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Drug release from hydroethanolic gels. Effect of drug's lipophilicity (log *P*), polymer–drug interactions and solvent lipophilicity

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ABSTRACT

We demonstrate drug release properties from hydroethanolic formulations as a function of the drug's lipophilicity (log *P*), solvent lipophilicity and drug–polymer interactions, for the first time.

A hydrophilic polymer, hydroxypropyl cellulose (HPC), provides the non-Fickian slower release of the lipophilic drug, lidocaine (log *P* = 2.6) and the burst (Fickian) release of hydrophilic drug, lidocaine hydrochloride (log $P \leq 0$). Thus, log *P* of drugs helps predict the drug release properties.

Hydrophobic Eudragit polymers provided the burst release of lidocaine. However, the cationic hydrophobic polymer (Eudragit E100) retained more lidocaine (~50%) topically than other hydrophobic polymers: Eudragit S100 (anionic) and Eudragit RLPO (cationic copolymer with quaternary ammonium group) (~25% lidocaine retention) which release lidocaine systematically. Thus, minute changes in functional groups of hydrophobic polymers help tune the lidocaine release topically or systemically.

An interaction between HPC and lidocaine as determined by FTIR helps the non-Fickian slower lidocaine release from HPC formulations. However, no interactions between lidocaine and hydrophobic Eudragit polymers explain the Fickian burst release of lidocaine from their formulations.

A lipophilic solvent, isostearyl alcohol which when replacing ethanol by 30%, slows the release rate and enhances the topical adsorption of lidocaine. Thus, solvent lipophilicity also modulates drug release properties.

1. Introduction

Lidocaine (Ld) and lidocaine hydrochloride (Ld·HCl) have been widely used as local anaesthetic agents (Nalamachu et al., 2008; Jorkjend and Skoglund, 1999; Affaitati et al., 2009). Different types of delivery vehicles such as patches (Nalamachu et al., 2008; Affaitati et al., 2009), gels (Wallace et al., 2001; Liu et al., 2007; Shin et al., 2004), gel foam (Hämäläinen et al., 1998), semisolids (Auner and Valenta, 2004; Jacques et al., 1997), films (Padula et al., 2003, 2007), polymer matrix (Fu et al., 2004; Miyajima et al., 1999), microemulsion (Yuan et al., 2008), and surfactants (Ganem-Quintanar et al., 1998) have been used for a diverse variety of hydrophilic and lipophilic drugs such as Ld·HCl and lipophilic drugs such as Ld. Furthermore, chemical enhancers have been used to improve the transdermal delivery of lidocaine (Lee et al., 2006).

Novel hydroethanolic gel formulations utilize hydrophilic and hydrophobic polymers and the water/ethanol ratio, in addition to other parameters such as pH, temperature and solution viscosity, to modulate the drug release rate of mainly lipophilic drugs (Tomlinson and Davey, 2001). Also Kim et al. (2001) have demonstrated testosterone transdermal delivery using a pressure-sensitive adhesive Duro-Tak patch comprising of ethanol/water (70:30), ethylene vinyl acetate (EVA) copolymer membrane and hydroxypropyl methylcellulose and skin permeation-enhancing agents.

Advantages with our hydroethanolic gels are that they do not need patches or skin permeation-enhancing agents, and protect the skin against water and abrasions, and rely more on hydrophobic and hydrophilic polymers to modulate the drug release rate. Upon application of hydroethanolic gels to the skin, ethanol evaporates and a polymer film forms on the skin, which helps to modulate drug release and protect the skin against abrasion and water (Tomlinson and Davey, 2001). For these reasons, hydroethanolic formulations are multi-functional systems, unlike other polymeric gels.

Ethanol acts as an antibacterial agent, and helps dissolve lipophilic drugs and polymers and helps polymers to form film. However, ethanol may sometimes induce skin irritation and burst release the drugs from formulations. Other volatile organic chemicals such as acetone, acetonitrile (ACN), silicone oils and chloroform can be employed instead of ethanol, but these solvents may contribute to skin dryness and irritation, may not dissolve some of the polymers, and may affect polymer film and drug release properties. To minimize above-said drawbacks of ethanol and other volatile

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solvent, there is a need to replace ethanol partially without affecting the release properties. We selected isostearyl alcohol (ISA) for the partial replacement of ethanol because ISA is long chain alcohol, forms film on the skin and is non-irritant. It has been extensively used for the transdermal drug delivery (Kang et al., 2005), and the delivery of topical cosmetic-actives using lipsticks (Egan and Hoffman, 1968) and antiperspirant sticks (Banowski et al., 2008).

Polymers play many crucial roles in hydroethanolic compositions such as forming the film, modulating drug release rate and modulating viscosity (Tomlinson and Davey, 2001). Although individual polymers or mixtures of polymers have been used to modulate the drug release properties (Fu et al., 2004; Miyajima et al., 1999; Padula et al., 2003, 2007; Liu et al., 2006; Tomlinson and Davey, 2001), the relationship of polymer–drug interactions and drug release properties has not been well established. This becomes a potential issue for hydroethanolic formulations because the drug would have different interactions with different polymers and would affect the drug release properties.

Lipophilicity of drug is represented by log *P* (Teitgen, 2006). Recently, Box and Comer (2008) and Fortenbach et al. (2008) have used for the classification of drugs and to understand the physiochemical properties in drug transport into skin compartments, respectively. Furthermore, log *P* of drugs has been used as one of the key parameters in the multivariate analysis of human jejunal permeability (*in vivo*) of drugs (Winiwarter et al., 1998).

The Franz cell is the most commonly used method to study the *in vitro* release of active ingredient from different formulations (Thakker and Chern, 2003; Siewert et al., 2003).

The Peppas equation (Peppas, 1985; Fu et al., 2004) is the most commonly used empirical equation to understand the drug release mechanism.

FTIR has been used to understand the drug–polymer interactions (Cantor, 1999) and to correlate drug–polymer interactions with drug release properties.

To the best of our knowledge, the relationship of drug lipophilicity–polymer chemistry–solvent lipophilicity–release properties is not well established particularly for hydroethanolic gels.

In the present article, we have studied relationships of drug lipophilicity–polymer chemistry–solvent lipophilicity–release properties using Franz cell release data and the Peppas equation.

2. Materials and methods

2.1. Materials

Water (Milli-Q, USA), anhydrous ethanol (CSR, Australia), hexylene glycol (Shell Chemical Co., USA), ISA (ISP technologies, USA), acetonitrile (Aldrich), lidocaine and lidocaine hydrochloride (Gufic Biosciences, India), hydroxypropyl cellulose (HPC) (trade name: Klucel G, Molecular weight of 370,000, Hercules Incorporation, USA), Ethocel standard 10 premium (EC), an ethyl cellulose polymer with ethoxyl content 48–49.5% and 9–11 cP viscosity of 5% solution (Dow chemicals), and Eudragit E100 (EE100) (cationic polymer with dimethylaminoethyl methacrylate as a functional group with molecular weight of 150,000), Eudragit S100 (EE100) (anionic polymer with methacrylic acid as a functional group with molecular weight of 160,000) and Eudragit RLPO (E-RLPO) (Meth-/acrylate copolymers with trimethyl-ammonioethylmethacrylate as a functional group with molecular weight of 150,000) (all from Degussa, Germany) were used without further purification. HPC and EC are hydrophilic whereas Eudragits are hydrophobic polymers.

A commercial HPC polymer Klucel G, is a versatile hydrophilic polymer which can be used as a film-former, thickener, stabilizer, suspending agent, film barrier, thermoplastic or protective colloid in a wide variety of formulations, including food, cosmetics, pharmaceuticals, coatings, adhesives, moldings, paper, paint removers, encapsulations and inks. EC, also a hydrophilic polymer, is most frequently used in controlled release and solid dosage formulations. These polymers are also useful as granulation binders, as film-formers to improve tablet integrity and appearance, and in taste masking of bitter actives. Eudragit polymers such as EE100, ES100 and E-RLPO are acrylic drug delivery excipients.

2.2. Method of preparation of hydroethanolic gel formulations

Hydroethanolic formulations were prepared by dissolving an appropriate amount of hydrophilic polymers and drugs in water phase and hydrophobic polymers and drugs in oil phase followed by mixing of these phases using a stirrer (600–1000 rpm) at room temperature.

2.3. Franz cell drug release experiments

In vitro drug release experiments were carried out using a Franz cell set up (Padula et al., 2007) which comprised 12 mL 0.01 M PBS solution, pH 7.0 (Aldrich) in the Franz cell receptor compartment, donor compartment and two 25 mm diameter, 0.1 μm pore size with 70% porosity, 125 μm thick hydrophilic Durapore™ (polyvinylidene fluoride (PVDF)) membranes (Millipore) were placed between receptor and donor compartments. The use of PVDF membranes for Franz cell drug release studies was reported by Fan et al. (2004). About 30–50 mg of formulation was placed on the membranes from the donor compartment. Concentrations of Ld and Ld·HCl were fixed at 5% (w/w) in all formulations. The concentrations of drugs, polymers and solvents in the present manuscript are represented as %w/w.

The temperature of the Franz cells was optimized and maintained at 30 °C. 200 μL of the receptor phase was drawn at certain time intervals and the drawn amount was replaced by the same amount of PBS buffer.

2.4. HPLC analysis

A reverse phase HPLC method using a cogent HPC column (75 mm × 4.6 mm id, 5 μm), PDA detector (210–300 nm range, detection at 220 nm), an isocratic elution at 1 mL/min with mobile phase containing 50% acetonitrile and 50% triethanolamine (TEA) buffer (0.1% TEA, pH 7.0). The retention time was about 4.5 min and total run time was 6 min. Methanol:H_2O = 50:50 was used as a diluent for the HPLC sample preparations. The standard deviation in the HPLC measurements was found to be between 2 and 5%.

The HPLC method was qualified for the determination of Ld concentration released into the receptor phase. The method accuracy and precision was evaluated by spiking Ld into the receptor phase at the concentrations that cover the typical range of lidocaine concentrations in the Franz cell samples from 30 min to 6 h. The method recovery was averaged at 100.8% for six samples. The precision was excellent with a relative standard deviation of 1%.

The detector linearity was demonstrated by analysing a series of diluted standard solutions containing about 0.008–0.32 mg/mL of Ld. The results showed that the detector response is linear with the correlation coefficient *R* of 0.9992.

2.5. FTIR analysis

Infrared spectra were recorded on Spectrum 100 (PerkinElmer) at RMIT University (Melbourne, Australia) using the KBr disk method.

3. Results and discussion

In general, hydrophilic drugs have log $P \leq 0$ whereas lipophilic drugs have log $P > 0$ (Wishart et al., 2008). Ld and Ld·HCl are selected as lipophilic and hydrophilic drugs, respectively because Ld has log P of 2.26, and Ld·HCl, being soluble in water, has log P of ≤ 0. These drugs have minor difference in their molecular weight but have drastic changes in the solubility. Results from the present study can be applied to a wide variety of drugs based on their log P values and help simplify the realization of effective controlled release formulations.

3.1. Drug release from individual polymers

The semi-empirical Peppas equation (Peppas, 1985) can be used to calculate n and k (1/min):

$$\frac{M_t}{M_\alpha} = kt^n \quad (1)$$

where M_t/M_α is the fractional drug release at time t. The initial drug loading present in the deposited formulation (on membrane) is considered as M_α. The constant k (1/min^n) (Rodriguez et al., 2000) is a kinetic constant measuring the velocity of drug release and n is a diffusional exponent that depends on the release mechanism and the shape of the matrix tested.

In the present study, the drug release occurred from the lateral layer of polymer(s) thin film deposited on the membrane, therefore one-dimensional radial release was considered. In general, Fickian diffusion defined by $n = 0.45$, anomalous (non-Fickian) transport by $0.45 < n < 0.89$, and case II transport (relaxation or swelling controlled systems by $n = 0.89$) (Ritger and Peppas, 1987a,b).

Fig. 1a and b depicts the effect of individual polymers on Ld release profiles and its partition between Franz cell receptor phase and membranes whereas Fig. 1c depicts the n and k values obtained using Eq. (1).

Representative release profiles of lidocaine from various polymeric formulations are depicted in Fig. 1a. When comparing the release properties of lidocaine from formulations comprising of hydrophilic polymers HPC and EC (Fig. 1a), the HPC formulation was found to provide continuous release (~4 h) of Ld compared to that of the EC formulation which provided ~1 h release of Ld.

The diffusion exponent, $n = 0.8$ was estimated for HPC indicating that the anomalous (non-Fickian) transport of Ld from the HPC formulation. The n value obtained for the HPC formulation is close to the characteristic n value of case II transport ($n = 0.89$) due to relaxation or swelling controlled systems. This can be attributed to the partial swelling of HPC thin film in the ethanol:water system. In comparison, n value of EC ($n = 0.28$) is almost 30% of that of HPC although there is not much difference in the chemical structures of these polymers. According to the EC specification (Dow Chemicals), EC is low viscosity polymer, which explains the quicker release of Ld from the EC formulation and attributed to the lower n value. The difference in the physical properties of HPC and EC is reflected in the k values, as the k value of EC is eight times higher than that of HPC. The change in the k values of EC and HPC is complimentary to their n values.

Hydrophobic cationic polymers, EE100 and E-RLPO have n values of 0.29 and 0.44, respectively, and k values of 0.17 and 0.11, respectively. These polymers show the Fickian release mechanism for the Ld release based on their n values. However, the difference in n and k values of these polymers can be attributed to difference in their structures because EE100 possesses secondary ammonium group and E-RPLO has tertiary ammonium group. To the best of our knowledge, such an effect of a small change in the chemical structure of polymers on the release properties of drugs has not been reported in the literature. Thus, the present study demonstrates

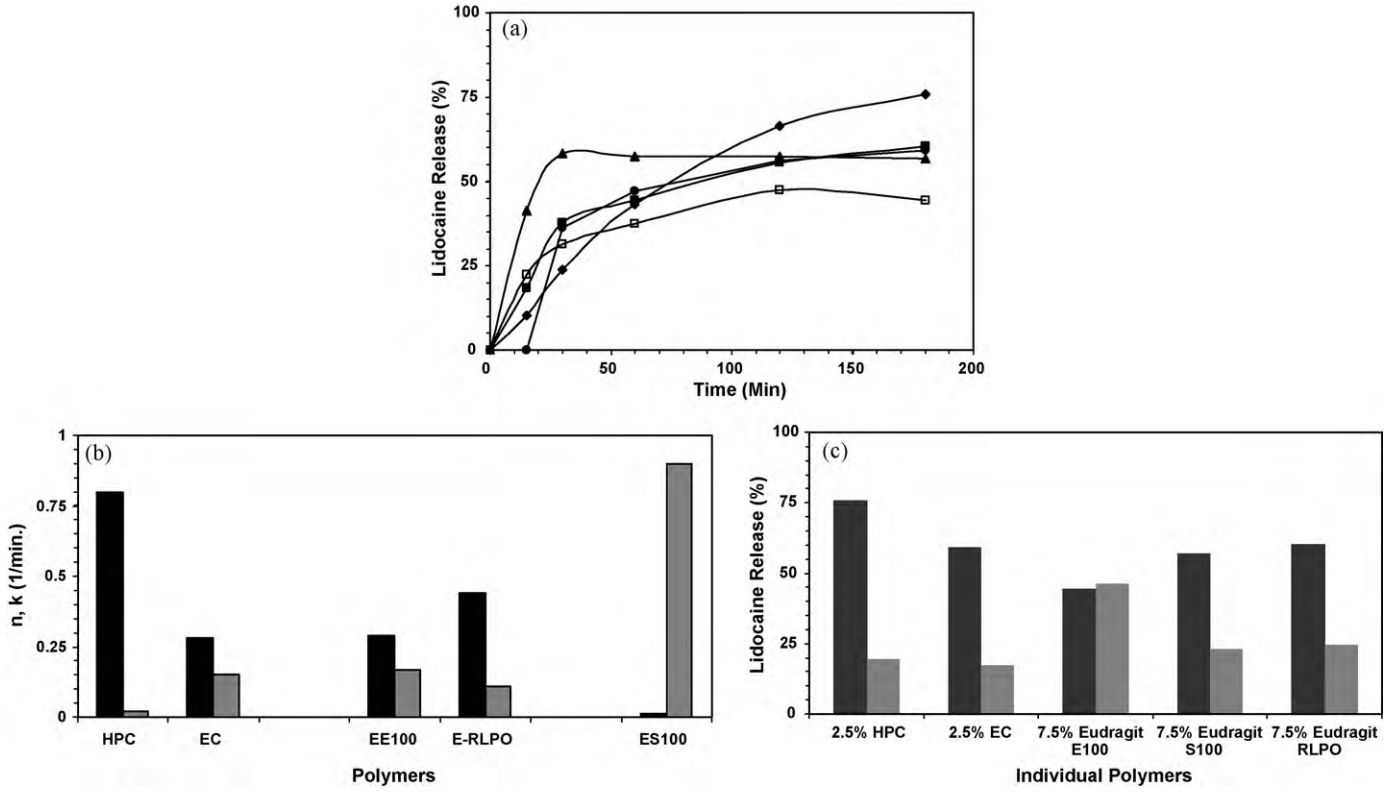

Fig. 1. (a) Effect of individual hydrophobic and hydrophilic polymers: hydroxypropyl cellulose (♦), Eudragit E100 (□), Eudragit RLPO (■), Eudragit S100 (▲) and ethyl cellulose (●) on the release profile; (b) diffusional coefficient, n (black bars) and kinetic constant, k (grey bars) and (c) lidocaine partitioned between the receptor compartment of the Franz cell (black bars) and membranes (grey bars).

for the first time that a minute change in the chemical structure can reflect change in the drug release properties.

Furthermore, ES100 which is also a hydrophobic Eudragit polymer, but with an anionic functional group, showed a very small value of n (=0.110) and a very large value of k (=1.05 min^{-1}.) which can be attributed to a faster Ld release rate than was observed for the cationic Eudragit polymers (EE100 and E-RLPO). These results again highlight an effect of a minute change in the chemical functionality of the polymer on the release mechanisms of drugs, which also has not been reported in the literature.

Small values of n and k obtained for hydrophobic polymers (EE100, E-RLPO and ES100), as compared to those of HPC, indicate that hydrophobic polymers did not interact with the Ld through ionic or covalent bondings and helped its burst release.

Additionally, the Ld adsorption onto the membrane from the HPC polymer was found to be 5% higher than from the EC polymer. The slower release of Ld from the HPC formulation may be related to either the higher viscosity of HPC or interactions of HPC with Ld. According to the EC specification (Dow Chemicals), EC is a low viscosity polymer, which accounts for the quicker release of Ld from the EC formulation.

When the effect of hydrophobic polymers on release properties of Ld was compared, the following trends were observed: Cationic E-RLPO having quaternary ammonium groups had a slower Ld release than EE100, which has cationic secondary ammonium groups. The anionic ES100 formulation released more of Ld in the receptor phase and exhibited less Ld adsorption on the membranes. Ld was partitioned almost equally between the receptor phase and membranes when applied using the cationic EE100 formulation. The EE100 formulation exhibited more Ld adsorption on the membrane compared to the ES100 formulation. Above results of Ld release from EE100 and ES100 polymers suggest that EE100 can be employed for the topical delivery of Ld and ES100 can be employed for the systemic release of Ld. It is difficult to know if Ld is trapped within EE100 film or completely precipitated on the EE100 film due to inherent roughness of polymer films. These results imply that we can select or tailor-makes suitable polymers to allow drug to either penetrate the skin (i.e. systemic release) or remain on the skin (i.e. topical release).

It is clear from Fig. 1a–c that the non-ionic hydrophilic polymer, HPC, enhances the release of more lipophilic drug, Ld, in a continuous fashion whereas cationic hydrophobic polymer, EE100, provides the burst release and lesser amount of the same drug.

3.2. Drug release from polymer mixtures

Fig. 2a depicts representative release profiles of lidocaine from formulations of HPC and EE100 and different ratios of HPC/EE100. To understand additional effects of HPC and EE100 on Ld release profiles, we reduced the ratio of HPC/EE100 and found that Ld release was indeed reduced without affecting the continuous release profile (Fig. 2a). Furthermore, Fig. 2b depicts n and k values obtained for different ratios of HPC and EE100 and individual polymers. As the ratio of HPC to EE100 changed from 5 (5% HPC + 1% EE100) to 0.33 (2.5% HPC + 7.5% EE100), the n value reduced by 1.4 whereas the k value increased by 0.37, the Ld release became more Fickian with an increase in the velocity of drug release. These effects highlight the retarding role of the cationic hydrophobic polymer EE100 for the Ld release. The above results can be explained as follows.

Hydroethanolic gels mentioned above are a uniform dispersion of two solid phases: (i) drug and (ii) polymers. The dissolution kinetics of these phases depends on the respective dissolution constant and surface composition. Upon contact with the external release environmental fluid (i.e. wet membranes) the drug starts diffusing, whereas polymers either swell (mostly hydrophilic polymers) or form a layer (mostly hydrophobic polymers) on the membranes. Consequently, the gel layer formation slows down the drug delivery and release kinetics depends on (a) drug dissolution and (b) drug diffusion through time dependent gel layer thickness. The gel layer thickness depends on polymer swelling and polymer erosion. Therefore, time evolution of the gel layer thickness is proportional to gel resistance to drug delivery. We can expect slow release of the drugs if the gel layer formation on the membrane is faster than the drug diffusion through gel layers, and vice versa. This is the case with Eudragit polymers, which would form the non-swellable hydrophobic layer on the membrane and may block the Ld diffusion. Therefore, these polymers, individually and in combination with HPC, offer resistance for the Ld release.

On the other hand, hydrophilic polymers, in particular HPC, may swell to some extent due to water in the solvent system while adsorbing onto the membrane and results in the slow release of hydrophobic Ld. HPC may not swell fully due to the presence of ethanol and the temperature of Franz cell experiments (30 °C) as HPC's solubility decreases with an increase in temperatures.

When a hydrophilic polymer (HPC) and a hydrophobic polymer (EE100) were mixed in different ratios in the formulations, a composite film of entangled polymers with possible precipitation of hydrophobic polymer (because of its lower concentration) in hydrophilic polymers (because of its higher concentration) would form on the PVDF membranes. The film would have hydrophilic as well as hydrophobic patches, which would provide competition for the Ld release as both these polymers have different release properties. Therefore, as the polymer ratio varies, the competition to release Ld also varies, which is evident from Fig. 2b.

Fig. 2b provides complimentary insights to Fig. 1a and b. It shows that 2.5% HPC facilitates the continuous Ld release with more of Ld present in the Franz cell receptor phase; leaving behind only 20% Ld on membranes. Also 7.5% EE100 provides burst release of Ld with almost equal partition of Ld between the Franz cell receptor phase and membranes. From the formulation containing 5% HPC and 1% EE100, the Ld is released continuously due to higher the HPC to EE100 ratio and also 10% higher than 2.5% HPC (without EE100). When the HPC/EE100 ratio is reduced from 5 to 0.33 by reducing HPC to 2.5% and increasing EE100 to 7.5% the Ld burst releases and ~20% Ld is retained on the membrane. This retention is 25% less than that obtained by 7.5% EE100 (without HPC). The results above demonstrate the HPC's function as a facilitator and EE100's function as a retarder for the Ld release and the competitive release of Ld and its retention on membranes from mixtures of HPC and EE100. These results are complimentary with the data presented in Fig. 1a and b.

Thus by varying the ratio of HPC (hydrophilic polymer) and EE100 (hydrophobic polymer), we can modulate the (hydrophobic) drug release properties.

3.3. Effect of log P on the release properties

Fig. 3a depicts representative release profiles of lidocaine and lidocaine hydrochloride from formulations of 30% ethanol + 5% HPC + 1% EE100. Fig. 3a shows a comparison of release profiles of hydrophobic Ld ($\log P = 2.26$) and hydrophilic Ld·HCl ($\log P = \leq 0$) from formulations of fixed ingredients.

Results from Fig. 3a showed that Ld·HCl had a burst release whereas Ld had a continuous release from their respective formulations.

Fig. 3b depicts the n and k values for these drugs. Due to the reduction of the log P value from 2.6 of Ld to log P of ≤ 0 of Ld·HCl, the n value drastically reduced by 21 whereas the k value increased by seven times. The n value for Ld was 0.42, which is close to 0.45 thus Ld may be released by anomalous (non-Fickian) transport mechanism. For Ld·HCl, the reduced n value (=0.02) is indicative of the

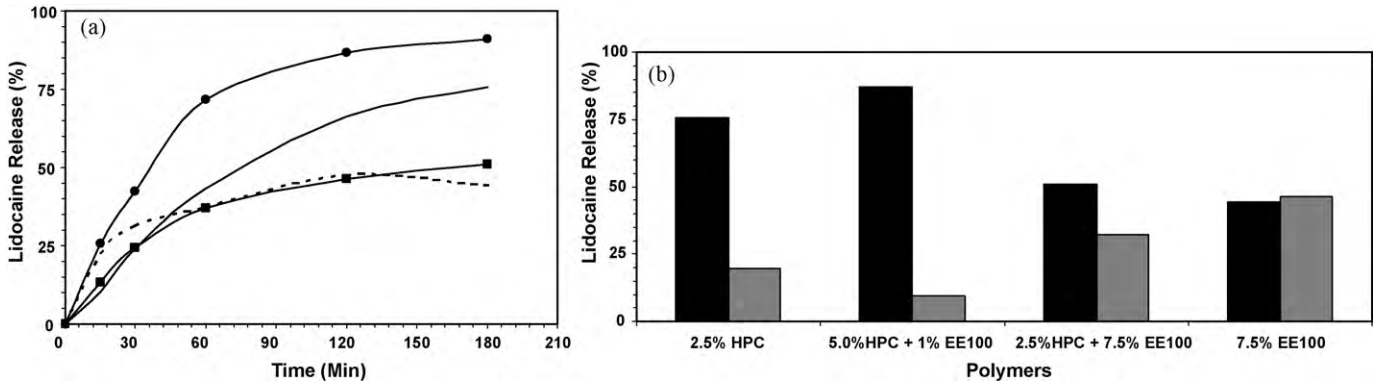

Fig. 2. Effect of different ratios of hydroxypropyl cellulose/Eudragit E100 on (a) the lidocaine release profile (2.5% hydroxypropyl cellulose (dark line), 7.5% Eudragit E100 (broken line), 5.0% hydroxypropyl cellulose/1% Eudragit E100 (●) and 2.5% hydroxypropyl cellulose/7.5% Eudragit E100 (■)); and (b) lidocaine partitioned between the receptor compartment of the Franz cell (black bars) and membranes (grey bars).

Fickian release. Also the higher k value for Ld·HCl is indicative of the burst release.

This can be attributed to the solubility and ionization of Ld·HCl in the ethanol:water (30:70) formulations. Due to these factors, HPC and low concentration of EE100 failed to retard the release of hydrophilic drug (Ld·HCl). Hydrophilic polymer, HPC, provided continuous release of (hydrophobic drug) Ld, whereas the excess amount of water from 30:70 ethanol:water rather than HPC hydroethanolic gel can be attributed to the burst release of Ld·HCl. Furthermore, the hydrophobic polymer EE100 may influence the release of hydrophilic drug, Ld·HCl. The influence of EE100 on Ld·HCl is apparent from Fig. 3c which suggests that almost 10% more of Ld·HCl than of Ld was retained on the membrane. After the burst release of Ld·HCl from the hydroethanolic solution, its release seems to be retarded by the hydrophobic coating of EE100 on the membrane. Both Ld and Ld·HCl released/adsorbed from formulations of fixed concentrations of HPC and EE100, and fixed ratio of ethanol:water. The only difference is the lipophilicity of these drugs. Therefore, different release behaviors of these drugs can be attributed to their log P values. Also from Fig. 1a we know that HPC delays Ld release whereas EE100 provides the burst release of Ld. Thus from Figs. 1a and 3a–c the relationship of log P of drug and hydrophobicity of polymers can be established under given experimental conditions.

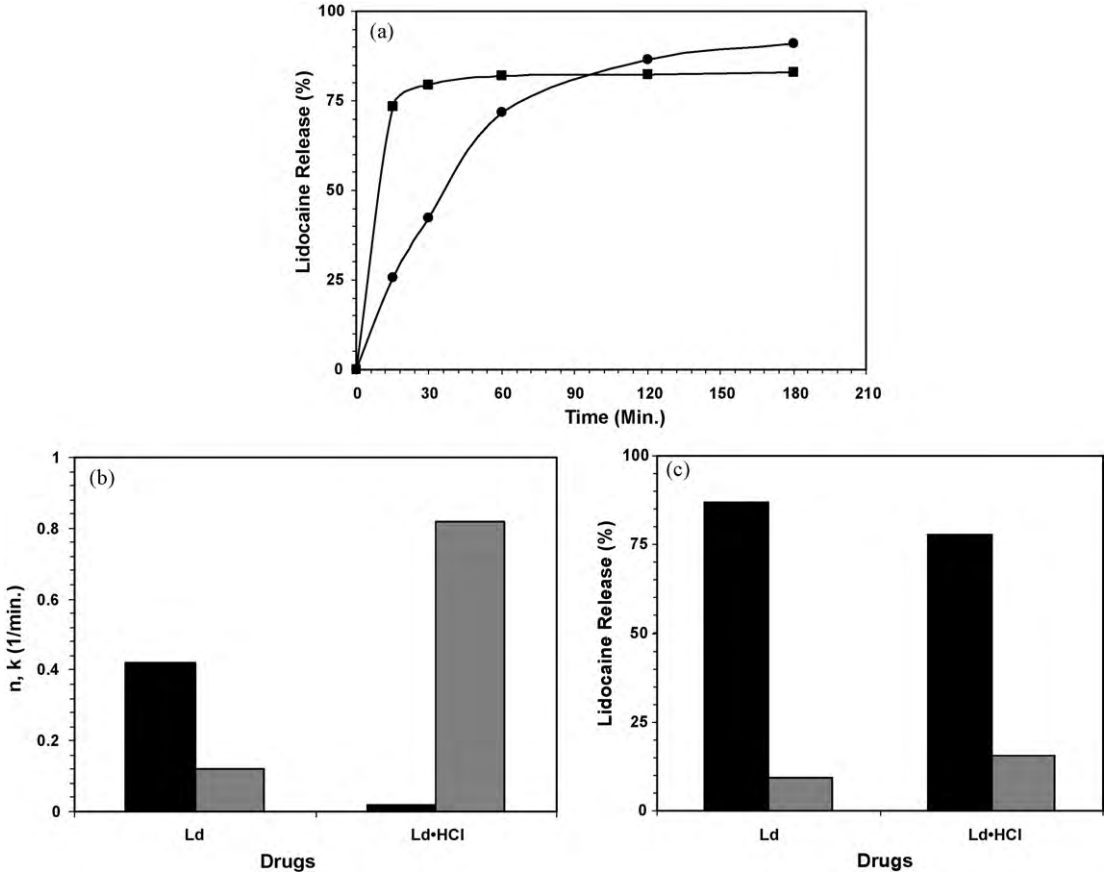

Fig. 3. (a) Release profiles of lidocaine (●) and lidocaine hydrochloride (■); (b) diffusional coefficient, n (black bars) and kinetic constant, k (grey bars) and (c) drugs partitioned between the receptor compartment of the Franz cell (black bars) and membranes (grey bars).

3.4. Effect of solvent lipophilicity on drug release properties

To understand the effect of the solvent lipophilicity on the drug release, ISA is employed. Solvent miscibility experiments showed that a maximum of 1/3 of ethanol can be replaced by ISA in the 30:30 ethanol:water formulations.

Fig. 4a–c is representative of Ld release properties and Ld partition between the membrane and the receptor phase of the Franz cell. As evident from these figures, the partial replacement of ethanol by ISA results in the extended continuous release (~more than 5 h.) of Ld (Fig. 4a), about 30% increase in n values (indicating an increase in non-Fickian transport of Ld), a reduction in k values to about 30% (indicative of slower transport of Ld through PVDF membranes) (Fig. 4b) and Ld accumulation on membranes is approximately doubled (Fig. 4c) as compared to the original ethanol based (non-ISA) formulation. Therefore, the partial replacement of ethanol by ISA may be utilized to transform a systemic formulation into the topical formulation. Note that the accumulation or topical delivery of Ld on the membrane would be different from that observed on the skin model. We assume that the accumulated Ld on membranes in the present study would either penetrate through membrane (or through the skin with time) or remain on the membrane (or on the skin) forever. ISA is a plasticizer and well-known film-former on the surface. Therefore, ISA acts as an additional film-forming component in the formulation, helping to reduce the ethanol concentration and extend continuous release, and retards the Ld release in the receptor phase of the Franz cell.

3.5. Understanding of polymer–drug interactions

To understand polymer–drug interactions, FTIR of Ld with HPC and ES100 was performed. To achieve maximum drug–polymer interactions, Ld was mixed with HPC and ES100 separately, in equal amounts, by dissolving Ld, ES100 in ethanol and HPC in water, followed by mixing of HPC with Ld and ES100 with Ld. Solvents then were evaporated, and the resultant powder was vacuum dried. The dried powder was used to form KBr pellets.

Infrared spectra of HPC, Ld and HPC–Ld (Fig. 5a) depict the formation of a doublet in the range of 3000–3400 cm^{-1} for HPC–Ld mixture. However, such a doublet is not present in the individual IR spectra of HPC and Ld. The formation of a doublet peak is indicative of chemical interactions between HPC and Ld, probably weak H-bonding between –OH group of HPC and –NH group of Ld. Both –OH and –NH bonds have characteristic peaks in the 3000–3400 cm^{-1} range. These interactions, in addition to the viscosity of the formulation imparted by HPC, account for the continuous release of Ld from the HPC formulation.

On the other hand, a mixture of Ld and EE100 (Fig. 5b) does not exhibit a doublet or any shift in other peaks representing interactions between the drug an polymer; therefore, EE100 may not bind the Ld ionically or covalently, accounting for the burst release of Ld from EE100. Also, the burst release of Ld from other Eudragits polymers may also be explained on this basis, as other Eudragit polymers may not have any interactions with Ld.

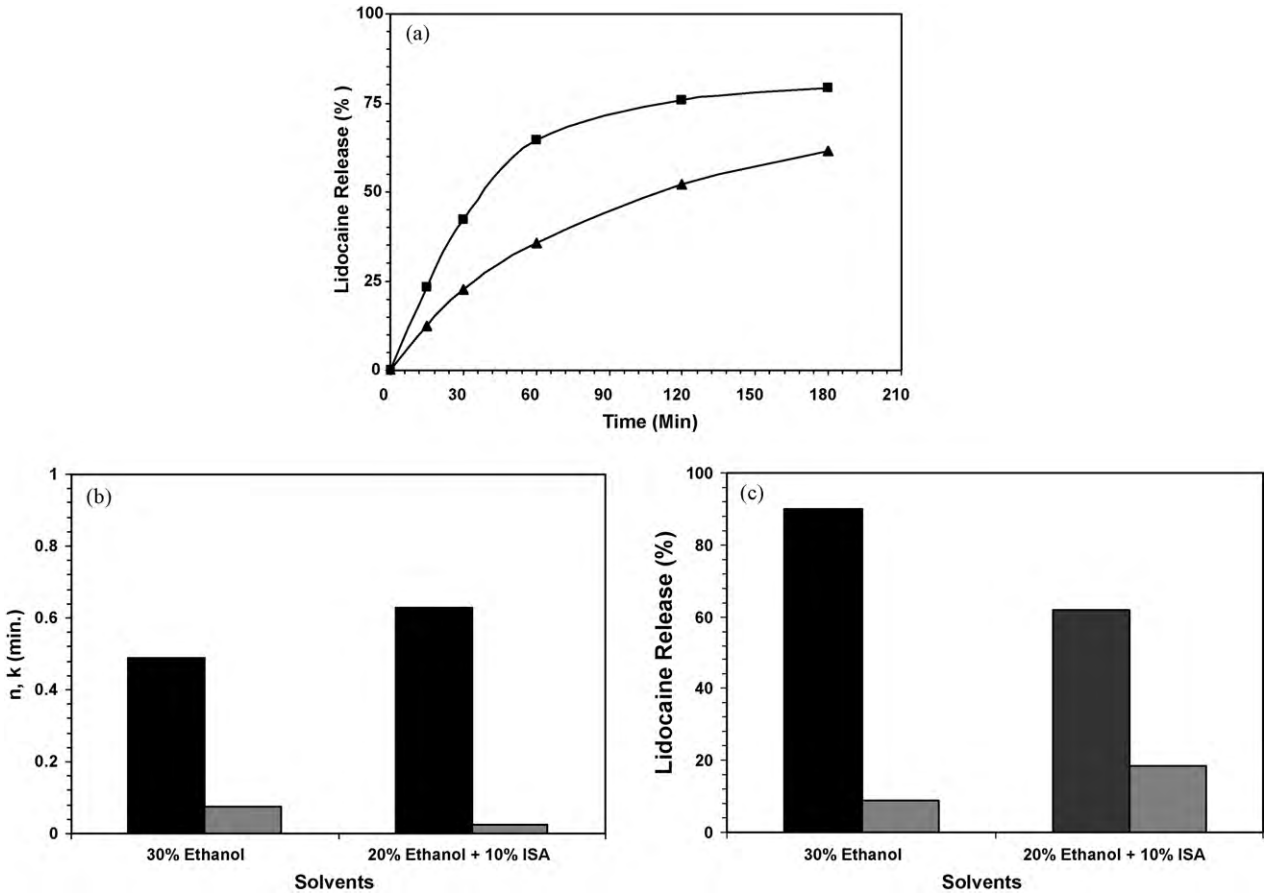

Fig. 4. Effect of solvent lipophilicity on lidocaine release from (a) the 30% ethanol containing formulation (■) and (20% ethanol + 10% isostearyl alcohol) containing formulation (▲); (b) diffusional coefficient, n (black bars) and kinetic constant, k (grey bars) and (c) lidocaine partitioned between the receptor compartment of the Franz cell (black bars) and membranes (grey bars).

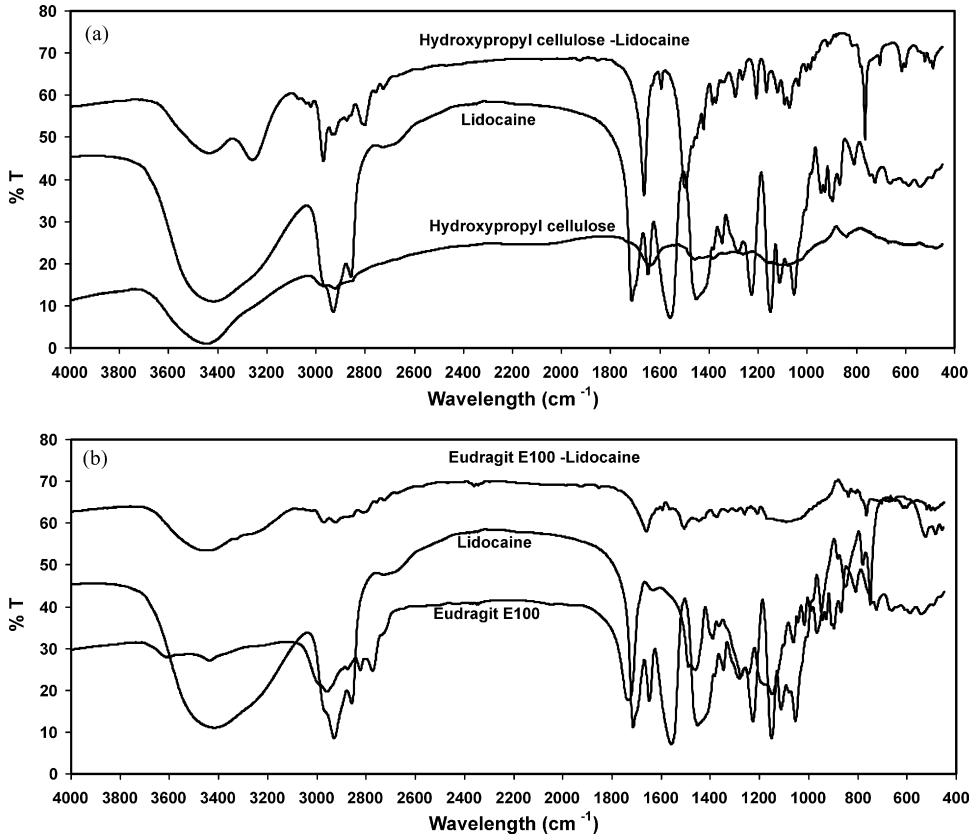

Fig. 5. FTIR analysis of (a) hydroxypropyl cellulose and (b) Eudragit E100 interactions with lidocaine.

4. Conclusions

We demonstrated drug release properties of hydroethanolic gel formulations as a function of drug's lipophilicity ($\log P$), polymer–drug interactions and solvent lipophilicity.

A hydrophilic polymer, hydroxypropyl cellulose (HPC) provides the non-Fickian slower release of the lipophilic drug, lidocaine ($\log P = 2.6$) and the burst (Fickian) release of the hydrophilic drug, lidocaine hydrochloride ($\log P \leq 0$). Thus, $\log P$ of drugs would help to predict the drug release properties.

Hydrophobic Eudragit polymers provided the burst (Fickian) release of lidocaine. However, the cationic hydrophobic polymer (Eudragit E100) retained more Ld (~50%) topically than other hydrophobic polymers: Eudragit S100 (anionic) and Eudragit RLPO (cationic copolymer with quaternary ammonium groups) (~25% lidocaine retention) which release lidocaine systematically. Thus, minute changes in functional groups of hydrophobic polymers help tune the lidocaine release topically or systemically.

An interaction between HPC and lidocaine (FTIR data) helps the non-Fickian slower lidocaine release from HPC formulations. In addition, the absence of an interaction between lidocaine and hydrophobic Eudragit polymers is consistent with the Fickian burst release of lidocaine from their formulations.

A lipophilic solvent, isostearyl alcohol, when it replaces 30% of the ethanol in a hydroethanolic solution, slows the release and enhances the topical adsorption of lidocaine. Thus, solvent lipophilicity also modulates drug release properties.

The present study would help to control the delivery of drugs either topically or systemically and to control the drug release rates based on $\log P$ of drugs, lipophilicity of solvents and drug–polymer interactions. These findings would aid in our understanding of many fundamental issues of pharmaceutical formulations – extending it in new directions – thereby considerably help boosting the quality of pharmaceutical products based on hydroethanolic gels. Furthermore, the present study would help to realize polymer or non-polymer formulations with desired release properties of existing hydrophilic or hydrophobic drugs (e.g. mupirocin or corticosteroids) as well as newly developed drugs. Additionally, it would help reduce dosing amount and time duration, and improve patient compliance.

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