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EVALUATION OF THE LOSS OF PROPYLENE GLYCOL DURING AQUEOUS FILM COATING*

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ABSTRACT

A Plackett-Burman study was used to determine the coating factors which can affect the loss of propylene glycol, a common water soluble plasticizer used in aqueous film coating, during the film coating process. The processing variables studied were: application rate of the aqueous film coating liquid, atomizing air pressure, drying time, amount of propylene glycol in the aqueous film coating liquid, temperature and the amount of aqueous film coating liquid applied. Analysis of the data shows that the amount of propylene glycol in the film was 81 to 96% less than the theoretical value when considering the amount of the propylene glycol in the aqueous film coating liquid. The loss of propylene glycol was independent of the variables studied. The loss of propylene glycol was also shown to occur in the Accela-Cota during the coating of tablets.

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INTRODUCTION

Film formers such as hydroxypropyl methylcellulose are used extensively in aqueous film coating of solid dosage forms. The physical properties, such as tensile strength, elasticity and adhesion, of a film made from hydroxypropyl methylcellulose can be modified by the addition of plasticizers. Some common plasticizers for aqueous film coating are: polyethylene glycols, propylene glycol and glycerol (1).The choice of plasticizer depends upon the ability of the plasticizer to modify the polymer-polymer interactions. In an aqueous film coating formulation, plasticizers are thought to act by inserting between the polymer chains causing a disruption of the forces holding the chains in an ordered rigid pattern. By disrupting these polymer-polymer bonds, the polymer matrix is softened and extended (2). The type and quantity of plasticizer should be optimized to achieve the desired film forming characteristics.

Preliminary work indicated that the polymer:propylene glycol ratio in dried films was different from the polymer:propylene glycol ratio in the aqueous film coating liquid used to make the films. This work involved quantifying the amount of propylene glycol lost and determining which spray coating variables influence this loss. Two other plasticizers, glycerin and polyethylene glycol 400, were tested similarly to the propylene glycol.

MATERIALS AND METHODS

A combination of three hydroxypropyl methylcellulose polymers of different viscosities were used as the basic aqueous coating

TABLE 1

Formula used to prepare the basic aqueous coating liquid

Item	Source	Amount (%w/w)
Hydroxypropyl Methylcellulose 2910, USP, 5 CPS	Methocel E 5 Dow Chemical	2.0
Hydroxypropyl Methylcellulose 2910, USP, 15 CPS	Pharmacoat 615 Shin Etsu	2.0
Hydroxypropyl Methylcellulose 2910, USP, 50 CPS	Metolose 50 Shin Etsu	1.0
FD&C Blue Dye No. 1	H. Kohnstamm	0.07
Distilled Water		Q.S.

liquid (Table 1). This combination of polymers, 5, 15, and 50 cps viscosity grades, provided an acceptable film without the addition of a plasticizer. This allowed for the spraying of films without plasticizer which could then be compared to the films which contained plasticizer.

FD&C Blue Dye No. 1 (Blue 1) was used in the aqueous coating liquid as a marker compound which provided for an indirect method of measuring the loss of propylene glycol during the formation of the films. The Blue 1 was assayed using a Hewlett-Packard Spectrophotometer. The amount of Blue 1 was determined in the aqueous coating liquid before spraying the films and each film was analyzed for the amount of Blue 1 per gram.

The amount of propylene glycol (Union Carbide) in the sprayed films or the aqueous coating liquids was determined using a gas chromatography assay based on USP assay for propylene glycol.

TABLE 2

Independent Variable	Low Level	High Level
1. Temperature (^{o}C)	40	60
2. Number of Dry Cycles	15	30
3. Flowrate (ml/min)	50	100
4. Atomizing Air Pressure (psi)	20	50
5. Propylene Glycol (%w/w)	2.0	5.0
6. Number of Sprays	40	80

Sprayed films were prepared using the spraybox apparatus (3) which simulates the spraying conditions of the Accela Cota. A Spraying Systems Model 1/4 JAUCO spray gun was used for spraying the films. Temperature and air velocity control in the range of interest for aqueous film coating were achievable and reproducible. A Masterflex Servodyne Controller was used to revolve the sample at 40 rpm which produces an exposure to the spray for about the same time as that seen for a tablet in a 24 inch Accela-Cota (4). The aqueous film coating liquids were sprayed on three and one-half inch squares cut from transparency film for infrared copiers (3M Company) which allowed for easy removal of the films.

The independent variables in the 12 run Plackett-Burman experimental design (5) are shown in Table 2. This design was chosen to determine which spray conditions affected the loss of propylene glycol. The prepared films were weighed and analyzed for the amount of propylene glycol and Blue 1 present per gram of the film. The result of each trial was reported as the amount of propylene glycol per gram of film and as the percent loss of propylene glycol from theoretical. The amount of Blue 1 present

TABLE 3

Ratio of polymers and viscosity of various aqueous coating liquids. All solutions contained 2% w/w propylene glycol.

Solution	%w/w 5 CPS	% w/w 15 CPS	%w/w 50 CPS	Viscosity (CPS)
1	2.0	2.0	1.0	248
2	2.4	2.4	1.2	327
3	1.8	1.8	0.9	194
4	1.6	1.6	0.8	154
5	3.0	1.0	1.0	143
6	4.0	1.0	0.0	74
7	2.0	1.0	2.0	239
8	0.0	4.0	1.0	261

was used to confirm the results of the amount of propylene glycol lost and calculate the amount of water in each film.

To study the affect of coating liquid viscosity, a second group of aqueous film coating liquids were prepared that contained 2% w/w propylene glycol and various amounts of the three HPMC polymers (Table 3). The viscosities of the eight coating liquids were measured with a Brookfield viscometer. Films were prepared in the spraybox from the eight solutions and again analyzed for the amount of propylene glycol and the amount of Blue 1. The spraybox coating conditions were the same as the high level for the Plackett-Burman study, except that the number of sprays was 50 and the atomizing air pressure was 40 psi.

Additional work included using the basic aqueous film coating liquid containing propylene glycol to coat placebo tablets in a 24 inch Accela-Cota and to prepare sprayed films from the basic aqueous film coating liquid using either polyethylene glycol 400 (Union Carbide) or glycerin (Proctor & Gamble) as the plasticizer.

This work was done to confirm the loss of propylene glycol in the actual coating of tablets and to determine if either of the other two plasticizers are lost during the coating process. No direct assay was developed for these two plasticizers but the loss was determined from the amount of Blue 1 present in the films.

RESULTS AND DISCUSSION

The results of the Plackett-Burman study are summarized in Table 5 and Table 6. The loss of propylene glycol calculated on a percent basis ranged from 81 to 96 percent of the theoretical amount considering the amount of propylene glycol in the aqueous film coating liquid. When using the percent loss of propylene glycol as the dependent variable, the only independent variable calculated to be significant at the 99% confidence level was the amount of propylene glycol in the aqueous film coating liquid. The amount of propylene glycol varied from 35 milligrams to 84 milligrams per gram of film. The data was also analyzed using the amount of propylene glycol per gram of film as the dependent variable and no independent variables were significant at the 90 percent confidence level. A ratio of polymer to propylene glycol was calculated in the sprayed films based on the amount of Blue 1 in each film. Analysis using this ratio as the dependent variable shows that none of the independent variables were significant at the 90 percent confidence level.

It is interesting to note how much water was retained in each film from the Plackett-Burman study.The amount of water was

TABLE 5

Results of Plackett-Burman Study expressed as milligrams per gram of film.

Trial	Blue 1	Polymer	Propylene Glycol	Water	% Propylene Glycol Lost
1	13.3	899	72	16	93
2	12.9	872	46	69	95
3	12.2	897	79	12	81
4	12.2	897	65	26	85
5	12.9	949	61	0	86
6	12.1	818	70	100	93
7	12.1	890	69	29	84
8	12.4	838	84	66	91
9	12.4	838	39	111	96
10	12.7	934	69	0	84
11	12.6	851	82	54	92
12	11.5	846	35	108	91

TABLE 6

Summary of the effects from Plackett-Burman Analysis looking at the amount of propylene glycol lost, milligrams of propylene glycol per gram of film, milligrams of water per gram of film, and propylene glycol/ polymer ratio.

Independent Variable	% Propylene Glycol Lost	Propylene Glycol	Water	Propylene Glycol / Polymer
1. Temperature	23.8	-0.83	-28.0	-0.72
2. Dry Cycles	13.2	4.2	-25.7	-1.0
3. Flowrate	-8.5	13.2	-22.9	-3.4
4. Atomizing Air Pressure	25.8	-3.8	-19.4	0.86
5. Propylene Glycol	555*	2.5	40.3	-1.0
6. No. of Sprays	4.83	17.2	-43.5**	-4.4

* Indicates a calculated statistically significant result at the 99% confidence level.

** Indicates a calculated statistically significant result at the 90% confidence level.

calculated using a mass balance on the amount of each ingredient in the film, assuming that the only four ingredients in the sprayed films were: hydroxypropyl methylcellulose polymers, Blue 1, propylene glycol and water. The amount of propylene glycol and Blue 1 were known from the assays of each. The amount of hydroxypropyl methylcellulose polymers was calculated based on the amount of Blue 1. Using these three values, the amount of water in each film could be determined. The calculated amount of water in each film ranged from approximately 0% water to almost 11% water by weight. Using the amount of water remaining in the film as the dependent variable, the number of sprays was the only significant independent variable at the 90 percent confidence level. This may be due to the fact that as a film gets thicker, more water can be retained in the film. It must be considered that an indirect method of determining the water content of each film was used so the significance of this result needs to be studied further looking specifically at the water content in the films.

The percent loss of propylene glycol and the amount of propylene glycol remaining in each film made from the eight aqueous film coating liquids of various viscosities are shown in Table 7. The loss of propylene glycol ranged from 71 to 84% and the amount of propylene glycol in the film ranged from 69 to 80 mg of propylene glycol per gram of film. The differences seen did not appear to depend on the viscosity of the aqueous film coating liquid. These results are similar to what was seen from the Plackett-Burman study except the range in the amount of propylene glycol remaining in the film was not as large. This may be due to

TABLE 7

Results of making aqueous coating liquids with different viscosities. Solutions are listed in increasing viscosity.

Solution	Mg Propylene Glycol Per Gram of Film	% Propylene Glycol Lost
6	76	80
5	77	80
4	80	84
3	75	77
7	70	71
1	76	78
8	72	72
2	80	83

the fact that these eight solutions were sprayed under one set of spraying conditions in the spraybox while the Plackett-Burman study had different spraying conditions for each run.

Films sprayed using either glycerin or polyethylene glycol 400 as the plasticizer in the basic coating liquid were dried to a constant weight at 40^{o}C to remove as much residual water as possible. Analysis of the Blue 1 content of these films indicated that little or no plasticizer was lost during the film making process.

When placebo tablets were coated in the 24 inch Accela-Cota, the results were similar to what was seen in the spraybox (Table 8). Four different coating runs were made in the Accela Cota using either a small oval or large oval tablet. For each run, 20 tablets were analyzed for the amount of propylene glycol and the amount of Blue 1. When 2% w/w propylene glycol was used in the basic aqueous coating liquid, the percent loss of propylene glycol was not as extensive and the amount of propylene glycol per gram of film

TABLE 8

Results of assays on tablets coated in 24 inch Accela Cota. The amount of propylene glycol is expressed as milligrams of propylene glycol per gram of film.

Results for 2% w/w propylene glycol in basic aqueous coating liquid

Large Ovaloid Tablets	Small Ovaloid Tablets
11.9 ± 0.89	12.0 ± 0.49

Results for 5% w/w propylene glycol in basic aqueous coating liquid.

Large Ovaloid Tablets	Small Ovaloid Tablets
16.8 ± 0.98	15.0 ± 1.1

was higher than what was seen in the Plackett-Burman study. When 5% w/w propylene glycol was used, similar results were obtained.

CONCLUSIONS

The amount of propylene glycol in the sprayed films ranged from 35 to 84 milligrams of propylene glycol per gram of film. This variation in the amount of propylene glycol is not dependent upon any of the commonly controlled factors in aqueous film coating that were looked at in this study. This work confirmed that the loss of propylene glycol occurs during the coating of tablets in the 24 inch Accela-Cota but the amount lost was not as extensive as what was shown to occur in the spraybox. This may be due to inherent differences in the spraybox versus the Accela-Cota. No loss was observed when polyethylene glycol or glycerin were used as the plasticizer.

Because the loss in the amount of propylene glycol was found to vary, the amount of propylene glycol in the film could differ from lot to lot when tablets are film coated using propylene glycol as a plasticizer. This variation in the amount of propylene glycol coupled with the fact that the amount of water in the film may not be the same could cause the physical properties of the films on the tablets to be different from lot to lot. Further work could be done to demonstrate whether or not this variation in propylene glycol and water content can be a potential problem in the coating of tablets.

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