is in the field of mucoadhesion. There is profuse scientific literature about the topic. An interesting and complete review was published by Caramella et al. [48] in the early nineties.

The task of dealing with the rheological aspects of mucoadhesión is rather intriguing, as is always the case when rheology is involved in explaining the behavior of a system. In this regard, mucoadhesive hydrogels represent no exception.

Most of muchoadhesive polymers are either a water-soluble cross-linked polymer with limited swelling capacity or a hydrophilic polymer that swells indefinitely and eventually undergoes complete dissolution.

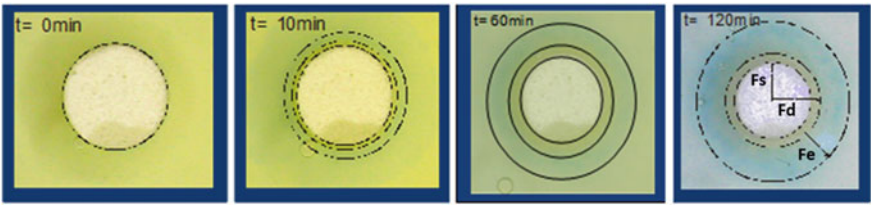

Fig. 19 Evolution in time of swelling fronts exhibited by matrices carbomer-atenolol$_{100}$ in aqueous media. *Fs* swelling front; *Fd* diffusion front; *Fe* erosion front

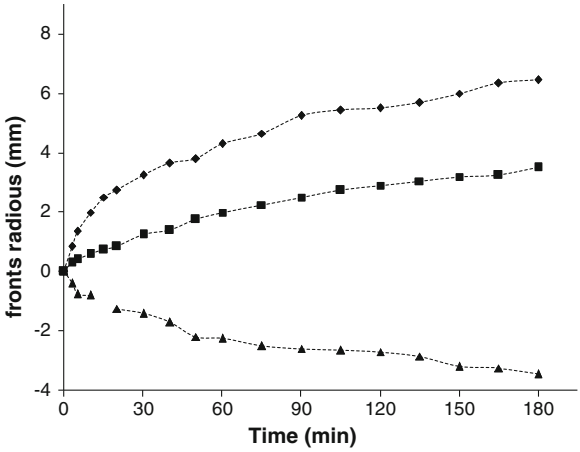

Fig. 20 Front movements of the C-atenolol$_{75}$ matrix in water: (*black diamond*) erosion front, (*black square*) diffusion front, (*black triangle*) swelling front. (*Data adapted from reference* [16])

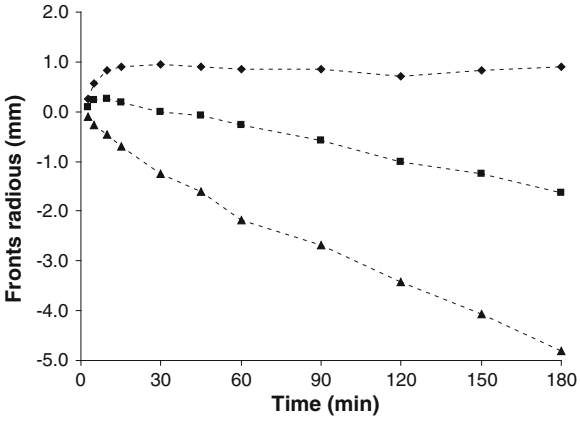

Fig. 21 Front movements of the AA-atenolol$_{50}$ matrix in water: (*black diamond*) erosion front, (*black square*) diffusion front, (*black triangle*) swelling front. (*Data adapted from reference* [42])

Mucoadhesion invariably involves the presence of a hydrated gel phase. The hydrogel may be applied as such to the mucosal surface or the hydrated gel phase can be formed in situ upon hydration of a solid mucoadhesive system in contact

with the mucus layer. As in the case of molecular weight, it can occur that mucoadhesivness increases with increasing viscosity up to a maximum value corresponding to optimal adhesion.

It has been reported that the viscoelastic nature of C gels is a good predictor of their adhesive properties. They also observed a substantial decrease in the rheological storage moduli for all samples, while no changes were observed in mucoadhession and proposed that a redistribution of cations between the polymer cluster and the bulk of medium is a possible additional mechanism of ageing of C hydrogels [49].

From a methodology point of view, the reological approach involves the investigation of the changes in rheological properties that mucoadhesive PE and hydrogels undergo when they are mixed with mucins.

There is plenty of experimental evidence to support that rheologic changes are observed when bioadhesive polymers and mucin are mixed. In this context it was shown that when a mucoadhesive polymer and mucin are mixed together there is a synergistic increase in viscosity. It is known that the viscosity of a mucin dispersion is the net result of the resistance to flow exerted by individual chain segments, physical chains entanglements and non-covalent molecular interactions, which are the same as the interactions involved in the process of mucoadhesion. Then, it has been proposed that the interaction forces involved in a mucin bioadhesive system could be evaluated by viscosity measurements since both, physical and chemical bonds in mucin-polymer mixtures cause changes in the shape or arrangements of macromolecules that are the bases for viscosity changes. It has been observed that there are variations in the elastic and viscous behavior. The balance between them is represented by tg δ (loss tangent). Thus, tg δ has been proposed as a suitable parameter to compare the viscoelastic behavior of polymers with different elastic and viscous profile. The more pronounced the elastic behavior with respect to the viscous one, the lower the loss tangent.

The measurement of the dynamic properties is useful for the differentiation of bioadhesive PE based on their interaction with mucin. The loss tangent parameter provides a complete characterization of these rheological changes. For homologous series or for similar PE the same order of mucoadhesion observed in the rheology will be found in the tensil strength.

Whenever the PE-mucin interaction produces a rheological synergism in the mixture a hardening of the gel in the corresponding interface will be observed.

Romero et al. [50] investigated the rheological properties of C971, C934 and C940 hydrogels loaded with ofloxacin (Table 4) and related them with their antimicrobial properties against both fluoroquinolone-sensitive and -resistant Pseudomonas aeruginosa.

The analysis of bactericidal index values after a short time of drug exposure confirms the higher potency of hydrogels compared with that of ofloxacin (Fig. 22).

The improved uptake in fluoroquinolone-resistant isolates was correlated with the viscosity of hydrogels. The performance of hydrogels seems to be related to

Table 4 Physicochemical and rheological properties of carbomer-ofloxacin hydrogels

Hydrogel	Ofloxacin concentration (mg/ml)	pH	Electrokinetic potential (ζ) (mV)	Viscosity (mPa.s), 37 °C
C971-ofloxacin	2.64	6.93	−52.67	910
C934-ofloxacin	2.68	7.03	−65.13	1,340
C940-ofloxacin	2.68	6.94	−53.22	28,970

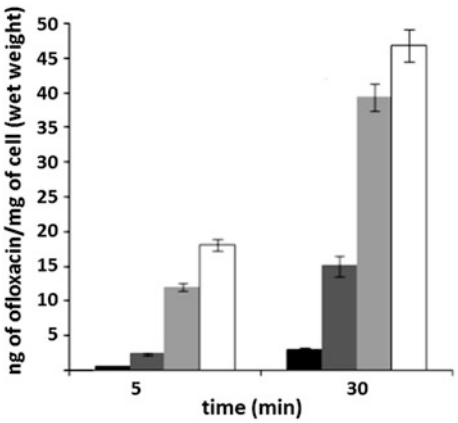

Fig. 22 Bacterial uptake of ofloxacin from (*black square*) ofloxacin solution, (*grey square*) C971-ofloxacin hydrogel, (*ash square*) C934-ofloxacin hydrogel and (*white square*) C940-ofloxacin hydrogel. (*Data adapted from reference* [19])

their bioadhesive properties that allow prolonged contact time and the release of an effective amount of drug close to bacterial cells.

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