Wurster Coated Aspirin I

Film-Coating Techniques

By VINCENT COLETTA and HOWARD RUBIN*

A method of coating aspirin crystals of various mesh sizes with mixtures of ethylcellulose and methylcellulose using the WARF (Wurster) air suspension apparatus is described. The results of varying the ratio of ethylcellulose to methylcellulose in the coating film have been explored. Rapidly disintegrating tablets of the coated crystals were prepared, and solubility studies were run. These showed excellent sustaining ability. Definite correlation between the solubility rate of aspirin and the ethylcellulose to methylcellulose ratio in the coating was found.

As PART OF the program of the study of dosage forms suitable for proprietary use, it was of interest to study release characteristics of crystalline drugs coated in the Wurster apparatus (1) to yield delayed release of these drugs. This paper deals with the coating of crystalline aspirin and its incorporation into rapidly disintegrating tablets. A companion paper correlates *in vitro* and *in vivo* release of certain of these preparations (2).

The Wurster apparatus was chosen because of its versatility. The coating process is not limited by particle size of the drug, the coating materials, or the solvent system; the machine has been documented as to its usefulness in applying coatings for the purpose of controlling drug release (1, 3). The 6-in. pilot model has a capacity of 0.5 to 4 Kg., and coating can be completed in 30 to 50 minutes. This chamber easily supplies quantities of material necessary for product development requirements.

The need for pH independent coatings suggested the use of combinations of ethylcellulose and methylcellulose (4), well known cellulose polymers, in different ratios as possible coating materials. It remained then to determine optimum particle size of the drug, applicable ratios of the two cellulose materials, percentage film coat, rate of application of the solubilized materials, and the particular machine settings to yield the most even continuous film coat.

EXPERIMENTAL

A typical data sheet with all operating conditions is illustrated in Table I. A soluble dye was added to the cellulose gum dispersions as a visual aid in the coating process. A large (1 gal.) Waring Blendor was used to disperse the gums. The spray run was completed in 30 minutes. By allowing the outlet temperature of the apparatus to climb to within a few degrees of the inlet temperature, there was assurance that all the solvent was evaporated off the granules. Agglomeration was prevented by adjusting air and liquid flow (5). The resultant products consisted mainly of individual crystals with a continuous coating of the polymers.

The conditions entered in Table I were standardized and used throughout the experiments. The solvent system, formulation, concentrations of plasticizer, and total cellulose polymers remained constant. In all cases, fast disintegrating tablets containing the coated aspirin—83%, cornstarch—15%, and talc—2% were prepared using $^{7}/_{16}$ in. S.C. punches. The tablets contained 325 mg. of acetylsalicylic acid. Disintegration time was less than 1 minute. *In vitro* solubility studies were run on all granules and tablets. The shells remaining after solubility studies were examined microscopically to determine degree of fracture of the coating and whether any aspirin remained in the intact shells.

Initial studies were done with 20-mesh aspirin (20–40 mesh) and 40-mesh aspirin (all pass 40 mesh). A 2.7% coating was applied to the 20-mesh material, and a 4.8% coating was applied to the 40-mesh material. The finer material required additional coating to yield approximately the same final film thickness.

Twenty-mesh aspirin crystals were selected for additional coating work; 6% coatings were applied to this material, starting with concentration of 50/50 ethylcellulose/methylcellulose with gradations to 100% ethylcellulose and 0% methylcellulose.

RESULTS AND DISCUSSION

In the first study (Table II) 20-mesh aspirin using 75% ethyl, 25% methylcellulose was the slowest, though not slow enough. It was decided to concentrate on the largest aspirin size (20 mesh) and increase the concentration of the coating material. The second series was started to determine the optimum ratio of ethylcellulose to methylcellulose.

Duplicate solubility runs indicate granulations, and tablets showed good reproducibility within the batch (2). Solubilities for duplicate coating and tablet preparations are shown in Table III. It is apparent that excellent replication was achieved in the final tablet. The accuracy of duplication from batch to batch depends only on the ability to follow through on the operating procedures of the apparatus. The Wurster apparatus is the ideal equipment for research quantities of coated drugs. The

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TABLE I.—WURSTER COATING AND GRANULATING PROCESS

Formula No.	133	*Date:*	10/17/61
Material Coated:	20–40 mesh aspirin crystals	*Quantity:*	2 Kg.
Coating:	50/50 ethylcellulose methylcellulose	*Quantity:*	120 Gm.
Coating, %:	6% based on wt. of aspirin 5.66% of total wt.		

Formula of Coating Solution:	*Quantity*
1) Methylene chloride	1800 ml.
2) Isopropyl alcohol	1800 ml.
3) Glycerin	24 ml.
4) Ethylcellulose N 10 (10 cps)	60 Gm.
5) Methylcellulose 50 Hg (50 cps)	50 Gm.
6) FD&C Green No. 3	50 mg.

Initial Coating Solution Temp.: 130° F. *Mixing Time:* 3 min.
Max. Air Flow: 96.0 c.f.m. *Recommended Air Flow:* 78.5 c.f.m.
Fluid Nozzle: 2050 *Air Nozzle:* No. 64
Atomization Pressure: 45 psig. *Coating Reservoir Pressure:* 15 psig.
Inlet Fluid Pressure: 5–9 psig. *Inlet Temp. Setting:* 125° F.
Inlet Temp. Range: 115–130° F. *Exhaust Temp. Range:* 90–110° F.
Yield: 98% *Humidity:* 45% R.H.

Remarks: Formula No. 134 tablets prepared with the coated aspirin. No agglomeration of crystals.

TABLE II.—SOLUBILITY OF ASPIRIN TABLETS

	Per Cent Dissolved (as a Function of Time— 4-hr. Recovery)			
	2.7% Coating—20 Mesh (20–40 Mesh)		4.8% Coating—40 Mesh (Pass 40 Mesh)	
	25 Ethyl 75 Methyl	75 Ethyl 25 Methyl	25 Ethyl 75 Methyl	75 Ethyl 25 Methyl
Time	134A	134B	134C	134D
1/2	42	47	77	97
1	79	65	90	98
2	94	88	100	99
3	100	94	100	99
4	100	100	100	100

use of other apparatus, *i.e.*, coating pan and hydraulic gun, is possible; but experience indicates that duplication on small batches is difficult (3).

Figures 1 and 2 clearly indicate the release rates obey first-order kinetics. The semilogarithmic solubility plots are linear. *In vitro* sustaining of acetylsalicylic acid is evident, and *in vivo* sustaining is also obtained (2).

Through the use of the Wurster apparatus and the cellulose polymers ethylcellulose and methylcellulose, it has become possible to vary the solubility release rates of aspirin crystals. The data clearly show that as the amount of ethylcellulose is increased in the ratio, the aspirin release rate is decreased. The procedure is considered very satisfactory since not only can the release be predicted but also the tablets prepared from the coated crystals give excellent duplication.

Microscopic examination of the residue after solubility determinations using stereo and polarizing microscopes indicates that most of the shells are largely intact with some fractured ones and some

TABLE III.—REPLICATION OF COATING AND TABLETING PROCEDURE

	% Dissolved as Function of Time	
	152	152A
5 min.	6	6
15 min.	13	13
30 min.	22	23
1 hr.	37	37
2 hr.	57	61
3 hr.	74	74
4 hr.	80	85

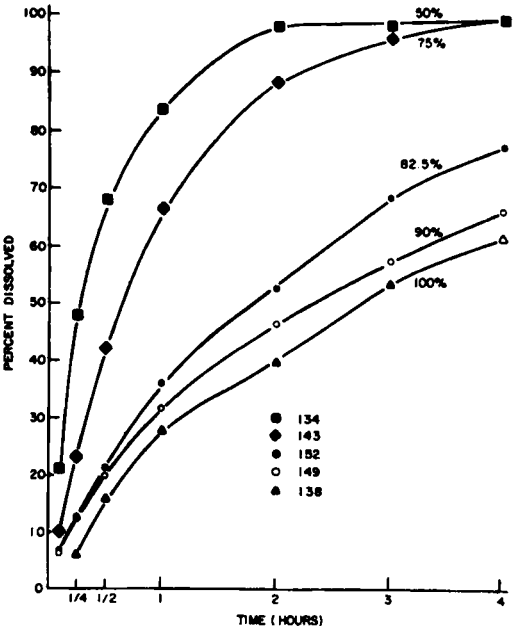

Fig. 1.—Effect of ethylcellulose content on solubility rate (6% coatings).

powdered cellulose mixture. The intact shells are free of all traces of crystalline aspirin. The variation in ratios of the two cellulose polymers with corresponding variation in solubility rate clearly

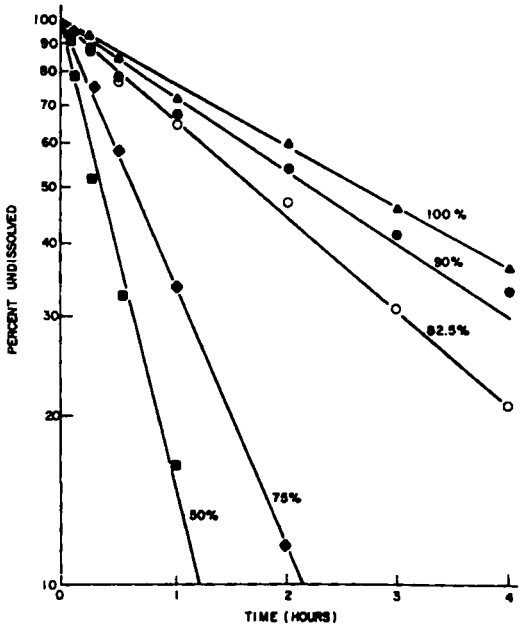

Fig. 2.—Semilog plot of per cent aspirin dissolved *vs.* time (data from Fig. 1 graph) illustrates solubility rate variations with concentration of ethylcellulose on coating.

indicates the mechanism is one of dialysis with ethylcellulose as the more impermeable film, though the literature indicates water vapor transmission through both films is similar (6). The combination of ethylcellulose and methylcellulose appears to be slowly soluble at the 50/50 level. This does not appear, however, during the length of the solubility run. The films containing the higher ratio of ethylcellulose seem to be dominated by the ethylcellulose and appear to be insoluble in the pH 4 buffer. Kanig and Goodman (6) show that this situation appears with ethylcellulose and polyvinyl pyrrolidone combinations; nevertheless, concentration changes as low as 7.5% increase in ethylcellulose and 7.5% decrease in methylcellulose (75/25 to 82.5/17.5) show a definite change in solubility rate. The influence on water vapor transmission and therefore the change in aspirin solubility seems to be significant for relatively smaller percentage changes in composition.

SUMMARY

From a purely practical pharmaceutical standpoint it is evident from the data presented that the Wurster apparatus is a valuable tool for preparing research quantities of sustained-release medications. Continuity of films and evenness of coating is possible and reproducible. The coated crystals are suitable for compression into fast disintegrating tablets that provide sustained release of aspirin. It has been shown that the solubility rate of aspirin coated with different concentrations of ethylcellulose and methylcellulose can be sustained. It has also been shown that the ratio of the two cellulose polymers affects the solubility rate, the solubility rate being inversely proportional to the concentration of ethylcellulose. This has been reflected in the solubility rate curves as shown.

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Physical Stability Testing of Pharmaceuticals

By JAMES E. TINGSTAD

The importance of physical stability of pharmaceuticals and methods of testing physical stability of tablets, capsules, suspensions, emulsions, solutions, and ointments are discussed.

Physical stability is an important problem to product formulators for three primary reasons.

Appearance.—Physicians, pharmacists, patients—all expect pharmaceutical products to look fresh, elegant, and professional no matter how long they sit on the shelf. Any slight change in physical appearance—like fading of a color—may cause these people to lose confidence in that particular product.

Uniformity.—Since most products are sold as multiple-dose packages, the formulator has to make sure that the patient receives the same amount of active ingredient in each dose. A cloudy solution or a broken emulsion means that the patient is in danger of being overdosed or underdosed.

Availability.—The formulator's ethical responsibility to the patient does not end with providing a uniform dose. If the active ingredient is not absorbed, he has failed that patient just as much as if he gave him a worthless placebo. Therefore, the formulator has to make sure that the active ingredient is just as

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