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Cost Evaluation of Alternative Pharmaceutical Tableting Processes by Simulation

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Abstract □ A simulation model and a subsequent computer program were developed as experimentation methods for evaluating tableting processes with respect to cost. These methods also allow estimation of the various times involved in a tableting operation (*e.g.*, the processing time). The model was programmed in FORTRAN using the GASP IV simulation language. After verification of the program, experiments were run that involved comparing different levels of specific input variables to determine which variable had an effect on the cost–time relationships of a particular processing method. Among the possible input variables chosen for evaluation were the drying method, the type of tableting machine, the batch size, the labor rate, and the operation of the equipment in the process. An analysis of variance was made, and three separate regression equations were developed that described the relationship between the input variables and the dependent variables of processing cost and time. Graphs were developed from the regression equations by manipulating them through series of different independent variables. These graphs then were used in determining minimum costs and times, breakeven points, and rates of change, as well as in simple evaluation of processes through graphic representation. By using the simulation program to run experiments and then by analyzing them, results can be obtained to help in making intelligent decisions about the cost–time relationships of a particular tableting procedure before it is implemented.

Keyphrases □ Tableting processes—cost evaluation, simulation model □ Models, simulation—cost evaluation of tableting processes □ Cost evaluation—tableting processes, simulation model □ Processing formulations—tableting procedures, cost evaluation, simulation model

The effects of alternative processing methods and formulations on the physical, chemical, and biological characteristics of tablet dosage forms (1, 2) have been discussed extensively. Although these alternative processes and formulations can affect the time and cost for tablet production, little information has been published on these time–cost effects. This paper describes a method for assessing various processing time and cost effects with specific alternative formulations and processing techniques. The general implications of these effects also are shown.

The basic element of this method is a computer simulation encompassing the various tablet-processing techniques. Although simulation has been used in the pharmaceutical industry for the development of a completely computerized tableting plant (3) and for various chemical and business operations, these simulations are specific for a particular company and application. Also, these simulations have been employed to answer specific questions.

The approach illustrated here is generalized to simulate virtually any tableting operation, and it is coupled with an example of an experimental design so that inferences can be made over numerous factors that change from one tableting operation to another. In this way, the individual simulation serves as a basic experimental unit, much as would an individual laboratory experiment. Results from such simulations thus can be used in process analysis, design, and performance evaluation with respect to cost–time information.

MODEL

Development—A general simulation model for the tableting of pharmaceutical products was developed. The model was constructed so that any of the three basic tableting methods (wet granulation, direct compression, and slugging) as well as variations in these methods could be simulated. The basic unit operations employed by these methods were arranged in linear fashion as shown in Part A of Fig. 1. To simulate a particular tablet processing technique, unit operations that are not part of the technique are excluded by having a zero time interval. In this way, a single model can simulate two or more tableting methods where any differences in the methods are inputted explicitly in the program.

General unit operation input variables are included in every step of the model (Fig. 1, Part B). The times involved in each unit operation are determined by the type of equipment used in that particular step. These times reflect the cost involved per unit operation. Power and depreciation are other cost components. Only linear depreciation is used in the model,

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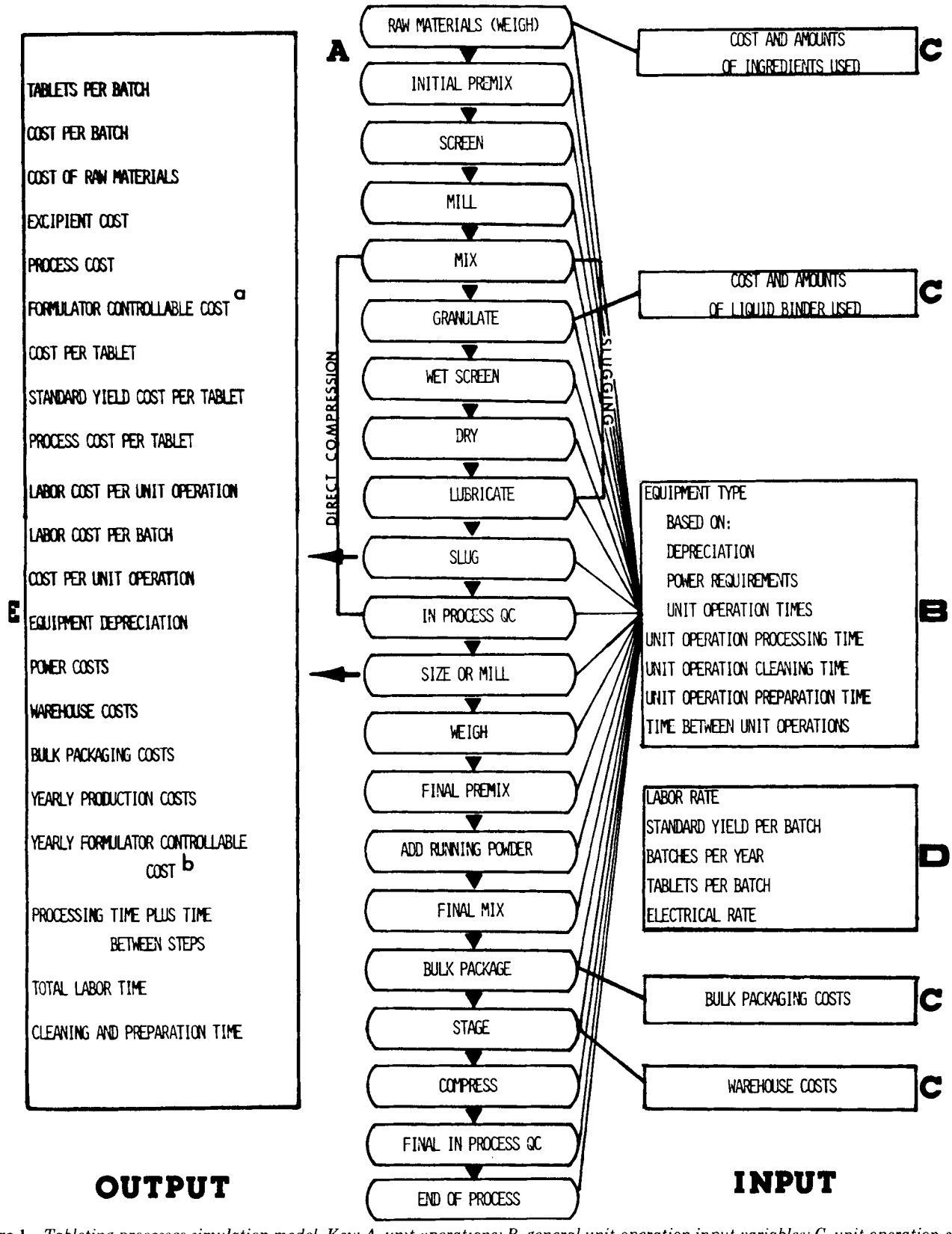

Figure 1—*Tableting processes simulation model. Key: A, unit operations; B, general unit operation input variables; C, unit operation-specific input variables; D, batch-specific input variables; and E, final cost–time output. [a]Process and formulation controllable cost. [b]Yearly process and formulation controllable cost.*

as noted in Table I, which also includes some of the important equations used in the model (4, 5). The utilization factor used here is unity minus the fraction of time the equipment is idle. The utilization factor adjusts the actual batch time to account for a proportional amount of the idle time for the equipment.

Unit operation-specific input variables that are used in only certain operations are given in Part C of Fig. 1. These variables include warehousing costs, but only those incurred during the staging operations before the final product is complete.

Batch-specific input variables that are used throughout the entire

Table I—Partial List of Basic Equations Used in the Model [a]

Computed Output	Equations	Variables
Power consumption cost per unit operation (PCC)	PCC = (HP) (UOPT) (ER) (0.012426432)	HP = Horsepower of the equipment in the unit operation UOPT = Unit operation processing time (minutes) ER = Electrical rate (dollars per kilowatt hour) 0.012426432 = Conversion factor
Labor cost per unit operation (LC)	LC = (PT + CT + UOPT + TBUO) (LR)	PT = Unit operation preparation time CT = Unit operation cleaning time UOPT = Unit operation processing time TBUO = Time between unit operations LR = Labor rate (dollars per hour)
Total cost per unit operation (TCUO)	TCUO = PCC + LED + LC + AC	PCC = Power consumption cost per unit operation LED = Linear equipment depreciation per unit operation LC = Labor cost per unit operation AC = Additional costs (*i.e.*, raw materials, bulk packaging costs, and warehouse cost)
Total cost per batch (TCB)	TCB = $\Sigma_{i=1}^{x}$TCUO, where x is the total number of unit operations in the process	TCUO = Total cost per unit operation
Processing cost per batch (PC)	PC = TCB − CRM	TCB = Total cost per batch CRM = Cost of raw materials
Process and formulation controllable cost (FCC)	FCC = (EC − PC)/SY	EC = Excipient cost PC = Processing cost SY = Standard yield per batch
Standard yield cost per tablet (SYCT)	SYCT = TCPT/SY	TCPT = Theoretical cost per tablet SY = Standard yield per batch
Linear equipment depreciation per unit operation (LED)	LED = [(IC − SV)/(SL × 525,960 × UF)] (UOPT + PT + CT)	IC = Initial cost of each piece of equipment in the process SV = Salvage value of each piece of equipment in the process SL = Service life of each piece of equipment in the process UF = Utilization of each piece of equipment in the process 525,960 = Conversion factor UOPT = Unit operation processing time PT = Unit operation preparation time CT = Unit operation cleaning time

[a] All times are in minutes.

simulation are given in Part D of Fig. 1.

The final cost–time output needed for process analysis and evaluation is denoted as Part E in Fig. 1. The *Appendix* gives detailed information regarding this output. In addition, various histograms and tables that show the cost breakdowns for individual unit operations are provided by the basic program to aid in specific process verifications and corrections.

The basic simulation model was kept simple to reduce computer costs and to make it easier for users to adjust to specific operational variations. Adjustments to the input data will be needed when the operation being simulated deviates from the assumptions made in constructing the basic model. These assumptions and some of the required adjustments include the following:

1. The time "between" unit operations is included in the cost of the successive operation.

2. If a unit operation is skipped, then the time between it and the successive unit operation is uniform. The time "between" unit operations is dictated by the unit operation being left, *not* by the next unit operation in the process. This convention allows variations in the sequences of unit operations.

3. Equipment depreciation for each unit operation in a process is based on the unit operation processing time, cleaning time, and preparation time. The batch depreciation is the sum of the individual depreciations of the unit operations.

4. Labor cost for a unit operation includes the time between the current and the previous unit operation, cleaning time, preparation time, and unit operation processing time multiplied by a single labor rate. If multiple labor rates are involved, then a single composite labor rate can be used.

5. The unit operation processing labor time is equal to the unit operation processing time, except in the drying step (tray drying only) and the staging step. In the drying and staging steps, the unit operation processing labor time is much less than the unit operation processing time.

6. Costs are assigned only to the particular batch being processed. Accordingly, the time a laborer works on more than one batch during any particular processing step is not included in the final cost estimates.

7. The laborer can do only one thing at a time. For example, if the mixing unit operation lasted 15 min, the laborer would be at this step for 15 min and would *not* be starting the next unit operation in advance. The only exceptions are the drying and staging unit operations, where the unit operation processing labor time differs from the unit operation processing time.

8. All equipment used is powered by electricity; or if it is powered by some alternative form of energy, it can be converted into equivalent electrical units (kilowatt hours).

Data—Data were collected from various pharmaceutical manufac-

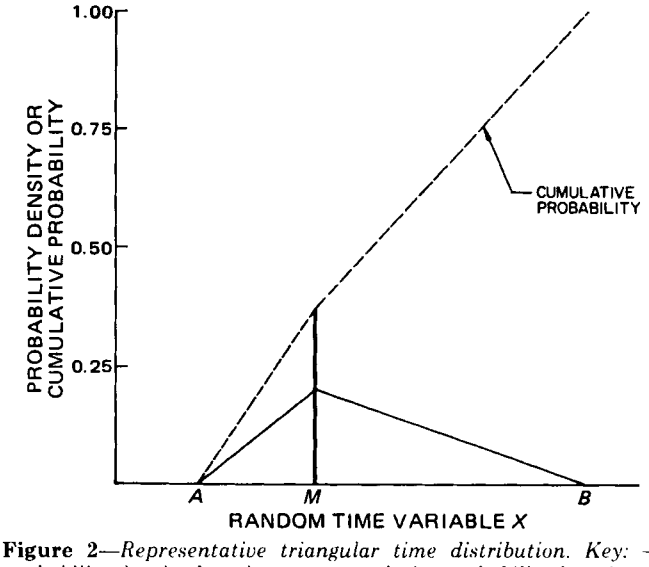

Figure 2—*Representative triangular time distribution. Key:* —, *probability density function;* - - -, *cumulative probability function;* A, *minimum;* B, *maximum; and* M, *mode.*

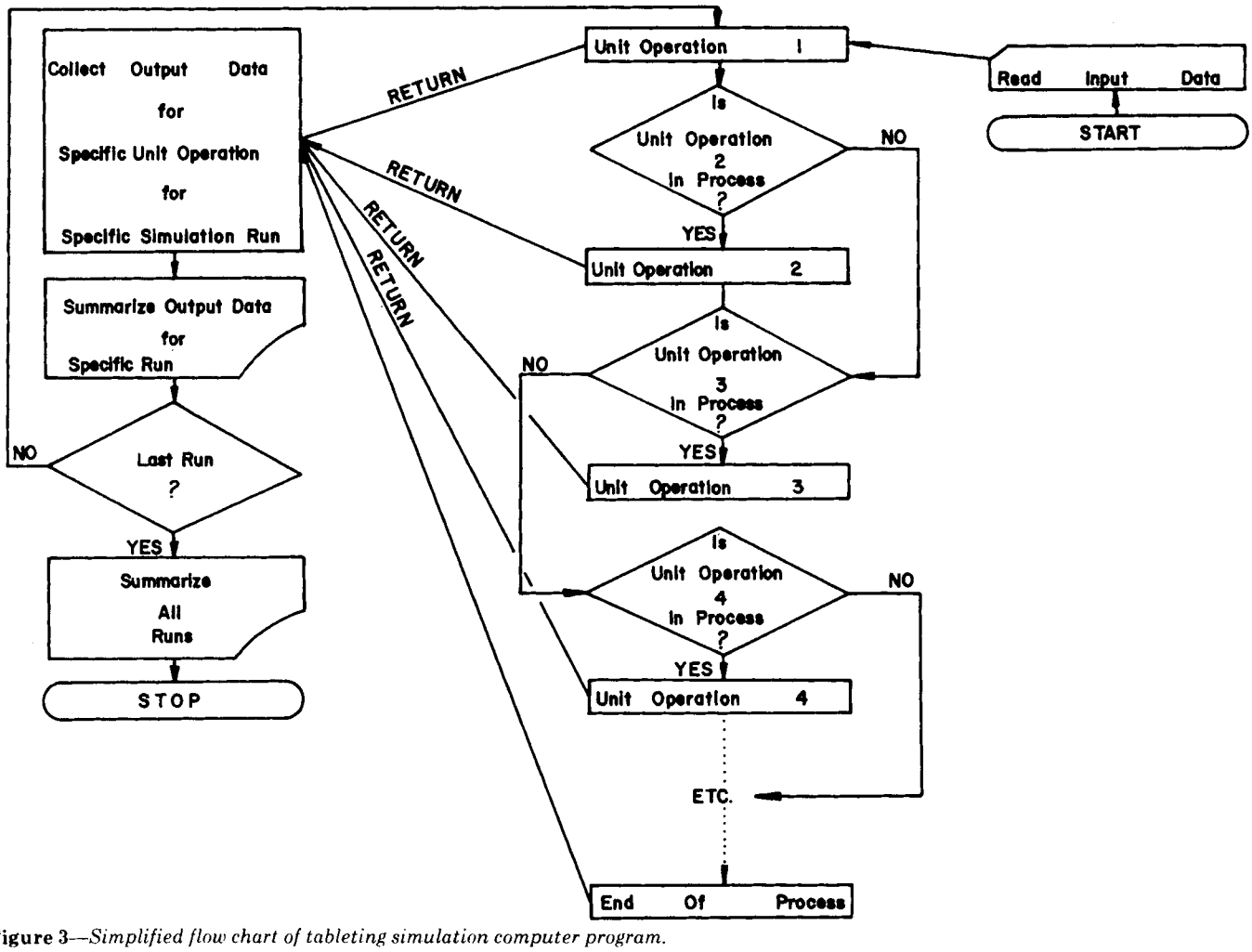

Figure 3—*Simplified flow chart of tableting simulation computer program.*

turing firms on specific operations performed, sequences of operations, equipment specifications and layouts, products made, manpower requirements, approximate time requirements, and other relevant features to assure reasonable generality of the model and to provide reasonable values and ranges for various parameters and coefficients.

Time and cost variations occur randomly in the unit operations, and an allowance was made in the basic model to include these uncertainties. Time data were collected in triangular distribution form to provide users with a consistent and highly intuitive method for including these uncertainties (6). With the triangular distribution, users must specify the minimum value, the most likely or modal value, and the maximum value for the random time variable being described. Distributions representative of the data collected were used in the program, but other distributions can be incorporated, if necessary, with a minimum of programming effort. Figure 2 shows the probability density and cumulative probability functions of the triangular distribution.

The probability density function is described by:

$$F(X) = \frac{2(X - A)}{(M - A)(B - A)} \qquad A \le X \le M \qquad \text{(Eq. 1}a\text{)}$$

$$F(X) = \frac{2(B - X)}{(B - M)(B - A)} \qquad M \le X \le B \qquad \text{(Eq. 1}b\text{)}$$

$$F(X) = 0 \qquad \text{otherwise} \qquad \text{(Eq. 1}c\text{)}$$

The cumulative probability function is described by:

$$F^*(X) = \frac{(X - A)^2}{(M - A)(B - A)} \qquad A \le X \le M \qquad \text{(Eq. 2}a\text{)}$$

$$F^*(X) = \frac{(M - A)}{(B - A)} + \frac{(B - M)^2 - (B - X)^2}{(B - M)(B - A)} \qquad M \le X \le B \qquad \text{(Eq. 2}b\text{)}$$

where X is the random time variable, A is the minimum value, B is the maximum value, and M is the modal (most likely) value. This distribution allows for asymmetry in the random variable, which often occurs in processing time requirements. In the computer program, a uniform random deviate is called and converted to a value of X through the cumulative probability function described by Eqs. 2*a* and 2*b*.

Programming—The model was programmed in FORTRAN with the

Table II—Example of the Printout Produced by the FORTRAN Simulation Program

Average Results of All Runs	Average	*SD*
Tablets per batch	250,000.00	
Cost per batch	$6,293.00	4.108
Cost of raw materials	$5,879.76	
Excipient cost	$59.13	
Process cost	$413.24	4.108
Process and formulation controllable cost	$476.18	4.141
Cost per tablet	$0.025172	0.00001643
Standard yield cost per tablet	$0.025375	0.00001656
Process cost per tablet	$0.001653	0.00001643
Labor cost per step	$25.73	0.270
Labor cost per batch	$385.98	4.047
Cost per step	$419.53	0.274
Equipment depreciation	$4.42	0.075
Power costs	$2.84	0.065
Warehouse costs	$0.00	
Package costs	$20.00	
Yearly production cost	$1,132,739.82	739.415
Yearly process and formulation controllable cost	$85,712.12	745.378
Processing time plus time between steps	46.999 hr	0.755
Total labor time	70.951 hr	0.744
Cleaning and preparation time	41.057 hr	0.850

Table III—Comparison of Actual *versus* Simulated Average Total Processing Time plus Time between Unit Operations

Product	Actual Time from Manufacturer, hr	Simulated Time from Program, hr	Percent Difference from Actual Time
1	5.12	5.57	8.79
2	33.0	36.7	11.2
3	17.0	16.0	5.88
4	26.5	27.2	2.64
5	39.5	33.4	15.4
7	28.5	29.3	2.81
7	41.0	37.0	9.76
8	39.5	36.4	7.85

aid of a computer simulation package called GASP IV (7). GASP IV allows users to build computer simulations with a minimum of effort. The programmer develops subroutines that interact with various GASP IV subroutines. Subroutines in the GASP IV package provide much of the statistical analysis used in the simulation and in creating the cost–time histograms in the program output. Each unit operation in the model was programmed as a separate subroutine so that users could incorporate additional cost–time features into any unit operation with a minimum of difficulty.

By using different initial uniform random deviates, a different stream of random numbers are generated with each simulation run and are converted to random variations in time and cost output through the specific forms of the triangular distributions. These variations take the form of an average and a standard deviation for each cost–time output of the model. This result is indicated in the simplified flow diagram of the computer program shown in Fig. 3.

Table II shows a sample of the output averages and standard deviations to illustrate the management information provided by the basic simulation program.

Verification—The model verification was accomplished in two steps. The first step involved inspection by pharmaceutical processing personnel, including tableting operation supervisors and directors of pharmaceutical manufacturing departments, of the model concept, assumptions, and variable values to assure that they were representative of actual tableting processes.

The second step involved taking various tablet products from different companies, running the simulation on them as specified by their processing sheets, and then comparing the average simulated processing times with the average time reported in the company's records. Table III shows the results of these comparisons and the percentage differences between the simulation and the actual processing times. No relationships between simulation errors and actual processing times were evident from these data when they were plotted on a scattergram. Final cost data comparisons could not be obtained for proprietary reasons.

Model Application—Numerous experiments were run using the simulation, especially those involving interprocess analysis. The experiment illustrated here is an example of an intraprocess analysis. The goal was to determine how different levels of specific processing variables affect the final processing time and processing cost of a particular wet granulation tableting technique.

Numerous variables affect the processing time and cost. The variables chosen for investigation were the type of drying (tray or fluid bed), the type of tableting machine, the batch size, the average utilization of all equipment in the process, and the labor rate.

Except for the variable of the type of drying, there are many options for each variable, so the number of combinations possible is extremely large. Consequently, investigation of even a small fraction of these combinations is economically unfeasible in a search for more economical

Table IV—Fixed Unit Operation Input [a]

Unit Operations in Process	Equipment Used in Unit Operation	Cost of Equipment in Unit Operation[b]	Horsepower of Equipment
1. Raw materials	Scales	$7,000.00	0.1
2. Premix	Small blender[c]	$20,000.00	3.0
3. Screen	Screens	$50.00	0.0
4. Mix	Mixer[d]	$30,000.00	2.0
5. Granulate	Mixer	$30,000.00	2.0
6. Wet screen	Screens	$50.00	0.0
7. Dry	—[e]	—[e]	—[e]
8. Dry screen or size	Hammer mill[f]	$10,000.00	10.0
9. Weigh	Scales	$7,000.00	0.1
10. Add running powder or lubricant	Scoop	$5.00	0.0
11. Final mix	Large mixer[g]	$43,000.00	15.0
12. Bulk package	Scoop	$5.00	0.0
13. Compress	—[e]	—[e]	—[e]
14. Final in-process quality control	Quality control	$2,000.00	0.1

[a] The additional inputs were: bulk packaging costs = $20.00; electrical rate = $0.025/kw hr; standard yield = 0.992; and batches per year = 100. [b] Service life of equipment is 15 years. [c] Patterson Kelly Co., Division of Harsco Corp., East Stroudsburg, PA 18301. [d] Day Mixing, Cincinnati, OH 45212. [e] Variable level input. [f] Fitzpatrick Co., Elmhurst, IL 60126. [g] General Machine Co. of New Jersey, Newark, NJ 97114.

Table V—Variable Unit Operation Input [a]

Levels	Drying Method	Tableting Machine	Utilization of All Equipment in Process, %	Batch Size, tablets	Labor Rate per Hour
1	Tray dried (stainless steel tray dryer) Horsepower = 3.0 Cost = $20,000.00 Tray drying processing time: mode = 1080.0, minimum = 960.0, and maximum = 1200.0 Tray drying labor time: mode = 60.0, minimum = 50.0, and maximum = 70.0	Tablet machine A Horsepower = 3.0 Cost = $43,000.00 Tablets per minute: mode = 2800.0, minimum = 1500.0, and maximum = 4100.0	100	500,000	$5.50
2	Fluid bed dried Horsepower = 25.0 Cost = $100,000.00 Fluid bed drying processing and labor time: mode = 32.5, minimum = 20.0, and maximum = 45.0	Tablet machine B Horsepower = 15.0 Cost = $90,000.00 Tablets per minute: mode = 7608.0, minimum = 4347.0, and maximum = 10,869.0	50	1,000,000	$11.00
3	—	—	—	1,500,000	$16.50

[a] All times are in minutes.

Table VI—Results of Analysis of Variance [a]

Processing Cost Model ANOVA Results	Processing Time Model ANOVA Results	
	Fluid Bed Dried	Tray Dried
B (Batch size)	B (Batch size)	B (Batch size)
L (Labor rate)	T (Tableting	T (Tableting
U Utilization factor	machine)	machine)
T (Tableting machine	BT (B–T	BT (B–T
D (Drying method)	interaction)	interaction)
LU (L–U interaction)		
BT (B–T interaction)		
LT (L–T interaction)		
UT (U–T interaction)		
LUT (L–U–T interaction)		

[a] Tested at 0.01 level of significance with pooled error term. Certain interactions were determined to be poolable into an error term after testing indirectly across the restriction error with the residual error at a 0.25 level of significance.

tableting methods. An alternative approach is to use an experimental design that analyzes the effect of entire variables and their interactions to identify those that affect the processing time and cost. This approach allows identification of those variables and interactions where processing times and costs do change significantly, thereby reducing the number of variables to be considered.

Once the significant variables and interactions are identified, a formula for describing the processing time and cost can be devised through regression methods to show the magnitude of these time and cost effects. Various decision rules then can be developed with these formulas to aid in the management of the tableting process, the potential purchase of new equipment, or the design of a new tableting process. Some of these features will be demonstrated here. In addition, optimization methods may be employed to find the most economic processing method following the concepts discussed previously (8–10). A variety of experimental designs, regression procedures, and optimization techniques can be employed in this conceptual approach, but the choice among these alternatives is beyond the scope of this investigation.

EXPERIMENTAL

The particular tableting technique being investigated, as well as the fixed unit operation input, is shown in Table IV. The levels of the fixed input remain the same throughout the entire experiment. Salvage values for all equipment were estimated to be zero at the end of the service life of 15 years.

The different levels of the variables of the drying method, tableting machine, utilization factor, batch size, and labor rate used in the experimental design approach are noted in Table V. All of the variables in Table V were assumed to be continuous between the levels tested, except for the drying method, which was considered discrete.

A five-way split–split plot experimental design was employed. This design allows the experimental conditions to be run twice using two separate sets of initial uniform random deviates, which are used to obtain random time variables from the different triangular time distributions. It was assumed that the effect of the two different sets of initial uniform random deviates would be statistically insignificant; consequently, the interactions involving this effect could be pooled together as an error term. This error term then could be used in an analysis of variance. A test was made on this assumption by rerunning the simulation strictly at the model value for all of the triangular time distributions and comparing the average processing time and cost output without variability to that obtained from the results using the different sets of initial uniform random deviates. Since there was an insignificant difference, this assumption was partially verified.

Before running an analysis of variance, the generated processing cost and time outputs were checked to assure homogeneous variances. Since the processing cost means were proportional to the cost variances, a logarithmic transformation of these data was made, and the Burr–Foster Q test (11) assured homogeneity at a 0.01 level of significance. Mean processing time data were separated into tray drying and fluid bed drying categories due to trends in the data within each method. The need for this separation was expected since drying method levels were considered discrete. Logarithmic and fourth-root logarithmic transformations on the tray drying and fluid bed drying processing time data, respectively, gave homogeneous variances at the 0.01 level of significance as confirmed by the Burr–Foster Q test.

An analysis of variance was performed separately on each of three data sets: (*a*) the processing cost with both drying methods, (*b*) the processing time using tray drying, and (*c*) the processing time using fluid bed drying. The results showed that the effects of the two different sets of initial uniform random deviates were insignificant. The main effects and interactions that were statistically significant in the analysis of variance are listed in Table VI.

A second-order stepwise regression analysis was performed on those variables found to be statistically significant in the analysis of variance. The equations developed by this analysis, as well as the squared correlation coefficients, are given in Table VII.

Table VII—Results of Regression Analysis [a]

Processing Cost Regression Equation		Processing Time Regression Equations	
Variable	B (Coefficent)	Variable	B (Coefficient)
L	0.781*e*-01	Tray Drying	
L^2	−0.179*e*-02	T	−0.146*e*-05
B	0.982*e*-07	B	0.126*e*-06
UT	−0.608*e*-05	BT	−0.106*e*-10
B^2T	0.161*e*-17	B^2	−0.500*e*-14
U	−0.411*e*-01	Constant	1.464
LU	0.245*e*-02	R^2 = 0.9999	
D	−0.555*e*-02	Fluid Bed Drying	
LUT	0.620*e*-06	T	−0.153*e*-05
B^2	−0.128*e*-13	B	0.585*e*-07
T	0.117*e*-04	BT	−0.374*e*-11
BT	−0.101*e*-10	B^2	−0.600*e*-14
LT	−0.922*e*-06	Constant	1.021
L^2T	0.302*e*-07	R^2 = 0.9998	
L^2UT	−0.243*e*-07		
Constant	2.146		
R^2 = 0.9998			

[a] B = batch size, L = labor rate, U = utilization factor, T = tablet machine, and D = drying method. Minimum F value for variable entry = 0.01, maximum F value for variable removal = 0.005, and tolerance = 0.001.

RESULTS AND DISCUSSION

Graphical Development—The regression equations in Table VII were programmed on a digital computer and manipulated through a series of over 100 points between the high and low levels of the factors tested. The graphs shown in Figs. 4–7 were selected for discussion from among the many that were developed using a computer plotting technique and the points generated from the regression equations.

Processing Time Analysis—The processing time increased as a function of increasing batch size (between 0.5×10^6 and 1.5×10^6 tablets/batch), as expected, but the rate of increase always was greater with tablet machine A[1]. The reason for this greater rate of increase was that tablet machine A had a lower speed than tablet machine B[2], so it took longer for tablet machine A to produce a fixed batch size of tablets than tablet machine B. Tray-dried batches made with tablet machine A always had longer processing times than fluid bed-dried and tablet machine B-produced batches. The most interesting feature of this test was that processing times were almost linear functions of the batch size, even though there were interactions and higher order terms in the regression equation.

Another test was made on the processing time as a function of the mean tableting rate for different batch sizes with different drying methods as shown in Fig. 4. The tray-dried processing time for a fixed batch size was offset by a constant processing time of ~27.8 hr more per batch than the fluid bed-dried[3] processing time. Beside the decrease of the batch processing time with increased tableting rates, the processing time effects also were marginally decreased (Fig. 4).

Although the effects of the examples follow the form of intuitive expectations, the magnitude of these effects would be difficult to anticipate without considerable data. However, use of the graph allows easy visual understanding of the trends caused by these effects as well as computation of their magnitude.

Processing Cost Analysis—Figure 5 illustrates how the processing cost decreases with increasing mean tableting rate using different combinations of drying methods and batch sizes. The processing cost change over the limits of the tableting rate (mean tablets per minute) becomes

[1] Model 541, Stokes Division, Pennwalt Corp., Philadelphia, Pa.
[2] Model M75MKIII, Manesty Machines Ltd., Speke, Liverpool, England.
[3] Model AG100, Aeromatic Inc., Bernardsville, NJ 07924.

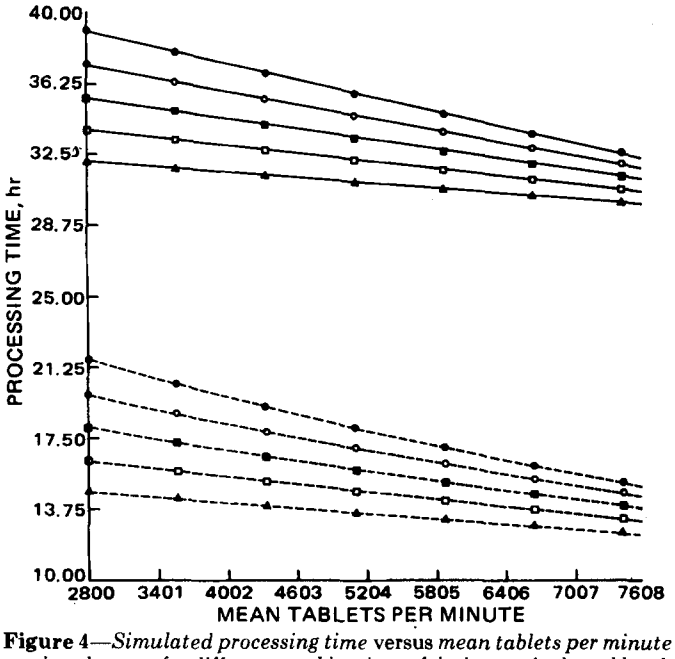

Figure 4—*Simulated processing time* versus *mean tablets per minute produced curves for different combinations of drying methods and batch sizes. Key: -●-, tray dried, 1,500,000 tablets; -○-, tray dried, 1,250,000 tablets; -■-, tray dried, 1,000,000 tablets; -□-, tray dried, 750,000 tablets; -▲-, tray dried, 500,000 tablets; --●--, fluid bed dried, 1,500,000 tablets; --○--, fluid bed dried, 1,250,000 tablets; --■--, fluid bed dried, 1,000,000 tablets; --□--, fluid bed dried, 750,000 tablets; and --▲--, fluid bed dried, 500,000 tablets.*

less as the batch size decreases. Breakeven points normally are observed when only one factor is changing, but the breakeven points shown here are between different batch sizes as well as between different drying methods. For example, at a production rate of ~7207 tablets/min, the processing cost per 1000 tablets is about 24¢ for a 1,500,000-tablet batch that is fluid bed dried compared to 28¢/1000 tablets for a 1,250,000-tablet tray-dried batch. To find a true cost breakeven point between these two curves, the mean tablets per minute *versus* the processing cost per fixed number of tablets (*i.e.*, per thousand) has to be plotted. This can be done easily using Fig. 5.

Figure 6 shows how the processing cost per batch increases with increasing batch size using different combinations of tableting machines, utilization factors, and drying methods. Processing costs with tablet

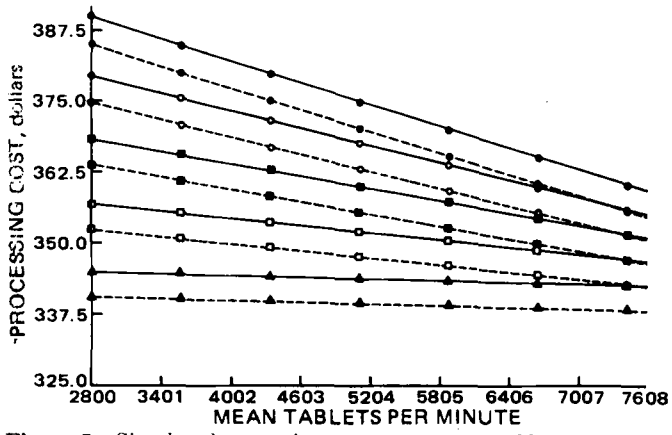

Figure 5—*Simulated processing cost* versus *mean tablets per minute produced curves for different combinations of drying methods and batch sizes at a fixed labor rate of $5.50/hr and utilization factor (UF) of 1.0. Key: -●-, tray dried, 1,500,000 tablets; --●--, fluid bed dried, 1,500,000 tablets; -○-, tray dried, 1,250,000 tablets; --○--, fluid bed dried, 1,250,000 tablets; -■-, tray dried, 1,000,000 tablets; --■--, fluid bed dried, 1,000,000 tablets; -□-, tray dried, 750,000 tablets; --□--, fluid bed dried, 750,000 tablets; -▲-, tray dried, 500,000 tablets; and --▲--, fluid bed dried, 500,000 tablets.*

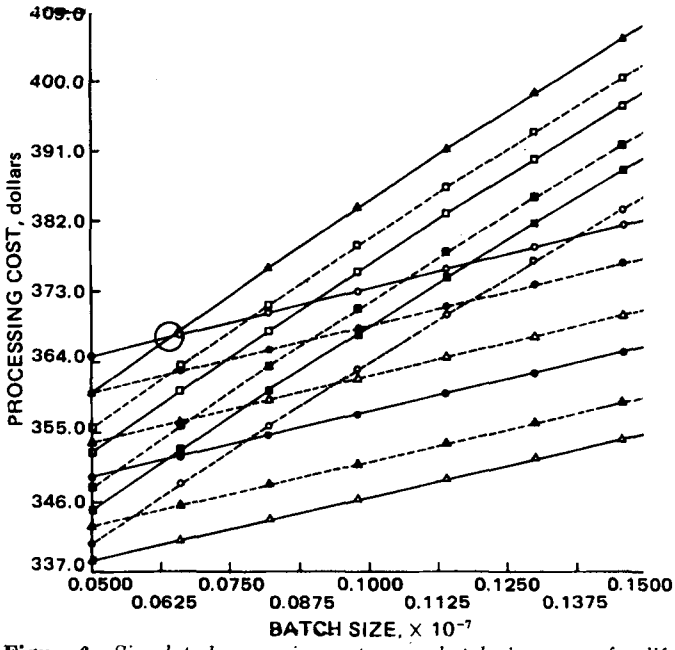

Figure 6—*Simulated processing cost* versus *batch size curves for different combinations of tableting machines, utilization factors (UF), and drying methods at a fixed labor rate of $5.50/hr. Key: -▲-, tablet machine A, UF = 0.5, tray dried; --□--, tablet machine A, UF = 0.5, fluid bed dried; -□-, tablet machine A, UF = 0.75, tray dried; --■--, tablet machine A, UF = 0.75, fluid bed dried; -■-, tablet machine A, UF = 1.0, tray dried; --○--, tablet machine A, UF = 1.0, fluid bed dried; -○-, tablet machine B, UF = 0.5, tray dried; --●--, tablet machine B, UF = 0.5, fluid bed dried; --△--, tablet machine B, UF = 0.75, tray dried; -●-, tablet machine B, UF = 0.75, fluid bed dried; --▲--, tablet machine B, UF = 1.0, tray dried; and -△-, tablet machine B, UF = 1.0, fluid bed dried.*

machine A are lower than tablet machine B with small batch sizes, but these costs increase at a greater rate with increasing batch sizes. As a result, there is a breakeven point with the batch size. For example at ~640,625 tablets/batch, the curves for tray-dried tablets with a utilization factor of 0.5 intersect. This breakeven point can be seen in the encircled area of Fig. 6. The only difference in these two curves is the type of tableting machine used. Tablet machine A is less expensive to operate at small batch sizes due to its smaller power cost and equipment depreciation charged per batch. However, as the batch size increases, tablet machine B becomes less expensive to operate due to its high production output and, thus, minimal tableting unit operation processing labor cost. The cleaning and preparation time for both tablet machines were assumed to be approximately the same. For a constant utilization factor, Fig. 6 shows that the breakeven batch size is the same for tray drying or fluid bed drying. As the utilization factor increases, the breakeven batch sizes decrease. Increases in processing cost with larger batch sizes are approximately linear with tablet machine B, but those with tablet machine A tend to be slightly marginally decreasing.

Figure 7 illustrates how the processing cost changes with increasing labor rate up to $8.25/hr using all combinations of drying methods, tableting machines, and utilization factors at a fixed batch size of 1,000,000 tablets. The processing costs increase with labor rate in a marginally increasing manner up to $8.25/hr. Figure 7 also shows that for a given utilization factor and a given tableting machine, fluid bed drying has a lower processing cost than tray drying. Figure 7 may be useful in evaluating processes as labor rates become inflated.

Processing Time–Processing Cost Interaction—By comparing the graphs where the dependent variable is processing time with graphs where the dependent variable is processing cost, it is evident that the drying method affects the processing time to a greater extent than does the tableting rate while the tableting rate affects the processing cost more than the drying method. This observation indicates that while the cost of either drying method varies little per batch, the time difference between the two is great. The time saved by using fluid bed drying over tray drying could be used for increased production of other product batches. Since the simulation only represents the cost–time variables for a single batch of a single product, multiple-batch and multiple-product considerations should be kept in mind.

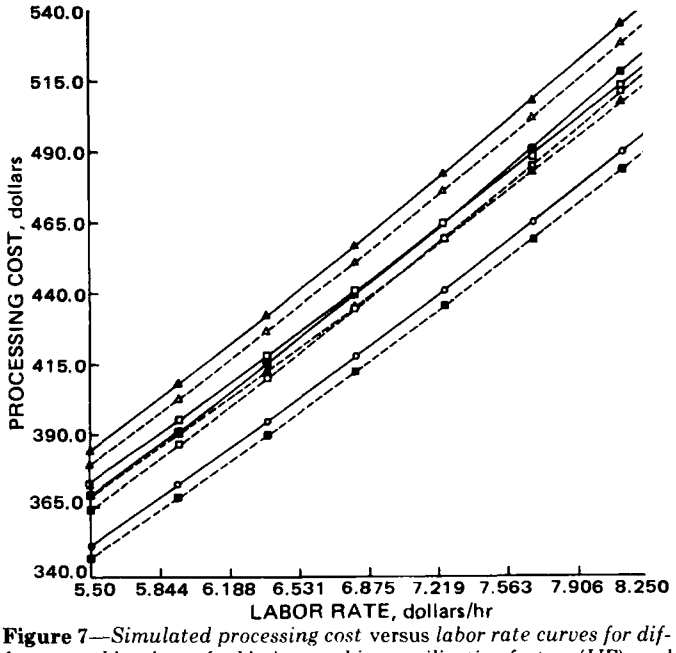

Figure 7—*Simulated processing cost* versus *labor rate curves for different combinations of tableting machines, utilization factors (UF), and drying methods at a fixed batch size of 1,000,000 tablets. Key: –▲–, tablet machine A, UF = 0.5, tray dried; --△--, tablet machine A, UF = 0.5, fluid bed dried; –■–, tablet machine A, UF = 1.0, tray dried; –□–, tablet machine B, UF = 0.5, tray dried; --□--, tablet machine A, UF = 1.0, fluid bed dried; --▲--, tablet machine B, UF = 0.5, fluid bed dried; –○–, tablet machine B, UF = 1.0, tray dried; and --■--, tablet machine B, UF = 1.0, fluid bed dried.*

CONCLUSIONS

1. The model and simulation program shown here can be used in intraprocess as well as interprocess cost and time evaluations.

2. The simulation program itself can be used as an experimentation method, with an almost unlimited number of experiments and manipulations possible at a fraction of the cost and time of the actual processing experiments.

3. Statistical methods as well as optimization techniques can be applied to the experimental simulation output to make optimal decisions about the results.

4. The model and simulation can be a tool in making management and process-engineering decisions concerning tableting cost and time considerations, especially with processes that are new or being updated.

APPENDIX

The following cost–time outputs for each run of the simulation program may be defined:

1. Tablets per batch—the number of tablets produced in a batch. It is the theoretical yield rather than the standard yield of tablets.

2. Cost per batch—the total cost per batch, including raw material cost, labor cost, equipment depreciation, power consumption costs, warehouse costs, and bulk packaging costs.

3. Cost of raw materials—the cost of both active and inactive ingredients in the formulation.

4. Excipient cost—the cost of the raw materials *minus* the cost of the active ingredients in the formulation.

5. Process cost—the total cost minus the cost of the raw materials.

6. Process and formulation controllable cost—the processing cost plus the excipient cost divided by the standard yield per batch. This cost will change if one uses a different process or a different formulation.

7. Cost per tablet—the total cost divided by the theoretical number of tablets.

8. Standard yield cost per tablet—the cost per tablet divided by the standard yield per batch.

9. Process cost per tablet—the process cost divided by the theoretical number of tablets produced.

10. Labor cost per unit operation—the average labor cost per step including the end-of-process step.

11. Labor cost per batch—the total labor cost per batch.

12. Cost per unit operation—the same explanation as in the section on labor cost per step applies here. This cost is the total *average* cost per step. It includes raw material costs.

13. Equipment depreciation—the total equipment depreciation that can be assigned to this particular batch.

14. Power costs—the cost of the energy consumed by the equipment during the process.

15. Warehouse costs—the total cost of using warehouse space to store a batch of unfinished product.

16. Package costs—the cost of bulk packaging the unfinished product to be stored or bulk packaging the final product to be stored. It is a fixed number in that the formulator must know the cost.

17. Yearly production cost—the total cost per batch multiplied by the number of batches produced per year.

18. Yearly process and formulation controllable cost—the per batch formulator controllable cost multiplied by the number of batches per year.

19. Processing time plus time between steps—the total time it takes to process a batch. This time does not include cleaning or preparation time; it only includes the time it takes to produce a batch if everything is prepared and cleaned.

20. Total labor time—the total labor time spent in producing a batch. It is the time that a laborer is paid for that can be assigned to a particular batch.

21. Cleaning and preparation time—the total cleaning and preparation time spent during the production of a batch.

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