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Estimation of 5-fluorouracil-loaded ethylene-vinyl acetate stent coating based on percolation thresholds

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Abstract

The drug percolation thresholds of 5-fluorouracil-loaded ethylene-vinyl acetate stent coatings were estimated to characterize their drug release behavior and mechanical properties. The stent coatings were prepared using 5-fluorouracil (5-FU) as antitumor drug and ethylene-vinyl acetate (EVA) as matrix forming material in different ratios. In vitro release assays were carried out exposing only one side of coating to pH 6.5 PBS. Based on the release profiles, the drug percolation thresholds were estimated as 0.21 of total porosity (corresponding to ca. 32%, w/w of the drug), which is in approximately agreement with the atomic force microscopy (AFM) result. Based on the coating tensible break strength and tear break strength data, the mechanical percolation thresholds of drug were obtained as 39.7 ± 0.3 and $37.5 \pm 1.4\%$ (w/w) of drug content, respectively.

Keywords: Stent coating; Ethylene-vinyl acetate; 5-Fluorouracil; Percolation threshold

1. Introduction

Percolation theory is a statistical theory that has a wide application in many scientific disciplines. It was first introduced in the pharmaceutical field by Leuenberger et al. (1987) to improve the characterization of solid dosage forms. The percolation theory deals with the formation of clusters and the existence of site and bond percolation phenomena. A cluster is defined as a group of neighbouring occupied sites in the lattice and the probability at which a cluster just percolates a system. The percolation threshold indicates the concentration at which there is the maximum probability of appearance of a continuous phase, and represents the critical value, close to which some properties of the system change suddenly (Stauffer and Aharony, 1992).

A few attempts have been made to apply percolation theory to the formation and release kinetics of matrix-type tablets, which have enabled new insights about their design and characterization (Leuenberger et al., 1995; Caraballo et al., 1996a,b; Leuenberger and Ineichen, 1997; Kuentz et al., 1999; Kuny and Leuenberger, 2003). However, percolation theory has seldom been used to estimate matrix-type membranes or films (Xu and He, 1998).

Bare and film-coated esophageal stents have been widely used in clinic (Sabharwal et al., 2005). However, their effective lifespan of the treatment was often shortened by the tumor ingrowth and overgrowth (Ell et al., 1994; Saxon et al., 1997; Rozanes et al., 2001; Sarper et al., 2003). Coating endoluminal stents with antitumor drug–polymer compound can prevent overgrowth (benign and malignant) and increase the efficacy and duration of clinical effectiveness of the device. For several decades, 5-fluorouracil (5-FU) has been one of the most effective chemotherapeutic agents with clinical activity against solid carcinoma such as esophageal cancer (Ciftci et al., 1997; Oettle et al., 2002). Due to erratic oral bioavailability, intravenous administration of this drug is currently in clinical use. However, such an administration mode causes severe gastrointestinal, hematological, neural, cardiac and dermatological toxic effects, due to its cytotoxicity. 5-FU has cytotoxic activity mainly against cells in S phase with a very short plasma half-life of approximately 11 min (Grem, 1990; Martel et al., 1998). EVA is a heat-processable, flexible and inexpensive material. Its safety and biocompatibility have been confirmed by its comprehensive application in the field of pharmaceutics

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(Maurin et al., 1992; Costantini et al., 2004). The EVA stent coating can also provide a physical barrier to malignant cell ingrowth.

The objective of the present work is to estimate the drug percolation thresholds that characterize the drug release behaviors and mechanical properties of the 5-FU-loaded EVA stent coatings.

2. Materials and methods

2.1. Materials

5-Fluorouracil was obtained from Nantong Jinghua Pharmaceutical Co., Ltd. (China) and micronized by a planetary ball mill. The sizes of drug particles were measured using a light microscope with an image analysis system (Winner 99 (3.02) Beta, Jinan Winner Science and Technology Co. Ltd.). Ethylene-vinyl acetate copolymer (EVA) was purchased from Shanghai Research Institute of Chemical Industry (China). All other chemicals and solvents were of reagent grade and used as received.

2.2. Preparation of 5-FU-loaded EVA coating

The coatings were prepared by fully blending 5-FU and melted EVA in different ratios and then compressing the blend into films with a heat source. In brief, 50 g of EVA was added into the chamber of HAAKE Rheocord System (Rheocord 90, HAAKE Mess-Technic GmbH, Germany) and heated until it was completely melted. Afterward a certain amount of the micronized 5-FU was added slowly into the melted EVA and blended at 95 °C for 2 h under stirring at 37 rpm. The EVA–5-FU blends were further processed by the Two-Roll Mill (S(X)K-160A, Shanghai Rubber Machinery Works) for 1 h. The 5-FU-loaded EVA coatings were obtained by compressing the processed blends at 105 °C on the Compression Moulding Machine (XLB-D, Shanghai No. 1 Rubber Machinery Factory). The obtained coatings are films of uniform thickness of 100, 150, 200, and 300 μm. The drug content was calculated from the weight ratio of the drug and the copolymer used. The blank EVA film was prepared in the same conditions except no drug was added.

2.3. In vitro release studies from the 5-FU-loaded EVA coating

Uniform disks with 1.1 cm^2 in area and 300 μm in thickness were cut from the 5-FU-loaded EVA coatings prepared in 2.2 and weighed accurately. The one side of disk was coated with a blank EVA film and another side was exposed to the dissolution medium. Each disk was placed in a vial of 5 ml pH 6.5 phosphate buffer solution (PBS) at 37 °C with shaking at a rate of 150 strokes min^{-1}. At predetermined time points the disk was removed and placed into another vial with fresh PBS to maintain sink conditions. The drug quantity released from the disk was measured spectrophotometrically at 266 nm. Six repetitions for each formulation were carried out.

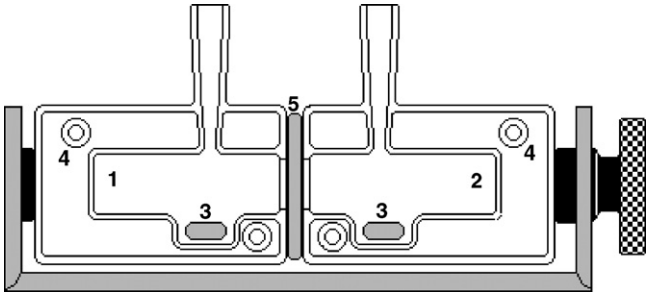

Fig. 1. Schematic diagram of apparatus for the test of diffusion coefficient of 5-FU in the EVA film. (1) Donor compartment; (2) receptor compartment; (3) stirbars; (4) to/from heater/recirculator ports; (5) tested film.

2.4. Determination of drug solubility (C_s)

Excess amounts of 5-FU were shaken in test tubes at 37 °C for 72 h. The saturated solution was centrifuged to remove undissolved drug particles and then filtered through a Millipore filter paper (0.45 μm). The 5-FU concentration was determined by the HPLC.

2.5. Measurement of diffusion coefficient of 5-FU in the EVA film (D_m)

The diffusion coefficient (D_m) of 5-FU in the EVA film was determined using V–C horizontal cell that has two compartments (Fig. 1). Each compartment has a volume of approximately 5 ml and an effective diffusion area of 0.64 cm^2. A piece of the blank EVA film was clamped between the two compartments of the cell. Five millilitres of the drug suspension in pH 6.5 PBS was filled into the donor compartment and 5 ml of pH 6.5 PBS into the receptor compartment. The assembled cell was stirred at 250 rpm to minimize the boundary effect and kept at 37 °C using a circulating water bath. The receptor solution was removed at the predetermined intervals and replaced with 5 ml of fresh solution. The amount of the drug permeated was determined by the HPLC. D_m was calculated by the equation (Siegel, 1986):

$$t_L = \frac{L_m^2}{6D_m}$$

where t_L is the lag time and L_m is the thickness of the film.

2.6. HPLC determination of 5-FU

5-FU was assayed by a HPLC method. The mobile phase was a combination of methanol:water (1:4). The column was Diamonsil C18 (5 μm, 4.6 mm × 250 mm) and the column temperature was maintained at 25 °C. A flow rate of 1.0 ml min^{-1} yielded an operation pressure of around 1000 psi. The UV detector was operated at 266 nm. Under these conditions, and the 5-FU peak appeared at the retention time of 4.22 min.

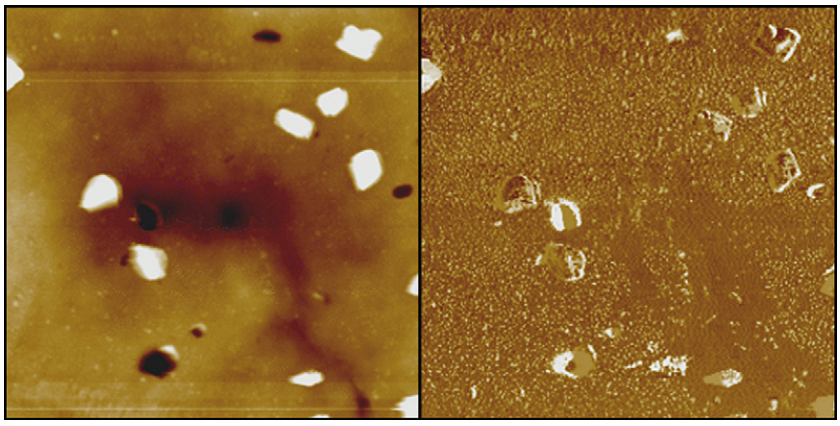

Fig. 2. AFM topography image (left) and phase image (right) from the surface of EVA coating loaded with 20% (w/w) of 5-FU before drug release (scan area, 18 μm × 18 μm).

2.7. Porosity

The porosities of drug and air for the 5-FU-loaded EVA stent coatings were calculated by the formula:

$$\varepsilon_d = \frac{V_d}{V}$$

$$\varepsilon_0 = \frac{V - V_d - V_e}{V}$$

where ε_0 is porosities of air spaces; ε_d the porosity of drug (volume fraction of drug); V the measured volume of the coating, calculated from its height and diameter by micrometer (apparent volume); V_d and V_e are the true volume of the drug and the EVA in the coating calculated by the ratios of weight and true density for 5-FU and EVA. The true density of 5-FU (ρ_d, 1.73 g cm^{-3}) and the true density of EVA (0.95 g cm^{-3}) were taken from literature (Xu and He, 1998) and supplier, respectively.

2.8. AFM

The morphologies of 5-FU-loaded EVA stent coatings were observed using atomic force microscopy (AFM) (Mukimock Naniste, DI Corporation, US) analysis. The AFM images were recorded with a Nanoscope III from Digital Instruments operated in the tapping mode in air using microfabricated Si (type NCH) cantilevers with a spring constant between 27 and 53 N m^{-1}, resonance frequency in the range of 301–365 kHz, and 1 and 2 Hz scanning speed.

2.9. Mechanical properties

2.9.1. Tensible test

Tensible test was performed on the coating sample using the Universal Electromechanical Tester (Instron 4465, Instron Corp., USA), at a speed of 300 mm min^{-1}. The geometry of the sample corresponds to the geometry for the membrane sample specified in the GB 1039-79, equivalent to the ISO standard (gauge total length equal to 50 mm and width at the center equal to 5 mm). The force is measured as a function of the elongation until the breakage of the sample. Six repetitions for each formulation were carried out in the test.

2.9.2. Tear test

Tear test was performed with the same instrument in 2.9.1, at a speed of 300 mm min^{-1}. The gauge total length is 150 mm, width 50 mm and the length of incision 75 mm. The geometry of the sample corresponds to the ISO standard 6383.1-1983. The tear strength (N mm^{-1}) was calculated by dividing average force by the thickness. Six repetitions were adopted for each formulation.

3. Results and discussion

3.1. 5-FU particles in the EVA coating

Fig. 2 is the AFM topography image (left) and phase image (right) of the coating with 20% (w/w) of 5-FU. It can be seen that there are some white juts and black holes in the topography image. The phase corresponding to the white juts is different from their neighborhood, indicating the white juts are drug

Table 1
Statistical parameters from the image analysis of the 5-FU powder by light microscope

n[a]	Shape factor	Aspect ratio	Max diameter (μm)	Min diameter (μm)	Mean diameter (μm)
295	0.790	1.004	8.7 ± 0.2	2.5 ± 0.3	5.0 ± 0.3

[a] n, number of cases.

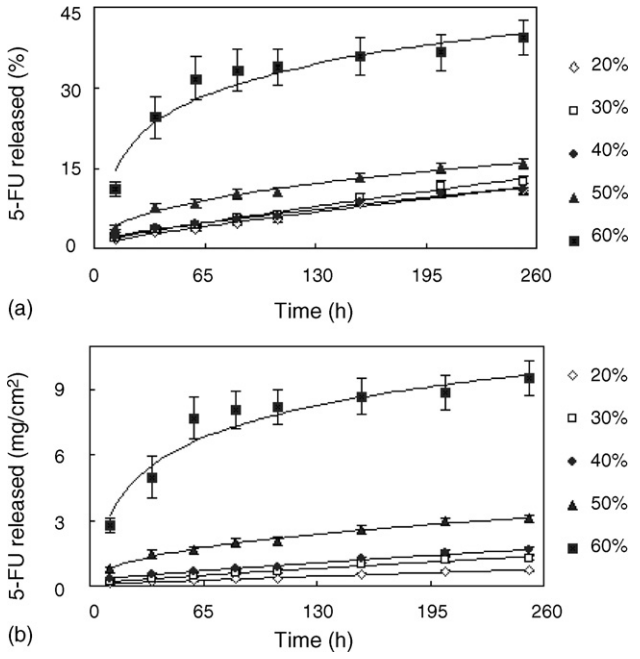

Fig. 3. Percentage (a) and amounts (b) of drug released vs. time for EVA stent coatings with different loadings of 5-FU.

particles. It is observed that the drug particles are quite uniformly dispersed and not clustered in the EVA matrix. The sizes of the drug particles in the EVA matrix are less than 1.5 μm, smaller than that of the original 5-FU powders (5 μm, see Table 1). This indicates that some drug powders are fragmentated into smaller particles in the preparation process. The drug size and shape have an important influence on the drug percolation threshold and mechanical properties of the matrix, and the percolation threshold was lower for finer drug powders (Caraballo et al., 1996b; Millán et al., 1998; Flandin et al., 2000).

3.2. Estimation of the drug geometrical threshold percolation based on drug release

Taking into account the percentage of drug released from the coatings, the drug release profiles are almost the same for the coatings containing up to 40% (w/w) of drug (see Fig. 3a). This fact can be attributed to the increase that the coating volume underwent during the release assay. After the 250-h release assay, the coatings showed a low but significant increase in volume (5%, v/v approximately). This increase in volume can be due to a little relaxation of the matrix structure that can result in the development of additional porosity and in the penetration by the dissolution medium. Therefore, water can percolate the region of the coating near to the free surface. As a consequence, the entire drug included in this region will be released, even if a drug infinite cluster does not exist in this coating. This process can mask the influence of the drug percolation threshold on the release profiles. Therefore, the drug percolation threshold cannot be deduced from the release profiles that were very similar for the coatings containing up to 40% (w/w), showing that the dissolution profiles were not sensitive to the drug load within this range. The similar result was also reported for morphine hydrochloride in Eudragit® RS–PM matrices (Melgoza et al., 1998; Melgoza et al., 2001; Aschkenasy and Kost, 2005). Alternative methods have been employed to estimate the drug percolation threshold in the studied matrices.

3.2.1. Estimation of the drug percolation threshold by AFM

The percolation threshold of the drug is the probability or volume fraction at which the drug starts to percolate the sample. Fig. 4a–e shows the topography images of the dissolution medium-exposed sides of coatings containing 20–60% (w/w) of drug after the 250-h release assay, respectively. From Fig. 4a and b, we can find, there are some black holes in the coatings with less drug contents (20 and 30%, w/w 5-FU) and the coating containing 30% (w/w) 5-FU has more holes. The sizes of holes observed in Fig. 4a are almost the same with those of the drug particles in Fig. 2, indicating that these holes are the voids formed by the release of drug particles. These holes are not connected, but separated each other, which is also consistent with the result shown in Fig. 2. However, for the coating containing 40% (w/w) of drug (Fig. 4c), the black holes appear to be connected each other and even form channels in the coating. This fact suggests the existence of a drug infinite cluster percolating the entire sample. Therefore, according to the AFM study, the 5-FU percolation threshold is expected to be about 40% (w/w) of drug. There are many interconnected channels in the coatings containing 50 and 60% (w/w) drug (Fig. 4d and e). It can be speculated that these channels are formed by the dissolution of clusters of drug particles.

3.2.2. Estimation of the drug percolation threshold using the method of Leuenberger and Bonny

The method of Bonny and Leuenberger (1991) is employed to estimate the drug percolation threshold for the 5-FU-loaded EVA coating:

$$\beta = b(2A - \varepsilon C_a)^{1/2} = \lambda\varepsilon - \lambda\varepsilon_c$$

where β is a property of the coating derived from the drug diffusion coefficient, b the slope of the Higuchi plot, A the concentration of the drug dispersed in the EVA matrix and C_a is the solubility of the drug in the permeating fluid. λ represents a

Table 2
Calculation of the property β and related parameters[a] in the coatings with different drug loading for estimation of ε_c using the method of Leuenberger and Bonny

Drug (%, w/w)	ε_0	ε	$b \pm$ S.E.	R	A	$\beta \times 10^3$
20	0.0135	0.1328	0.0513 ± 0.00262	0.970	2.066	2.53
30	0.0121	0.1996	0.0901 ± 0.00827	0.975	3.246	3.54
40	0.0058	0.2733	0.1077 ± 0.01352	0.983	4.630	3.55
50	0.0066	0.3586	0.2146 ± 0.01476	0.998	6.093	6.16
60	0.0224	0.4638	0.4886 ± 0.0396	0.951	7.640	12.53

[a] b, Higuchi constant (mg $h^{-1/2}$ cm^{-2}); R, linear correlation coefficient; A, concentration of drug dispersed in the coating (mg cm^{-3}); β, coating property ($g^{1/2}$ $cm^{-1/2}$ $h^{-1/2}$).

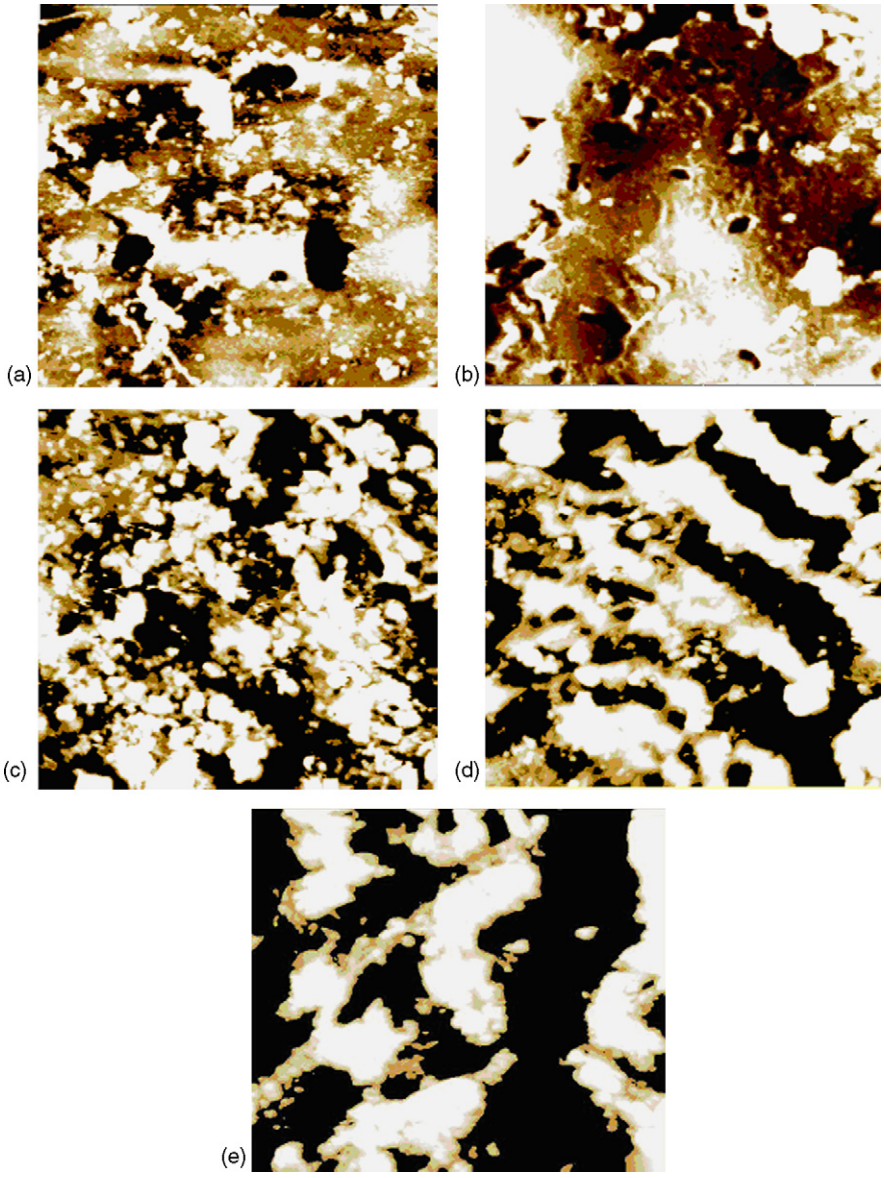

Fig. 4. AFM images of the EVA coatings with different drug loads after 252 h of dissolution. Drug loads (w/w) and scan sizes (a): 20%, 11 μm × 11 μm; (b): 30%, 11 μm × 11 μm; (c): 40%, 11 μm × 11 μm; (d): 50%, 11 μm × 11 μm and (e): 60%, 18 μm × 18 μm.

constant, ε the total porosities summing the drug porosity and air porosity, and ε_c denotes the critical porosity (the drug percolation threshold).

The results obtained for the property β and the related parameters are shown in Table 2. Because the dissolution profiles were not sensitive to the drug load within 20–40%, the drug percolation threshold is estimated based on the drug release behaviors of the coatings containing 40–60% of 5-FU (Fig. 3b). As Fig. 5 shows, the percolation thresholds or critical porosity of 5-FU is obtained from the regression of the β values, which exhibited a linear behavior versus ε (solid squares in Fig. 5). The obtained value for the critical porosity, the intercept with the abscissa, was 0.211 ± 0.020, considering a 95% confidence interval ($P = 0.05$). This value corresponds to a 5-FU content of ca. 32% (w/w). The AFM observations are approximately in agreement with this result.

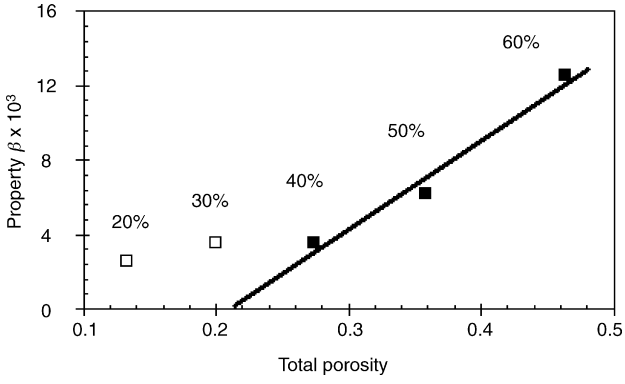

Fig. 5. Estimation of the drug percolation threshold of the coatings using the method of Bonny and Leuenberger.

Table 3
Some parameters of 5-FU for estimation of ε_c using the bi-diffusion model

C_a (mg ml^{-1})	C_m (mg ml^{-1})[a]	D_a (cm^2 s^{-1})[b]	D_m (cm^2 s^{-1})
17.132	0.240	3.127×10^{-5}	1.036×10^{-9}

[a] Cited from Ping and William (1987).
[b] Cited from Xu and He (1998).

3.2.3. Estimation of the drug percolation threshold using the bi-diffusion model

In the system of the 5-FU/EVA coating, as 5-FU is a hydrophilic drug with small molecular weight, the diffusion of 5-FU in hydrophobic EVA matrix might be matrix and/or pore controlled. In this case, a modified kinetics equation for matrix-pore bi-diffusion process was established by Xu and He (1998):

$$Q_t = \sqrt{[2\rho_d\varepsilon_d - (1-\varepsilon)C_m - \varepsilon C_a][(1-\varepsilon)D_m C_s + D_B C_a]t}$$

where D_m is the diffusion coefficient in the matrix, C_m the solubility in the matrix and D_B is the bulk diffusion coefficient, which can be calculated from the slope of the release curve.

When the conductivity scaling law and the percolation concepts are applied, the relationship between diffusivity D and critical porosity ε_c is established:

$$D = \frac{D_B}{D_a} = \alpha(\varepsilon - \varepsilon_c)^2$$

where α is a proportionality constant, and D_a is the diffusion coefficient in the permeating fluid.

The calculated D and related data are listed in Tables 3 and 4 and the plot of square root D versus ε for the studied coatings was shown in Fig. 6. The ε_c is calculated to be 0.213 ± 0.015 ($P = 0.05$), which is almost the same with the result using the method of Leuenberger and Bonny.

3.3. Investigation of mechanical properties based on percolation theory

The esophageal stent coating should withstand the rigor of tearing, compression and expansion during its deployment and subsequent peristaltic movements in lumen. The mechanical properties of the coatings such as tensible break strength and tear break strength are important.

According to percolation theory, different properties have different percolation thresholds. For each type of lattice there is a site and a bond percolation threshold. When the diffusivity and conductivity of composites are studied, the concept

Table 4
D_B, D and ε_d values determined as a function of drug loading for estimation of ε_c using the bi-diffusion model (Xu and He, 1998)

C_d (mg cm^{-3})	ε_d	$D_B \times 10^6$ (cm^2 h^{-1})	$D \times 10^5$
206.6	0.119	2.920	0.296
324.6	0.187	6.148	0.637
463.0	0.267	6.190	0.645
609.3	0.352	19.399	1.690
764.0	0.441	81.188	8.076

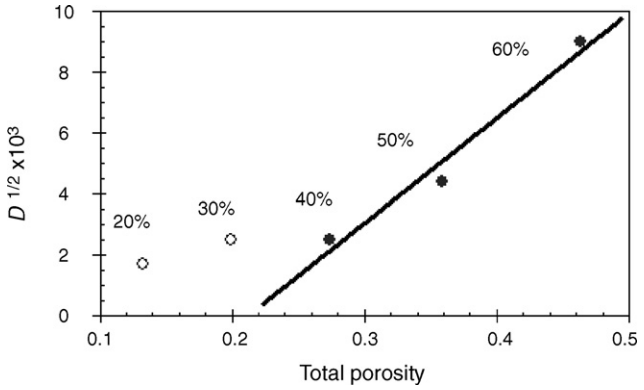

Fig. 6. Estimation of the drug percolation threshold of the coatings, employing the bi-diffusion model.

of site percolation is used. On the other hand, concerning the mechanical properties such as elasticity and tensible strength, the bond percolation is applied for explaining the interaction between the particles (Stauffer and Aharony, 1992; Leuenberger and Ineichen, 1997). Herein, we use the bond percolation to investigate the mechanical properties of 5-FU-loaded EVA stent coating.

According to a model explaining the relationship between solid fraction and mechanical properties of the binary system based on bond percolation theory (Holman and Leuenberger, 1988), a similar relationship between tensible break strength (T) or tear break strength (S), and volume fraction of one component was applied in the 5-FU-loaded EVA coating system:

$$\log S = K_1 P$$

$$\log T = K_2 P$$

where P is the probability, corresponding to volume fraction of EVA, and K_1, K_2 are the proportionality constants.

Fig. 7 illustrates the relationship between the logarithm of tensible or tear break strength and P based on percolation theory, indicating the mechanical properties of the coatings are not only dominated by EVA, but also influenced by drug particles. At a

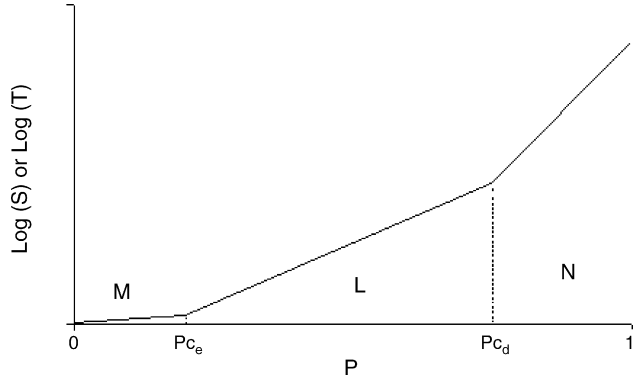

Fig. 7. The relationship between the logarithm of tensible or tear strength at break and P (EVA volume fraction). Pc_e: percolation threshold of the EVA. Pc_d: percolation threshold of the drug, 5-FU. M, L and N represent the regions of percolating clusters of drug particles and isolated EVA, percolating clusters of both drug and EVA, isolated drug particles and percolating clusters of the EVA, respectively.

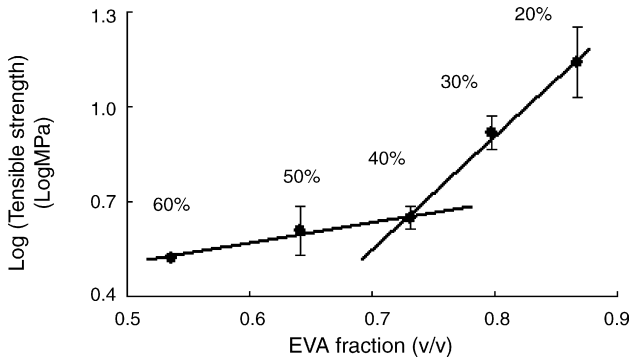

Fig. 8. Semi-logarithmic plot of tensible strength at break against EVA volume fraction for the EVA stent coatings loaded with 20, 30, 40, 50 and 60% (w/w) of 5-FU.

certain volume of drug particles (Pc_d), far above the percolation threshold of EVA (Pc_e), the drug particles clusters become finite from infinite, i.e. from interconnected to discontinuous or isolated. According to the percolation theory, something peculiar should presumably happen at Pc_d. This transition from infinite to finite cluster of drug particles manifests itself by effecting a change in the degree of change of logarithmic tensible strength ($\log S$) or logarithmic tear strength ($\log T$) for P-values above Pc_d. Thus, the change of $\log S$ or $\log T$ with changes in P is different for values of P below and above Pc_d. A semi-logarithmic plot of S or T against P for all values of P should thus show an inflexion at Pc_d. Similarly, another inflexion appears when EVA starts to percolate the system (Pc_e).

Figs. 8 and 9 show plots of $\log S$ and $\log T$ as a function of the volume fraction of EVA in the coatings. There is only one point of inflexion in Figs. 8 and 9, which should corresponding to the drug percolation threshold (Pc_d), because the EVA matrix containing 60% (w/w) of drug still can maintain matrix integrity. Based on the points of inflexion, the percolation thresholds (Pc_d) for S and T of the matrices are 39.7 ± 0.3 and 37.5 ± 1.4% (w/w) of drug, which are corresponding to ca. 72.9 and 74.7% (v/v) of EVA, respectively. The mechanical percolation thresholds of drug are a little higher than the geometrical percolation thresholds, which is consistent with the relevant report (Melgoza et al., 2001).

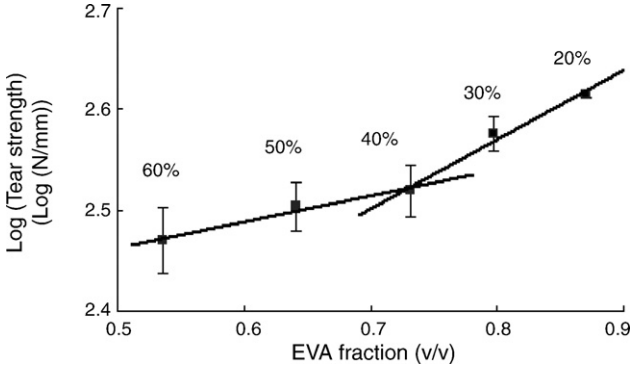

Fig. 9. Semi-logarithmic plot of tear strength at break against EVA volume fraction for the EVA stent coatings loaded with 20, 30, 40, 50 and 60% (w/w) of 5-FU.

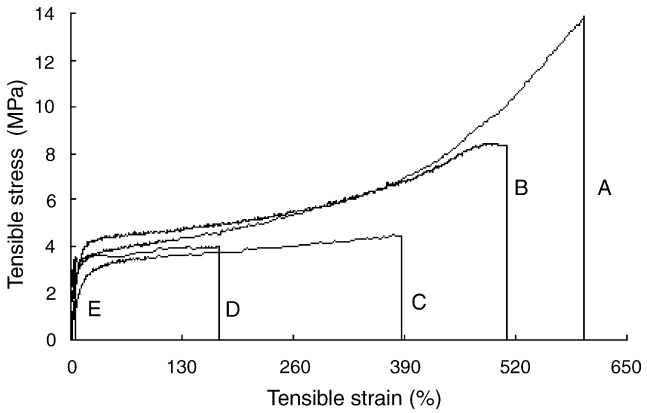

Fig. 10. Tensible stress–strain curves of the EVA stent coating loaded with: (A) 0% (w/w); (B) 20% (w/w); (C) 30% (w/w); (D) 40% (w/w); (E) 50% (w/w) and (F) 60% (w/w) of 5-FU.

The strain–strength curves of the coatings with various drug contents are shown in Fig. 10. At the same strain, the strength of the coating with 20 or 30% (w/w) of drug is much bigger than that of the coating containing 40–60% (w/w) of drug, which also indicates that a mechanical percolation threshold of drug appears at the drug concentration of 30–40% (w/w).

4. Conclusion

The drug release behaviors and mechanical properties of 5-FU-loaded EVA stent coatings were studied and characterized by estimating drug percolation thresholds. Based on the drug release profiles, the geometrical percolation threshold of the drug was obtained as ca. 32% (w/w) of drug. This result is in approximately agreement with the AFM observations. Based on the tensible break strength and tear break strength of the coatings, the drug percolation thresholds were 39.7 ± 0.3 and 37.5 ± 1.4% (w/w) of drug respectively.

Acknowledgement

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