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Controlled release of lidocaine hydrochloride from polymerized drug-based deep-eutectic solvents†

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This work takes advantage of the transformation of lidocaine hydrochloride into deep-eutectic solvents (DESs) –ionic liquid analogues– to incorporate polymerizable counterparts into DES, such that polymer-drug complexes are synthesized by free-radical frontal polymerization without the use of solvent. DESs are formed through hydrogen bonding of an ammonium salt and a hydrogen-bond donor (HBD). It is demonstrated that lidocaine hydrochloride -as ammonium salt- is able to form DESs with acrylic acid and methacrylic acid. The properties of DESs allow frontal polymerization in bulk with full conversion achieved in a one-pot synthesis, yielding monoliths of polymers loaded with a high concentration of drug. In *in vitro* experiments, the sustained release of the drug takes place in a controlled manner triggered by the pH, ionic strength and solubility of the drug in the medium. Such control is owed to the swelling of polymers as well as to the specific interactions between the drug and the polymers already established in the DES precursor. Finally, it is noteworthy that different monomers (as HBD) and crosslinkers can be used, thus expanding the possibilities of drug delivery systems for transdermal technologies by exploiting the DES chemistry.

Introduction

Polymers have been used extensively in the development of smart drug delivery systems by which the active pharmaceutical ingredient (API) can be administered with prolonged and good control.[1] On the other hand, currently major attention has been paid to polymorphism of APIs because, aside from the economic issues derived from patenting, it can have a profound impact on the way the API is processed, stored and delivered.
Formation of API-based eutectics (mixtures having a melting point lower than that of the individual components) is a well-known strategy to enhance the pharmacological performance of a given API, while favoring their processability and synergistic effects;[2] e.g. lidocaine/prilocaine eutectic cream.[3] More recently, API transformation into ionic liquids has proven to be useful to overcome polymorphism, opening new patents of already commercialized API and tuning their liphophilicity/hydrophobicity in order to enhance their transmembrane transport.[4]
APIs require the aid of excipients to protect them for degradation before reaching their target and to modulate their release profiles. The incorporation of drugs into excipients has restrictions dictated by the physicochemical properties of each system.[5] Polymers are frequently used as excipients owing to their compositional versatility, thermal properties and easy storage.[6] The main advantage of amorphous molecular level dispersions of APIs in polymers is that they prevent the crystallization of low Tg amorphous APIs over pharmaceutically-relevant time scales. Also they improve the dissolution rate, and hence possibly the bioavailability of the API. Nevertheless the amount of drug that can be efficiently dispersed in these systems requires time-consuming techniques such as directly mixing the two molten components, melt extrusion, and dissolution of each component in a mutual solvent followed by solvent removal.[7]
In contrast to solid blends of drugs and polymers, the direct polymerization of monomers in the presence of drugs allows synthesizing in situ polymers with a specific molecular weight or architectures required for the intended drug delivery systems. Meanwhile, the drugs are homogeneously integrated into the matrix, and their release can be controlled depending on their "phase stability" in the pre-polymerized mixture and more importantly in the resulting polymer.[8] In this regard different methods of polymerization have been explored, which include interfacial polymerization,[9] anionic polymerization,[10] free radical polymerization[11] and frontal polymerization.[12] Polycondensation of silica precursors in the presence of ibuprofenate-based ionic liquid have proven to be an efficient technique to produce drug-releasing systems with kinetics controlled by the nature of the silica wall.[13] Whereas in another approach, the synthesis of poly(diol-co-citrate) polyester by polycondensation was carried out under mild conditions thanks to the formation of deep-eutectic solvents with lidocaine or ammonium salts and one of the precursor of the polyester.[14] Thus the lidocaine and ammonium salts integrated in the polyester were released depending on the biodegradable character of the resulting elastomer.[15] The more obvious advantage that those approaches offer is the creation of drug delivery systems in one step such that the chance of losing drug activity by processing is minimized.
Deep-eutectic solvents (DESs) are ionic liquids analogs formed from the association of hydrogen-bond donors and ammonium or phosphonium salts, which are capable of forming eutectic mixtures with melting point often below room temperature.[16] DESs exhibit many of the properties of ionic liquids but require no complicated synthesis.[17] DES are prepared by mixing

together the components and heating until melting (usually below 100°C). Upon cooling, a liquid with a melting point far below the melting points of the constituents is obtained. DESs offer certain advantages versus ILs and can replace them in many applications.[18] By varying the molar ratio of the components or the nature of the ammonium salt and the hydrogen bond donor, it is possible to tune the physico-chemical properties of DES, such as viscosity, density and melting point.[19]

Recently our group showed that it is possible to control the exothermicity of frontal polymerization of highly reactive monomers such as acrylic acid, methacrylic acid and acrylamide by means of their complexation with ammonium salts and transformation into DESs.[20] Frontal polymerization is a way to produce polymers in unstirred reactors where a localized thermal initiation generates a polymerization front that propagates through the reactor.[21] Convective instabilities that interfere with front propagation can be avoided using inert fillers which increase the viscosity of the reaction mixture.[22] The bubbles due to boiling of monomer are also avoided using solvents having high boiling points (e.g. DMSO or DMF).[23] In our case, the ammonium salts (the active fillers) pose a dual role considering that they can modify the viscosity of the monomers by forming DESs and they are also the releasable molecules from the polymer after full conversion in solventless conditions.[24]

Frontal polymerization of this type of polymerizable DES containing lidocaine hydrochloride was first described previously by our group.[20b] In the current work frontally polymerized DESs containing lidocaine hydrochloride as a drug delivery system are studied. For that, two DESs containing acrylic acid and methacrylic acid, as hydrogen-bond donors (HBD), and lidocaine hydrochloride, as the ammonium salt, were polymerized by free-radical frontal polymerization. After polymerization, the effects of pH and ionic strength on the kinetics of drug release were studied. This work expands the types of drug delivery systems that can be prepared exploiting DES chemistry, since the monomers (HBD and crosslinker) can be selected and copolymerized depending on the desired properties of the final drug delivery system suitable for transdermal technologies.

Results and discussion

Drug-based DES

Ionic liquids have been used within pharmaceutical sciences for tuning the polarity of the active pharmaceutical ingredient (API) in a way that the concentrations of sparingly-soluble APIs are enhanced in aqueous media or lipophilic membranes.[4d] In the current work the transformation of API into DESs is used as a strategy to control the reactivity of acrylate monomers in free-radical polymerization[25] to obtain drug delivery systems. Recently our group reported that the complexation of monomers by ammonium salts results in control over the exothermicity of free-radical polymerization of acrylates in bulk, e.g. in frontal polymerization.[20a] It is therefore crucial to ensure that the mixtures of API and monomers –the polymerizable DESs– exhibit the characteristic properties of DESs. For that, modulated DSC was used to study the thermal properties of mixtures of monomers and API, namely acrylic acid (AA), methacrylic acid (MAA) and lidocaine hydrochloride (LidHCl), respectively (Figure 1).

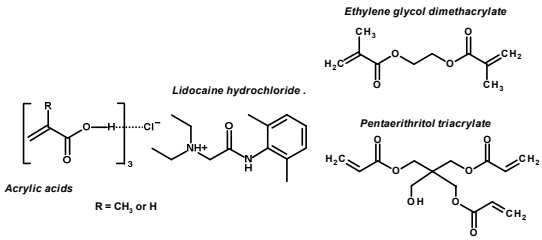

Figure 1. Structures of the polymerizable DESs and crosslinkers used in this work.

The compositions of the DESs were optimized such that the viscosity and the density of double bonds exhibited by DESs were adequate to sustain frontal polymerization.[20b, 26] That means that even when the mixtures used in this work might not correspond to the eutectic point, the combination of viscosity and density of double bounds (ratio monomer/salt) was selected to achieve frontal polymerization (Table 1). However, API-based eutectic mixtures still show melting point or glass transitions below the melting point of their pure components, (Figure S1), so they match one the principal characteristics of a DES;[16-17] thus, they will be referred as DESs throughout.

Table 1. Viscosity and melting point (mp) of polymerizable DESs and their components.

DES (HBD /Ammonium salt)	DES ratio / mol	Viscosity / mPa·s	DES mp(T_g) / °C	HBD mp / °C	Ammonium salt mp/ °C
AA-LidHCl	3 : 1	231	(-78.4)	13	80-82
MAA-LidHCl	3 : 1	315	6.8	16	80-82

Fourier transform infrared (FTIR) spectra of DESs disclose intermolecular hydrogen-bond interaction between the HBD and ammonium salt mainly in the carbonyl region. For instance, in AA-LidHCl DES, the carbonyl band of acrylic acid originally located at 1696 cm^{-1} in pure acrylic acid, shifts and broadens as a result of the disruption of the acrylic acid dimer by creating a new type of hydrogen bond. The bands at 1688 and 1722 cm^{-1} are related to the carbonyl in DES and the free form respectively, as described elsewhere.[20b] Also the band at 1432 cm^{-1}, which correspond to CH_2, shifts toward lower wavenumbers because of the HBD nature of the acrylic acid. In the case of MAA-LidHCl the carbonyl band notably decreases its intensity and becomes broader, revealing its association in a DES complex (Figure S2). It is worth noting that the N-H bending vibration and C-N stretching at 1543 cm^{-1}, from LidHCl does not shift after forming DESs with acrylic acids. This suggest that DES association is mainly due to an anion-HBD complex (Figure 2, Figure S3).[27]

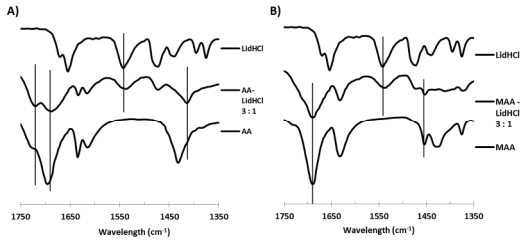

Figure 2. ATR-FTIR spectra of polymerizable DESs and their components in the range of 1350 to 1750 cm^{-1}.

Polymerization of DESs

The main drawback of free-radical polymerization in the bulk of API-monomer mixtures is that undesirable side-reactions between the API and the monomer can occur due to the high temperatures. On the other hand, the presence of remaining monomers (that might be toxic) and the need of post purification steps make of this approach difficult to perform. Thus, complete conversion is necessary. In this regard, mixtures of acrylamide and diclofenac sodium salt frontally polymerized in water with high conversion have been reported.[12] The resultant drug delivery systems showed a heterogeneous appearance due to the poor control of the exothermicity of the reaction that led to boiling of the water causing irregular surfaces; hence the release of diclofenac was difficult to control, unless a high amount of crosslinker was added (up to 40 wt %).

It was already pointed out that the presence of the non-polymerizable counterpart helps to reduce the temperature of the acrylate polymerization, but it is also plausible that the formation of DES through hydrogen-bonding prevented an eventual degradation of the API caused by high temperatures during polymerization.[14]

Frontal polymerization of DES containing lidocaine hydrochloride was performed as reported.[20a] The high viscosity of the polymerizable DESs allowed ascending frontal polymerization without buoyancy-driven convection. The experimental setup and results from polymerization of DESs are listed in the Table 2.

Table 2. Experimental setup and polymerizations results.

DES	Initiator (% mol to monomer)	Crosslinker (% mol to monomer)	Front temperature (°C)	Front velocity (mm s^{-1})
AA-LidHCl	1	0.7	138	0.49
MAA-LidHCl	2	0.7	135	0.22
AA-LidHCl / MAA-LidHCl [a)]	2	0.7	131	0.19

[a)] 1 : 1 mol

The rapid polymerization coupled with the DES nature of the components produced homogeneous and solid monoliths, i.e. no segregation of lidocaine hydrochloride occurred during polymerization (Figure S4).

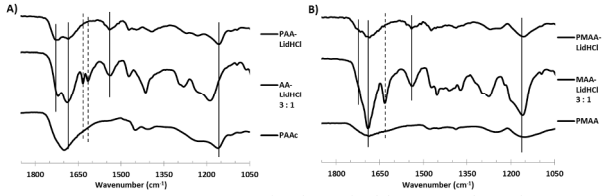

Figure 3. ATR-FTIR spectra of polymerizable DESs, the polymer complexes resulting after polymerization of DESs and the pure polymers. Some important bands are marked with solid lines while the monomer bands are marked with dashed lines.

Figure 3 shows that the spectrum of pure poly(acrylic acid) (PAA), does not match the corresponding bands of PAA in the spectrum of PAA-LidHCl monolith in the carbonyl region; the same occurred for PMAA. Thus, the resultant polymers-API can be considered as complexes due to the strong interactions between their components,[28] which are showed by the FTIR spectra. See for instance the band at 1700 cm^{-1} in the PAA in Figure 3A that corresponds to the carbonyl. It is shifted because it is involved in a polymer-API complex through H-bonding (e.g. it splits and shifts to 1722 cm^{-1} in the PAA-LidHCl complex), resembling the DES precursor;[26] the same occurs with PMAA-LidHCl. However the band at 1157 cm^{-1} that corresponds to bending in the plane of CH_2 [29] does not change in shape nor in intensity compared with bare PAA due the lack of any interaction with LidHCl during its polymerization. It is also clear the disappearance of the bands related to monomers (acrylate double bond) in the polymer complexes due to complete polymerization of DESs, in accordance with gravimetric and thermogravimetric analyses (Figure S5). Those bands are located at 1634 and 1613 cm^{-1} in acrylic acid, and at 1637 cm^{-1} in methacrylic acid.

Kinetics of APIs release

From Figure 4 it can be seen that both polymer systems – PMAA and PAA – under every condition studied (pH and ionic strength), released the maximum theoretical amount of API present in the DES within ca. 30 hours or less. The ^{1}H NMR spectra of the released compounds reveal that only lidocaine hydrochloride (Figure S6) was released, and it remained unaffected by the polymerization process.

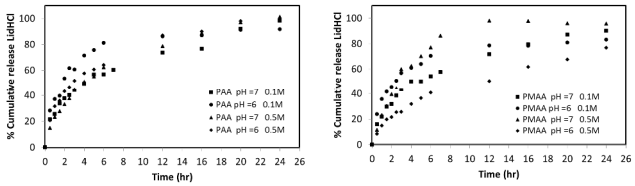

Figure 4. Kinetics of the release of lidocaine·HCl from poly(acrylic acid) (PAA) and poly(methacrylic acid) (PMAA) crosslinked with ethylene glycol dimethacrylate in phosphate buffer at different pH and ionic strength under sink conditions at 24°C.

Polyacrylic acids are a well-known class of polyelectrolytes that are pH responsive. As hydrogels, their swelling depends on the protonation state of the pendant carboxyl groups. In consequence, swelling in these systems is due to electrostatic repulsion. The pKa of PAA is around 4.8 - 6.7 constrained by the molecular weight and the crosslinking degree,[30] while for PMAA it is between 6.4 - 7.[31] Regarding the ionic strength, the general behavior is that increasing the salt concentration in the hydrogel increases the degree of electrostatic screening. Therefore, the electrostatic repulsion between hydrogel charges, which causes swelling, is prevented by the presence of the counterions of the salt.[32]

Herein, the experiments were conducted at pH 6 and pH 7 to show how the amount of drug release can be controlled by the pH of the medium.

It is expected that both the pH and the ionic strength would have a strong impact on the kinetics of the release of APIs. The release of drugs from this class of hydrogels has been well studied, and it is generally accepted that diffusion and swelling are the phenomena that govern the drug release from the hydrogels.[33] Lidocaine hydrochloride (LidHCl), a local anesthetic, is the type of API whose degree of ionization is also pH dependent, i.e. the efficiency of dissolution and delivery varies with pH. Such dependence means that, in the case of LidHCl (pKa = 7.16), an increase in the pH of the medium results in conversion of positively charged molecules into

electrically neutral species, reducing their solubility in aqueous media.[34]

In the present case, the kinetics of the API's release involves not only the simultaneous absorption of water and desorption of drug via swelling-controlled diffusion, but also API dissolution that is pH-dependent. Thus the kinetics depicted in Figure 4 are the result of the competition of different mechanisms operating at the same time, although under certain pH and ionic strength some phenomena become more relevant and are the predominant mechanisms. By comparing the kinetics of swelling and the drug release, the overall kinetics can be dissected in two regimens depending of polymer swelling and drug solubility, which will be discussed below.

The first stage of the release involves the swelling of the polymer-API complex from the glassy state to the swollen state, which is accompanied by diffusion of the API. In the case of poly(acrylic acid)-LidHCl, the 60% of the cumulative release of LidHCl occurs within the first 3 to 6 hours depending on the pH and the ionic strength of the media; whereas it takes 4 to 16 hours for the poly(methacrylic acid)-LidHCl depending on the pH and ionic strength. The first stage of the release fit well to the Fickian model for all cases ($R^2 > 0.9$, Figure S7), such that the process can be considered mainly as swelling-controlled mechanism following the Equation 1.[35]

$$\frac{M_t}{M_\infty} = kt^n \qquad (1)$$

Where M_t and M_∞ are the amounts of drug released at time t, and at equilibrium, respectively; k is proportionality constant and n is the diffusional exponent, which is 0.5 for the Fickian model.

It is worth noting that the amount of LidHCl released at pH 6 is higher than at pH 7, irrespective of ionic strength in the PAA case, and at low ionic strength in the PMAA case. This could be considered as an anomalous behavior due to the fact that polyacrylic acids swell more in basic than acid media, and in consequence the release should be higher at pH 7 than 6. In order to disregard this mechanism, the diameter of cylinders of PAA-LidHCl (as a function of volume) was measured over time at pH 6 and 7 at fixed ionic strength (Figure 5). It is clear that the swelling follows Fickian behavior ($R^2 > 0.99$), which indicates that the incorporation of API does not interfere with the macroscale swelling of poly(acrylic acid) hydrogels containing LidHCl (Figure S8).

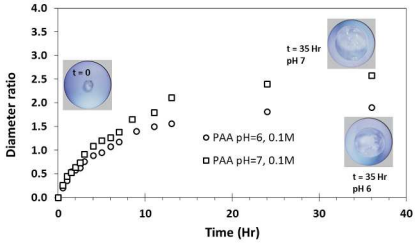

Figure 5. Swelling behavior of poly(acrylic acid) crosslinked with ethylene glycol dimethacrylate in phosphate buffer at different pH.

However, the dissolution of the API in aqueous media, and hence its ionization, plays a crucial role in the release. As mentioned above, the pKa of LidHCl makes the molecule soluble at pH 6 due to its ionization to LidH+ and Cl- ions as follows.

$$LidHCl + H_2O \leftrightarrow LidH^+ + Cl^- \qquad (2)$$

$$LidH^+ \xleftrightarrow{pKa=7.16} Lid + H^+ \qquad (3)$$

During the onset of swelling, the dissolution rate of the LidHCl becomes more relevant to finally being the controlling factor due to the high concentration of drug in the network.[36] The ionic strength also affects the trend of the first stage of the release by diminishing the swelling of PAA but also increasing the solubility of LidHCl via the diverse ion effect (Figure 6 A-B). [37] This double effect is notable in the Figure 6B in which both phenomena seem to nullify themselves in a sort of "buffering effect".[38] On the other hand, the release of LidHCl from the PMAA is higher at pH 6 only with low ionic strength (Figure 6C). At 0.5 M the charge screening causes the release to be controlled by the swelling rather than by the API dissolution; as a result, the release rate is considerably higher at pH 7 (close to PMAA pKa) enhanced by the diverse ion effect (Figure 6D).[32]

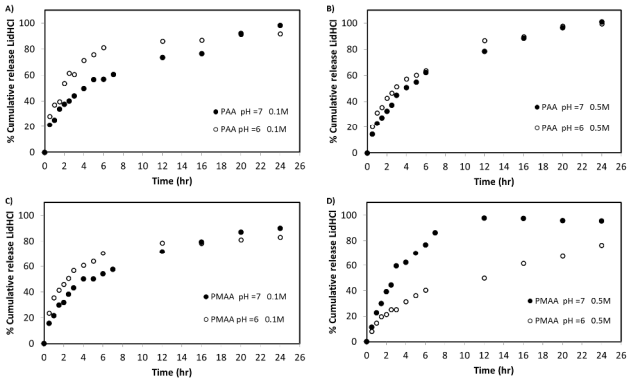

Figure 6. Effect of pH and ionic strength on the release of lidocaine·HCl from poly(acrylic acid) and poly(methacrylic acid) crosslinked with EGDMA in phosphate buffer under sink conditions at 24°C.

Nevertheless, in all cases after 10-12 hours the swelling reaches a constant rate, and the amount of LidHCl release seems to follow zero-order kinetic, as previously reported for drug delivery systems based on poly(acrylic acid).[39] This second stage in the release is associated with a diffusion-controlled process of the API from the already swelled matrix.[40]

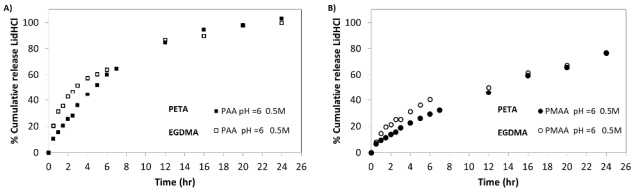

Figure 7. Effect of crosslinkers on the release of lidocaine·HCl from A) poly(acrylic acid) and B) poly(methacrylic acid) in phosphate buffer under sink conditions at 24°C.

In order to further control the swelling of the polymers, two types of crosslinkers with different functionalities were used, and their effect on the release was studied. Ethylene glycol dimethacrylate (EGDMA) possess two methacrylate groups, whereas pentaerithrytol triacrylate (PETA) possess three acrylate groups; both are able to undergo free-radical polymerization to form networks (Figure 1). The amount of crosslinker used in this work is very low (0.7% mol to monomers), though adequate to form hydrogels. Since PETA is a trifunctional monomer, the degree of crosslinking of the resultant hydrogel is higher compared with the hydrogel crosslinked with EGDMA, and then the swelling in the former case is slower at fixed pH and ionic strength. Hence the release is controlled during the first stage by modifying the relaxation of the network, i.e. its swelling by water absorption (Figure 7).

Another way to control the relaxation of the polymer is through copolymerization. In this way different functionalities can control different properties yielding a tailored performance. Although, it can be seen in Figure 8 that the random copolymerization of acrylic acid and methacrylic acid in a 1:1 ratio results in a copolymer whose release kinetic resembles more the PAA homopolymer than the PMAA one at pH 6. Interestingly the use of PETA gives rise to the Case II transport mechanism at pH 6 and 0.5 M, i.e. n = 1 in the Equation 1 and hence controlled by the rate of polymer relaxation, which follows zeroth order kinetics.[33]

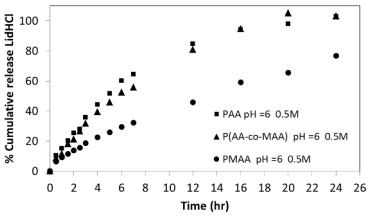

Figure 8. Release of lidocaine·HCl from poly(acrylic acid), poly(methacrylic acid) and poly(acrylic acid-co-methacrylic acid), all crosslinked with PETA in phosphate buffer under sink conditions at 24°C.

Furthermore, by their proper combination of bioadhesive poly(acrylic acid) and poly(methacrylic acid),[30, 41] a series of copolymers with tailored surface properties that ultimately control their bioactivity and release mechanisms can be easily envisaged by the use of polymerizable DESs.

Experimental Section

DESs preparation and characterization

All chemicals were purchased from Sigma-Aldrich and used as received. Deep-eutectic mixture counterparts were mixed together in the proper ratio and heating at 80°C until a homogeneous liquid was obtained. For example, 1 mL (14.57 mmol) of acrylic acid and 1.4 g (43.71 mmol) of lidocaine hydrochloride monohydrate were mixed in a vial and placed in oven at 80°C for 1 hr. The viscosity of the different DESs was measured with a Brookfield Digital Rheometer DV-III at 24 °C. Modulated differential scanning calorimetry (DSC) was performed with a TA Instruments Model DSC Q-100 system, under a nitrogen atmosphere, with a scan rate of 5 °C min^{-1}. DSC scans showed the melting point (T_m) and the glass transition temperature (T_g) of the DESs. TGA was performed with a Hi-Res Modulated TGA 295 Thermogravimetric Analyzer under nitrogen atmosphere and a heating rate of 10 °C min^{-1}. FTIR spectra were collected on a Perkin–Elmer spectrophotometer using an ATR accessory in the range 4000–650 cm^{-1} at room temperature with a resolution of 4 cm^{-1}, and the spectra shown are an average of 32 scans. The API released was characterized by proton-nuclear magnetic resonance (^{1}H NMR) spectroscopy using a Bruker DRX-500 spectrometer.

Polymerization of DESs

Frontal polymerization was carried out by dissolving 1,1-bis(tert-butylperoxy)-3,3,5-trimethylcyclohexane (Luperox 231®), as thermal initiator and ethylene glycol dimethacrylate (EGDMA) or pentaerithrytol triacrylate (PETA), as crosslinkers, in the different DESs. The resulting solutions after stirring were transferred to a long test tube (70 mm length and 6 mm diameter), and bubbled with nitrogen gas. The reactor was covered for thermal isolation. Then, the bottom part of the tube was heated with an electrical resistance (ca. 200 °C) for thermal initiation, whereas the upper end of the reactor remained open to atmospheric pressure (Figure S9). After initiation, the exothermic nature of acrylic polymerizations promoted an increase in the temperature at the bottom portion of the reactor such that polymerization occurred upwards through the entire reactor without buoyancy-driven convection and with constant velocity.

Polymer-drug characterization

Once the polymerization front reached the top of the DES in the reactor, the conversion was calculated dividing the dry polymer weight after soaking in distilled water (to wash out unreacted acrylates and the API) by the theoretical weight of the polymer that would result from full monomer-crosslinker polymerization. Those results were further verified by the loss weight of monomer (unreacted acrylic acid or methacrylic acid) in the temperature range between 140 and 200 °C following the derivative weight curve in a thermogravimetric analysis, and by the disappearance of the bands related to monomer in FTIR spectra. The specific interactions between the components of the DESs were studied by FTIR. The polymer-APIs were subjected to the same characterization.

Release experiments

The monoliths were soaked in deionized water until all the API was wash out, and the media was then lyophilized. The solid residue was analyzed by ^{1}H NMR to identify the API entrapped in the polymer during the polymerization. The controlled release of the drugs from the polymers was carried under sink conditions at 24°C. The effect of pH and ionic strength on the release was tested in phosphate buffer pH= 6 and 7, with two different ionic strengths (0.5 and 0.1 M). At predetermined time intervals, samples were withdrawn and immediately replaced with an equal volume of dissolution medium to keep the volume constant. Lidocaine hydrochloride concentration was determinated by UV-Vis spectroscopy at 263 nm (Figure S10).

Conclusions

This work showed that taking advantage of the DES chemistry, the exothermicity of acrylate free-radical polymerization in bulk (e.g. frontal polymerization) can be controlled by means of their complexation with APIs. Polymer-API complexes can be easily synthesized in a one-pot synthesis with a minimum consumption of energy, full conversion and in solventless conditions, preserving the API from degradation. The tailored composition of DESs allowed designing polymer and copolymer complexes that are pH responsive such that the entrapped API can be released in a controlled manner.

With in vitro experiments, the sustained release of lidocaine hydrochloride (as model drug) was controlled by the pH, ionic strength and solubility of the drug in the medium. During the first stages, the mechanism governing the release is the dissolution and diffusion of the API through the polymer. However, as the swelling develops, the mechanism turns into a sustained release controlled by diffusion. Those mechanisms can be tuned by the appropriate combination of monomers (i.e. different DESs) and crosslinkers.

The amount of lidocaine hydrochloride homogenously integrated in the stable polymer complexes is, to the best of our knowledge, the highest ever reported in poly(acrylic acid) and

poly(methacrylic acid). This is due to the fact that the API is one of the components of the polymerizable DESs. Therefore the specific interactions between the components that are formed and maximized in the DES precursor result in homogeneous polymer complexes.
Finally, it was demonstrated that different monomers can play the role of hydrogen bond donor and by means of its copolymerization a new type of polymerizable DESs was achieved. These results significantly expand the possibilities of drug delivery system preparation by exploiting the DES chemistry.

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