International Journal of Drug Delivery 5 (2013) 206-213
http://www.arjournals.org/index.php/ijdd/index

Original Research Article

ISSN: 0975-0215

Formulation and multivariate optimization of microcrystalline cellulose pellets of highly water soluble drug

Ravindra Tiwari[1], Sunil Kumar Agarwal[2] and Shweta Tiwari[3]

*Corresponding author:

Ravindra Tiwari

[1]Department of Pharmaceutical science, Singhania University, Pacheri Bari, Jhunjhunu. Rajasthan. India.
[2] Dr. Reddys Laboratories Limited, Hyderabad, India.
[3]Govt Girls college, sector 14 gurgaon India.

Abstract

Microcrystalline Cellulose (MCC) pellets containing highly water soluble compound A was formulated with highest pellet usable yield of 86%, aspect sphericity that is (aspect ratio less than 1.1 and roundness greater than 0.85), minimum friability of 0.33% by extrusion and Spheronization technique. A Central Composite Design (CCD) was executed to estimate the effect of formulation and process variable namely water (21-41%), spheronization time (1-9 min) and Spheronization speed (200-800) to maximize responses i.e, usable yield, Sphericity aspect ratio and roundness. Least square regression analysis using response surface methodology permit the identification and optimization of variables that shows significant effect on selected responses. Polynomial model fitted to the data were used to predict the responses in the desired value. A generalized desirability function is used to get maximum achievable target for responses. The optimum values for variables were water 31%, Spheronization Time of 5 min and Spheronization speed of 500 rpm. These results confirmed the usefulness of Multivariate analysis to identify the critical variables and their interactions on the characteristics of pelletization

Keywords: Microcrystalline Cellulose, Pelletization, Central composite Design, Response Surface Methodologhy

Introduction

Pellets are increasingly being used as multiple unit dosage forms [1]. Suitable excipients and fillers can be used to produce pellets with the desired characteristics [2]. Spherical pellets possess many advantages, including a low surface area–to-volume ratio, good flow properties, and uniformity in packing [3]. This ideal shape of pellets makes them excellent substrates for coating as desired for aesthetic purposes or to control the reproducible release of active ingredients [4]. Pellets possess many pharmacological advantages as they disperse freely in the gastrointestinal tract, maximize drug absorption, reduce peak plasma fluctuations and minimize potential side effects without appreciably lowering the bioavailability [5]. They avoid high local concentrations of bioactive agents, which may inherently be irritative or anesthetic to stomach [6]. Additionally they reduce intra and inter subject variability of plasma profiles by reducing variations in gastric emptying rates and overall transit times. Pellets are spherical beads that are between 0.5 and 1.5 mm in mean diameter and have a narrow size distribution [7]. Their reproducible particle surface is ideal for coating. Therefore, pellets have gained considerable attention in the development of modified-release dosage forms [8].

One of the most widely used pelletization process in the pharmaceutical industry is extrusion and Spheronization, which is suitable for formulation with high doses of drug [9]. Spheronization or merumerization is the process of making extrudes in round shape. Extrusion spheronization follows mainly five steps that is mixing or blending, extrusion, spheronization, coating and finally drying, which can be explained/described as; dry mixing of ingredient to achieve homogenous powder dispersion followed by wet massing to produce a sufficient plastic mass and then extrusion to form rod shaped particles of uniform diameter followed by spheronization to round off these rod shaped particles into spherical particles with narrow size distribution. This is followed by drying to achieve desired final moisture content and finally screening to obtain desired size of spheres/pellets [10]. The formulation and conditions used to prepare pellets are somewhat important for extrusion and spheronization. Every single step in the process of pelletization by extrusion/ spheronization affects the properties of the resulting pellets [11, 12].

Use of suitable excipients and fillers can be made to produce pellets of desirable quality. Such dosage forms may also optionally consist of several inert materials, referred to as excipients, in addition to the active ingredient, which is present in amounts sufficient to accomplish the desired pharmaceutical effect. Microcrystalline cellulose (Microcrystalline Cellulose) is the most popular excipient for the production of beads by extrusion spheronization. Microcrystalline Cellulose can hold large amount of

water and is plastic enough to yield to the shear force of extrusion and spehronization. It facilitates removal of most of the water easily on drying it leads to the formation of round spheres with desirable characteristics [13, 14]. The high water holding capacity and compressibility and compactibility characteristics of Microcrystalline Cellulose make it suitable for the process of extrusion spheronization of highly water soluble drug thus Microcrystalline Cellulose has been considered a crucial excipient for the production of beads by extrusion spheronization [15, 16].

The purpose of pelletization process is to produce spherical particles of acceptable size and size distribution along with good mechanical strength and desired release properties. The common way for the delivery of pellets is by filling them in hard gelatin capsules. Also, they may be coated to produce desired drug release profile. Therefore, it is important to determine the pellet size, size distribution, shape, abrasion resistance and mechanical strength as these parameters determine the quality of pellets produced. Also, filling in hard gelatin capsules is uniform, and their coating procedure becomes successful [17].

In the current study, the influence of water level, spheronization time and spheronization speed on the critical pellet properties of Compound A pellets were studied.

The application of statistical experimental design for formulation and process development is highly recommended due to high degree of interactions studied between variables [18]. In the present investigation, the experimental plan chosen was central composite design (CCD) regression model which permits the prediction of system properties by response surface methodology [19, 20]. The main aim was to evaluate the interactions between the various formulation and process variables on the properties of pellets.

Materials and Methods

Material

The following chemicals were obtained from commercial suppliers and used for experiment Compound A (Arti Drugs India) a salt with a molecular weight of 313.84 and solubility 100 mM in water and to 50 mM in DMSO, Microcrystalline cellulose (Avicel PH 101, FMC biopolymer Nederland), Hydroxy propyl cellulose (L-HPC, Shin-Etsu Chemical, Japan), were of EP standard and were used as received. Water freshly demineralised was used as a liquid binder.

Preparation of Pellets

A batch size consisted of 250 grams in weight was kept for all the experiments. All the ingredients were weighed and passed through BSS no. 22. The sieved ingredients were mixed well for 10 minutes in Rapid mixer Granulator. All dry ingredients were granulated with demineralised water in a Rapid mixer Granulator (2 liter capacity) with an impeller and chopper (General mechanical industries ltd. Mumbai, India) for 5-6 minutes till granulation end point was reached. To ensure uniform water distribution during wet massing, the material adhering to the mixing bowl was regularly removed. The wet granulate was extruded at the extrusion speed of 25 rpm using single extruder. The extruder used was screw feed with radial extrusion (Fuji Paudal Co. Ltd, Tokyo Japan, model-MG 55). Spheronization was done at speed of 200 to 600 rpm for 1 min to 9 min on a spheronizer with cross-hatch disk (Fuji Paudal Co. Ltd, Tokyo Japan, model QJ 230 T-1). The spheronised part was dried using Fluidized Bed Drier (Retsch Gmbh & Co., Haan Germany, model-TG 100) operating at 60^0C for 20 min in 2 sets of air speeds, initially minimum and than increased to avoid the fragmentation of pellets.

Experimental design and data investigation

Central composite design has advantages as it reduces the number of trials needed to attain the highest amount of information on product properties. The influence of one formulation variable and two process variable was tested at five levels as per design (Table 1). The formulation variable was granulating fluid i.e. water (X_1, % w/w of dry blend) process variables including spheronization Time (X_2 min), spheronization speed (X_3 rate per min) whereas dependent variables or the responses were % usable yield (Y_1,), Aspect ratio (Y_2), Roundness (Y_3) and friability (Y_4) were investigated. The selection of variables and their ranges was based on the results of preliminary experiments. The levels for each parameter are represented by (-1) sign for low level, (+1) sign for the high level for factorial points, (0) for mid point and (+2) & (-2) for the axial points (star points).

Table 1: Factors and their levels used in the experimental design

Factors	units	(-2)	(-1)	(0)	(+1)	(+2)
Water (X1)	%	21	26	31	36	41
Spheronization Time (X2)	Min	1	3	5	7	9
Spheronization speed (X3)	RPM	200	350	500	650	800

Central composite design (CCD) with two center point and an alpha level of ±2 (table 1) was employed to estimate the extended effect of the formulation and process variables X1, X2 and X3 on responses i.e., Usable yield (Y1), Aspect Ratio (Y2), Roundness (Y3) and Friability (Y4) in an extended spherical domain.. The responses were evaluated for each trial of the experimental design and results were analyzed using Design Expert version 8.0.7.1 software (Stat-Ease, Inc.). A second order polynomial equation was fitted to the CCD result data for each responses using least square regression analysis.

Analysis of Variance (ANOVA) was performed for each response at 0.05 level of significance (=0.05). The simultaneous optimization technique was chosen for optimization of the responses. This method is based on the utilization of desirability functions. Each response is converted into an individual desirability function.

Model was generated using CCD and variables were optimized using best combination as per desirability for responses. Lack of Fit

Test was applied to check any significant difference between the predicted and observed responses.

Pellets characterization

Usable % yield (Particle size distribution)

The size and size distribution of the pellets produced was determined by agitation for 10 min with sieve shaker[11]. 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), and 0.71 mm (BSS sieve no. 22) to 0.5 mm (BSS sieve no. 30). The results were taken as percentage of weight retained on each sieve size. The fraction of pellets passed from BSS sieve no. 18 (0.853 mm) and retained on to BSS sieve no. 22 (0.71 mm) was reported as usable yield.
Usable yield: The Usable yield was calculated using the formula

(Weight of dried pellets X 100) / Weight of excipients (250gm)

Pellet shape

The shape and the area of pellets were investigated by optical microscopic image analysis. Fifty pellets from each batch were placed on black backgrounds and a top cold light source was used to reduce the influence of shadow on the image processing. The image analyzer consisted of a computer system linked to a camera (Nikon Ecliose, model E600POL, Stage micrometer Olympus Tokyo 0.01mm) interfaced via a Nikon camera (model Nikon Coolpix 4500), to a personal computer loaded with a commercially available software program (Image Pro Plus 5.1 Version. The Roundness of the pellets is calculated by the software using the following relationship:

Roundness = Area / $(dmax/2)^2$

Aspect ratio = max feret diameter / min feret diameter

The image analysis is based on the consideration that a perfect sphere has a shape factor of 1.000.The sphericity of all the pellets under study was normalized taking nonpareil seeds as standard. The sphericity index of the Compound A pellets of is given in Table 2, and their microscopic images were 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 measurements.

Friability

Beads weighing 3 g, along with 25 glass beads (3mm in diameter), were placed in a Model 1805 Roche friabilator (Vankel Industries, Inc., Edison, NJ) that was then operated for 100 revolutions at 25 rpm. Glass beads were separated by screening with a 12-mesh sieve and the beads collected on a BSS 22-mesh sieve with its 0.71-mm aperture, after smaller particles were allowed to pass through, were weighed. The friability was determined as the percentage loss of mass of the beads. Each batch was assessed in duplicate

Loss on Drying

The loss on drying 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.

SEM photographs

Pellets were coated for 200 s under an argon atmosphere with gold–palladium (Poloron SC6740) and then observed with a scanning electron microscope (Carl Zeiss EVO 40 at 20 KV, Germany).

Result and Discussion

The purpose of pelletization process is to produce spherical particles of acceptable size and size distribution along with good mechanical strength and desired release properties. The appropriate use and level of each excipient was determined by conducting preliminary studies. In the subsequent preliminary trials with water as the wet massing liquid, all materials were successfully extruded: spheronized, however, the pellets exhibited very high friability. The pellets crumbled back to powder during drying and subsequent handling. In order to avoid this problem, HPC has been used as binder.
Our preliminary work revealed that the amount of granulating fluid along with Spheronization speed and Spheronization time may be the significant variables influencing the formulation of Microcrystalline Cellulose pellets containing Compound A. Thus, optimization of core pellets was further investigated in depth in order to draw maximum advantage from its potential effectiveness for drug release.
In the present study, Response Surface Methodology (RSM) was oppressed systematically for evaluating the effect of varying the amount of granulating fluid; water, spheronization speed and spheronization time as well as to highlight any interaction among the components on the usable yield, Aspect ration, Roundness of pellets, and friability of pellets. This will facilitate the identification of the most significant factors influencing these properties and establishing their best levels for optimizing the considered experimental responses. Mathematical relationship was generated between the factors and responses for determining the levels of factors, which yield optimum responses.

Table 2: Experimental matrix for Central Composite Design (in coded levels)

Exp. S.N0.	Combinations		X_1 (%w/w)	X_2 (min)	X_3 (rpm)	% usable yield (Y_1)	AR (Y_2)	Roundness (Y_3)
1	1		-	-	-	64.4	1.18	0.702
2	x1		+	-	-	58.8	1.09	0.838
3	X2		-	+	-	70.0	1.22	0.669
4	X1X2	Factorial points	+	+	-	62.1	1.13	0.782
5	X3		-	-	+	68.8	1.17	0.727
6	X1X3		+	-	+	58.0	1.06	0.888
7	X2X3		-	+	+	71.9	1.11	0.79
8	X1X2X3		+	+	+	38.0	1.05	0.903
9	Mid point		0	0	0	85.5	1.03	0.935
10	Mid point		0	0	0	88.9	1.04	0.922
11	X1At – 2 L		-2	0	0	40.2	1.14	0.774
12	X1At + 2 L		+2	0	0	12.0	1.03	0.936
13	X2At – 2 L	Axial points	0	-2	0	78.4	1.15	0.744
14	X2At + 2 L		0	+2	0	58.0	1.18	0.715
15	XAt – 2 L		0	0	-2	79.0	1.22	0.671
16	X3At + 2 L		0	0	+2	68.0	1.05	0.907

Usable yield (Particle size distribution)

One determinant of the success of pelletization process is the percentage yield in the desired size range. A high yield can ensure a cost-effective production. The yield in the targeted 1mm (BSS sieve no. 16), to 0.71 mm (BSS sieve no. 22) fraction, indicating a strong influence of formulation and process variables and ultimately the success of the process.

The response plots for usable yield as a function of % water, spheronization speed and spheronization time, it was seen that the yield is affected most by % water and the lower yield values are obtained at the highest water levels.

Table 3: ANOVA results for model fitting for usable yield, Aspect ratio and Roundness

Source	Usable yield	Aspect ratio	Roundness
R^2	0.9738	0.9389	0.9291
R^2 Adjusted	0.9346	0.8474	0.8228
Model P - value	0.0004	0.0052	0.0079
Lack of Fit P - Value	0.3287	0.1855	0.1547

The response surface design gives more information regarding the curvilinear change in the responses with changing variable levels. The model was checked for appropriateness by examination of sequential model sum of squares and correlation parameters. The high R^2 (coefficient of determination) (Table 3) indicated that the quadratic model was suitable for describing the data. Lack of fit was insignificant as p value >0.05 for all the responses. The correlation parameters of for the quadratic model (Table 3) suggested a good fit to the data. The reduced regression equation for the usable yield in terms of coded factors is:

$$\text{Usable yield} = 86.075 - 7.162X_1 - 3.050X_2 - 15.275X_1^2 - 4.750X_2^2 - 3.425X_3^2 \quad (1)$$

Figure 1 demonstrate the changes in usable yield by variation of the process parameter. It was observed that the maximum usable yield was near the central region. Taken together with Eq.(1), surface maximum may reached when the level X1 and X2 are 30.04 and 4.59 respectively.

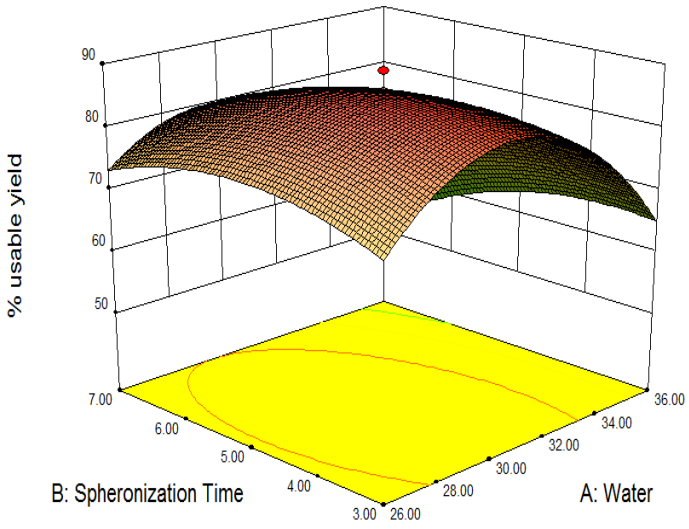

Figure 1: influence of % water and spheronization time on %usable yield

Our results also indicate that a greater reduction in the usable yield was observed with increase in water level and long spheronization time levels. However spheronization speed did not have any significant effect on usable yield (p>0.05). All two factor

interactions were insignificant but all quadratic terms were significantly affected usable yield (Table 4). At the highest water level and spheronization time, the pellets becomes sticky and over wetted due to excessive fluid present, respectively, which results in agglomeration into larger than desired beads, and the usable yield decreases.

Table 4: ANOVA results (p value): parameter estimates of responses for usable yield (Y1), Aspect ratio (Y2) and Roundness (Y3)

Source	Response: Usable yield (Y1)		Response: Aspect Ratio (Y2)		Response: Roundness (Y3)	
	Coefficient	Prob > F	Coefficient	Prob > F	Coefficient	Prob> F
% water(26,36)	-7.1625	0.0012*	-0.035	0.0016*	-0.0356	0.0021*
Spheronization Time(3,7)	-3.05	0.0495*	0.004	0.5299	0.0043	0.6887
Spheronization Speed(350,650)	-2.5375	0.0872	-0.035	0.0016*	-0.0356	0.0030*
% water *Spheronization Time	-3.175	0.1209	0.006	0.5259	0.00625	0.5629
% water *Spheronization Speed	-3.9	0.0683	0.001	0.8973	0.00125	0.8365
Spheronization Time *Spheronization Speed	-3.225	0.1162	-0.018	0.0900	-0.01875	0.2000
% water *% water	-15.275	<.0001*	0.0125	0.1056	0.0125	0.1233
Spheronization Time *Spheronization Time	-4.75	0.0087*	0.0325	0.0026*	0.0325	0.0028*
Spheronization Speed *Spheronization Speed	-3.425	0.0330*	0.025	0.0089*	0.025	0.0145*

*Means significance (p-value of Prob > F less than 0.05)

Further reduction in the water level resulted in moderate reduction of the usable yield. This was attributed to the binding properties of water as well as the production of good extrudate. As the water level was decreased, the extrudate displayed substantial shark skinning and resulted in the production of fines or undersized pellets, thus decreased the percentage of pellets in the desired size range.

Longer spheronization time increased the particle to particle interactions in the spheronizer and encouraged the formation of agglomerates and oversized beads. This results in a reduction in the yield in the desired size range. Decreasing the water level in the formulation increased the usable yield up to a certain extent by imparting necessary plasticity and lubricity to the wetted mass. Beyond the optimum water level with increased water levels decreased in the usable yield due to over wetting and agglomeration that leads to oversized pellets.

Pellets Shape

Aspect Ratio and Roundness of pellets

It is desirable to obtain high yields of beads in the desired size range, the shape that is critical for a number of processing advantages of beads, such as flow ability and uniformity in coating.

Bead shape was evaluated based on two parameters - aspect ratio (AR) and Roundness of pellets (RP)

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

ANOVA results for the quadratic model for Aspect ratio and roundness (table 3) suggested a good fit to the data. Lack-of-fit was insignificant ($p>0.05$). The second order polynomial regression equation for the aspect ratio and roundness in terms of coded factors was:

$$\text{Aspect ratio } Y_2 = 1.045 - 0.035X_1 - 0.035X_3 + 0.032X_2^2 + 0.025X_3^2 \quad (2)$$

$$\text{Roundness } Y_3 = 0.909 + 0.052X_1 + 0.049X_3 + 0.049X_2^2 + 0.034X_3^2 \quad (3)$$

The effect of the formulation and process variables on the responses i.e., Aspect ratio and Roundness were evaluated by studying the design parameters. Each of the variables except spheronization time had a statistically significant influence ($p < 0.05$) on the aspect ratio and roundness of the pellets (Table 4) no two factor interaction were statistically significant, however quadratic product of spheronization time and spheronization speed were significant. Figure 2 and 3 illustrate the relationship between the corresponding responses and factors. It was found that the

maximum roundness of 0.968 was proposed by model at 38.54% water, 4.97 min spheronization time and 615.45 rpm of spheronization speed. Similarly aspect ratio of 1.008 was predicted by the model at 37.96 % water, 4.98 min spheronization time and 601.29 rpm of speed.

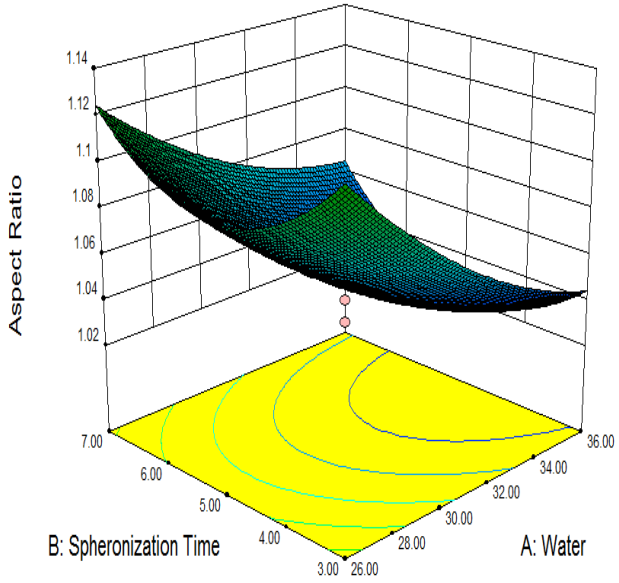

Figure 2: influence of % water and spheronization time on Aspect Ratio

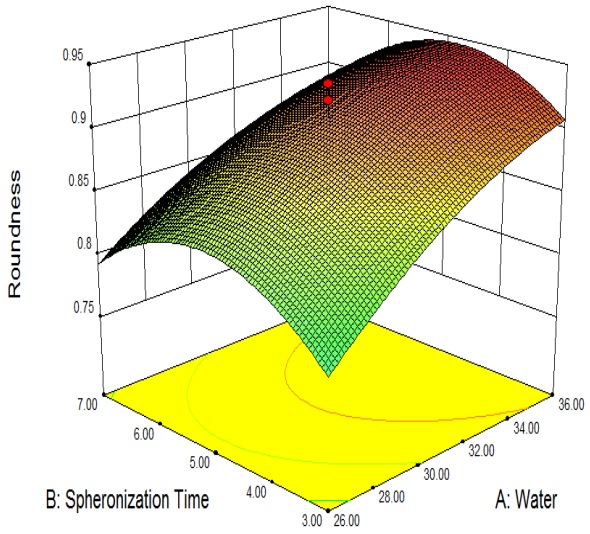

Figure 3: influence of % water and spheronization time on Roundness

From the regression equation, it can be observed that the pellets aspect ratio and roundness is most sensitive to water levels and spheronization speed. The average pellet diameter is at a minimum when water level and spheronization speed was at optimum and maximizes when they both are high level. The change in the bead size is more pronounced at higher speed and longer spheronization time. At high water levels the beads size tend to increase by way of agglomeration as more water is expressed to the surface of the beads due to higher speeds and agglomeration due to further particle to particle interactions occurs with longer times. At lower spheronization speeds, the bead size also found to increase with longer spheronization times. This is because, at low speeds, the longer particle to particle interactions facilitate the agglomeration of fines and smaller sized beads resulting in an increase in the average bead size.

Loss on drying

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.

Friability

Pellets with low friability are more rugged and thus more likely to maintain their integrity upon subsequent handling and coating processes. Each of the batches produced beads that exhibited low friability (<1%). However, friability exhibited a wide variation in the range 0.04–1.71%.

Spheronization for longer times results in higher friability of the beads. At high spheronizer speeds, where abrasive forces are high, increasing the water content does not reduce the friability of the beads. When spheronization speed is lowered along with an increase in the water, ruggedness of the beads is improved as depicted by the lower friability values.

SEM results

The external morphology of pellets is shown in figure 4. The surfaces of Extruded pellets were rougher. According to the SEM images (taken at magnitude of 92), a smooth surface for the hot-air dried pellets (Figure. 4) were observed.

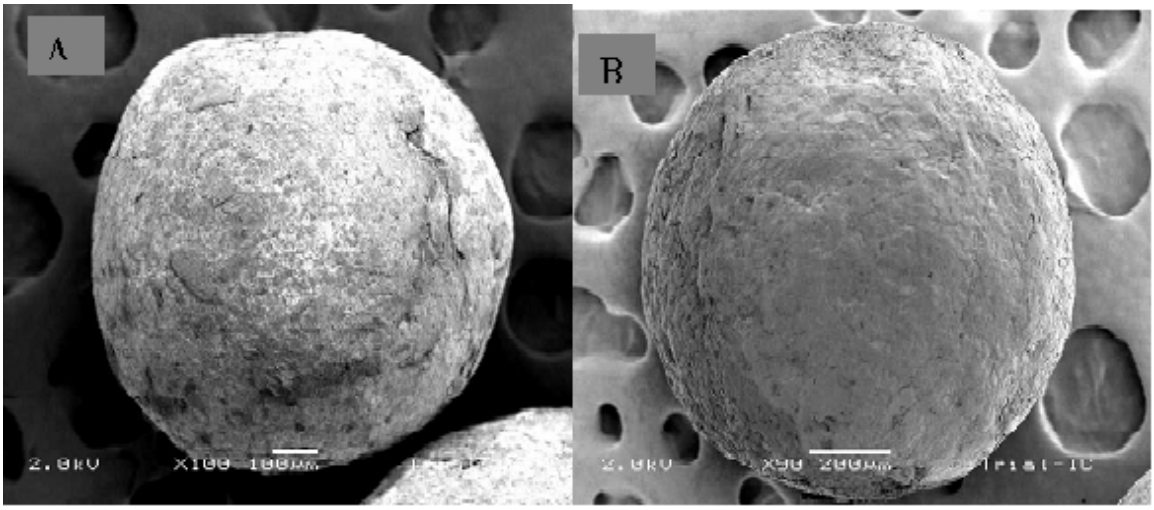

Figure 4: Scanning electron microscopy pictures of Extruded pellets from formulation Exp 9 and 10.

Conclusions

MCC pellets containing Compound A were successfully be prepared by extrusion and Spheronization technique. The result of Central Composite Design (CCD) revealed that % water was the major key factor for all responses. Spheronization time significantly affect the usable yield and friability, whereas Spheronization speed was responsible for sphericity (Aspect ratio and roundness). Residual were normally distributed and high R^2 value for all responses proved the efficiency of model to predict responses. Observed responses for the optimized product were in close agreement with the predicted values, thereby demonstrated the feasibility of the optimization procedure. The best batch of pellets shows maximum usable yield of 83.07%, optimum aspect ratio of 1.052, and optimum roundness of 0.927. Finally it proved that design of experiments with statistical analysis and modeling were useful tools for the characterization and optimization of the pelletization processes.

Acknowledgments

The authors wish to thank Shin-Etsu Chemical, Japan, who kindly provided the samples of Hydroxy propyl cellulose and Singhania University Pacheri Bari Jhunjhunu for motivation and support.

.

References

[1]. Sinha VR, Agrawal MK and Kumria R. Influence of Formulation and Excipient Variables on the Pellet Properties, Prepared by Extrusion Spheronization. Current Drug Delivery. 2005; 2: 1-8.

[2]. Mehta KA, Kislalioglu MS, Phuapradit W, Malick AW, Shah NH. Effect of formulation and process variables on porosity parameters and release rates from a multi unit erosion matrix of a poorly soluble drug. J Control Release. 2000; 63:201-211.

[3]. Kojima M, Nakagami H. Development of controlled release matrix pellets by annealing with micronized water-insoluble or enteric polymers. J Control Release. 2002; 82: 335-343.

[4]. Elchidana PA, Deshpande SG. Microporous membrane drug delivery system for indomethacin. J Control Release. 1999; 59: 279 - 285.

[5]. Fekete R, Zelko R, Marton S, Racz I. Effect of the formulation parameters on the characteristics of pellets. Drug Dev. Ind. Pharm, 1998; 24: 1073-1076.

[6]. Ghebre- Shellasie I. Pellets: a general overview. In: Ghebre- Shellasie I, ed. Pharmaceutical Pelletization Technology. New York, NY: Marcel Dekker Inc; 1989: 6-7.

[7]. Rekki, G. S., Porter, S.C. and Jambhekar, S.S., .Factors affecting the Release of Propranolol Hydrochloride from Beads Coated with Aqueous Polymeric Dispersions. Drug Dev. Ind. Pharm. 1995; 21: 709.

[8]. Gandhi, R., Kaul, C.L. and Panchagnula, R..Extrusion and spheronization in the development of oral controlled-release dosage forms. Pharm Sci Tech Today. 1999; 2: 160.

[9]. Schmidt C and Kleinebudde P. Influence of the Granulation Step on Pellets Prepared by Extrusion/Spheronization. Chem. Pharm. Bull. 1999; 47(3): 405-412

[10]. Thoma K and Ziegler I. Investigations on the Influence of the Type of Extruder for Pelletization by Extrusion-Spheronization. I. Extrusion Behavior of Formulations. Drug Deve. Ind. Pharm. 1998; 24: 401 - 411

[11]. Koo OMY, Heng PWS. The influence of microcrystalline cellulose grade on shape and shape distributions of pellets produced by extrusion-spheronization. Chem Pharm Bull (Tokyo). 2001; 49: 1383-1387

[12]. Neau S. H., Chow M. Y., Durrani M. J. Fabrication and characterization of extruded and spheronized beads containing Carbopol 974P, NF resin. International Journal of Pharmaceutics. 1996; 131: 47-55.

[13]. Neau S. H., Chow M. Y., Hileman G. A., Durrani M. J., Gheyas F., Evans B. A. Formulation and process considerations for beads containing Carbopol 974P, NF resin made by extrusion- spheronization. International Journal of Pharmaceutics 2000; 199: 129-140.

[14]. Gouldson MP, Deasy PB. Use of cellulose ether containing excipients with microcrystalline cellulose for the production of pellets containing metformin hydrochloride by the process of extrusion-spheronization. J Microencapsul. 1997; 14: 137-153.

[15]. Agrawal AM, Howard MA, Neau SH. Ext ruded and spheronized beads containing no microcrystalline cellulose: influence of formulation and process variables. Pharm Dev Technol. 2004; 9: 197-217.

[16]. Rowe RC, Sheskey PJ and Owen SC, Handbook of Pharmaceutical Excipients, 5th edition, Published by the Pharmaceutical Press; 2006. p. 132-135, 389-395, 449-453, 96-99, 731-733, 336-340, 611-615

[17]. Seth AK and Misra AN. Mathematical modeling of preparation of acyclovir liposomes: Reverse phase evaporation method. J. Pharm. Pharm. Sci. 2002; 5: 285-291

[18]. Sanchez-Lafuente C, Furlanetto S and Fernandez-Arevalo M. Didanosine extended-release matrix tablets: optimization of formulation variables using statistical experimental design. Int. J. Pharm. 2002; 237: 107-118

[19]. Boza A, De la Cruz Y, Jordan G, Jauregui-Haza U, Aleman A and Cataballo I. Statistical optimization of a sustained release matrix tablet of lobenzarit disodium. Drug Dev. Ind. Pharm. 2000; 26: 1303-1307