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COMMUNICATION

The Use of β-Cyclodextrin as a Pelletization Agent in the Extrusion/Spheronization Process

A. Gazzaniga,[1,*] M. E. Sangalli,[1] G. Bruni,[2] L. Zema,[1] C. Vecchio,[3] and F. Giordano[4]

[1]*Instituto Chimico Farmaceutico, Università di Milano, viale Abruzzi, 42, 20131 Milano, Italy*
[2]*Dipartimento di Chimica Fisica, Università di Pavia, viale Taramelli 16, 27100 Pavia, Italy*
[3]*Pharmaceutical Technologies R&D, via Comignano 2B, 28010 Revislate Veruno (NO), Italy*
[4]*Dipartimento Farmaceutico, Università di Parma, viale delle Scienze, 43100 Parma, Italy*

ABSTRACT

The use of β-cyclodextrin for the preparation of pellets by the extrusion/spheronization process is described for different formulations and processing conditions. Sieve analysis and friability tests were performed to assess the physical and technological characteristics of pellets. Satisfactory products were obtained with β-cyclodextrin contents up to 90% by weight.

INTRODUCTION

The use of pellets offers definite advantages in the preparation of conventional and modified-release solid dosage forms. Among pelletization processes, the extrusion/spheronization technology has been shown to produce high-quality materials for pharmaceutical applications. In this respect, several excipients have been tested for processing characteristics. Microcrystalline cellulose (MCC) was found to be a determinant for the plasticity of the wetted mass and for the binding properties which are necessary for conferring strength to pellets.

* To whom correspondence should be addressed. Fax: +392 29514197. e-mail: gazza@imiucca.csi.unimi.it

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The extrusion/spheronization process can produce pellets with high contents of active ingredient (up to about 80% w/w) (1–4). This feature can be of particular interest when one faces the problem of formulating drug/cyclodextrin (CD) inclusion compounds which consist, in the majority of cases, of large amounts of these special active ingredients. The main limiting factor is represented by the dose weight to be administered; considering the average molecular weights of drugs and CDs, 100 mg of a hypothetical inclusion compound can contain approximately 5–20 mg of the guest. This means that the formulation design is rather limited and conditioned by the large weight percentage which must be reserved for use by the inclusion compound, and by its physical characteristics. The overall technological behavior of the powdered inclusion compound, because of the existing weight ratio of drug/CD, can be reasonably ascribed mainly to the physical characteristics of CD (5–7).

On the basis of these premises, the investigation of the extrusion/spheronization process was applied to CD-containing formulations.

In the present work, the preparation and the physical properties of pellets obtained by processing formulations containing MCC and increasing amounts of β-CD were studied. In particular, data concerning morphology, particle size distribution, and friability of pellets as a function of composition and processing parameters are reported and discussed.

MATERIALS AND METHODS

Pellets made of β-CD (Roquette Frères, Lestrem, France) and MCC (Avicel PH 101, FMC Corp., Philadelphia, PA) in differing ratios were prepared by multistage processing (blending, wet granulation, extrusion, spheronization, and drying). Each batch (3 kg) was blended and granulated in a high-speed granulator (Solid Processor, Lab 4, Patterson Kelley Co., East Stroudsburg, PA).

Wetting was accomplished by adding purified water in quantities sufficient to achieve the proper mass consistency for extrusion. The wetted mass was divided in five portions for processing at differing conditions (feeding and agitating speeds for extrusion, plate rotational speed, and residence time for spheronization). The extrusion was carried out by forcing the mass through the radial screen extruder (hole diameter 1.0 mm; screen thickness 1.25 mm, NICA, type E4, Sweden) to produce cylindrical extrudates to be processed in the spheronizer (NICA, type S2-450) to produce pellets.

Pellet Evaluation

Physical tests on pellets prepared from different formulations and processing conditions included sieve analysis (sample size 100 g, JEL [J. Engelsmann, Germany] Sieve Shaker 200, 5 min) and friability testing (sample size 10 g, Roche (Erweka, Germany) friabilator, 25 glass spheres, 7 mm diameter, 10 min). The pellets were then placed on a 0.250-mm sieve and shaken for 5 min on a JEL 200 Sieve Shaker.

All tests were performed in triplicate.

RESULTS AND DISCUSSION

To evaluate the behavior of β-CD within the process of extrusion and spheronization, MCC/β-CD granulations with increasing β-CD contents were prepared and tested. MCC was chosen as the basic component owing to its generally accepted superiority in promoting pellet formation. In Table 1, codes and compositions of MCC/β-CD mixtures are reported together with the quantity of fluid required to adequately wet the powder mass.

It can be seen that in these preparations the progressive substitution of MCC by β-CD led to a consequent decrease of the amount of water needed to obtain good quality extrudates, as assessed in a series of preliminary trials. The presence of a water-soluble component, such as β-CD (water solubility ~ 1.8% w/v), clearly influenced the efficiency of the wetting process (8). A positive linear relationship between the amounts of fluid added and β-CD present in the formulation was found: the relevant plot is shown in Fig. 1.

The granulations obtained from formulas reported in

Table 1

Preparation[a] Codes and Relevant Formulation Parameters

Code	MCC Parts by Weight	β-CD Parts by Weight	Water (kg)	Water/MCC Ratio
MB1.0	1	0	3.60	1.20
MB2.1	2	1	2.64	1.32
MB1.2	1	2	1.62	1.62
MB1.5	1	5	1.22	2.45
MB1.8	1	8	1.15	3.47
MB2.1bis	2	1	2.24	1.12

[a]The processed amount for all MCC/β-CD mixtures was 3 kg on a dry weight basis

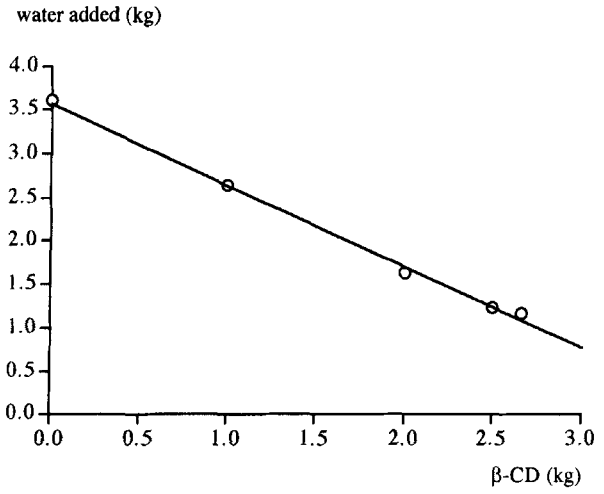

Figure 1. Relationship between the amount of water and β-CD present in the formulation.

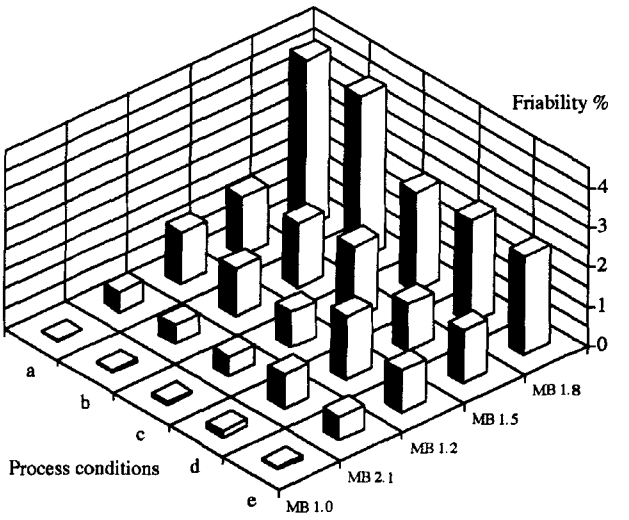

Figure 2. Friability of pellets as a function of formula composition and process conditions.

Table 1 were then processed for extrusion and spheronization.

Feeding and agitation speed (extrusion), plate rotational speed, and residence time (spheronization) were used as the processing variables to provide more information on the effect of extrusion and spheronization conditions on the final pellet quality (see Table 2).

For all formulations and operating conditions adopted, the process was successful and yielded pellets of spherical shape estimated on the basis of visual inspection. Friability and size distribution parameters were determined in order to assess the quality of the finished products: Fig. 2 shows percent friability as a function of both composition and processing conditions.

The presence of β-CD led to pellets with a significant increase of friability which, except for MB1.8 preparations, was rather constant and averaged below 2%. These results can be considered satisfactory in view of possible subsequent handling of the pellets. With respect to the dimension of pellets, a narrow size distribution in most cases was obtained.

Figure 3 shows the weight percent of the size fractions within the range (0.71–1.4 mm) generally accepted for classifying pellets of good quality versus different compositions and operating conditions (9).

Table 2

Processing Conditions

	Extrusion		Spheronization	
Code	Feeding Speed (rpm)	Agitator Speed (rpm)	Plate Rotation Speed (rpm)	Time (min)
a	35	25	580	3
b	35	25	580	6
c	35	25	800	3
d	75	50	580	6
e	170	100	580	6

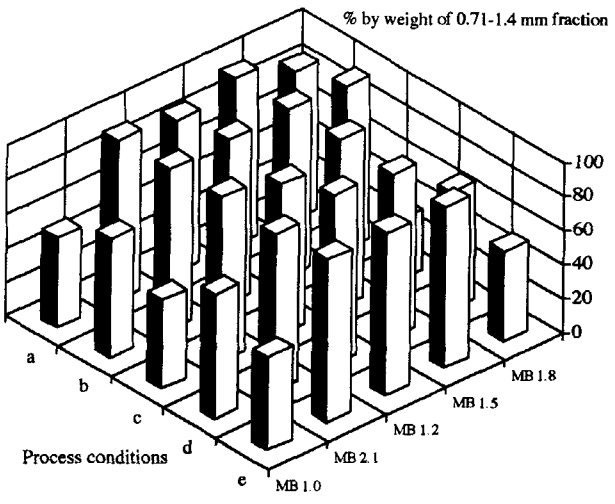

Figure 3. Weight percent of the 0.71–1.4 mm size fraction as a function of pellet formulation and process conditions.

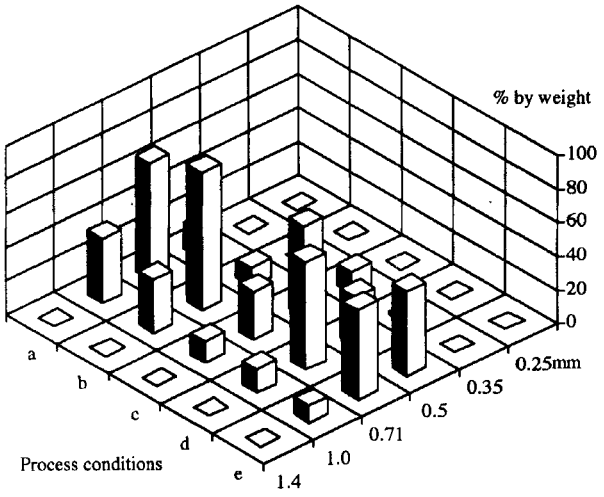

Figure 4. MB1.8 composition: particle size distribution.

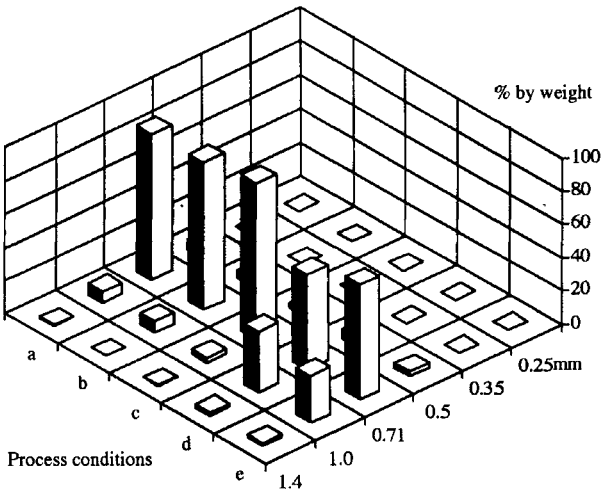

Figure 5. MB2.1 composition: particle size distribution.

In particular, this granulometric fraction for pellets prepared from formulations MB2.1, MB1.2, and MB1.5 (β-CD contents from 33.3 to 83.3%) showed values of weight percent above 90, thus indicating a substantial homogeneity irrespective of both extrusion and spheronization conditions. A greater variability was found for pellets with 88.9% of β-CD (MB1.8), which can be reasonably ascribed to the lower plasticity and mechanical resistance of the extrudate. Particle size distribution of MB1.8 pellets was generally shifted toward smaller size fractions; this was more evident for MB1.8c pellets spheronized at 800 rpm (Fig. 4).

MB1.0 pellets (from MCC alone) prepared under the same operating conditions exhibit an average particle diameter smaller than that of other preparations. This can be partially referred to as the sponge-like behavior of the MCC extrudates which allows water expulsion from granules during spheronization (10,11). On the other hand, the presence of β-CD, a component more water-soluble than MCC, seems to favor the holding of fluid within the granules, thus resulting in pellets with larger diameter.

The recognized significant influence of fluid amount on the entire process is well documented by the differences in particle size and friability shown by two preparations (MB2.1 and MB2.1 bis, water/MCC ratios 1.32 and 1.12, respectively) obtained after the powder mass was wetted with different quantities of water (Figs. 5, 6, and 7).

Concerning the ability of β-CD alone to form pellets using water as the wetting fluid, the poor quality of extrudates, in terms of plasticity and sticking, invariably led to irregularly shaped pellets and agglomerates with broad size distribution. In this respect, preliminary promising results were obtained by lowering the solubility of β-CD in the wetting fluid through the use of water/ethanol mixtures. This probably improves the plasticity of the wetted mass and thus the feasibility of the overall process.

In conclusion, β-CD can be formulated in pellets by means of the extrusion/spheronization technology using small amounts of MCC, which proved to be important to ensure plasticity of the wetted powder mass. The amount of granulating fluid was confirmed to be a critical factor capable of significantly influencing the feasibility of the

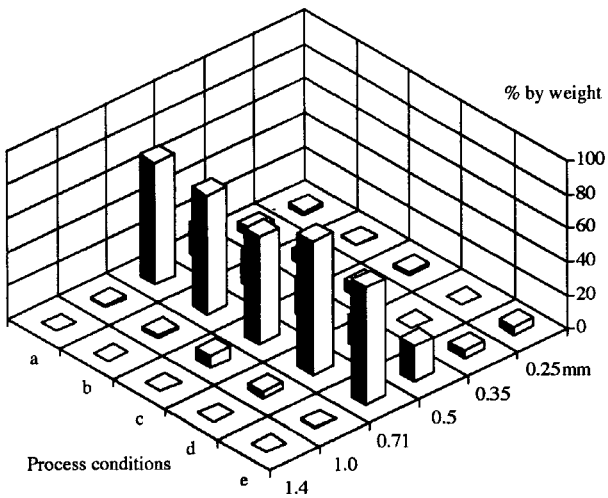

Figure 6. MB2.1bis composition: particle size distribution.

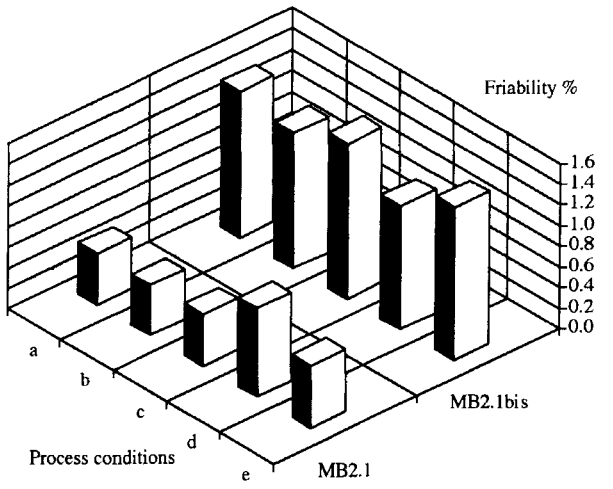

Figure 7. Friability of MB2.1 and MB2.1bis preparations wetted with different quantities of water.

overall process; in particular, it was found to be strictly dependent on the quantity of MCC present in the formulation. The pellets obtained generally showed acceptable friability and good roundness characteristics along with a very narrow particle size distribution.

Pellets with satisfactory physical characteristics could also be prepared using drug/β-CD mixtures with MCC contents below 20% on a dry weight basis, thus confirming the expected and desired possibility of vehicling large amounts of active (12).

Investigations are in progress regarding a comprehensive technological and biopharmaceutical characterization of pellets prepared from MCC/CD/drug and MCC/inclusion compound systems.

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