DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 6(3), 237-253 (1980)

TABLETING PRODUCTION TIMES, COSTS AND RISKS THROUGH SIMULATION

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ABSTRACT

As the methods of preparation of pharmaceutical compressed tablets are examined, it becomes evident that there are a number of cost factors which may be significant. These cost factors may be of paramount importance in decision making as to the method of preparation. A comparative study was done to evaluate costs involved in the preparation of tablets by direct compression or the wet granulation procedure at two batch sizes. A simulation model for the processing was used for analysis of the system to optimize batch size, procedure and cost.

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INTRODUCTION

Tablets can be produced through a variety of alternative processes and formulations. It is well recognized that the resulting tablet characteristics are affected by these alternatives. There is a large literature on this topic (1,2). However it is also known that these alternative processes and formulations affect the production time, processing costs, and the variations in each, but little is written about these time-cost effects. This paper addresses this latter topic and a recently devised method for quickly assessing production times and costs for batch production using various formulations and methods of processing.

Three general tableting methods are wet granulation, dry granulation, and direct compression. Numerous variations exist within each type depending upon the type of equipment used and the detailed manufacturing practices employed. With each tablet product management must select a specific formulation, a batch size, the equipment to be used, and a particular manufacturing method that fulfills the objectives of producing a quality product which meets consumer needs at a low cost. Accordingly, the proposed method of assessing batch production costs and processing times serves as a management aid in this decision making. Prospective new products or changes in equipment, excipients, or methods can be evaluated using this technique. Not only does this method describe the average cost and processing time, it also shows the variation of cost and time expected from batch-to-batch for an assessment of the risk associated with the prospective changes.

The heart of the proposed method is a general (computer) simulation program of unit tableting operations. Users of this program provide information on the particular operations for a specific tablet product and the program manipulates these data over the entire processing sequence to show the statistics of costs and processing time. Cumulative costs and times over the processing sequence are also shown by this program to aid in checking specific steps. When changes in the formulation, equipment, batch sizes, manufacturing or methods are contemplated, only the revised input information needs to be changed and the program may be rerun in order to assess the time, cost, and risk effects (3).

THE TABLETING MODEL

Of the three general methods of tableting, the wet granulation method contains the most numerous processing steps. Direct compression and dry granulation both contain several but not all of the steps used in wet granulation with the exception of the slugging (chilsonating) step in dry granulation. Table 1 shows the processing steps of these tableting methods. A simulation program was written which contains all twenty processing steps shown in this table but with the provision that any step which is inappropriate for the type of tableting under consideration could be by-passed. In this way, a single program could be used to capture virtually any sequential method of tableting to show the cost-time build-up over the processing sequence. The reason for using a single program was to reduce the chances of omissions and to prevent any inadvertent programming bias between these general methods of

Table 1

Unit Operations and Cost/Time Information Inputs
for the General Tableting Model

UNIT OPERATIONS	INPUTTED COST & TIME INFORMATION	
	SPECIFIC UNIT OPERATIONS	UNIT OPERATIONS
Weigh raw materials	Cost of ingredients	
Initial premix		Power requirements
Screen		Type of equipment
Mill		Step processing time
Mix		Step cleaning time
Granulate	Cost of binder	Step preparation time
Wet screen		Time between steps
Dry		Labor rate
Lubricate		Equipment depreciation
Slug		Standard yield
Quality control check		Batches per year
Size or mill		Equipment utilization
Weigh		Tablets per batch
Final premix		
Add running powder (lubricant)		
Final mix		
Bulk package	Bulk packaging costs	
Stage	Warehouse costs	
Compress		
Quality control check		
End of process		

tableting. Users must, of course, supply input data for this program and some of these input data are illustrated in Table 1. The program then performs all the bookkeeping and statistical calculations and reports the results.

Some important assumptions were made in the development of this program which are important to the inputted data. In the case of equipment depreciation,it was assumed that straight-line depreciation is employed over the cleaning, preparation, and processing time of the equipment. Most equipment in this industry is not utilized 100 , nor is it dedicated to a single product and so the fair distribution of equipment-wear costs must be apportioned to a batch of tablets in some reasonable manner. We opted for simplicity in the program, allowing users to make allowances in their input data by incorporating a "utilization factor" into the depreciation equations (4). A second important assumption was that the labor time for a processing step consisted of the entire time of that step, the time between the previous and the current step, the cleaning, and the preparation time; all at a constant labor-cost rate. Here again users can adjust the cleaning and/or preparation time as well as the time periods between steps or within a step when more or less labor time is required. Also, if different labor rates are used for the cleaning, preparation, between steps, and during operating times, then a single proportionately-weighted labor-cost rate can be used. It should be pointed out that the single exception to this labor-time assumption is with the staging and drying steps (tray drying only) where the labor time is not assumed to cover the entire step time. A

third assumption was that power consumption was 0.0124 kilowatt-hours per horsepower per minute of use, following standard energy conversion rates. Efficiency adjustment can be made by users in the horsepower requirements or the time used. A fourth assumption of this model was that minor changes in the operational sequence would not affect the total time or cost estimates. We tested several cases of sequence changes and could not find any reason to suspect a cost or time change purely for this reason. Consequently, we constructed a single time-cost model in the simulation program so that it would be easier for users to adjust the complexities of the real situation to be compatable with the model.

Since the processing time, cleaning time, preparation time, and time between steps varies from batch-to-batch with the same product, it was necessary to include these time and cost variations in the program in order to denote risk characteristics. Expected time variations create risks in production control and the consequential cost variations imply economic risks. In order to obtain time variation from the program in a consistent and easily used manner, we adopted the triangular distribution which provides wide flexibility in use (5). This distribution also conforms easily to human intuition for estimating the time parameters and interpreting the meaning. Users need to identify the minimum, most likely, and the maximum values of the time variable which changes from batch-to-batch in the processing. The program automatically computes the probabilities associated with a random variable according to the triangular distribution. The probabilities increase uniformly

from the minimum value to the most likely and then decrease uniformly to the maximum value. In the simulation, random numbers are selected according to this distribution as the value of that time variable for a given run. The program performs all the bookkeeping and statistical computations and then it presents the results for management decision making (6).

DATA INPUTS AND MANAGEMENT INFORMATION

Users of this simulation program are required to input data for the specific process and formulation under question. Table 2 shows an example of such input data for the direct compression of a multivitamin product.

After these input data are in the program and the program is run, various forms of management information are generated in the data output of this program. A number of runs of this program are required in order to obtain the risk effects in terms of standard deviations. Table 3 illustrates the type of management information available from this program. Since there was no staging step in direct compression where partially processed materials are stored, there is no warehousing cost shown. It should be noted that warehousing of finished goods inventories are not included in this program. The total cost per batch includes the cost categories of raw materials (including excipients) and process cost; whereas the formulator controlled cost consists of only the excipient and process costs divided by the standard yield, which in this case is 98%. Further components of the processing cost shown are the costs associated with labor, equipment de-

Table 2
Example Program Input Data

Processing Steps	Processing Time Requirements (Min)		
	Minimum	Most Likely	Maximum
1. Prepare Raw Materials	50.0	60.0	70.0
2. Pre-Mix	10.0	15.00	20.0
3. Size or Mill	25.0	30.00	35.0
4. Final Mix	13.0	15.00	17.0
5. Bulk Package	18.0	20.0	22.0
6. Compress	270.0	270.0	270.0

Ingredients in Batch	$/Gram	No. of Grams
16 Active Ingredients	.008282 Ave.	448,984
Calcium Stearate	.001936	3,500
Excipient (s)	.000331	125,000

Packaging Cost = $20.00
Tablets/Batch = 700,000
Electricity Rate = $0.025/kilowatt-hour
Labor Cost Rate = $5.50/hour

Processing Step	Equipment	Original Cost ($)	Salvage ($)	Service Life (yrs)	Horsepower
1	Scales	7,000	1,400	10	0.1
2	Mixer	5,000	1,000	20	2.0
3	Mill	8,000	1,600	10	10.0
4	Blender	5,000	1,000	20	3.5
5	Misc.	5	1	20	0.0
6	Tableting Machine	12,000	2,400	20	1.5

Utilization Factor (all Equipment) = 1.0

Warehouse Costs = 0

Standard Yield = 98%

Number of Batches Annually = 100

Table 3

Final Output for Ten Runs of the Simulation

Output		Average	Standard Deviation
Tablets per Batch		700,000.00	
Cost per Batch	$	4,003.87	5.184
Cost of Raw Materials	$	3,766.68	
Excipient Cost	$	48.15	
Process Cost	$	237.19	5.134
Formulator Controllable Cost	$	291.16	5.289
Cost per Tablet	$	.005720	.00000741
STD Yield Cost per Tablet	$	.005837	.00000756
Process Cost per Tablet	$	.000339	.00000741
Labor Cost per Step	$	30.73	.733
Labor Cost per Batch	$	215.13	5.134
Cost per Step	$	471.98	.741
Equipment-Depreciation	$	1.83	.052
Power Costs	$	.23	.004
Warehouse Costs	$	0.00	
Package Costs	$	20.00	
Yearly Production Cost		$400,386.53	518.366
Yearly Formulator Controllable Cost	$	29,115.98	528.945
Processing Time Plus Time Between Steps	Hr	9.017	.122
Total Labor Time	Man-Hr	39.114	.933
Cleaning and Preparation Time	Man-Hr	30.097	.911

preciation, power, warehousing, and packaging. Processing time in man-hours is also shown along with the two components of the actual time to process a batch, including the time between processing stages and the cleaning and preparation time. With this particular direct compression method of processing, these two time components simply add to give the total processing time but this is not the case for a tray-dried wet granulation. Ten simulation runs were made for this example of tableting in order to obtain the standard deviations shown in Table 3. The average value plus and minus a standard deviation represents the expected variation about 68 percent of the time. For an expected variation about 95 percent of the time, simply multiply 1.96 times the standard deviation, then add and subtract that value from the average. In the Table 3 example, the total cost per batch would be expected to vary from $3993.73 to $4014.03 for ninty five percent of the batches. When the actual costs are above or below this range, then special notifications can be sent to management where these exception cases may be investigated. The simulation results can be used in the manner shown above in order to set cost or time ranges for exception reporting. Other forms of reports, such as histograms of the total or labor costs over the process sequence, are also generated when needed as an aid for tracking down discrepencies. It is, however, extremely important to validate the simulation results with the cost and processing time of well known products before using this technique extensively as a management aid.

PROGRAM EXPERIMENTS AND MANAGEMENT DECISIONS

Besides the ongoing management applications shown above, this production time, cost, and risk model provides a vehicle for experimenting with prospective management actions. Numerous questions arise on alternative processing methods, batch sizes, equipment modification, or changes in the formulations and methods. When such questions arise, the input information can be altered to reflect the change and the program may be rerun in order to evaluate the effects of these changes. The program serves to provide a means for obtaining a low-cost rapid response to such management questions. However, it should be pointed out clearly that the effects on the tablet quality must be estimated by other means.

In order to illustrate the use of this simulation program in experiments which aid in management decision making, let us consider another multivitamin product. Two different methods of tableting (direct compression and wet granulation) and two different batch sizes (200K and 1500K tablets) were considered. The input data is not shown here. Table 4 shows the various costs and standard deviations for these four conditions of this particular product. It is clearly seen in this case that direct compression has a lower expected cost for either batch size. Further, it is easy to test if these batch costs are significantly different in a statistical sense by multiplying 1.96 times the standard deviation, adding this amount to the lower cost and subtracting this amount from the upper cost; the results are the upper and lower limits which would be expected to hold for

Table 4

Results of Four Simulations on a Product Made by Two Different Tableting Techniques with Two Different Batch Sizes

		DIRECT COMPRESSION No. of Tablets/Batch		WET GRANULATION No. of Tablets/Batch	
		200,000	1,500,000	200,000	1,500,000
Average Batch Costs	Total Cost	$1,109.64 (100%)	$7,210.06 (100%)	$1,169.46 (100%)	$7,351.42 (100%)
	Raw Materials	$ 927.98 (84%)	$6,959.86 (97%)	$ 934.90 (80%)	$7,011.76 (95%)
	Processing Cost	$ 181.66 (16%)	$ 250.20 (3%)	$ 234.56 (20%)	$ 339.66 (5%)
Average Tablet Costs & Standard Deviations	Expected Total $/Tablet	.005548	.004807	.005847	.004901
	Standard Deviation	.000030	.0000059	.000027	.0000041
	Expected Processing $/Tablet	.000908	.000167	.001173	.000226
	Standard Deviation	.000030	.0000058	.000027	.0000041
Labor time, Variability, & Cost/Batch	Total Labor Time	32.958 MH	45.236 MH	42.145 MH	61.021 MH
	Standard Deviation	1.106	1.582	1.007	1.106
	Labor Cost/Batch	$ 181.27	$ 248.80	$ 231.80	$ 335.62

ninty five percent of the batches of this product; assuming that costs vary normally. In the example at hand at a 200K tablet batch size, the upper 97.5 percent limit per 1000 tablets by direct compression is 5.548 + 1.96 (0.030) =$5.607, whereas the lower 97.5 percent confidence interval for wet granulation on the same basis is $5.848 - 1.96 (0.027) = $5.794. Assuming that costs vary normally, there is less than a 2½ percent chance that the direct compression cost will exceed $5.607/1000 tablets and less than 2½ percent chance that 1000 tablets by wet granulation will be less than $5.794; consequently there is little reason to doubt that direct compression of this product will be less costly than wet granulation at this batch size. The results at the larger batch size are similar but less distinct. Accordingly, management can reasonably expect that direct compression is the less costly method for batch sizes in the range examined.

Although it is evident from the analysis above that direct compression is the lower cost method of tableting this particular product for the batch sizes examined, it is unclear what the economic batch size should be. The answer to this batch size question depends not only on the annual production cost savings but also on the annual costs of finished goods inventories and these costs must be estimated outside of the production cost model. As larger batches are made there are usually decreases in both the production costs and the production frequency per year. These cost savings per year are offset by increased quantities of finished goods inventoried per year; creating greater warehousing

costs. If the total sales for this product is 1200K tablets per year and 400K tablet batches are made, then each of the three batches made per year raise this inventory immediately following production and the disbursements from warehousing cause the inventory to drop between batches. When the disbursement rate is uniform over the years and the next batch is run near the end of the inventory level, the average inventory level is equal to one half the batch size. An increase of batch size to 600K tablets for this production results in one less batch per year, an increase in the average inventory of this product to 300K tablets, and an added (or marginal) cost with this larger inventory. There is also an expected cost savings per year due to the smaller production cost per tablet and the fewer batches per year If the total annual savings in production per year by increasing the batch size is greater than the added annual costs of inventory, then a batch size increase is economically attractive. This same argument follows for another potential increase in batch size and so forth. When the marginal annual costs for larger inventories is equal to the marginal cost savings from larger batches, then the optimum economic batch size is obtained. Results from the simulation with increasing batch sizes provide the means for computing the total batch costs and these costs multiplied by the number of batches required per year yield the total annual cost with increments in batch sizes. Decreases in these total annual costs with batch size increments are the marginal production cost savings. These savings can be compared with the added inventory

costs per year caused by the increase in batch size. While many products do not have a uniform disbursement from the warehouse over the year and therefore do not have average inventory levels set at one-half of the batch size, this assumption, or one similar, can often be used as a reasonable approximation. If should be noted, however, that the analytical approach to finding economic batch sizes does not account for many practical limitations caused by equipment restrictions or dating implications to inventory costs.

Numerous other management questions exist in tableting operations where this program can aid the decision makers. When the processing equipment limits the batch size well below the economic limit, then the program can be revised to reflect larger processing capacity equipment and rerun to see if the investment in larger equipment is justified by the cost savings. New formulations may be investigated and various "what if" questions can be addressed and answered quickly.

ACKNOWLEDGEMENTS

This study was supported by a grant from the FMC Corporation, Food & Pharmaceutical Products Division.

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