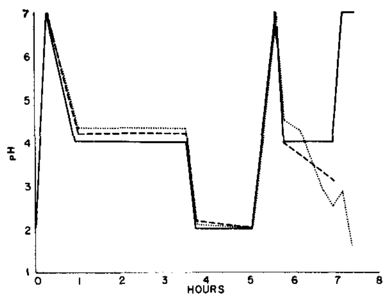

Fig. 6.—Transmitting capsule linearity response *vs.* time. Key: ————————, actual pH; – – – – – – – – –, kilocycle value; ...., chart value.

The results of varied pH media are given in Table IV and Fig. 6.

Response interval of the transmitting capsule to different buffers was found to be less than 5 min.

CONCLUSIONS

1. The Heidelberg capsules provide an accurate and sensitive means of telemetric recording of hydrogen-ion concentration of a surrounding medium.
2. Individual transmitting capsules vary in sensitivity and must be individually standardized.
3. The useful life span of a transmitting capsule is approximately 6 to 8 hr.
4. Linear response of the capsule is limited to between pH 2.0 and 7.0.
5. On the basis of the *in vitro* evaluation of the instrument and transmitting capsule, the Heidelberg capsule merits consideration for *in vivo* determinations of gastric pH.

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Evaluation of a High-Efficiency Solids–Solids Blender

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Solids–solids blending of pharmaceuticals is a time-consuming batch operation. Modern techniques using high-efficiency mixing devices as a method of process time-saving and cost reduction are becoming of prime concern. The Littleford-Lodige mixer was evaluated as a method of achieving rapid high-efficiency solids–solids blending; its application as a wet granulation device was also briefly investigated. The data obtained using the Littleford-Lodige mixer as a solids–solids blender is presented. Evaluation of the data indicate complete mixing is obtained in approximately 30 sec. Preliminary evaluation of this equipment as a method of wet granulation indicates granulation times in the order of 5 to 10 min. or less, depending on mixing characteristics and ingredients. Based on the results of this work, the Littleford-Lodige mixer appears to be a promising method of achieving rapid dry blending and wet granulation in one piece of equipment. Its use in the field of blending and wet granulation is worthy of further investigation.

Solids–solids blending and the incorporation of liquids into dry solids is an important unit operation in many processes. In the field of pharmaceuticals, the blending of materials in the past has routinely been handled using the standard process equipment—namely, ribbon blenders, Hobart mixers, twin-shell blenders, etc. Mixing in these types of equipment, although adequate, generally is time consuming and of a batch nature. Today, with the ever-present problems of cost reduction and time savings being critically evaluated, the unit operation of blending is being reviewed for possible methods of time reduction and/or continuous operation.

In the past several years, high-efficiency equip-

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TABLE I.—DRY BLENDING STUDY

Run[a]	Plow Speed, r.p.m.	Chopper Speed, r.p.m.	15 sec.	30 sec.	45 sec.	1 min.	5 min.	10 min.	15 min.	35 min.
			Mixing Times — Results Acetaminophen Concn., mg./300 mg.[b]							
1	120	3600	28.14	29.48	29.34	30.43	30.09	29.92	...	...
2	170	3600	30.71	33.45	30.59	30.57	30.84	30.60	...	...
3	240	3600	28.14	30.53	30.56	30.71	30.37	30.73	...	...
4	170	3600	30.65	30.56	30.48	30.41	30.61	33.45	30.57	...
5	120	0	White powder and dye agglomerates observed throughout mixing cycle							30.72
6	240	0	Similar to run 5					30.69	30.40	33.32

[a] Not in order of experimentation. [b] Average of four assay results; theoretical result 30 mg./300 mg.

TABLE II.—GRANULATION STUDY

Run[a]	Plow Speed, r.p.m.	Chopper Speed, r.p.m.	Quantity Granulating Material, No./No.	Time Required for Granulation, min.	Time Required for Initial Pasting, min.	Time Required for Overworking, min.
1	120	3600	0.3	2–3	3–4	5
2	150	3600	0.3	1–1.5	2.5	3
3	180	3600	0.3	0.5–1	1.5	2–2.5
4	240	3600	0.3	0.25–0.5	0.5–0.75	1
5	150	3600	0.3	1–1.5	2–3	3–4
6	150	0	0.3	No satisfactory granulation	...	2–2.5
7	150	3600	0.4	Not observed	3	3.5–4
8	150	3600	0.2	None after 7 min.[b]	...	...
9	150	3600	0.2+ Water to 0.3 level	1.5–2	2.5–3	3–4

[a] Not in order of experimentation. [b] Water to 0.3 level added after 7 min.; pasting occurred 0.5 min. after water addition.

ment has become available which greatly reduces the time required for uniform mixing or accomplishes the blending operation continuously. One of the more versatile pieces of equipment available today is the Littleford-Lodige mixer. The object of this paper is to report the results obtained when this mixer was used as a solids–solids blender and also some cursory results obtained when the mixer was used for wet granulation of the dry powder blends.

EXPERIMENTAL

Equipment.—The equipment used in the experimental work was the Littleford-Lodige mixer model FM-130. Figure 1 is a schematic diagram of a typical Littleford-Lodige mixer showing the essential parts. The experimental unit consists of a horizontal cylindrical shell equipped with a series of plow-shaped mixing tools and a high-speed blending chopper assembly mounted at the bottom rear of the mixer. For the addition of liquids, an injection tube terminating in a spray nozzle is provided. This nozzle is located immediately above the chopper assembly.

In operation, the plow-shaped mixing tools revolve at variable speeds from 120–240 r.p.m. and maintain the contents of the mixer in an essentially fluidized condition. At the same time, the plowing device provides a high volume rate of transfer of material across the blender. When liquid or granulating solutions are to be added to dry powders, the liquid enters the mixer under pressure through the liquid injection nozzle immediately above the chopper assembly. This assembly consists of blades mounted in a tulip-shaped configuration rotating at 3600 r.p.m. As the liquid impinges in the area of the chopper, it is immediately dispersed. By varying the mixing cycle, the particle size of the granulation may be controlled. A secondary function achieved by the chopper assembly is a milling or grinding operation due to the high peripheral speed of the blades.

Test Blend.—The test blend used in the solids–solids experimentation was made up of 215 parts lactose, 50 parts cornstarch, 30 parts acetaminophen, and 5 parts FD&C Green No. 2 Lake.

For the wet granulation, the dry blend of the above composition was used; a 10% w/w aqueous starch paste was used as the granulating medium.

Experimental Technique.—In the dry solids blending experimentation, all runs were made using a batch charge of 45 lb. All of the powders were charged to the mixer, and mixing was started using the designated experimental conditions. At time intervals of 15, 30, and 45 sec. and 1, 5, and 10 min. (in some runs 15 and 35 min.) mixing was stopped. Samples were taken for chemical analysis and visual evaluation. For chemical analysis, 1-oz. samples were taken. The sampling technique used was to take a sample from both ends and the center of the mixer. The three samples for each time interval were assayed. A randomly selected duplicate analysis of one of the samples at each time interval was also made. The four assay results for each sampling time were arithmetically averaged, and the average result is reported in Table I.

For the wet granulation experiments, after dry blending of the solids, the starch paste for granulating was added to the batch in one addition. During the subsequent mixing for granulation, the blender was stopped at various time intervals for visual inspection and evaluation of the granulating process.

Experimental Evaluation.—Two methods were used for the evaluation of the dry blending. The primary method was a chemical assay for acetamino-

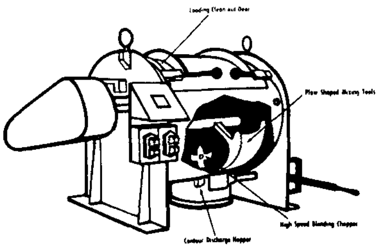

Fig. 1.—Littleford-Lodige (model FM-130) batch type mixer.

phen. The method used was the comparison of a test sample diluted in water and read at 243 mμ against water on the Zeiss spectrophotometer. The observed reading then was compared to a standard curve. No correction was necessary for the powder base less acetaminophen since no absorption was found for the base at 243 mμ.

Visual inspection of the dry blend was used as a secondary evaluation. This method was primarily for observation of dye particle dispersion. The method consisted of spreading a small amount of the dry mix over a white Patapar paper surface with a spatula. After spreading, the blend was inspected for streaking of both dye particles and acetaminophen agglomerates.

The evaluation of the wet granulation was limited to a visual inspection. Since the purpose of the work presented was to show the versatility of the Littleford-Lodige mixer, no drying and compressing of the granulation was performed.

DISCUSSION OF RESULTS

Dry Blending.—The data obtained for dry blending are presented in Table I. As can be observed from the data, complete mixing is obtained in approximately 30 sec. when the combination of the chopper and plow blades are used. There is apparently little effect of speed of the plow blades, although at the lower speed slightly longer mixing time (approximately 60 sec.) appears to be required to obtain the theoretical concentration of acetaminophen.

Without the use of the chopper blades, as in runs 5 and 6, a visual inspection of the mix at various intervals indicated a uniform distribution of material throughout the blend. However, there were considerable white powder agglomerates and dye specks. As mixing proceeded, the white agglomerates were dispersed; however, further reduction of the dye particles was not observed.

Visual inspection of the runs when the chopper mixer was used indicated that any white powder agglomerates present at the start of a run were dispersed after approximately 1 min. of mixing. However, dispersion of the dye particles was considerably more difficult, and almost complete dispersion of the dye particles was not observed for approximately 10 min. In none of the runs were the dye particles completely dispersed.

Visual inspection for color intensity was also made. In all instances, except those when the chopper was not used, color intensity was completely developed between 5 and 10 min. of mixing, with no noticeable color changes after 10 min. of blending. Without using the chopper blades, color development was not complete after 35 min. of mixing.

A temperature rise of 10–15°F. was observed during dry blending. In operation, approximately two-thirds of the observed temperature rise occurred in the first 5 min. of dry blending. The remaining rise in temperature was noted in the next 5-min. mixing period. No noticeable temperature rise was noted after 10 min. of dry blending.

Wet Granulation.—Table II summarizes the data obtained in the wet granulation experiments. As can be readily observed from the data, the time required to produce a satisfactory granulation is inversely proportional to the speed of the plow-shaped mixer. Depending on the speed of the plow mixer, a formulation can be granulated in less than 30 sec. or up to 3 min. or more, depending on the formulation needs. The data also show the importance of the role of the chopper in producing a granulation. Without using the chopper, no satisfactory granulation was achieved.

The effect of decreasing the granulating solution was evaluated. In these experiments no granulation was obtained with reduced granulating solution. However, when additional water was added, equivalent to that used in runs at 0.3 lb. of granulation solution per pound of powder, the granulating time correlated nicely.

In the experimentation, a temperature rise during granulation was noted. In a complete granulating cycle, after the addition of the granulating agent, a temperature rise of less than 5°F. was noted. Apparently, the work input due to mixing was lessened by the temperature of the granulating agent being lower than the powder batch after dry blending.

An interesting point was observed during the granulating experimentation. The Littleford-Lodige blender was equipped with an amperage gauge, as shown in Fig. 1. During all of the granulating experiments, it was noted that as the granulating cycle proceeded the current required, a measure of the work input increased to a constant level in each run at the point of proper granulation. As mixing continued and pasting occurred, the amperage required would increase. Based on these observations, apparently the granulation cycle is capable of being instrumented, thus relieving the necessity of the operator to determine the point of proper granulation.

CONCLUSIONS

The Littleford-Lodige mixer is well adapted for solids–solids blending and/or solids–liquid blending. In either case, blending times of less than 1 min. can yield satisfactory products, depending on the rotational speed of the plow-shaped mixer. The chopper blade plays an important part in the mixing operation; it is required to give satisfactory wet granulation. However, the use of the chopper blade for dry blending is not so critical and may not be necessary for satisfactory dry blending. Using the chopper blade may eliminate the necessity of auxiliary pulverization of dyestuffs or similar materials.

In the experimentation there is evidence that the Littleford-Lodige mixer could be instrumented to eliminate the necessity of the operator to determine when a granulation cycle is satisfactory.