



INFLUENCE OF PROCESS AND FORMULATION VARIABLES ON PHYSICAL PROPERTIES OF THE PELLETS USING A 2³ FACTORIAL DESIGN

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ABSTRACT

This aim of the present study was to evaluate the effects of spheronizer speed, spheronization time and amount of water content, on physical properties and appearance of pellets. Microcrystalline cellulose is the main ingredient in the formulation as it has ideal rheological properties for extrusion-spheronization. A 2³ factorial design was used to study the effect of significant factors and their interactions in the response. The selected process variables were studied and their influence on usable yield, sphericity, density and moisture content was determined. Regularity in shape and size, which is obtained by optimization of several production variables, promotes the functional coating efficiency. The pellets of optimum size range were obtained with high amount of water and spheronization time. Optimal amount of water gave spherical pellets. Pellets obtained from higher spheronizer speed were more spherical than those from low spheronizer speeds. Good sphericity and smooth surface were obtained with higher spheronizer speeds.

Keywords: Extrusion-spheronization, Pelletisation, Factorial design, microcrystalline cellulose, pellet sphericity, spheronization speed, spheronization time.

INTRODUCTION

Pellets are systematically produced, geometrically defined agglomerates of bulk drugs and excipients. They are small, free-flowing, spherical or semi-spherical solid units which are in the size range of 0.5-2.0 mm. Extrusion-spheronization is the most commonly used technique for pelletization¹. Extrusion-spheronization is a process of wet-extrusion, followed by spheronization, used to produce a wide variety of engineered, controlled release drugs. The excipients for pelletization by extrusion/spheronization are very limited because of the characteristics desired from wet masses. The main desired property for the extrusion process is to form a cohesive plastic mass on wetting^{2,3}. The wet mass should be mechanically strong to ensure handling and collection, and brittle enough to survive broken into short lengths in the spheronizer⁴. Microcrystalline cellulose is used as main ingredient in the formulation as its rheological properties are very well suited for extrusion-spheronization⁵. It imparts sphericity to the pellets⁶. It has a very high internal porosity and a large surface area because of randomly arranged filamentous micro crystals. This provides high absorbent and moisture retaining properties which are important for extrusion process. The retained moisture acts as a lubricant during extrusion, and helps to manipulate the pellet shape during spheronization^{3,7}.

Extrusion-spheronization is a multi-step mechanical process which involves: dry mixing, wet massing, extrusion, spheronization, drying and screening¹.

The application of statistical experimental design for formulation and process development is highly

recommended due to high degree of interactions studied between variables⁸. In the present investigation, the experimental plan chosen was the factorial design. The main aim was to evaluate the interactions between the various formulation and process variables on the properties of pellets.

MATERIALS AND METHODS

Materials

Microcrystalline cellulose (Avicel PH 101) was obtained from FMC Corp, Little island, Cork, Ireland. HPC-L (Hydroxypropylcellulose low substituted) was obtained from Nippon Soda Co Ltd, Tokyo, Japan. All ingredients were of analytical grade. Demineralised water was used as a granulating fluid and a liquid binder.

Methods

Pellet production

Pellets were prepared by extrusion-spheronization method. Process variables have huge impact on the pellet properties. In the present study, the process and formulation variables were used for preparation of pellets and their impact on the pellet properties was evaluated by statistical design. Pellets were prepared using 250g of Avicel PH 101, 2.5g of HPC-L (i.e. 1%). The process and formulation parameters were varied according to the factorial design as described in Table 2.

1. Wet massing (Rapid mixer granulator, Sainath Boilers and Pneumatics, Mumbai) kneading parameters: impeller speed slow, 5min, chopper speed slow, 2min, dosing speed 20ml/min



2. Extrusion (single screw radial extruder, Fuji Paudal Co Ltd, Tokyo, Japan) Diameter of die: 1mm, extrusion speed: 50 rpm.
3. Spheronization (Fuji Paudal Co Ltd, Tokyo, Japan) equipped with a rotating plate of regular cross hatch geometry was used for spheronization.
4. Drying (Fluidized bed dryer, Restch, Germany) at 50°C for 20 min.

Experimental Design

Experimental design is applied to reduce the number of trials, and is needed to attain the maximum information on the product properties. The first step of experimental design is the selection of parameters and the choice of responses. The variables (i.e. factors) included the spheronization speed, spheronization time and amount of water. The percentage yield, sphericity, residual moisture and densities were used separately as the responses in the mathematical modeling. This would help in the identification of the most significant factor influencing the properties¹¹.

A mathematical model was generated between the factors and responses, for determining the levels of factors, which yield optimum responses. A 2³ full factorial design was used to study the effect of the formulation and process variables. The studied factors were: the amount of granulating fluid i.e. water (X₁, % w/w of dry blend), spheronization speed (X₂, revolutions per minute, rpm) and the spheronization time (X₃, min). The responses which were studied: percentage yield (usable yield, Y₁,%), sphericity factor (Y₂), loss on drying (Y₃, %) and density (Y₄, g/ml).

The levels of factors are discussed in table 1. The level for the each parameter is assigned (-) sign for low level and (+) sign for high level. The experimental matrix of the factorial plan is represented in represented in table 2.

Table 1: Experimental design

Level	Water Content (% w/w)	Spheronization speed (rpm)	Spheronization time (min)
(-)	95.04	400	3
(+)	110.89	800	7

Table 2: Formulations as per 2³ full factorial design

Formulation Run	X ₁	X ₂	X ₃
SK1	-	-	-
SK2	+	-	-
SK3	-	+	-
SK4	+	+	-
SK5	-	-	+
SK6	+	-	+
SK7	-	+	+
SK8	+	+	+

A first order polynomial regression equation that fitted to the data is:

$$Y = a_0 + a_1X_1 + a_{ij}X_iX_j + a_{ijk}X_iX_jX_k$$

Where, Y is the response, a₀ is the intercept which represents the arithmetic averages of all the quantitative outcomes of eight experimental runs. a_i is the main effect coefficient of the interaction effect, X_i, X_j and X_k are the parameters. This equation enables us to study effects of each factor and their interactions over the responses. The coefficients with factor represent the effect of particular factor and the coefficient with more than one factor represent the interaction between the factors. The positive sign of the coefficient indicates synergistic effect while negative sign indicates antagonistic effect of the factors.

Pellet characterization

1. Usable yield (Particle size distribution)

The size and size distribution of the pellets produced was determined by agitation for 10 min with sieve shaker³. A sieve shaker (Jayant laboratory instruments), vibrating at 1mm amplitude was used. Pellets were put on the top of the sieve with series of openings ranging from 1mm (BSS sieve no. 16), 0.853 mm (BSS sieve no. 18), 0.71 (BSS sieve no. 22) to 0.5 (BSS sieve no. 30). The results were taken as percentage of weight retained on each sieve size. The fraction of pellets sieved from BSS sieve no. 18 to BSS sieve no. 22 was reported as usable yield.

2. Sphericity factor

The shape of pellets was examined with light microscope (Olympus microscope) at 10X magnification, connected to a camera. Major and minor axes of 50 particles of each composition were measured. The sphericity factor, the ratio of major and minor axes of pellets was determined as mean of 50 measurements⁸.

3. Moisture analysis

The moisture content of the dried pellets was analyzed with a moisture content analyser (Mettler Toledo Ltd., Switzerland). Two grams of pellets were used for the test. The percentage loss of moisture during the test was determined. The results were calculated as mean value of three measurements.

4. Bulk density and tapped density

The bulk density and tapped density were determined from the weight of a 40 g sample charged into a 100 ml graduated cylinder, and the volume was recorded. The pellets were tapped 1250 times until a constant volume was obtained and tapped density was calculated. Both densities were averaged from three determinations. Bulk density was calculated as: M/V₀, where M is weighed mass and V₀ is unsettled apparent volume. Tapped density was calculated as: M/V_f, Where M is weighed mass and V_f is final tapped volume.

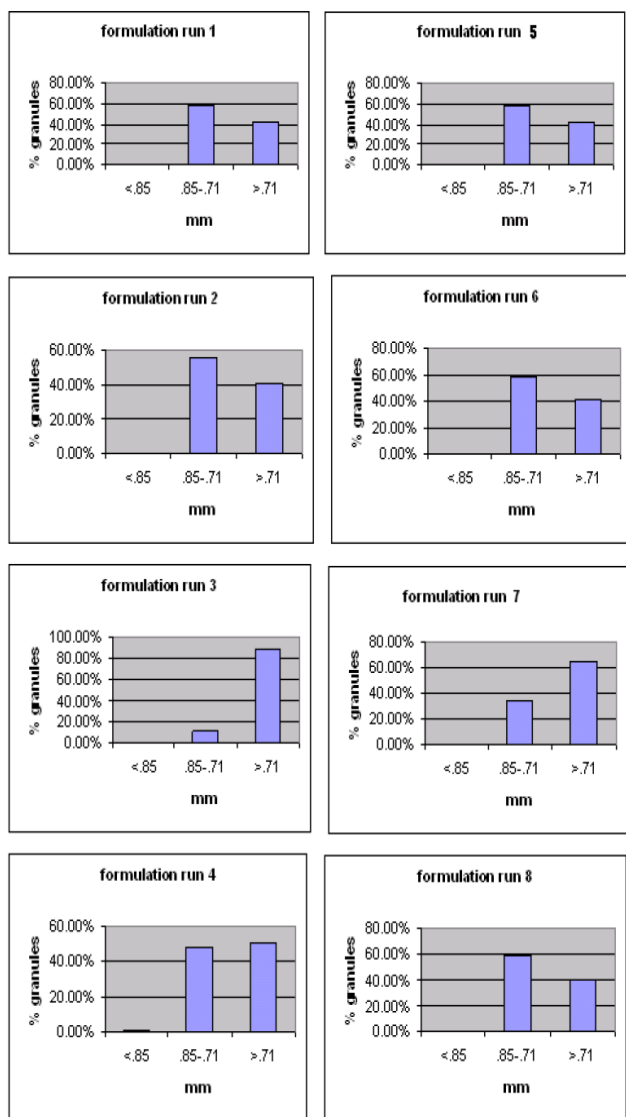


RESULTS AND DISCUSSION

1. Usable yield, pellet size distribution

For a successful extrusion-spheronization process, a high percentage of pellets should be produced within a desired size range⁸. Size distribution is an important factor to be considered if the pellets are to be coated for modifying drug release. It also reduces the variation in full weight. Figure 1 lists the results of the particle size distribution. The largest pellets are the ones made with high amount of water and spheronization time. This implies that the solvent influences the packing of particles during processing. This is evident from the highest positive term X_1 . The positive sign of the coefficient indicates an increasing effect, whereas the negative sign refers to a decreasing effect on the corresponding response⁹. In addition, the usable yield is inversely influenced by spheronization speed. When spheronization time was increased, pellets combined with fine particles during process.

Figure 1: Graphical representation of particle size distribution of all experiments



Moreover, interaction term X_1X_2 significantly contributed to the pellet size, even though, X_2 was seen to have negative influence. This means that each factor tends to modify the effect of another towards the pellet size.

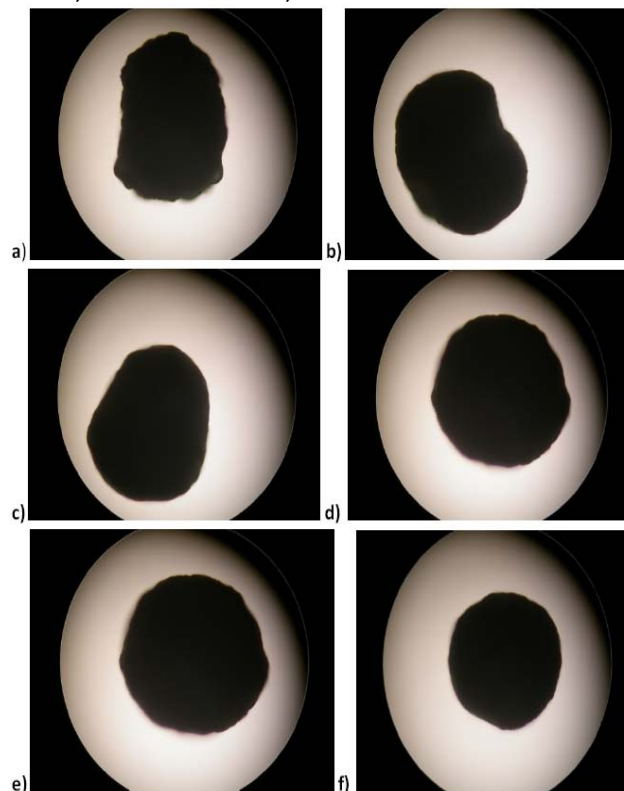
Subsequently, treatment according to the mathematical model was carried out. This was done in order to determine the role played by each of the factors studied.

$$Y_1 = 46.71 + 8.75 X_1 - 8.20 X_2 + 3.52X_3 + 6.77 X_1X_2 + 0.1 X_1X_3 + 5.08 X_2X_3 - 3.03 X_1X_2X_3$$

2. Sphericity factor

Pellet shape can vary from rounded cylinders to dumbbells and ellipsoids as shown in figure 2. Sphericity of the pellet is a critical parameter as it has processing advantages like free flowing, uniformly coated product. It is the work of spheronizer to fragment the extrudate with the frictional plate and subsequently, smoothen the fragments into spherical pellets.

Figure 2: Photomicrographs of pellets a) formulation SK6; b) formulation SK1; c) formulation SK3; d) formulation SK4; e) formulation SK7; f) formulation SK8



The reduced regression equation for sphericity factor is:

$$Y_2 = 1.6338 - 0.2662X_2$$

The results in Table 3 show that an optimal amount of water gave pellets. When low amount of water was used spherical shaped pellets were not obtained. Spheronization speed also had an impact on the sphericity. Pellets obtained from higher spheronizer speed were more spherical than those from low spheronizer speeds. Good sphericity and smooth surface were obtained with higher spheronizer speeds.

3. Loss on drying

As mentioned in Table 3, Pellets were found to have low moisture content ranging from 1.6 to 1.8%. The difference in moisture content of pellets was very small and thus, it was statistically insignificant. This indicated that even though the initial water content of the pellets was different, the drying process efficiently removed the free water added during the initial wet massing.

4. Densities

The results of densities have been concluded in Table 3. The analysis of interaction indicated that for a given amount of water, on increasing the spheronization speed, there is increase in overall sphere density. On increasing moisture content, overall density increases.

Table 3: Densities, sphericity factor, loss on drying obtained by different spheronization speeds, spheronization times and amount of granulating fluid.

FORMULATION	BULK DENSITY (g/ml)	TAPPED DENSITY (g/ml)	SPHERICITY FACTOR	LOSS ON DRYING (%)
SK 1	0.6	0.65	1.32	1.61
SK2	0.61	0.76	1.11	1.74
SK3	0.62	0.66	1.09	1.69
SK4	0.75	0.83	1.07	1.78
SK5	0.6	0.66	1.19	1.62
SK6	0.71	0.93	1.08	1.76
SK7	0.6	0.64	1.07	1.66
SK8	0.71	0.96	1.02	1.79

CONCLUSION

The study illustrated that spheronization speed, spheronization time and the amount of water had a significant effect on the physical characteristics and appearance of pellets. Optimization of process variables promoted to determine the influence of the factors and interactions between them. The pellets of optimum size range were obtained with high amount of water and spheronization time. Optimal amount of water gave spherical pellets. Pellets obtained from higher spheronizer speed were more spherical than those from low spheronizer speeds. Good sphericity and smooth surface were obtained with higher spheronizer speeds.

REFERENCES

- Kandukuri J.M., Allenki V., Eaga C.M., Keshetty V., Jannu K.K., Pelletization techniques for oral drug delivery, *International Journal of Pharmaceutical Sciences and Drug Research*, 1(2), 2009, 63-70.
- Chatlapalli R., Rohera Bhagwan D., Physical characterization of HPMC and HEC and investigation of their use as pelletization aids, *Int. J. Pharm.*, 161, 1998, 179-193.
- Podzcek F., Knight P.E., Newton J.M., The evaluation of modified microcrystalline cellulose for the preparation of pellets with high drug loading by extrusion/spheronization, *Int. J. Pharm.*, 350, 2008, 145-154.
- Tomer G., Podzcek F., Newton J.M., The influence of model drugs on preparation of pellets by extrusion/spheronization: II spheronization parameters, *Int. J. Pharm.*, 231, 2002, 107-119.
- Dukic A, Mens R, Adriaensens P, Foreman P, Gelan J, Remon JP, Vervae C, Development of starch-based pellets via extrusion/spheronization, *Eur. J. Pharm. Biopharm.*, 66, 2007, 83-94.
- Alvarez L, Concheiro A., Gomez-Amoza L., Souto C., Martinez-Pacheco R., Effect of Microcrystalline cellulose Grade and process variables on pellets prepared by Extrusion-spheronization, *Drug Dev. Ind. Pharm.*, 28(4), 2002, 451-456.
- Pund S., Joshi A., Vasu K., Nivaskar M., Shishoo C., Multivariate optimization of formulation and process variables influencing physico-mechanical characteristics of site-specific release isoniazid pellets, *Int. J. Pharm.*, 388, 2010, 64-72.
- Mehta K.A., Rekhi G.S., Parikh D.M., *Handbook of Pharmaceutical Granulation Technology*, 2, 2005, 333-363
- Sinha V.R., Agarwal M.K., Kumria R., Influence of operational variables on the pellet properties prepared by Extrusion spheronization, *Current Drug Delivery*, 2, 2005, 1-8.
- Fetete R., Zelko R., Marton S., Racz I., Effect of the formulation parameters on the characteristics of pellets, *Drug Dev. Ind. Pharm.*, 24(11), 1998, 1073-1076.
- Ye G., Wang S., Sia heng P.W., Chen L., Wang C., Development and optimization of solid dispersion containing pellets of itraconazole prepared by high shear pelletization, *Int. J. Pharm.*, 337, 2007, 80-87.
- Manivannan R., Parthiban K.G., Gummudavelly S., Ayyasamy B., Senthilkumar N., Multiparticulate drug delivery systems: Pellet & pelletization technique, *Drug Invention Today*, 2(5), 2010, 223-237.

