Permeability Study on Cellulose Acetate Butyrate Coating Film

Please note: This article is the original unedited version of the article that was featured in *Drug Delivery Technology,* Vol. (8), NO. (2), 46-51 (2008).

Authors: Jinghua Yuan*, Doug Dunn, Nancy M. Clipse, and Ray J. Newton, Jr.

Formulation Products Lab
Pharmaceutical Formulations Group
Eastman Chemical Company
Kingsport, Tennessee 37662

Jinghua Yuan: Principal Technical Service Representative
Tel: (423) 229-8627
Fax (423) 224-0414
jinghua@eastman.com

**To whom all correspondence should be addressed.*

Introduction

Cellulose acetate butyrate (CAB) belongs to cellulose ester family. CAB could be used for tabletting as a matrix material (1) or taste-masking when combined with cellulose acetate (CA) and hydroxypropyl cellulose (2), and has been reported in patents for semi-permeable membrane in osmotic drug delivery systems (3,4). Particularly, CAB could be used in extended release due to its more hydrophobic nature.

Little work has been reported related to the permeability of CAB films. Recently, a group of researchers from Alza conducted a study to characterize CAB membrane properties with respect to performance of OROS® systems. Typically, the release rate of drugs from an OROS® is controlled by semipermeable membranes composed of cellulose acetate. They found that the CAB membrane matched the CA membrane in robustness but had superior drying properties, offering particular advantages for thermolabile formulations (5).

The objectives of this study were to investigate the effects of formulation variables on CAB coating film performance, to examine CAB lot to lot variation effects on the permeability of the coating films and to compare the permeability of CAB coating film with those of CA coating film at the similar formulation and under the same coating processing conditions.

Experimental

Materials.

Cellulose acetate butyrate CAB-171-15NF and cellulose acetate CA-398-10NF/EP (Eastman Chemical Company, Kingsport, TN) were used in the study. The typical physical properties of CAB are listed in Table I.

Table I. Typical Physical Properties of CAB-171-15NF.

Property	**Range**
Viscosity (sec)	14 - 24
Acetyl (wt%)/ DS	29.5 / 2.0
Butyryl (wt%) / DS	17.0 / 0.7
Hydroxyl (wt%) / DS	1.1 / 0.3
Melting Range (°C)	230 - 240
Glass transition temperature (Tg, °C)	152

Note: 1. properties reported here are typical of average lots. Eastman makes no *representation that the material in any particular shipment will conform exactly to the listed properties.*

2. *DS: degree of substitution.*
3. *Tg is obtained from the second heating scan by DSC.*

A coating formulation included CAB-171-15NF or CA-398-10NF/EP (CA), polyethylene glycol 3350 (PEG 3350, Sigma Aldrich, St Louis, MO) as the plasticizer (Pz), acetone (high purity solvent, B&J Brand, Burdick & Jackson, Muskegon, MI) and deionized water (NANOpure water system, Barnstead, Van Nuys, CA) as the solvent system. The model tablets to be coated consisted of 98.5% of POLYOX water-soluble resins with a molecular weight of 5,000,000 (Dow Chemical, Midland, MI); 0.5% of colorant (Sensient Technologies Corp., St. Louis, MO), and 1.0% of magnesium stearate (Mallinckrodt Baker Inc., Phillipsburg, NJ). All of the materials were used as received.

Methods.

Preparation of model tablets. POLYOX with a molecular weight of 5, 000,000, blue dye, and magnesium sterarate were blended in a v-blender (The Patterson Kelly Co. Inc, East Stroudsburg, PA) for three minutes with the intensifying bar on for 15 seconds. The above mixture was then compressed into 250.0 mg tablets on a rotary tablet press (D3B 16 station, Manesty, England) under 400 lb compression force.

Preparation of CAB coating solutiona. A CAB coating solution, with 6.0 wt% solid content, was prepared by dissolving Pz, if any, in water for 1. 5 hours, then add most of the needed acetone. Finally add CAB gradually under stirring. After all CAB dispersed, continue to stir for another two hours. Add a calculated amount of acetone to compensate the loss due to evaporation during the dissolving process. Twelve formulations listed in table II were investigated.

Table II. Coating Formulation Investigated.

Formulation ID	CAB (g)	PEG 3350 (g)	Water (g)	Acetone (g)	PEG/CAB ratio	% Water
1	71.05	8.95	66.67	1186.66	0.13	5.00
2	71.05	8.95	133.33	1120.00	0.13	10.00
3	80.00	0.00	0.00	1253.33	0.00	0.00
4	80.00	0.00	66.67	1186.66	0.00	5.00
5	71.05	8.95	66.67	1186.66	0.13	5.00
6	62.02	17.98	66.67	1186.66	0.29	5.00
7	71.05	8.95	40.00	1213.33	0.13	3.00
8	62.02	17.98	53.33	1200.00	0.29	4.00
9	71.05	8.95	66.67	1186.66	0.13	5.00
10	80.00	0.00	133.33	1120.00	0.00	10.00

11	**62.02**	**17.98**	**133.33**	**1120.00**	**0.29**	**10.00**
12	**71.05**	**8.95**	**66.67**	**1186.66**	**0.13**	**5.00**

Procedures of performing CAB coating. 800.0 g of tablets were coated with a CAB coating solution in each run. All of the coating runs, with a theoretical coating weight of 10.0 wt% relative to the tablet weight, were performed in a pan coater (COMPU-LAB, Thomas Engineering, Inc., Hoffman Estates, IL) with one spray gun under the processing conditions indicated in Table III. All of the coating formulations were repeated twice.

Table III. Coating Processing Conditions.

Factor	**Condition**
Equipment	12 " Pan coater (COMPU-LAB, Thomas Engineering)
Nozzle	35100-ss
Substrate	250.0 mg tablets
Pan charge	800.0 g
Inlet temperature	25.0 °C
Air flow rate	175.0 cfm
Pan rotate speed	15.0 RPM
Atomized air pressure	15 psi
Spray rate	20.0 ml/min for 5 min; increased to 25.0 ml/min for another 5 min; and maintained at 30.0 ml/min for the rest of the run

Measurement of the permeability of CAB coating film. The permeability of CAB coating film was determined by performing a water uptake test. Eight tablets from each run were randomly selected and tested in 1000 ml of deionized water at 37 °C using a standard USP disintegration tester. At selected time intervals, the tablets were taken out, dried gently with a tissue, and weighed. The water uptake at time "t" is the tablet weight at time "t" minus the tablet weight at time zero (tablet weight before testing). The testing was terminated after 9 hours. The average value of eight tablet results was used in analysis.

Results and Discussions

Pz and water effect on the permeability of CAB coating film. CAB coated tablets were tested in D.I. water to determine water uptake as a function of time. It was observed that the water uptake rate is greater in the first hour, then the uptake rate decreases slightly and is maintained at the rate for the rest of the testing. Figure 1 shows an example of water uptake changing with time.

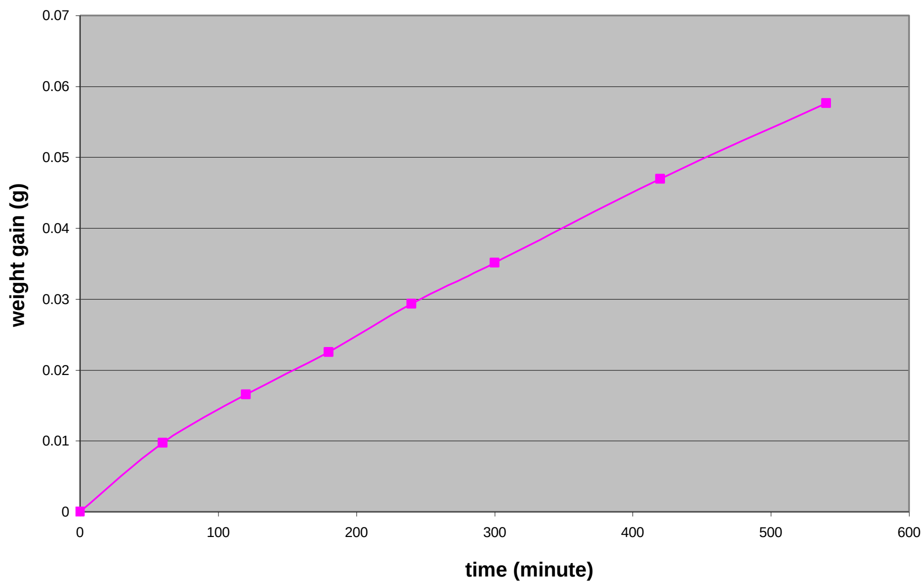

Figure 1. Water uptake of CAB coated tablets changes with time.

The observed shift in water uptake rate may be due to a change in the mechanism of water transport through the coated film. In the beginning of the experiment, water starts to penetrate the film by occupying the pores in the film; water may start to diffuse through the film simultaneously, but at a very low rate. When all pores are filled with water, water penetrates through the film only by diffusion. Since the diffusion step is slow, the water uptake rate decreases. After the first hour, the water uptake rate remains constant at the diffusion controlled rate.

Based on the fact that the water uptake rate changes within the testing range, two models were established to fit the experimental data. Design Expert ®software (Design Expert V7., Stat-Ease, Inc., Minneapolis, MN) was employed to analyze the data. The water uptake rates are predicted as follows:

For the first region (about the first hour),
Water uptake rate (g/min) =

+6.50370E-005	
-1.05288E-006	* PEG
-4.91641E-006	* Water
+2.54453E-006	* PEG * Water
+1.02019E-005	* PEG^2
+9.62682E-007	* Water^2

For the second region (beyond the first hour),
Water uptake rate (g/min) =

+1.07750E-004	
-6.48804E-007	* PEG
-7.22356E-006	* Water
+3.73240E-006	* PEG * Water
+1.53744E-005	* PEG^2
+1.29684E-006	* Water^2

Here: PEG and water are the corresponding concentration in the formulation in %.

The models indicate that Pz and water level affect the permeability of CAB coating significantly, visually it is shown in Figures 2 and 3.

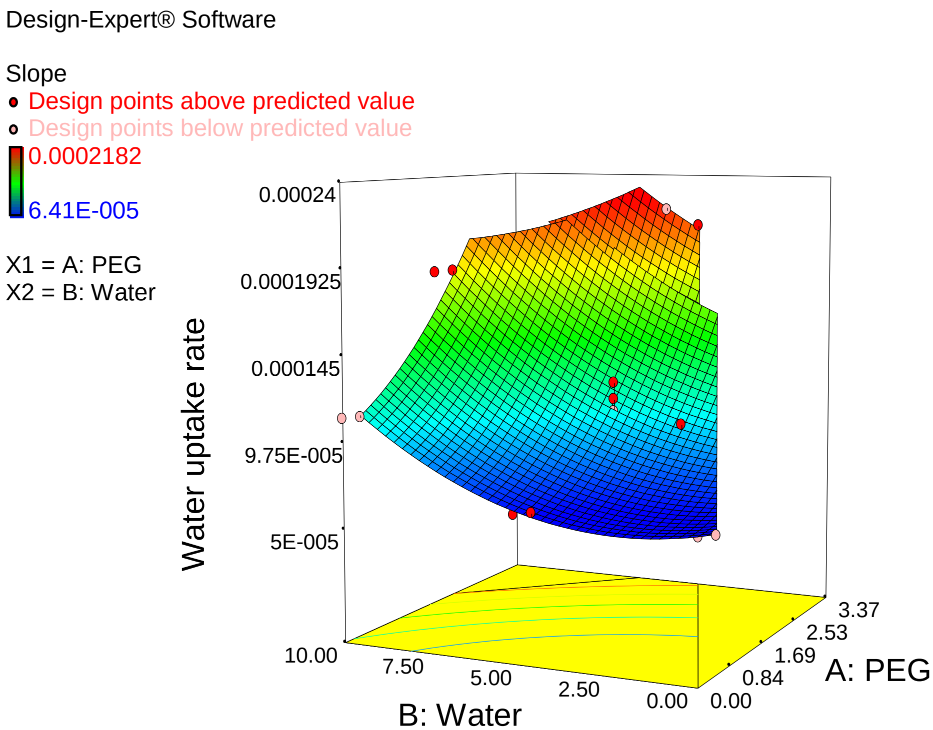

Figure 2. Water uptake rate changed with Pz and water in the beginning of the testing.

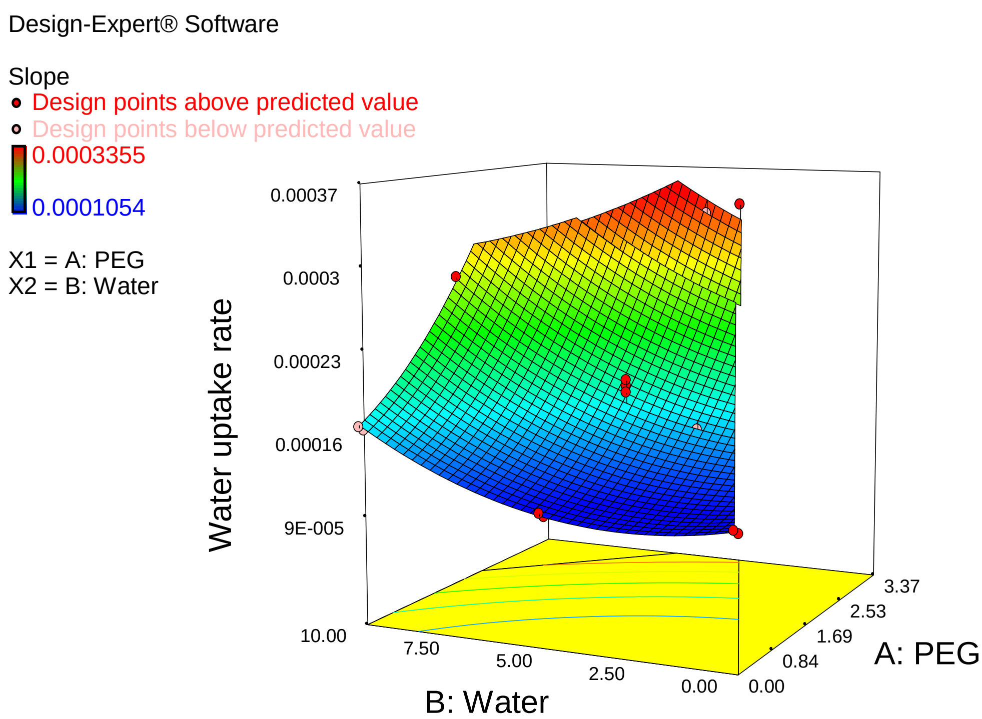

Figure 3. Water uptake rate changed with Pz and water in the second region of the testing.

Figure 4 shows an example of the model predicted results and experimental data. The agreement between the prediction and experimental data is clearly shown.

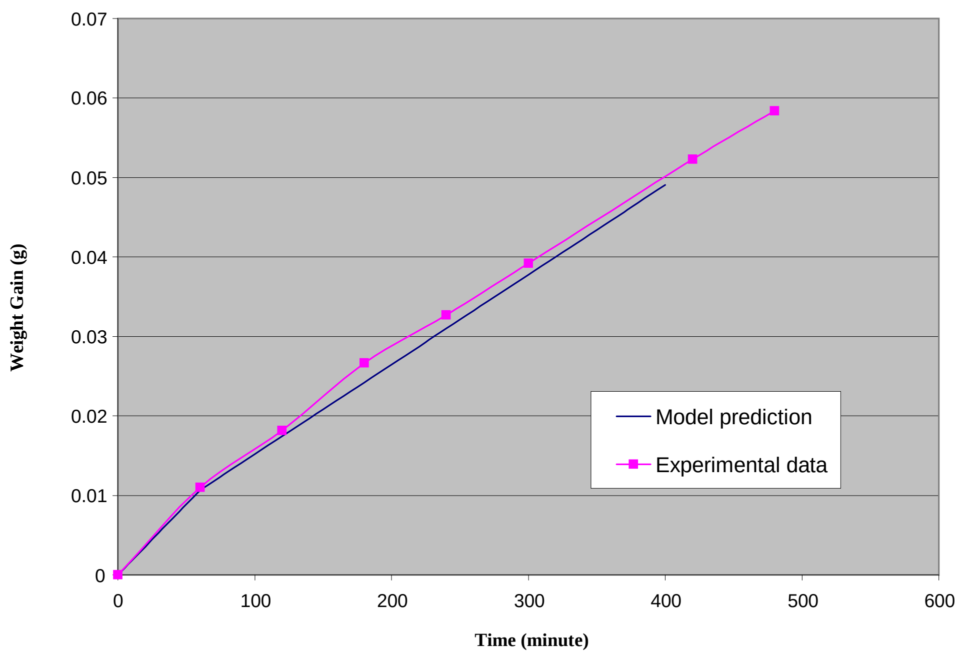

Figure 4. Comparison of model predicted results and experimental data.
Formulation: Pz/CAB = 13%; water = 5.00%.

CAB lot variation effect on the permeability of CAB coating film. To examine the effects of variation in CAB lot on the permeability of CAB coating films, three CAB lots were selected. Table IV lists the product information of three CAB lots.

Table IV. Product Information of Three CAB Lots.

Test	Lot 1	Lot 2	Lot 3	**Specification**
ASTM-A Viscosity, sec	21.32	18.80	16.84	14.0-24.0
Butyryl by GC, wt%	17.06	17.48	17.31	16.5-19.0
Free Acidity by IC, %	0.0101	0.0147	0.012	< 0.1
Acetyl by GC, wt%	30.08	30.48	30.14	28.0-31.0
Hydroxyl by Titration, wt%	1.10	1.07	1.03	0.8-1.4
NF Water, wt%	0.81	0.93	0.90	< 5.0

The same model tablets were coated with these three CAB lots under the same coating conditions as described before with an exception of atomized air pressure being 20 psi instead of 15 psi used in other coating runs. The coating formulation was Pz/CAB=13%, water =5.00% (formulation #1 in Table II).

For each lot of CAB, two separate coating runs were performed. Water uptake experiments were conducted with eight randomly selected tablets. The average value was reported. Figure 5 displays the water uptake results.

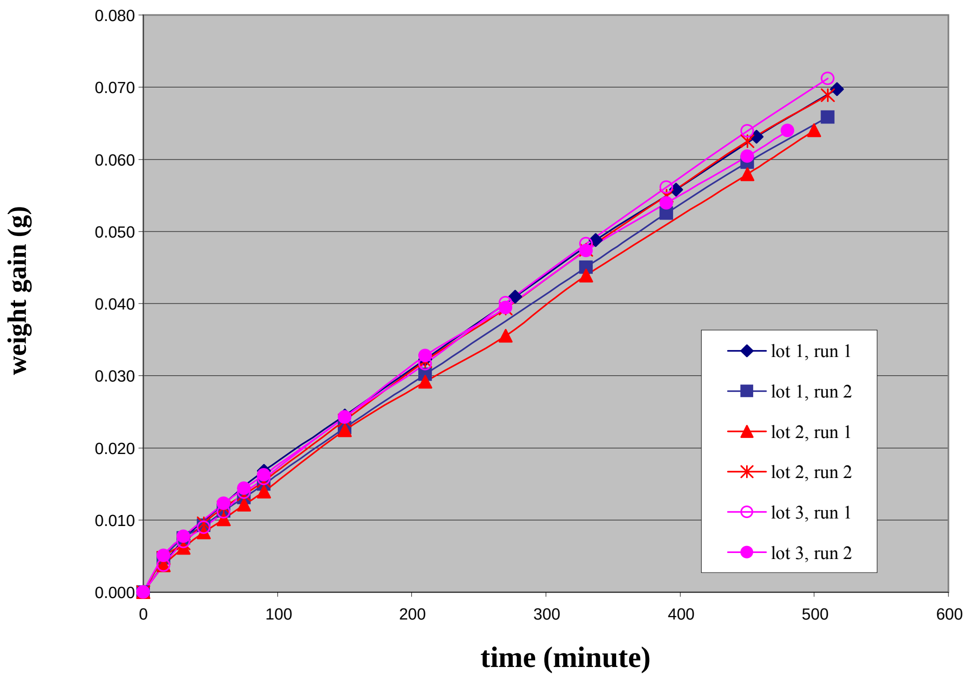

Figure 5. Water uptake results from three CAB lots.

To determine the lot to lot variation, statistical analysis was performed on center points in the experimental design. There were four center points in the design; formulation #1, #5, #9 and #12. Table V lists the water uptake data variation at 500 minutes. The variation was calculated as: variation = (run2 – run1)/ run1 *100%

Table V. Statistical Analysis of Lot Variations.

	Run 1	**Run 2**	**Variation (%)**
Center Point #1	0.060	0.064	6.7
Center Point #2	0.058	0.056	3.4
Center Point #3	0.061	0.062	1.6
Center Point #4	0.058	0.057	1.7
Lot 1	0.069	0.066	4.3
Lot 2	0.068	0.064	5.9
Lot 3	0.071	0.068	4.2

The variation results from the center point formulation indicate that the water uptake difference at 500 minute between two runs could be up to 7% for the same coating formulation under the same coating conditions.
The water uptake variations of three CAB lots between two runs are also listed in Table V. The data suggest that the variation of lot to lot is within the experimental errors. So, it is concluded that the variation of CAB lots in the studied range doesn't significantly impact on the permeability of the coated films.

<u>Comparison of permeability of CA and CAB coating film.</u> The model tablets were coated with CA or CAB using the same formulation, and the permeability of CA or CAB coating film was determined by water uptake tests. Figures 6 and 7 are the results.

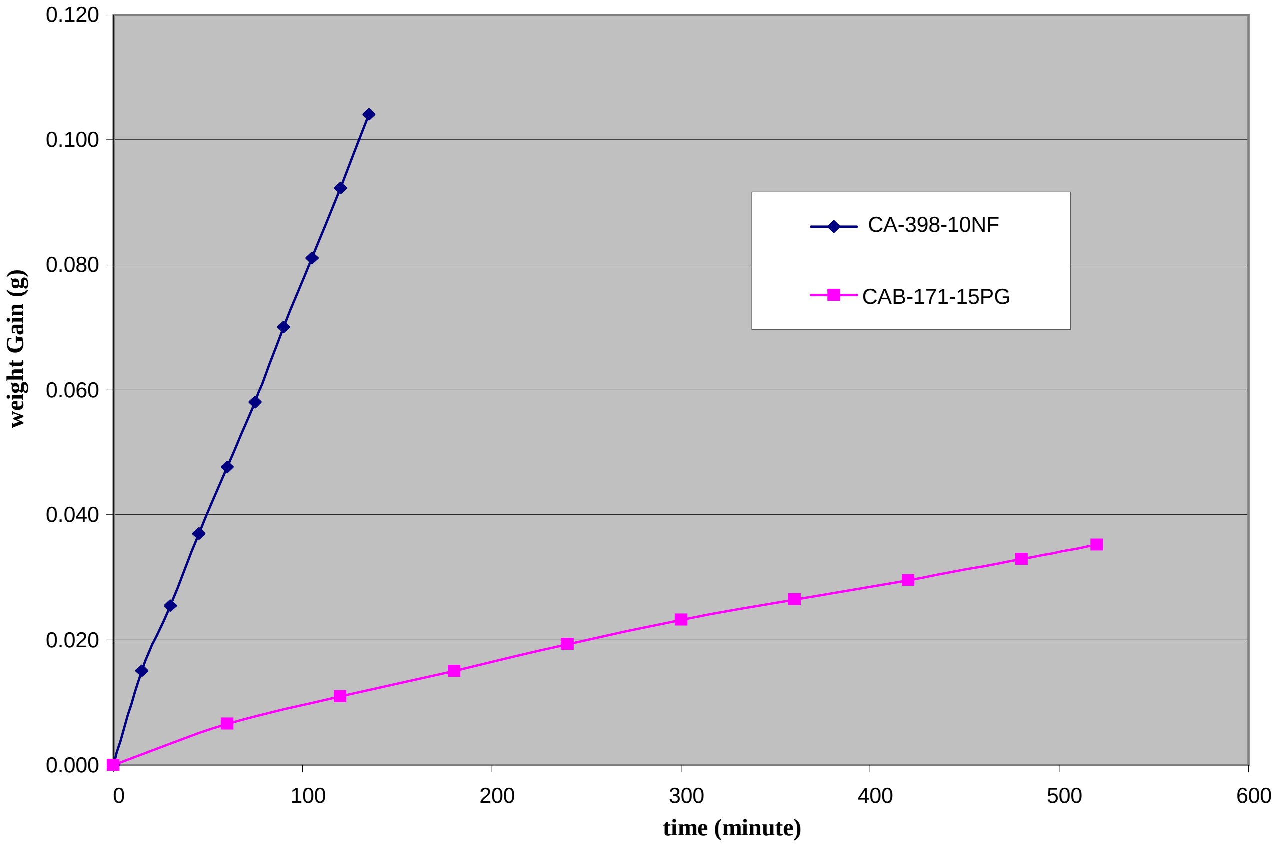

Figure 6. Comparison of water uptake between CA and CAB coating.
Formulation: Pz/polymer = 0%; water = 0.00%.

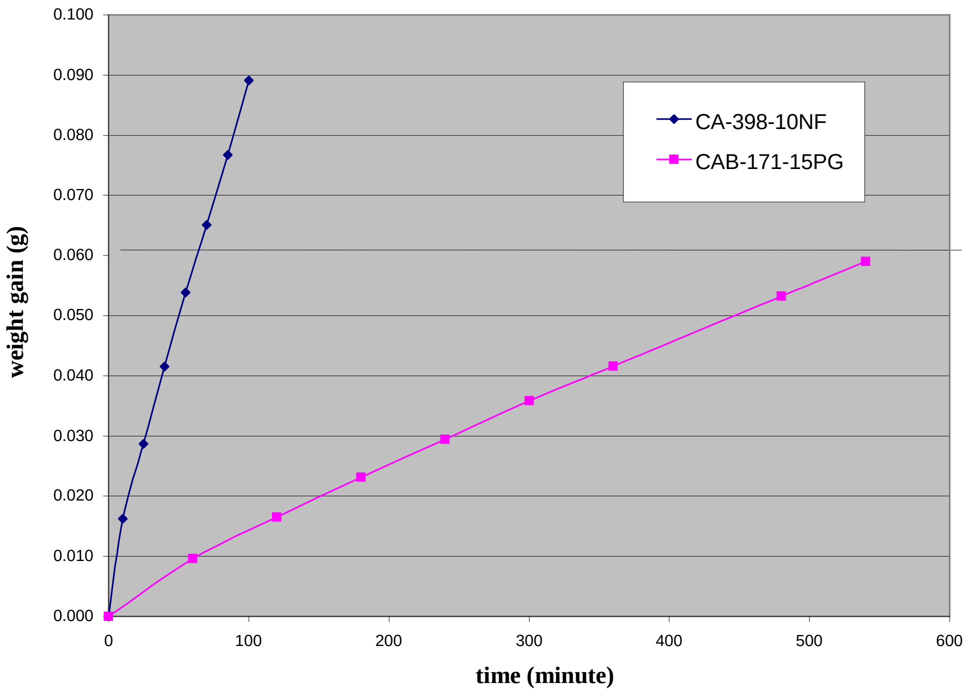

Figure 7. Comparison of water uptake between CA and CAB coating.
Formulation: Pz/Polymer = 13%; water = 5.00%.

It is not surprising that CAB coating has lower permeability due to its hydrophobic nature. SEM images showed that no obvious differences in morphology of the coating films between CA and CAB (see Figures 7 and 8). So, the difference in water uptake between CA and CAB coating are mainly determined by two factors: 1. the nature of the polymers - The more hydrophilic type of polymer CA would allow water fast diffuses through the coating film, which gives higher water uptake. 2. the differences in molecular weight of the polymers - CA has a lower molecular weight. At the same amount of coating weight, the lower molecular weight polymer has more free volume which enables water diffuses through the film at a higher rate. Combining these two factors, it is expected that water uptake from CA coating film would be much higher than CAB coating film.

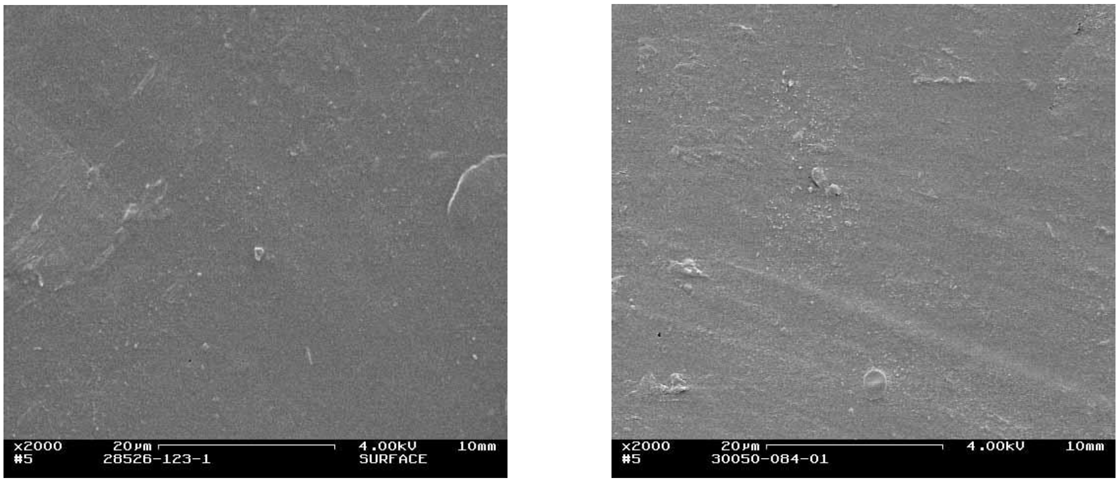

Figure 8. SEM surface images. Left: CA coating film; right: CAB coating film.

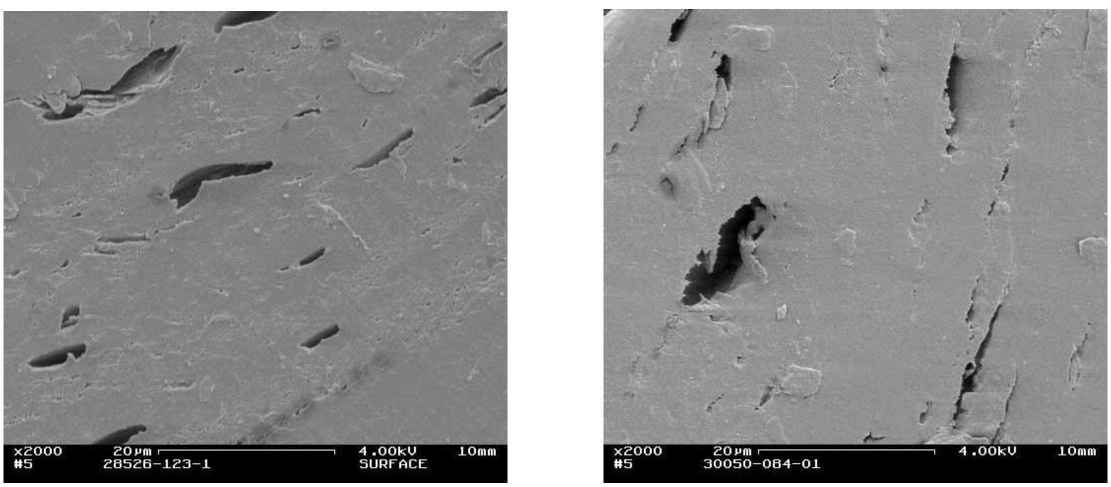

Figure 9. SEM cross-section images. Left: CA coating film; right: CAB coating film.

Conclusions

The study has demonstrated that formulation variables, such as, plasticizer level and water level will affect the permeability of the CAB coating films. It seems that PEG has a major influence. CAB lot variation doesn't seem to have significant impact on the permeability of the coated films. Comparison of the permeability between CA and CAB coated films suggests that CA film is more permeable. One could design a desirable permeability of a membrane by selecting formulation variables and the type of a polymer.

References

1. J. Yuan and S.H. Wu, "Sustained-Release Tablets via Direct Compression: A Feasibility Study Using Cellulose Acetate and Cellulose Acetate Butyrate," *Pharm. Technol.* **24** (10), 92-106 (2000).
2. E.J. Roche, "Taste Masking and Sustained Release Coatings for Pharmaceuticals," US Patent 5074114 (1991).
3. C.M. Chen, C.S.L. Chiao and J. Suarez, "Controlled Release Tablet Formulation," US Patent 5458887 (1994).
4. G.M. Zentner, G.S. Rork and K.J. Himmelstein, "Controlled Porosity Osmotic Pump," US Patent 4968507 (1990).
5. A. Shanbhag, B. Barclay, J. Koziara and P. Shivanand, "Application of Cellulose Acetate Butyrate-based Membrane for Osmotic Drug Delivery," *Cellulose* **14**, 65-71 (2007).