Formula Modifications in a Solvent-Free Tablet Film Coat

PAUL A. TUERCK and DUNCAN E. McVEAN▲

Abstract □ Solvent-free formulations suitable for use as film coatings are described. Coatings are applied by spraying molten mixtures onto tablets in a conventional coating pan. The effects of a series of 17 additives on two representative basic formulations are evaluated. Results are presented relative to appearance, disintegration, friability, and uniformity. Desirable characteristics imparted by the additives may be easily selected from tables and used in the formulation of subsequent coating compositions. The concentration of shellac in the basic formulations was found to govern the rapidity of disintegration of the coatings regardless of additives. Of the additives evaluated, only castor oil, cocoa butter, and isopropyl myristate improved the basic formulations.

Keyphrases □ Tablet coating—solvent-free shellac polyethylene glycol 4000 formulations, effects of 17 additives, molten mixture spraying □ Shellac-polyethylene glycol 4000 solvent-free tablet film coatings—formulation, effects of 17 additives, molten mixture spraying □ Film coatings—formulation of solvent-free shellac-polyethylene glycol 4000 films for molten mixture spraying of tablets, effect of 17 additives

The use of coatings on tablets and pills is well documented. For example, "Remington's Pharmaceutical Sciences" lists a bibliography of 322 references pertaining to the subject (1). Those familiar with the art of tablet coating are acquainted with the reasons for coating and advantages and disadvantages of the application methods.

Until recently, sugar coating was overwhelmingly preferred and it still provides tablets of exceptional esthetic qualities. But for reasons of economy, both with respect to labor and material costs, other methods have gained popularity. Film-type coatings, in particular, offer reduced labor and material costs, are thin enough that embossed emblems are retained, mask tastes and odors, offer improved stability over sugar coatings, provide increased resistance to abrasion, and provide increased luster when compared to compressed tablets (1).

Unfortunately, it is necessary that most newer film coatings be applied with the film-forming material dissolved or suspended in volatile solvents such as acetone, chloroform, and alcohol. While these solvents evaporate quickly and make it possible to complete the coating operation in a short period, they also have many disadvantages. These solvents evaporate quickly, necessitating the use of large quantities which are either lost completely during the drying cycle or are partially recovered with expensive recovery systems. Elaborate precautions are sometimes necessary to protect against their inherent toxicity. The associated hazards of explosion and fire from local concentrations of vapors also must not be ignored. Furthermore, it is sometimes necessary to alternate the coating applications with drying cycles, since the use of solvent tends to dissolve portions of the coating already applied, resulting in sticking and clumping of tablets in the coating pan.

Film coating may also be accomplished by other methods, such as the Wurster air-suspension technique. This unique method also involves volatile solvents as vehicles for the film-forming materials (2, 3).

Pan coating remains one of the most widely used methods for applying film coats. Numerous modifications of methods exist for applying the coating materials and include the time-honored method of pouring on solutions in frequent and divided portions with intermittent drying cycles; spraying, using air pressure for atomization; and airless spraying, using hydraulic pressure alone for atomization. All these methods have been automated in part or *in toto* (4).

A recently issued patent (5) is concerned with some basic, novel coating compositions of dry shellac with polyethylene glycol. It is possible to apply these combinations as molten solutions to tablets with the aid of steam-jacketed pneumatic spray heads.

The purpose of this experimental work was to conduct screening studies to determine the effect of various additives on two basic film coating compositions containing 10 and 20% shellac in polyethylene glycol 4000 (I). The method and formulas described obviate the use of volatile organic solvents and the attendant hazards of toxicity or explosion.

EXPERIMENTAL

Preliminary feasibility work indicated that satisfactory coatings could be expected from application of any one of several basic formulas described in the patent (5). Two basic formulations containing pharmaceutical grade shellac (10 and 20%) and I were selected. Since little is known concerning the solvent properties of the molten I–shellac mixtures, selection of materials for screening could not be made on this basis. Therefore, approximately 50 materials were selected with different properties, *i.e.*, hydrophobic, hydrophilic, or surface active. Each was also believed not to represent a toxicological hazard should it be considered for future use.

Each additive was first prepared as 1 and 10% (by weight) solutions or dispersions in the molten mixture to determine miscibility. Approximately 60% of the additives were miscible at both levels. This group, in general, included alcohols, acids, esters, and glycols. Saccharides as a group were insoluble. Only 17 additives are included in this report. The others were eliminated, since, during later trials, their inclusion made application of satisfactory film coats impossible.

Materials that appeared soluble in the basic coating mixture at 110–140° included cocoa butter, castor oil, stearic acid, oleic acid, abietic acid, I, polyethylene glycol 6000, glycerin, propylene glycol, glyceryl monostearate, acetylated monoglycerides[1], tristearin, benzyl benzoate, polyoxyethylene-polyoxypropylene block polymers of molecular weight 2500[2] (II) and 8350[3] (III), polyoxyethylene lauryl ether[4], and polysorbate 80. Carnauba wax, cetyl alcohol, and stearyl alcohol were soluble at 140° but insoluble at 110°. Materials insoluble at 100–140° included paraffin, mineral oil, corn oil, beeswax, solid petrolatum, mannitol, carboxypolymethylene,

[1] Myvacet, Type 7-00, Distillation Products Industries, Division of Eastman Kodak Co., Rochester, N. Y.
[2] Pluronic L 62, Wyandotte Chemical Corp., Wyandotte, Mich.
[3] Pluronic F 68, Wyandotte Chemical Corp., Wyandotte, Mich.
[4] Brij 35, Atlas Chemical Ind., Wilmington, Del.

Table I—Effects of Additives to 10% Shellac–90% I Base on Tablet Film Coatings

Additive (10% w/w)	—Disintegration, sec.— Median of Range[a]	Range[b]	Coating Weight[c]	$(SD)_c$[d]	SD[e]	Friability[f]	α[g]	Disintegration Factor[h]	Initial Appearance[i]
Abietic acid	380	80	29.2	4.57	3.67	0	13	13	3
Acacia	415	330	39.6	8.17	7.70	0	19	10	18
Acetylated monoglycerides	385	90	50.3	4.13	3.11	0.025	6	8	17
Benzyl benzoate	360	60	35.5	4.01	2.95	0	8	10	1
Polyoxyethylene lauryl ether	345	90	32.7	4.59	3.70	0	11	11	12
Castor oil	445	150	55.7	4.63	3.75	0.005	7	8	9
Cocoa butter	425	90	37.5	5.02	4.22	0 (1)	11	11	6
Glycerin	365	70	24.4	3.43	2.09	0.01	9	15	4
Isopropyl myristate	465	170	48.0	4.46	3.53	0 (1)	7	10	1
Oleic acid	580	200	74.5	9.44	9.04	0.008	12	8	16
Polyethylene glycol 400	320	40	47.3	4.00	2.93	0	6	7	6
Polyethylene glycol 6000	410	60	27.8	7.25	6.72	0 (1)	24	15	5
II	385	150	48.1	6.04	5.39	0.01	11	8	9
III	340	40	25.2	4.64	3.76	0	15	13	6
Polysorbate 80	378	55	43.3	5.52	4.80	0.01	11	9	13
Propylene glycol	438	105	38.8	5.08	4.29	0.01	11	11	9
Stearic acid	545	50	66.3	6.69	6.11	0.03	9	8	14
Coated control	375	130	29.9	3.74	2.57	0	9	13	15
Uncoated control	323	75	—	2.72	—	2.8 (1)	—	—	—

[a] Median of the range of 12 tablets disintegrated as described in USP XVII. [b] Range encountered in disintegration of 12 tablets as described. [c] Average coating weight in milligrams based on an average of 30 tablets as compared to an average weight of 30 uncoated control tablets. [d] Standard deviation in milligrams based on 30 individual weights of coated tablets (or an uncoated control). [e] Standard deviation in milligrams of the coat; obtained from $SD = \sqrt{(SD)_c^2 - (SD)_u^2}$, where $(SD)_c$ = standard deviation of coated tablets, and $(SD)_u$ = standard deviation of uncoated tablets. [f] Percent loss—20 tablets rotated for 4 min. in a Roche friabilator. (1) signifies splitting. [g] Coefficient of variation (of coat) = $\sqrt{(SD)_c^2 - (SD)_u^2}/W_c \cdot 100$, where W_c = weight of coat. [h] A number indicating the delay in disintegration contributed by a unit weight of applied coating. Units of this number are seconds per milligram. The lower the number, the faster the coat will disintegrate. [i] Average point-score rating of six people familiar with tablet dosage forms (1 = excellent and 18 = very poor). Tablets were inspected for smoothness, mottling, shine, and general appearance.

lactose, sucrose, dextrose, corn syrup solids, sorbitol, ethylcellulose (50 cps.), microcrystalline cellulose, sodium alginate, sodium carboxymethylcellulose, sodium lauryl sulfate, hydroxypropyl methylcellulose, polyvinylpyrrolidone, cetylpyridinium chloride, urea, sorbitan tristearate[6], hydroxypropyl cellulose[6], and gelatin. Isopropyl myristate and acacia, while insoluble, were readily suspendable and sprayable. Glyceryl monostearate and tristearin, while soluble, were eliminated because they imparted poor spraying characteristics to the basic formulations.

EQUIPMENT, MATERIALS, AND METHODS

A rotary tablet machine[7] (16 station) equipped with 0.95-cm. (0.375-in.) deep cup punches was used to compress placebo tablets. Tablets were prepared by direct compression from anhydrous lactose USP, direct tableting grade[8], and lubricated with 1% magnesium stearate. Tablets were compressed at a weight of 250 mg. each.

Two basic coating mixtures were prepared. One consisted of a 10% solution, by weight, of pharmaceutical grade dry shellac[9] with 90% I. The second was a mixture of 20% shellac, by weight, with 80% I. Approximately half the required amount of I was melted, shellac was added with constant stirring, and heat was applied until solution was complete. Heat was then discontinued, and the remainder of I was added and mixed. The molten mass was cast into paper cups and allowed to harden. The resulting ingots were later remelted and mixed with other ingredients. At this time, 0.5% of D&C Yellow No. 10 was added to define more easily areas of application and to evaluate the uniformity of the coat during the spraying operation.

During the coating process, the tablets were rotated in a stainless steel coating pan having a diameter of approximately 16.51 cm. (6.5 in.) at a rate of 43 r.p.m.

The coating compositions were applied to the rotating tablets by spraying molten material at 110–140° through a steam-jacketed pneumatic spray head[10]. Low pressure (12 psig.) steam was introduced into the steam jacket to keep the spray head hot during the operation. In each instance, the spray coat was applied to batches of 175 g. of tablets for 5 min. Air pressure for atomization was regulated at 15 psig.

Within 10 days after they were coated, the tablets were evaluated initially for friability, appearance, disintegration, and tablet-to-tablet uniformity of coat. Since these were screening studies, factors such as the additives being capable of assuming more than one crystalline form on cooling were not considered. These factors could be defined later should an additive appear promising as a result of this preliminary evaluation. Weights of tablets were obtained using a balance[11], and friability was determined[12] (6). Disintegration times were determined using the Stoll–Gershberg apparatus, with disks, and 37° distilled water as described in the USP XVII (7). The appearance of the coats before and after storage for 9 months at ambient room temperature was checked visually. In addition, the tablets were inspected for sticking (clumping), fading, and general appearance.

Tables I and II record disintegration times (in seconds) presented as a median of the range of 12 tablets for each formula modification presented, the range of disintegration times (in seconds), the coating weight, friability, appearance, coefficient of variation of the coat, and a factor derived from the other physical parameters.

The range of disintegration times, in general, may reflect uniformity or nonuniformity of the coat, with the more uniform coat exhibiting the narrowest range.

The weight of the coat is an index of the sprayability of the coating material. Since the time of application is uniform, the increase in coating weight over that of the coated control indicates increasing sprayability and vice versa. Since the weight of the coat varied from additive to additive and with the coated control, a normalizing

[6] Arlacel 60, Atlas Chemical Ind., Wilmington, Del.
[6] Klucel, Hercules Powder Co., Wilmington, Del.
[7] Stokes B-2 model 512.
[8] Sheffield Chemical Co., Division of National Dairy Products Corp.
[9] Mantrolac R 49, Mantrose Co., New York, N. Y.

[10] 1/4 JBCJ spray head equipped with a No. 2850 fluid nozzle and a No. 70 air nozzle supplied by Spraying Systems Co., Bellwood, Ill.
[11] Type H6T, Mettler Instrument Corp., Hightstown, N. J.
[12] Using a Roche Friabilator.

Table II - Effects of Additives to 20% Shellac–80% I Base on Tablet Film Coatings

Additive (10% w/w)	—Disintegration, sec.— Median of Range[a]	Range[b]	Coating Weight[c]	$(SD)_c$[d]	SD[e]	Friability[f]	α[g]	Disintegration Factor[h]	Initial Appearance[i]
Abietic acid	800	200	39.5	4.24	3.25	0	8	20	17
Acacia	525	170	38.2	3.88	2.77	1.0	7	14	18
Acetylated monoglycerides	515	90	39.5	5.06	4.27	0	10	13	5
Benzyl benzoate	720	360	41.9	4.21	3.21	0	8	17	11
Polyoxyethylene lauryl ether	483	115	36.7	5.14	4.36	0	12	13	8
Castor oil	530	40	31.8	4.45	3.52	0	11	17	4
Cocoa butter	515	150	31.6	4.02	2.96	0 (1)	9	16	9
Glycerin	438	185	21.1	2.79	0.20	0	1	21	7
Isopropyl myristate	570	160	39.2	5.03	4.23	0	11	15	1
Oleic acid	603	145	35.3	5.05	4.26	0	12	17	14
Polyethylene glycol 400	485	110	44.8	5.05	4.26	0	10	11	15
Polyethylene glycol 6000	355	50	16.7	3.44	2.11	0 (1)	13	21	13
II	405	150	30.4	5.42	4.69	0	15	13	6
III	480	200	39.6	5.10	4.32	1.0	11	12	13
Polysorbate 80	370	40	27.8	3.70	2.51	0	9	13	4
Propylene glycol	550	160	34.1	3.36	1.97	0	6	16	2
Stearic acid	470	80	20.9	3.94	2.95	1.0	14	22	16
Coated control	530	100	31.1	3.57	2.31	0 (1)	7	17	11
Uncoated control	323	75	—	2.72		2.8 (1)	—	—	—

[a–i] See footnotes to Table I.

factor, called a disintegration factor (D.F.), was developed to aid comparison among modified coatings as follows:

$$\text{D.F.} = \frac{t}{W_c} \qquad \text{(Eq. 1)}$$

where t = median of the disintegration time of 12 tablets (seconds), and W_c = average weight of the coat (milligrams). A comparison of the disintegration factor for a modified coating material with that of the coated control indicates the effect of the additive upon the apparent rate of solution of the basic coating formulation.

DISCUSSION

Throughout the experiment, attempts were made to keep variables at a minimum. The objective was to determine the effects of individual additives on the coating. Although certain additives such as carnauba wax, cetyl alcohol, and stearyl alcohol were miscible with the basic coating formulations, these materials raised the melting points of the formulations to such an extent that acceptable coats could not be achieved when these additives were used in 10% concentrations.

Other additives such as isopropyl myristate and acacia were not miscible with the coating compositions. However, they were suspendable to some degree and were included since they did not interfere with the sprayability of the coats. Isopropyl myristate formed a temporary emulsion and greatly improved the performance of the spraying operation as well as the appearance of the finished tablets.

It was generally observed that the series consisting of 10% shellac–90% I could be applied much more easily and resulted in tablets of a more elegant appearance than the series containing 20% shellac–80% I (last column, Tables I and II).

Examination of tablets stored 6 weeks at 45° revealed that all tablets had faded except those containing cocoa butter, castor oil, oleic acid, or glycerin. The mechanism of the stabilizing effect of these additives on the D&C Yellow No. 10 is not clear at this time. Tablets stored 9 months at room temperature did not exhibit the same degree of color instability.

Tablets stored 6 weeks at 45° containing benzyl benzoate, polyethylene glycol 400, propylene glycol, or II had softened to the point where they had clumped together. Here, again, tablets stored 9 months at room temperature presented a slightly different picture.

In general, the 9-month room temperature evaluation was more revealing than the high temperature study. The coated control

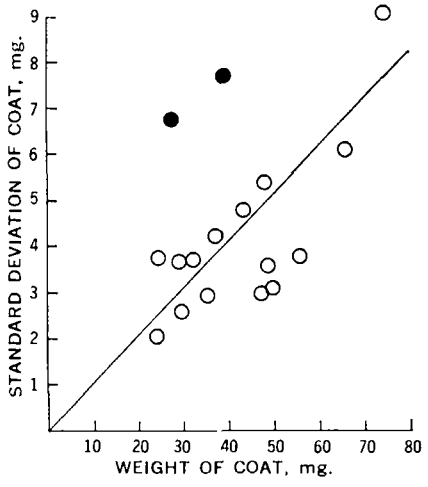

Figure 1—*Dependence of the standard deviation of the coat upon the weight of the coat illustrated for the 10% shellac–90% I system. Key: ●, parameters of additives that are statistically different from the parameters of the other additives;* i.e., *the process is out of control.*

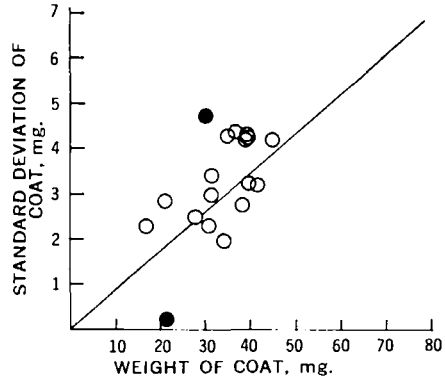

Figure 2—*Dependence of the standard deviation of the coat upon the weight of the coat illustrated for the 20% shellac–80% I system. Key: ●, parameters of additives that are statistically different from the parameters of the other additives;* i.e., *the process is out of control.*

Table III—Comparative Rank of Acceptable Additives According to Descriptive Factors

Additive	Disintegration Factor		Coefficient of Variation		Appearance		Row Total
	A[a]	B[b]	A[a]	B[b]	A[a]	B[b]	
Castor oil	1	3	1	3	4	2	14
Cocoa butter	3	2	4	2	3	3	17
Isopropyl myristate	2	1	1	3	1	1	9
Polyethylene glycol 6000	5	5	5	5	2	5	27
Coated control	4	3	3	1	5	4	20

[a] A = 10% shellac–90% I base. [b] B = 20% shellac–80% I base.

tablet exhibited a slight degree of clumping, and tablets could easily be separated with one or two gentle shakes of the container. This was also the case with all tablets found to exhibit clumping, with the exception of those containing benzyl benzoate, polyethylene glycol 400, polysorbate 80, propylene glycol, II, abietic acid, and acetylated monoglycerides, which required slightly more vigorous shaking.

Coatings composed of the 10% shellac–90% I base with cocoa butter, polyethylene glycol 6000, or isopropyl myristate additives exhibited no clumping or fading after 9 months of storage at room temperature.

Coatings composed of the 20% shellac–80% I base with castor oil, polyethylene glycol 6000, isopropyl myristate, or cocoa butter additives performed in a like manner. With respect to clumping and fading, these additives provide an improvement over the coated control.

As a result of the 9-month room temperature evaluation, only four of the 17 miscible additives were found to be useful as modifying agents to the basic formulations. These additives are castor oil, cocoa butter, isopropyl myristate, and polyethylene glycol 6000.

Regarding weight, the coefficients of variation (α) of the coats are listed in Tables I and II and were calculated by:

$$\alpha = 100 \cdot \frac{\sqrt{(SD)_c^2 - (SD)_u^2}}{W_c} \qquad \text{(Eq. 2)}$$

where $(SD)_c$ = standard deviation of coated tablets, $(SD)_u$ = standard deviation of uncoated tablets, and W_c = average weight of coating. An F test shows acacia and polyethylene glycol 6000 to be significantly different from the remainder when the data in Table I are considered; glycerin and II are likewise significantly different from the remainder when the data in Table II are considered. The coefficient of variation *for the process* can be obtained from a plot of standard deviation of coats, SD, *versus* W_c (with the constraint of zero intercept), and the coefficient of variation for the process emerges in the slope of the line (Figs. 1 and 2).

A least-squares fit yields $\alpha = \Sigma SD \cdot W_c / \Sigma W_c^2 = 0.0952$ or 9–10% for Fig. 1 and 0.0988 or 9–10% for Fig. 2. These values are, of course, close to the coefficient of variation for the coated control, showing that, within statistical limits, the substances tested (other than acacia and polyethylene glycol 6000 in Table I and glycerin and II in Table II) are not detrimental to the uniformity of the coat.

The disintegration factor, coefficient of variation of the coat, and appearance rating for each additive were ranked in relation to the others and to those of the coated control. The order of rank was assigned on the basis of the lowest number in each category being assigned first order in rank, *etc.* The results of this ranking are in Table III. Note that each additive is ranked for each criterion in each of the two basic formulations.

To select an order of preference for the use of these additives, the ranks which each additive held in each category and for each basic formulation were summed ("Row Total" column of Table III). Again, the lower the sum the more desirable is the effect of the additive upon the basic formulation. From Table III, it can be seen that isopropyl myristate, castor oil, and cocoa butter all improved the basic formulations while polyethylene glycol 6000 ranks lower than the coated control.

The disintegration factor for each additive to the 10% shellac–90% I basic formulation was divided by the corresponding factor in the 20% shellac–80% I basic formulation. The quotients were then summed and averaged, and their standard deviation was computed. When this average, 0.66 ($SD = \pm 0.15$), is compared to the quotient obtained from a like division of the disintegration factors for the coated controls, 0.76, the conclusion can be made that shellac is the controlling factor with regard to disintegration of this type of coating composition.

A similar treatment was applied to the coefficients of variation. The ratio for glycerin was aberrent to those obtained for the other additives. When the ratio for glycerin is eliminated, the average of the ratios for the remaining additives, 1.17 ($SD = \pm 0.58$), was, within statistical limits, consistent with that for the coated controls, 1.3. Examination of the quotients for individual additives reveals that glycerin, acacia, polyethylene glycol 6000, and propylene glycol effect a considerable increase in uniformity with increasing concentration of shellac. These agents probably act as plasticizers for the shellac and should be considered as such when used in combination with shellac. Since only one concentration of each additive was evaluated with each of two concentrations of shellac, a more comprehensive factorial analysis of the data was not attempted. However, the results of these screening studies did elucidate additives suitable for future work.

SUMMARY AND CONCLUSIONS

1. A novel method was described for application of tablet coatings. Tables citing the effect of various additives to the two basic coating compositions described were presented.

2. A disintegration factor was developed to aid comparison of basic coating formulations and the effect of additives upon them in conjunction with the use of the coefficient of variation. Use of these factors resulted in the selection of three additives that favorably modify the basic formulations described herein. Based on an overall appraisal, improvements in the basic coats were attained by addition of 10% (w/w) castor oil, cocoa butter, or isopropyl myristate to a shellac–polyethylene glycol 4000 mixture. These additives not only improved stability with respect to clumping and fading but also with respect to disintegration, friability, uniformity of coat, and appearance.

3. The concentration of shellac in the basic formulation appears to control disintegration regardless of additives.

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ACKNOWLEDGMENTS AND ADDRESSES

Received November 9, 1972, from the *Pharmaceutical Research and Development Laboratories, Merrell-National Laboratories, Division of Richardson-Merrell, Inc., Cincinnati, OH 45215*

Accepted for publication April 17, 1973.

The authors thank Mr. George F. Graman for his technical assistance and Dr. J. T. Carstensen, University of Wisconsin, for his critical and editorial comments on this manuscript.

▲ To whom inquiries should be directed.