Drug Development and Industrial Pharmacy, 24(11), 1007–1015 (1998)

RESEARCH PAPER

Hydrophilic-Lipophilic Drug Carrier Systems of Bead Cellulose and Isopropyl Myristate

B. Wolf

University of Leipzig, Faculty of Biological Sciences, Pharmacy and Psychology, Institute of Pharmacy, Department of Pharmaceutical Technology, Schönauer Straße 160, D-04207 Leipzig, Germany

ABSTRACT

Solid carrier systems of bead cellulose (BC) and isopropyl myristate (IPM) as a lipophilic excipient showed high release rates for low prednisolone and high IPM content and decreasing rates for increasing drug and decreasing IPM content. The release of griseofulvin was decreased by increasing IPM content. The release was controlled by the solubility of the drugs in IPM and water, the crystalline state of the drugs, and the weight ratio of the components and was varied in a wide range by change of the prescriptions. The products were prepared according to a dispersion-coevaporation process and were received as flowable powders consisting of spherical porous particles. IPM with dispersed drug was incorporated into the pores of the beads and also precipitated on the bead surface. Depending on the ratio of IPM to drug, more or less crystalline drug particles were suspended in the liquid IPM film or the drug was amorphous dissolved. Investigations of wettability and water uptake gave hints to more lipophilic properties. The advantage of the coprecipitates was the combination of a hydrophilic carrier and a lipophilic excipient as a flowable system for controlled release.

INTRODUCTION

In earlier investigations, the drug release rate was changed in a wide range by use of coprecipitates of bead cellulose (BC) as a solid carrier; polyethylene glycols, Poloxamer, and polysorbate 80 as hydrophilic solubilizers; and hydroxypropyl methylcellulose as a film former in variable composition (1–3). Acceleration was achieved with high solubilizer content and retarded release with products containing film former or with

slightly soluble and crystalline dispersed drugs. The advantage of these controlled-release products of BC and hydrophilic excipients was the good flowability, therefore producing good handling.

Microspheres, nanoparticles, nanospheres, and liposomes (4–7) have been investigated and sometimes already are used as carriers for hydrophilic, as well as lipophilic, drugs. No information exists about products of BC as solid hydrophilic carriers and lipophilic drugs and/or lipophilic excipients or solvents. For this reason, BC coprecipitates with strong lipophilic liquids (white mineral oil, oenotheric oil, olive oil, juniper berry oil, and peanut oil) were prepared (8). The products were flowable, possessed hydrophobic properties, and consisted of spherical porous particles. Compared to BC coprecipitates with a fourfold uptake of hydrophilic solubilizers (1,2), the maximum content of lipophilic oils was limited.

In the present study, BC coprecipitates were prepared with isopropyl myristate (IPM) as lipophilic solvent and prednisolone and griseofulvin as model drugs. The aim was to obtain flowable carrier systems with hydrophobic properties, high content of lipophilic solvent, and controlled drug release.

EXPERIMENTAL

Materials

Swollen, raw BC (Sächsische Kunstseiden GmbH, D-Pirna) was available as water-swollen, never-dried porous spheres with a water content of 90% and the following particle size distributions: 10–50 μm, 6%; 50–100 μm, 70%; >100 μm, 24% (9). Isopropyl myristate (Cosnaderm GmbH, D-Ladenburg; viscosity, 6.38 mPa·s; surface tension, 28.1 $mN \cdot m^{-1}$; specific gravity, 0.853 $g \cdot cm^{-3}$), ethyl alcohol, the drugs prednisolone and griseofulvin (both micronized, German Pharmacopoeia quality) (10), and demineralized water (specific conductivity $<0.06\ \mu S \cdot cm^{-1}$) were used.

Methods

Preparation of Bead Cellulose/Isopropyl Myristate Coprecipitates

For example, to prepare the coprecipitate BC:IPM: prednisolone = 1:3:0.75 (w/w), the water amount of 20.0 g swollen, never-dried BC was exchanged for ethanol on a frit (pore size 40 μm). Excess ethyl alcohol was removed by the vacuum of a water jet pump for 1 min. The ethyl alcohol containing BC was suspended in the solution of 4.8 g IPM and 1.2 g prednisolone in 20.0 g ethyl alcohol and vigorously mixed. Ethyl alcohol was evaporated under agitation by infrared (IR) radiation (red IR lamp, 250 W, distance 30 cm) to constant weight of the product. A yield of 7.45 g = 98% dry product was obtained.

Flow Properties

Bulk and tap densities were examined according to the methods of the German Pharmacopoeia 1996 (10). Thus, 100 g substance was filled into a 250-ml graduated cylinder (bulk density). Tap density was obtained from the volume after 1760 steps of tapping (tap volumeter, Erweka, D-Heusenstamm). Flowability was characterized by Carr's index:

$$\text{Carr's index} = (\text{tap density} - \text{bulk density}) \cdot 100\%/\text{tap density}.$$

The flow time of a defined substance amount from a funnel (rim diameter 100 mm, stem length 50 mm, inner diameter 10 mm, angle 60°) was measured.

To investigate the angle of repose, a glass funnel (rim diameter 120 mm, stem length 30 mm, inner diameter 16 mm) was located 20 mm above the crosswires on a graph paper. The outflow of the funnel was shut, and it was filled with a sufficient amount of substance. The outflowing powder formed a cone, with the top filling up the outflow of the funnel. The radii r_i of the cone were measured in four directions. The angle of repose was calculated from the mean with regard to the distance and the inner stem diameter:

$$\text{Angle of repose} = \arctan(20/(r - 8))$$

Sedimentation Volume

For sedimentation volume, 1.5 g substance was suspended in water under agitation and left for swelling and sedimentation in a 25-ml graduated cylinder for 3 days.

Mean Bead Diameter and Microscopic Bright Field Investigation

An Amplival (Carl Zeiss, D-Jena) microscope was used and was equipped with a ground-glass screen and 200× magnification. Dry preparations were dispersed in silicone oil on an object slide. With the help of a stencil, 500 particles were counted and classified into 8 particle size classes by the method of equivalent diameter. The mean bead diameter was calculated from the frequencies per class.

Polarization Microscopy and Microphotography

The Amplival microscope was equipped with two polarizators, photo projection, tube, a basic unit (Carl Zeiss, D-Jena), and camera Exakta (Ihagee, D-Dresden). The magnification was 80×; the distance of network lines on the microphotographs was 40 µm. Exposure time was 4 sec.

Scanning Electron Microscopy

Scanning electron microphotographs (SEMs) were available from a scanning electron microscope Cam Scan CS 24 (Cambridge Scanning Company Ltd., GB-Cambridge). The samples were sputtered with silver; the magnification was 150× to 600×; and the voltage 15 kV.

X-Ray Powder Diffractometry

Crystallinity data were obtained from an x-ray powder diffractometer (XPD) D 5000 (Siemens, D-Berlin) 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 from 5° to 50° with steps of 0.05°.

Differential Scanning Calorimetry

A differential scanning calorimeter DSC-PL (Polymer Laboratories Ltd., GB-Loughborough) was used with a silver furnace. The samples were sealed into closed aluminum pans; an empty pan was used as a reference. The measuring range was −50°C to 280°C, with a heating rate of 10 $K \cdot min^{-1}$.

Thermogravimetry

Thermogravimetry analysis (TGA) was measured with a TG-PL oven (Polymer Laboratories Ltd., GB-Loughborough) from room temperature to 500°C with a heating rate of 10 $K \cdot min^{-1}$ under nitrogen atmosphere.

Capillary Ascending Rate and Contact Angle

The capillary ascending rate was measured with the microprocessor tensiometer K12 (Krüss GmbH, D-Hamburg). According to Ref. 8, 1.0 g dry BC product was filled into a scaled glass tube (length 60 mm, inner diameter 8 mm) with a frit on the bottom (pore size 40 µm) and vibrated for 10 min by a sieve vibrator (THYR 1, Labortechnik, D-Ilmenau) at medium intensity to produce a homogeneous and reproducible powder bed. The test liquid was filled into a crystallization dish (diameter 65 mm, height 40 mm) and brought to a temperature of 20°C. The frit bottom of the glass tube was immersed in the liquid, and the solvent uptake by the powder bed was measured per time. The contact angle was calculated from the data of the capillary ascending rate (solvent uptake) considering the density, viscosity, and surface tension of the solvent according to a modified Washburn equation with the help of the computer program K121 (Krüss GmbH, D-Hamburg). Swelling of the powder was characterized by the increase of powder volume (in %) after 15 min of solvent uptake; wetting was expressed as humidified volume compared to swelling volume (in %) after solvent uptake.

Dissolution Study

Release experiments were performed in the manner of earlier investigations (2) in 1.0 L purified water at 37°C ± 0.3°C with a paddle stirring rate of 50 rpm and 6 replicates using a dissolution tester DT6 (Erweka, D-Heusenstamm) according to the German Pharmacopoeia (10). After 10, 20, 30, 60, 180, and 360 min, 5.0 ml liquid were withdrawn for analysis and refilled with 5.0 ml water. The sample amounts of the coprecipitates for release experiments were adjusted to defined drug doses of 10, 20, 50, or 75 mg.

Griseofulvin and prednisolone were analyzed by high-performance liquid chromatography (HPLC) using two pumps, a spectrophotometer Lambda 1000, an injection syringe (Bischoff Analysentechnik und -geräte GmbH, D-Leonberg), and a reversed-phase column, the Kromasil® C18, which was 5 µm, 250 mm × 4.6 mm. The eluents were methyl alcohol:water = 70:30 and 80:20 (v/v), and the wavelengths were 291 nm and 240 nm for griseofulvin and prednisolone, respectively. The eluents were degassed prior to application by an ultrasonic device and the weak vacuum of a water jet pump for 5 min. The flow rate of the eluents was 1 $ml \cdot min^{-1}$. For calibration, methanolic solutions of the drugs (50.0 $mg \cdot L^{-1}$) and dilutions were investigated. The released amounts were calculated from the drug peak areas using the program Hyperdata Chromsoft (Bischoff Analysentechnik und -geräte GmbH, D-Leonberg).

RESULTS AND DISCUSSION

Physical and Flow Properties

Compared to the coprecipitates with fatty oils (8), BC is able to take up a threefold amount of IPM, preserving the spherical shape and with only slight adhesiveness and

Table 1

Weight Ratio and Properties of BC/IPM Coprecipitates Without Drugs

Preparation	Weight Ratio PC:IPM	Bulk Density[a] (g/ml) (n = 3)	Sedimentation Volume[a] (ml/g) (n = 3)	Mean Bead Diameter[a] (μm) (n = 500)
Pure BC	—	0.633 ± 0.043	7.2 ± 0.3	37.16 ± 1.59
M1	1:0.5	0.455 ± 0.038	12.0 ± 1.1	45.56 ± 1.38
M2	1:1	0.500 ± 0.021	15.6 ± 0.8	53.96 ± 1.61
M3	1:2	0.500 ± 0.033	18.0 ± 1.2	72.28 ± 2.15
M4	1:3	0.571 ± 0.043	19.2 ± 1.0	74.56 ± 2.34
M5	1:4	0.336 ± 0.029	19.0 ± 1.1	78.84 ± 2.52

[a]Mean ± confidence interval ($2P$ = .05).

Table 2

Flow Properties of BC Preparations

Physical Value	Coprecipitate BC:IPM = 1:3	Coprecipitate BC:PEG 400 = 1:4	Pure BC
Bulk density (g/ml)	0.571	0.498	0.632
Tap density (g/ml)	0.641	0.561	0.699
Carr's index	10.9	11.2	9.5
Angle of repose (°)[a]	31.3 ± 2.0	40.7 ± 4.8	32.2 ± 1.5
Flow time (sec)[a]	36.0 ± 1.8	—	13.4 ± 0.6

[a]Mean ± confidence interval of five determinations ($2P$ = .05).

a low agglomeration tendency (Table 1). The product with a fourfold IPM amount is not flowable and somewhat sticky. With increasing IPM content, the values of sedimentation volume and mean bead diameter ascend.

Carr's index of coprecipitate M4 with high IPM content is in the range of good powder flow properties and is similar to those of a high loaded hydrophilic coprecipitate (1) and of pure BC (Table 2). Flow time value is high due to slight cohesion of the beads; the angle of repose of 31.3° indicates good-to-passable flow.

Because of technical difficulties in the course of SEM specimen preparation (evaporation and partial decomposition of IPM during exposure to gold steam under vacuum), the SEM investigation showed black surface layers and blurred outlines of the beads at low magnification. Under the light microscope, in analogy to pure BC and BC coprecipitates with PEG 400 (1), pores and holes up

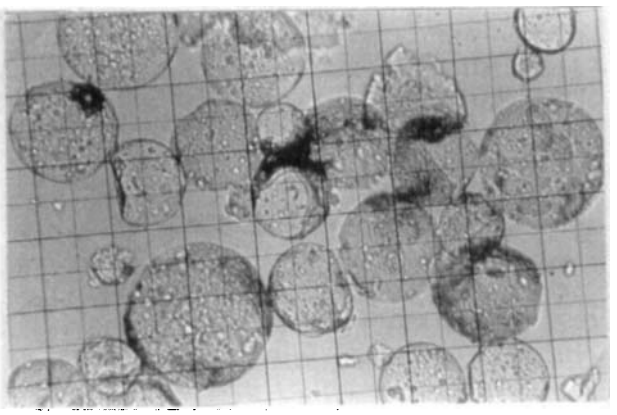

Figure 1. Microphotograph of coprecipitate BC:isopropyl myristate:griseofulvin = 1:3:0.1 (M13); distance of network lines is 40 μm.

Table 3

Weight Ratio and Crystallinity of BC/IPM/Drug Coprecipitates

Preparation	Weight Ratio PC:IPM:Prednisolone	Weight Ratio IPM:Prednisolone	Crystallinity by POL Microscopy
M6	1:1:0.1	10:1	Crystalline
M7	1:2:0.1	20:1	Amorphous
M8	1:3:0.1	30:1	Amorphous
M9	1:3:0.2	15:1	Poor crystalline
M10	1:3:0.5	6:1	Strong crystalline
M11	1:3:0.75	4:1	Strong crystalline
	PC:IPM:Griseofulvin	IPM:Griseofulvin	
M12	1:1:0.1	10:1	Crystalline
M13	1:3:0.1	30:1	Poor crystalline

to a diameter of 5 μm were visible (Fig. 1). IPM is deposited as a transparent film on the beads and also is incorporated into the pores, thus preventing the beads from shrinking and sintering during ethyl alcohol evaporation in the preparation process.

Crystallinity

Under the polarization microscope, cellulose crystallinity occurs at a weight ratio of BC:IPM of 1:0.5 (M1), which refers to incomplete surface films on the beads; at higher IPM content, the coprecipitates appear amorphous. At low prednisolone concentration (solubility in IPM of 120 $mg \cdot L^{-1}$ at 25°C), the drug is completely dissolved or amorphously dispersed, at an IPM:prednisolone ratio of 15:1 (M9), and at a higher prednisolone concentration, small crystals are formed at the bead surface (Table 3). Griseofulvin (solubility in IPM of 166 $mg \cdot L^{-1}$ at 25°C) crystals are visible at the surface of the beads at an IPM:griseofulvin ratio of 30:1 (M13, Fig. 1), as well as 10:1 (M12).

The crystal signals of the coprecipitates are distinguished regarding their origin by x-ray powder diffractometry. Pure BC shows crystalline signals at Bragg

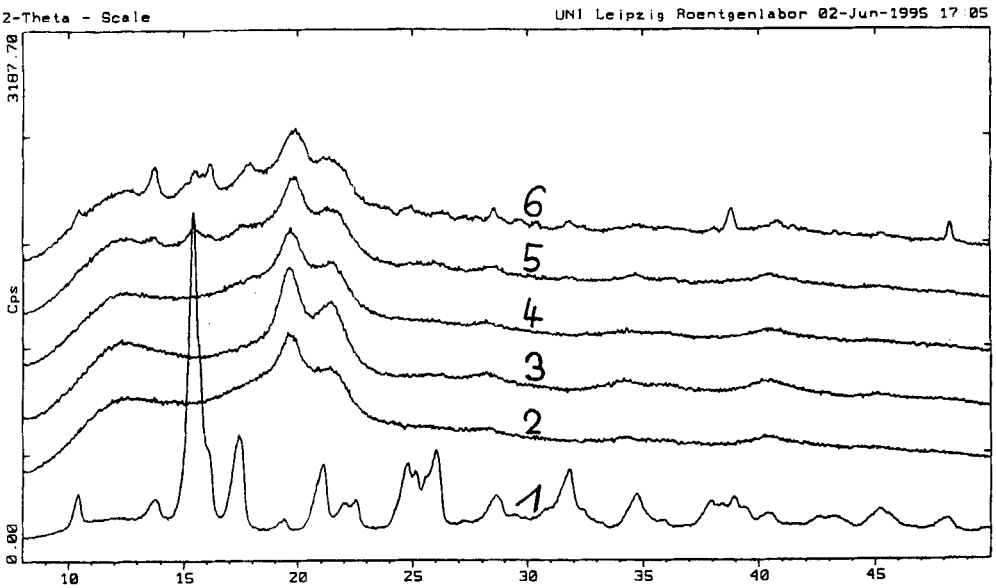

Figure 2. X-ray powder diffractograms of (1) prednisolone and coprecipitates with increasing prednisolone content (2) M4, (3) M6, (4) M9, (5) M10, and (6) M11.

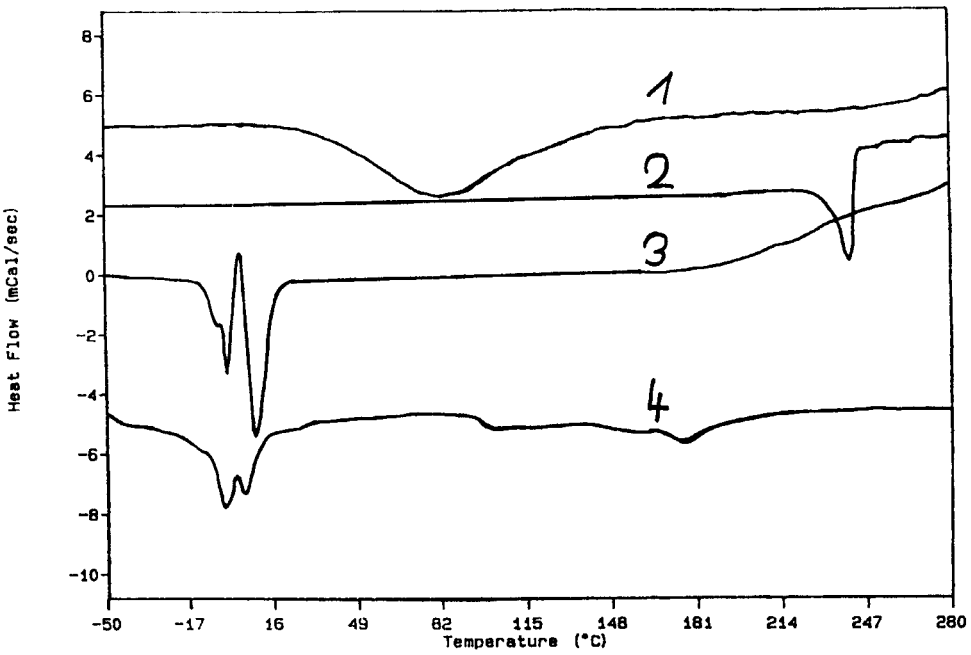

Figure 3. DSC scans of (1) pure BC, (2) prednisolone, (3) IPM, and (4) coprecipitate M10.

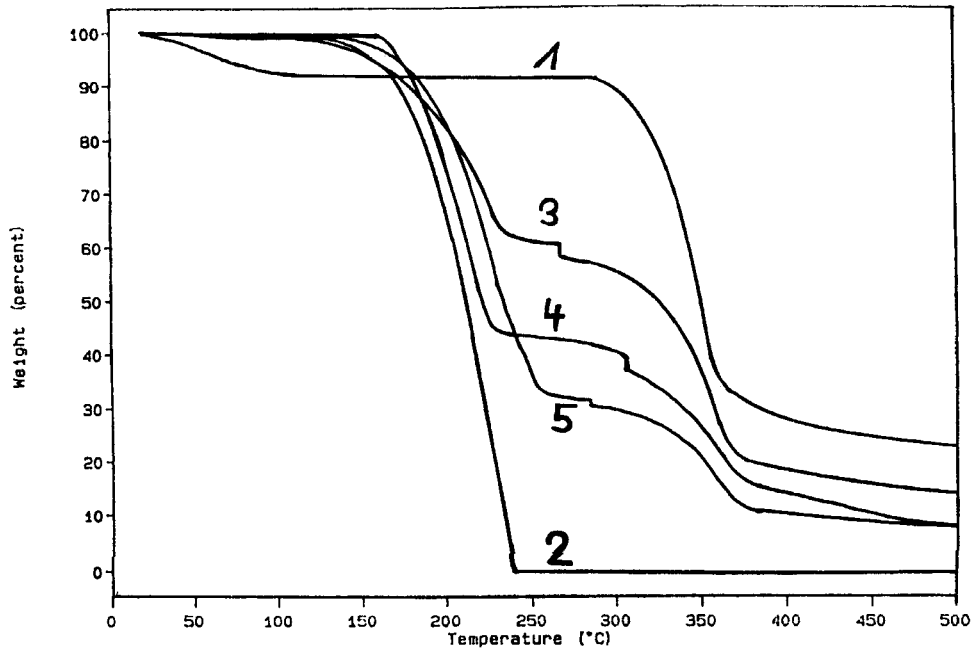

Figure 4. TGA scans of (1) BC, (2) IPM, and coprecipitates (3) M2, (4) M4, and (5) M11.

Table 4

Wettability and Contact Angle of BC Preparations at 20°C

Preparation	Liquid	Capillary Ascending Rate[a] (g^2/sec)	Contact Angle[a] (°)	Swelling (%)	Wetting (%)
BC:IPM = 1:3	Water	2.23E-04 ± 1.05E-04	89.7	0	28
Pure BC	Water	9.26E-03 ± 1.19E-03	72.6 ± 2.3	86	100
BC:IPM = 1:3	IPM	2.52E-03 ± 3.50E-04	Approx. 0	0	100
Pure BC	IPM	1.14E-03 ± 3.01E-04	47.0 ± 14.6	0	100

[a]Mean ± SD of three determinations.

angles of 19.8° and 21.9° (1). Increasing the content of IPM in coprecipitates had no significant influence on the position and the intensity of the cellulose crystal signals (Fig. 2). There are no crystal effects visible other than those of *pure* cellulose. Crystal signals of prednisolone occur at coprecipitates with IPM:prednisolone ratios of 6:1 and 4:1; for lower prednisolone contents, only cellulose signals are visible.

Thermal Properties

The broad endotherm due to water desorption from cellulose (Fig. 3) does not occur at the coprecipitate M9; the melting peak of prednisolone is reduced and shifted to lower temperatures (180°C). The melting process of IPM gives two peaks because of a blended substance of different esters (9). The peaks are not shifted at the coprecipitate compared to pure IPM. At room temperature, the coprecipitates consist of solid cellulose beads with liquid IPM layers.

The IPM evaporation and decomposition at 150°C–240°C (Fig. 4) is not shifted at coprecipitates; unsteadiness in the plots arises from burst effects. The inflexion point of cellulose decomposition arises at 330°C–350°C for BC, as well as for the coprecipitates.

Solvent Adsorption and Contact Angle

The capillary ascending rate of water is distinctly lower at coprecipitate M4 compared to pure BC (Table 4). The high contact angle of 90° indicates poor wetting. On the other hand, the rate of IPM uptake by M4 is 10-fold that of water, and wetting is complete regarding the contact angle of 0°. IPM coprecipitates possess lipophilic properties. For pure BC, water is adsorbed with a higher rate than IPM due to lower viscosity, higher surface tension, and hydrophilic properties. BC is wetted by both liquids, with corresponding contact angles of 72.6° and

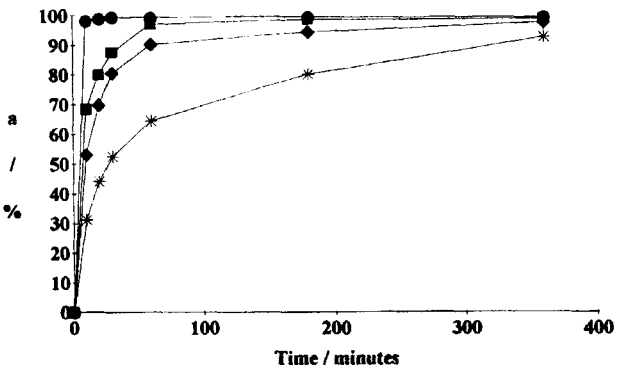

Figure 5. Prednisolone release (amount *a* in %) from coprecipitates with high IPM content and increasing prednisolone content: (●) M8; (■) M9; (◆) M10; and (*) M11.

47° for water and IPM, respectively, in spite of distinctly different hydrophilicity and the assumption of a more hydrophilic cellulose surface. The relatively high value of the calculated contact angle of the system pure BC/water compared to BC/IPM can be explained by swelling of BC during water uptake and the therefore limited validity of the Washburn equation. IPM uptake by BC surpasses that of white mineral oil (8). The solvents are incorporated into the pores of BC by capillary forces.

Drug Release

The drug release rate is high in the case of coprecipitates with low prednisolone content (M6-M8) due to dissolved or amorphous dispersed prednisolone. With increasing content, prednisolone crystallizes, and the release is more and more retarded, so that a value of 90% is obtained for M11 only after 6 hr (Fig. 5). With the highest prednisolone dose of 75 mg, the value is distinctly below the saturation concentration in water, and

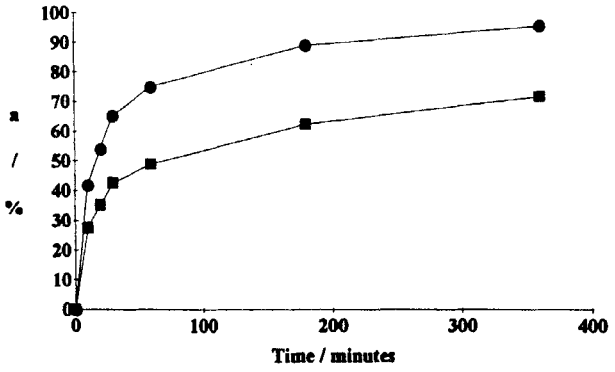

Figure 6. Griseofulvin release from coprecipitates with increasing IPM content: (●) M12 and (■) M13.

the release is not influenced by solubility. The rate-limiting processes in the initial phase are the wetting of the bead surface by the aqueous dissolution liquid; penetration of water into the pores of the beads, which are filled with hydrophobic IPM; dissolution of prednisolone crystals at higher drug content; and diffusion of prednisolone molecules from the IPM film or droplets to the aqueous phase by a concentration gradient. In the terminal phase, the swelling of the cellulose gel matrix and the diffusion of prednisolone molecules from the inner part of the pores to the bead surface are important and cause lower rates.

Griseofulvin is expected to have a release profile influenced by the poor solubility (15 $mg \cdot L^{-1}$ in water at 37°C) and low dissolution rate. The release from BC coprecipitates is relatively high in the first hour and reaches about 75% of the 6-hr values (Fig. 6). The initial drug amount derives from dispersed substance in the IPM film at the bead surface. In the later course, griseofulvin molecules from the inner parts of the beads are released by the same processes as prednisolone. The release is also slow at a low griseofulvin content because of crystalline dispersed drug and poor solubility in water, and it is retarded with increasing IPM content due to better solubility in IPM than in water.

Linearization of Drug-Release Curves

The release-rate profiles are linearized by the Weibull function. The shape parameters are in the range of 0.37 to 0.57, indicating biphasic kinetics in all cases (Table 5). The initial fast release in the first hour is followed by slower release. The scale parameters and the characteristic values $t(63,2\%)$ of prednisolone release increase with decreasing release rate. The parameters of griseofulvin release are distinctly lower compared to prednisolone release from coprecipitates of an analogous prescription but have similar tendencies.

CONCLUSIONS

The coprecipitates of BC and IPM are preferred carrier systems for oily soluble drugs or for drugs with intended retarded release. The products have good flowability and are therefore suitable for further handling, for example, as filling material for hard gelatin capsules. The advantage over the BC coprecipitates with fatty oils is the much higher IPM amount that can be taken up, preserving the granular and good flow properties. The release rates of prednisolone and griseofulvin from BC/IPM coprecipitates can be varied by changing the weight ratio of IPM to drug.

Table 5

Weibull Function Parameters of Drug Release from BC/IPM Coprecipitates

Preparation	Shape Parameter b[a]	Scale Parameter a[a]	Correlation Coefficient r	$t(62,3\%)$[a] (min)
BC:IPM:Prednisolone				
M8	After 10 min > 98% released		0.9318	—
M9	0.4478 ± 0.0930	2.4516 ± 1.2613	0.9665	6.403 ± 4.369
M10	0.4098 ± 0.0407	2.8827 ± 0.6602	0.9594	12.904 ± 4.473
M11	0.5243 ± 0.0296	8.5586 ± 1.2225	0.9937	59.501 ± 8.400
BC:IPM:Griseofulvin				
M12	0.5688 ± 0.0880	7.2641 ± 2.2246	0.9811	30.891 ± 3.417
M13	0.3748 ± 0.0204	7.0640 ± 0.9503	0.9907	182.036 ± 31.455

[a]Mean ± SD of six determinations.

ACKNOWLEDGMENT

The authors wish to thank Dr. W. Schmitz, Institute of Mineralogy, Crystallography, and Material Science of the University of Leipzig for the x-ray diffractometer measurements.

REFERENCES

1. B. Wolf, W. Schmitz, and H. Schneider, Int. J. Pharm., 139, 87 (1996).
2. B. Wolf, I. Finke, and W. Schmitz, Pharmazie, 51, 104 (1996).
3. B. Wolf, Int. J. Pharm., 156, 97 (1997).
4. G. V. Betageri, S. A. Jenkins, and D. L. Parsons, *Liposome Drug Delivery Systems*, Technomic, Lancaster, 1993.
5. D. D. Lasic, *Liposomes: From Physics to Application*, Elsevier, Amsterdam, 1993.
6. P. Johnson and J. G. Lloyd-Jones, *Drug Delivery Systems. Fundamentals and Techniques*, VCH Weinheim, New York, 1987.
7. M. Rosoff, *controlled Release of Drugs: Polymers and Aggregate Systems*, VCH Weinheim, New York, 1989.
8. B. Wolf, Pharmazie, to be published.
9. B. Wolf, W. Horsch, and I. Finke, Pharmazie, 46, 788 (1991).
10. Deutsches Arzneibuch 1996, Deutscher Apotheker Verlag Stuttgart, Govi-Verlag GmbH Frankfurt a.M./Eschborn, 1996.
11. H. P. Fiedler, *Lexikon der Hilfsstoffe*, Editio Cantor Aulendorf, 3. Auflage, Aulendorf, 1989.