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COMMUNICATION

Studies of the Drug Permeability and Mechanical Properties of Free Films Prepared by Cellulose Acetate Pseudolatex Coating System

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ABSTRACT

Free films produced with cellulose acetate (CA) pseudolatex were prepared by the casting method. The effects of plasticizer concentration, drying temperature, and drying time on drug permeability and mechanical properties of free films were investigated by three-factor spherical second-order composite experimental design. The results were analyzed by the multivariable regression method. The experimental results indicated that plasticizer concentration, drying temperature, and drying time had complex effects on free film permeability and mechanical behavior. These results probably arise from the film-forming ability of CA pseudolatex particles at various conditions and the evaporation of plasticizer during the film-forming process.
Key Words: *Cellulose acetate; Mechanical property; Permeability; Pseudolatex; Salbutamol sulfate.*

INTRODUCTION

Cellulose acetate (CA) is a kind of cellulose ester derivative that has been used as a coating material for many controlled-release formulations. Traditionally, CA has been applied using a solvent-based system; however, the advent of latex/pseudolatex technology in the pharmaceutical industry has provided a means for applying the polymer using an aqueous vehicle. Thus, problems associated with a solvent-based system such as flammability, toxicity, and environmental contamination can be eliminated using a latex/pseudolatex system (1).

The most notable difference between solvent-based and a latex/pseudolatex coating system lies in the mechanism of film formation. For a solvent-based coating system, the film formation is associated with the formation of polymer gels after the evaporation of the solvent. The formation of films from a latex system is associated with

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the overcoming of particle-particle repulsion due to electrostatic forces and particle rigidity. This process requires energy. Capillary forces resulting from the high surface tension produced as water between latex spheres evaporates provide much of the energy required for film formation (2). In addition, some researchers pointed out that the continuous film could not form without the presence of plasticizer. At the same time, drying temperature was also vital to the film formation (3).

At present, the latex/pseudolatex coating plays an important role in controlled-release formulation development (4–8). However, the availability of information on the factors that influence the mechanical properties and drug permeability of free film prepared by CA pseudolatex were very limited. The main object of this work was to study the effects of plasticizer concentration, drying time, and drying temperature on the free film permeability and mechanical properties. These results should be useful in formulating films for optimum performance in microporous osmotic pump tablets coated with CA pseudolatex.

MATERIALS AND METHODS

Materials

Cellulose acetate (39.8% acetylation) was generously supplied from Eastman Company Limited (Kingsport, TN). Diacetin was purchased from the Beijing Chemical Factory. Salbutamol sulfate was purchased from Lisheng Pharmaceutical Factory (Tianjin, China). Sodium lauryl sulfate and ethyl acetate were purchased from Shenyang Chemical Company (Shenyang, China). The other chemicals used were analytical grade.

Preparation of Free Films

The CA pseudolatex was prepared by an emulsion-solvent evaporation method with ethyl acetate–ethanol (95:5) mixture as the solvent and 0.05% sodium lauryl sulfate as the surfactant. Diacetin was used as the plasticizer. To avoid coagulation, the plasticizer was slowly poured into the CA pseudolatex under mild stirring. The free films were prepared by a casting method and dried at various conditions. Plasticizer concentration (based on CA content), drying temperature, and drying time were selected as the causal factors to make the free film according to three-factor spherical second-order composite experimental design (see Table 1).

Leaching of Water-Soluble Materials

According to the method mentioned by Peter, Ingunn, and Peter (9), the fraction of water-soluble materials leached from free film is determined by weight. Dry film samples of about 100 mg weight (m_1) were immersed in 25.0 ml of distilled water at 37°C. After 24 hr, the sam-

Table 1

Experimental Design for the Preparation of Cellulose Acetate Pseudolatex Free Film

Formulation	X_1	Plasticizer Concentration (%)	X_2	Drying Temperature (°C)	X_3	Drying Time (hr)
1	1	130	1	80	−1	18
2	1.7	150	0	70	0	24
3	−1	70	1	80	1	30
4	−1	70	−1	60	−1	18
5	1	130	1	80	1	30
6	0	100	0	70	−1.7	12
7	1	130	−1	60	1	30
8	0	100	0	70	1.7	36
9	−1.7	50	0	70	0	24
10	0	100	1.7	87	0	24
11	0	100	0	70	0	24
12	0	100	0	70	0	24
13	1	130	−1	60	−1	18
14	0	100	0	70	0	24
15	0	100	−1.7	53	0	24
16	−1	70	−1	60	1	30
17	0	100	0	70	0	24
18	−1	70	−1	60	−1	18

ples were carefully dried with paper and weighed again (m_2). The free films were put in a vacuum chamber above silica gel until the weight became constant (m_3). For each film formulation, three determinations were made ($n = 3$). The fraction of water-soluble materials leached from the films f_1 was calculated according to the following equation:

$$f_1 = [(m_1 - m_3)/m_3] \times 100\% \quad (1)$$

The fraction of water uptake by the free films f_2 could be found by the following equation:

$$f_2 = [(m_2 - m_3)/m_3] \times 100\% \quad (2)$$

Drug Permeability of Free Films

The drug permeability tests of the CA pseudolatex free films were performed in a standard 3-ml side-by-side diffusion cell system at 37°C. Before each permeability experiment was performed, the thickness of the film was measured with a micrometer. The cells were clamped to prevent leakage and bathed with 37°C water. In the donor cell, saturated salbutamol sulfate solution was placed, while distilled water was added to the received cell. To reduce boundary layer effects, stirring bars were placed in both cells.

After a certain time interval, 0.2 ml of solution in the received cell was sampled, and the same amount of distilled water was compensated. The content of salbutamol sulfate in the sample was detected by a high-performance liquid chromatography (HPLC) method with an ultraviolet detector at a 276-nm wavelength (Jasco Co., Ltd., Tokyo, Japan). The salbutamol sulfate permeability of CA pseudolatex free film could be calculated from

$$P_s = (dm/dt)[h/(A \cdot \Delta C)]$$

where P_s is the salbutamol sulfate permeability of the CA pseudolatex films, A is the surface area of the film that contacts the solution, h is the thickness of the film, ΔC is the concentration difference between the two diffusion cells, and dm/dt is the rate of salbutamol sulfate content change with time in the received cell.

Mechanical Evaluation of Free Films

All tests were conducted under controlled environmental conditions of 25°C ± 1°C and 60 ± 2% RH. Before the measurement of the mechanical properties, film specimens (10 × 150 mm) were cut using a sharp blade. The thickness of the specimen was measured at various points using a micrometer, and the mean thickness was used for the computation of mechanical properties.

A servopulser hydropulse test system (Shimadzu, Tokyo, Japan) was used for the measurements. The film specimen was clamped using an upper and a lower flat-faced metal grip laminated with cardboard to prevent film damage. The distance between the grips, and therefore the effective length of the film under stress, was kept constant at 50 mm. A cross-head speed of 0.5 mm/min and a chart paper/cross-head ratio of 5:1 were used for the measurements. The load-displacement profile was recorded with an *X*-*Y* recorder. An average of at least 3 measurements was taken for each kind of specimen. The typical load-displacement profile is shown in Fig. 1.

Three mechanical properties, namely, tensile strength, percentage elongation, and elastic modulus, were computed from the load-displacement profile. Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be computed from the applied load at rupture as a mean of three measurements and the cross-sectional area of fractured film as described from the following equation:

$$\text{Tensile strength} = \text{Load at failure}/(\text{Film thickness} \times \text{Film width})$$

Elastic modulus is the ratio of applied stress and corresponding strain in the region of approximately linear portion of elastic deformation on the load-displacement profile and can be calculated using the following equation:

$$\text{Elastic modulus} = \text{Slope}/(\text{Film thickness} \times \text{Film width} \times \text{Cross-head speed})$$

where slope refers to the slope of the elastic deformation portion on the load-displacement profile.

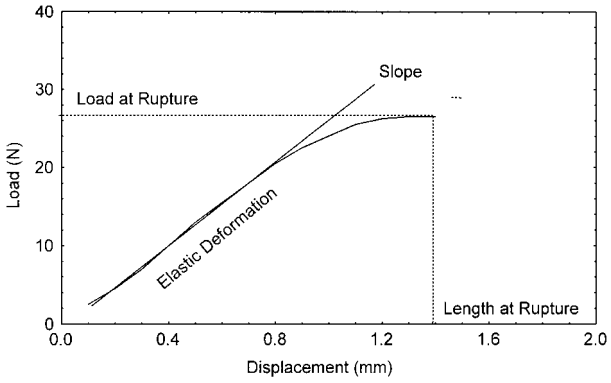


Figure 1. The typical load-displacement profile of CA pseudolatex free film.

Percentage elongation can be obtained by the following equation:

$$\%\text{elongation} = [(\text{Specimen length at rupture} - \text{Original specimen length})/\text{Original specimen length}] \times 100$$

RESULTS AND DISCUSSION

Data Analysis

All the experimental results are shown in Table 2. By employing multivariable regression, a series of second-order polynomial equations composed of the combination of causal factors X_1, X_2, X_3 and film properties could be obtained:

$$\text{Leaching materials}(\%) = 6.6237X_1 - 8.1971X_2 + 5.3200X_3 - 4.0523X_1^2 - 1.0021X_2 - 2.0921X_3^2 + 2.0682X_1 \times X - 0.4343X_2 \times X_3 + 0.1747X_1 \times X_3 + 36.1726 \quad (R^2 = .9635)$$

$$\text{Permeability} = -3.0330X_1 - 49.2211X_2 - 3.1512X_3 - 8.8898X_1^2 + 3.9129X_2^2 - 11.3985X_3^2 - 32.3858X_1 \times X_2 + 35.1108X_2 \times X_3 - 22.9332X_1 \times X_3 + 51.6659 \quad (R^2 = .8708)$$

$$\text{Tensile strength} = -0.6354X_1 + 6.9300X_2 - 5.6445X_3 + 4.0374X_1^2 + 3.7744X_2^2 - 1.2536X_3^2 - 6.4756X_1 \times X_3 - 6.4281X_2 \times X_3 + 8.7697X_1 \times X_3 + 22.4031 \quad (R^2r = .7881)$$

$$\%\text{elongation} = 2.7045X_1 + 1.2751X_2 + 0.5987X_3 + 0.9950X_1^2 + 0.5971\ X_2^2 - 0.2161X_3^2 + 1.8623X_1 \times X_2 - 2.9671X_2 \times X_3 + 1.4888X_1 \times X_3 + 2.7795 \quad (R^2 = .9351)$$

Table 2

Experimental Result of Cellulose Acetate Pseudolatex Free Films Properties Study

Formulation	Fraction of Leached Material (%)	Water Uptake Fraction (%)	Drug Permeability Coefficient ($\times 10^{-9}$cm^{2}s^{-1})	Mechanical Properties		
				Tensile Strength (kg/mm^2)	% Elongation	Elastic Modulus (kg/mm^2)
1	21.70	25.85	5.0	48.37	4.30	1758
2	32.07	37.11	22.9	28.79	10.2	796
3	13.50	18.26	11.7	22.67	2.40	653
4	23.33	27.95	215.4	34.64	1.80	2379
5	39.74	32.02	3.57	21.52	16.0	914
6	23.50	26.90	1.6	20.16	2.20	1350
7	48.10	46.70	3.9	45.72	2.20	2054
8	36.21	38.90	13.7	25.64	3.00	1778
9	16.31	24.84	6.9	33.10	2.00	2345
10	20.09	24.19	0.1	44.90	6.50	2364
11	35.62	41.38	71.3	23.01	2.70	1749
12	36.90	34.25	57.8	24.46	2.70	1777
13	39.59	40.05	126.2	27.34	4.50	874
14	36.96	35.92	64.7	20.32	2.37	1789
15	45.92	39.50	103.7	15.47	3.40	1045
16	41.40	33.21	122	1.45	[a]	[a]
17	35.27	36.24	15.3	22.51	3.25	1763
18	26.08	24.06	92.0	28.44	8.40	952

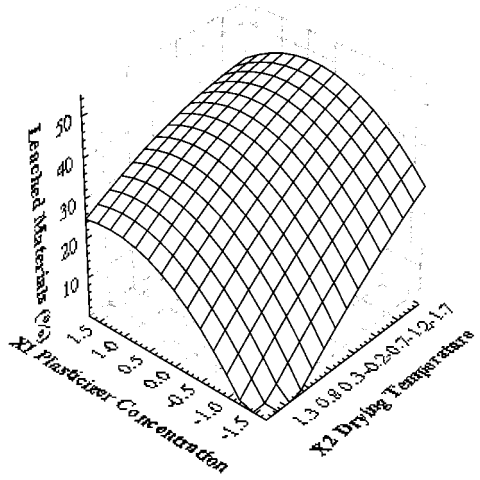
[a] Means could not be measured.

$$\text{Elastic modulus} = -327.2323X_1 - 162.3000X_2 - 99.7588X_3 - 63.1728X_1^2 - 16.8060X_2^2 - 65.4219X_3^2 - 63.2743X_1 \times X_2 - 587.4849X_2 \times X_3 + 346.7845X_1 \times X_3 + 1768.6434 \quad (R^2 = .7657)$$

Leaching of Plasticizer

Since the water uptake by the free film and the fraction of leached materials of the film had a good linear relationship ($r = .8973$), the leached materials of the film were composed mainly of water-soluble materials. The free film contained CA, diacetin, and sodium lauryl sulfate (0.05%). CA cannot dissolve in water, and the sodium lauryl sulfate content was too low to be responsible for the weight loss of the film alone. Therefore, the weight loss can represent the content of plasticizer leached from the film. Leaching of plasticizer from the film could make the film porous and turn the transparent films opaque. Therefore, leaching of plasticizer contributed to the drug permeability of the free films.

Figure 2 shows the three-dimensional diagram of leached materials as a function of any two factors among X_1 (plasticizer concentration), X_2 (drying temperature), and X_3 (drying time) while the other factor is kept constant. As the plasticizer concentration X_1 increased from 50% to 150%, the leached materials showed an obvious increase in their value. This is simply because plasticizer was the main leached material in the free films, while the higher drying temperature X_2 resulted in less leached plasticizer. The reason is twofold. First, the plasticizer evaporated easily under the higher drying temperature, and less plasticizer remained in free films to be leached out. Second, the continuous films were formed under the higher drying temperature when plasticizer concentration was 100%; it is difficult for water to permeate into the films. Drying time could result in more leached materials from the free films under certain drying temperatures. If the free films were placed under certain drying temperatures for a long time, defects would be found on the films



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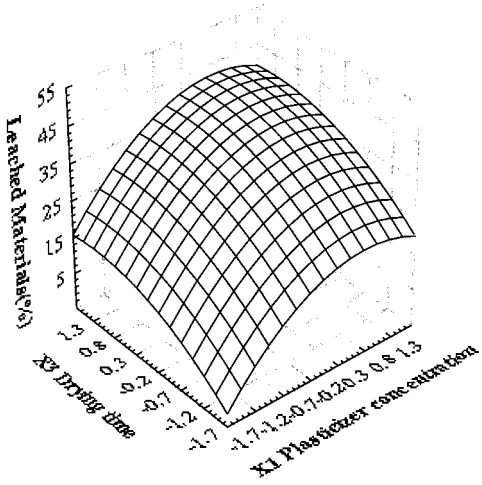

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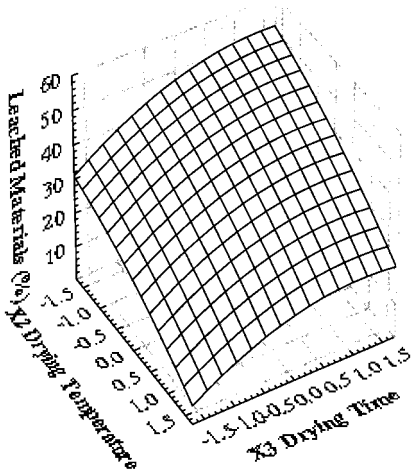

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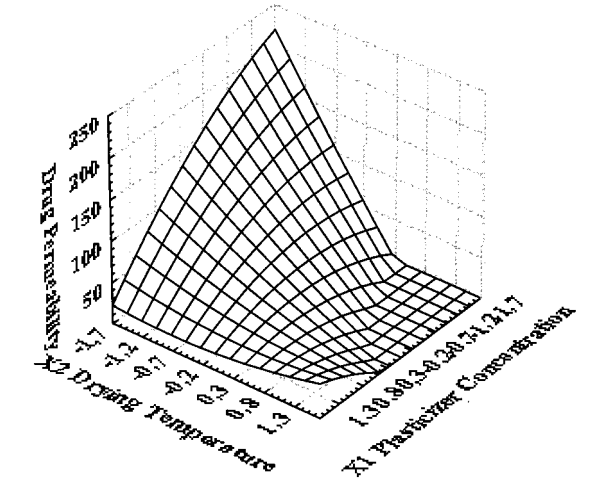
Figure 2. The three-dimensional diagram of leached materials as a function of any two factors among X_1 (plasticizer concentration), X_2 (drying time), and X_3 (drying temperature): (a) drying time kept constant at 24 hr; (b) drying temperature kept constant at 70°C; (c) plasticizer concentration kept constant at 100%.

due to the loss of plasticizer. So, water could easily permeate into the free films. The plasticizer leached from the cracks overcomes the plasticizer loss caused by evaporation. Therefore, the total effect of the drying time was to increase the amount of leached materials.

Drug Permeability

Figure 3 shows the three-dimensional diagram of drug permeability as a function of any two factors among X_1 (plasticizer concentration), X_2 (drying temperature), and X_3 (drying time) while the other factor is kept constant. The results indicate that plasticizer had a significant effect on the drug permeability of the free films, and its effect depended on the drying temperature. When the drying temperature was extremely low (e.g., 53°C), the drug permeability decreased with increasing plasticizer concentration. It is because the plasticizer could dramatically decrease the minimum film formation temperature (MFT) (2). If the plasticizer concentration was 70% and the drying temperature was 53°C, the continuous film could not be formed because the environment temperature was below the MFT. Therefore, the drug permeability of the film was high. Along with the increasing plasticizer concentration, the continuous film formed more easily because of the decreasing MFT, and the drug permeability decreased dramatically. But, for the drying temperature of 87°C, it was another case. The drying temperature was above the MFT, and continuous films could form as the plasticizer concentration was 50%. The drug permeability showed an increasing tendency when the plasticizer concentration increased. This is because more plasticizer remained in the films if the original plasticizer concentration was high. More water-soluble plasticizer certainly makes the film porous and enhances the drug permeability.

Drying temperature and drying time may have had the same effect on the drug permeability of the films. A longer drying time can dramatically reduce the drug permeability at 53°C, but it could cause a slight increase of permeability at 87°C. The reason is that a longer drying



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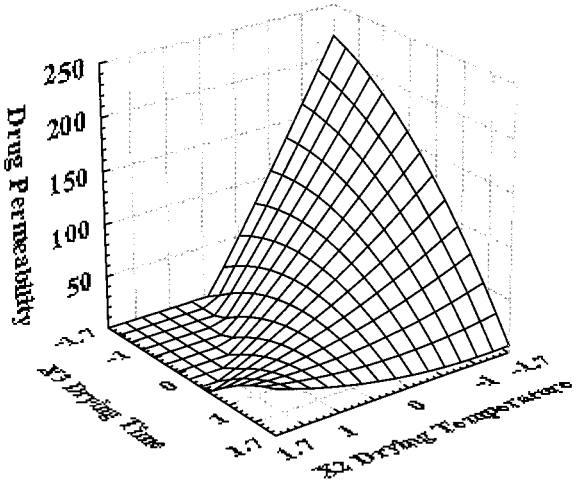

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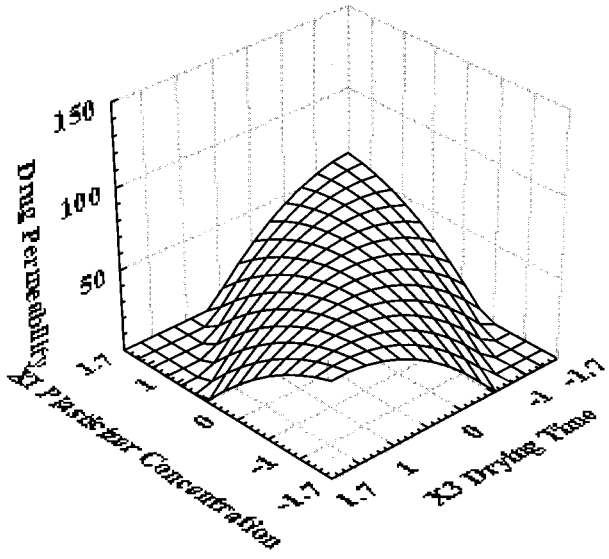

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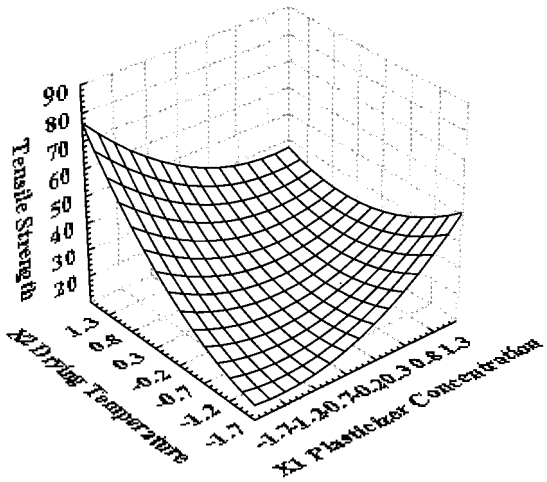
Figure 3. The three-dimensional diagram of drug permeability as a function of any two factors among X_1 (plasticizer concentration), X_2 (drying time), and X_3 (drying temperature): (a) plasticizer concentration kept constant at 100%; (b) drying time kept constant at 24 hr; (c) drying temperature kept constant at 70°C.



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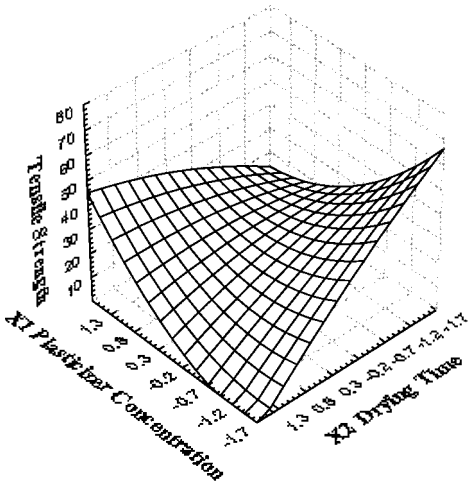

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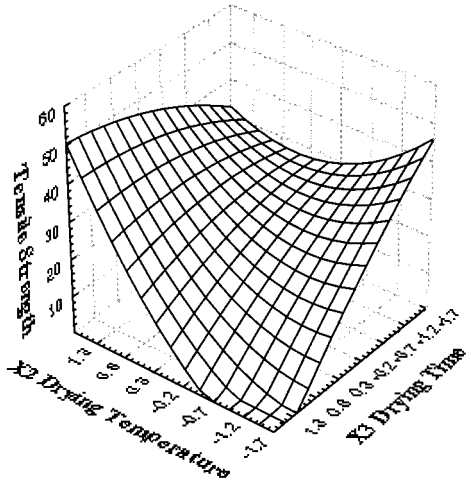

(c)

time at a lower drying temperature could evaporate the water and help the film formation. At a higher drying temperature, the free film could form easily at a shorter drying time. Longer drying time could only cause more evaporation of plasticizer and lead to defects in the films. Drug permeability increased if defects were present in the film. On the other hand, if the drying temperature was above the MFT and the drying time was kept constant, the higher drying temperature caused the decrease of drug permeability because of continuous film formation. However, for a longer drying time (i.e., 36 hr or longer), the higher drying temperature caused the formation of cracks on the films and led to higher drug permeability. Figure 3c shows the drug permeability as a function of drying time X_3 and plasticizer concentration X_1 for a drying temperature of 70°C. From the graph, we could draw the conclusion that all kinds of formulations could form continuous films at the drying temperature. When the plasticizer concentration is 50%, the longer drying time may cause evaporation of plasticizer, and cracks may form on the free films. Therefore, the drug permeability increased with the increasing drying time at low plasticizer concentration. If the plasticizer concentration was 150%, the drug permeability may be caused mainly by the presence of plasticizer. The longer drying time may lead to more evaporation of plasticizer and reduce the drug permeability.

Mechanical Properties

To prepare microporous osmotic pump tablets, the films produced with the CA pseudolatex coating system must endure high osmotic pressure promoted by the tablet cores. Tensile strength is the most important mechanical property that could represent the function of the film coated outside the tablet core. In this paper, more emphasis was paid to the factors that affect tensile strength of free films. Figure 4 shows the three-dimensional diagram of tensile strength as a function of any two factors among X_1 (plasticizer concentration), X_2 (drying temperature), and X_3 (drying time), while the other factor is kept constant. When the drying temperature was low, (e.g., 53°C),

Figure 4. The three-dimensional diagram of tensile strength as a function of any two factors among X_1 (plasticizer concentration), X_2 (drying time), and X_3 (drying temperature): (a) drying time kept constant at 24 hr; (b) drying temperature keep constant at 70°C; (c) plasticizer concentration kept constant at 100%.

the increasing plasticizer concentration would lead to the decrease in tensile strength. The same result was also obtained when the drying time was 12 hr and the drying temperature was kept constant at 70°C. The reason is that more plasticizer would remain in the film if the original plasticizer concentration was high. Plasticizer modified the physical properties of the polymers to improve film-forming behavior. In particular, plasticizer converts a hard, brittle polymer into a softer, more flexible material by reducing the glass transition T_g and MFT. Nevertheless, for a higher drying temperature and longer drying time, the result may be different. More plasticizer evaporated if the film was cured at a higher temperature or for a long time. The loss of plasticizer would lead the film to become hard and brittle. As the drying temperature increased from 53°C to 87°C, the tensile strength also increased if the plasticizer was kept constant at 50%. It is essential for the drying temperature to exceed MFT to form continuous films. Therefore, a higher drying temperature would help film formation and increase the tensile strength of the film. However, if the plasticizer concentration was 150%, the film could form at 53°C, and the increase of drying temperature had little effect on tensile strength.

Drying time also influenced the tensile strength of the films. If the drying temperature was kept at 70°C and the original plasticizer concentration was 50%, the longer drying time evaporated the plasticizer and made the film brittle. A longer drying time resulted in decrease of the tensile strength, while for films prepared with 150% plasticizer, it was another case. The plasticizer was enough for film formation, and excessive plasticizer made the film softer. For these circumstances, a longer drying time evaporated the plasticizer and made the tensile strength increase.

CONCLUSION

The plasticizer content, drying time, and drying temperature could affect the permeability and mechanical properties of CA pseudolatex free films. Drying temperature and drying time were essential for the film formation. However, plasticizer evaporation would occur during the drying process. Plasticizer reduces the MFT and T_g of the polymer. Excessive plasticizer reduces the tensile strength of the films. In addition, high plasticizer also increases the drug permeability of the film. Systematic consideration must be paid to the coating formulation when preparing the microporous osmotic pump tablets with CA pseudolatex.

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