Permeability Study on the Coating Film Consisting of
CA-398-10 NF/EP and CA- 320S NF/EP

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INTRODUCTION

Cellulose esters form the most suitable semipermeable membranes for osmotic drug delivery systems. Eastman produces several types of cellulose esters, in which CA-398-10 NF/EP and CA-320S NF/EP are the most commonly used for the application. CA-398-10 NF/EP and CA-320S NF/EP could be used alone (1-3) or combined to form the membrane (4). CA-398-10 NF/EP and CA-320S NF/EP have different acetyl content (CA-398-10 NF/EP: 39.8% vs. CA-320S NF/EP: 32.0%) and physical properties (5). These differences in properties result in different permeability of the coating films. One would expect that the permeability of the coating films could be tailored by adjusting the ratio of two polymers in the coating solution to fit particular needs.

The objectives of this study were to investigate the effects of the ratio of CA-398-10 NF /EP to CA-320S NF/EP on the permeability of the coating films, to investigate the effects of plasticizer level and molecular weight on the permeability of the coating films, and to address the effect of acetyl content variation in CA-398-10 NF/EP polymer on the permeability of the coating films.

MATERIALS

To determine the permeability of coating films, the designed coating solution was coated on model tablets. The model tablets consisted of POLYOX water-soluble resins with a molecular weight of 5,000,000 (Dow Chemical, Midland, MI), colorant (Sensient Technologies Corp., St. Louis, MO), and magnesium stearate (Mallinckrodt Baker Inc., Phillipsburg, NJ). For coating solutions, CA-398-10 NF/EP with an acetyl content at 39.4% (CA-NF, Eastman Chemical Company, Kingsport, TN), CA-398-10 TG (technical grade) with an acetyl content at 40.3% (CA-TG, Eastman Chemical Company) and CA-320S NF/EP (Eastman Chemical Company) were used in the study. Plasticizers (Pz) investigated were polyethylene glycol 400 (PEG 400) and polyethylene glycol 3350 (PEG 3350) (Sigma Aldrich, St Louis, MO). High purity acetone (B&J Brand, Burdick & Jackson, Muskegon, MI) and deionized water (NANOpure water system, Barnstead, Van Nuys, CA) were used as the solvent system. All of the materials were used as received.

METHODS

<u>Experimental design of coating formulation</u>

Four groups of coating formulations were designed. Table 1 lists one group (Group 1) of formulations having CA-320S NF/EP and low acetyl content of CA-398-10 NF/EP with PEG 400 as the plasticizer. The table is color coded so that one color region has the same ratio of CA-398-10 NF/EP to CA-320S NF/EP with changing plasticizer concentration. Group 2 is the formulations having CA-320S NF/EP and low acetyl content of CA-398-10 NF/EP with PEG 3350 as the plasticizer. The water concentration is kept at 10.0% in the total solution for all formulations. The other two groups of formulations were the same compositions as Group 1 and 2, except high acetyl content of

CA-398-10 TG was used to replace the low acetyl content CA. There were 36 formulations in total.

Table 1. Formulations Having CA-320S NF/EP and Low Acetyl Content of CA-398-10 NF/EP with PEG 400 as the Plasticizer.

Sample ID	CA	Total CA (g)	PEG 400(g)	Water (g)	Acetone (g)	PEG/CA
1	50% NF + 50% CA 320S	80.00	0.00	133.33	1120.00	0.00
2	50% NF + 50% CA 320S	72.00	8.00	133.33	1120.00	0.10
3	50% NF + 50% CA 320S	64.00	16.00	133.33	1120.00	0.20
4	75% NF + 25% CA 320S	80.00	0.00	133.33	1120.00	0.00
5	75% NF + 25% CA 320S	72.00	8.00	133.33	1120.00	0.10
6	75% NF + 25% CA 320S	64.00	16.00	133.33	1120.00	0.20
7	90% NF + 10% CA 320S	80.00	0.00	133.33	1120.00	0.00
8	90% NF + 10% CA 320S	72.00	8.00	133.33	1120.00	0.10
9	90% NF + 10% CA 320S	64.00	16.00	133.33	1120.00	0.20

Preparation of model tablets and coating solutions

The model tablets and coating solutions were prepared according to the procedures described in a previous work (6).

Procedures of performing coating

A quantity of 800.0 g of tablets was coated with one 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 a previous work (6). The inlet temperature was controlled at 25 °C and the bed temperature was 21 °C. All of the coating formulations were repeated twice.

Determination of the permeability of coating films

The permeability of coating films was determined by a water uptake test (7). The test was terminated when the water uptake by the tablet caused the internal pressure to increase to a point where the film coating ruptured. The average weight gain of eight tablets was used in the data analysis.

RESULTS & DISCUSSIONS

Permeability of the coating films is determined by water uptake experiments. The faster water uptake rate indicates the film is more permeable. It was observed that the water uptake rate changed from fast to slightly slower around the first five minutes during a water uptake experiment. The shift in uptake rate may be due to the change in mechanism of water transporting through the film. In the beginning of the testing, by capillary action water will occupy the pores or small channels formed during coating; after that water will penetrate through the membrane by diffusion. Because the diffusion step is slower, the water uptake rate governed by diffusion is slower.

Water uptake results were analyzed with statistical tools. Design Expert® software (Design Expert V7., Stat-Ease, Inc., Minneapolis, MN) was employed to establish models to predict water uptake rates. Because water uptake rates changed during the course of testing, two models were obtained to describe the water uptake rates for one group of formulations. There are eight models developed for four groups of formulations. The models are displayed in Table 2.

Table 2. Established Models to Predict Water Uptake Rates.

Acetyl content of CA-398-10 (%)	Plasticizer	Water uptake rate model	
		To 5 minutes	Beyond 5 minutes
39.4	PEG 400	0.001231032 + 5.65762E-05 * CA320S +1.71733E-05* CA_NF +0.000375182 * PEG -1.07434E-06* CA320S * CA_NF -2.72024E-07* CA320S * PEG -4.09833E-06 * CA_NF * PEG	0.000622234 -7.68814E-06 * CA320S +1.84631E-06 * CA_NF +0.000182026* PEG +5.34942E-07*CA320S * CA_NF -1.11611E-06* CA_NF * PEG
40.3	PEG 400	0.001377644 +5.71842E-05 * CA320S +2.02306E-05 * CA_TG +0.00040116 * PEG -1.07434E-06 * CA320S * CA_TG -2.65677E-06* CA320S * PEG -4.09833E-06* CA_TG * PEG	0.000622234 -7.68814E-06 * CA320S +1.84631E-06* CA_TG +0.00014694* PEG +5.34942E-07* CA320S * CA_TG -1.11611E-06* CA_TG * PEG
39.4	PEG 3350	0.001326205 +5.89555E-05* CA320S +1.71733E-05 * CA_NF +0.000373997 * PEG -1.07434E-06* CA320S * CA_NF -2.15027E-06 * CA320S * PEG -4.09833E-06 * CA_NF * PEG	0.000617775 -7.68814E-06 * CA320S +1.73484E-06* CA_NF +0.00023638 * PEG +5.34942E-07 * CA320S * CA_NF -2.50565E-06* CA_NF * PEG
40.3	PEG3350	0.001820165 +6.82472E-05* CA320S +2.02306E-05 * CA_TG +0.000376468* PEG -1.07434E-06 * CA320S * CA_TG -1.02092E-06* CA320S * PEG -4.09833E-06* CA_TG * PEG	0.000617775 -7.68814E-06* CA320S +1.73484E-06* CA_TG +0.000201294* PEG +5.34942E-07* CA320S * CA_TG -2.50565E-06* CA_TG * PEG

CA_NF: CA-398-10 NF/EP
CA_TG: CA-398-10 TG

The ratio of CA-398-10 NF/EP to CA-320S NF/EP effect on the water uptake of the coating films

To study the ratio of CA-398-10 NF/EP to CA-320S NF/EP effect on the permeability of the coating films, three ratios of CA-398-10 NF/EP to CA-320S NF/EP - 90/10, 75/25, and 50/50 (wt %), were investigated in the study. Figure 1 shows the results having CA-398-10 NF/EP with 39.4% acetyl and 11.1% of PEG 400 relative to the CA polymers weight in the formulations.

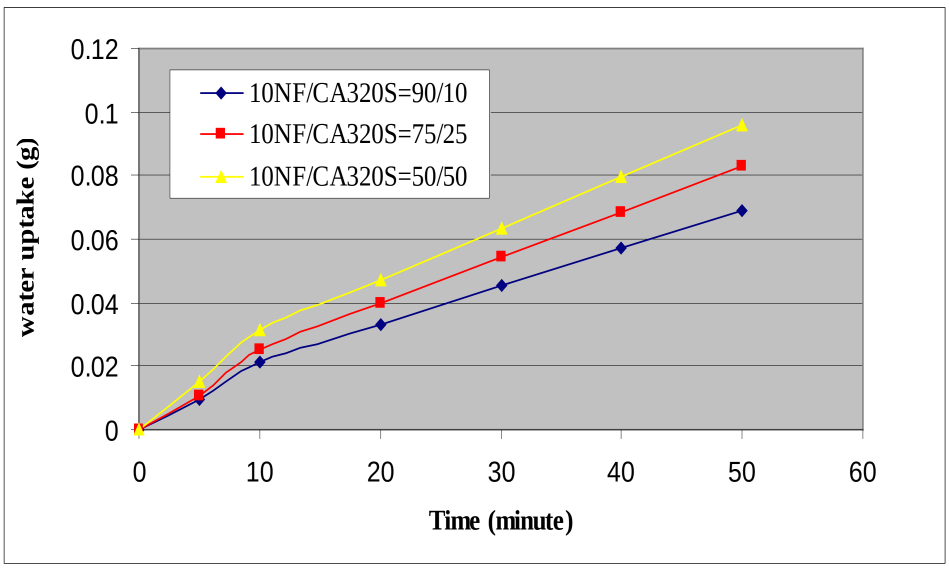


Figure 1. The ratio of CA-398-10 NF/EP to CA-320S NF/EP effect on the permeability of the coating films (PEG400 = 11.1% in the formulations).

It is known that the permeability of a CA film increases with decreasing acetyl content in the polymer (5). CA-320S NF/EP has acetyl content at 32%; its film is more permeable compared to a CA-398-10 NF/EP film with acetyl content at 39.8%. So, the more CA-

320S NF/EP in the formulation, the faster the rate of the water uptake. The trend maintains the same when PEG 3350 was used in the formulation.

The significant implication of this finding is that one can readily adjust the desired rate of water uptake in an osmotic drug delivery system by selecting the appropriate ratio of CA-398-10 NF/EP to CA-320S NF/EP to use in the coating formulation. Thus one can control the rate at which a drug is released from an osmotic tablet by controlling the rate of internal osmotic pressure buildup which is a direct function of the rate of water uptake by the tablet. Indeed this concept is already used commercially (8).

<u>Effect of PEG level and PEG molecular weight on the water uptake of the coating films</u>

PEG 400 and PEG 3350 at 0.0%, 11.1% and 25.0% relative to total CA polymer weight were studied to investigate the effect of PEG level and PEG molecular weight on the water uptake of coating films.

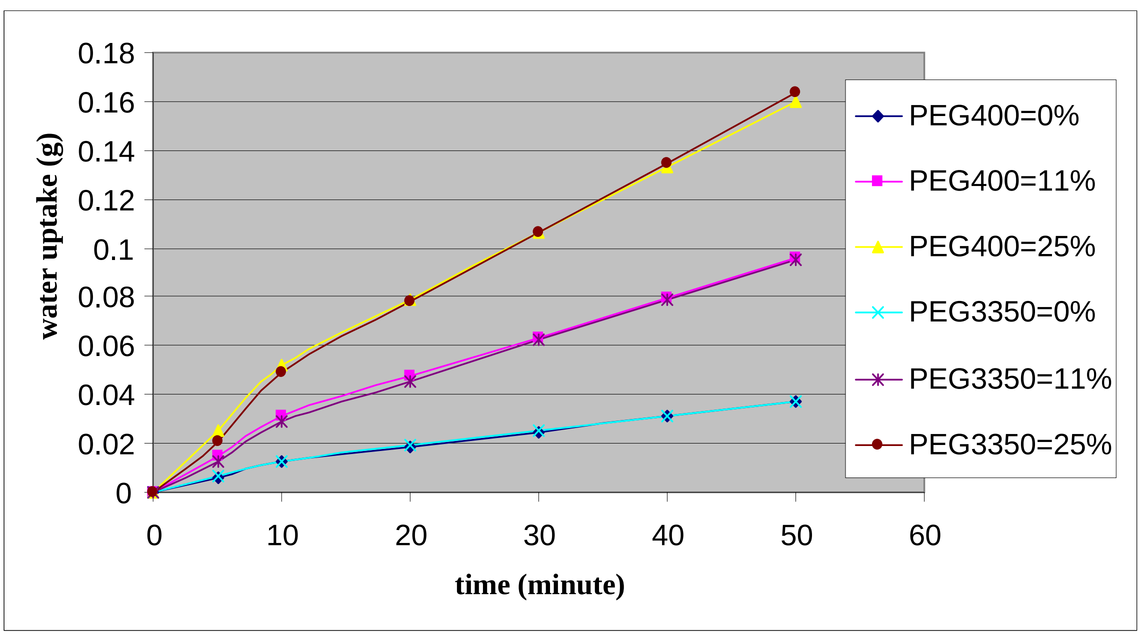


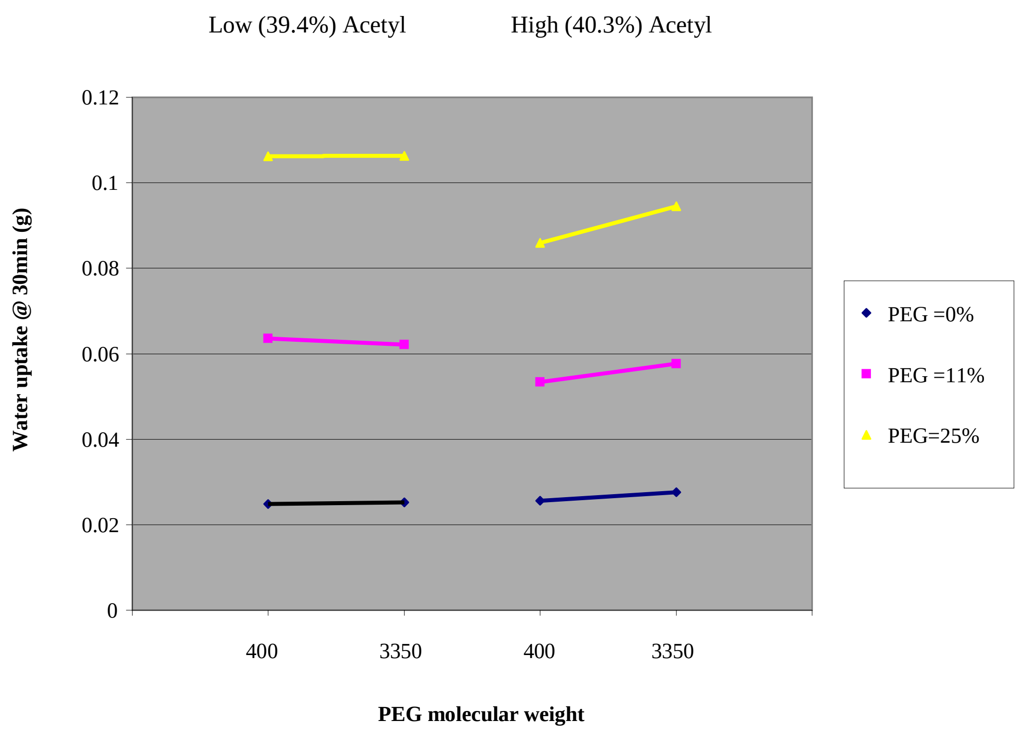
Figure 2. PEG level and molecular weight effect on the permeability of the coating films. CA-398-10 NF/EP/ CA-320S NF/EP = 50 /50; acetyl in 10 NF/EP = 39.4%.

Figure 2 displays the effect of PEG level and PEG molecular weight on the water uptake while the ratio of CA-398-10 NF/EP to CA-320S NF/EP was maintained at 50/50%. The results of this study show that PEG molecular weight has little, if any, impact on the rate of water uptake. However, PEG level has a significant effect as is seen from the 8 fold increase in the water uptake when the PEG is increased from 0 to 25% of the total CA polymer weight. Based on past research with cast films, it is expected that increasing the level of a hydrophilic plasticizer such as PEG would increase water uptake because these type plasticizers make the chains of polymers more flexible and more permeable.

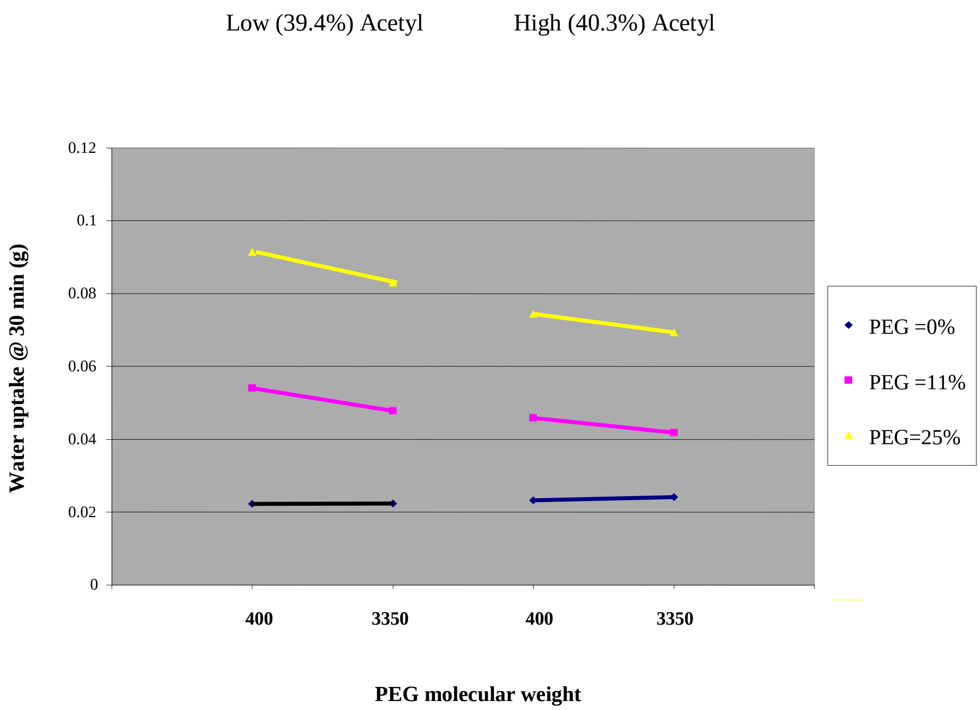
The effect of PEG molecular weight on the rate of water uptake of coating films is more complicated; it depends on other formulation factors, such as, ratio of CA-398-10 NF/EP to CA-320S NF/EP, and the acetyl content in CA-398-10 NF/EP. To better address the effect, consideration on the ratio of CA-398-10 NF/EP to CA-320S NF/EP must be included. It will be discussed next.

Effect of acetyl variation in CA-398-10 NF/EP polymer on the water uptake of coating films

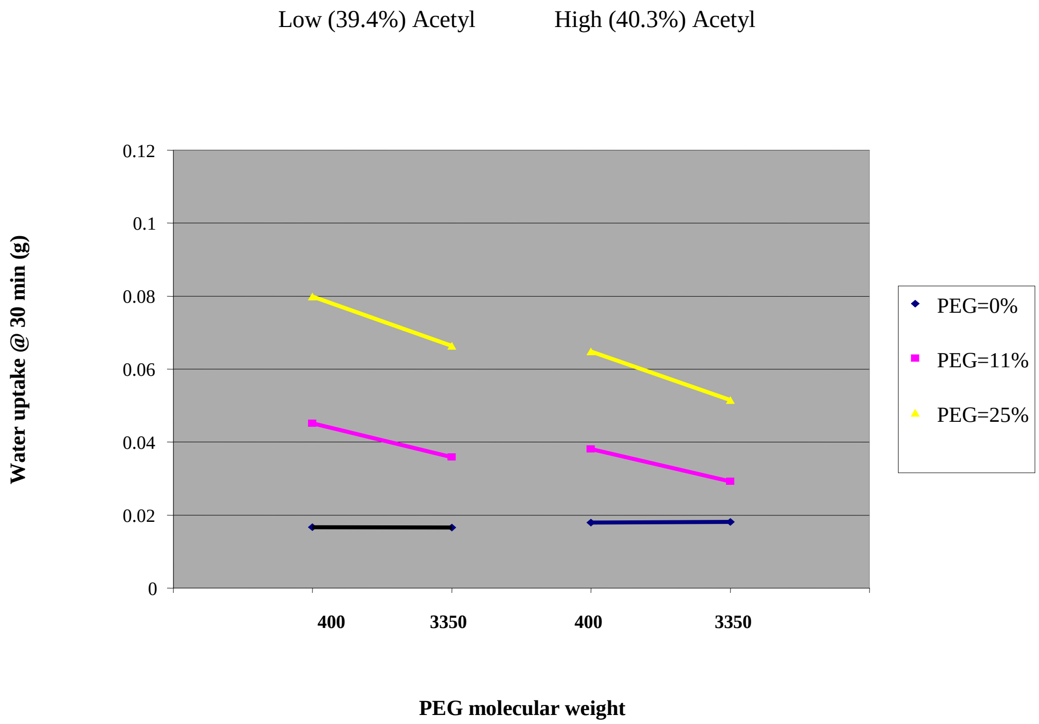
In this study, two acetyl contents of CA-398-10 were used; they were 39.4% (CA-NF) and 40.3% (CA-TG). Design Expert ®software was employed to establish models to predict water uptake rates (see Table 2). Based on the models, water uptake at 30 minutes for each formulation is predicted. The results are presented in Figure 3.



3a: CA-398-10/CA320S = 50/50
Left lines: low acetyl CA 398-10 was used; right lines: high acetyl CA 398-10 was used.



3b: CA-398-10/CA320S = 75/25
Left lines: low acetyl CA-398-10 was used; right lines: high acetyl CA-398-10 was used.



3c: CA-398-10/CA320S = 90/10

Left lines: low acetyl CA-398-10 was used; right lines: high acetyl CA-398-10 was used.

Figures 3a-3c. Predicted water uptakes at 30 minutes to show the effects of PEG level and PEG molecular weight, and acetyl variation in CA-398-10 polymer on the water uptake of the coating films.

It is observed that at a fixed ratio of CA-398-10 to CA-320S and without PEG in the formulations, a 1% acetyl variation (low to high - introduced by the CA-398-10) does not have a significant impact on the rate of water uptake, which is supported by the straight lines in Figure 3a – 3c. When PEG is present in the formulations and the ratio of CA-398-10 to CA-320S is greater than 50/50, the water uptake from PEG 400 plasticized films is slightly higher than those plasticized with PEG 3350. This is consistent with the results that have been published before (3). It is surprising that PEG molecular weight doesn't show significant influence on the water uptake when the ratio of CA-398-10 to CA-320S is at 50 /50. In this case, the water uptake is influenced mainly by the presence of the high level of CA-320S; therefore, it is impossible to distinguish any additional effect from PEG 400 versus PEG 3350.

The results in Figure 3 suggest when PEG was present in the formulations, lower acetyl CA-398-10 gives higher water uptake; the differences due to acetyl variation are shown in Table 3.

Table 3. Difference in Water Uptake at 30 Minutes due to Acetyl Variation.

Ratio of NF/CA320S	PEG Type	PEG level (%)	Water uptake (g)@30 min, 39.4% acetyl	Water uptake (g)@30 min, 40.3% acetyl	% Difference in water uptake due to acetyl
90/10	PEG400	0	0.0167	0.0179	7.2
		11	0.0451	0.0381	15.5
		25	0.0799	0.0648	18.9
	PEG3350	0	0.0166	0.0181	9.0
		11	0.0359	0.0292	18.7
		25	0.0664	0.0515	22.4
75/25	PEG400	0	0.0223	0.0233	4.5
		11	0.0541	0.0459	15.2
		25	0.0914	0.0744	18.6
	PEG3350	0	0.0224	0.0242	8.0
		11	0.0478	0.0419	12.3
		25	0.0830	0.0693	16.5
50/50	PEG400	0	0.0248	0.0256	3.2
		11	0.0636	0.0534	16.0
		25	0.1062	0.0859	19.1
	PEG3350	0	0.0252	0.0276	9.5
		11	0.0621	0.0577	7.1
		25	0.1063	0.0945	11.1

The data in Table 3 indicates that acetyl content variation in CA-398-10 polymer over 0.9% (within CA specification) range could influence the rate of water uptake of the coating films to a certain degree; especially the formulations that have higher levels of CA-398-10 NF/EP and PEG 400 as the plasticizer. At the 11% PEG400 level and when the ratio of CA-398-10 to CA- 320S = 50 /50, the data suggest that on average one would expect a 1.5% increase in the rate of water uptake for each 0.1% decrease in the acetyl content in the CA-398-10.

CONCLUSIONS

This study demonstrates that one can readily adjust the desired rate of water uptake in an osmotic drug delivery system by selecting the appropriate ratio of CA-398-10 NF/EP to CA-320S NF/EP to use in the coating formulation. Thus one can control the rate at which a drug is released from an osmotic tablet by controlling the rate of internal osmotic pressure buildup which is a direct function of the rate of water uptake by the tablet. Additionally, it has been confirmed that plasticizers also play a very important role in determining the permeability of the coating films with higher levels of plasticizer in the formulation giving increased permeability. Finally, variation in acetyl content of the CA-398-10 can also contribute to the film permeability with the lower acetyl levels giving increased permeability in formulations that also include a plasticizer. All of these factors should be considered when designing an osmotic drug delivery system for tablets coated with a mixture of these two cellulose acetates.

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Captions for tables and figures:

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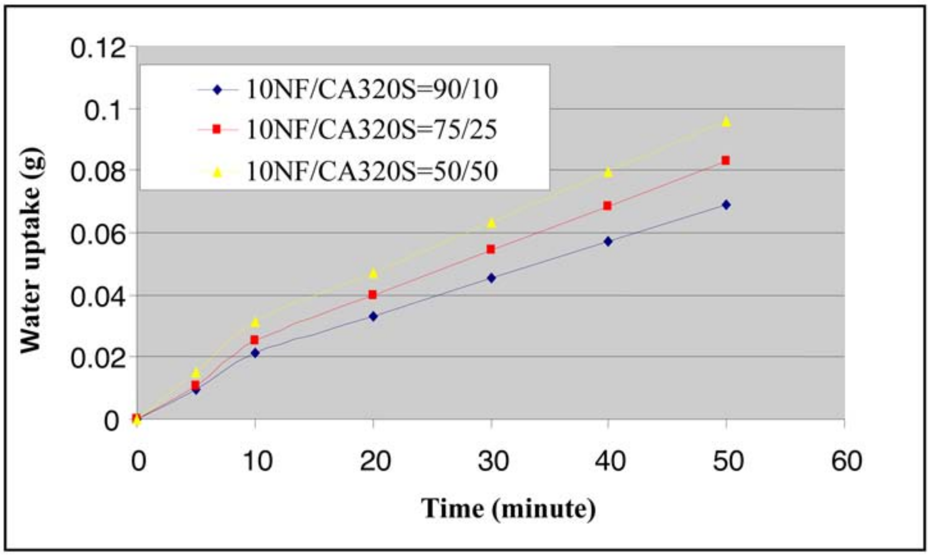
Authors’ Biography:

Dr. Jinghua Yuan is Principal Technical Service Representative at Eastman Chemical Company, responsible for pharmaceutical excipient products. Dr. Yuan has more than 20 years experience in formulation development and drug delivery systems. Prior to joining Eastman, Dr. Yuan worked as a Research Associate at Purdue University and University of Virginia. Dr. Yuan earned her PhD from Tianjin University, China in 1989.

Doug Dunn joins Eastman Chemical Company in 2005 and has more than 25 years of laboratory experience, 18 of those in pharmaceutical industry. Prior to joining Eastman, Mr. Dunn worked as a development scientist for GlaxoSmithKline Pharmaceuticals in a R&D analytical laboratory. Mr. Dunn received an Associate of Science degree in Chemical Technology from Northeast State Technical Institute, Tennessee in 1981.

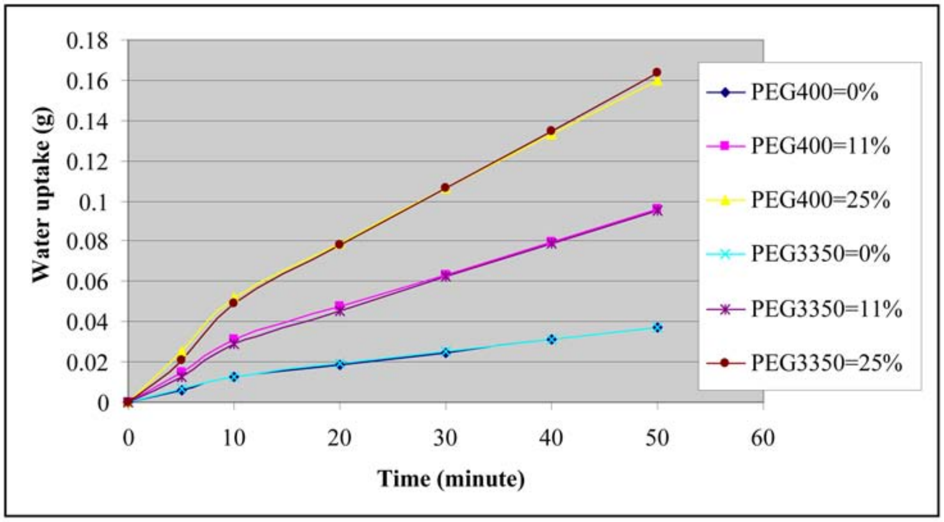
Ms. Nancy Clipse is a Lab Analyst. She has more than 40 years with Eastman Chemical Company and more than 20 years experience in formulation and drug delivery. She attended East Tennessee State University in 1968 and 1982.

Dr. Ray Newton is retired and was the Group Leader of the Formulation Products Lab. His career at Eastman included a wide range of duties, including R&D, manufacturing technical support, manufacturing supervision, and new business development. Dr. Newton earned his BS in 1974 from Lee University and his PhD in 1978 in Organic Chemistry from the University of Tennessee, Knoxville.



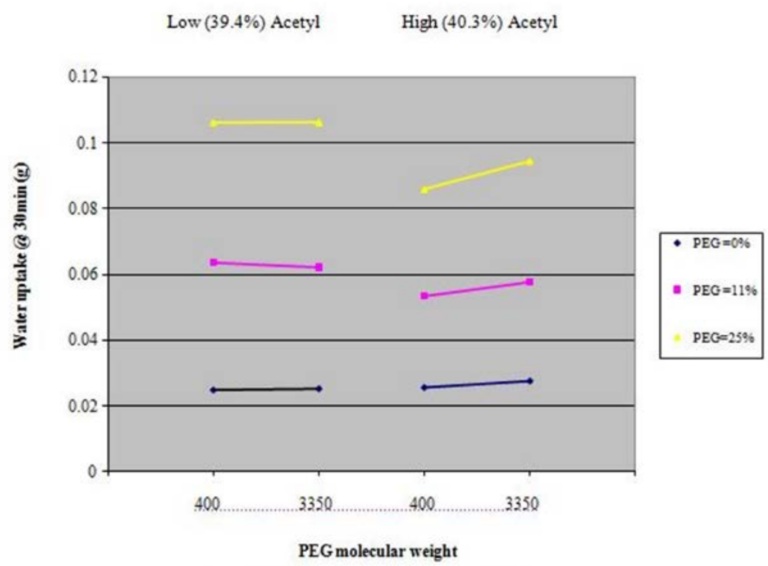
0.12
0.1
0.08
0.06
0.04
0.02
0
Water uptake (g)
10NF/CA320S=90/10
10NF/CA320S=75/25
10NF/CA320S=50/50
0
10
20
30
40
50
60
Time (minute)

Figure1.

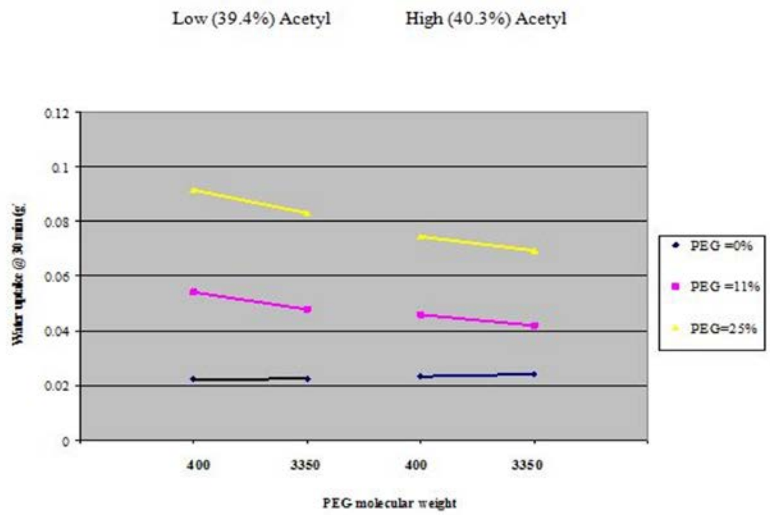


0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
Water uptake (g)
0
10
20
30
40
50
60
Time (minute)
PEG400=0%
PEG400=11%
PEG400=25%
PEG3350=0%
PEG3350=11%
PEG3350=25%

Figure 2.



3a: CA-398-10/CA320S = 50/50
Left lines: low acetyl CA 398-10 was used; right lines: high acetyl CA 398-10 was used.



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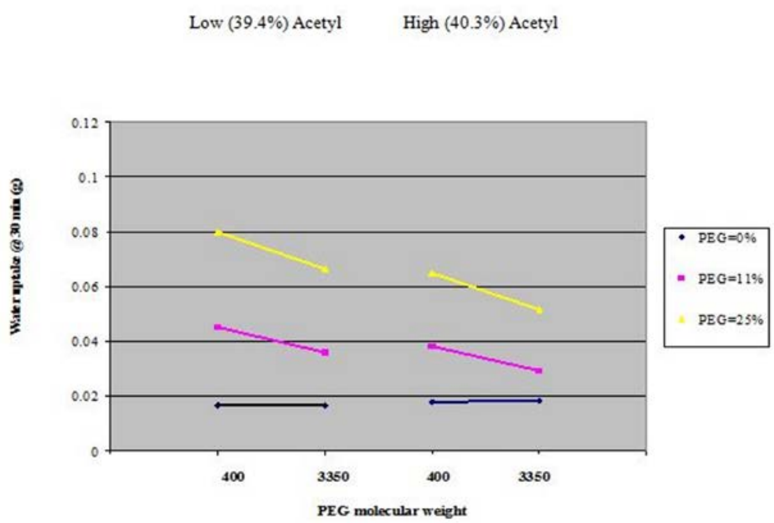

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Figure 3.