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Drug release from cast films of ethylene vinyl acetate (EVA) copolymer: Stability of drugs by ^{1}H NMR and solid state ^{13}C CP/MAS NMR

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The study utilizes an oral biocompatible material based on ethylene vinyl acetate copolymer (EVA) designed to release drugs *in vitro* at therapeutic levels over several days. We examined the drug stability during film casting process using proton and solid state NMR techniques. The drug-loaded EVA films were prepared from the dry sheet obtained by solvent (dichloromethane) evaporation of polymer casting solutions. Drugs tested include chlorhexidine diacetate (CDA), doxycycline hydrochloride (DOH), tetracycline hydrochloride (TTH) and nystatin (NST). Drug release from the films was examined for at least 14 days in 10 ml ddH_2O (NST in water/ethanol (4:1)) which was replaced daily. Changes in optical density were followed spectraphotometrically. Effect of temperature on rate measurements was studied and the energies of activation (E^*) were calculated using Arrhenius plots. Effect of EVA copolymer composition on CDA release rate was also investigated. The enhanced rates with temperature increase may be attributed to the formation of channels with increased geometry in the polymer. The highest E^* observed for CDA compared to DOH and TTH may be related to their average molecular weights. Spectral analyses for CDA and NST revealed that the chemical and physical structures of the drugs remained unaffected during the film casting process.

1. Introduction

This paper is an extension of our earlier publication dealing with the development of a simple method involving a biocompatible copolymer (ethylene vinyl acetate (EVA)) to deliver drugs of effective concentrations at constant rate for an extended period of time [1].

The use of polymer based drug delivery systems in dentistry is a relatively new area of research with an exception to the release of fluoride ions from polyalkenoate cements and their predecessors silicate cements inhibiting secondary caries and promoting bone growth [2, 3].

The control of *candida albicans* is another area of research, where drug loaded polymeric materials are being used to avoid repeated mouth washes [4, 5]. More recently, certain types of composite filling materials the so-called compomers [6, 7], some orthodontic adhesive resins containing fluorides [8] and a few methacrylate based copolymer systems [1] were reported to release fluoride ions in order to reduce dental caries.

The rationale behind this study is that wide applicability and versatility of thermoplastic material prompted us into optimizing precast EVA polymers as an intraoral drug delivery system. Several oral infectious organisms are protected by the oral biofilm which contains glycocalyx and is highly resistant to antimicrobial, antifungal or antiviral agents delivered systemically [9, 10]. Local drug delivery systems using other vehicles including biodegradable polymers have been successfully developed to manage periodontal infection [11]. However, these delivery systems have not been expanded to incorporate antifungal or antiviral agents and are currently limited to subgingival delivery. The present study was undertaken to overcome some of existing problems.

The main objective of this study was to determine whether a bio-compatible copolymer based on ethylene vinyl acetate (EVA) could deliver drugs of effective concentrations in controlled release for prolonged periods of time. In this study using both proton NMR

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and ^{13}C CP/MAS solid state NMR techniques, we examined whether or not the released drug from drug-loaded films remained unchanged during film casting process. Finally the study also included the effect of copolymer composition on the rate of drug release.

2. Experimental procedures

2.1. Materials

The materials used in this study are detailed in Table I.

Double distilled water for water soluble drugs such as CDA, DOH and TTH, and water/ethanol (4:1) for water insoluble nystatin (NST) as extracting media were used in the present study. All the solution NMR spectra were run in D_2O (99.9%).

2.2. Methods

2.2.1. Preparation of polymer thin films

Drug loaded EVA polymer films were prepared according to the method used in our earlier study [12].

Drug loaded polymer square films (30 mm × 30 mm × 1 mm) were cut from dry films, and a minimum of three separate squares were used to follow the kinetics of drug release. A volume of 10 ml distilled water or water-ethanol system (4:1) was used as the extracting media. Fresh samples of 10 ml of the media were used daily for at least 14 days and the extracts were analyzed in terms of decreases in concentrations by measuring the optical density (OD) spectrophotometrically (Beckman Du® -70 Spectrophotometer) at wavelength where we showed maximum absorption occurred (λ_{max}). The values of average molecular weight and λ_{max} for all the drugs used in the study are summarized in Table II.

TABLE I Material codes and suppliers

Material	Code	Supplier
Chlorhexidine diacetate	CDA	Sigma-Aldrich Chemicals
Doxycycline hydrochloride	DOH	Sigma-Aldrich Chemicals
Tetracycline hydrochloride	TCH	Sigma-Aldrich Chemicals
Nystatin	NYT	Sigma-Aldrich Chemicals
Ethylene vinyl acetate	EVA	DuPont
Dichloromethane	DCM	Mallinckrodt Baker Inc.
Deuterium oxide	D_2O	Sigma

TABLE II Average molecule weight and λ_{max} (maximum absorption wavelength in nm) for the drugs

Drug	Average M. wt	λ_{max} (nm)
Chlorhexidine diacetate (CDA)[a]	626	257.5
Doxycycline hydrochloride (DOH)[a]	481	275.7
Tetracycline hydrochloride (TTH)[a]	481	276.7
Nystatin (NST)[b]	926	306

[a]Water medium.
[b]Water-ethanol (4:1).

The values of λ_{max} for CDA (257.5 nm), DOH (275.7 nm), TTH (276.7 nm) and NST (306 nm) were determined separately by spectral measurements from 220 to 400 nm. Using standard plots between drug concentration and optical density (OD), decreases in drug concentration were determined each day [12].

2.2.2. Time release profiles

Values of near constant release rates of all the three individual drugs were determined using the plots obtained from the drug release at various time intervals (days). The observed drug release profiles conformed to the usual trend representing initially first order followed by zero-order kinetics. A typical drug release

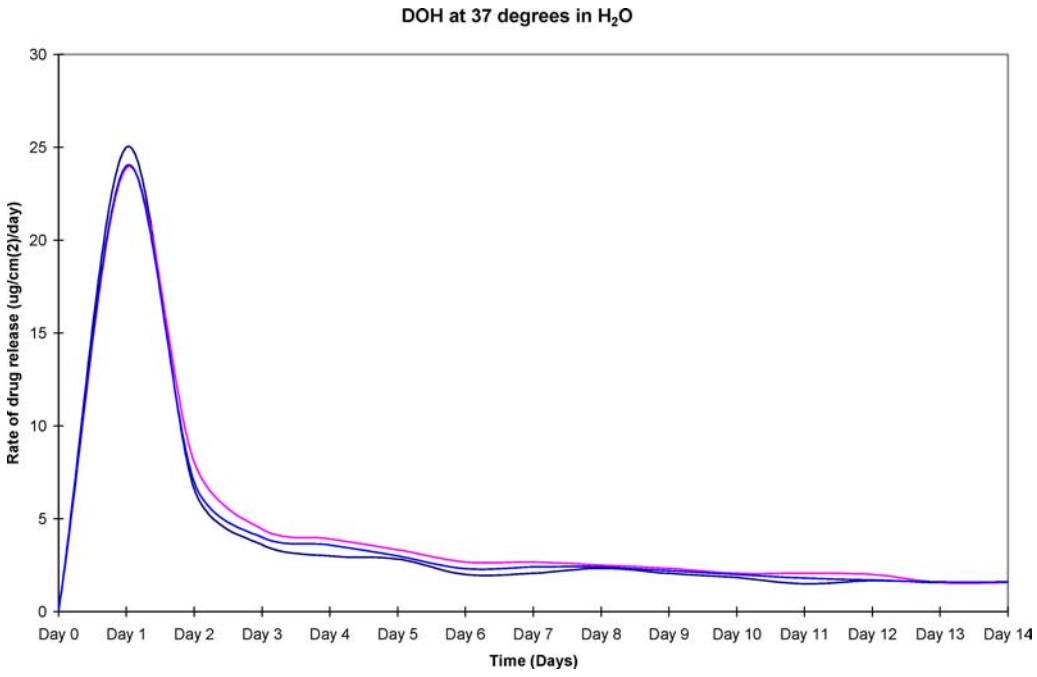

Figure 1 A typical time release profile for doxycycline hydrochloride (DOH) at 37 °C in H_2O.

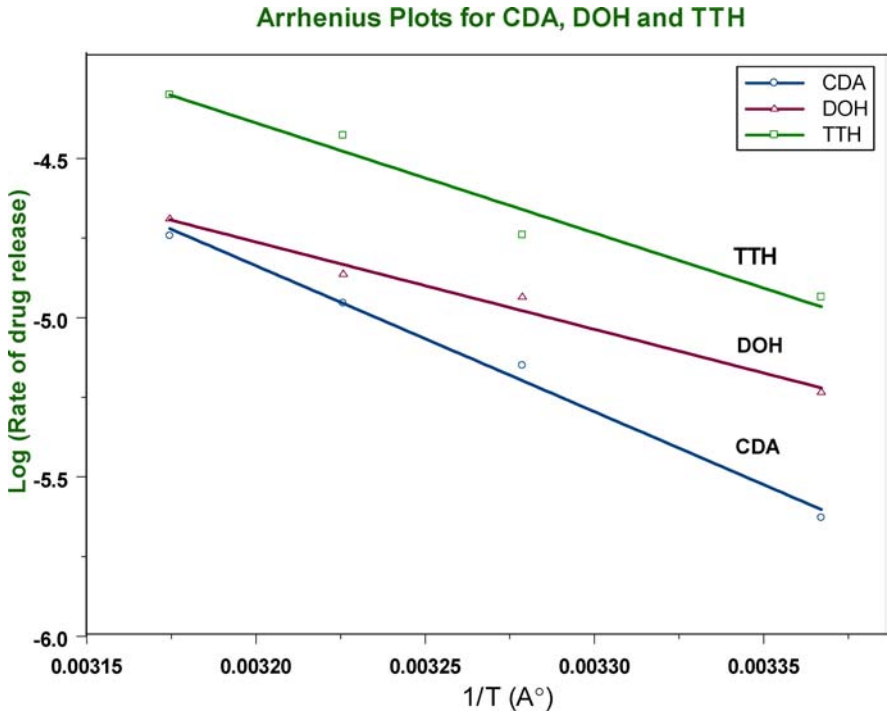

Figure 2 Arrhenius plots drawn between log k vs. $1/T$ for the drugs tetracycline hdrochloride (TTH), DOH and chlorhexidine diacetate (CDA).

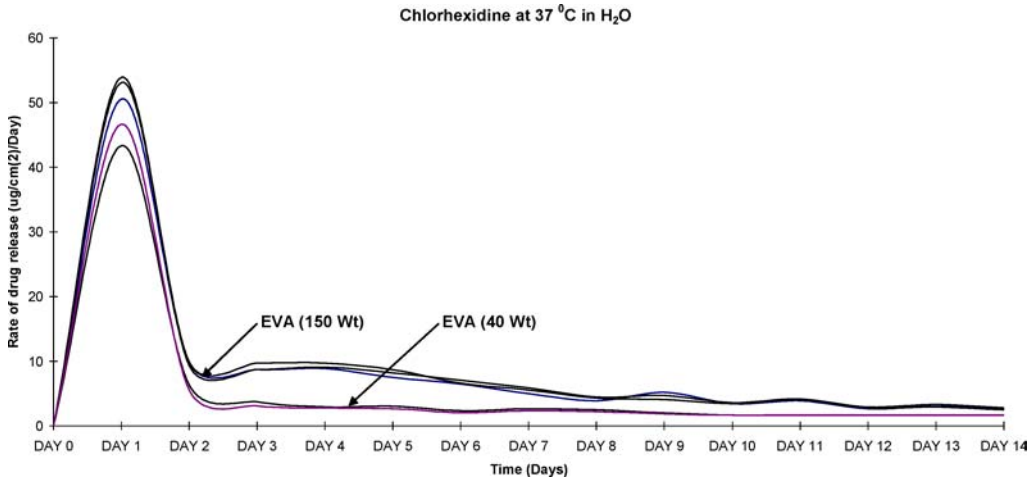

Figure 3 Time release profiles of CDA at two different ethylene vinyl acetate copolymer (EVA) compositions 40 and 150 Wg in water at 37 °C.

profile with reference to DOH at 37 °C is shown in Fig 1. Arrhenius plots drawn between log k vs. $1/T$ for the drugs TTH, DOH and CDA were shown in Fig. 2. Time release profiles of CDA at 37 °C for two different EVA compositions 40 and 150 Wg in water are shown in Fig. 3.

2.2.3. *Stability of drug incorporated into EVA films using proton NMR and ^{13}C CP/MAS + TOSS (Cross Polarization/ Magic Angle Spinning + Total Sideband Suppression) solid state NMR technique*

^{1}H nuclear magnetic resonance (NMR) analysis: CDA was analyzed using solution ^{1}H-NMR spectrometer (Bruker DRX-400) to determine the stability of drugs extracted from films.

Single-resonance, solution ^{1}H NMR spectra were collected (Fig. 4(a)–(c)). Figs 4(a)–(c) represent spectra respectively of EVA, CDA alone and CDA extracted from the drug loaded film. The spectrometer, (Bruker DRX-400) operated at 400 MHz, proton. The temperature was 293.0 K and 22.5 μs was required for a 90 ° pulse. In both cases, the solvent was D_2O. In these spectra, signal intensity is plotted versus the chemical shift, measured in ppm. The chemically different protons (^{1}H nuclei) in the sample resonate at different frequencies because they are shielded more or less by the electrons that surround them. The NMR spectrum is treated like a fingerprint of the chemical structure of the molecule. The strong line at ∼4.65 ppm in both spectra arises from the small amount of residual HDO in the solvent. If H_2O is used as solvent, instead of D_2O, the corresponding line would be so large that it would obscure the spectrum of the analytical sample.

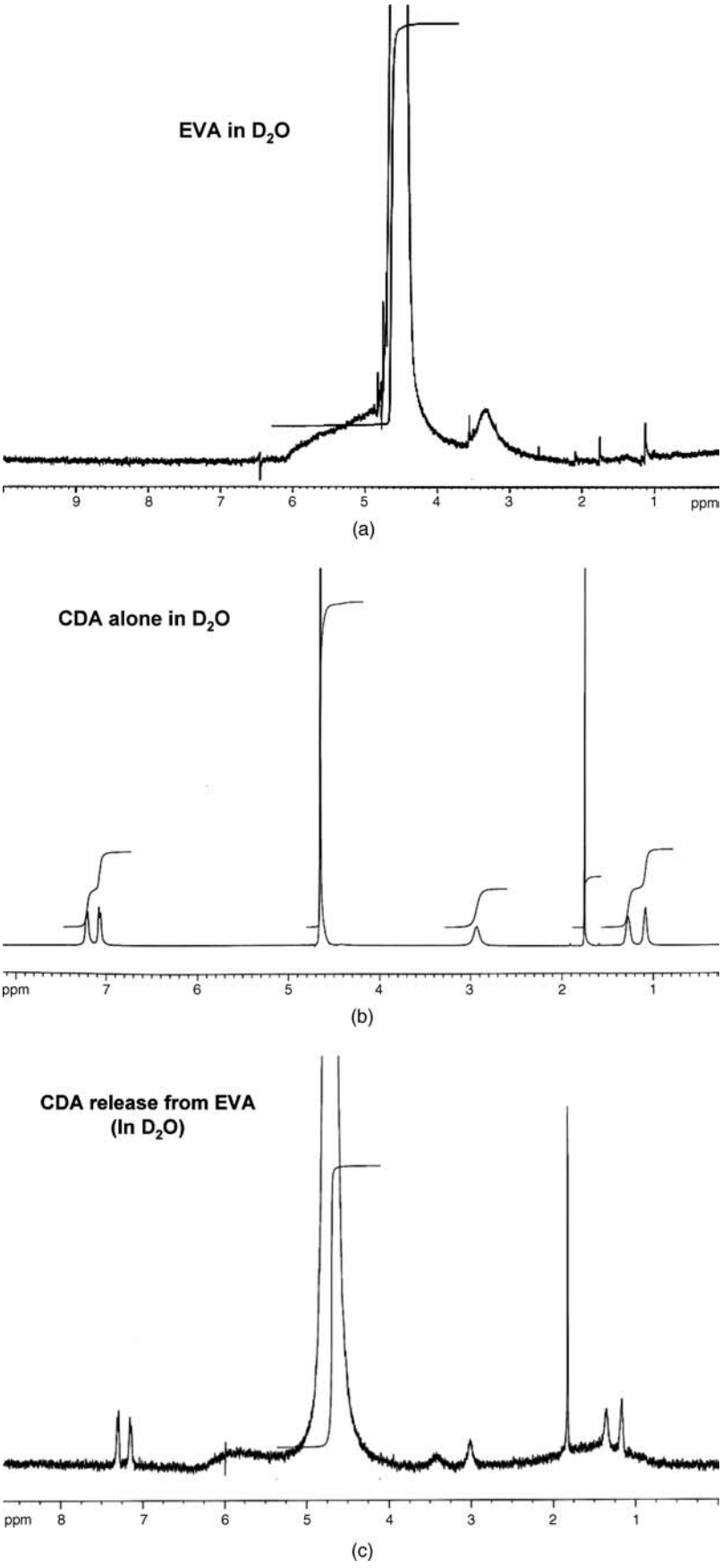

Figure 4 ^{1}H NMR solution spectra in D_2O of EVA (Fig. 4(a)); CDA alone (Fig. 4(b)); CDA released from EVA (Fig. 4(c)).

2.2.4. 13C CP/MAS solid state NMR spectral analysis

^{13}C CP/MAS solid state spectra were obtained for EVA film (Fig. 5(a)), NST alone (Fig. 5(b)), and nystatin loaded EVA film (Fig. 5(c)) using the Bruker DSX300 (300 MHz proton, 75 MHz carbon) with 7 mm rotor. All the spectra were run using CP/MAS + TOSS while spinning at 5.000 kHz. All the spectra of the films

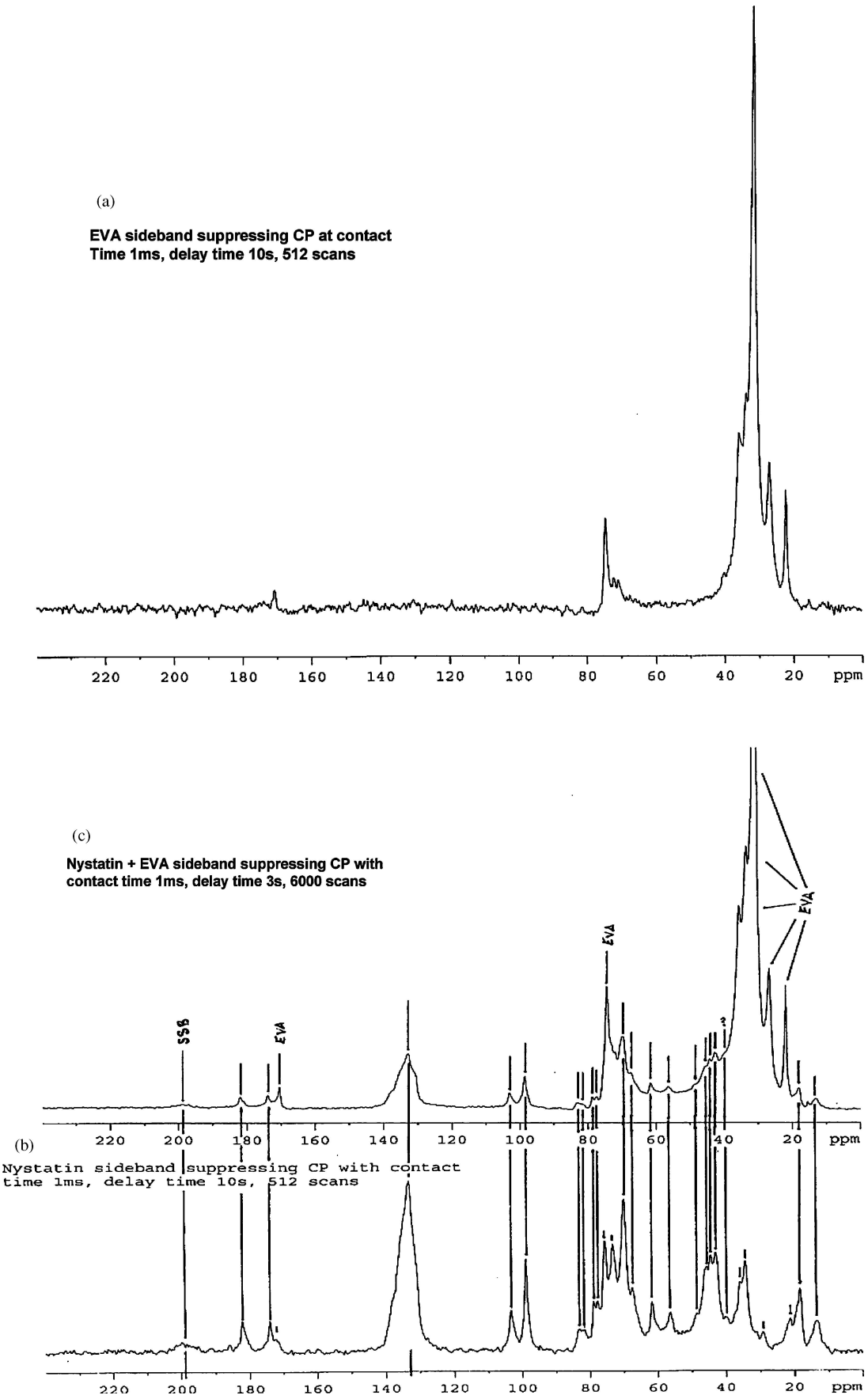

Figure 5 Spectra of ^{13}C CP/MAS solid state NMR of EVA (Fig. 5(a)); Nystatin alone (Fig. 5(b)); Nystatin + EVA (Fig. 5(c)).

were run with the same contact time (1 ms) in order to favor proton-carbon magnetization transfer in rigid molecules such as NST. In other words, a short contact time makes the experiment preferentially sensitive to the more rigid NST which is then more visible against the EVA background.

2.3. Statistical analysis

Two-way analysis of variance was applied to rate data extractable drug release versus time transformed to the log scale to achieve approximate normality and variance homogeneity. The main effects of drug and temperature as well as their interaction were assessed with statistical significance defined at the .05 level. Pairwise comparisons among drugs and different levels of temperatures were assessed with Bonferroni adjustment for multiple comparisons.

3. Results

The values near constant release rate in water as extracting medium for a minimum of 14 days and energies of activation (E^*) of CDA, DOH and TTH at four different temperatures, i.e., 24, 32, 37 and 47 °C, are shown in Table III. These rate measurements were extended to include NST at 24 °C in water/ethanol (4:1) medium. Water/ethanol (4:1) medium system was used as the NST is insoluble in aqueous medium. The near constant rate of drug release value was determined to be 0.21 ± 0.01 μg/cm^2/day at 24 °C for NST.

Fig. 1 represents a typical time release profile for DOH involving commonly observed initial "burst" followed by a pattern showing near constant rate of drug release.

The following three equations were used in the determination of E^*, the energy of activation. E^* is defined as the energy required to overcome the "energy barrier" for diffusion or translocation of the drug molecules through the channel present in the polymer matrix.

$$\text{Log}k = \log A - E^*/(2.303 \times RT) \quad (1)$$

$$\text{Slope} = -E^*/2.303 \times 1.987 \quad (2)$$

$$\text{Activation energy} E^* = (\text{Slope} \times 2.303 \times 1.987) \quad (3)$$

where k is the rate of chemical process, A is the frequency factor, E^* is the energy of activation (cal·mole^{-1}), T is the absolute temperature and R is the gas constant (1.987 cal·degree^{-1} mole^{-1}).

Fig. 2 represents Arrhenius plots were drawn between log k vs. $1/T$ at 24, 32, 37 and 47 °C for all the three drugs i.e. CDA, DOH and TTH (see the Equation 1). Slopes of these plots are used in Equations 2 and 3 to calculate E^*.

Even though the mean rate data in Table III show a consistent pattern (they increase from left to right within rows and increase from top to bottom within columns), the two-way ANOVA resulted in a statistically significant interaction between drug and temperature. Accordingly, pairwise comparisons among drugs are made separately for each temperature level, and similarly, pairwise comparisons among temperature levels are made for each drug separately. In total, 30 pairwise comparisons are made with a Bonferroni adjusted p-value of $.05/30 = .0017$ defining statistical significance. For CDA, all six possible pairwise comparisons of temperature level were statistically significant. The same held for TTH. For DOH, 5 of 6 pairs were statistically different; rates at temperature levels of 32 and 37 °C were only marginally significantly different from one another ($p = .0241$). For temperature of 24 or 32 °C, each of the three drug pairs had statistically significantly different rates. For temperature of 37 °C, TTH differed statistically from both CDA and DOH. However, CDA and DOH were only marginally significantly different ($p = .0077$). For temperature of 42 °C, rates for TTH differed statistically from both CDA and DOH. However, CDA and DOH were not significantly different ($p = .0891$). Rate measurements for CDA at two EVA copolymer compositions i.e. 40 and 150 Wg (DuPont Grade) and the corresponding time release profiles at 37 °C were shown in Table IV and Fig. 3.

3.1. ^{1}H NMR spectral analysis

Three ^{1}H NMR solution spectra with the complete analysis of the leaching of CDA from EVA film were collected. First we have a spectrum in D_2O of whatever leaches out of uncompounded EVA film (Fig. 4(a)). Then we have a spectrum of CDA in D_2O before it is introduced into the film (Fig. 4(b)). Finally there is a D_2O spectrum of the substances that leach out of EVA film compounded with CDA (Fig. 4(c)). It is to be noted that Fig. 4(c) represents the spectrum of released CDA from EVA obtained after

TABLE III Values of near constant release rates in water at 24, 32, 37 and 42 °C and energies of activation (E^*) with reference to CDA, DOH and TTH

	Rate in water (μg/cm^2 per day) [b]				
Drug[a]	24 °C	32 °C	37 °C	42 °C	E^* (kcal/mol)
CDA	0.53 ± 0.01	1.90 ± 0.39	2.52 ± 0.12	4.07 ± 0.08	20.69
DOH	1.31 ± 0.04	2.61 ± 0.15	3.08 ± 0.08	4.60 ± 0.03	12.56
TTH	2.57 ± 0.12	4.09 ± 0.16	8.41 ± 0.40	11.26 ± 1.98	15.83

E^*: Energy of Activation (calculated from slopes of Arrhenius plots).
[a]Drug in EVA (2.5%).
[b]Rate was expressed in terms of mean (SD).

TABLE IV Effect of EVA copolymer composition on the rate of CDA release at 37 °C in water

Grade	EVA copolymer composition (wt%)	Rate of CDA release (μg/cm^2/day)
40 Wg	40 vinyl + 60 ethylene	2.52 ± 0.02
150 Wg	32 vinyl + 68 ethylene	5.45 ± 0.05

subtracting the spectrum (Fig. 4(a)) collected for EVA. This allows us to have a spectrum due only to the released drug alone and eliminates signals due to impurities leached out from EVA and the signal due to HDO present in D_2O.

3.2. ^{13}C CP/MAS solid state NMR spectral analysis

Figs. 5(a), (b) and (c) represent the spectra collected for EVA (Fig. 5(a)), NST alone (Fig. 5(b)) and NST-loaded EVA (Fig. 5(c)).

The following three spectra were collected: (1) EVA film, 512 scans with a recycle time of 10 s (Fig. 5(a)); (2)Nystatin powder, 512 scans with a recycle time of 10 s (Fig. 5(b)); (3) EVA film with 11% added Nystatin, 6000 scans with a recycle time of 3 s (Fig. 5(c)). The 7 mm rotor held 320 mg of this film. The EVA film shows 9 distinct peaks, including a small one at 170 ppm. This arises from the >C=O in the acetate. The Nystatin powder shows 27 distinct peaks. The EVA/Nystatin film shows 7 distinct peaks attributable to EVA and 20 distinct peaks attributable to the Nystatin. The spectral overlap is too great in the regions around 30, 75 and 170 ppm to separate the two spectra. That is where all the lost lines fall. Many of the Nystatin peaks are quite small. This same study on a film with less than 2.5% Nystatin would probably not show more than 2 or 3 Nystatin peaks. If 2.5% film was placed in a smaller volume rotor, the NST might not be visible at all. In the spectrum of nystatin incorporated in EVA film (Fig. 5(c)) resonances were identified with chemical shifts similar to the NST alone (Fig. 5(b)). A comparison of both the spectra (Fig. 5(b) and (c)) revealed that the match between the relative intensities and the line shapes is quantitatively convincing, suggesting that both the chemical and physical structure of NST remains unaffected during the film casting process.

4. Discussion

This study demonstrates that each of these therapeutic agents shows a sustained rate of drug release from EVA over extended periods of time and that the drug remained unaffected during film casting process. This study also shows that the rate of drug release increases with the increasing temperatures. Energy of activation (excess energy required by a drug molecule to surmount the energy barrier before the diffusion or translocation occurs in the polymer matrix through the channel) was also discussed.

Rate data presented here are based on the part of the curve after the onset of initial burst. The initial burst is attributed to the surface-bound drug [13–17]. Release profiles usually reveal an initial "burst" of drug at short intervals followed by a longer period of continuous release. The initial drug "burst" is due to the porosity present in the matrix or liberation of surface-bound drug [18, 19]. However, the release characteristics can be controlled through proper device design. Constant release of a drug, without an initial burst can often be achieved by appropriate selection of polymers and fabrication methods [14–17]. In many therapeutic programs, the rate of release should be relatively constant or a zero order time dependence, that is, the rate of release is independent of time [16–18].

4.1. Effect of the temperature

It is generally known that increase of temperature invariably results in an increase of rate of diffusion of molecules either in liquids or in solids [20, 21]. The same observation can be extended to include drug delivery process involving the diffusion (translocation) of the drugs through the channels in thin polymer films when immersed in extracting medium. Consistent with this, it is seen in Table III that all the drugs studied exhibited an increase in rate values with increasing temperature from 24 to 42 °C for the diffusion of drug molecules in EVA polymer matrix. A useful rough generalization is that the rate is doubled by a rise in temperature of 10 °C [20]. In accordance with this, it was seen that the rate of drug release was almost doubled by a rise in temperature from 32 to 42 °C (Table III, column 3 & 5). This may be attributed to the enhanced diffusion of drug molecules through the channels at higher temperature leading to relatively higher rates. Among all the drugs studied, TTH exhibited the highest near constant rate of release value (8.41 μg/cm^2 per day) at body temperature (37 °C) and that CDA showed the least value of drug release (2.5 μg/cm^2 per day). Similar trend was observed with reference to the values obtained for all the three drugs studied at temperature 24, 32, 37 and 42 °C.

Among the critical factors that are responsible for the diffusion of drug molecules in the polymer matrix, drug particle size, geometry, drug-drug interactions, drug-polymer matrix interactions, length and size of the channel, play a major role in the translocation of these drug molecules. The rate at which drug molecules diffuse through the channels [3] or interconnecting porous network [22, 23] of the polymer matrix, can be increased by decreasing the average molecular weight of the drug in the polymer matrix [24].

It was seen from the analysis of the values of E^* (Table III) that the energy associated with diffusion of CDA molecules through the channels was found to be 20.69 k·cal/mole compared to DOH (12.56 k·cal/mole) and TTH (15.83 k.cal/mole). The relatively higher value of E^* for CDA is perhaps due to its average molecular weight of 626 which is higher than those for TTH (481) and DOH (481) (see Table II). As the latter two drugs have almost similar values of average molecular weight (481), one needs to explain the difference in the E^* values obtained for the two drugs in terms of sizes of the drug molecules which may be

undergoing association leading to dimerization or trimerization. In order to explain the observed energy differences, it was speculated that more TTH molecules were involved in association process relative to DOH molecules. For larger size molecule to diffuse (translocate) through a given geometry of channels, more energy is required to surmount the "energy barrier", resulting in a higher energy of activation of 15.83 k.cal/mole than that for DOH (12.56 k·cal/mole). In other words, when the size of the molecule due to association increases, energy required for the diffusion (translocation) of the drug molecules is higher as was seen in case of TTH (15.83 k·cal/mole).

4.2. Effect of EVA copolymer composition

Analysis of data in Table IV strongly indicated that a change in the composition of EVA copolymer from 40 to 150 Wg resulted in an increase of rate of CHD release by a little more than two times. There are several factors that are responsible for the observed enhanced rates of diffusion of molecules when composition is changed, drug solubility in one of the component polymer of the copolymer system is perhaps the most important factor responsible for setting up a concentration gradient between copolymer matrix and the surrounding extracting medium. This results in a rapid diffusion (translocation) of drug molecules through the channels formed due to the interconnecting pores in the polymer matrix. Consistent with this and more strikingly enough, the observed increase in rate value is perhaps due to the greater solubility of CDA in one of the component polymer of EVA, i.e., ethylene polymer component relative to vinyl acetate component. This facilitates a rapid diffusion of the drug molecules.

4.3. Results of ^{1}H NMR and ^{13}C CP/MAS solid state NMR spectral analysis

A comparison of relative intensities and the ^{1}H chemical shifts of spectra obtained for solution of EVA (Fig. 4(a)), CDA alone (Fig. 4(b)) and CDA + EVA (Fig. 4(c)) suggest strongly that the chemical structure remained unaffected during the film casting process. In other word, this spectrum (Fig. 4(c)) is so nearly a simple addition of the two previous spectra (Fig. 4(a) and (b)) that no further analysis is necessary to conclude that the CDA comes out of the film with the same structure as the one that was incorporated into EVA.

A further confirmation that the extractable drug is unchanged comes from studies showing that the drug is effective as antimicrobial/antifungal agent.

In the solid-state spectra of (EVA: Fig. 5(a); NST: Fig. 5(b); NST+EVA: Fig. 5(c)) there is similar correspondence between the spectra. Judging from the similarity between the lines (both shape and position) in the NST powder and in the mixture, it is suggested that the NST is dispersed in the film as small crystallites rather than in a true solid solution. This phase separation probably occurs during the last part of the drying process.

5. Conclusions

1. NMR spectral analysis of drugs extracted from polymer films suggested that the chemical structures and all the drugs studied remained unaffected during film casting process and release. A further confirmation stems from studies showing that the drug is effective as antimicrobial, antifungal an antiviral agent.

2. Among all the drugs investigated, TTH loaded EVA samples exhibited the highest near constant rate of release values.

3. The activation energy (E^{*}) required for the translocation (diffusion) of CDA molecules was found to be the highest of the drugs tested.

4. Changing the composition of EVA copolymer from 40 wt% vinyl to 32 wt% vinyl component resulted in an increase in the rate of release of CDA by about a factor of two.

6. Significance

Significant feature of this polymeric system is that the use of EVA-based materials as a deliver system has structural integrity that promotes longer oral drug delivery by serving as prosthetic or removable appliances. Furthermore, the development of a novel delivery system will permit the use of specific topically active agents that are not absorbed by the gastrointestinal tract and that can not be easily delivered intraorally over a prolonged period of time due to salivary clearance. Rate of drug release can easily be altered by simply changing the composition of EVA copolymer. Finally drug stability remains unchanged physically and chemically during casting process of this dental prosthesis. Such a new delivery system would provide optimal pharmacokinetic and pharmacodynamic drug release. The study has a great clinical potential in providing useful treatment strategies for oral diseases.

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