surfactants discussed previously, emulsions stored at 5° containing polyoxyethylene sorbitan mono-oleate, when compared to those without it, were found to have a greater degree of droplet coalescence and lower apparent viscosities in spite of the stabilizing influence of refrigeration temperature.

It is interesting to note that although allergenic materials theoretically require refrigeration to maintain their potency, repository w/o emulsions after intramuscular injection are maintained at body temperature for periods of up to 1 year with no reported decrease in effectiveness.

The unqualified success of repository emulsion therapy may well depend upon elucidation of the specific agent responsible for individual allergic reactions, since the formulation of a stable w/o emulsion, consistent with the desired objectives, certainly is not insurmountable when the exact chemical composition of the components is known. Difficulties arise from the introduction of the unknown variables that undoubtedly exist in current antigenic extracts. The production methods for the extracts are a consideration since they are not standardized. The units of potency measurement constitute another variable since 3 different systems are in common use among allergists. The product may also vary as a result of variation in the amount of active principle in the raw material.

Considering the tremendous number of variables involved in the techniques of preparing and standardizing extracts of pollen and the extremely wide variations reported by physicians in the emulsification and administration of the extracts in repository form, the success that has been achieved is remarkable.

SUMMARY

This investigation has been concerned primarily with an evaluation of aqueous dispersions in light mineral oil stabilized with mannide mono-oleate and prepared under a set of standard conditions. The results obtained indicate the following.

1. Inorganic electrolytes, at concentrations as low as 0.01 *M*, in the aqueous internal phase of w/o emulsions, increase the apparent viscosities, hinder sedimentation, and have a marked stabilizing influence. This electrokinetic effect appears to be directly related to the valency of the anion.

2. The addition of water-soluble surfactants to the internal phase of w/o emulsions facilitates emulsification. However, these agents decrease stability and tend to cause inversion.

3. The storage of w/o emulsions at 5° has a definite stabilizing influence when compared to room temperature storage.

REFERENCES

(1) Fox, C. D., and Shangraw, R. F., *J. Pharm. Sci.*, **55**, 318(1966).
(2) Brown, E. A., *Rev. Allergy Appl. Immunol.*, **15**, 589 (1961).
(3) *Ibid.*, **16**, 74(1962).
(4) Albers, W., and Overbeek, J. T. G., *J. Colloid Sci.*, **14**, 501, 510(1959).
(5) *Ibid.*, **15**, 489(1960).
(6) Schulman, G. H., and Cockbain, E. G., *Trans. Faraday Soc.*, **36**, 651(1940).
(7) Verwey, E. J. W., *ibid.*, **36**, 192(1940).
(8) Brown, E. A., *Rev. Allergy Appl. Immunol.*, **16**, 171 (1962).
(9) Brown, E. A., *Ann. Allergy*, **21**, 432(1963).
(10) Rapaport, H. G., *N. Y. State J. Med.*, **61**, 2731(1961).
(11) Brown, E. A., *Ann. Allergy*, **20**, 126(1962).
(12) Gaillard, G. E., Schellin, R., and Mayers, R. A., *ibid.*, **21**, 69(1963).
(13) *Ibid.*, **21**, 378(1963).

Technical Articles

Critical Evaluation of the Compactor

By R. COHN, H. HEILIG, and A. DELORIMIER

With the assistance of a suitably prepared experimental design a compactor was optimized to prepare a basic granulation to which other drugs could be added and directly compressed into tablets. An IBM 1620 computor was employed to evaluate the data and to extrapolate additional information for the preparation of contour charts. The contour charts permitted a simple and accurate interpretation of the data and allowed selection of a set of optimum processing conditions. Additional trials confirmed the reliability of this technique.

A NUMBER OF investigations (1–3) in the chemical processing industry have employed continuous compacting equipment for the unit operation of particle size enlargement. They have shown the compaction process to be useful in the conversion of fine powders into larger agglomerated units. These particulates generally exhibited a reduced tendency to cake, improved flowability, increased bulk density, less dust, and

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a modified dissolution rate. On the basis of these earlier studies, it was expected that the compaction process would be applicable for the preparation of pharmaceutical granulations in large volumes.

A study was undertaken to utilize a compactor[1] for the preparation of a basic granulation to which other drugs would be added and directly compressed into tablets. Potassium chloride, which is a major component of a number of this company's marketed products, was selected as the test material.

The facilities of the Squibb Scientific Computing Center were employed for the preparation of an experimental design and the interpretation of the resultant data.

A photograph of the compactor utilized is presented in Fig. 1.

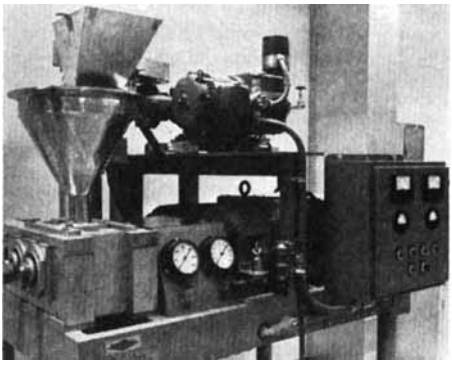

Fig. 1.—Photograph of the compactor.

EXPERIMENTAL

The experimental design permitted controlled modifications to be made on the 4 primary processing variables shown in Table I.

TABLE I.—PHASE *A* PROCESSING VARIABLES AND THEIR RANGES FOR THE COMPACTOR

Variable	Ranges
Oil pressure	220–800 p.s.i.
Roll speed	20–80% (10–40 r.p.m.)
Feed screw speed	20–80 (23–92 r.p.m.)
Added moisture	0–1%

Moisture evaluation of the test material was limited to the range of 0–1%, since it was observed that the addition of more than 1% moisture impeded material flow from the hopper of the compactor to the compacting rolls.

The criteria that were used to evaluate the quality of the granulation and the compressed tablets subsequently produced in the first phase study are shown in Table II.

The flow properties of the granulations were measured as a function of their angle of repose (4). Particle size distributions were obtained by sieve analysis. Loss on drying after 3 hr. at 160° F. under vacuum was used to define the moisture content of the granulation. The term "per cent fines" refers to the amount of potassium chloride that sifted through the compactor without being compacted.

TABLE II.—CRITERIA FOR EVALUATING PHASE *A* RESPONSES

Granulation	Tablet
Particle flow	Weight uniformity
Particle size distribution	Individual tablet assay
Moisture content	Binding
Per cent fines	Picking
	Capping
	Hardness
	Friability
	Disintegration time

A Colton 216 tablet machine was employed for the preparation of the tablet cores. The criteria referred to as binding, picking, capping, hardness, friability, and disintegration time were determined by standard procedures. Statistically sampled tablets were separately weighed on an analytical balance. To determine drug distribution, individual tablet assays were performed on 10 tablets selected at random from each trial.

On the basis of the data obtained from the full replicate factorial design of 18 runs shown in Table III, the IBM 1620 computer was able to extrapolate a total of approximately 2000 responses. Satisfactory correlations were obtained between the theoretical computer responses and the actual trial results.

A statistical analysis of the data obtained from these first 18 trials indicated that, aside from the moisture content of the granulations, the per cent fines, and the tablet hardness, all responses listed in Table II met the proposed specifications over the entire range of the experiment. Hence, these were not considered to be of primary importance in planning the second phase of the study.

During the course of the experiment, it was noted that under certain processing conditions the

TABLE III.—PHASE *A* EXPERIMENTAL DESIGN FOR THE COMPACTOR EVALUATION

Trial	Oil Pressure, p.s.i.	Roll Speed, %	Feed Screw, %	Moisture, %
1	800	80	80	0
2	220	80	20	0
3	220	20	80	1.0
4	800	80	80	1.0
5	800	80	20	0
6	220	80	20	1.0
7	510	50	50	0.5
8	800	20	80	0
9	800	20	20	0
10	800	20	80	1.0
11	220	20	20	0
12	220	80	80	0
13	220	20	20	1.0
14	800	80	20	1.0
15	220	20	80	0
16	510	50	50	0.5
17	220	80	80	1.0
18	800	20	20	1.0

[1] Model SN Chilsonator, manufactured by the Fitzpatrick Co.

amperage sensor on the drive motor indicated that the motor was being overloaded. It thus became apparent that the motor amperage response would become a very significant factor in the selection of an optimum processing condition. Hence, the responses for this factor were recorded for each trial and were used in the preparation of the contour charts.

Plotting of several contour charts from the tabulation of phase *A* responses led to the design for phase *B*. It was determined from analysis of phase *A* data that satisfactory responses for moisture, fines, hardness, and motor amperage could be obtained within the limits of the processing variables as shown in Table IV.

TABLE IV.—PHASE *B* PROCESSING VARIABLES AND THEIR RANGES

Variable	Range
Oil pressure	300–500 p.s.i.
Roll speed	70–90% (35–45 r.p.m.)
Feed screw speed	50–70% (57–80 r.p.m.)
Added moisture	0 %

RESULTS AND DISCUSSION

Data from the phase *B* trials were combined with those from phase *A* for a comprehensive analysis and determination of an optimum operating condition. The selected data are listed in Table V.

The perusal of the initial trial responses indicated that the factors of primary concern were *per cent fines, motor amperage,* and tablet hardness. Hence, these responses were evaluated for the preparation of a contour chart.

In order to prepare this type of descriptive diagram it was necessary to fix 2 of the 4 processing variables listed in Table I. Due to the inherent simplicity of processing dry powders and the lack of any significantly enhanced responses, moisture was held at a level of 0%. With added moisture fixed at 0%, roll speed could be set at 80% of the maximum. The results indicated that at these settings the most satisfactory set of responses would be attained and in addition, maximum throughput of material could be achieved in the shortest period of time.

Figures 2–4 illustrate the preparation of a contour chart and its use in determining optimum processing conditions. The contour lines are drawn by connecting responses of equal magnitude. For clarity the numerical responses that were obtained from the computer were removed from Figs. 3 and 4.

It can be observed from Fig. 2 that there was a relatively simple relationship between amperage data and the processing variables. It was observed that as the effective throughput of material or the forces acting on the compression rollers were increased, more power had to be expended. Since this work was measured as a function of motor amperage, any increase in either or both of these factors causes a corresponding increase in amperage levels. The maximum amperage at which the drive motor could be satisfactorily operated was 17. Hence, any set of processing conditions which would result in an amperage reading of less than 17 was satisfactory.

TABLE V.—SELECTED DATA EMPLOYED FOR THE PREPARATION OF CONTOUR CHARTS

Moisture..... 0%
Roll Speed.....80%

Oil Pressure	Feed Screw Speed	Amperage	Hardness	Fines
100	40	7.36	15.00	34.67
200	40	8.92	15.20	34.43
300	40	10.60	15.23	34.11
400	40	12.40	15.10	33.72
500	40	14.31	14.80	33.26
600	40	16.34	14.34	32.72
100	50	7.71	14.93	33.43
200	50	9.32	15.15	33.06
300	50	11.03	15.20	32.61
400	50	12.87	15.09	32.09
500	50	14.82	14.82	31.50
600	50	16.88	14.38	30.84
100	60	8.22	14.97	33.26
200	60	9.86	15.21	32.76
300	60	11.61	15.29	32.18
400	60	13.49	15.20	31.53
500	60	15.48	14.95	30.81
600	60	17.58	14.53	30.01
100	70	8.88	15.14	34.15
200	70	10.56	15.40	33.52
300	70	12.35	15.50	32.81
400	70	14.26	15.43	32.03
500	70	16.29	15.20	31.18
600	70	18.43	14.80	30.26
100	80	9.69	15.43	36.11
200	80	11.41	15.71	35.35
300	80	13.25	15.83	34.51
400	80	15.20	15.78	33.60
500	80	17.26	15.57	32.62
600	80	19.44	15.19	31.56
100	90	10.66	15.83	39.14
200	90	12.42	16.14	38.24
300	90	14.29	16.18	37.27
400	90	16.28	16.25	36.23
500	90	18.38	16.06	35.12
600	90	20.60	15.71	33.94

Hardness values have been superimposed on the amperage graph in Fig. 3.

The hardness data were obtained by measuring 20 individual tablets for each trial on a pneumatically

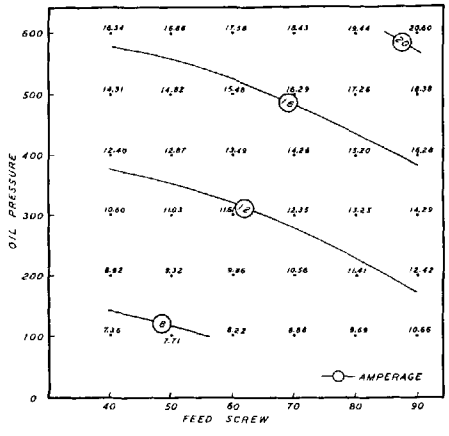

Fig. 2.—Amperage responses plotted as a function of feed screw speed and oil pressure. Moisture, 0%; roll speed, 80%.

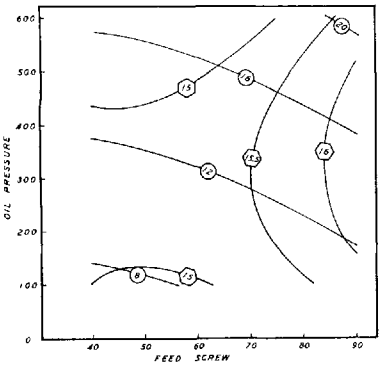

Fig. 3.—Tablet hardness values superimposed on the amperage plot. Moisture, 0%; roll speed, 80%. Key: O, amperage; ○, hardness.

operated Strong-Cobb hardness tester. Although one would hardly expect a significant difference in tablet quality for hardness values of 15.5 and 16.0, due to the relatively large number of samples (approximately 400), a noticeable trend was observed. That is, although the individually reported results did not appear to be significantly different, the data that were obtained to arrive at these numbers were different.

A perusal of this figure indicated that a simple relationship between the variables and the responses

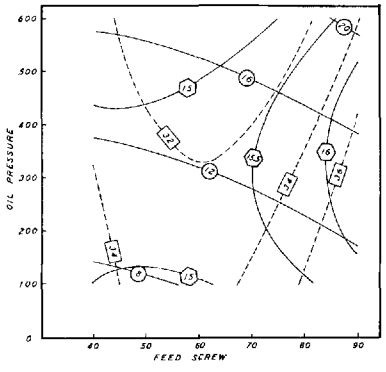

Fig. 4.—Per cent fines, amperage, and tablet hardness values displayed as functions of roll speed and oil pressure. Moisture, 0%; roll speed, 80%. Key: O, amperage; ○, hardness; □, fines.

did not exist, although a review of the tables of data confirmed that maximum feed screw speed was important to maximize this response.

The responses measured as functions of the processing variables were fairly difficult to interpret for the analysis of the amount of fines that sifted through the compactor without being compacted. It was observed that reduced feed screw speed tended to reduce the magnitude of this result. Since one of the major difficulties of the compactor was leakage of powders between the roller seals, as less material was brought in contact with the seals, less was forced through without being compacted. The assumption that increased pressure prevented or reduced the tendency of material to pass between the rollers without compression is probably incorrect. It was the authors' experience that a better fit of the compactor roller and seals was obtained under increased pressure, as less fines were observed under conditions of higher oil pressure. In actual usage, the fines were recycled back to the compactor and did not effect later processing elements.

Thus, as can be observed from Fig. 4, for the following fixed levels of moisture, 0%, and roll speed, 80%, the variable processing conditions of feed screw speed, 65%, and oil pressure, 400 p.s.i., yielded a product which manifested the maximum number of satisfactory responses.

A second and third series of contour charts were drawn with moisture fixed at 0%, but with roll speed fixed at 70 and 90%, respectively, at maximum conditions. The resultant data indicated that at optimum conditions the responses were slightly inferior to those obtained at a fixed roll speed of 80%.

A confirmatory trial was performed at the machine settings suggested by an analysis of the contour charts at moisture, 0%, roll speed, 80%, feed screw, 65%, and oil pressure, 400 p.s.i., with the result that satisfactory correlations of the actual responses to theoretical values were obtained. Excellent tablets were prepared when portions of the aforementioned compacted material were employed for the preparation of other potassium chloride-containing products.

REFERENCES

(1) Evans, P. E., and Smith, G. C., *Powder Met.*, **3**, 26 (1959).
(2) Kurtz, B. E., and Barduhn, A. J., *Chem. Eng. Progr.*, **56**, 67(1960).
(3) Gregory, H. R., *Trans. Inst. Chem. Engr.*, **40**, 21 (1962).
(4) Nelson, E., *J. Am. Pharm. Assoc., Sci. Ed.*, **44**, 135 (1955).