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EFFECT OF SPHERONIZATION TECHNIQUE ON DRUG RELEASE FROM UNCOATED BEADS

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ABSTRACT

Spheronization techniques are finding increased utility in pharmaceutical research and production. In this investigation emphasis is on the effect of two different spheronization methods (pan versus marumerizer) on drug release from uncoated beads containing acetaminophen and microcrystalline cellulose at a 1:1 ratio. Drug release from the pan beads is much faster than that from the marumerizer beads. The pan beads disintegrate during the dissolution testing, while beads made via the extruder and marumerizer appear to behave as an inert matrix system.

INTRODUCTION

In view of the advantages of spherical particles containing drugs the study of the manufacturing process is of great interest, particularly when developing dosage forms of the controlled release type for oral administration. Several approaches to the development of spheres for subsequent coating with a drug release-controlling membrane were reviewed in the literature.[1-4] Spheronization techniques involved are extrusion/marumerization, pan method, air fluidization, and granulation in specific granulators. The ability to shape a material by its passage through a die has been utilized by the pharmaceutical industry in the extrusion/marumerization process, which has been described in detail by Reynolds.[2] The traditional method of building up cores, which include crystals, nonpariel seeds and granules, for spheronization is by the use of conventional coating pans.[4] Effects of spheronization processing variables and materials on resultant beads have also been investigated.[5-7]

The present work deals with two different spheronization methods; they are (1) the pan method and (2) the extruder/ marumerizer method. The purpose of this work is to compare bead products prepared by two methods. Specifically, bead properties and dissolution behavior will be discussed.

MATERIALS AND METHODS

Materials — Microcrystalline cellulose, USP, (Avicel PH 101), cornstarch, USP, and acetaminophen, USP, (APAP), were supplied by FMC Corporation (Philadelphia, PA). Powdered sucrose (food grade) was used in one formulation and distilled water was utilized as the granulating solvent.

Bead preparation — Beads were prepared from a powdered mixture using two manufacturing methods; they are (1) the pan method and (2) extruder/marumerizer technology. The formulations listed in Table 1 were used in this study. Each formula contains 50% active drug and 50% fillers.

1. Pan method

The pan method is a two step method where 30/40 mesh seeds are prepared and then dried or used directly to further build beads to the desired size by a powder layering technique. (A screening and size selection step for the seeds is required between the two steps.)

The drug and filler(s) were dry blended and then placed into a 6 inch conventional coating pan rotating at 30 rpm. Distilled water was sprayed onto the powder mixture to moisten it as the pan rotated. The size selection of seeds is performed in the

TABLE 1: Formulations of Spheres

Formula No.	1	2
Acetaminophen (g)	500	500
Avicel PH-101 (g)	500	
Sucrose (g)		170
Cornstarch (g)		330
Distilled Water* (ml)	870	220

* for the granulating process

screening step. The 30/40 mesh seeds may be directly used in the bead preparation or dried in an oven at 40°- 45°C for 20 hours. The same technique as in the seed preparation was performed to produce the beads. The seeds in the pan were wetted by spraying distilled water. A part of the powder mixture was dusted onto the seeds. After the powder covered the moistened seed surface uniformly, the operation was repeated continuously until the seeds were built up to spheres of the desired size.

2. Extruder/marumerizer method

The extruder/marumerizer method is a three step process of wet granulation, extrusion and spheronization to produce the beads. (No size screening is usually performed between the three steps.)

The ingredients in the formula were dry blended in a planetary mixer (Hobart) for 5 minutes and were granulated by

adding distilled water continuously over 25 minutes. The wet mass was passed through the extruder operating at 50 rpm and equipped with a 1.5 mm screen. The extrudate was spheronized in the marumerizer at a 1000 rpm plate rotational speed and a 1 minute residence time.

The resulting spheres from both methods were dried in a hot air oven at 40°C - 45°C for 20 hours.

Test methods — Bead size and size distribution were determined using conventional sieve analysis.[8] The sphere density was calculated based on the average sphere weight and the mean diameter of 100 spheres. Friability testing was performed with the Erweka Friabilator on a 10 gram bead sample with 200 glass spheres (4 mm diameter).[9] Dissolution studies were performed on 14/16 mesh uncoated beads using the USP/NF dissolution apparatus 1 with a 50 rpm basket rotational speed. Distilled water was used as the dissolution medium (900 ml). The concentration of drug released in the medium was determined using UV spectroscopy at 249 nm.

RESULTS AND DISCUSSION

Bead Preparation

Beads or spheres were successfully prepared from the microcrystalline cellulose formula (formula 1) by both

manufacturing methods. To produce solid spheres using the extrusion/marumerization technique, the extrudate must break into short segments and the short cylinders must be plastic enough to be rounded into a spherical shape. It was found that materials which break into short cylinders but do not have sufficient plastic properties do not yield a spherical product.[1,8,10,11]

The starch/sucrose formula (formula 2) was included in this study as a traditional pan formula. Although spheres were successfully produced in the pan with this formula, the spheronizer method was not successful; a loose, friable extrudate was generated which could not be spheronized in the marumerizer. One possibility for this observation is that the materials lack the inherent cohesive and plastic properties to form a desired extrudate mass for marumerization; these results support the results described by Miyake et al.[11] In the pan mathod, the spheres are built up without strong friction between beads when the pan was rotated. Therefore, the binding force of components in formula 2 is sufficient to overcome the friction and collision force between spheres in the pan. Cornstarch and sugar could not be extruded and spheronized because of their low elasticity.[11] Therefore, the results and discussion below refer only to the microcrystalline cellulose formula, since it was successful in both techniques.

Bead Size Distribution

The effect of the different spheronization techniques on the bead size distribution for formula 1 is shown in the histogram in Figure 1. The results indicate that the pan method may give spheres with a more narrow size distribution than the marumerizer spheres. The steps to accomplish this, however, are more involved. In the pan method, the bead size uniformity completely relies on the processes which include the nucleation (seed formation) and sphere growth (bead preparation) relating to the seed size uniformity, application rates of the powder and the volume of water in the process. In the second step of the pan method, the bead preparation, extremely uniform seeds were used in this study. Past experience indicates that a one step process in the pan method without sieving seeds would yield a very wide size distribution of beads. The two step process is traditional. Therefore, the size distribution of pan beads partially depends on the seed uniformity.

Drug Release

The results of dissolution testing for acetaminophen beads of formula 1 are shown in Figure 2; the results show that the dissolution of APAP from the uncoated beads made in the pan is faster than the dissolution of the drug from the uncoated beads made in the marumerizer. For the pan beads, more than 80% APAP dissolved in 30 minutes, which is equal to the amount of APAP dissolved from the marumerizer beads in 2 hours.

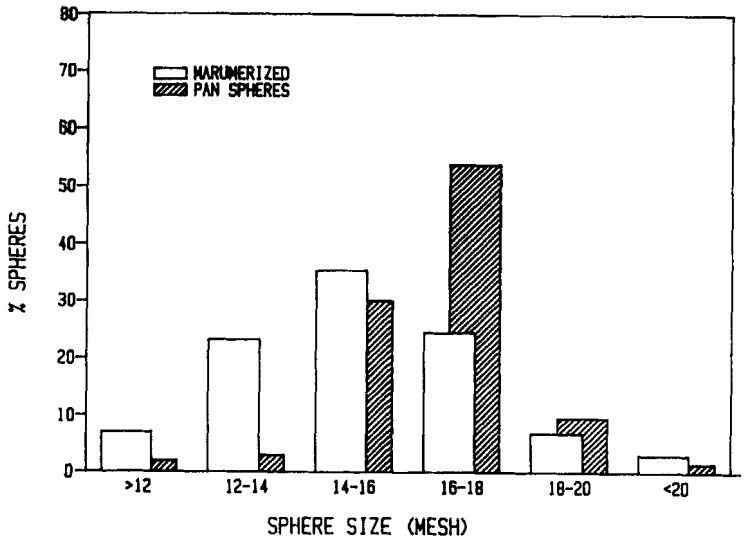

FIGURE 1

Effect of spheronization technique on bead size distribution.

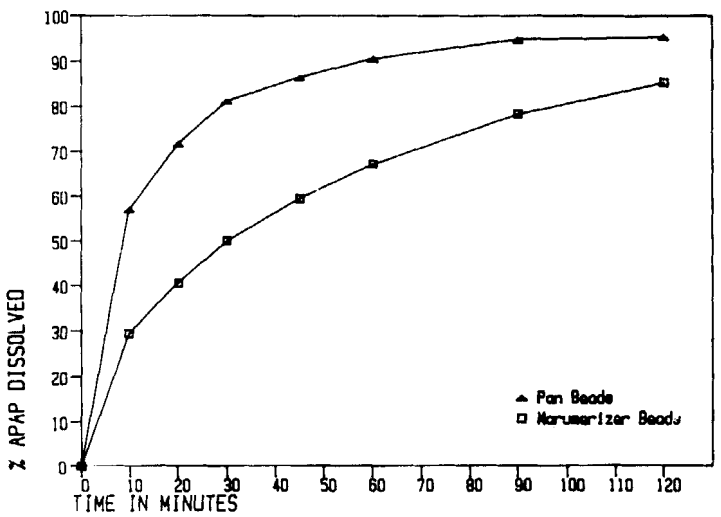

FIGURE 2

Dissolution profiles for acetaminophen uncoated beads.

One obvious explanation is the fact that the pan beads disintegrate, while the marumerizer beads remain intact in the dissolution test. The surface area which is exposed to the dissolution medium is a reasonably important factor affecting the dissolution rate; and the larger the surface area, the faster the drug release. The pan beads disintegrate into small particles during the dissolution testing, resulting in larger surface area, hence increasing the dissolution rate.

Figure 3 shows that the dissolution profile of uncoated beads made in the marumerizer has the typical characteristics of a straight line for the percentage of APAP released versus the square root of time. Therefore, the drug release from uncoated beads made in the marumerizer can be mathematically expressed by means of the following model:[12,7]

$$Q = \sqrt{DC_s(\varepsilon/\tau)(2A - \varepsilon C_s)t} = kt^{1/2}$$

where Q is the cumulative amount of the drug released per unit surface area in time t; D is the diffusion coefficient of the drug in the dissolution medium; C_s is the solubility of the drug in the medium; A is the drug concentration in the beads or drug loading; ε is the porosity; τ is the tortuosity of the pore or capillary system and k is the dissolution rate constant based on the square root relationship.

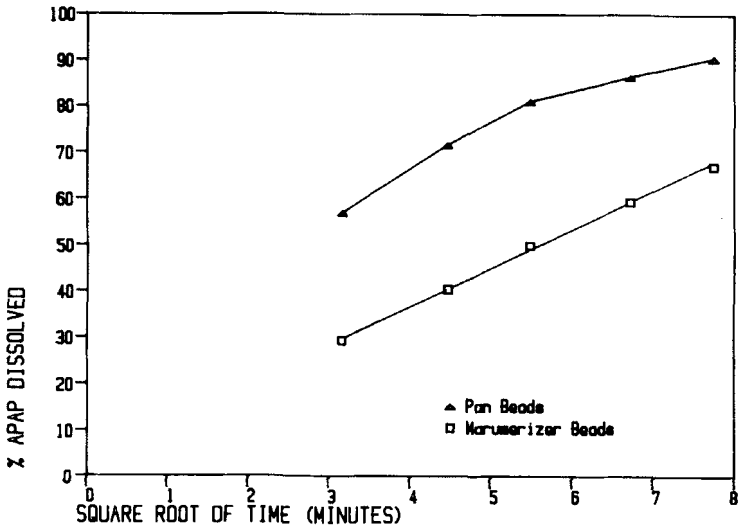

FIGURE 3

Dissolution data for acetaminophen uncoated beads plotted as percent released *versus* the square root of time (minutes)$^{1/2}$.

This equation represents drug release from an inert porous matrix. In this case the drug was dispersed in the water insoluble inert matrix material (Avicel PH 101). The porosity, ε, may represent the channels through which the drug is released. The pores in the matrix are formed from two sources. One of them is the void volume due to air existing in the matrix before the dissolution testing. The other is created during the dissolution testing by leaching of the drug and soluble excipients into the penetrating medium and forming a depletion area. Therefore, the pore controlled release mechanism can be used to describe the dissolution behavior of the drug from uncoated spheres made in the marumerizer, as has been discussed by previous workers.[7]

TABLE 2. Physical Properties of Beads

Sample (14/16 mesh)	Bed Density (g/ml)	Sphere Density (g/ml)	Friability (%)
Marumerizer beads	0.70	1.66	9.0
Pan beads	0.52	1.12	13.0

Acetaminophen release from pan beads does not fit this square root model because the disintegrating beads are not classified as an inert matrix system. The disintegration is dependent on the consolidation process of the beads which can be influenced by the spheronization techniques. Extrusion and marumerization are processes in which energy is applied to the substrate to generate strongly bound beads. The results of density testing, shown in Table 2, indicate that the beads made in the marumerizer have a lower pore volume than the beads made in the pan. In general, the cohesive force of the powder in beads is related to the number of contact points, which is related to the porosity, and the intersurface distance between individual particles or molecules in the sphere. The results of the sphere density calculations possibly imply that the number of contact points in the consolidation of pan spheres is smaller than that of marumerizer spheres and the interface distance of powder in pan spheres is longer than that in marumerizer spheres. In the pan method, the binding of powder in the beads probably results from the chemical nature of the materials in the formula and

water acting as a liquid bridge. In the marumerizer method, the binding force is not only from these, but also possibly from the added mechanical force during the process. Therefore, the binding force in the marumerizer spheres is too strong to be broken during the dissolution testing.

This conclusion is further supported by additional experimentation in terms of friability testing, as shown in Table 2, which indicates that the sphere strength is different for beads prepared in the pan and in the marumerizer.

A bead is an aggregate of component particles that is held together by the presence of bonds of finite strength. In general, the dried beads have strong bonds resulting from fusion or recrystallization of particles and curing of the adhesive or binder.[13] One of common methods of studying bead strength is the friability measurement. The lower the friability, the stronger the binding force, which is affected by the base material, the amount of binder and the spheronizing equipment used. The experimental results of friability measurements support the observation that the pan method results in weaker bonds in beads than does the marumerizer method; hence disintegration takes place during dissolution testing.

SUMMARY AND CONCLUSIONS

Beads containing microcrystalline cellulose were successfully produced by both the pan and the extruder/marumerizer methods, whereas the more traditional starch/sucrose beads could not be processed by the marumerizer.

The bead physical properties and the dissolution behavior are influenced by the spheronization methods, the pan method and the marumerizer method, although the same formulation was used in this study. The two types of spheres behave differently in disintegration, resulting from the different degree of interparticle cohesion and adhesion probably due to the energy applied in the spheronization processes. The marumerizer beads were intact during the dissolution testing. The drug release from marumerizer beads was described using the pore controlled release mechanism and the square root of time relationship..

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