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Porous cellulose matrices – a novel excipient for the formulation of solid dosage forms

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Summary

A novel pharmaceutical aid prepared from a specially processed cellulose is presented. The material, which consists of highly porous spherical cellulose beads, is regarded as having a considerable field of application in dry pharmaceutical formulation. Primarily, the material may act as a multiple unit carrier and release controlling system as well as an additive for the compression of multiple unit preparations in the form of compressed and disintegrating tablets. This paper describes formulation possibilities, and presents some of the essential characteristics and preliminary results on some applications.

Introduction

Cellulose is a well-known and widely used pharmaceutical excipient, whether as a tabletting aid giving good bonding and disintegration properties or for the manufacture of pellets. Particularly this latter application has been of growing interest as it has been demonstrated that better product performance is often obtainable from, e.g., controlled-release pellet-based systems than from single unit controlled-release tablet systems. Typically, one can expect advantages in overall absorption, attenuation of local irritant effects, and better reproducibility (Bogentoft et al.,1978). There are numerous processes available for the production of multiple-unit (MU) cores, however, it is generally highly desirable to obtain particles of uniform shape with a well defined and narrow size range, and thus uniform surface area distribution, in order to obtain good handling properties, good dose uniformity and accurate control of the release properties (Ragnarsson and Johansson, 1988). This usually leads to complex processes which include, usually at a late stage, a sizing operation which will lead to waste and possible environmental hazards. One possible alternative is to produce and size the inert pellets before the considerably value-adding incorporation of the drug substance, thus the whole process of traditional granulation and sizing can be neatly by-passed. The material presented in this paper consists of highly porous cellulose beads of normal pellet size that can be used to incorporate

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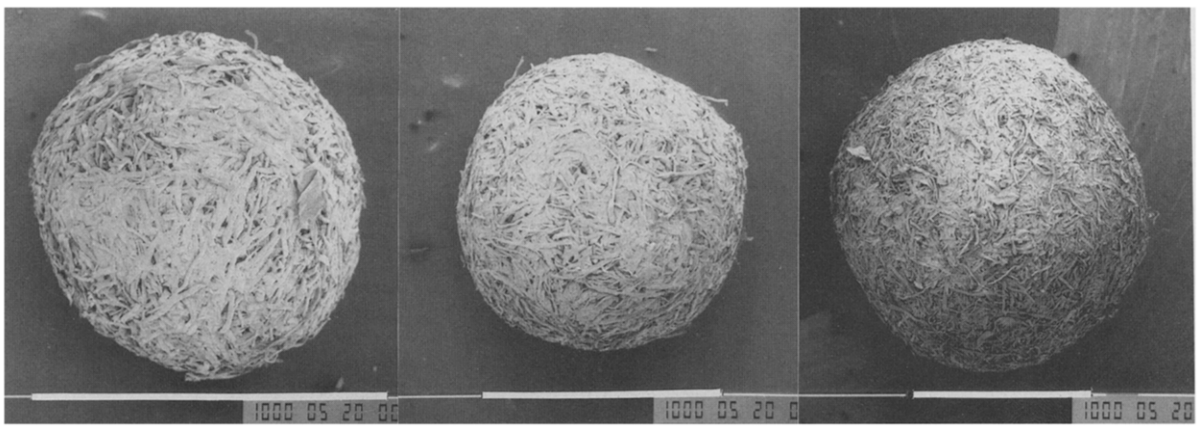

Fig. 1. Special cellulose beads, diameters ≈ 0.95, 1.25, and 1.75 mm. Scale bars represent 1 mm in each case.

drugs into well-defined units. The concept of using highly porous cellulose beads for this and other pharmaceutical applications is the subject of a recent patent application (WO91/18590, 1991) and is at present undergoing further development at Kabi Pharmacia AB.

Materials and Methods

Description of the material

The material consists of spherical or near-spherical beads of a specially processed cellulose (special cellulose, SC). The SC is mixed with water, extruded through 1.6–2.5 mm openings, partially dried in an air vortex and dried in a conventional hot-air oven to constant weight. Other methods of preparation have been successfully tried, however, this discussion will focus on material prepared as outlined above. Typical porous beads of this material are shown in Fig. 1.

Beads have also been manufactured from commercial microcrystalline cellulose (MC) by the same method, however, their characteristics are quite different as would be expected considering the differences in raw material (Fig. 2).

Fundamental characteristics of the special cellulose beads

Structurally, the beads are essentially balls of tangled more or less close-fitting fibres, the surface being a reasonably regular fibrous case whilst the inside appears to be slightly less close-packed in scanning electron micrographs of beads that have been cut open. They are in fact very difficult to cut open as they tend to deform under pressure rather than fragment, but they can be prised apart (Fig. 3). The beads have a high total porosity, voidage, or as we prefer to call it, accessible free space (A.F.S., defined as the proportion of the total volume of the bead not occupied by cellulose but accessible to gases or liquids) that can to some extent be varied by using different raw materials (Patent application WO91/18590, 1991) and to some extent by the manufacturing parameters. Under radial compression the beads exhibit essentially plastic properties.

Fig. 2. Microcrystalline cellulose beads, ≈ 1.6 mm diameter. Scale bar represents 1 mm.

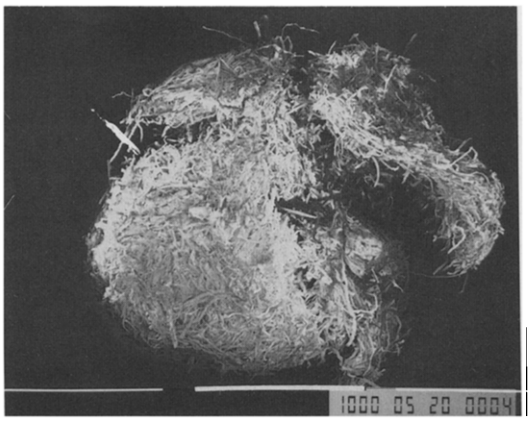

Fig. 3. Special cellulose bead, 1.1 mm diameter, prised apart. Scale bar represents 1 mm.

Preparation of the material

Starting materials

The SC was as defined in the specifications, batch S-20. MC (Avicel PH – 101 FMC Corp., DE, U.S.A.) was used as a reference. Water was the granulation fluid employed in all cases.

SC specifications

The SC specifications were as follows: chemical purity to USP-NF XVII (Powdered Cellulose) standards; tap bulk volume within the range 160–500 ml/10 g (as defined in patent application WO91/18590, 1991); degree of polymerization values within the range 2500–3500 (SCAN-CM 15:88); fibre length with a mean value by weight within the range 0.3–0.8 mm and maximum of 2 mm (SCAN-C18, 10 000 rev. tapwater).

Methods

For our experiments the cellulose and water were mixed in a planetary mixer for a predetermined period and screened through an oscillating granulator with mesh openings of 1.6–2.5 mm. Due to the fibrous nature of SC a considerably greater amount of water is required than with MC in order to obtain a workable mass.

The screened material is then fed into a vortex equipment which forces the particles of wet mass to circulate and collide at relatively high speed losing water and acquiring shape and size distribution. The water content at the end of this process is about 60% of the original amount of water incorporated. The beads are collected from the equipment and spread out on trays for the final drying in a hot-air oven in conditions that produce a constant final weight. The beads are then sized using a set of close-series sieves (DIN 4188) in order to study the size distribution and to obtain fractions within narrow size ranges for future studies.

Results

Particle size distribution

The size distributions obtained are particularly interesting, as under high-yield conditions the population appeared to follow an almost normal distribution with SC and an asymmetric distribution with MC (Fig. 4). For SC the cumulative weight percentages were converted to probits allowing us to express the results from particle size and size distribution in process reproducibility trials simply as a median and standard deviation values.

The medians as obtained for six batches yield an average value of 679 μm with a standard deviation of 27.6 μm corresponding to $\pm 4\%$ relative S.D. This indicates that under these conditions the method is reproducible in terms of particle size. The correlation coefficient of 0.9838 of the common probit linear regression is also highly significant ($P \geqq 0.999$, $n = 54$).

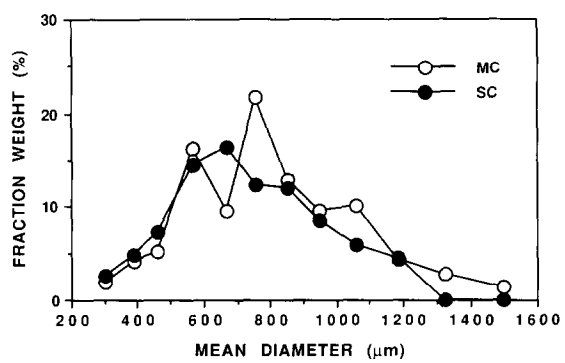

Fig. 4. Particle size distribution: comparison between beads from microcrystalline cellulose (MC, mean of three batches) and special cellulose (SC, mean of six batches).

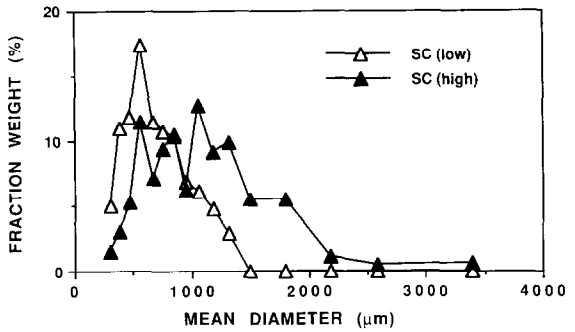

Fig. 5. Particle size distribution: comparison between special cellulose (SC) beads prepared with 140% (high) and 68% (low) of the normal water content; means of three batches in each case.

Alterations to the basic parameters of production make it possible to obtain larger populations of small or large diameters of beads, however, for SC the distributions were no longer normal, but appeared to be two or more normal, or pseudo-normal distributions set very closely together, the probit lines acquiring distinct 'breaks'. Thus, it appears that to obtain a relatively narrow particle size distribution it becomes necessary to keep within rather small process variations. The same comparisons that were made for the 'standard' situation could not be easily made here, and so the conclusion was that it is possible to alter the size distribution by altering the manufacturing parameters but exactly how this was brought about has not been entirely elucidated (Fig. 5).

Porosity / accessible free space

In order to determine the total A.F.S. air pycnometry measurements (Air pycnometer model 930, Beckman Instruments Inc., CA, U.S.A.) were carried out. The geometrical volume of the sample was calculated by estimating the individual volume of each bead, assuming it to be a sphere, and determining the total number of beads in the sample by weight. Comparing this volume with the volume read on the instrument the A.F.S. was obtained. The A.F.S. values for SC were in the range 65–75%, for MC the results being between 24 and 28%. These relatively low values of A.F.S. for MC beads associated with other properties that will be described later led us to conclude that this material is unsuitable for the production of high porosity beads by this process. A fuller comparison was not carried out as it was thought that it would serve no useful purpose. Other measurements included the use of an automatic helium pycnometer (AccuPyc 1330, Micromeritics Instrument Corp., GA, U.S.A.) which yielded results comparable with air pycnometry.

Scanning electron microscopy

Scanning electron micrographs were obtained in a Jeol JSM T-200 (Jeol- Technics Co. Ltd, Tokyo, Japan) after gold-sputtering (Jeol JFC-1100). SC beads were first mounted on conductive paint, whilst MC beads were mounted on commercial epoxy resin, heat-cured and cut by abrasion as these beads are very difficult to cut with a scalpel blade. The film employed was Polaroid type 55 (Polaroid Corp., MA, U.S.A.). Beads prepared from SC have already been presented (Fig. 1) and should be compared with the photographs of the exterior of a large MC bead (Fig. 2) and a large MC bead cut open (Fig. 6). It should be noted that the surface of the intact bead is relatively smooth and compact, certainly very different from the beads in Fig. 1. The interior of the bead revealed in Fig. 6 shows one apparently single, large irregular cavity, possibly the result of contraction on drying. Access to this cavity would be difficult and it would not provide

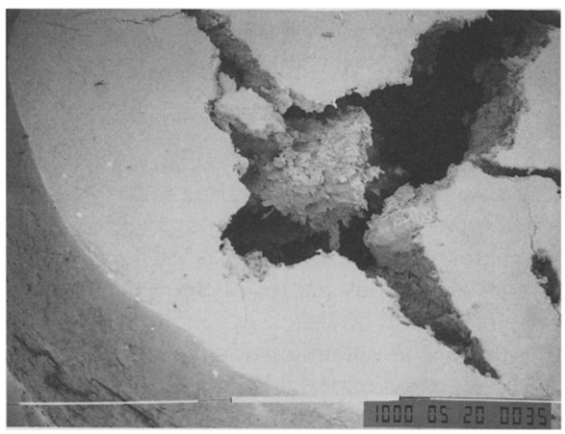

Fig. 6. Microcrystalline cellulose bead, ≈ 4 mm diameter, cut open. Scale bar represents 1 mm.

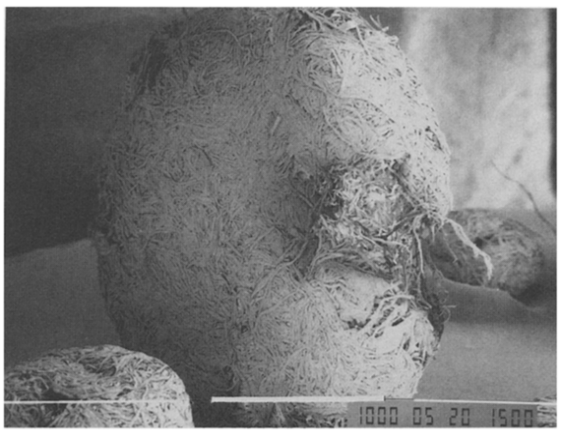

Fig. 7. Special cellulose bead, ≈1.8 mm diameter, after compression to 50 N. Scale bar represents 1 mm.

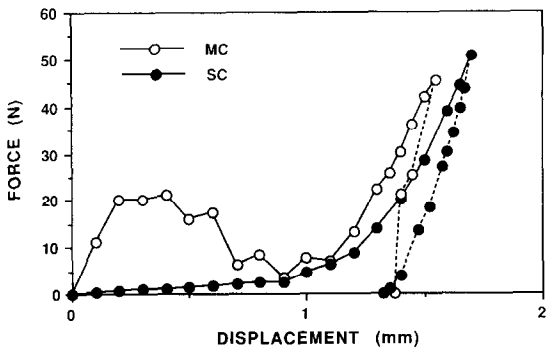

Fig. 8. Force-displacement curves for a microcrystalline cellulose (MC) bead, diameter 2.15 mm and for a special cellulose (SC) bead, diameter 1.87 mm. Displacements given as mm from point of contact. Dashed lines represent the recovery phases.

the large surface area required for drug deposition homogeneously distributed. Such cavities are less evident in smaller beads, long internal cracks being more usual.

Behaviour under compression

The different structure is well illustrated by the compression characteristics of the beads: those from SC deform readily under pressure offering relatively little resistance up to a point at which resistance increases and the deformation becomes almost totally plastic with very little residual elasticity. At the highest pressures the beads end up disc-shaped with peripheral ruptures, but still reasonably whole (Fig. 7).

When beads from MC are subjected to radial compression they start to fragment at compression forces of about 20 N, yielding an irregular force-displacement curve as the fragmentation continues. Finally, there is a sharp increase in resistance as the sample ends up like a little cake of powder and flakes. Two typical force-displacement curves are given in Fig. 8. The force gauge employed was an AccuForce Cadet, 0–50 N, from the Mansfield & Green Division, FL, U.S.A. The deflection of the sensor element was not corrected for as it is linear with respect to the force applied and at 50 N is only about 0.18 mm.

Other experimental data

Water sorption and bulk density determinations were also carried out, and these data provide perhaps the clearest illustration of the variation of physical properties with different types of SC. These experiments are described in the patent application (WO91/18590, 1991) and were performed on beads manufactured from small experimental batches of cellulose with varying levels of hydrolysis (Fig. 9).

Potential applications

Some results relating to the possible applications of highly porous cellulose beads have al-

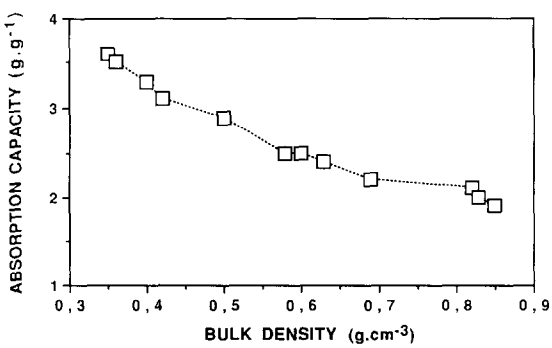

Fig. 9. Water sorption capacity as a function of bulk density for several batches of beads prepared from different special celluloses.

ready been presented at the annual meeting of the Swedish Pharmaceutical Association in 1991.

These relate to the use of the beads as a pharmaceutical aid in the tabletting of sensitive coated granules (Björk et al., 1991), where the authors demonstrate that this material can be employed in this fashion with encouraging results. Another presentation dealt with the loading of the beads with terodiline and observing the release with and without the inclusion of a retarding agent, *n*-hexadecane (Björk and Nyqvist, 1991)). The authors demonstrate that it is possible to load these beads on a small scale and to investigate the release pattern, more as a research tool than as a objective in itself, however, the principles governing both situations are the same and so this reference essentially illustrates one of the possible application situations.

Conclusions

This paper describes a novel pharmaceutical aid consisting of beads of pure pharmaceutical grade cellulose having a very high porosity, typically about 75%. The method of manufacture here described is reproducible and parameter manipulation will, within limits, yield predictable results. The properties of the finished beads are very much dependent on the starting material. Microcrystalline cellulose, which is commonly used in pellet formulations, is not suitable for this particular purpose as the beads thus produced have a considerably lower porosity, as well as unfavourable mechanical properties. These highly porous cellulose beads may be employed either in their unloaded state as compression accessories, as has been exemplified by Björk et al. (1991), or as drug carriers. In this latter application, the important aspect to consider is the concept of a carrier that is produced and sized in its empty state and loaded to a given degree with drug substance. This loading may even be performed as part of the drug manufacturing process, cutting down on overall processing costs and leading to environmentally safer manipulation. One of the major advantages would be the possibility to incorporate semi-solids or materials that do not readily form crystals, opening up new possibilities in solid formulation. The loaded beads may be employed as a multiple unit system in their own right if the drug release profile thus obtained is favourable, or alternatively it would be possible to incorporate release modifying agents. Another possibility would be the coating of these beads with a suitable film thus achieving the required release profile.

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