Influence of Certain Factors on the Coating of a Medicinal Agent on Core Tablets

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The influence of core tablet shape, mixing of coating powders, dilution ratio of diluent to medication, and composition of diluent on the efficiency in the coating of a medicinal onto core tablets by the conventional method was investigated. It was found that tablet shape and type of mixing did not influence the efficiency in this procedure. The overall percent recovery of medicament depending on the variations introduced was from 85 to 90.9 percent in the procedure. Significant factors were drug to diluent ratio and composition of the diluent. Two new methods of drug application were employed, namely, the air-atomized system and the airless-spray-coating system. The air-atomized system was found less efficient than the conventional coating procedure. The airless-spray-coating system, on the other hand, showed a nearly 100 percent efficiency in medication coating.

PROCESSES AND TECHNIQUES employed in the coating of tablets have been surrounded with secrecy. Only one specific report was found in the literature about the efficiency of coating a medicinal agent onto solid cores. Welti (1) investigated the efficiency of applying medication onto pellets on a small scale by the conventional coating method. He found that losses of medication are considerably smaller when the medicament is applied in a powder mixture to previously wetted pellets than when the medicament is applied in the form of a suspension. In general, Welti experienced a loss of medicament ranging from 18 to 44.8%. The loss was dependent on the size of the coating pan, the method of application, and the type of drying.

It was the purpose of this study (*a*) to investigate the efficiency of coating a medicament onto solid cores by the conventional coating procedure, (*b*) to present two new film-coating methods of medicament coating and to show their efficiency, and (*c*) to evaluate some factors influencing the efficiency of medicament coating with respect to the conventional coating procedure and the two new methods.

It was hoped that a comparison between these three methods of application would reduce the general loss of medication as experienced by Welti and give a better way for medicament coating.

Received May 8, 1967, from Eli Lilly and Co., Indianapolis, IN 46206

Accepted for publication February 14, 1968.

Presented to the Industrial Pharmaceutical Technology Section, APhA Academy of Pharmaceutical Sciences, Las Vegas meeting, April 1967.

Abstracted from a thesis presented to the Graduate Division of Butler University College of Pharmacy, Indianapolis, by Werner M. K. Seidler in partial fulfillment of the requirements for the degree of Master of Science.

The author wishes to thank Eli Lilly Research Laboratories, Indianapolis, Ind., for the supply of chemicals and use of equipment.

EXPERIMENTAL

Two types of tablet shape were used in all experiments: Type 1—round deep concave, and Type 2—elliptical. The tablet weight was in both cases 365 mg. The tablets were subcoated with four applications of a coating solution consisting of sucrose (35% w/v) and acacia (27% w/v) and a coating powder consisting of talc (87%) and acacia (13%) in the conventional manner before medication coating was applied. The medicament used in these experiments was quinine hydrochloride. Each tablet was coated with 15 mg. of quinine hydrochloride, theoretically. No excess was used in any of the experiments.

Conventional Coating Procedure—Twenty-four experiments were carried out to investigate the conventional coating procedure. In each experiment 5,000 subcoated tablets were placed into a 14-in. pear-shaped copper coating pan rotating at 24 r.p.m. The tablets were wetted with an aqueous sucrose-acacia solution after which a powdered diluent–medicament mixture was applied. Alternate wetting and powdered diluent–medicament application was continued until all of the powdered medicament mixture was applied. This was followed by two applications of syrup. Drying was accomplished after each addition with warm air and full exhaust. The tablets were then dried for 24 hr. at room temperature. Ten tablets were picked at random from each experiment and a single tablet assay performed for quinine hydrochloride.

The variations introduced in the conventional coating procedure involved (*a*) the ratios 50:50, 20:80, and 5:95 of powdered diluent to medicament, (*b*) the mixing of the components in a twin-shell blender and in a ball mill for 5 hr. in both cases, and (*c*) the use of two different powdered diluent–medicament mixtures. The composition of the powdered diluent formulas was as follows:

1.	Calcium sulfate	49% w/w
	Milk sugar	49% w/w
	Magnesium stearate	2% w/w
2.	Calcium carbonate	44.5% w/w
	Starch powder	6.0% w/w

Calcium sulfate	44.5% w/w
Silicon dioxide	5.0% w/w

The diluents were chosen as being representative of those commonly used in the pharmaceutical industry.

Film-Coating Procedure—In the film-coating procedure, utilizing the air-atomized system and the airless-spray system, quinine hydrochloride was incorporated in the film-forming solution. The two film-forming solutions used in the experiments consisted of:

1. Hydroxypropyl methylcellulose 10	3.0% w/v
Glycerin	0.3% v/v
Quinine hydrochloride	5.0% w/v
Methylene chloride and methanol 50:50 v/v, a sufficient quantity	
2. Polyvinylpyrrolidone	4.0% w/v
Acetylated monoglycerides type 9-40	1.0% v/v
Acetylated monoglycerides type 5-00	3.0% w/v
Quinone hydrochloride	7.5% w/v
Isopropanol and methylene chloride 40:60 v/v, a sufficient quantity	

For the application of quinine hydrochloride film-coating solution in the air-atomized system, a De Vilbiss spray gun with the spray nozzle No. 92 was used. A variation introduced in the air-atomized system involved a change in air pressure (10 p.s.i. and 25 p.s.i., respectively). The pan size, pan speed, and batch size were the same as in the conventional coating procedure. The coating solution was continuously sprayed onto a moving bed of tablets. The spray rate for Solution 1 was 17.2 ml./min.; for Solution 2 it was 11.4 ml./min., both at 10 p.s.i. At 25 p.s.i. the spray rate of Solution 1 was 23 ml./min.; for Solution 2 it was 19 ml./min. Sufficient exhaust was provided on the outside of the pan to carry off the solvent vapors during the spraying. After drying the tablets for 24 hr. at room temperature, 10 tablets were picked at random from each of eight experiments and assayed for quinine hydrochloride content.

In the airless-spray system the film-coating material to be applied was pumped under high pressure through a special nozzle. In four experiments a Nordson pump model No. 100 060 (16:1 pressure ratio) with a Nordson Versa gun was used. Nozzle 9C11 was used for coating Solution 1 with an air pressure of 500 p.s.i.; nozzle 6C7 for coating Solution 2 with an air pressure of 800 p.s.i. All experiments utilized a noncirculating system. To better accommodate the spray to the coating pan and to the tablets the lot size was increased to 7,500 subcoated tablets per experiment. The pan size and the pan speed were the same as in all previous experiments. The Nordson system did not allow a continuous spray, as was the case with the air-atomized system, since no air to facilitate drying was introduced during the actual spray cycle into the pan. A cycle of 3 sec. spraying time and 25 sec. drying time was established. No exhaust or hot air was used during the actual spray cycle. Again, after 24 hr. drying at room temperature, 10 tablets were selected at random from each experiment and assayed for quinine hydrochloride content.

Assay Procedure—The quinine hydrochloride content of each tablet was determined spectrophotometrically. Correction for the interference due to the water-soluble film-forming agent was determined from a placebo tablet subjected to the entire assay procedure.

RESULTS AND DISCUSSION

A total of 36 experiments was carried out (24 for the conventional coating procedure, 8 for the air-atomized system, and 4 for the airless-spray-coating system), and 358 single-tablet assays were performed. Table I gives the averages for the conventional coating procedure according to the variations introduced. The assay range differential is understood to be the difference in assay results between the lowest and the highest assay in this grouping. It can be seen that the type of mixing and tablet shape did not have any significant influence on the coating efficiency as shown by the percent recovery or on the assay range differential. The variations which were found to be significant are (*a*) the medicament ratio and (*b*) the type of powder diluent formula used. There was little difference between powdered medicament–diluent in the ratio of 50:50 and 20:80, but the 5:95 ratio showed the highest assay results and the least assay range differential. Powder diluent Formula 1 showed greater percent recovery than powder diluent Formula 2; however, the assay range differential was higher. The overall percent recovery in the conventional coating procedure, depending on the variations introduced, was from 85.0 to 90.9%.

Table II gives the averages for the film-coating procedures. In the air-atomized system the nature of the film-forming solution and the pressure applied have a significant influence on the quinine hydrochloride content of the finished tablets. The higher the pressure the greater the medicament loss. The overall recovery of quinine hydrochloride in this system ranges from 69.4 to 74.0%, depending on the air pressure and the film-forming solution used. The assay range differential is about the same regardless of the variations introduced.

In the airless-spray-coating system, the tablet shape seems to have an influence on the actual amount of quinine hydrochloride found on the tablet. Also, film-forming Solution 2 shows a greater percent recovery and a smaller assay range differential than film-forming Solution 1. However, it must be recalled that a larger nozzle and a lower pressure was required for film-forming Solution 1 in order to obtain a satisfactory spray. The range of the individual assay results was the greatest in the airless-spray-coating system compared to either the conventional coating procedure or the air-atomized system; however, the actual amount of quinine hydrochloride found on tablets was close to theory.

Statistical Evaluation—Analysis of variance showed (Table I) that in the conventional coating procedure the powder diluent–medicament ratios and the powder diluent formulas are factors which influence medicament coating. In the air-atomized system the pressure and, to a lesser degree, the film-forming solution are factors which influence medicament coating (Table II). In the airless-spray-coating system (Table II) the variations used appear to make no difference in the results.

TABLE I—AVERAGES FOR CONVENTIONAL COATING PROCEDURE AND STATISTICAL EVALUATION

Variation	Recovery, %	Assay Range Differential, mg.	Assay, mg.	Source of Variation	SS	df	MS	FP(F)
Shape				Shape	0.22	1	0.22	0.15
Round	87.2	2.7	13.1					
Ellipt.	87.5	3.1	13.1					
Mixing				Mixing	0.52	1	0.52	0.37
Twin-shell	86.6	2.8	13.1					
Ball mill	88.3	3.1	13.2					
Medicament ratio				Medicament ratio	33.11	2	16.56	$11.65 < 0.001^a$
50:50	85.8	3.3	12.9					
20:80	85.6	3.4	12.8					
5:95	90.9	2.0	13.7					
Powder diluent formula				Powder diluent formula	47.25	1	47.25	$33.23 < 0.001^a$
1	90.3	3.3	13.6					
2	85.0	2.5	12.7					
				Residue and error	329.84	232	1.422	
				Total	410.94	237		

[a] Statistically significant differences.

TABLE II—AVERAGES FOR FILM-COATING PROCEDURES AND STATISTICAL EVALUATION

Variation	Recovery, %	Assay Range Differential, mg.	Assay, mg.	Source of Variation	SS	df	MS	FP(F)
Air-Atomized System								
Shape				Shape	0.38	1	0.38	0.38
Round	71.6	2.9	10.8					
Ellipt.	72.5	2.1	10.9					
Film-form. solution				Film-form. solution	6.86	1	6.86	$6.88 < 0.01^a$
1	74.0	2.5	11.1					
2	70.1	2.5	10.5					
Air pressure, p.s.i.				Air pressure	12.81	1	12.91	$12.85 < 0.001^a$
10	74.8	2.4	11.2					
25	69.4	2.6	10.4					
				Residue and error	75.75	76	0.997	
				Total	95.80	79		
Airless-Spray System								
Shape				Shape	5.70	1	5.70	$2.52 > 0.05$
Round	103.2	3.9	15.6					
Ellipt.	98.6	5.6	14.8					
Film-form. solution				Film-form. solution	2.35	1	2.35	$1.04 > 0.05$
1	99.3	7.0	15.0					
2	102.5	3.1	15.4					
				Residue and error	83.54	37	2.26	
				Total	91.59	39		

[a] Statistically significant differences.

SUMMARY AND CONCLUSIONS

The following conclusions are drawn from this study:

1. In the conventional coating procedure the medicament loss was found to range from 0.7 to 24.3% based on individual assay.

2. The type of mixing of the powdered diluent–medicament mixture and the tablet shape did not influence the efficiency of the conventional coating procedure.

3. Best yields and smallest tablet-to-tablet variations in medicament content were obtained with the highest powder diluent–medication ratio.

4. Two new methods of application were employed, namely, the air-atomized coating system and the airless-spray-coating system.

5. With the two new methods it was found that the tablet shapes used in this study did not influence the drug content of the tablets.

6. The air-atomized system gave a more consistent range in tablet-to-tablet medicament content than either the conventional coating procedure or the airless-spray-coating system; however, the percent recovery of the applied medicament was the lowest, in the range of 65 to 75%, depending on the air pressure used.

7. The airless-spray-coating system was found

to be the most efficient method of medicament application to a tablet core. Nearly 100% quinine hydrochloride recovery was obtained with this method.

8. Of the three methods investigated, the air-atomized coating system showed the greatest loss of medicament. The airless-spray-coating system showed hardly any loss of medicament. The conventional coating procedure was intermediate in medicament content with respect to the atomized systems.

From this study there appears to be an advantage in applying medication by the airless-spray system. Such a system eliminates the excess medication which must be added in the conventional coating procedure and would thus result in a savings in labor and material.

REFERENCE

(1) Welti, H., *Pharm. Acta Helv.*, **39**, 139(1964).

Keyphrases

Core tablets—drug coating
Physical parameters, effect—coating core tablets
Powder, sucrose–acacia solution—coating
Drug–diluent ratio, effect—core coating
Film coating—airless-spray, air-atomized systems

Notes

Enhanced Mortality of Selected Central Nervous System Depressants in Hypoexcretory Mice

By B. A. BECKER, K. L. HINDMAN*, and J. E. GIBSON

The mortality of nine central nervous system depressant drugs was compared in normal and hypoexcretory mice. Anuria was produced in mice by penile ligation; cholestasis was produced by bile duct ligation. The intraperitoneal administration of prochlorperazine, trifluoperazine, perphenazine, meprobamate, and chloral hydrate produced significantly elevated mortality rates in anuric mice whereas promazine, perphenazine, and meprobamate showed elevated mortality rates in cholestatic mice. The mortality of chlorpromazine and phenobarbital was not altered in hypoexcretory mice.

CHOLESTATIC OR anuric mice may be more susceptible to some pharmacologic agents than mice without excretory impairment as shown by Gibson and Becker (1). In that work the acute lethality of ouabain was found to be enhanced in cholestatic mice; digoxin and digitoxin had higher mortality rates in anuric mice. Possible alteration in acute lethality of nine central nervous system depressant drugs were similarly studied in cholestatic and anuric mice: five phenothiazine tranquilizers (Table I) including two from the propyldimethylamine subgroup, promazine and chlorpromazine; three from the propylpiperazine subgroup, prochlorperazine, trifluoperazine, and perphenazine; the nonphenothiazine tranquilizer, meprobamate; and three sedative-hypnotics, pentobarbital, phenobarbital, and chloral hydrate.

METHODS

Male Swiss-Webster mice weighing 25–40 Gm. and allowed free access to food and water throughout the experiment were rendered anuric by penile ligation under light ether anesthesia by the method of Becker and Gibson (2). Cholestasis was induced by ligation of the common bile ducts of other male mice of the same strain under ether anesthesia. The surgical wound was closed by 9-mm. wound clips. The general experimental procedure followed that previously reported (1). Preliminary experiments were performed on intact mice to determine suitable dosages of the test agents. Since the anticipated responses were enhancement or no change in mortality rates, dosages were sought which would be in the low lethal range, *e.g.*, LD_{10}–LD_{50}, as enhancement of mortality rates by dosages in the high lethal range, LD_{50}–LD_{99}, would be difficult to demonstrate with any degree of statistical confidence. The selected drugs were administered intraperitoneally in aqueous solution or 0.5% sodium carboxymethylcellulose suspension. The desired dosage of the selected agent was administered 2 hr. after penile ligation (PL) or 24 hr. after bile duct ligation (BDL); sham-operated animals, similarly treated, served as standards. Vehicle-treated operated and sham-operated mice served as controls. Since none of the control animals died under the conditions used, control data were eliminated from

Received October 18, 1967, from the Department of Pharmacology, College of Medicine, University of Iowa, Iowa City, IA 52240

Accepted for publication December 11, 1967.

This research was supported in part by grant No. GM-12675 from the National Institutes of Health.

* Recipient of a College of Medicine Summer Fellowship.