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Idris M. El-Mahdi,
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Three-Dimensional Presentations of Factorial Experimentation Data of Extrusion – Spheronization

Idris M. El-Mahdi[(1)], and Tariq A. El-Shehebia[(2)]

[(1)] Department of Pharmaceutics, Faculty of Pharmacy, Arab Medical University, Benghazi, Libya. P.O. Box 5341, Correspnding author Email: idrispharmacy@yahoo.com. [(2)] Department of Computer, Faculty of Information Technology, Garyounis University, Benghazi, Libya.

ABSTRACT

Extrusion – spheronization technology is one of the major methods for production of multiparticulates in the pharmaceutical industry. The difficulty in this method is how to develop a formulation which provides high drug load and high yield of product of the desired size. In any spheronization operation, loss of significant amount of the formula to very large fraction or fine fraction is unavoidable. The aim of this work is to analyze the data obtained from 3 x 3 factorial experiment prepared using mixes of microcrystalline cellulose (MCC), ketoprofen, and water at three levels for each factor on production of large pellets, pellets, and fines. The factors studied were water content, spheronization speed, and spheronization time. The product obtained in each experiment was subjected to sieving analysis to three fractions, and the data was analyzed with the use of modified computerized method to allow for immediate analysis of such complex 3 X 3 experiment. The new 3-D plots allow for easy identification of the optimum conditions to allow for the maximum production of pellets and capable of identifying the possible interactions between the factors studied in the experiment. The data showed that the significance or non-significance obtained for the studied factors at their respective levels was observed during all the triplicate experiments which may provide for the desired "controlled spheronization". Based on this work it was concluded that 3-D plots of factorial experiments are of great benefit to formulator than any other 2-D plots, especially in spheronization technology.

INTRODUCTION

Spheronization is a rapid process for pellets preparation and offers the potential to achieve controlled release properties within the cores, which can be further modified by microencapsulation or even compressed in a tablet form. The extrusion – spheronization process comprises a number of individual unit processes namely, dry blending, wet granulation, extrusion, spheronization and drying. Each process is associated with several processing variables . The process is capable of producing fine particles of high drug content (as high as 90% load), and high sphericity. Factorial experiments followed by statistical analysis are of great significance on optimization of yield of the desired size, reduce loss of formulation to large or fine fractions, and to identify the significance of each factor and their levels on the yield of the desired size (pellets) [1, 2].

The aims of this work are to use modem statistical packages to analyze the factorial experiments for extrusion-spheronization data. Also, to attempt a new way of graphical presentation to data obtained by extrusion – spheronization technology.

METHODS

1. Mixing

100 g of a powder mix containing the drug ketoprofen and Avicel PH-101 was loaded into a Kenwood chef planetary mixer. Powders were mixed at speed 1.0 using a 'k' shaped mixing arm (Kenwood Chef Excel, UK). The powders were pre-blended for 10 min and mixing was continued for a further 4 min after slowly adding the required amount of water. The-mixer was stopped every 2 min to scrape any powders from the wall with a spatula. The wet mass was placed into an airtight container and allowed to stand overnight for 24 hr to allow the powders and added water to reach equilibrium.

2. Extrusion

The wet mass was extruded using a\rotary gravity-fed cylinder-type extruder (Alexanderwerk, Type-GA65, Germany) fitted with a 7.0 cm diameter, 14.8 cm long perforated cylinder. The perforations were 1 mm in diameter and the cylinder wall was 4-mm thick. The perforations were spread evenly and centrally over 8.3-cm length of the cylinder wall. The perforated cylinder was placed against a solid cylinder in the extruder and was capable of rotating from 20 to l00-rpm.

3. Spheronization

The extrudate was spheronized on a *5* inch (120 mm) diameter spheronizer (Caleva Model 120, UK), using a cross-hatch friction plate for a specific period of time. The spheroids were allowed to dry at room temperature, followed by drying at 45°C for 48 hr in a forced air circulation oven (Memmert Type UL4O, Germany), after which they were removed and evaluated.

4. Sieve Analysis

Sieve analysis was performed using a nest of standard sieves. These sieves were placed on top of each other, the largest aperture sieve at the top with the decreasing apertures as the sieve nest approached the base plate. The sieve used were 1680, 1180, 850 and 300 pm. A batch of pellets was placed onto the nest of Endecott sieves, which was securely mounted on an Endecott test sieve shaker (MK11, UK). The sieve shaker was set to agitate the nest for 15 min, during which time the pellets fell through the sieves until the aperture of the sieves was smaller than the size of the individual pellets. The weight of sieves was subsequently separated and their retained fractions weighed. The weight of each sieve function was expressed as percentage of the weight of dry solids added to the sieves. In this work, the desirable size range of pellets was taken to be between the 850 and 1180 □m and any spheronized product occurring within this size range is referred to as 'pellets'. Pellets occurring above this size are described as 'large pellets', while any product occurring below this range is referred to as 'fines'. In this work, the terms pellets, beads, beadlets, microspheres or millispheres are used to describe solid particles or agglomerates of particles with a high degree of sphericity having a diameter of around 1 mm.

5. Factorial Design of Experiments

It is evident that there are too many factors that can influence the production of pellets by the process of extrusion-spheronization. Preliminary experiments are essential in order to set the main levels of the factors, which can influence pellet production. Usually such experiments are done randomly but the factor of previous experience with such technique is a helping factor. After preliminary attempts completed it is time for the systemic designed experiments to be conducted, such experiments are termed factorial experiments. These experiments are arranged to study the relation between water level, spheronizer speed, and spheronization time. The number of required experiments (N) is calculated using the formula:

$$N=L^k$$

Where **L** is the number of levels and K is the number of factors. It should be noted that most statistical programs cannot analyze complex factorial experiments of 3 X 3 order or higher, and data will have to be divided into groups to facilitate their analysis [3]. Also, the method of Armstrong & James [4] will be used to show the interaction between the three variables and their levels.

RESULTS & DISCUSSION

1. Production of Pellets

Table 1 shows the yield of pellets from the (3 X 3) factorial experiment. The yield of pellets ranged from 30 to 90 %. The highest % of pellets yield was observed at the following conditions: 5 2.5% water content, 1000 rpm spheronization speed and after 5 mm of spheronization time. The lowest production rate was observed at the extreme value of each variable. The non-factorial experiment conducted was useful in determining the range of levels which could be applied to the various and indicated the relative importance of the factors in terms of the spheronized product characteristics. The formulations were initially composed of ketoprofen, Avicel PH101 and lactose. The results indicated that a high level of Avicel was required in order to produce satisfactory yields. Lactose was then excluded from the formulations and the pellets were composed solely of the drug and Avicel. The yield of pellets was 82% up to 60% ketoprofen content, while lower yields were obtained when drug content was increased above that level. Apparent density determinations showed no significant changes between the different formulations which was attributed to the similar densities of the materials used. The sphericity factor score for all preparations was below 1.2, which implied that the pellets were very spherical and possibly without any major surface defects [5, 6, 7].

A 3^3 full factorial experiment with subsequent statistical analysis was used to evaluate the optimization process (Table 1). The yield data obtained was subjected to ANOVA (Table 2), revealing significant effects and interaction terms for the three factors involved. The three main factors of water content, spheronization speed and spheronization time were found to contribute to the yield of pellets. An increase in water content from 47.5% resulted in enhanced yield of pellets at all speed / time levels, while at 57.5% the yield progressively decreased. Increasing water content would eventually exceed "bound water" in the pellet formulation, resulting in an increase in "free water" on the surface of the pellets promoting agglomeration.

An increase in all three factors gave rise to the greatest degree of agglomeration, manifested by high large pellets production (> 60%). The below optimum water content was associated with high production of fines. At 52.5% of hydration level, the yield of pellets was maintained in the range of 81-90% under conditions of 1000 or 1250 rpm and 5, 10 or 15 min levels. The high speed of 1500 rpm was mostly accompanied by a reduction in pellets yield when spheronization times were increased. Controlled spheronization behavior was evident at 52.5% level as the mixes showed no significant changes in the

Corresponding author: idrispharmacy@yahoo.com

pellets production upon prolongation of spheronization times.

loss of yield with longer spheronization time, which is probably due to the migration of excessive moisture to the

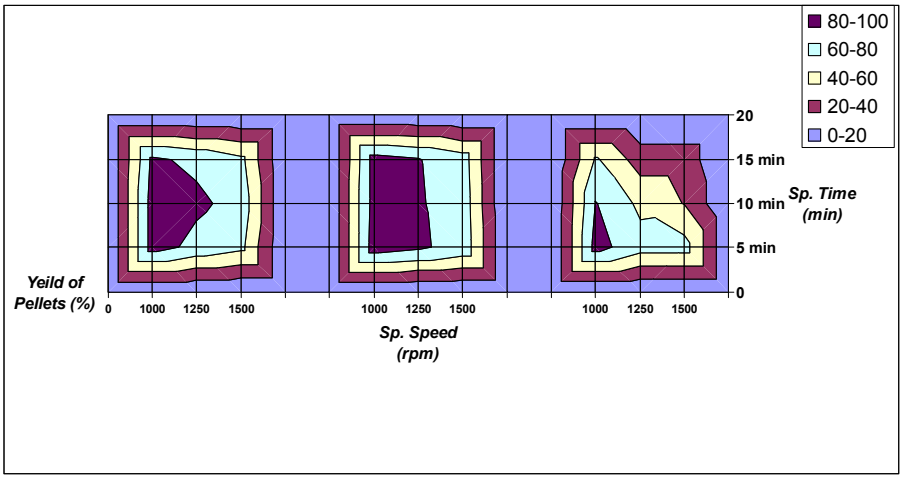

Figure 1a. Surface representation of results from factorial experiments for the yield of pellets (%) as a function of speed/water content.

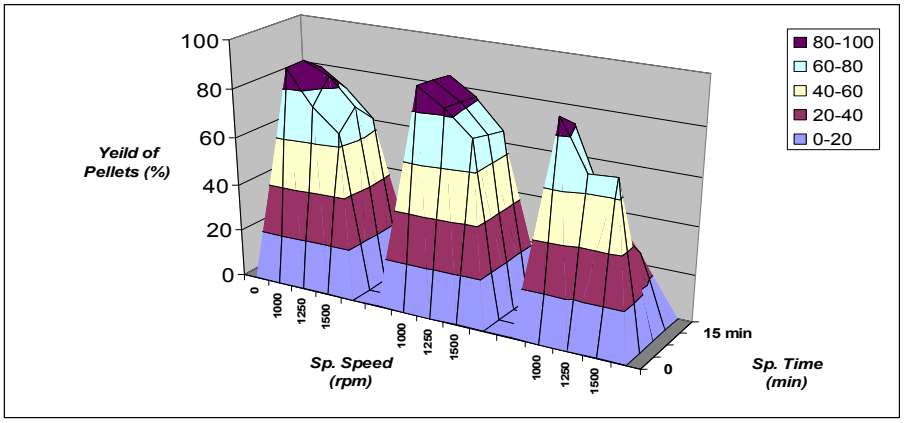

Figure 1b. Three-D representation of results from factorial experiments for the yield of pellets (%) as a function of speed/water content.

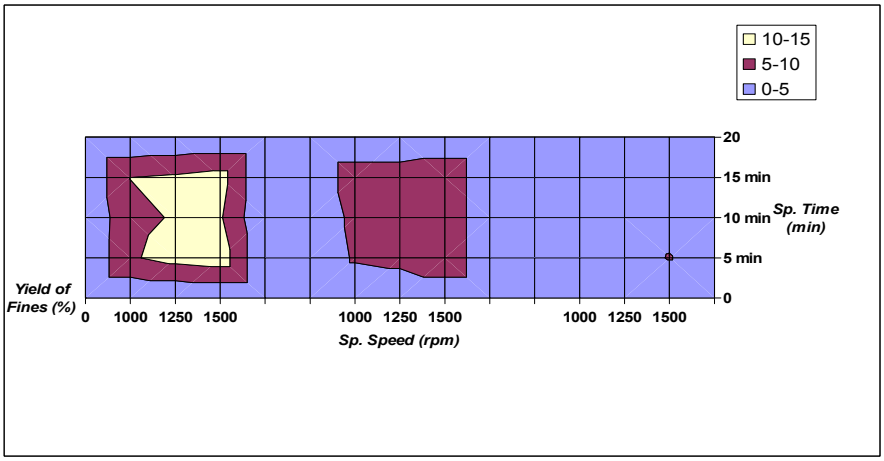

Figure 2a. Surface representation of results from factorial experiments for the yield of fines (%) as a function of speed/water content.

Fielden *et al.* [8] considered optimum spheronization conditions were achieved when controlled spheronization was observed. Uncontrolled spheronization refers to the surface of the pellet which aided the production of large pellets.

Corresponding author: idrispharmacy@yahoo.com

Below optimum water level can show uncontrolled spheronization by losing the yield of pellets to fines, because of the abrasive contact of the pellets with each other and the wall of the spheronizer. Such behavior was observed at 47.5% water level.

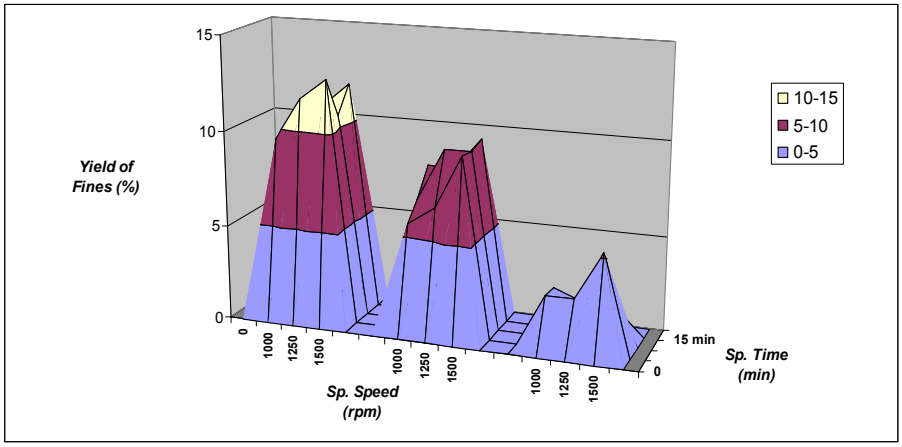

Figure 2b. Three-D representation of results from factorial experiments for the yield of fines (%) as a function of speed/water content.

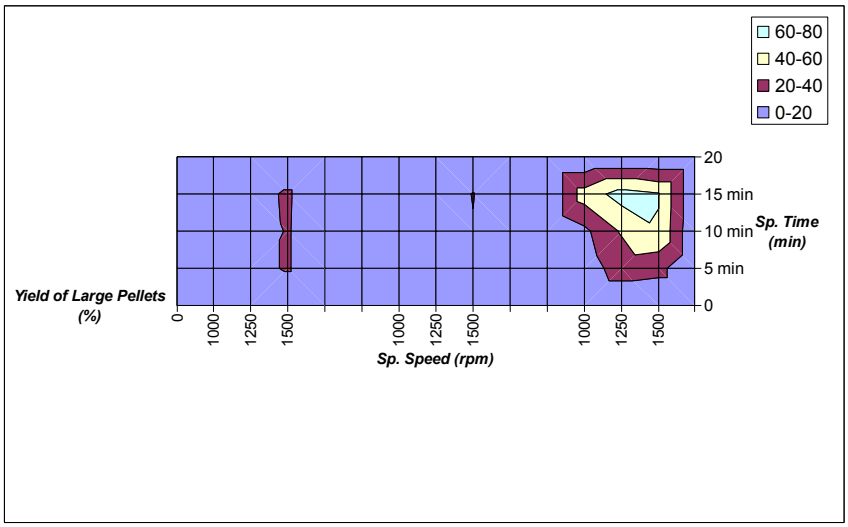

Figure 3a. Surface representation of results from factorial experiments for the yield of Large Pellets (%) as a function of speed/water content.

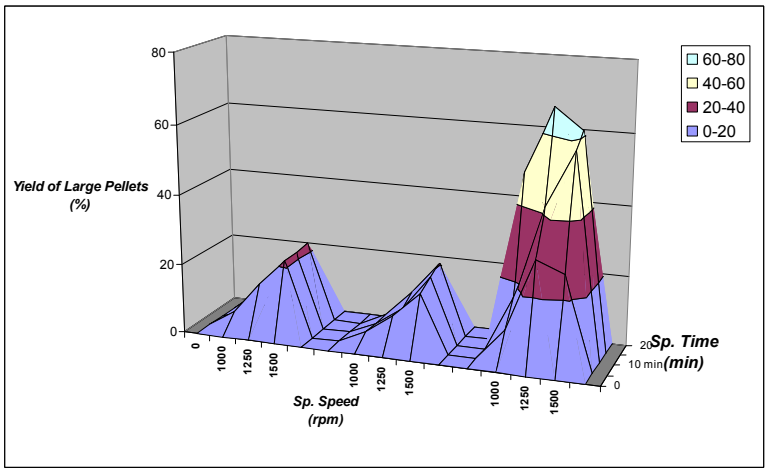

Figure 3b. Three-D representation of results from factorial experiments for the yield of Large Pellets (%) as a function of speed/water content.

Corresponding author: idrispharmacy@yahoo.com

Table.1. The effects of water content and spheronization speed/time on the yield of pellets.

Water Level	*Sp Speed (rpm)*	*Spheronization Time*		
		5 min	*10 min*	*15 min*
47.4 %	**1000**	88.44	88.69	82.98
	1250	74.17	84.00	76.15
	1500	65.47	73.30	65.56
52.5 %	**1000**	90.51	89.72	88.34
	1250	83.91	82.30	81.01
	1500	73.82	71.70	69.70
57.5 %	**1000**	87.97	81.54	63.16
	1250	67.5	56.02	30.93
	1500	68.27	39.46	30.63

NB: **Sp = Spheronization**

The statistical analysis at 5% significance level of the three variables and their interactions (Table 2) revealed that the main factors had significant effects on pellets production , and interactions were observed to occur between water level and spheronization speed or time, while not significant for the speed/time interaction term. In general, the results depend to a large extent on the formulation examined and equipment employed in the process. Comparison between the works of various authors could be difficult because of the various processing equipment employed [9].

Table 2 . ANOVA for the yield of pellets from 33 factorial experiment.

Source	*df*	*SS*	*MS*	*F*	*F Crit P=0.05*
A	2	2684.3	1324.14	80.96	4.46
B	2	2268.3	1134.17	68.42	4.46
C	2	697.92	348.96	21.05	4.46
AB	4	376.31	94.07	5.67	3.84
AC	4	1051.1	262.77	15.85	3.84
BC	4	50.44	12.61	0.76	3.84
ABC	8	132.61	16.57		
Total	26	7561			

NB: A = water level;, B = spheronization speed; C = spheronization time; df = degree of freedom; SS = sequential sum of squares; MS = adjusted sum of squares; F & F-Crit. are the F-calculated & F-tabulated, respectively.

When the value of F-calculated is more than the F-tabulated this indicates a significant statistics.

The obtained data is illustrated as surface plots in two forms: 2-D or 3-D graphs (Fig. 1 to 3) for pellets, fines and large pellets, respectively. The 2-D surface plots are the commonly used presentation to show the results from factorial experiments. It was evident that the 3-D plots give clearer picture to the state of spheronization. The 3-D plots also show the formation of a new sector for pellets production above 90 % which cannot be identified in the 2-D plots.

GENERAL CONCLUSION

Extrusion — spheronization is an important method for microencapsulation of drugs. The application of statistical analysis to the yield of spheronized product is associated with optimization of production conditions to limit the loss of starting materials. The analysis of variance (ANOVA) is a good tool for the characterization and prediction of interactions in spheronization process, and to identify the limits for optimum production of pellets in the size range of 1 mm in diameter. The results obtained by the statistical package EXCEL were compared to those obtained by calculation methods and both were in agreement. The use of surface plots was found to be a good representation to show the data after slight modification.

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Corresponding author: idrispharmacy@yahoo.com