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Research Article

The Use of ß-Cyclodextrin in the Manufacturing of Disintegrating Pellets with Improved Dissolution Performances

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Abstract. It has recently been highlighted that the release behavior of pellets containing microcystalline cellulose (MCC) as the spheronizing agent may be impaired by the lack of disintegration. Although alternative spheronizing excipients have been proposed, their overall advantages have not thoroughly been assessed. In the present work, the possible use of β-cyclodextrin (βCD) was therefore explored for the manufacturing of pellets with a potential for effective disintegration and immediate release of poorly soluble active ingredients. MCC/βCD powder formulations containing no drug or model drugs with different water solubility, able to form inclusion compounds with the employed cyclodextrin, were pelletized by agglomeration in rotary fluid bed equipment. By applying successive statistical experimental designs, the most critical formulation and operating parameters were identified and optimal manufacturing processes were ultimately set up. High yields of pellets provided with satisfactory physical-technological characteristics were obtained using powder formulations with up to 80% βCD. Based on dissolution testing results, the suitability of βCD for the preparation of disintegrating MCC-containing pellets with improved dissolution performance was finally demonstrated.

KEY WORDS: β-cyclodextrin; design of experiments; microcrystalline cellulose; pellets; rotary fluid bed.

INTRODUCTION

Pelletization by means of agglomeration is a size enlargement process where powders are aggregated into free-flowing, high density and low-porosity pellets (1). Agglomeration can be promoted by the use of wetting/binding liquids, such as in the case of extrusion-spheronization (ES) and rotary processing (RP) techniques, leading to the formation of spherical and/or pseudospherical units with smooth surface (2). Although moistening, agglomeration/densification and spheronization are all required for the manufacturing of pellets, their peculiar characteristics chiefly depend upon the spheronization step. Unlike ES, in RP all these phases occur simultaneously in a one-step process that is carried out in a single equipment (3). Moreover, when using rotary fluid bed granulators, the drying phase can also be performed in the same equipment as well as a possible subsequent coating process aimed at the achievement of modified release multiple-unit dosage forms. Finally, rotary fluid bed equipments may be exploited for the manufacturing of spherical particles via other techniques such as solution/suspension layering or powder layering.

Pelletization by agglomeration in rotary fluid bed is based on three forces, centrifugal, gravitational and fluidizing, acting all together to promote the typical rope-like motion of the bulk (3). Centrifugal forces are generated by the rotational plate motion and tend to push the material towards the product chamber wall. The inlet air, flowing through the gap between the rotating plate and the chamber wall, drives the bulk upwards (fluidization). As the distance rises, the airflow rate decreases and the gravitational force starts to prevail. Thus the bulk is carried downwards and inwards. The nebulising system is located in the lower part of the chamber wall; the nozzle position is such that the moistening liquid is sprayed tangentially concurrent to the moving bulk. The rotating plate (rotor) is responsible for the distribution and mixing of the moistening liquid. Also, it is expected to promote densification of agglomerates and provide frictional forces for an effective spheronization step. Although a smooth rotor surface would be preferable to avoid adhesion, it might fail to supply sufficient shear for speronization (4).

To produce pellets with good technological properties by the RP technique, a cohesive yet plastic mass should be obtained after moistening, while a certain degree of brittleness should be pursued during the spheronization step. A so-called spheronization aid is generally needed to provide the moistened bulk (paste) with the above-stated rheological properties (5). In this respect, microcrystalline cellulose (MCC) is widely regarded as a key excipient due to its potential for retaining large amounts of moistening liquid that imparts binding, lubricating and plasticizing properties to the

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mass (1,6–8). This attitude is chiefly related to such inherent morphological characteristics of the material as high porosity and broad surface area. Nevertheless, some disadvantages of MCC-based pellets have been highlighted, the most critical of which is the lack of disintegration that may result in a prolonged drug release via diffusion through an insoluble inert matrix (9–12). This behaviour not only prevents the development of fast-disintegrating dosage forms, but also may prove detrimental to delivery systems containing poorly soluble drugs, particularly when an immediate release performance is expected after the coating has ceased from operating (e.g. enteric-coated pellets, pulsatile-release or colon-specific multiple unit dosage forms). Spheronization aids other than MCC have so far been proposed, such as hydrated aluminium silicates (10), pectinic acid (9,13), cross-linked polyvinylpyrrolidone (5), k-carrageenan (11,14,15), chitosan combined with sodium alginate (16), starch-dextrin mixtures (17) or modified high-amilose starch (12,18). The ability of these materials to confer fast-disintegration properties to the product and/or promote the release of poorly soluble drugs has generally been emphasized. On the other hand, their suitability for pelletization does not seem to be always satisfactory as for MCC. Based on the aptitude of MCC as a spheronizing agent, a different approach has also been followed, which involves the use of additives in pellet formulation that may counterbalance the lack of disintegration this excipient can bring about even when present in low amounts. For example, weak bases and acids (hydroxides and carbonates, citric and fumaric acids) (19) as well as superdisintegrants (20) have been proposed to enhance the disintegration/dissolution performance of pellets prepared by ES. In this respect, the use of functional excipients such as cyclodextrins (CDs) could be of great interest according to their well-known ability to increase the apparent water solubility of drugs, thus possibly improving their dissolution and bioavailability outcome (21,22). This functionality is primarily related to the formation of drug/cyclodextrin inclusion complexes. However, further solubilizing mechanisms have more recently been described including the ability to participate in various types of non-inclusion complexes, the formation of aggregates and the ability to form and stabilize supersaturated drug solutions (23,24). Moreover, from a regulatory point of view, consensus appears to be building around the classification of CDs as excipients, i.e. aids in the manufacturing of dosage forms and not part of the drug substance. In particular, β-cyclodextrin has recently been added to the FDA list of GRAS (generally regarded as safe) food additives.

On the basis of these considerations, the aim of the present work was the evaluation of CDs as possible excipients for the manufacturing of pellets with potential for fast disintegrating/dissolving performances and immediate release of poorly soluble drugs. As CDs are high-molecular weight compounds, they generally add bulk to the formulation, thus possibly impacting the manufacturing process. When CDs are used as complexing agents, their amount depends on the drug/CD interaction ratio and on the drug dose, the most critical conditions being interaction ratios ≤1 and/or highly dosed active compounds. In previous studies, the ability of β-cyclodextrin (βCD) to act as a filler in ES was demonstrated, and pellets with good technological properties were manufactured even with a restrained MCC content (≥10%) (21). Therefore, the possibility of preparing pellets with high βCD content by agglomeration in a rotary fluid bed was first investigated in the absence of an active ingredient starting from binary formulations with MCC. Furthermore, the influence of βCD on the release of a model drug from the optimized formulation with the minimum MCC content was evaluated. As the manufacturing process and the final properties of pellets prepared by RP technique are known to be strongly affected by a variety of parameters, a sequential statistical experimental approach was undertaken in both stages for optimizing the product development (25).

MATERIALS AND METHODS

Materials

Acetaminophen, AAP (ACEF SpA, I), 95%<100 μm; Ketoprofen, Keto (Cosma, I), 90%<7.5 μm, 50%<3.0 μm; β-cyclodextrin, βCD (Kleptose, Roquette Italia SpA, I), sieved fraction<125 μm; microcrystalline cellulose, MCC (Avicel PH 101, FMC-B.H. Shilling SpA, I). Distilled water of EP grade.

Methods

Preparation and Characterization of Pellets

Pellets were prepared by agglomeration in a rotary fluid bed granulator (Glatt GCPG1.1, Glatt GmbH, D) equipped with a smooth-surface plate. Different phases in the pelletization process can be distinguished: powder mixing, moistening liquid addition, wet massing and drying.

Powder mixing was carried out inside the product chamber of the rotary processor preheated by running without product for about 10 min (26). Powders were introduced separately in the chamber and mixed for 3 min under the conditions reported in Table I.

The moistening liquid (water) was sprayed tangentially into the moving powder through a nebulizing nozzle (1.2-mm diameter) by a peristaltic pump (Flocon 1003, Glatt GmbH, D). The nozzle was equipped with a 3-mm air dome spacer ring. During the water addition phase, the air gap pressure difference was maintained approximately 1,000 Pa, while the

Table I. Process Parameters

Phase	Parameter	
Powder mixing	Air gap pressure difference (Pa)	1,000
	Air flow rate (m^3/h)	60
	Inlet air temperature (°C)	30
	Plate rotational speed (rpm)	700
Water addition	Defined in the experimental designs	
Wet massing	Air gap pressure difference (Pa)	1,000
	Air flow rate (m^3/h)	50
	Inlet air temperature (°C)	30
	Plate rotational speed (rpm)	500
Drying	Air gap pressure difference (Pa)	1,000
	Air flow rate (m^3/h)	70
	Inlet air temperature (°C)	60
	Plate rotational speed (rpm)	200

values of the other process parameters were defined by means of sequential statistical experimental designs.

The need for a wet massing phase at the end of water addition was evaluated within the sequential optimization study. When provided by the design, it was carried out under the conditions reported in Table I.

Pellets were finally dried in the same rotary fluid bed equipment for 15 min (Table I).

The particle size distribution of pellets was estimated by sieve analysis (Octagon 2000, Endecotts Ltd., UK; 5 min, amplitude 4) of approximately 100 g samples. ASTM standard sieves were used in the 180- to 2,800-μm range. From the distribution by weight of diameters, geometric mean diameter (d_{geo}) and geometric standard deviation (σ_{geo}) were calculated.

Process yield was calculated as the percent ratio between the amounts of obtained pellets and starting materials. Moreover, a useful yield was defined as the percent of product in the 500- to 1,400-μm range.

Resistance of pellets to abrasion was evaluated through a procedure that was adapted from *Ph. Eur. 6th Ed.* friability test for uncoated tablets (21). 10 g of pellets were introduced in a Roche friabilator along with 25 glass beads (7-mm diameter) and rotated for 4 min at 25 rpm. Loss of powder <180 μm was determined and friability was calculated as the percent ratio between the amount of powder <180 μm and the initial sample weight.

Photographs of pellets from the selected 500- to 1,400-μm size fraction were taken by optical microscope (Panagor, D). The shape of pellets was evaluated by their aspect ratio, i.e. the mean ratio (n=30) between the longest Feret diameter measured on pellet images and its orthogonal (11).

Dissolution Test

Dissolutions were carried out in a USP 29 paddle apparatus (Dissolution System 2100B, Distek, North Brunswick, NJ, USA) at the stirring rate of 100 rpm. Samples of pellets containing 200 mg of acetaminophen and 30 mg of ketoprofen, respectively, were placed in 1,000 ml distilled water thermostated at 37±0.5 °C. Medium samples were automatically withdrawn at predetermined time points and spectrophotometrically analyzed for drug concentration. Acetaminophen and ketoprofen were assayed (Lambda 25, PerkinElmer, Monza, MI, I) at 248 and 260 nm, respectively. Tests were performed in triplicate. Bars in figures represent standard deviation.

Disintegration Test

Disintegration of pellets was evaluated through a procedure that was adapted from *Ph. Eur. 6th Ed.* disintegration test for tablets and capsules. A three-position disintegration apparatus (DT3, Sotax AG, Basel, CH; six replicates) was used with a 125-μm porous membrane placed at the bottom of the basket-rack assembly (11,18). Fifty milligrams of pellets were inserted in each tube, and two discs per tube were added. The basket-rack assembly moved at the rate of 31 cycles per minute in a vessel containing 800 ml of distilled water thermostated at 37±0.5 °C.

Table II. Experimental Setting of the Trials Provided by the 2_{IV}^{8-4} Factorial Design and Relevant Response Values

	Factor								Response		
	A	B	C	D	E	F	G	H			
Exp. no.	Powder load (g)	Water/powder ratio (g/g)	Spraying rate (g/min)	Atomizing air pressure (bar)	Air flow rate (m^3/h)	Inlet air temperature (°C)	Plate rotational speed (rpm)	Spheronization time (min)	d_{geo} (μm)	σ_{geo}	Friability (%)
1	500	3.5/5	30	1.5	40	30	1,000	5	1,606	1.25	3.10
2	500	2.5/5	20	2.0	40	40	1,000	5	244	1.29	13.56
3	500	3.5/5	20	1.5	70	40	700	5	269	1.32	6.67
4	500	2.5/5	30	2.0	70	30	700	5	263	1.31	24.09
5	750	3.5/5	20	2.0	40	30	700	5	1,195	1.30	6.36
6	750	3.5/5	30	2.0	70	40	1,000	5	551	1.43	6.71
7	750	2.5/5	30	1.5	40	40	700	5	353	1.34	8.60
8	750	2.5/5	20	1.5	70	30	1,000	5	263	1.23	17.35
9	750	3.5/5	30	2.0	70	40	1,000	0	490	1.45	1.79
10	750	2.5/5	30	1.5	40	40	700	0	388	1.38	13.05
11	750	3.5/5	20	2.0	40	30	700	0	1,052	1.77	6.90
12	500	3.5/5	30	1.5	40	30	1,000	0	1,692	1.54	1.41
13	500	2.5/5	20	2.0	40	40	1,000	0	260	1.28	11.33
14	500	3.5/5	20	1.5	70	40	700	0	251	1.26	13.36
15	750	2.5/5	20	1.5	70	30	1,000	0	244	1.27	11.92
16	500	2.5/5	30	2.0	70	30	700	0	419	1.40	5.17

Table III. Regression and Correlation Coefficients of the 2_{IV}^{8-4} Factorial Design for Response Polynomials

	d_{geo}		σ_{ge}		Friability	
	Regression coefficients and significant p values					
Polynomial term	Coefficient	p value	Coefficient	p value	Coefficient	p value
b_0	596.22	<0.0001	1.363	<0.0001	9.46	<0.0001
b_A	−29.19	–	0.033	–	–	–
b_B	292.01	<0.0001	0.051	–	−3.67	0.0086
b_C	124.00	<0.0001	–	–	−1.47	–
b_D	−37.00	0.0399	0.040	–	–	–
b_E	−252.58	<0.0001	−0.032	–	1.42	–
b_F	−185.58	<0.0001	–	–	–	–
b_G	71.49	0.0014	–	–	–	–
b_H	–	–	−0.056	–	1.34	–
	Correlation coefficients					
R^2_{adj}	0.985	0.288	0.416			

Experimental Design and Process Optimization

Based on a MCC 20%/βCD 80% by weight mixture, a sequential statistical experimental design was settled including a 2_{IV}^{8-4} factorial design (screening design) and a central composite design (CCD) with two replicates of the center point. When a model drug was introduced in the powder formulation (MCC 20%, drug/βCD 80% by weight), a new CCD was performed. Dependent variables (responses) involved by the experimental designs were product characteristics such as size (d_{geo}), size distribution (σ_{geo}) and mechanical resistance (friability). Pellet aspect ratio was also included in the case of CCDs together with the useful yield ($yield_{500–1,400}$).

Statistical analysis was carried out by means of a software package (JMP 6.0—SAS Institute, Cary, NC, USA). The least-squares method was used to estimate coefficients of successive polynomials. R^2 adjusted (R^2_{adj}) was calculated in order to evaluate the fitting of polynomials. *F*-statistics was used to identify statistically significant terms. Significant effects were evaluated with p value<0.05. Less significant regression coefficients were progressively eliminated to maximize the R^2_{adj} parameter (27).

In order to find out the experimental conditions for the achievement of the optimal product, i.e. the best response values, the desirability function approach, as described by Derringer and Suich, was applied (28). Individual and overall desirability as well as optimized factor levels were calculated using the above software package. Because pellet size (d_{geo}) is a satisfactory response, i.e. it lies between two threshold values, the 500–1,400 μm range was chosen for the calculation of the desirability function. The maximization desirability function was used for $yield_{500–1,400}$, while size distribution, friability and aspect ratio were minimized.

RESULTS AND DISCUSSION

In a previous work, we investigated the impact of β-cyclodextrin (βCD) on the manufacturing process and physical-technological properties of microcrystalline cellulose (MCC)-based pellets prepared by the extrusion-spheronization (ES) technique (21,29). Binary MCC/βCD mixtures were processed using water as the moistening liquid. By progressively replacing MCC with βCD, a good-quality product was attained with up to 90% amounts of the latter filler. The first aim of the present work was the development of an analogous pelletization process using a rotary fluid bed equipment starting from powder blends with the highest possible percentage of βCD. The ability of this functional excipient to enhance drug dissolution performances, in fact, is strictly related to its content in the formulation (with respect to any possible drug).

Pelletization by agglomeration in rotary fluid bed shares important features with the ES process, especially with regard to the spheronization step. However, differences in the mechanism of spheroid formation have been highlighted, which may affect the final product (2). In particular, less water seems to be required for an effective spheronization when operating in fluid bed, and pellets with a wider size distribution, lower sphericity but higher mechanical resistance can be obtained. Nucleation, agglomeration and coalescence of agglomerates have been recognized as the main mechanisms involved in the formation of spheroids by rotary processing (RP), whereas attrition and layering seem to be predominant in ES.

Preliminary trials performed in a rotary fluid bed apparatus pointed out the advantageous possibility of using the previously employed basic MCC/βCD formulation when the minimum amount of MCC was adjusted to 20% by weight and the equipment was provided with a smooth-surface rotor that limited the wet mass tendency to adhesion. With respect to further formulation and process variables that might

Table IV. Process Parameters of the Water Addition Phase Selected by the 2_{IV}^{8-4} Factorial Design

Parameter	
Powder load (g)	750
Spraying rate (g/min)	20
Atomizing air pressure (bar)	2.0
Inlet air temperature (°C)	30

Table V. Factors and Levels of the CCD Performed on the MCC/βCD Formulation

Factor		Level				
		−1.682	−1	0	+1	+1.682
B	Water/powder ratio (*g*/*g*)	2.83/5	3/5	3.25/5	3.5/5	3.67/5
E	Air flow rate (m^3/h)	43	50	60	70	77
G	Plate rotational speed (rpm)	650	700	775	850	900

influence the manufacturing process and product features, their overall number would have led to countless experimental trials. Therefore, a screening design was initially undertaken for identifying the most significant factors, which would be used as the basis for subsequent process optimization steps. Eight main independent variables were selected including one single formulation variable, i.e. the amount of water added as the moistening liquid with respect to the powder load (factor B). Most of the screened process parameters were relevant to the water addition phase, i.e. powder load (factor A), spraying rate (factor C), atomizing air pressure (factor D), air flow rate (factor E), inlet air temperature (factor F) and plate rotational speed (factor G). Finally, the possible effect of an additional spheronization step, i.e. a wet massing phase at the end of water addition, was also taken into account (spheronization time, factor H). Provided that factor interactions were negligible, a Plackett–Burman saturated screening design could be undertaken, in which every experiment performed is associated with a model term (30). This kind of design allows simple first-order mathematical models with no interaction terms to be calculated. Nevertheless, if interactions exist, they might be confounded with main effects. To reduce biased estimation of first-order effects, a 2_{IV}^{8-4} factorial design was selected, which was built by folding over a design of resolution III and confounding main effects with the interactions that involved the rotor speed, whenever possible (31,32). Among the factors under study, the plate rotational speed was, in fact, *a priori* defined as the one that would less probably interact with the others. A low and a high levels were fixed for each factor under study and 16 trials were performed in a randomized sequence. Responses including the dimensional characteristics and mechanical resistance (friability) of the product were evaluated in order to find out the best parameter for the screening of such factors. The experimental settings and values of the obtained responses are reported in Table II. ANOVA was then performed on the results, and effects with p values<0.05 were considered statistically significant (Table III). Among the investigated responses, the best correlation with the screened factors was achieved for the pellet size, d_{geo} ($R^2_{adj} = 0.985$). Moreover, the analysis showed that almost all variables significantly impacted ($p<0.05$) on the product mean size, the most effective being water/powder ratio and air flow rate.

Based on the screening phase, an additional experimental design (central composite design, CCD) was set up to further investigate rotary fluid bed pelletization of the MCC/βCD 20/80% *w*/*w* mixture. Along with water/powder ratio (factor B) and air flow rate (factor E), plate rotational speed (factor G) was also selected for evaluation in this design, even

Table VI. Experimental Setting of the Trials Provided by the CCD Performed on the MCC/βCD Formulation

	Factor			Response				
	B	E	G					
Exp. no.	Water/powder ratio (*g*/*g*)	Air flow rate (m^3/h)	Plate rotational speed (rpm)	d_{geo} (μm)	σ_{geo}	Friability (%)	$Yield_{500–1,400}$ (%)	Aspect ratio
1	−1	−1	−1	918	1.47	1.65	87.2	1.25
2	1	−1	−1	1,480	1.53	1.12	33.6	1.16
3	−1	1	−1	763	1.65	5.01	84.0	1.21
4	1	1	−1	721	1.48	1.18	86.4	1.25
5	−1	−1	1	596	1.37	2.86	73.9	1.21
6	1	−1	1	1,321	1.52	3.14	43.5	1.18
7	−1	1	1	303	1.29	4.18	2.0	1.22
8	1	1	1	618	1.37	3.36	77.6	1.24
9	−1.682	0	0	594	1.39	5.86	73.8	1.22
10	1.682	0	0	1,123	1.35	1.35	80.1	1.20
11	0	−1.682	0	1,059	1.42	3.30	81.9	1.21
12	0	1.682	0	358	1.38	5.89	12.4	1.21
13	0	0	−1.682	852	1.52	1.27	85.7	1.29
14	0	0	1.682	488	1.43	3.94	53.2	1.27
15	0	0	0	587	1.38	3.27	71.4	1.23
16	0	0	0	538	1.32	2.83	75.4	1.21
17	0	0	0	640	1.34	3.31	69.5	1.22

Table VII. Regression and Correlation Coefficients of the CCD Performed on the MCC/βCD Formulation for Response Polynomials

Polynomial term	d_{geo}		σ_{geo}		Friability		$Yield_{500–1,400}$		Aspect ratio	
	Regression coefficients and significant p values									
	Coefficient	p value	Coefficient	p value	Coefficient	p value	Coefficient	p value	Coefficient	p value
b_0	582.87	<0.0001	1.346	<0.0001	3.169	<0.0001	71.73	<0.0001	1.221	<0.0001
b_B	179.57	<0.0001	0.003	–	−0.916	0.0017	−0.34	–	−0.007	–
b_E	−226.17	<0.0001	−0.011	–	0.682	0.0096	−7.69	–	0.009	–
b_G	−121.38	0.0003	−0.052	0.0053	0.663	0.0111	−10.90	0.0265	−0.004	–
b_{BE}	−126.76	0.0012	−0.036	–	−0.550	–	20.25	0.0044	0.022	0.0083
b_{BG}	64.94	0.0369	0.042	–	0.477	–	12.05	–	–	–
b_{EG}	–	–	−0.045	0.0497	–	–	−10.92	–	–	–
b_B^2	114.42	0.0008	0.017	–	–	–	–	–	−0.008	–
b_E^2	61.23	0.0233	0.027	–	0.339	–	−9.36	–	−0.008	–
b_G^2	47.68	–	0.054	0.0114	−0.365	–	–	–	0.017	0.0146
	Correlation coefficients									
R^2_{adj}	0.949	0.662	0.746	0.666	0.637					

though it was proven not to markedly influence d_{geo}. Indeed, contradictory conclusions about its role in spheronization-based processes were found in the literature, and no actual confirmation was drawn on its *a priori* assumed poor chances of interaction with other factors (3,25). By means of the CCD, first- and second-order effects as well as interactions of the three main factors were evaluated. The five levels required for the parameters under study and the conditions fixed for the others were defined based on the results of the screening trials (Tables IV and V). The additional spheronization step, in particular, was omitted given the fact that it proved ineffective in certain cases and too critical with regard to the formation of oversized aggregates (lumps) in certain others. The experimental settings of the 17 trials performed are reported in Table VI. For each batch, the amount of pellets in a useful range of dimensions (500–1,400 μm) was determined, and the product was characterized in terms of mean diameter and size distribution as well as friability and shape (Table VI). All these parameters were subsequently included in the regression analysis leading to the calculation of polynomial coefficients and of ANOVA data reported in Table VII.

The amount of product in the 500–1,400 μm range was generally >70%. Only in two cases (trials 7 and 12) the mean particle size of pellets was approximately 300 μm. Presumably, the combination of experimental conditions did not promote aggregation and coalescence. In another case (trial 2), uncontrolled agglomeration occurred and pellets with mean particle size >1,400 μm were produced. The size distribution of the RP products was confirmed to be rather wide (2). Moreover, their aspect ratio typically was within the 1.16–1.29 range.

The correlation between the selected factors and relevant responses was generally good, thus indicating the consistency of the approach (Table VII). As previously observed in the case of the screening design, the best fitting was obtained for experimental data relevant to d_{geo} (higher R^2_{adj} value and number of significant regression coefficients). In particular, factor B showed positive first- and second-order coefficients with respect to the pellet size. Generally, an exponential increase in pellet dimensions is expected as the water/powder ratio is increased. Only when a very low amount of water is added is a decrease in d_{geo} expected. With respect to factor B, both air flow rate (factor E) and plate rotational speed (factor G) have an opposite impact. In fact, both contribute positively to d_{geo}. In particular, by raising the rotor speed, attrition/abrasion phenomena should normally be enhanced, thus reducing the product size. The same result should be brought about by an increase in the air flow rate as a consequence of reduced moisture available for the formation of liquid bonds on the particle surface. On the other hand, at low levels of these factors, pellet dimensions would be expected to increase with increasing rotor speeds or air flow rates. The contribution of centrifugal forces and air flow to the formation of solid interparticle bridges, should

Table VIII. Predicted and Experimental Values of Responses and of Overall Desirability Relevant to the Trial Performed Under the Optimal Combination of Factor Values (Water/Powder Ratio, 4.25/5 *g*/*g*; Air Flow Rate, 61 m^3/h; Plate Rotational Speed, 756 rpm)

		Predicted value	Experimental value	Relative error
Response	d_{geo} (μm)	844	874	−3.6
	σ_{geo}	1.37	1.35	1.3
	Friability (%)	1.87	1.63	13.1
	Yield (%)	73.2	79.0	−8.0
	Aspect ratio (%)	1.21	1.20	−1.1
Desirability		0.733	0.737	−0.52

Relative error = [(predicted value − experimental value)/predicted value] × 100

Table IX. Experimental Setting of the Trials Provided by the CCD Performed on the MCC/AAP–βCD Formulation

	Factor			Response				
	B	E	G					
Exp. no.	Water/powder ratio (*g*/*g*)	Air flow rate (m^3/h)	Plate rotational speed (rpm)	d_{geo} (μm)	σ_{geo}	Friability (%)	$Yield_{500–1,400}$ (%)	Aspect ratio
1	3.75/5	50	700	955	1.50	2.86	82.7	1.28
2	4.25/5	50	700	1,615	1.46	0.77	28.1	1.31
3	3.75/5	70	700	362	1.37	1.16	10.5	1.37
4	4.25/5	70	700	688	1.37	4.03	86.0	1.26
5	3.75/5	50	850	774	1.39	3.50	89.7	1.27
6	4.25/5	50	850	662	1.36	4.05	83.6	1.32
7	3.75/5	70	850	249	1.35	15.39	5.00	1.24
8	4.25/5	70	850	374	1.34	13.22	11.2	1.31
9	3.58/5	60	775	339	1.37	15.87	8.40	1.31
10	4.42/5	60	775	1,050	1.36	2.41	86.6	1.27
11	4.00/5	43	775	972	1.95	2.04	48.2	1.25
12	4.00/5	77	775	248	1.34	12.02	4.80	1.33
13	4.00/5	60	650	276	1.36	17.02	4.30	1.26
14	4.00/5	60	900	452	1.32	8.28	32.7	1.26
15	4.00/5	60	775	734	1.40	3.26	87.5	1.35
16	4.00/5	60	775	590	1.35	5.21	73.9	1.29
17	4.00/5	60	775	687	1.38	4.18	80.6	1.31

prevail in this case. With reference to the other responses, the number of statistically significant coefficients was markedly reduced. Hence, any factor-response relationship might have become a questionable issue.

The results achieved so far indicated that, when employing the RP technique, βCD exhibits a good aptitude for spheronization, thus confirming its suitability for being exploited, even in high amounts, in the formulation of pellets. However, to further support the potential of this special filler for improving the disintegration and dissolution performances of the product, a model drug-containing preparation was considered. Due to the need for setting up the new manufacturing process, the previous one underwent optimization. The desirability approach was applied to the manufacturing of MCC/βCD-containing pellets in order to identify the optimal combination of variables, i.e. those leading to the best possible product. The optimal levels calculated for factors through the defined overall desirability function were: water/powder ratio 4.25/5 *g*/*g*, air flow rate 61 m^3/h and plate rotational speed 756 rpm. For the purpose of validating the approach, an additional experiment was performed under these conditions, and results were compared with the predicted values. A good agreement was found for all responses and for the overall desirability (Table VIII).

With respect to the investigated formulation, the optimal levels for air flow rate and rotor speed turned out to be located in the middle of the experimental space, whereas the optimal amount of water lay beyond this area, thus indicating that higher water/powder ratios could be more effective. Preliminary trials carried out with a MCC/model drug (acetaminophen, AAP)–βCD formulation under the same process conditions as in the optimal experiment confirmed

Table X. Regression and Correlation Coefficients of the CCD Performed on the MCC/AAP–βCD Formulation for Response Polynomials

	d_{geo}		σ_{geo}		Friability		$Yield_{500–1,400}$		Aspect ratio	
	Regression coefficients and significant *p* values									
Polynomial term	Coefficient	*p* values	Coefficient	*p* values	Coefficient	*p* values	Coefficient	*p* values	Coefficient	*p* values
b_0	717.63	<0.0001	1.336	<0.0001	4.95	0.0102	70.45	0.0001	1.303	<0.0001
b_B	160.78	0.0144	−0.0007	–	−2.82	0.0164	11.18	–	0.001	–
b_E	−259.95	0.0007	−0.095	0.0023	3.98	0.0024	−17.91	0.0300	0.007	–
b_G	−92.75	–	−0.023	–	−0.17	–	2.18	–	−0.002	–
b_{BE}	–	–	–	–	−1.59	–	17.82	–	–	–
b_{BG}	−121.70	–	–	–	1.58	–	–	–	0.018	–
b_{EG}	88.42	–	–	–	–	–	−17.88	–	–	–
b_B^2	–	–	–	–	1.06	–	–	–	–	–
b_E^2	–	–	0.092	0.0032	–	–	−15.11	–	–	–
b_G^2	−85.95	–	–	–	2.31	0.0476	−12.28	–	−0.014	–
	Correlation coefficients									
R^2_{adj}	0.688	0.612	0.634	0.497	0.059					

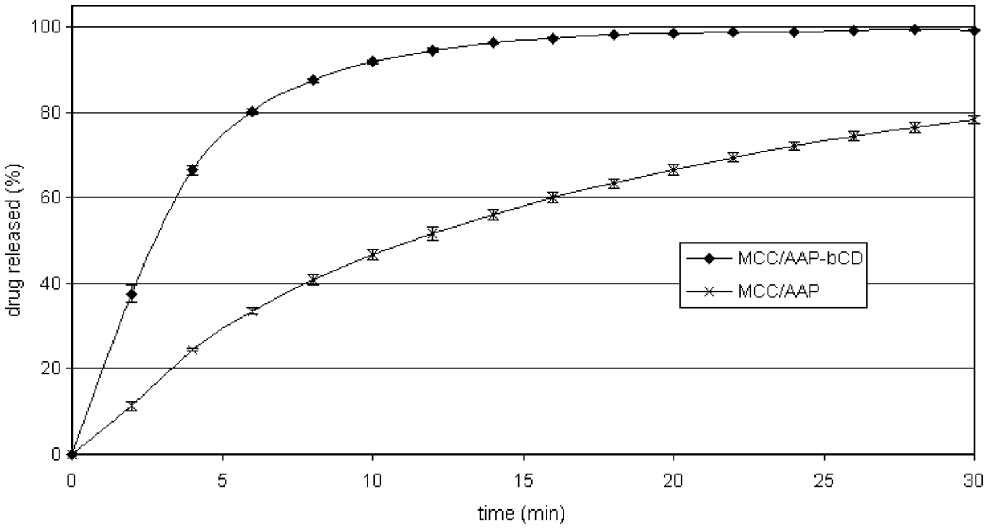

Fig. 1. Dissolution profiles of acetaminophen from pellets obtained by the MCC/AAP and the MCC/AAP–βCD powder formulations, respectively

this hypothesis. The powder formulation contained 20% MCC, 9.4% AAP and 70.6% βCD *w/w* resulting in a drug/βCD 1:1 molar ratio. AAP was used as the model drug for its well-known ability to form interaction compounds with the selected cyclodextrin (1:1 mol) (33–35). RP technique is known to be largely affected by the chemical–physical and physical–technological characteristics of the starting materials. Therefore, the addition of AAP to the powder formulation was supposed to be critical suggesting the possible benefits of undertaking a new experimental design. Once again, a CCD was constructed based on previous factors and levels except for water/powder ratios, each numerator being 0.75 g above the preceding one. The experimental settings of the trials performed on the MCC/AAP–βCD formulation and the obtained responses are reported in Table IX, while the relevant ANOVA data can be found in Table X.

Water amount, air flow rate and rotor speed (independent variables) were still proven to influence the defined responses, even if R^2_{adj} values were generally lower. Moreover, fewer coefficients of the second CCD turned out significant. In regard to the manufacturing process development, a more in-depth investigation should be carried out with special attention to the particle size and solubility characteristics of the drug and to the binding properties of the formulation. However, the disintegration/dissolution performances of the obtained product seemed worth investigating to find out whether an improvement had been achieved and to assess the role played by the complexing agent. Of all acceptable batches (high yields of product with good technological properties), batch 1 was subjected to *in vitro* testing. The relevant dissolution profiles were compared with those of purposely prepared pellets without βCD (AAP–βCD 1:1 molar mixture replaced by AAP only). The two products (batch 1 and reference) were analogously manufactured and showed comparable physical-technological properties. As expected, βCD was able to improve drug dissolution rate resulting in 100% AAP dissolved within 20 min as opposed to about 1 h (Fig. 1). Moreover, a change in the morphology of the βCD-containing product was observed during the dissolution test. While MCC/AAP pellets were shown to maintain

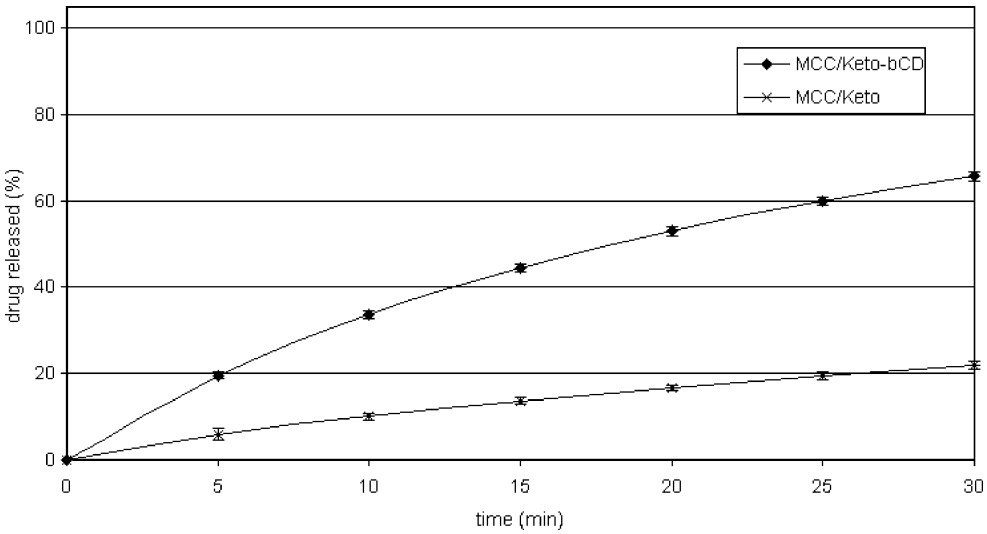

Fig. 2. Dissolution profiles of ketoprofen from pellets obtained by the MCC/Keto and the MCC/Keto–βCD powder formulations, respectively

their original dimensions or swell slightly, the MCC/AAP–βCD ones rapidly decreased in size thus making it difficult to distinguish any potential fragmentation process. However, differences in the inherent ability of pellets to disintegrate were also confirmed through a specific test performed in a modified disintegration apparatus intended for tablets and capsules. The βCD-containing product was disintegrated within 30±4 min (mean ± SD), whereas no disintegration was undergone by MCC/AAP pellets in 6 h.

In order to confirm the potential of βCD as a filler, another active ingredient was taken into account, ketoprofen (Keto), with a lower water solubility as compared to AAP, a similar molar weight and, again, the ability to form 1:1 molar ratio inclusion compounds with βCD (36). MCC/Keto 20/80% and MCC/Keto–βCD 20/14.6–65.4% powder formulations were pelletized, and dissolution studies were carried out on selected pellet samples with similar physical–technological characteristics (Fig. 2). As expected for matrix-like systems such as the MCC-based pellets, the dissolution performance of the product containing ketoprofen alone was strongly affected by its poor solubility. However, the ability of βCD to enhance drug dissolution rate by offsetting the lack of disintegration of MCC-based pellets was highlighted also in the case of Keto (42±3 min disintegration).

The contribution of both disintegration and drug/βCD interaction to the performances of pellets containing βCD needs further investigation. However, the formulation strategy based on the use of βCD might prove advantageous in enhancing the dissolution performance of MCC-containing pellets, especially when poorly soluble drugs are involved.

CONCLUSIONS

The use of cyclodextrins was proposed to overcome the lack of disintegration typically shown by pellets based on MCC as the spheronization agent. Indeed, the resulting matrix-like behavior may affect their dissolution/release performance, thus possibly hindering the development of modified-release formulations containing poorly soluble drugs.

The aptitude of βCD as a spheronization adjuvant in rotary fluid bed pellettization was initially assessed, and the manufacturing process was optimized with a MCC/βCD 20/80% powder mixture. The possibility of preparing pellets with elevated amounts of complexing agent may turn out advantageous in the design of high-strength dosage forms. Subsequently, pellets containing model drugs with different solubility were prepared. In particular, a CCD was undertaken for setting up the manufacturing process of the AAP-containing product. The potential of βCD for enhancing dissolution/release performances was confirmed by *in vitro* testing.

As MCC still represents the spheronization agent of choice, a formulation strategy aimed at improving the functionality of pellets based on this filler may be regarded as promising and worthy of further investigation.

REFERENCES

1. I. Ghebre-Sellassie. Pellets: a general view. In I. Ghebre-Sellassie (ed.), *Pharmaceutical Pelletization Technology*, Marcel Dekker, New York, NJ, 1989, pp. 1–13.
2. C. V. Liew, S. M. Chua, and P. W. S. Heng. Elucidation of spheroid formation with and without the extrusion step. *AAPS Pharm. SciTech*. **8**(1):Article 10 (2007).
3. L. Gu, C. V. Liew, and P. V. S. Heng. Wet spheronization by rotary processing—a multistage single-pot process for producing spheroids. *Drug Dev. Ind. Pharm.* **30**(2):111–123 (2004).
4. R. Pišek, O. Planinšek, M. Tuš, and S. Srčič. Influence of rotational speed and surface of rotating disc on pellets produced by direct rotor pelletization. *Pharm. Ind.* **62**:312–319 (2000).
5. C. V. Liew, L. Gu, J. L. P. Soh, and P. W. S. Heng. Functionality of cross-linked polyvinylpyrrolidone as spheronization aid: a promising alternative to microcrystalline cellulose. *Pharm. Res.* **22**(8):1387–1398 (2005).
6. C. Vecchio, G. Bruni, and A. Gazzaniga. Preparation of indobufen pellets by using centrifugal rotary fluidized bed equipment without starting seeds. *Drug Dev. Ind. Pharm.* **20**:1943–1956 (1994).
7. J. Vertommen, and R. Kinget. The influence of five selected processing and formulation variables on the particle size, particle size distribution, and friability of pellets produced in a rotary processor. *Drug Dev. Ind. Pharm.* **23**:39–46 (1997).
8. J. Kristensen, T. Schaefer, and P. Kleinebudde. Direct pelletization in a rotary processor controlled by torque measurements. II: effect of changes in the content of microcrystalline cellulose. *AAPS PharmSci*. **2**(3):Article 24 (2000).
9. I. Tho, S. A. Sande, and P. Kleinebudde. Pectinic acid, a novel excipient for production of pellets by extrusion/spheronization: preliminary studies. *Eur. J. Pharm. Biopharm.* **54**:95–99 (2002).
10. J. Kristensen, T. Schæfer, and P. Kleinebudde. Development of fast-disintegrating pellets in a rotary processor. *Drug Dev. Ind. Pharm.* **28**(10):1201–1212 (2002).
11. M. Thommes, and P. Kleinebudde. Use of κ-carrageenan as alternative pelletisation aid to microcrystalline cellulose in extrusion/spheronization. I. Influence of type and fraction of filler. *Eur. J. Pharm. Biopharm.* **63**:59–67 (2006).
12. A. Dukić, R. Mens, P. Adriaensens *et al.* Development of starch-based pellets via extrusion/spheronization. *Eur. J. Pharm. Biopharm.* **66**:83–94 (2007).
13. I. Tho, S. A. Sande, and P. Kleinebudde. Disintegrating pellets from water-insoluble pectin derivative produced by extrusion/spheronization. *Eur. J. Pharm. Biopharm.* **56**:371–380 (2003).
14. M. Bornhöft, M. Thommes, and P. Kleinebudde. Preliminary assessment of carrageenan as excipient for extrusion/spheronisation. *Eur. J. Pharm. Biopharm.* **59**:127–131 (2005).
15. M. Thommes, and P. Kleinebudde. Use of κ-carrageenan as alternative pelletisation aid to microcrystalline cellulose in extrusion/spheronization. II. Influence of drug and filler type. *Eur. J. Pharm. Biopharm.* **63**:68–75 (2006).
16. N. Charoenthai, P. Kleinebudde, and S. Puttipipatkhachorn. Use of chitosan-alginate as alternative pelletization aid to microcrystalline cellulose in extrusion/spheronization. *J. Pharm. Sci.* **96**(9):2469–2484 (2007).
17. S. Almeida Prieto, J. Blanco Méndez, and F. J. Otero Espinar. Starch-dextrin mixtures as a base excipients for extrusion-spheronization pellets. *Eur. J. Pharm. Biopharm.* **59**:511–521 (2005).
18. A. Dukić-Ott, J. P. Remon, P. Foreman, and C. Vervaet. Immediate release of poorly soluble drugs from starch-based pellets prepared via extrusion/spheronization. *Eur. J. Pharm. Biopharm.* **67**(3):715–724 (2007).
19. M. F. L. Law, and P. B. Deasy. Effect of common classes of excipients on extrusion-spheronization. *J. Microencapsul.* **14**:647–657 (1997).
20. C. Souto, A. Rodríguez, S. Parajes, and R. Martínez-Pacheco. A comparative study of the utility of two superdisgregants in microcrystalline cellulose pellets prepared by extrusion-spheronization. *Eur. J. Pharm. Biopharm.* **61**:94–99 (2005).
21. A. Gazzaniga, M. E. Sangalli, G. Bruni, L. Zema, C. Vecchio, and F. Giordano. The use of β-cyclodextrins as a pelletisation agent in the extrusion/spheronisation process. *Drug Dev. Ind. Pharm.* **24**:71–75 (1998).
22. L. Palugan, M. Cerea, C. Vecchio *et al.* Optimization of direct pelletization process of a beta-cyclodextrin/microcrystalline cellulose mixture in fluidized bed rotor granulator. *Boll. Chim. Farm.* **138**(3):79–85 (1999).

23. T. Loftsson, and D. Duchêne. Cyclodextrins and their pharmaceutical applications. *Int. J. Pharm.* **329**:1–11 (2007).
24. E. Brewster, and T. Loftsson. Cyclodextrins as pharmaceutical solubilizers. *Adv. Drug Deliv. Rev.* **59**:645–666 (2007).
25. J. Bouffard, H. Dumont, F. Bertrandt, and R. Legros. Optimization and scale-up of a fluid bed tangential spray rotogranulation process. *Int. J. Pharm.* **335**:54–62 (2007).
26. L. Gu, C. V. Liew, J. L. P. Soh, and P. W. S. Heng. Feasibility of eliminating premixing for the production of pellets in a rotary processor. *Pharm. Dev. Tech.* **11**(2):159–165 (2006).
27. D. C. Montgomery. Accostamento di modelli per regressione. In D. C. Montgomery (ed.), *Progettazione e analisi degli esperimenti*, McGraw-Hill, Milan, Italy, 2005, pp. 433–471.
28. G. Derringer, and R. Suich. Simultaneous optimization of several response variables. *J. Qual. Tech.* **12**(4):214–219 (1980).
29. A. Gazzaniga, F. Giordano, and inventors. Roquette, assignee. Micro-granules obtenus par etrusion/spheronisation contenant une cyclodextrine. FR patent 2705677, December 2, 1994.
30. R. L. Plackett, and J. P. Burman. The design of optimum multifactorial experiments. *Biometrika.* **33**(4):305–325 (1946).
31. G. E. P. Box, W. G. Hunter, and J. S. Hunter. Fractional factorial designs at two levels. In G. E. P. Box, W. G. Hunter, and J. S. Hunter (eds.), *Statistics for Experimenters. An Introduction to Design, Data Analysis, and Model Building*, Wiley, New York, NY, 1978, pp. 374–409.
32. Experimental design (industrial DOE). Available at: http://www.statsoft.com/textbook/stexdes.html. Accessed December 6, 2007.
33. S. Y. Lin. Effect of humidity on the formation and stability of acetaminophen-β-cyclodextrin inclusion complexes. *Drug Dev. Ind. Pharm.* **15**:2221–2241 (1990).
34. A. Gazzaniga, M. E. Sangalli, P. Benelli, U. Conte, G. Bettinetti, and F. Giordano. Interaction between acetaminophen and β-cyclodextrin by powder compaction. *STP Pharma. Sci.* **4**(6):421–424 (1994).
35. M. R. Caira, and D. R. Dodds. Inclusion of nonopiate analgesic drugs in cyclodextrins. II X-ray structure of a 1:1 β-cyclodextrin–acetaminophen complex. *J. Incl. Phenom.* **38**(1–4):75–84 (2000).
36. I. Orienti, A. Fini, V. Bertasi, and V. Zecchi. Inclusion complexes between non-steroidal antiinflammatory drugs and β-cyclodextrin. *Eur. J. Pharm. Biopharm.* **37**:110–112 (1991).