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The Influence of Post Coating Thermal Treatment on Film Properties and Drug Release from Ethylcellulose Barrier Membrane Coating Systems

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PURPOSE

Ethylcellulose aqueous dispersions are widely used in the formulation of modified release oral drug delivery systems. Drug release from aqueous dispersion (latex) coated dosage forms may be affected by variables influencing the coalescence of the polymer particles and hence the film formation process[1, 2]. Post thermal treatments or curing conditions to obtain reproducible drug release profiles have been widely investigated[3, 4]. The objective of this study was to investigate the effect of post coating thermal treatment on the physico-mechanical properties of ethylcellulose (EC) films and subsequent drug release from EC-coated multi-particulates.

METHODS

Free films from both aqueous EC dispersion (Surelease® aqueous ethylcellulose disperson, E-7-19040) and plasticized organic EC (ETHOCEL™ premium ethylcellulose polymer, Standard 20 cP Premium, Dow Chemical Co., USA) were prepared, as described below. Aqueous EC and plasticized organic EC dispersions were also coated on drug layered (Table 1) 18-20 mesh (850-1000 µ) pellets.

Table 1. Model Drugs and Physical Characteristics

Model drug	Solubility (mg mL^{-1})†	Solubility Term†	Molecular Weight†	pKa†
Acetamino-phen	14	Very Slightly Soluble	151.2	9.5
Metoprolol Succinate	100	Freely Soluble	652.8	9.2
Propranolol HCl	33	Soluble	295.8	9.5
Tolterodine Tartrate	12	Sparingly Soluble	475.6	9.9

† Obtained from The Merek Index and the Physicians Desk Reference.

Three post coating thermal treatment variables (Table 2) were investigated using a temperature and humidity controlled chamber (SH-241, ESPEC, USA).

Table 2. Experimental Process Variables

Variable	Units	Low Level	High Level
Temperature	ºC	40	70
Humidity	%	45	75
Treatment Duration	Hours	12	72

A structured formal experimental design was developed using design of experiment (DOE) software (Fusion Pro, S-Matrix Corporation). Thirteen thermal treatments including three replicates, for purposes of determining experimental error, were conducted. Five different response variables were examined (Table 3) for both aqueous and plasticized organic EC free films and coated multi-particulates.

Table 3. Experimental Response Variables

Response Variable	Units
Tensile Strength	MPa
Elongation at Break	%
MVTR	g H_2O/day/sq m
Thermal Analysis (T_g)	ºC
Drug Release	%min^{-1}

Preparation of Free Films

Aqueous EC dispersions (Surelease), 20% solids content, were cast on a Melinex (Du Pont Teijin Films, U.K. Ltd., UK) substrate using a draw knife (Gardner Casting Knife, Silver Spring, USA) with a targeted dry film thickness of 150 µm ± 10%. Films were dried at 40ºC for approximately 60 minutes.

Organic EC dispersions, plasticized with dibutyl sebacate and oleic acid in the same ratio as the aqueous EC dispersion, were prepared at 10% solids content with a 90:10 ratio of isopropyl alcohol and de-ionized water. Dispersions were then cast on glass plates to a targeted dry film thickness of 150 µm ± 10%. Films were dried at room temperature overnight in a chemical safety hood.

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Evaluation of Mechanical Properties

Tensile strength (σ) and elongation at break testing were carried out to assess the mechanical properties of cast films both before and after curing. Mechanical properties of cast films were evaluated using a tensile testing instrument (Mini 44, Instron, USA) at an extension rate of 1 mm/min. Test films were cut into rectangular strips of 10 mm x 70 mm (n=10). Elongation at break was calculated by the following equation: $(I_2 - I_o) / I_o$, where I_o is a constant of 25 mm (test area of the rectangular strip) and I_2 is the sum of the displacement (mm) of the crosshead after testing and I_o.

Determination of Water Vapor Permeability

Water vapor permeability of cast films was determined using a water permeability analyzer (WPA-100, VTI Corporation, USA). Experiment temperature parameters were 25ºC/80%RH with an air flow rate of 200 cc/min. Tests were conducted for an average of 90 minutes or until equilibrium was achieved.

Thermal Analysis (Tg)

Film samples were analyzed using differential scanning calorimetry (Q100 DSC, TA Instruments, USA). Approximately 10 mg of sample were sealed in standard aluminum pans and heated from 25°C to 150°C at a heating rate of 20°C min^{-1} in an atmosphere of nitrogen.

Drug Release

Dissolution testing was carried out for all aqueous and organic plasticized EC coated multi-particulate samples to assess the effect of post coating thermal treatment conditions on drug release characteristics. Twelve-hour dissolution testing in a USP apparatus I (baskets), with USP media at 37±0.5°C and 100 rpm, was carried out for all samples (n=3). Dissolution profiles were compared using time to 50% drug release (t_{50}), maximum drug release ($\%_{max}$), and similarity factor (f_2).[5, 6]

All samples, whether cast films or coated multi-particulates, were allowed to equilibrate in a controlled environment laboratory (23ºC/55%RH) for 24 hours prior to testing.

RESULTS

Film Properties

EC films prepared from both aqueous and organic dispersions appeared transparent, smooth, homogenous and free from defects. A summary of physico-mechanical film properties from thermally-treated aqueous and organic plasticized EC films illustrates a wide range of values (Table 4).

Table 4. Film Property Values

Variables	Units	Aqueous Ethylcellu-lose	Organic Plasticized Ethylcellulose
Tensile Strength	MPa	4.9 - 7.4	5.1 - 8.1†
Elongation at break	%	6.2 - 33.9	9.7 - 15.7†
MVTR	g H_2O/day/sq m	97 - 110†	112 - 122†

† Experimental DoE Outer points

Treatment of aqueous EC films exhibited an approximate 25% to 500% increase in elongation at break compared to untreated films, while treated organic EC films exhibited a 33% to 62% increase in elongation at break (Table 5).

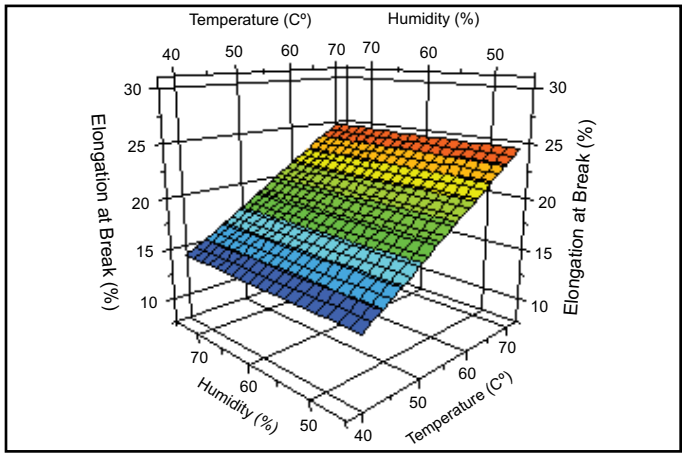
Table 5. Elongation at Break (%)

Treatment Condition†	Aqueous Ethylcellulose Average	Organic Plasticized Ethylcellulose Average
Control	6.206 (1.093)	9.652 (3.447)
70°C, 75%RH, 72hr	16.451 (2.187)	12.836 (4.026)
70°C, 45%RH, 48hr	21.442 (2.221)	12.953 (3.153)
40°C, 75%RH, 48hr	11.603 (2.483)	14.633 (3.773)
40°C, 45%RH, 72hr	8.499 (2.143)	15.675 (3.682)

† Experimental DOE outer points.

Greatest increases in elongation at break were seen when aqueous EC films were exposed to elevated temperatures, 70ºC, for 12 hours. Longer duration, 72 hours, at these temperatures resulted in decreased elongation at break in aqueous films. As for organic plasticized EC films, lower temperatures, 40ºC, increased elongation at break slightly. Surprisingly, humidity did not affect film properties (Figure 1).

Figure 1. Aqueous Ethylcellulose Disperson Elongation at Break; Time = 48 hrs



Water Permeation Analysis

At equilibrium, moisture permeation rates of aqueous and organically-cast EC films remained primarily unchanged following treatment (Table 6).

Table 6. Water Permeation Analysis (g H_20/day/sq m)

Treatment Condition†	Aqueous Ethylcellulose Average	Organic Plasticized Ethylcellulose Average
Control	109 (2)	116 (5)
70°C, 75%RH, 72hr	110 (2)	122 (9)
70°C, 45%RH, 48hr	97 (2)	120 (7)
40°C, 75%RH, 48hr	104 (2)	114 (3)
40°C, 45%RH, 72hr	102 (2)	112 (5)

† Experimental DOE outer points.

Thermal Analysis

Endothermic transitions, expressed by onset, inflection and end point (Table 7), remained unchanged for treated and untreated (control) films for both aqueous and organic EC systems regardless of treatment conditions.

Table 7. Glass Transition Temperature (°C)

Treatment Condition†	Aqueous Ethylcellulose		
	Onset	Inflection	End
Control	46.05 (1.19)	49.46 (2.50)	52.47 (1.64)
70°C, 75%RH, 72hr	45.30 (0.44)	46.84 (0.70)	49.91 (0.19)
70°C, 45%RH, 48hr	45.81 (1.49)	49.42 (0.65)	53.41 (0.73)
40°C, 75%RH, 48hr	45.35 (1.13)	46.30 (1.20)	53.26 (1.11)
40°C, 45%RH, 72hr	46.43 (1.21)	47.32 (1.13)	53.66 (0.63)
Treatment Condition†	Organic Plasticized Ethylcellulose		
	Onset	Inflection	End
Control	48.27 (1.13)	50.50 (0.64)	54.49 (2.89)
70°C, 75%RH, 72hr	46.42 (0.88)	47.55 (0.18)	51.23 (0.98)
70°C, 45%RH, 48hr	47.38 (1.17)	49.39 (0.52)	52.44 (0.29)
40°C, 75%RH, 48hr	46.43 (1.61)	47.83 (0.84)	52.09 (0.90)
40°C, 45%RH, 72hr	46.07 (1.36)	47.52 (1.24)	52.97 (0.78)

† Experimental DOE outer points.

Drug Release

Drug release profiles for treated and untreated EC coated pellets were examined and a summary of t_{50}, $\%_{max}$ and f_2 results are shown in Table 8. The data show a wide range of values illustrating both small and large changes in the coated pellets, as a result of treatment conditions for each model drug.

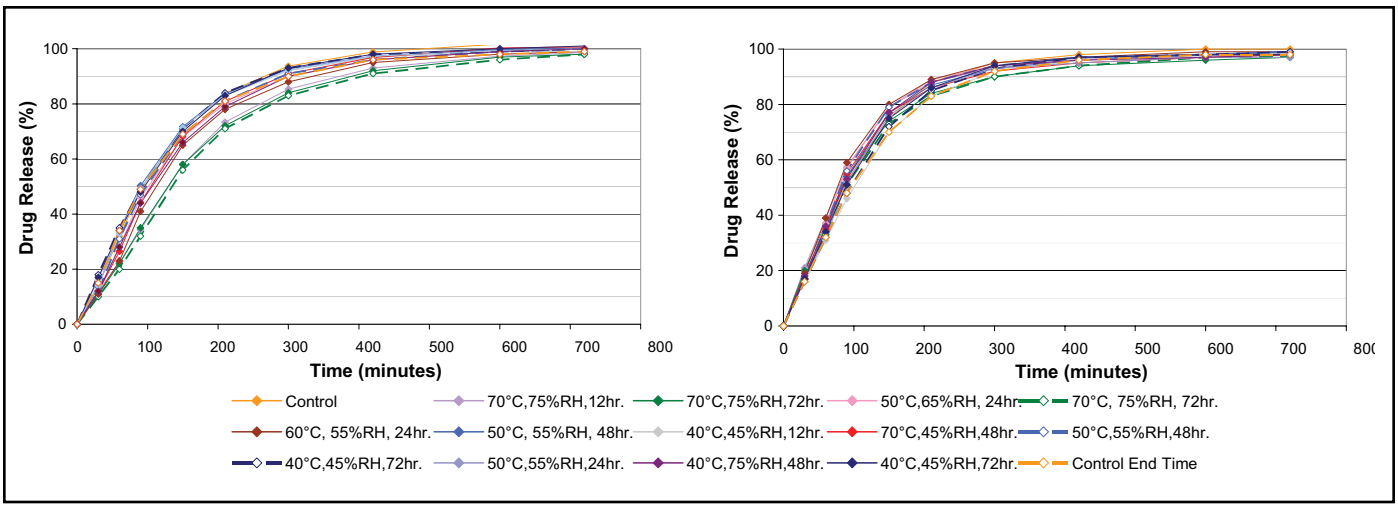
Table 8. Model Drug Release

Model Drug	Aqueous Ethylcellulose		
	$T_{50\ (min)}$	$\%_{max\ (min)}$	f_2
Acetaminophen	89 - 145	98 - 101	48.1 - 88.2
Metoprolol Succinate	197 - 357	68 - 87	41.9 - 86.6
Propranolol HCl	226 - 320	76 - 89	46.8 - 92.5
Tolterodine Tartrate	-	41 - 68	55.6 - 94.9
Model Drug	Organic Plasticized Ethylcellulose		
	$T_{50\ (min)}$	$\%_{max\ (min)}$	f_2
Acetaminophen	77 - 100	97 - 99	72.9 - 88.9
Metoprolol Succinate	0 - 522	42 - 89	22.7 - 84.4
Propranolol HCl	195 - 650	54 - 87	23.6 - 62.9
Tolterodine Tartrate	-	34 - 48	61.8 - 83.2

For aqueous EC coated Acetaminophen (APAP) multi-particulates, drug release slowed when treated at high temperatures, 70°C, as illustrated by an increase in t_{50} from 89 to 145 minutes (Figure 2). Drug release for APAP coated with organic plasticized EC, was unaffected by treatment conditions (Figure 3). Overall extent of drug release remained unchanged for both systems regardless of treatment conditions.

Figure 2. Aqueous Ethylcellulose Acetaminophen Dissolution 5%WgT ; 15% Solids

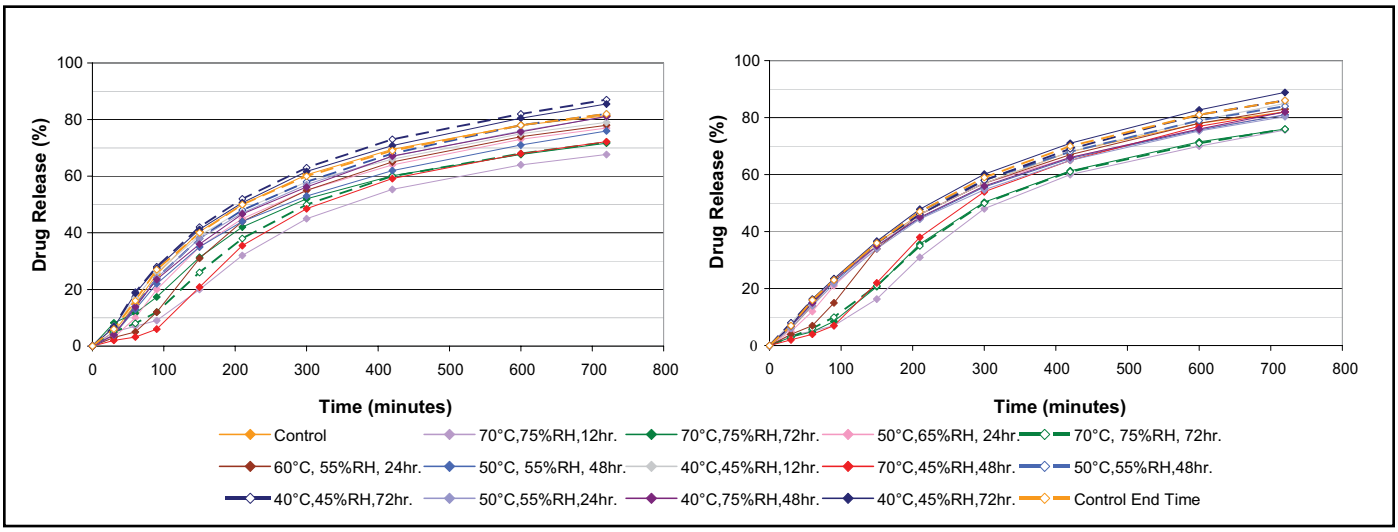
Figure 3. Organic Plasticized Ethylcellulose Acetaminophen Dissolution 5%WgT ; 7% Solids



For both aqueous coated metoprolol succinate and propranolol HCl multi-particulates, treatment at higher temperatures, 70°C, resulted in an increase in t_{50} and decrease in overall extent of drug release (Figures 4 & 5). Significant increases in lag time can be seen for both model drugs. No significant change in drug release was noted for organic EC coated systems (Data is not shown here).

Figure 4. Aqueous Ethylcellulose Metoprolol Succinate Dissolution 10%WgT ; 15% Solids

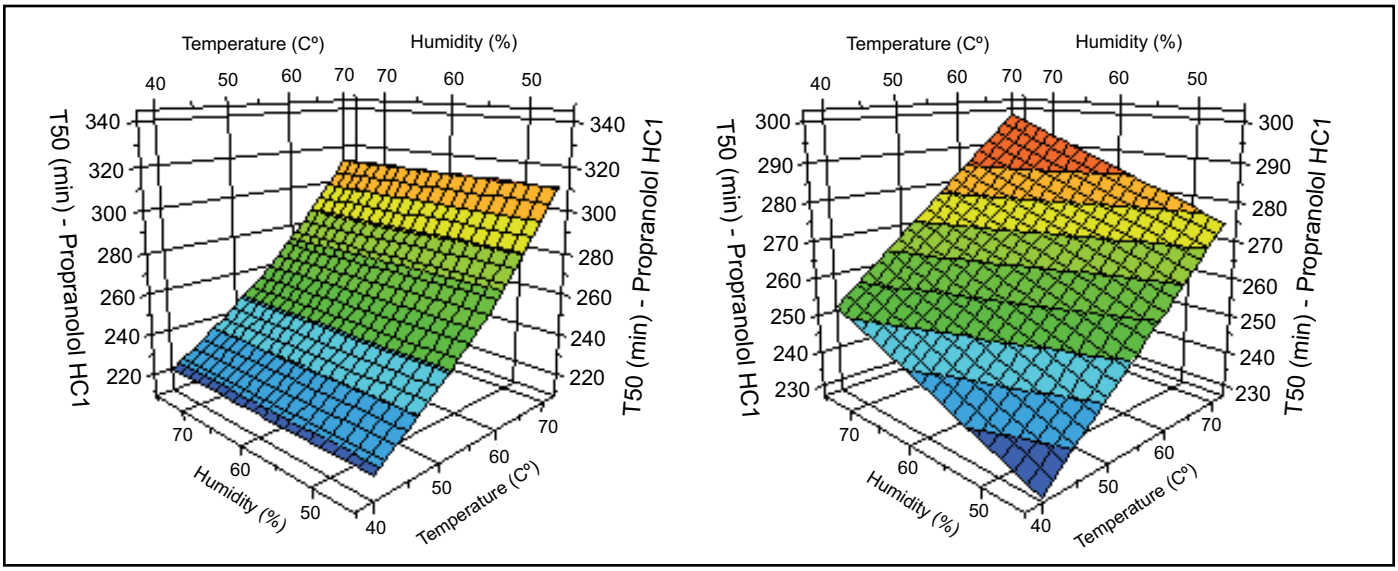
Figure 5. Aqueous Ethylcellulose Propranolol HCl Dissolution 7%WgT ; 15% Solids



For metoprolol succinate, only temperature treatment played a role in the changes noted (Figure 6). However, both temperature and humidity treatment, accounted for the differences seen in propranolol HCl coated multi-particulates (Figure 7). Treatment duration had no effect on drug release in either case.

Figure 6. Aqueous Ethylcellulose Dispersion Time Till 50% Drug Release (T50) - Metoprolol Succinate

Figure 7. Aqueous Ethylcellulose DispersionTime Till 50% Drug Release (T50) - Propranolol HC1



In the case of tolterodine tartrate coated multi-particulates, while no change in lag time was noted, the extent of drug release decreased for both aqueous and organic plasticized EC coatings (Figure 8 & 9). The extent of drug release, $\%_{max}$, decreased under most treatment conditions for aqueous EC (Figure 10) as well as for organic plasticized EC but to a lesser extent (Figure 11).

Figure 8. Aqueous Ethylcellulose Tolterodine Tartrate Dissolution 5%WgT ; 15% Solids

Figure 9. Organic Plasticized EthylcelluloseTolterodine Tartrate Dissolution 5%WgT ; 7% Solids

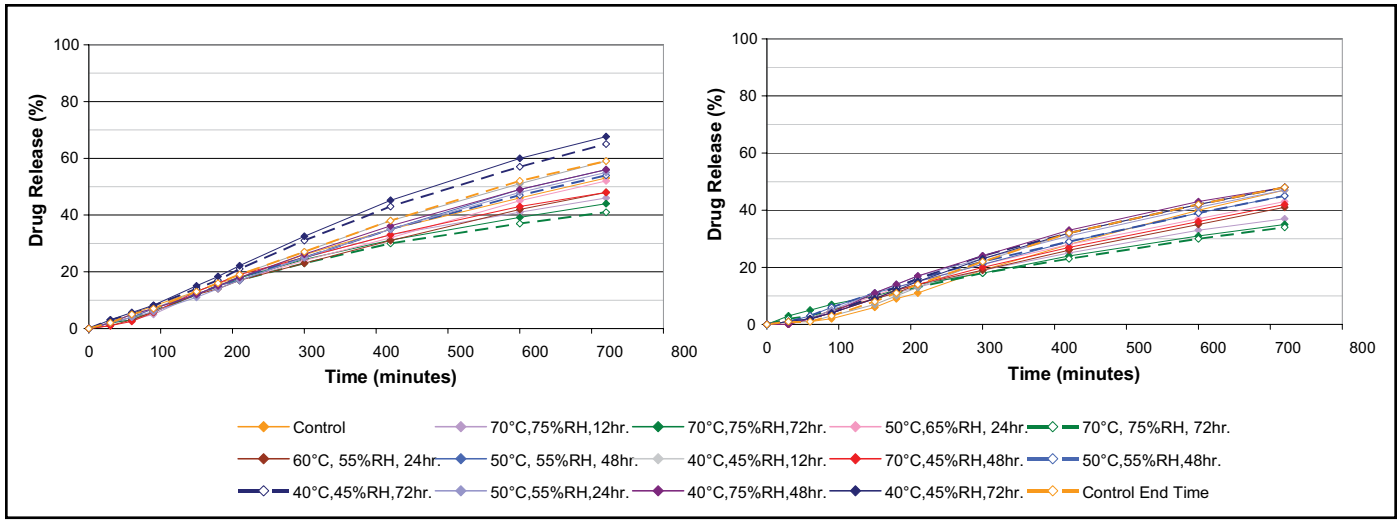
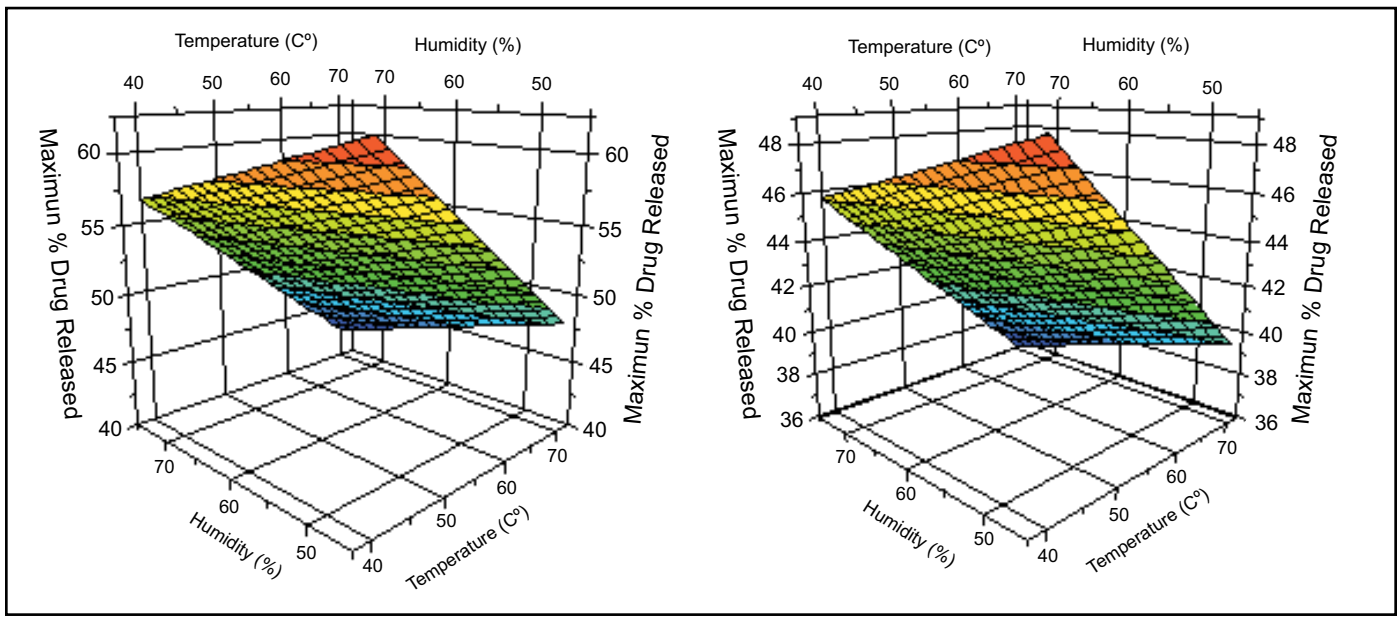


Figure 10. Aqueous Ethylcellulose Dispersion Maximun % Drug Release - Tolterodine Tartrate

Figure 11. Plasticized EthylcelluloseMaximun % Drug Release - Tolterodine Tartrate



CONCLUSIONS

The results demonstrated that post coating treatment can affect both physico-mechanical properties of EC films and drug release from EC-coated multi-particulates. The changes for the aqueous EC system may be attributed to a further gradual coalescence of latex polymer particles, thereby creating a more cohesive barrier membrane. Further work is underway to examine coating process recommendations that would overcome or minimize the need for post coating treatment.

REFERENCES

1. I. Ghebre-Sellassie, et al., Characterization of a new water-based coating for modified-release preparations, *Pharm. Technol.* 12(9):96 (1988)
2. M. Harris, et al., A water-based coating process for sustained release, *Pharm. Technol.*, 10(9), 102-107 (1986)
3. F.W. Goodhart, et al., An evaluation of aqueous film forming dispersions for controlled release, *Pharm. Technol.*, 8(4), 64-71 (1984)
4. I. Ghebre-Sellassie, Pellets: A general overview, *Pharmaceutical Pelletization Technology*, Marcel Dekker, New York (1989)
5. Federal Registar, Food and Drug Administration, Vol. 60, NO.230, p. 51542 (1995)
6. J. W. Moore, and H. H. Flanner, Mathematical comparison of curves with an emphasis on dissolution profiles, *Pharm. Technol.*, 20 (6), 65-74 (1996)

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