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Bead cellulose products with film formers and solubilizers for controlled drug release

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Abstract

Flowable bead cellulose (BC) coprecipitates were prepared for controlled release, consisting of spherical BC as carrier, the film former hydroxypropyl methylcellulose (HPMC), the hydrophilic solubilizers polyethylene glycol 6000 (PEG 6000) or Poloxamer, the plasticizers dimethyl phthalate and dioctyl phthalate and the model drugs prednisolone and griseofulvin. Coprecipitates of BC/HPMC/drug or BC/HPMC/plasticizer/drug without solubilizer showed fast and complete release of prednisolone due to the dispersed crystalline state and sufficient solubility of the drug and retarded release of griseofulvin due to poor solubility. The drugs crystallized during coprecipitation and were partially incorporated as well as HPMC and plasticizer into the pores of the beads and precipitated on the bead surface. IR-dried coprecipitates of BC, high solubilizer content and low HPMC content (or absence of HPMC) showed high release rates due to the amorphous or solid dispersed state of the drugs in the coprecipitates, therefore fast dissolution due to the solubilizing effect of PEG 6000 or Poloxamer. On the other hand, with increasing HPMC content and decreasing solubilizer content the release rates were diminished due to increasing crystallinity of the drugs and therefore slow dissolution, reduced solubilization, swelling of HPMC and hindered drug diffusion. The IR-dried coprecipitates with solubilizers were flowable and consisted of spherical particles. Freeze-dried coprecipitates of similar composition consisted of beads and separate HPMC and solubilizer particles. The advantages of the BC coprecipitates are the variation of the release rates in a wide range by changing the ratio of solubilizer, HPMC and drug and their favourable physical and flow properties. © 1997 Elsevier Science B.V.

Keywords: Bead cellulose; Hydroxypropyl methylcellulose; Polyethylene glycol 6000; Poloxamer; Coprecipitates; Controlled release; Flow properties

1. Introduction

High porous bead cellulose (BC) or BC derivatives have been used as carriers for drugs with the

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aim of increasing or retarding the release, improvement of stability of several drugs or to bring the drug into a suitable technological and flowable formulation (Lenfeld and Štamberg, 1987; Štamberg, 1988; Okuma et al., 1988a,b; Wolf and Horsch, 1991). The release of ionic drugs adsorbed onto ionic BC derivatives was fast and complete after a short time (Wolf and Finke, 1992a), that of a covalent bonded drug to oxidized BC (Wolf and Finke, 1992b) was slow and incomplete. BC coprecipitates with hydrophilic solubilizers (polyethylene glycols, Poloxamer and polysorbate 80) showed high release rates of slightly soluble drugs (Wolf et al., 1996a). The products were spherical, flowable, not or only slightly cohesive (Wolf et al., 1996b) and therefore suitable for direct use or for further manufacturing. With these products and excipients no retardation of drug release but a distinct accelerated release was achieved.

Several authors have reported coprecipitates of slightly soluble drugs with different release kinetics. Nifedipine was released with increased rate from coprecipitates with polyvinylpyrrolidone (Sugimoto et al., 1981) and from lactose beads covered with a film of nifedipine and polyvinylpyrrolidone or HPMC (Sugimoto et al., 1982). On the other hand prolonged release was achieved with coprecipitates of ibuprofen (Khan et al., 1995) or ketoprofen and Eudragit® S 100 (Khan et al., 1996). The release rate of hydrochlorothiazide from coprecipitates with polyvinylpyrrolidone and microcrystalline cellulose depended on the weight ratio of the components and could be accelerated as well as retarded (Simonelli et al., 1995). In most cases the coprecipitates were obtained as solid products which required further treatment, for example milling and sieving.

The aim of this paper was the preparation of spherical coprecipitates of BC, the solubilizers PEG 6000 and Poloxamer, the film former HPMC and the model drugs prednisolone and griseofulvin with variable drug release rates and with good flow properties. The solubilizers were used to increase the release rates, HPMC was used to decrease the release rates and the solubilizers and HPMC were combined to vary the releases rate between these extremes.

2. Materials and methods

2.1. Materials

Water swollen regenerated bead cellulose (porous spheres; particle size distribution: 10–50 μm: 6%; 50–100 μm: 70%; >100 μm: 24%) (Sächsische Kunstseiden GmbH, D-Pirna) is described elsewhere (Wolf et al., 1991), hydroxypropyl methylcellulose (Methocel® 90 HG, 4000 CP, crystalline substance, Fluka AG, CH-Buchs), polyethylene glycol 6000 (Lipoxol® 6000, Hüls AG, D-Marl), Poloxamer (Pluronic® PE 6800, BASF AG, D-Ludwigshafen), dimethyl phthalate (Aromatic, D-Leipzig) and dioctyl phthalate (Chemische Werke Miltitz, D-Leipzig) were used to prepare the coprecipitates. Griseofulvin and prednisolone (Jenapharm, D-Jena) were both obtained in micronized form, acetone and methyl alcohol were received in quality of German Pharmacopoeia (Deutsches Arzneibuch, 1996).

2.2. Preparation of coprecipitates of bead cellulose, hydroxypropyl methylcellulose, plasticizers and drugs

All products were prepared according to a dispersion- coevaporation process previously described (Wolf et al., 1996b). For example, to prepare coprecipitate BC:HPMC:dimethyl phthalate:prednisolone = 1:0.1:0.1:0.1, HPMC (0.16 g), prednisolone (0.16 g) and dimethyl phthalate (0.16 g) were dispersed and dissolved in 15 g of a 1:1 mixture (w/w) of methyl alcohol:methylene chloride one after the other. The inner bulk water of 20.0 g swollen BC was exchanged for methyl alcohol. Excess methyl alcohol was removed by weak vacuum of a water jet pump. The methyl alcohol containing BC was suspended in the solution of the components and vigorously mixed for 10 min. The solvent mixture was evaporated under agitation by infrared radiation (red IR lamp, 250 watt, distance 30 cm) to constant weight. Yield: 2.04 g = 98% dry coprecipitate.

2.3. Preparation of coprecipitates of bead cellulose, hydroxypropyl methylcellulose, hydrophilic solubilizers and drugs

2.3.1. One-step coprecipitates

For preparation of coprecipitate BC:PEG 6000:HPMC: prednisolone = 1:4:1:0.1, PEG 6000 (6.4 g), HPMC (1.6 g) and prednisolone (0.16 g) were dissolved and dispersed in 40 g of a 1:1 mixture (w/w) of methyl alcohol:methylene chloride one after the other. Methyl alcohol containing BC (20.0 g) was dispersed in the solution. The evaporation procedure was completed as above (Section 2.2). Yield: 9.50 g = 97% dry coprecipitate.

2.3.2. Two-step coprecipitates

For the preparation of the IR-dried coprecipitate BC:PEG 6000:HPMC:prednisolone = 1:4:1:0.1, in the first step, a coprecipitate of BC, PEG 6000 and prednisolone was prepared. Thus, PEG 6000 (6.4 g) and prednisolone (0.16 g) were dissolved and dispersed in 15 g methyl alcohol one after the other. BC (20.0 g) was handled as above and dispersed in the solution. Coprecipitation was obtained as above by IR drying. The yield of the first step was 8.0 g (98% dry coprecipitate). In the case of griseofulvin acetone was used instead of methyl alcohol as solvent.

In the second step the product (8.0 g) was placed into an evaporating dish and the solution of HPMC (1.6 g) in the 1:1 mixture of 40 g methyl alcohol:methylene chloride was added in 4 portions to the product step by step under continuous agitation and evaporation of the solvent by IR radiation. Yield: 9.6 g = 98% dry coprecipitate.

Freeze-drying in the second step: The coprecipitate from the first step (8.0 g) was dispersed in an aqueous HPMC solution (1.6 g in 50 ml water). The suspension was immediately frozen to −20°C and finally freeze-dried (Freeze-drying apparatus ALPHA 2–4, Christ GmbH, D-Osterode) at −20°C to constant weight. Yield: 9.6 g = 98% dry coprecipitate.

2.4. Physical and analytical methods

Investigation of bulk volume, tap volume, CARR index, sedimentation volume, angle of repose, flow time, mean bead diameter and microscopic brightfield investigation, polarization microscopy (POL) and microphotography, scanning electron microscopy (SEM), X-ray powder diffractometry (XPD), differential scanning calorimetry (DSC) and thermogravimetry (TGA) are described in detail elsewhere (Wolf et al., 1996a,b).

2.5. Dissolution study

Release experiments were performed in a manner to the earlier investigations (Wolf and Finke, 1992a) in 1000 ml purified water at 37 ± 0.3°C with paddle of stirring rate 50 rpm and 6 replicates, by use of a dissolution tester DT6 (Erweka, D-Heusenstamm) according to German Pharmacopoeia (Deutsches Arzneibuch, 1996). After 10, 20, 30, 60, 180 and 360 min 5.0 ml liquid were withdrawn for analysis and refilled by 5.0 ml water. The sample amounts of the coprecipitates for release experiments were adjusted to defined drug doses (10, 20, 40 or 80 mg drug).

Griseofulvin and prednisolone were analysed by HPLC by use of 2 pumps, spectrophotometer LAMBDA 1000, injection syringe (BISCHOFF Analysentechnik und -geräte GmbH, D-Leonberg) and a reversed phase column Kromasil® C_{18}, 5 μm, 250 × 4.6 mm. The eluents were methyl alcohol:water = 70:30 (v/v) and 80:20 and the wavelengths 291 and 240 nm for griseofulvin and prednisolone, respectively. The eluents were degassed prior to application by an ultrasonic device and weak vacuum of a water jet pump for 5 min. The flow rate of the eluents was 1 ml/min. For calibration, methanolic solutions of the drugs (50.0 mg/l) and dilutions were investigated. The released amounts were calculated from the drug peak areas by use of the programme Hyperdata Chromsoft (BISCHOFF Analysentechnik und -geräte GmbH, D-Leonberg).

3. Results and discussion

3.1. Macroscopical properties and morphology

3.1.1. Preparations without solubilizers

The limiting factor in the preparation procedure of the coprecipitates was the poor solubility

Table 1
Proportions and properties of one-step preparations without solubilizers; tolerance limit (TL) for $n = 500$ and $2P = 0.05$; standard deviation (S.D.) for $n = 3$

	Prescription (weight ratio)	Mean bead diameter (μm)	Bulk density (g/ml)	Sedimentation volume (ml/g)
		$\pm$TL; $n = 500$	$\pm$S.D.; $n = 3$	$\pm$S.D.; $n = 3$
	BC:HPMC			
F1	BC:HPMC = 1:0.05	39.36 $\pm$ 1.48	0.50 $\pm$ 0.03	5.50 $\pm$ 0.32
F2	BC:HPMC = 1:0.1	41.20 $\pm$ 1.52	0.45 $\pm$ 0.04	5.20 $\pm$ 0.28
F3	BC:HPMC = 1:0.2	47.24 $\pm$ 1.53	0.45 $\pm$ 0.02	7.40 $\pm$ 0.27
	BC:HPMC:griseofulvin			
F4	HPMC:griseofulvin = 1:0.1:0.05	43.25 $\pm$ 1.56	0.50 $\pm$ 0.01	4.80 $\pm$ 0.26
F5	HPMC:griseofulvin = 1:0.2:0.1	48.80 $\pm$ 1.58	0.56 $\pm$ 0.04	6.32 $\pm$ 0.30
	BC:HPMC:plasticizer:prednisolone			
F6	BC:HPMC:prednisolone = 1:0.05:0.05	44.12 $\pm$ 1.63	0.63 $\pm$ 0.03	5.06 $\pm$ 0.29
F7	BC:HPMC:dimethyl phthalate:prednisolone = 1:0.1:0.1:0.1	44.40 $\pm$ 1.63	0.56 $\pm$ 0.02	5.30 $\pm$ 0.11
F8	BC:HPMC:dioctyl phthalate:prednisolone = 1:0.05:0.05:0.05	46.78 $\pm$ 1.61	0.50 $\pm$ 0.01	6.44 $\pm$ 0.33
F9	BC:HPMC:dioctyl phthalate:prednisolone = 1:0.1:0.1:0.1	47.24 $\pm$ 1.70	0.45 $\pm$ 0.03	7.41 $\pm$ 0.34

of HPMC and the sol-gel transition at higher concentration. Products of BC, HPMC and drugs coprecipitated from aqueous solutions or from acetone showed strong agglomeration, forming a fused mass and the porosity of BC was lost. The best results with reference to good flow properties of the final products were obtained with a mixture of methyl alcohol:methylene chloride = 1:1 (w/w). Up to a concentration of 4% the HPMC solution was a sol. Swollen BC was dispersed in this sol forming a flowable homogenous suspension used for the coprecipitating process.

Coprecipitates with a weight ratio of BC:HPMC:drug of 1:0.1:0.1 (Table 1) were flowable, only slightly agglomerated and consisted of spherical, porous particles (Fig. 1). Higher film former content yields agglomerated and strong sintered products. It was not possible to increase the HPMC content by addition of plasticizers such as dimethyl phthalate and dioctyl phthalate, otherwise the fine-grained properties were lost. The values of particle size and sedimentation volume of the coprecipitates were only slightly higher than the values of pure BC (Wolf et al., 1996b) because of low content of HPMC, drug and plasticizer. There was no distinct dependence of the bulk density on different plasticizer and HPMC content in the coprecipitates.

3.1.2. Preparations with solubilizers

At one-step preparations (Table 2) the mixture of HPMC, solubilizer and drug was precipitated into the pores and also on the surface of the

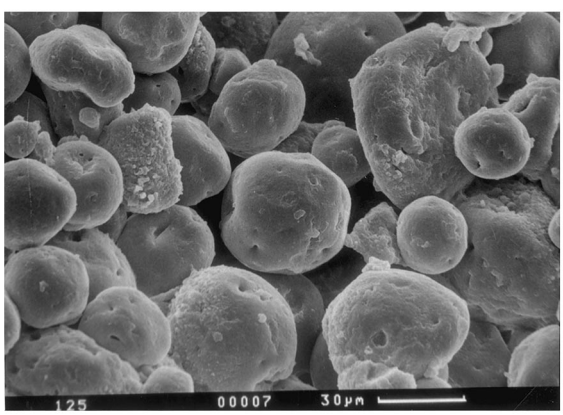

Fig. 1. Scanning electron microphotograph of coprecipitate F4.

Table 2
Proportions and properties of one-step preparations with solubilizers

	Prescription (weight ratio)	Mean bead diameter (μm)	Bulk density (g/ml)	Sedimentation volume (ml/g)
		$\pm$TL; $n = 500$	$\pm$S.D.; $n = 3$	$\pm$S.D.; $n = 3$
	BC:PEG 6000:HPMC			
F10	1:0.5:0.5	66.12 ± 1.51	0.50 ± 0.03	10.90 ± 0.81
F11	1:0.5:1	69.56 ± 1.69	0.53 ± 0.02	10.20 ± 0.72
F12	1:4:0.5	77.32 ± 2.31	0.50 ± 0.03	16.10 ± 1.10
	BC:PEG 6000:HPMC:prednisolone			
F13	1:0.5:1:0.1	69.56 ± 1.96	0.53 ± 0.01	10.20 ± 0.75
F14	1:1:0.5:0.1	64.16 ± 1.74	0.45 ± 0.02	11.96 ± 0.45
F15	1:4:1:0.1	78.00 ± 2.19	0.50 ± 0.02	18.90 ± 1.21
F16	1:2:1:0.1 (freeze-drying)	69.40 ± 2.06	0.12 ± 0.01	18.40 ± 0.94

beads. Comparing the products of the first and the second step of two-step coprecipitates (Table 3) HPMC was precipitated on the surface of the beads or occurred as separate fibrous and rod-shaped particles.

The one-step and two-step coprecipitates were flowable with only a few agglomerates, especially at high solubilizer content. The high content of solubilizer enabled the addition of a much larger amount of film former and drug in comparison to the coprecipitates without solubilizers. Bead diameter and sedimentation volume increased with solubilizer content (Table 2, Table 3). The magnitude of the bulk density did not significantly depend on the excipient content.

At high solubilizer and increasing HPMC content (Table 3; F18–F21), no change of bead size, bulk density and sedimentation volume was observed. The dominating influence of the solubilizer excess on the physical properties became obvious compared to the values of the preparation without HPMC (F17). The flow parameters of coprecipitate F21 (angle of repose $31.1 \pm 0.45°$; flow time 19.0 ± 1.4 s; tap density 0.69 ± 0.04 g/ml and CARR index $11.4 \pm 0.7\%$) differed only slightly from the values of coprecipitate BC:PEG 6000 = 1:4 (Wolf et al., 1996b).

Coprecipitates with distinct different properties were derived from freeze-drying in the second step. The products were obtained as very light and voluminous powders with loose agglomerates, low density and good flow characteristics.

3.2. Crystallinity

Coprecipitates without solubilizers appeared poorly crystalline under the polarization microscope with portions of crystalline HPMC and drug precipitated into the pores and separate HPMC particles in the form of rods and fibres. Bead agglomerates were connected by crystallized HPMC. In spite of the low concentration, the film former was not completely incorporated into the beads during the coprecipitation process. Because of poor solubility, a portion precipitated at the beginning of the solvent evaporation, forming separate, more or less crystalline particles. For comparison films of aqueous and methyl alcohol/methylene chloride HPMC solutions were prepared. The films obtained were transparent and amorphous when cast from a solution with undisturbed drying, but HPMC crystallized when the solutions were stirred during solvent evaporation.

IR-dried coprecipitates of BC, HPMC, higher amounts of PEG 6000 or Poloxamer and drugs consisted of strong crystalline beads. The crystallinity derived first of all from the solubilizers. Freeze-dried coprecipitates consisted of crystalline beads and amorphous or weak crystalline fan-shaped particles of solidified HPMC and solubilizer.

The diffractogram of HPMC showed a weak crystalline signal between Bragg angles of 17–22° (Fig. 2a, plot 2) what was superimposed by BC signals at 20° and 22° at coprecipitate F4 without

Table 3
Proportions and properties of two-step preparations with solubilizers

	Prescription (weight ratio)	Mean bead diameter (μm)	Bulk density (g/ml)	Sedimentation volume (ml/g)
		$\pm$TL; $n = 500$	$\pm$S.D.; $n = 3$	$\pm$S.D.; $n = 3$
	BC:PEG 6000:HPMC			
F17	1:4 without HPMC	70.00 ± 1.98	0.56 ± 0.03	19.00 ± 0.94
F18	1:4:0.25	73.48 ± 1.95	0.56 ± 0.02	21.90 ± 0.88
F19	1:4:0.5	81.00 ± 2.04	0.56 ± 0.04	17.30 ± 1.00
F20	1:4:0.75	77.28 ± 1.99	0.53 ± 0.02	22.20 ± 0.93
F21	1:4:1	72.76 ± 2.21	0.50 ± 0.02	18.10 ± 1.03
	BC:PEG 6000:HPMC:prednisolone			
F22	1:4:0.25:0.5	73.48 ± 2.05	0.56 ± 0.03	21.90 ± 1.02
F23	1:4:0.75:0.1	77.28 ± 1.99	0.53 ± 0.01	13.60 ± 0.89
F24	1:4:1:0.1	84.04 ± 2.18	0.45 ± 0.02	24.70 ± 1.33
	BC:PEG 6000:HPMC:griseofulvin			
F25	1:4::0:0.1 without HPMC	76.00 ± 2.16	0.56 ± 0.04	16.32 ± 0.56
F26	1:4:1:0.5:0.1	81.16 ± 1.99	0.50 ± 0.02	20.16 ± 0.66
F27	1:4:1:0.1	74.04 ± 1.98	0.50 ± 0.01	18.30 ± 0.73
	BC:Poloxamer:HPMC:prednisolone			
F28	1:0.5:0.5:0.1 freeze drying	—	0.13 ± 0.01	5.88 ± 0.27
F29	1:1:0.5:0.1 freeze drying	54.88 ± 1.38	0.10 ± 0.005	—
F30	1:3:0.5:0.1 freeze drying	—	0.22 ± 0.006	16.56 ± 0.69

solubilizer (plot 3). Crystalline effects of griseofulvin occurred only weakly at the coprecipitate first of all due to low concentration (4.3% w/w) and less to amorphous griseofulvin. The formation of an amorphous structure did not take place at a weight ratio of HPMC:griseofulvin of 1:1 or 2:1. Diffractograms of BC coprecipitates with prednisolone and HPMC also showed crystallinity of the drug.

The PEG 6000 signals at 19° and 24° superimposed the HPMC signals (diffractogram of coprecipitate F24, consisting of BC, PEG 6000, HPMC and prednisolone, Fig. 2b, plot 3). Prednisolone crystal signals (plot 1) were not visible in the coprecipitate because the drug was dissolved or present as an amorphous dispersion.

3.3. Thermal properties

Broad endotherms in the DSC scans of HPMC (Fig. 3, plot 1) and coprecipitate F8 (plot 3) at 50–150°C derived from evaporation of capillary bonded water in the cellulose gel and water desorption (Ford and Timmins, 1989). The absence of the melting peak of prednisolone at 240°C in the DSC scan of coprecipitate F8 resulted from high dispersion degree of small prednisolone crystals. In the scan of coprecipitate F24 the melting peak of PEG 6000 arose at 60°C and a distinct exothermic shift above 130°C when open aluminum pans were used. This effect was very weak in the case of closed pans. No melting peak of prednisolone was detectable because of amorphous or solid dispersed drug and low concentration corresponding to the diffractogram (Fig. 2). At high solubilizer and HPMC content the coprecipitates were solid at room temperature. Similar results were found for coprecipitates when Poloxamer replaced PEG 6000.

Thermogravimetric investigations (Table 4) showed weight loss of BC and HPMC with intercepts near 350°C resulting from thermal decomposition of cellulose with the higher value for HPMC due to oxidation of hydroxypropyl groups. PEG 6000 was evaporated and decomposed at 425°C. These values also occurred at the coprecipitates. The height of the steps corresponded to the weight part of the components in the coprecipitates.

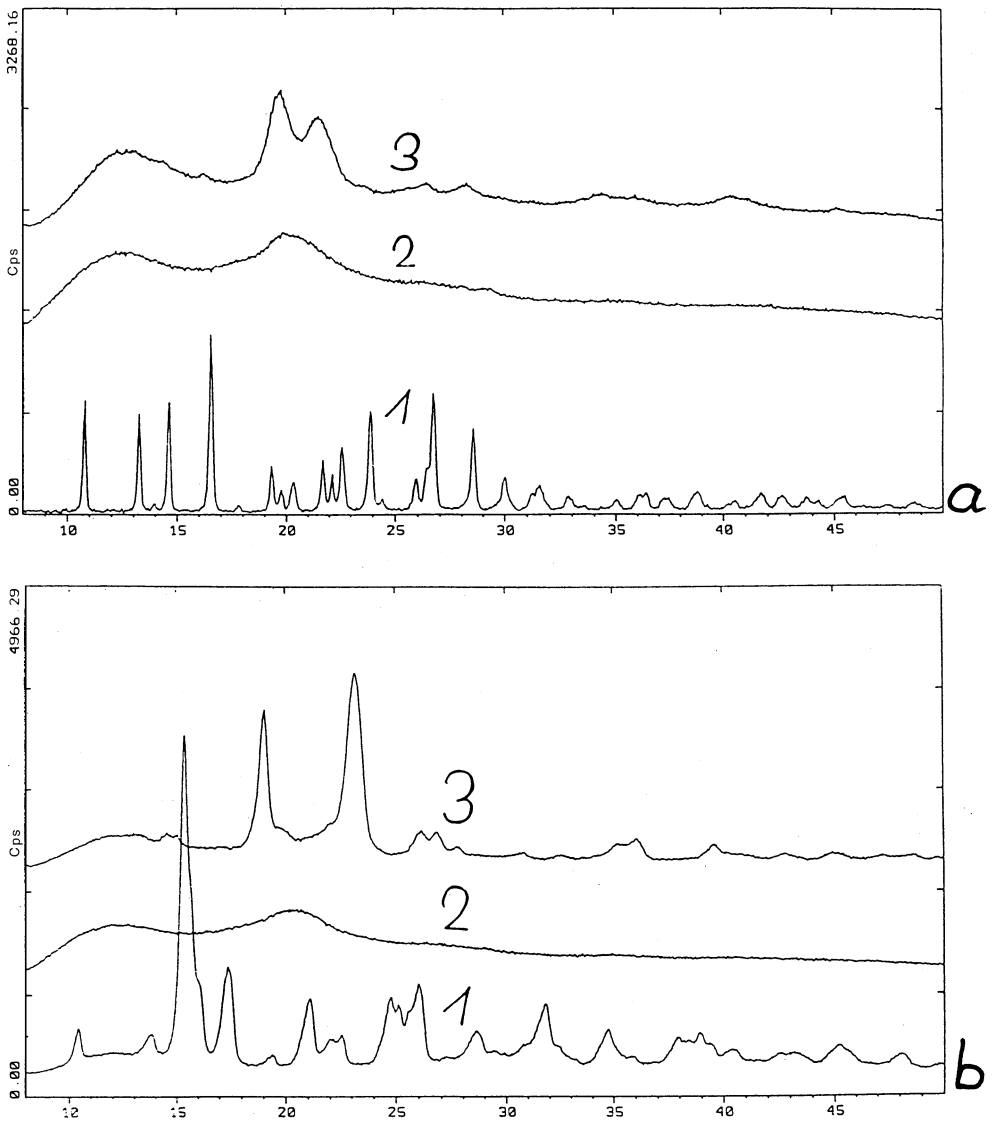

Fig. 2. X-ray powder diffractogram of a) griseofulvin (1); HPMC (2) and coprecipitate F4 (3); b) prednisolone (1); HPMC (2) and coprecipitate F24 (3).

3.4. Drug release

Griseofulvin is nearly insoluble in water (15 mg/l at 37°C) and prednisolone is a slightly soluble drug (1 g/l at 37°C). The investigated quantities (10–80 mg) within the beads were below the saturation concentration in the dissolution medium, so that sink conditions could be assumed.

The release of prednisolone from coprecipitates of BC, HPMC and plasticizers (F6–F9) was complete after 10–20 min. Prednisolone was predominantly crystalline but as a fine dispersion and, therefore, dissolved and released at a high rate. Film forming and envelopment of the beads by HPMC was not detectable. A ratio of HPMC to prednisolone of 1:1 was not sufficient for retardation.

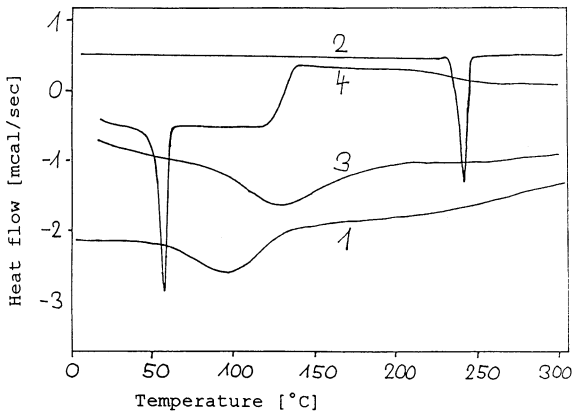

Fig. 3. DSC scans of HPMC (1); prednisolone (2), coprecipitates F8 (3) and F24 (4).

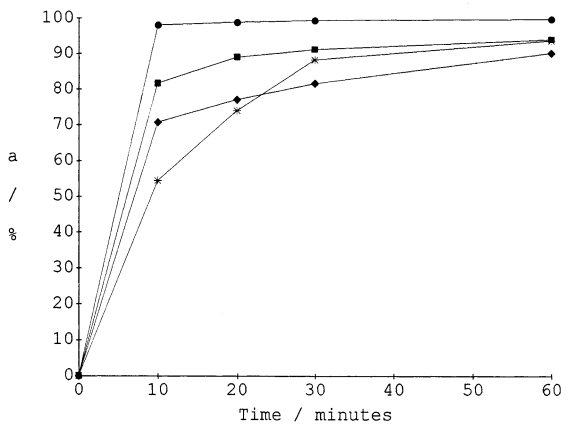

Fig. 4. Prednisolone release (amount a in %) from one-step IR-dried coprecipitates: – • –, F15; – ■ –, F13; – ◆ –, F14 and – × –, F16 freeze-dried.

From IR-dried one-step coprecipitates with high PEG 6000 content (Fig. 4, F15, mean values of $n = 6$) prednisolone was rapidly released due to the amorphous state and solubilization. On the other hand, especially during the first 30 min, the release was retarded with decreasing PEG 6000 content (F13, F14) and increasing influence of the film former. A slight prolongation was observed for freeze-dried coprecipitate F16. Products with Poloxamer instead of PEG 6000showed analogous release profiles.

Prednisolone release from IR-dried two-step coprecipitate F24 (Fig. 5, F24) was retarded due to a cover of HPMC on the beads compared to the analogous one-step coprecipitate F15 (Fig. 4). The release rate increased with decrease HPMC content (F23, F22). The same tendency was observed for freeze-dried coprecipitates with increasing Poloxamer content (Fig. 6).

Griseofulvin was distinctly retarded released from IR-dried coprecipitates without solubilizer (Fig. 7, F4, F5) due to low dissolution rate of the crystals formed during coprecipitation and to swelling of the HPMC. The dissolution of pure griseofulvin was faster because of small particle size of the drug. The release rate was more than 95% after 10 min from coprecipitate G5 with PEG 400/polysorbate 80 without HPMC (Wolf et al., 1996a) (Fig. 8) and retarded from coprecipitates with PEG 6000 and HPMC (F25–27). By com-

Table 4
TGA scans of pure substances and IR-dried BC preparations

Preparation	Cellulose pyrolysis and decomposition		PEG 6000 evaporation and decomposition	
	Inflexion point (°C)	Weight loss (%)	Inflexion point (°)	Weight loss (%)
BC	351	63	—	—
HPMC	350	78	—	—
F4	353	67	—	—
F7	349	69	—	—
PEG 6000	—	—	425	97
F10	353	54	421	28
F12	338	18	429	73

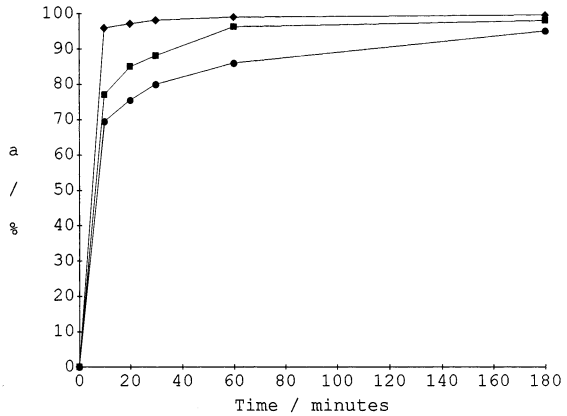

Fig. 5. Prednisolone release (a in %) from IR-dried two-step coprecipitates with decreasing HPMC content: – • –, F24; – ■ –, F23 and – ◆ –, F22.

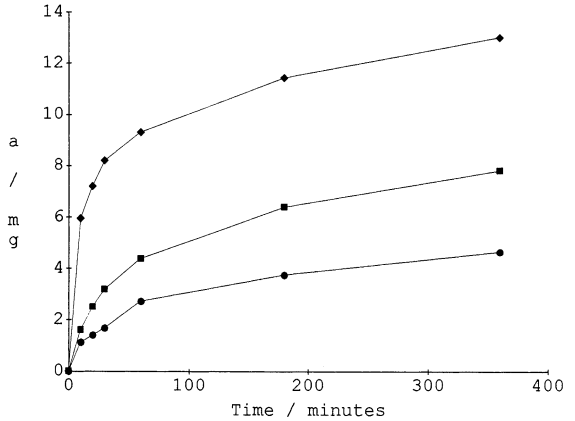

Fig. 7. Griseofulvin release (a in mg) from coprecipitates without solubilizers: – • –, F4 and – ■ –, F5 and dissolution of pure griseofulvin, – ◆ –.

parison with the plot of F4 it is obvious that the release was controlled by variation of the weight ratio of solubilizer and film former.

The release profiles were linearized by Weibull distribution (Table 5). The shape parameters were in the range of 0.2 to 0.7, indicating fast initial and slower terminal release. Scale parameter and characteristic release value t(63.2%) were low for high release rates (F14, F23, F24, F30) and vice versa high in the case of retarded release (F4, F5, F27, F28). In the initial part solubilized drug molecules and dissolved drug particles at the surface were released. In the later cases, the solubilizers in the pores were dissolved by penetrating water and drug molecules diffusing outside the pores by concentration gradients. The terminal phase was determined by swelling of HPMC and BC and slow release and diffusion of drug molecules from the gel skeleton. The latter process was the rate limiting process during the whole release from coprecipitates without solubilizers F4 and F5. Assuming matrix controlled release, the square root interpretation showed single-phase course and nearly straight lines with rate con-

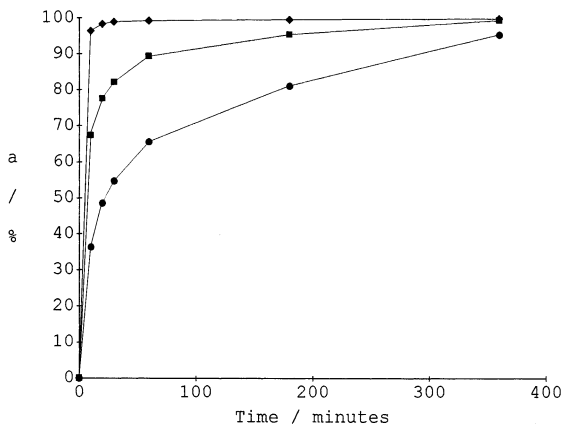

Fig. 6. Prednisolone release (a in %) from freeze-dried two-step coprecipitates with increasing Poloxamer content: – • –, F28; – ■ , –F29 and – ◆ –, F30.

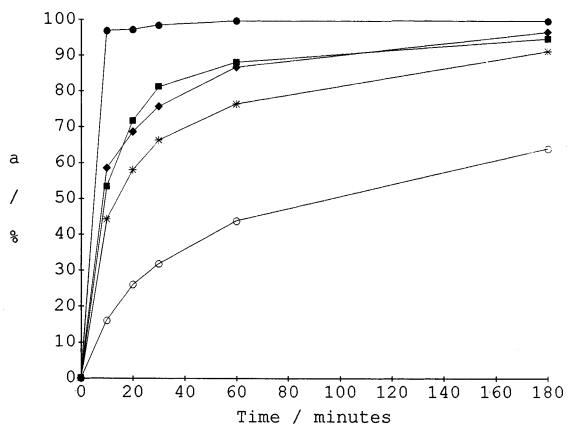

Fig. 8. Griseofulvin release (a in %) from IR-dried coprecipitates with increasing HPMC content: – • –, G5; – × –, F27; – ◆ –, F26; – ■ –, F25 and – ◦ –, F4.

Table 5
Probability parameters of the Weibull distribution from in vitro release profiles

Preparation	Shape parameter b	Scale parameter a	Correlation coefficient (r)	t(63.2%) (min)
BC:HPMC:griseofulvin				
F4	—	20.4864 ± 2.9630	0.9889	94.535 ± 20.145
F5	0.5929 ± 0.0447	21.4394 ± 4.0875	0.9966	169.239 ± 9.180
One-step preparations				
BC:PEG 6000:HPMC:prednisolone, IR-dried				
F13	0.6984 ± 0.0501	5.2812 ± 1.5160	0.9563	10.439 ± 2.370
F14	0.2103 ± 0.0441	0.8983 ± 0.1118	0.8893	0.641 ± 0.389
F15	After 10 min >95% released		0.7717	—
F16	0.5939 ± 0.1054	4.5255 ± 1.6199	0.9619	11.830 ± 1.691
Two-step preparations				
BC:PEG 6000:HPMC:prednisolone				
F22	After 10 min >95% released		0.8931	—
F26	0.3564 ± 0.0200	1.5147 ± 0.3000	0.9776	3.203 ± 2.200
F24	0.3226 ± 0.1052	1.5794 ± 1.1504	0.9698	3.531 ± 5.013
BC:PEG 6000:HPMC:griseofulvin, IR-dried				
F25	0.4079 ± 0.0518	3.0851 ± 0.4399	0.9729	15.716 ± 2.247
F29	0.5264 ± 0.0750	4.1129 ± 0.6222	0.9853	14.777 ± 2.599
F30	0.5712 ± 0.0654	6.7514 ± 1.4893	0.982	27.563 ± 5.226
BC:Poloxamer:HMPC:prednisolone, freeze-dried				
F28	0.5505 ± 0.1607	9.4211 ± 4.6921	0.9801	48.324 ± 14.584
F29	0.5279 ± 0.1960	3.3459 ± 2.1264	0.9157	7.220 ± 4.012
F30	0.1942 ± 0.0863	0.4229 ± 0.1402	0.8418	0.051 ± 0.089
$n = 6$	r' ($2P = 0.05$; $f = 4$)		0.8114	

stants of 4.8 ± 0.5 and 4.1 ± 0.4 [$1/\sqrt{\text{min}}$], respectively.

4. Conclusions

Coprecipitates of BC as carrier, HPMC, plasticizers and prednisolone showed fast and complete release due to fine dispersed drug crystals and good solubility, analogous preparations with griseofulvin showed retarded release due to low dissolution rate of the drug crystals and low solubility. The maximum loading degree of BC with HPMC was quite low, at higher HPMC amounts the dried products were agglomerated.

Prednisolone as well as griseofulvin release from coprecipitates with high solubilizer content was fast and complete after 30 min due to the release promoting properties of PEG 6000 and Poloxamer. On the other hand the release was retarded at high HPMC content and low solubilizer content due to retarding properties of HPMC. By combination of different amounts of solubilizers and HPMC the release rate was variable in a wide range. The release rate was also influenced by the applied preparation method (IR- or freeze-drying), the crystalline state of the drug in the coprecipitates and the resulting solubility. The coprecipitates were flowable, consisted of spherical particles and were, therefore, suitable for further manufacturing, for use as granules or as capsule filling materials.

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