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Composites of bead cellulose and hydrophilic solubilizers[1]

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Abstract

Composites of regenerated bead cellulose (BC) and hydrophilic solubilizers were prepared by coprecipitation from common solvents. Infrared-drying was used for evaporation of organic solvents and freeze-drying for water. Infrared (IR)-dried BC coprecipitates with polyethylene glycols 400 or 6000 (PEG 400 and 6000) or Poloxamer were spherical, granulous and flowable up to a weight ratio of BC to solubilizer of 1 : 4. The solubilizers were completely incorporated into the pores of the BC and precipitated on the bead surface. Freeze-dried coprecipitates with solid solubilizers were received as loose voluminous powders of beads and leaf-shaped particles, those with PEG 400 as uniform spherical granules. Coprecipitates with PEG 6000 or Poloxamer showed strong crystallinity in contrast to the amorphous products with PEG 400. The melting points of the solubilizers in the coprecipitates were shifted to lower temperatures compared with the pure substances.

The coprecipitates have the advantage over similar PEG or Poloxamer coprecipitates with drugs due to their good flow properties and favourable handling, and should be used as drug carriers for controlled release.

Keywords: Bead cellulose; Polyethylene glycols; Poloxamer; Polysorbate 80; Coprecipitation; Flow characteristics

1. Introduction

Bead cellulose (BC) (Štamberg, 1988) is a regenerated spherical porous cellulose, manufactured by a special dispersing method. It is used as a carrier for drugs by adsorptive, ionic or covalent bonds (Wolf and Horsch, 1991).

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In water-swollen undried raw BC (Wolf et al., 1991), solvent exchange to methyl alcohol, acetone or cyclohexane (Štamberg et al., 1979) is possible without essential loss of porosity, reduction of large specific surface area or diminishing of high solvent adsorbing capacity. During evaporation of the solvents, especially of water, the beads shrink and sinter, lose their spherical shape and show decreased porosity. These effects can be partially prevented by incorporating excipients into the pores of the beads so that porosity and flowability are preserved. Another reason for addition of selected excipients is the manufacturing of cellulose carriers with specific properties.

The preparation of loaded BC products can be achieved in two ways:

1. The excipients can be added to the viscose solution previous to the dispersing and bead forming process. Examples of macromolecular excipients are polypropylene glycols and block polymers (Berek et al., 1988) and mixtures of polyethylene glycol 4000 (Okuma et al., 1988a) or sodium polyacrylate (Okuma et al., 1988b) and liquid ammonia. Requirements for the yield of spherical, unsintered and flowable products are good miscibility of the excipient with the viscose solution and the possibility of a suitable forming and drying process.

2. The beads are formed from viscose solution and regenerated to pure cellulose. The excipients are added to the undried swollen beads. In this way, cellulose beads were stabilized with polyethylene methacrylate polymers (Štamberg et al., 1985) or polyethylene glycol 600 and sodium carboxymethyl cellulose (Rote Liste, 1994). The excipient molecules should be of moderate molecular mass so that they can penetrate into the pores of the beads, they must possess sufficient wettability for the hydrophilic surface of cellulose beads and they must be stable during exposition to higher temperatures in the drying process. Under these circumstances, solutions of the excipients in a volatile solvent removed during drying should be successful for bead loading.

In the present study, BC was loaded with liquid and solid hydrophilic solubilizers (PEG 400, PEG 6000, Poloxamer and mixtures with polysorbate 80) by a method of solvent deposition or so-called co-evaporation (Sucker et al., 1991) to prepare composites which feature the favourable properties of BC and overcome simultaneously the lack of flowable PEG/drug coprecipitates (Lo and Law, 1996). Several volatile solvents and two different drying methods were investigated with regard to the potential use of the BC-solubilizer coprecipitates as carriers for poorly soluble drugs. The physicochemical properties of coprecipitates with different weight ratios of BC to solubilizer were investigated and compared with pure BC treated under analogous conditions. The coprecipitates were characterized by bulk volume, tap volume, Carr index, angle of slope, flow rate, sedimentation volume and mean bead diameter. Crystalline state was investigated by polarization microscopy and X-ray powder diffractometry (XPD), thermal properties by differential scanning calorimetry (DSC) and thermal gravimetry. The thermal properties of the pure substances PEG 400, PEG 6000 and Poloxamer, and of the co-melts with polysorbate 80 were measured, for comparison with the BC coprecipitates.

2. Materials and methods

2.1. Materials

Raw BC (Sächsische Kunstseiden GmbH, D-Pirna) was available as water-swollen, undried BC (Wolf et al., 1991). The excipients used were: polyethylene glycol 400 and 6000 (Lipoxol® 400 and 6000, Hüls AG, D-Marl); Poloxamer (Pluronic® PE 6800, BASF AG, D-Ludwigshafen), polysorbate 80 (Tween 80®, Fluca AG, CH-Buchs); methyl alcohol p.a. and acetone p.a. (Laborchemie, D-Apolda) and purified water.

2.2. Bulk volume, tap volume, powder compressibility, flowrate and angle of slope

Flow properties were examined according to the methods of the German Pharmacopoeia (Deutsches Arzneibuch, 1996).

2.3. Sedimentation volume

A defined product amount is left for swelling and sedimentation in water for 3 days. During this time the solubilizers are completely dissolved so that the volume corresponds to the sedimented pure cellulose beads.

2.4. Microscopy and mean bead diameter

Microscope AMPLIVAL (Carl Zeiss, D-Jena) was equipped with two polarizators, photo projective, tube, basic unit (Carl Zeiss, D-Jena) and camera EXAKTA (Ihagee, D-Dresden). A ground-glass screen was used for estimation of particle size.

2.5. Scanning electron microscopy (SEM)

SEM was measured with a scanning electron microscope Cam Scan CS 24 (Cambridge Scanning Company, GB-Cambridge). The samples were sputtered with silver, the magnification was 150–600 × and the voltage 15 kV.

2.6. X-ray powder diffractometry (XPD)

X-ray powder diffractometer D 5000 (Siemens, D-Berlin) was equipped with a copper anode providing K_α radiation (45 kV, 35 mA) and a reset graphite monochromator. The measuring range of the Bragg angle was 5–50° with steps of 0.05°.

2.7. Differential scanning calorimetry (DSC) and thermogravimetry

From Polymer Laboratories, a DSC-PL and a TG-PL apparatus were used. The first was equipped with a silver furnace. The samples were sealed into closed aluminum pans with an empty pan as reference. The measuring range was −80–+180°C with a heating rate of 10 K min^{-1}. TGA curves were measured from room temperature up to 500°C with the same heating rate under nitrogen atmosphere.

2.8. Manufacturing of BC-solubilizer coprecipitates

In water-swollen, undried washed BC, water was exchanged against acetone and the mixture of PEG 400 or PEG 6000 (and mixed with polysorbate 80) and acetone was added under agitation. Acetone was removed by IR-drying up to constant weight. In the case of Poloxamer, methyl alcohol was used instead of acetone as volatile solvent. Freeze-dried coprecipitates were manufactured by suspending water-swollen BC in the aqueous solution of the solubilizers under agitation and freeze-drying to constant weight (freeze-drying apparatus ALPHA 2-4, Christ GmbH, D-Osterode).

3. Results and discussion

3.1. Macroscopical and flow properties

3.1.1. IR-dried coprecipitates

Preliminary trials showed that it is not possible to prepare spherical flowable products of BC and PEG 6000 or Poloxamer by fusion coprecipitation, i.e. by melting of the solid solubilizers, suspending swollen or dried BC in the melt and removing of excess solubilizer, because solid crystalline cake was obtained. In the same manner, agglomerated and unflowable products were received by suspending swollen BC in PEG 400 and removing the excess liquids.

While IR- as well as freeze-dried BC without excipients consisted of hard, agglomerated and aggregated particles of irregular shape (Wolf and Horsch, 1991), the IR-dried coprecipitates of BC and solubilizers were received as white, fine-grained products with small agglomeration tendency. Up to a weight ratio of solubilizer to BC of 4 : 1, the particles are spherical and flowable. Beads with PEG 400 and its mixtures with polysorbate 80 are soft and slightly adhesive, the products with PEG 6000 and Poloxamer and their mixtures with polysorbate are solid and not adhesive.

With increasing content of solubilizers, the values of mean bead diameter ascend continuously

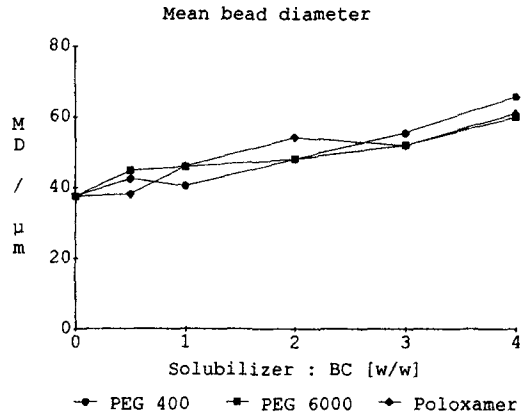

Fig. 1. Mean bead diameter of IR-dried BC coprecipitates with increasing solubilizer content.

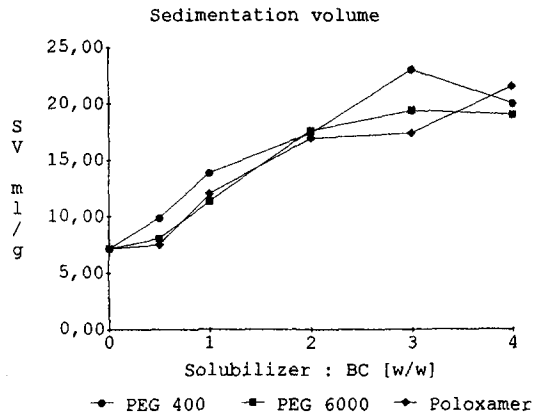

Fig. 3. Sedimentation volume of IR-dried BC coprecipitates with increasing solubilizer content.

(Fig. 1). The bulk volume values (Fig. 2) of BC/PEG 400 coprecipitates are somewhat higher than those of BC/solid solubilizer coprecipitates, owing to weak adhesiveness and probable cavities in the bulk. Coprecipitates with high solubilizer content exhibit high sedimentation volumes (Fig. 3). High values of sedimentation volume and bead diameter result not only from high solubilizer content, but also from reduced shrinking of the beads during drying compared with pure BC and low-loaded coprecipitates, owing to embedded solubilizers in the pores.

The values of angle of slope, Carr index and flow rate (Table 1) vary due to the different influence of excipient density, surface adhesiveness and solidity of the beads. Very good flow properties occur for coprecipitates with Poloxamer and the mixture Poloxamer/polysorbate.

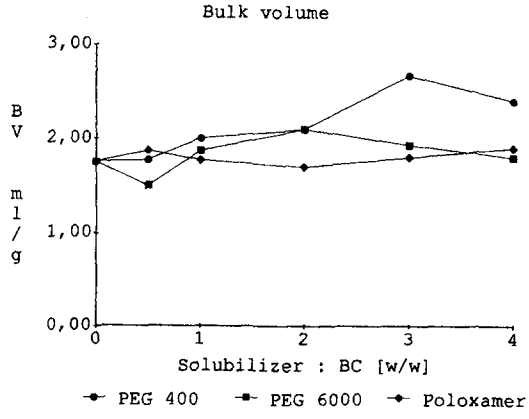

Fig. 2. Bulk volume of IR-dried BC coprecipitates with increasing solubilizer content.

3.1.2. *Freeze-dried coprecipitates*

Freeze-dried coprecipitates (Table 2) appear as fluffy, flowable and only slightly agglomerated powders of low density and high volume in relation to the more granulous IR-dried coprecipitates. Bulk volumes, tap volumes, sedimentation volumes and mean bead diameters of the coprecipitates are significantly higher than those of pure freeze-dried BC, owing to solubilizer content.

3.2. *Morphology*

Under the light microscope, swollen undried BC (Fig. 4), as well as BC/PEG 400 coprecipitates with a transparent PEG 400 layer, show surface structures referring to numerous pores of different size. Independent of loading degree and drying method, the latter consist of spheres with small cavities or holes at the surface (Fig. 5). IR-dried coprecipitates with PEG 6000 or Poloxamer are also spherical but covered by non-transparent solubilizer layers. Separate irregular particles consist of excess solubilizer. This is also valid for freeze-dried coprecipitates with high solid solubilizer content.

Table 1
Flow properties of IR-dried BC-coprecipitates with high solubilizer content

Preparation	Angle of slope (°)	Carr index (%)	Flow time [100 g] (s)
Pure BC	32.2	9.5	13.4
BC : PEG 400 = 1 : 4	40.5	11.4	—
BC : PEG 400 : Polysorbate = 1 : 2 : 2	34.5	6.5	15.9
BC : PEG 6000 = 1 : 4	28.4	10.4	15.5
BC : Poloxamer = 1 : 4	30.3	7.1	10.2
BC : Poloxamer : Polysorbate = 1 : 2 : 2	29.6	6.2	11.5

Table 2
Flow and physical properties of freeze-dried BC-coprecipitates with high solubilizer content

Preparation	Angle of slope (°)	Bulk volume (ml/g)	Tap volume (ml/g)	Carr index (%)	Sedimentation volume (ml/g)	Mean diameter (μm)	Flow time [100 g] (s)
Pure BC	18.3	1.61	1.34	16.80	3.50	43.38	22.8
BC : PEG 400 = 1 : 4	37.5	1.77	1.65	6.80	16.00	60.52	15.6
BC : PEG 400 : Polysorbate = 1 : 2 : 2	34.0	2.17	1.94	10.60	17.25	61.36	12.3
BC : PEG 6000 = 1 : 4	38.5	4.60	3.83	16.70	15.50	76.20	—
BC : Poloxamer = 1 : 4	37.3	2.96	2.46	16.90	14.50	57.84	—
BC : Poloxamer : Polysorbate = 1 : 2 : 2	37.8	2.48	2.18	12.10	17.25	83.40	20.7

3.3. Crystallinity

Under the polarization microscope, swollen undried BC appears completely amorphous. Dried pure BC shows, independently of drying method, a weak crystallinity which originates in crystalline areas of ordered cellulose molecules (Schleicher and Kunze, 1988; Blaschek, 1990; Suzuki et al., 1994; Matsumoto et al., 1994). Coprecipitates with PEG 400 are amorphous and, with PEG 6000 or Poloxamer, strongly crystalline (Fig. 6), respectively.

Fig. 4. Polarization microphotograph (POL) of pure undried BC suspended in water, distance of network lines 40 μm.

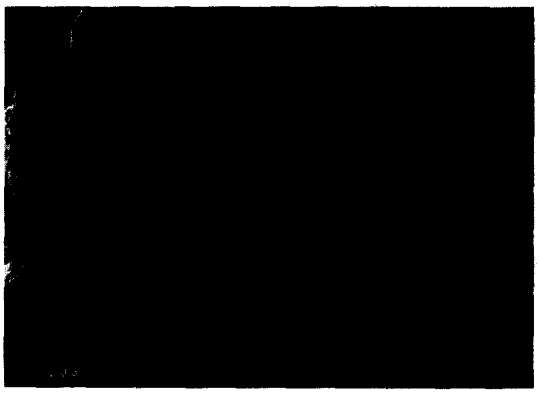

Fig. 5. Microphotograph (SEM) of coprecipitate BC : PEG 400 = 1 : 4, IR-dried from acetone.

Fig. 6. Microphotograph (POL) of coprecipitate BC : PEG 6000 = 1 : 4, IR-dried from acetone.

The origin of crystalline effects was distinguished by X-ray diffractometry. IR-dried pure BC shows distinct crystalline signals at Bragg angles of 19.8° and 21.9°. Comparison with freeze-dried BC verifies that the drying method has no influence on the position of cellulose crystal signals but intensity is lower with freeze-drying.

Increasing content of PEG 400 and polysorbate 80 does not shift the position of the cellulose crystal signals, but their intensity decreases. There are no other crystal effects visible than those of cellulose. Powder diffractograms of BC/Poloxamer coprecipitates (Fig. 7, plots 2–5) show, besides the signals of crystalline cellulose, two distinct Poloxamer signals at 19.0° and 23.2° (plot 1). According to this tendency, the intensity of Poloxamer signals increases with content while cellulose signals decrease. In the course of coprecipitation a part of the amorphous swollen cellulose forms crystalline domains. Polysorbate 80 has no detectable influence on the signals of cellulose, PEG 6000 or Poloxamer.

3.4. Thermal properties

DSC patterns of pure BC (Fig. 8, plot 1) exhibit a very broad endotherm between 100 and 150°C after IR- as well as freeze-drying, owing to residual unbound water loss in analogy to other kinds of cellulose like microcrystalline cellulose (Sonaglio et al., 1995). The melting peaks of BC/PEG 400 coprecipitates are shifted to distinct lower temperatures (plots 3 and 4) in comparison with pure PEG 400 (plot 2). An exotherm in the range −50– −45°C arises according to pre-crystallization of PEG 400 before melting. With BC/PEG 6000 or BC/Poloxamer coprecipitates, the melting points are also shifted to lower temperatures in relation to the pure solubilizers and co-melts with polysorbate. Nevertheless the coprecipitates are solid at room temperature, even

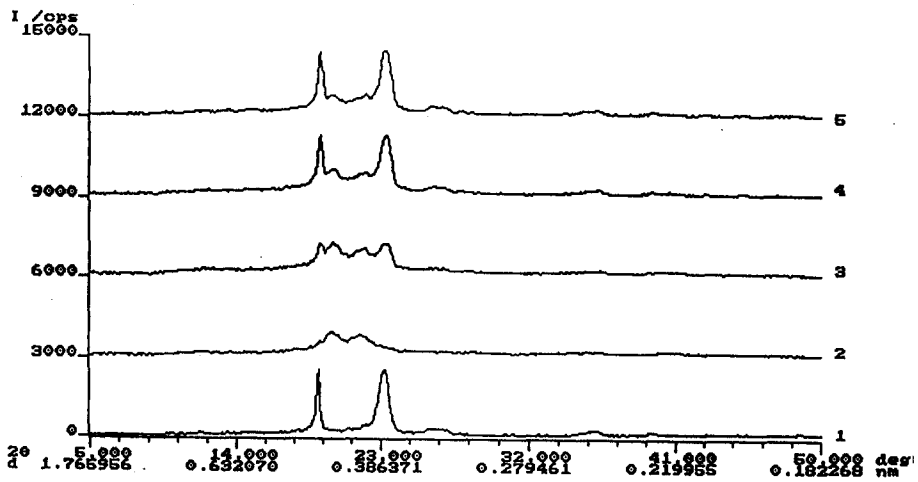

Fig. 7. XPD of pure Poloxamer (1) and IR-dried coprecipitates BC : Poloxamer = 1 : 0.5 (2), BC : Poloxamer = 1 : 1 (3), BC : Poloxamer : polysorbate = 1 : 2 : 0.5 (4), BC : Poloxamer = 1 : 3 (5).

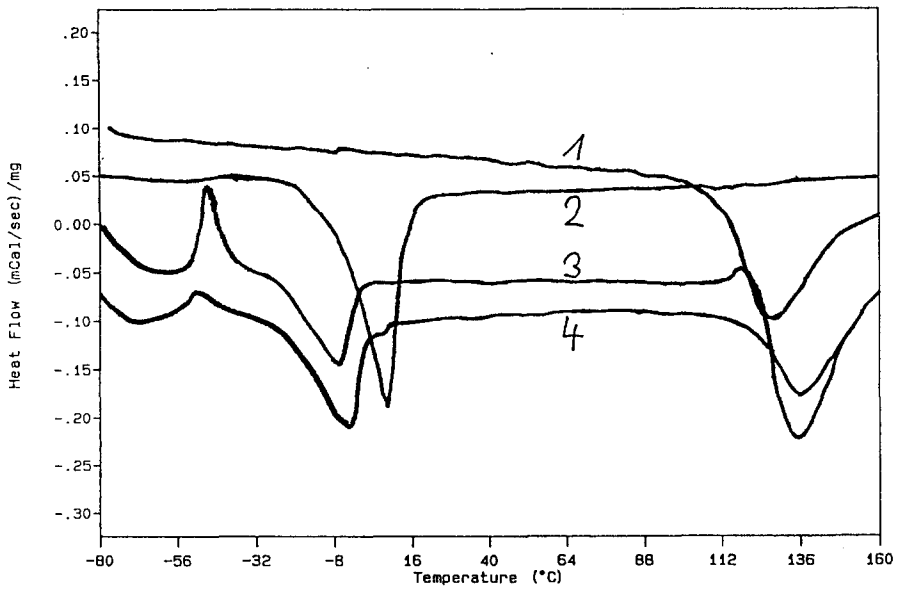

Fig. 8. DSC of freeze-dried BC (1), pure PEG 400 (2) and coprecipitates BC : PEG 400 = 1 : 4, IR-dried (3), BC : PEG 400 = 1 : 4, freeze-dried (4).

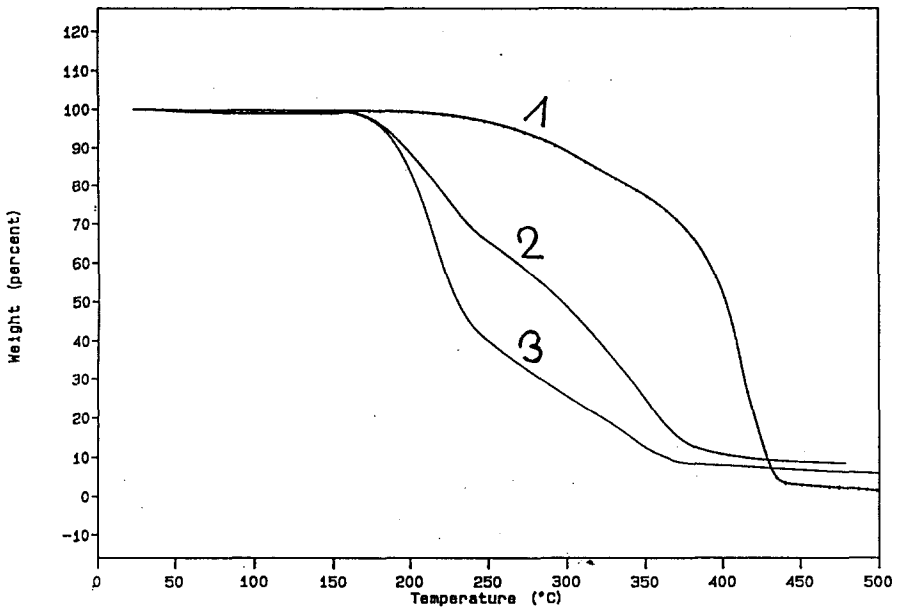

Fig. 9. TGA plots of PEG 6000 (1) and coprecipitates BC : PEG 6000 = 1 : 4, IR-dried (2), BC : PEG 6000 = 1 : 4, freeze-dried (3).

in 1 : 1 co-melts with polysorbate (Morris et al., 1992).

TGA plots of IR-dried as well as of freeze-dried BC shows water loss of about 8% between 50 and 100°C and decomposition at 350°C. Evaporation and decomposition of PEG 400 is shifted to dis-

tinct lower temperatures with a coprecipitate as compared with the pure substance. The same tendency is obvious for a coprecipitate with PEG 400 and polysorbate 80 in relation to the pure substances. Evaporation and decomposition of PEG 6000 in coprecipitates begins at 180°C (Fig. 9, plots 2 and 3) independent of drying regime; the pure substance shows an inflexion point at 400°C (plot 1).

4. Conclusions

Bead cellulose was loaded with solid and liquid hydrophilic solubilizers forming mechanical stable, spherical and flowable products up to a weight ratio of BC to solubilizer of 1 : 4. For this reason, BC is a suitable solid carrier for PEG/drug coprecipitates for direct use as granules, powders or filling material for hard gelatine capsules.

IR-dried products are destined for incorporation of slightly water-soluble drugs in an amorphous or solid dispersed state to improve solubility, dissolution rate and, finally, drug release. Coprecipitates freeze-dried from water are suitable as carrier for temperature-sensitive drugs. Depending on the final preparation and the addition of other excipients, controlled drug release should be achieved. This will be the topic of further papers.

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