The Effect of Isopropanol Addition on Enhancement of Transdermal Controlled Release of Ibuprofen from Ethylene Vinyl Acetate Copolymer Membranes

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ABSTRACT: This work reports the study of the addition of isopropanol on controlled release of ibuprofen from ethylene vinyl acetate (EVAc) copolymer membranes. An EVAc solution in cyclohexane (4% w/v) containing triethyl citrate (7% w/v) as plasticizer was mixed with ibuprofen at three different concentrations of 4, 6, and 8%. Isopropanol was mixed with each of the previous mixtures to form solutions of 1, 3, and 5% isopropanol concentrations. Samples were solvent cast on glass petridishes to form membranes. Home-made diffusion cells were used for *in vitro* study. These cells were composed of two compartments, donor (exposed to ambient conditions), and receptor (including buffer solution maintained at 37°C). Each cell was equipped with a sampling port and water in and out system. An ultraviolet spectrometer at 222 nm was used to measure release rates of obtained membranes. The diffusion mechanism for drug release was examined by zero-order, first-order, Higuchi and Korsmeyer-Peppas theories to confirm the obtained membranes follow the matrix-type system. By increasing the drug concentration from 4 to 8%, drug release (cumulative amount) was improved from 20 (47.5%) to 30 (36%) μg/cm^2 after 24 h. Addition of 5% isopropanol to the above samples (4 and 8% loading) further increased drug release to 24 and 43 μg/cm^2. Results were in good agreement with the Korsmeyer-Peppas theory for samples with 4 (% w/w) of ibuprofen. The highest percentage of drug release after 24 h was 59% for the sample with 4% drug loading compared to 50% for the sample with 8% drug loading, both with 5% isopropanol. J Appl Polym Sci 122: 3048–3054, 2011

Key words: ethylene vinyl acetate copolymer; ibuprofen; transdermal controlled release

INTRODUCTION

Transdermal drug delivery systems have been introduced for controlled release of drugs that need to be used for a long time. Transdermal delivery has many advantages over conventional modes of drug administration; in particular, it avoids hepatic first pass metabolism and improves patient compliance.[1]

Intensive research has shown that the transdermal route is a potential mode of delivery of lipophilic drugs.[2] Ibuprofen is a lipophilic and nonsteroidal anti-inflammatory drug (NSAID) that is used in the management of mild to moderate pain and inflammation for conditions such as musculoskeletal and joint disorders, rheumatoid arthritis and soft-tissue disorders such as sprains and strains and it is degradable in the liver.[3] Oral administration of ibuprofen has adverse effects on the gastro-intestinal tract. Ibuprofen and other NSAIDs can cause dyspepsia, nausea, and vomiting, gastrointestinal bleeding, and peptic ulcers and perforation (USP 28). Therefore, the development of a transdermal drug delivery system for ibuprofen without the adverse effect of frequent oral administration is important. It has been shown that the concentration of ibuprofen after transdermal administration in synovial fluid, muscle, and subcutaneously is more than that in plasma.[4]

Polymeric matrices are a way of controlling drug release rate for a long time. In a matrix type device, drug is dispersed or dissolved in an inert polymer and diffuses through the polymer matrix.[5,6]

Ethylene vinyl acetate (EVAc) copolymer has been known as a biomaterial for artificial hearts and as an antithrombogenic material. It is a heat processable and inexpensive material whose properties can be changed by varying the content of vinyl acetate or by adding plasticizer.[7,8]

The rate and mechanism of drug release from membranes can be predicted from different models such as those by Higuchi,[9,10] and Korsmeyer and Peppas.[11,12]

In this study, the release of ibuprofen from the EVAc matrix were evaluated and the effect of isopropanol on

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TABLE I
Membranes with Different Drug and Isopropanol Loadings

Isopropanol (% v/w)	Ibuprofen (% w/w)	Formulation Number
0	4	C40
1	4	C41
3	4	C43
5	4	C45
0	6	C60
1	6	C61
3	6	C63
5	6	C65
0	8	C80
1	8	C81
3	8	C83
5	8	C85

the membrane structure as an enhancer on release rate of ibuprofen were investigated.

EXPERIMENTAL

Materials

Ethylene-vinyl acetate copolymer with 28% vinyl acetate was obtained from Hyundai Seetec, Korea. Cyclohexane (solvent), triethyl citrate (TEC, plasticizer), potassium dihydrogen phosphate (PDHP), and sodium hydroxide (NaOH) were purchased from Merck (Germany), with PDHP and NaOH used to produce phosphate buffer saline based on USP 28 instructions. Dialysis tubs with 32 mm diameter were purchased from Sigma (Germany). Ibuprofen was donated by Rouzdarou Pharmaceutical (Iran). Isopropanol was purchased from Scharlua (Spain) and was used to increase the ibuprofen solubility. Acronal® V210, a 70% aqueous dispersion of carboxylated copolymer based on acrylate in combination with vinyl acetate, was obtained from BASF (Germany) for use as an adhesive. A transparent film made of polyurethane, as a backing layer, was donated by ChitoTech (Iran).

Drug-containing EVAc matrix preparation

EVAc matrix containing ibuprofen was prepared by a solvent casting process. Briefly, 2 g of EVA polymer beads were dissolved in 50 mL cyclohexane in a beaker with vigorous stirring. TEC (0.14 mL), as a plasticizer, was dissolved in this polymer solution as well. Drug loading weights were varied from 4 to 6 and 8 wt %. Isopropanol was mixed with the previous mixture to form solutions of 1, 3, and 5% isopropanol concentrations for each ibuprofen concentration.

The above solutions were poured onto a glass plate and the solvent was allowed to evaporate at 25°C in oven for 28 h. The matrix was removed from the petri-dish and dried at room temperature for 12 h. The thickness of the matrices were measured randomly at 10 points using a micrometer to test uniformity in the thickness (132 ± 12 μm) for all concentrations.

A pressure sensitive adhesive (Acronal®) was applied uniformly over the EVAc matrix with help of a film applicator with 75 mm gap width, and allowed to dry in the air at room temperature (25°C). The thickness of the adhesive itself was measured randomly at 10 points using a micrometer (20 ± 6 μm). A backing layer of polyethylene was

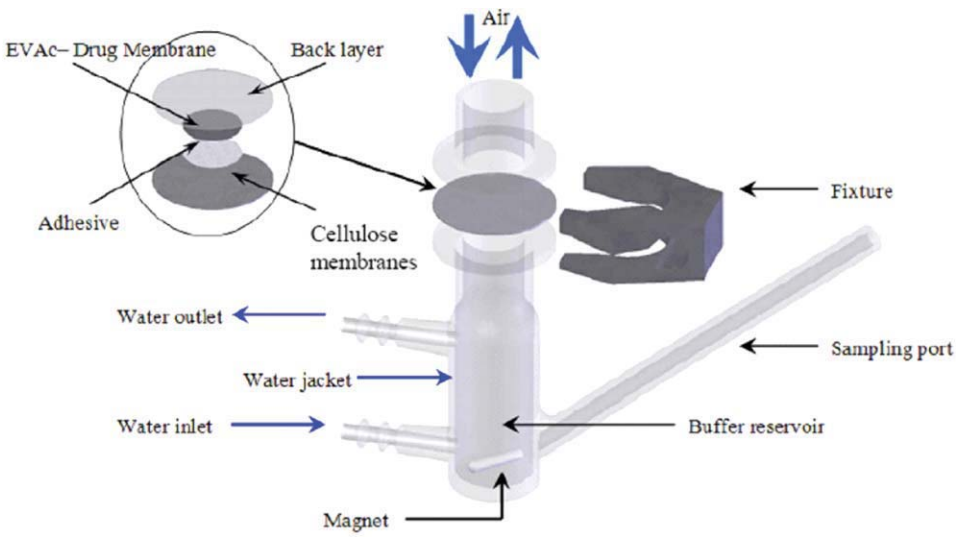

Figure 1 Diffusion cell used to measure drug release. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

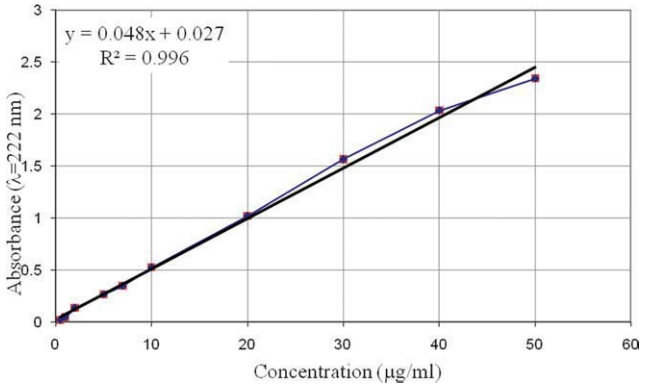

Figure 2 Calibration curve at different ibuprofen concentrations (0.5–50 µg/mL) in phosphate buffer at pH = 7.4, after 24 h dissolution in a shaking instrument at 37°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

adhered to the other side of the matrices. Table I shows the prepared membranes formulation at different drug loading and isopropanol concentrations.

In vitro release studies

The *in vitro* release of ibuprofen from the EVAc matrix was examined for 24 h by using a modified Franz diffusion cell.[13,14] Three diffusion cells (Fig. 1) including donor (exposed to ambient condition), and receptor (including buffer solution maintained at 37°C) compartments were built in house. These cells were equipped with double walls (water jacket), sampling port, and water in and out system. They were mounted on stirrers and piped to a water bath for temperature control.

EVAc membranes were cut in circular shape (2.5 cm^2) and placed in the diffusion cell. Cellulose membranes with molecular cut-off of 12,000 Daltons were used to prevent direct contact between the receptor compartment and the membranes. The cellulose membranes were cut to EVAc membrane size and allowed to soak overnight in buffer solution. The buffer solutions were continuously stirred with small magnetic bars to homogenize the temperature at 37°C with the circulating water jacket. At predetermined time intervals, 0.2 mL samples were withdrawn from the receptor compartment and replenished with fresh medium. An ultraviolet spectrometer (Milton Roy Spectronic 601) set at 222 nm, the value for the maximum absorption in the 200–300 nm wave length range, was used to measure the release data. A calibration curve (Fig. 2) was determined at different ibuprofen concentrations (0.5–50 µg/mL) in phosphate buffer at pH = 7.4, after 24 h dissolution in a shaking instrument at 37°C. The ibuprofen concentration in the solution was corrected for sampling

TABLE II
Applied Release Models

Model	Equation
Zero-order	$M_t = M_0 + k_0 t$
First-order	$M_t/M_\infty = (1/e^{\infty k_f t})$
Higuchi	$M_t/M_\infty = k_H \times t^{1/2}$
Korsmeyer-Peppas	$M_t/M_\infty = k \times t^n$

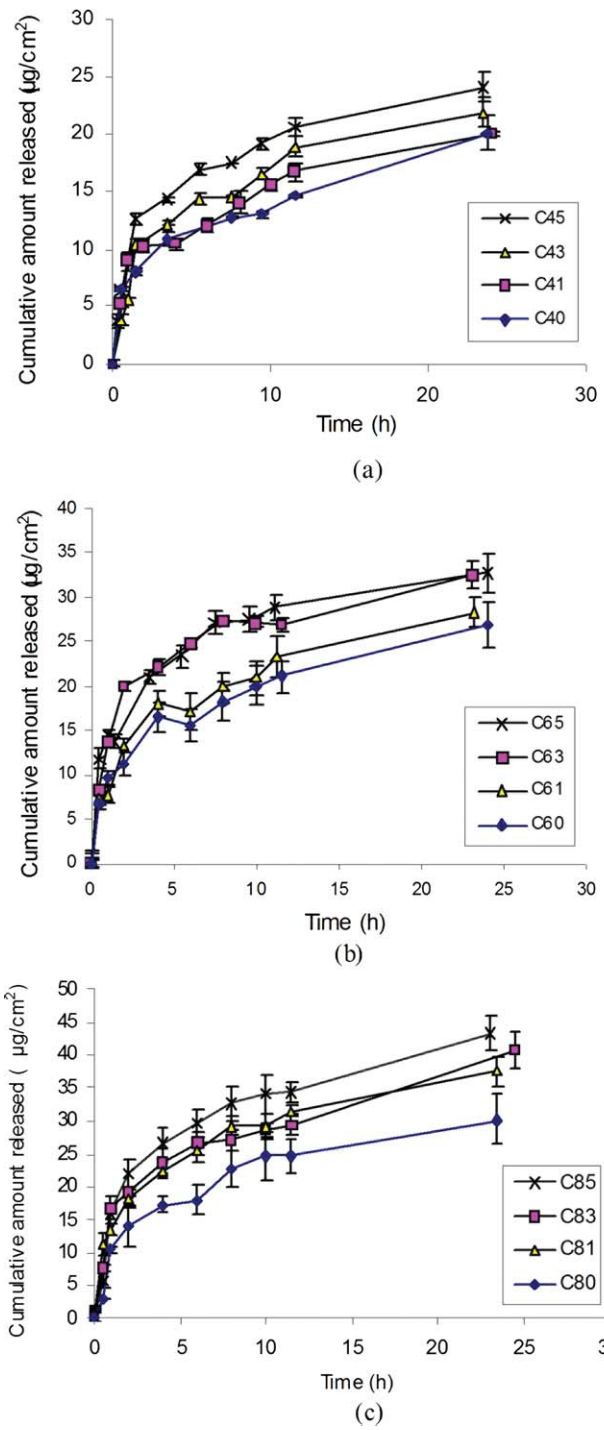

Figure 3 Drug release profiles of samples loaded with 4% (a), 6% (b), and 8% (c) of ibuprofen at different concentrations of isopropanol. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE III
Fitting Results of the Experimental Ibuprofen Release Data to Different Kinetic Equations, for Several Formulations

	Zero-order		First-order		Higuchi		Korsmeyer–Peppas		
	k_0	R^2	k_f	R^2	k_H	R^2	n	k	R^2
C40	0.68	0.80	0.04	0.85	0.10	0.89	0.28	1.79	0.97
C41	0.68	0.74	0.04	0.69	0.11	0.85	0.31	1.79	0.94
C43	0.83	0.74	0.06	0.57	0.12	0.91	0.44	1.97	0.92
C45	0.89	0.69	0.06	0.52	0.13	0.86	0.40	1.74	0.93
C60	0.94	0.77	0.05	0.72	0.07	0.90	0.34	2.22	0.98
C61	1.12	0.62	0.04	0.53	0.1	0.75	0.33	1.88	0.91
C63	1.05	0.75	0.05	0.67	0.08	0.91	0.37	2.22	0.96
C65	1.10	0.64	0.04	0.66	0.10	0.76	0.29	1.81	0.97
C80	1.17	0.74	0.07	0.48	0.07	0.92	0.52	2.60	0.86
C81	1.33	0.73	0.05	0.70	0.09	0.87	0.33	1.94	0.99
C83	1.34	0.73	0.05	0.58	0.09	0.86	0.36	2.00	0.90
C85	1.62	0.71	0.06	0.49	0.11	0.88	0.46	2.07	0.87

effects,[15] according to the equation described by Hayton and Chen[16]:

$$C_n^1 = C_n[V_T/(V_T - V_S)](C_{n-1}1/C_{n-1}) \quad (1)$$

where C_n^1 is the corrected concentration of the nth sample, C_n is the measured concentration of ibuprofen in nth sample, C_{n-1} the measured concentration of the $(n-1)$th sample, V_T the volume of receiver fluid, and V_S the volume of sample drawn (0.2 mL).

Kinetic mechanism

The kinetics of ibuprofen release from EVAc's base formulations were determined by finding the best fit of the dissolution data (cumulative drug released vs. time) to different models. These models are shown in Table II.

Here, M_t is the amount of drug released at time t, M_0 is the initial amount of drug, M_∞ is the total amount of drug in the matrix, M_t/M_∞ is the fraction of drug released at time t and the release rate constants are the k_0, k_f, k_H, and k (comprising the structural and geometric characteristics of the tablet) for zero order, first order, Higuchi and Korsmeyer-Peppas equations, respectively. The release exponent, n, is a parameter, which depends on the release mechanism.[12] The release data were fitted by models provided in Table II to find the best one of them with the least square analysis.[17–19]

Determination of drug solubility

An excess amount of ibuprofen was equilibrated with 5 mL of phosphate buffer saline solution at 37°C for 48 h with constant shaking in a shaking incubator. Then, the solution was centrifuged and the supernatant was removed. After appropriate dilution, the concentration was assayed spectrophotometrically at 222 nm. The maximum solubility of ibuprofen in phosphate buffer at 37°C was 10 mg/mL.

Scanning electron microscopy (SEM)

A scanning electron microscope (model XL30, Philips, Eindhoven, The Netherlands) was used to study the morphology of the membranes. Samples for SEM were prepared by dipping the membranes in liquid nitrogen and then fracturing them to permit imaging the cross section of the membranes, after coating with gold sputtering.

RESULTS AND DISCUSSION

Figure 3 shows the ibuprofen release for samples with 4, 6, and 8% (45, 85, and 98 μg/cm^2) drug loading at three different isopropanol concentrations. By increasing isopropanol concentration drug release was increased up to 44 μg/cm^2 at 24 h for the sample with 8% ibuprofen and 5% of isopropanol. By increasing the isopropanol concentration, ibuprofen solubility in EVAc and drug release was increased. Isopropanol may have an effect on reducing drug crystal formation. Isopropanol addition hinders crystal formation and since concentration of added isopropanol was low, therefore, the isopropanol release was negligible. In addition, drug crystals may have been an effect of isopropanol on the adhesive. Increasing numbers of crystals reduces diffusion of drug molecules in the matrix. However, higher isopropanol concentration may leach out more easily. Furthermore, as shown in Figure 3, the burst effect for all three drug loadings were limited to the first 2.5 h, and it varied between $\sim$ 15 and 30 μg/cm^2. Nevertheless, the presence of contact adhesive layer may have potential effects on the overall release results. Drug partitioning into this layer will contribute to the initial burst in proportion to the layer thickness and the solubility of drug in the contact

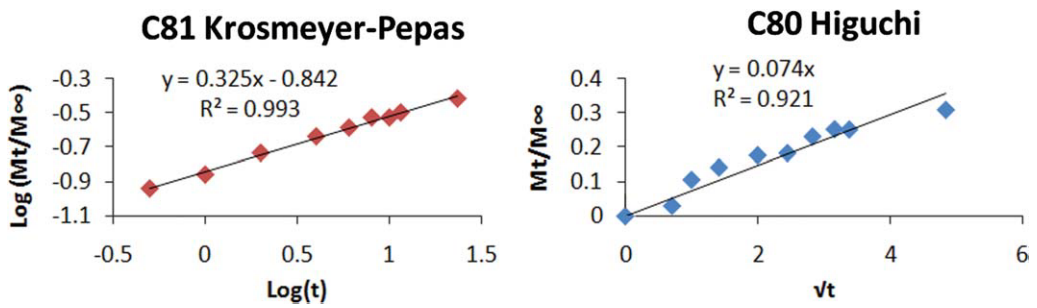

Figure 4 Two representative, Higuchi (C80, $R^2 = 0.92$) and Krosmeyer-Peppas (C81, $R^2 = 0.99$) fitting curves.

adhesive. Moreover, IPA will partition into the adhesive and plasticize this layer as well. Furthermore, it is assumed that all films contain drug at a saturation plus excess level. If any films release sufficient drug such that no crystalline drug remains, the mechanism of release will revert to Fickian release. It is possible that this occurred in the 4% drug films and the film concentrations of drug and isopropanol are assumed to be on a dry weight basis.

Kinetic mechanism

Table III indicates the results obtained from mathematical modeling. R squared values show data points are in best agreement with the Korsmeyer-Peppas theory. The best fitting model was defined based on the R^2 values not "k" and "n" alone. The origin of oscillation of "n" and "k" in the Korsmeyer-Peppas model despite the larger value of R^2 is unknown; it should be observed in the context of R^2 values, which oscillates similarly. Although, based on the R^2 values, the Korsmeyer-Peppas model does give the best fit. However, Higuchi model is easier to use, since it requires much smaller variation in the constants to achieve essentially the same R^2 values, and since the process of drug release is essentially the same for all films, one may prefer the simpler model. Two representative fitting curves are shown in Figure 4.

TABLE IV
Diffusion Coefficient and Drug Released Percentage After 24 h

Formulation Number	Diffusion coefficient ($\mu m^2\ min^{-1}$)	Percentage of drug released after 24 h
C40	0.56	47
C41	0.64	49
C43	0.78	54
C45	1.01	59
C60	0.31	38
C61	0.36	39
C63	0.56	44
C65	0.57	48
C80	0.30	36
C81	0.50	43
C83	0.50	48
C85	0.66	50

Apparent diffusion coefficient

Diffusion coefficients (apparent), were obtained for 60% release by the early time approximation of Fick's second law of diffusion according to Baker and Lonsdale.[20]

$$M_t/M_\infty = 4(D_t/\pi l^2)^{1/2=k\times t^n} \quad (2)$$

Where D is the diffusion coefficient (apparent) and l is the thickness of the membrane. Table IV shows diffusion coefficients and percentage of drug released after 24 h. As seen, by increasing isopropanol concentration, the D values are increased. As an example, for the sample with 4% ibuprofen, the diffusion coefficient was increased from 0.56 μm^2/min for C40 to 1.01 μm^2/min for C45. In addition, the percentage of drug release after 24 h was 59% release for C45 compared to 48 and 50% release for the C65 and C85 samples, respectively. Since the drug needs to be dissolved in the matrix to reach the surface, lower initial concentration of drug may decrease drug crystals formation and consequently increase the drug diffusion rate. Enhancement in

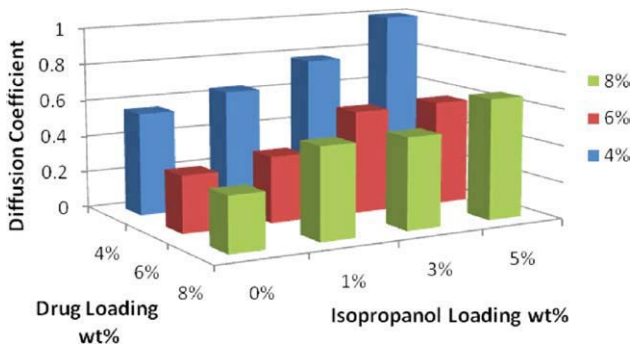

Figure 5 Diffusion coefficient of samples loaded with 4, 6, and 8% of ibuprofen at different concentrations of isopropanol. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

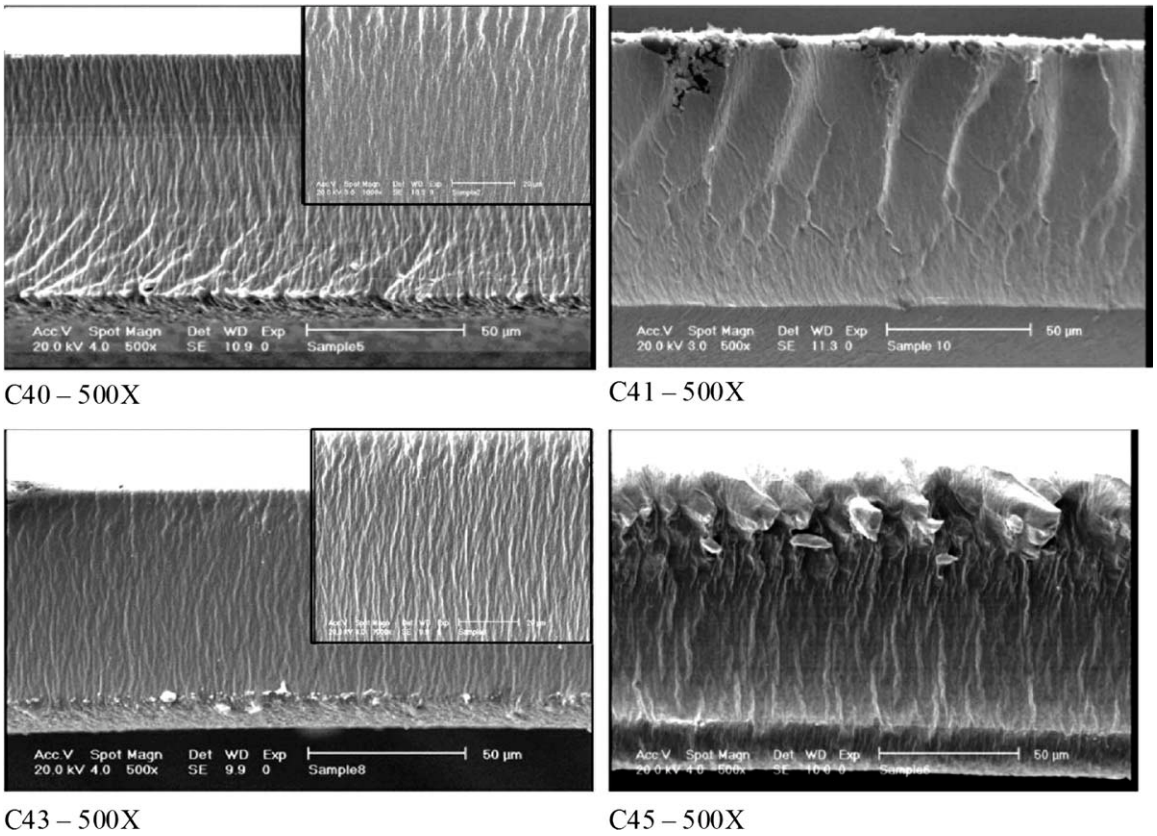

Figure 6 SEM micrographs of samples loaded with 4% ibuprofen and various isopropanol concentrations (insert figures show 20 μm scale).

drug diffusion coefficient is shown in Figure 5. However, the enhanced D for 4% means it is a greater percentage of a lower initial amount; therefore, less drug is supplied. Since total release is not simply a function of the calculated D, it is not surprising that the film with the lowest drug content releases the lowest mass of drug. Moreover, changes to the drug structure itself (in addition to matrix microstructure) may also be important in controlling drug diffusion.

Microstructure study

Scanning electron micrographs of samples loaded with 4% ibuprofen at various isopropanol concentrations are shown in Figure 6. At 4% drug loading, by increasing the isopropanol concentration, the porosity, and the average length of channels traversing the matrix was increased. In addition, isopropanol, a solvent of ibuprofen, may plasticizes the EVA and probably adhesive and increase the number of pathways to the outside of the membrane.

CONCLUSIONS

Ibuprofen, a predominant oral route administered drug, with potential painful transit in the gastro intestinal tract to the targeted organ, was loaded in matrix type EVAc transdermal systems. Drug and isopropanol (solublizer) concentration was varied from 4 to 6 and 8% (w/w) for the drug and 1, 3, and 5% (v/w) for the isopropanol. Cumulative release versus time showed the burst effect in the first 2.5 h for all of the samples and drug release improvement in 24 h up to 59 $\mu g/cm^2$ for the sample with 4% drug loading and 5% isopropanol. The fraction of drug released versus time was in good agreement with the Korsmeyer-Peppas's model. Scanning electron microscopy showed that, by increasing isopropanol concentration, the average length of channels through the membranes was increased.

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