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Research paper

The ophthalmic lyophilisate carrier system (OLCS): development of a novel dosage form, freeze-drying technique, and in vitro quality control tests

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Abstract

The ophthalmic lyophilisate carrier system (OLCS) is a novel dosage form for delivery of pharmacologically active ingredients or other substances improving the structure of the tear film to the eye. A drop of lyophilisate containing the drug and bulk forming water-soluble or swelling excipients is attached to a flexible hydrophobic carrier. Placebo OLCS and OLCS containing several drugs commonly used in ophthalmology were compared to conventional eye drops containing the same ingredients. A novel lyophilization procedure for the production of this dosage form is described, which allows stricter control of the freezing and drying conditions and shortens the production cycle by at least an order of magnitude. In clinical studies it was found that OLCS are easy to administer and well tolerated if the force of adhesion between lyophilisates and carrier strips and the structural firmness of the lyophilisates themselves are well controlled. These parameters are critical for convenient administration and complete delivery of the dose of active ingredients incorporated, therefore suitable in vitro tests were developed with which their values can be determined for the purpose of process validation. A study of fluorescein OLCS in humans indicated that concentration profiles in the cornea and anterior chamber are significantly higher than after administration of equal doses of the diagnostic in conventional eye drops.

Keywords: Lyophilization; Ophthalmic drug delivery; Bioavailability; Adhesive strength; Freezing rate; Pupillometry; Laser fluorimetry

1. Introduction

In spite of their broad use, conventional aqueous eye drops in multi-dose containers are a dosage form fraught with problems. In order to maintain their microbiological quality during use, preservatives must be added, which are known to cause damage to the cornea and conjunctiva [1,2]. For active ingredients undergoing hydrolysis, the pH is frequently adjusted to unphysiologically low values in order to achieve sufficient stability at the expense of optimal physiologic tolerability [3]. Low-viscosity eye drops are rapidly drained, particularly if the drops are large, and the absorption of active ingredients from the nasolacrimal duct may give rise to adverse systemic effects [4]. Many patients are unable to administer the correct dose in the right place and it is not unusual that the drop is placed on the cheek, that more than one drop is administered or that the patient contacts the cornea with the dropper tip, which may cause injuries. In order to deliver a drop to the eye, the head must be reclined. This makes visual control upon self-administration difficult, and the reclined posture is inconvenient, particularly for many elderly people.

There have been several attempts to eliminate one ore more of the problems associated with the microbiological quality and the ease of administration of eye drops. Examples are administration aids, single dose containers, the COMOD system [5], which do not contain preservatives and the double-chamber vial of Timpilo® eye drops, where

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the pH of the drug solution is 3.5 during storage for stability reasons. Prior to use, the pH is raised to 6.6 by breaking the seal of a buffer chamber and mixing the solutions [6]. One of the most remarkable innovative products was New Ophthalmic Delivery System (NODS), introduced by Smith and Nephew in 1996, in which the dose was administered as an ophthalmic insert attached to a paper strip handle by a pre-formed soluble breakpoint [7,8]. The system was marketed but lacked acceptance by patients and ophthalmologists because the insert did not separate easily and reliably from the handle. Still, the basic idea was the starting point for the development of the OLCS (Fig. 1) described below [9,10,11] in which a single dose of active ingredient is dissolved or dispersed in a drop of aqueous solution of a hydrophilic polymer, which is freeze dried on a soft hydrophobic carrier membrane attached to a paper handle. Upon administration, the lyophilisate is stripped off its carrier by a wiping motion over the lower eyelid, adheres to the conjunctiva and dissolves in the tear fluid. The physicochemical properties of hypromellose lyophilisates for ophthalmic use have been investigated by Zatloukal [12], but there is no information available on human studies of these insert-type dosage forms.

A summary of general features of OLCS compared to those of multi-dose eye drops is given in Table 1.

The development of production and testing techniques was spurred by observations made during clinical studies and problems that became apparent in the evaluation of their outcomes. All studies in humans were carried out at the Center of Ophthalmology at the University of Cologne with consent from the institutional review board.

2. Materials and methods

2.1. Materials

Hypromellose Ph. Eur. 2000 (Methocel E4M®, Dow Chemicals, Midland, MI, USA); fluorescein Ph.Eur. (Synopharm, D-Barsbüttel); polytetrafluoroethylene sheet, thickness 100 μm, relative density 1.6 (3 P Performance Plastic Products, D-Karben); Sekuroka autoclave indicator tape for OLCS handle (Roth, D-Karlsruhe).

Fig. 1. Administration of an ophthalmic lyophilisate carrier system (OLCS).

Table 1
Comparison of OLCS and conventional eye drops in multiple-dose containers

Characteristic	OLCS	Eye drops
Preservative required	No	Yes
pH adjustment to unphysiological values for the sake of stability	No	Frequently required
Precision of dosage	Good	Poor
Convenience of handling	Good	Poor (reclination, lack of visual control)
Risk of injury upon administration	Absent	Present
Ocular clearance and risk of systemic side effects	Low	High

2.2. Components

Standard vacuum components of the lyophilizer assembly were stainless steel. The parts in contact with liquid nitrogen were of diameter DN 40 with aluminum seals. Drying chambers were custom made of borosilicate glass with DN 25 fittings. For the vacuum system DN 16 steel components were used throughout. In the parts kept at or slightly below room temperature, perbunane O-rings were used as seals. Needle valve: EVN 116 (Pfeiffer Vakuumtechnik, D-Aslar), absolute pressure sensor: MKS Baratron Type 626A11MQE (MKS Instruments, D-München), Thermocouple: Type 901221, (JUMO, D-Fulda).

2.3. Freeze dryer

The lyophilization technique described below was developed in steps over a period of about 10 years as clinical studies indicated that the strength of adhesion between the lyophilisate and the carrier as well as the structural firmness, i.e. the mechanical resistance of the lyophilisate to compression and shearing are critical for both convenience of administration and bioavailability. Although these quality-determining characteristics depend upon several factors, the most important one is control of the freezing and drying process. Since most intermediate steps of the development are no longer of interest, only the initial method by which OLCS were produced for early clinical studies and the latest stage of development are described in detail.

Initially, small batches of five to 50 OLCS were prepared in conventional laboratory freeze dryers as follows (method I): a drop containing the drug and a hydrophilic polymer was placed on each of the pre-sterilized strips under aseptic conditions in a cylindrical stainless steel container. The container was closed with a lid containing a large opening covered with a 0.2 μm cellulose filter and

the solution was frozen and lyophilized after transfer into the freeze drier. In OLCS prepared by this method, the adhesion force between lyophilisates and hydrophobic carriers was variable both between and within batches. This was attributed to the lack of control of the freezing and drying process and to the inhomogeneity of temperature profiles within the drying chambers. The wide range of adhesion forces caused some lyophilisates to fall off their carrier strips during storage, while others would stick tenaciously and could only be stripped off with difficulty upon administration or not at all. Less important but also a point of concern were long drying times in excess of 20 h. These problems led to the development of both an in vitro test for quantification of the adhesion force and a new freeze drying technique.

In order to obtain more homogenous product characteristics, a mini-freeze dryer was developed, which allows better control of the freezing and drying conditions and reduces the length of the production cycle (method II). Remarkable features are the low investment for the single unit, small size and separation of the drying chamber from the bulk of the cooling system, which allows operation in either a laminar-flow workbench or an isolator, and the ease of handling.

In the latest version, the drying chamber is made of borosilicate glass and has five ports with standard vacuum fittings. Most parts of the lyophilizer except the coolant reservoir, the condenser finger and the drying chamber, are commercially available standard vacuum components.

2.4. Procedure

In the process development phase, all operations are carried out manually under aseptic conditions in a laminar flow bench. The carrier strip is charged with a drop of sterile aqueous or organic solution containing the drug, a hydrophilic polymer and other ingredients as required (Fig. 2a) are loaded on a small tray into the horizontal port (b) of the drying chamber so that the drop is located at its center. A finger-shaped condenser (c) is housed in a slightly inclined tube on the opposite side and can be fitted with a removable tongue-shaped extension that reaches below the carrier tray (d). The vertical bottom port (e) is attached to the vacuum system with a needle valve (f), vacuum pump, and pressure sensor (g). It can also be connected to a supply of filtered nitrogen gas (h) at a pressure of about 50 mbar for loading and unloading the chamber. The two ports above the center are set at equal angles with respect to the vertical and are fitted with an infrared heater (i) of which only the electric connections are visible in this figure, and an infrared-transmissive window (j). The latter is the viewing port for an external infrared temperature sensor suitable for non-invasive control of the freezing and drying cycle. For process development and validation, the temperature in the drop can also be measured by a mini-thermocouple attached to a special tray. If this

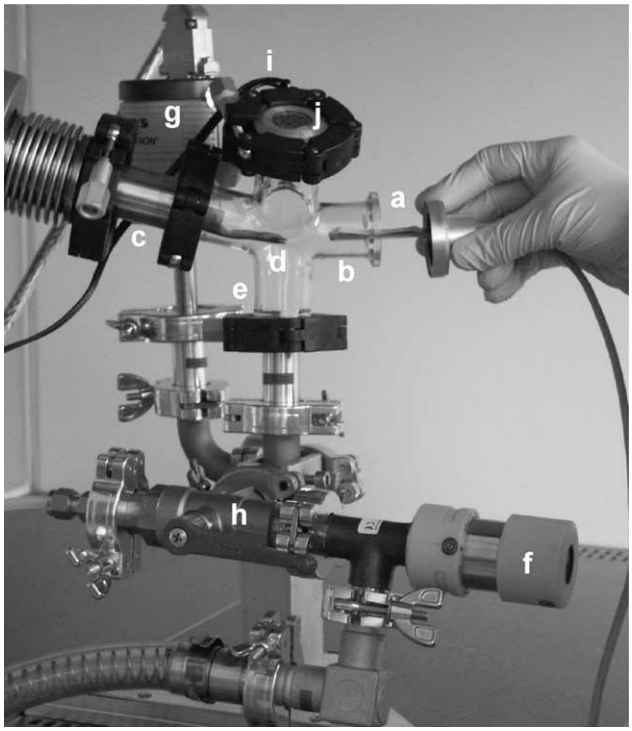

Fig. 2. Loading of mini-lyophilizer (method II).

device is used, the carrier strip is perforated before being placed on the tray, the tip of the thermocouple is inserted into the puncture, and the drop is deposited on top of it. If both the thermocouple and the infrared sensor are available, the temperature inside the drop and on its surface can be measured simultaneously.

When the extension is attached to the cold finger, it serves as the condensing surface. Since it can be replaced at the end of a drying cycle when so much ice has accumulated that the drying rate is reduced, it can be de-iced externally and the drying operation can be repeated indefinitely without interruption. If the extension is not used, ice can also be removed mechanically from the condenser finger, thus eliminating the necessity to heat the condenser surface between production cycles in order drain the condensate.

2.5. Operating conditions

Presently, the condenser is cooled by liquid nitrogen (b.p. 77 K). After insertion of the carrier with the liquid drop weighing about 25 mg, freezing is induced by evacuation of the drying chamber. Depending upon the evacuation rate, the solution is supercooled to about 265 K and freezes within 12–64 s (Fig. 3). During the primary drying period, the gas pressure is reduced to about 0.01 mbar, and the sample is heated by infrared radiation emitted by a hot wire delivering approximately 5 W. Bulk water evaporates completely within about 20 min and the end of the primary drying phase is recognized by an increase of product temperature. At this point, the heating power is increased to about 10 W and

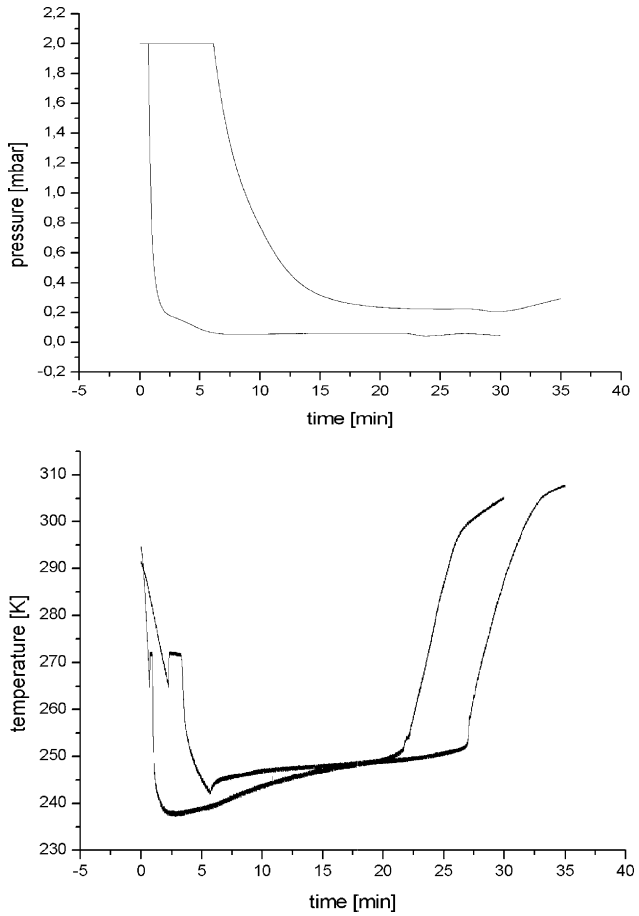

Fig. 3. Pressure and temperature cycles during OLCS lyophilization. Left, fast evacuation, rapid freezing; right, slow evacuation, slow freezing.

drying is terminated when the product temperature reaches 313 K. Upon completion of the drying cycle, the chamber is flooded with nitrogen, the OLCS is removed and transferred aseptically to a sterile tube for storage.

Since only simple movements are involved, the process can be automated and would then preferably be run in an isolator.

2.6. Measurement of adhesion force and compressibility

The adhesion force is measured using a precision balance attached to a motor-driven clamp mechanism (Fig. 4). The carrier strip is inserted into the 200-μm-wide clamp slit so that the lyophilisate is positioned just below the slit. The paper handle is firmly attached by a rod to the bottom eye of the electronic balance and the clamp is pulled down at a rate of 0.59 mm/min by a small motor. The force is converted into a digital weight signal and recorded as a function of time. The adhesion force cannot be measured reliably if the lyophiliates are very soft because they can be compressed and drawn into the slit. Since attempts to administer extremely compressible OLCS fail for similar reasons, even this type of negative test result is of practical relevance.

The adhesion force tester can be used in an alternative mode to test the compressibility of lyophilisates. For this purpose, the clamp is removed and the platform on which it rests is lowered to its bottom position. The lyophilisate is placed flat on the platform, a 200-g weight is suspended by a rod from the eye of the balance and the table is moved up at the same rate as in the adhesion force measurement. Again, the weight signal is recorded as a function of time.

2.7. Clinical studies

Four types of OLCS have been tested in humans with authorization by the institutional review board of the university clinics of Cologne. Both eye drops and OLCS were administered by an ophthalmologist.

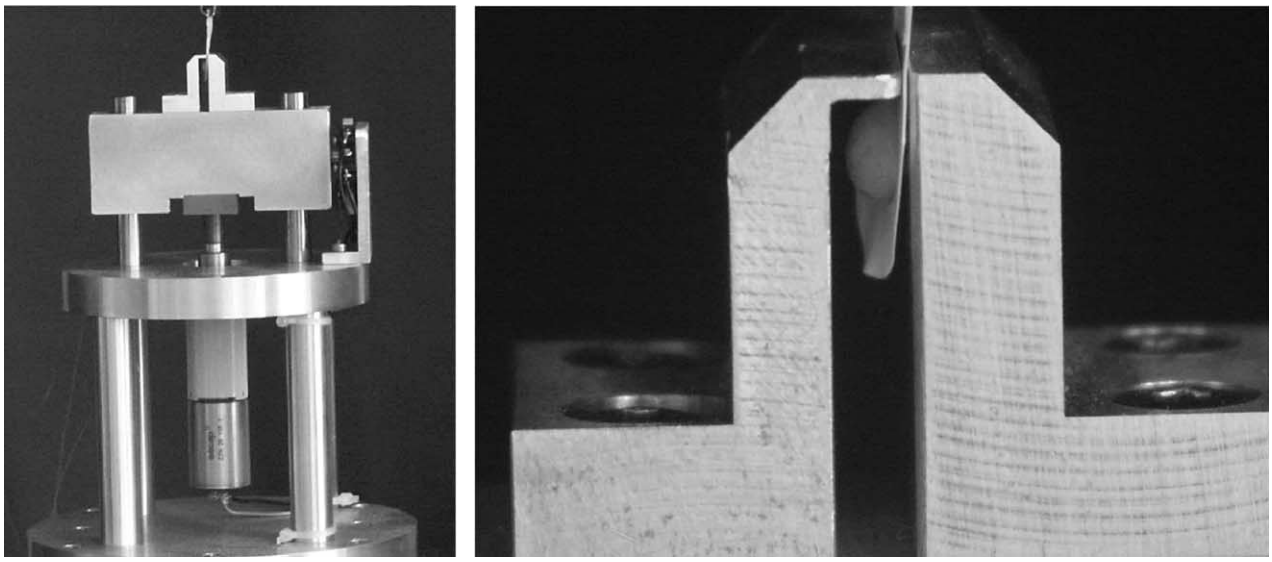

Fig. 4. Adhesion force and compressibility tester.

- Drug free lyophilisates prepared from 0.5% solutions of hypromellose [9,10] were studied in 32 healthy volunteers to assess the tolerability of the dosage form, who graded the sensation upon contact of the lyophilisate with the cornea on a visual analogue scale ranging from 0 (neutral) to 10 (extremely painful).
- The extent of miosis after administration of conventional pilocarpine eye drops OLCS was studied as an indicator of local bioavailability in 16 volunteers [13, 14] using a modified infrared pupillograph CIP 900 (Amtech, D-Weinheim).
- For the same purpose, the mydriatic effect of Tropicamide after administration of eye drops and OLCS was assessed in two studies in eight and 10 healthy volunteers[13,15].
- Concentration profiles of fluorescein in the cornea and anterior chamber were determined by fluorophotometry in an open label parallel study of eye drops (Fluorescein Thilo 0.17%, Alcon, D-Freiburg) and OLCS [17,18] using a scanning fluorimeter Fluorotron® Master (Coherent Inc., Palo Alto, CA, USA).

3. Results

3.1. Tolerability

OLCS prepared from 0.5% Hypromellose solution in water for injection were administered to 32 subjects. Conventional Hypromellose eye drops (Lacrisic®, Alcon-Thilo, D-Freiburg) administered simultaneously to the contralateral eye were used as a reference [10]. The sensoric perception was quantified on visual analogue scales ranging from 0 to 1. Subjects recorded their perceptions 0.5, 2, 5, and 10 min after administration. Differences between the dosage forms were statistically not significant. In general, the initial discomfort was slightly higher for conventional eye drops. Later, the ocular sensation of the rehydrated polymer was more pronounced and decreased at a lower rate (Fig. 5).

3.2. Bioavailability of pilocarpine

The time course of miosis after exposure to a light stimulus was measured. The magnitude of the pharmacological effect before and 5, 10, 15, 30, 45, 60, 120, 180, 240 and 360 min after administration was quantified by the area between the baseline pupil diameter and its decrease profile after a standard light stimulus. At each time point, the time course of miosis after a standard light stimulus was measured for 2 s. The area between the level of the initial value of the pupil diameter and the subsequent profile of reduced diameters was computed automatically and divided by the initial value in order to compensate for interindividual differences of mean pupil diameters (Fig. 6). In pupillometry, this is called the relative amplitude. The area

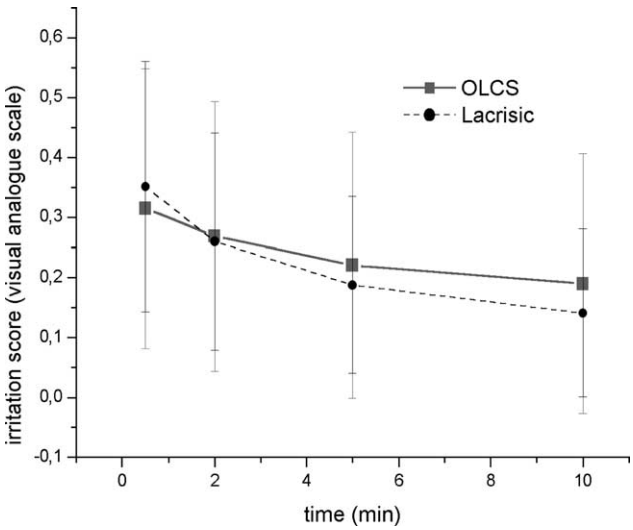

Fig. 5. Mean irritation scores of placebo OLCS and Lacrisic® eye drops (Bars: S.D., $n = 32$).

between the baseline value of the relative amplitude measured before the experiment and the values measured between 5 and 360 min divided again by the baseline value was taken as a measure of total bioavailability estimated from the pharmacological effect. Corresponding values for OLCS as the test formulation (A_L) and conventional eye drops as the reference (A_D) and their quotients are given in Table 2 together with pertinent statistics.

The mean area under the time–effect curves of the lyophilisates amounts to only about 40% of the corresponding value for the eye drops, indicating a low bioavailability. An assessment of intermediate results after administration to subjects 1–4 indicated that incomplete delivery was the probable cause, therefore the residual amount of pilocarpine remaining on the carrier strips after administration was assayed for the OLCS administered to subjects 5–16. Results are given in column 5 of Table 2 and indicate that the mean fraction delivered was only about 20%. A correlation between the amount recovered and the area under the effect vs. time curve was not found.

Evaluation of the data as paired observations indicates that the mean A_L/A_D ratio is 1.8 and therefore strongly in favor of OLCS. This is, however, an artifact due to the high variability of responses after administration of the reference dosage form. It may be noted that the coefficient of variation of the effect measure, which is therapeutically more relevant than the mean bioavailability, is nearly equal for OLCS and eye drops, with a slight tendency in favor of the former.

3.3. Bioavailability of tropicamide

The pupillographic procedure and the data evaluation method were identical to those used for the pilocarpine preparations described above. Measurements were taken before and 15, 30, 45, 60, 120, 360 and 480 min after

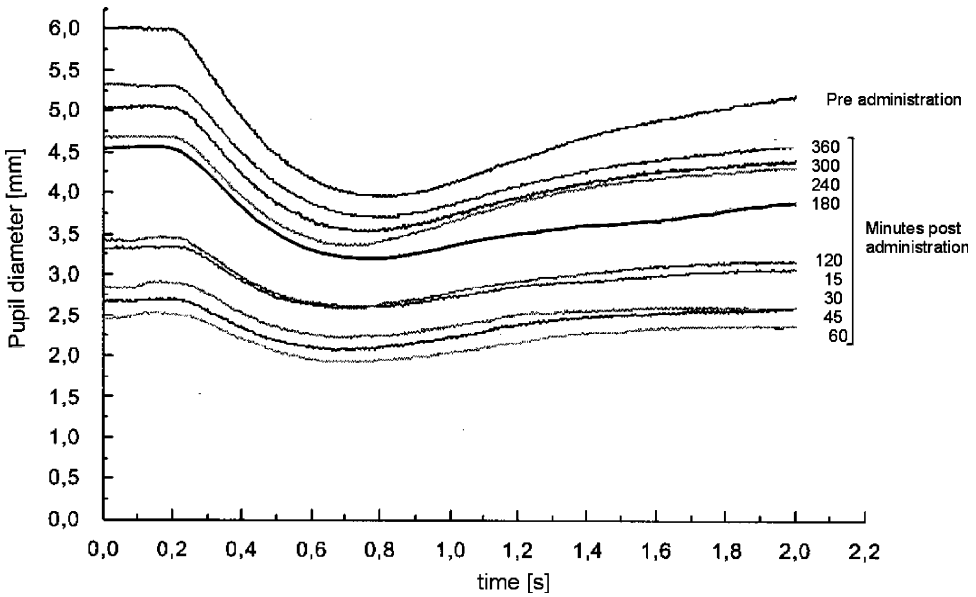

Fig. 6. Time course of miotic pupil reactions to standard light stimulus after administration of pilocarpine eye drops in one subject.

administration. In this instance, the reduction rather than the increase of the miotic response to a standardized light stimulus was measured as a function of time [15]. Initially, a comparative study of tropicamide eye drops and one batch of OLCS produced by method I with Hypromellose as the only water soluble lyophilisate-forming polymer had been scheduled. An intermediate evaluation of data from the first eight subjects indicated obvious problems with the ease of administration and consequently reduced bioavailability. Therefore, for the second half of the study in 10 subjects, a different experimental batch was used, where mannitol and sodium hyaluronate were used as bulk-forming excipients (Table 3).

At this time, methods to quantify the adhesion force and the compressibility of lyophilisates had not yet been developed, but assessment by touch indicated that the latter lyophilisates were both less compressible and easier to separate from the PTFE carrier strip.

3.4. Bioavailability of fluorescein

One OLCS containing 68 μg of fluorescein was administered to one eye of each of 20 subjects, while three drops of conventional eye drops, each containing the same dose, were administered at intervals of 15 min to the contralateral eye. The drug concentration was measured fluorimetrically in the corneal stroma and the mid-anterior chamber. Concentration profiles at both sites are given in Fig. 7. Mean fluorescein concentrations in the cornea were up to 11.3 times higher (at 15 min) after administration of OLCS compared to eye drops (Fig. 7).

Table 2
Effect–time profiles of miotic pupil reaction after administration of a nominal dose of 0.3 mg pilocarpine in OLCS[a] and eye drops[b]

Subject	A_L (min)[c]	A_D (min)[d]	A_L/A_D	Recovered (%)[e]
1	9.70	10.97	0.884	Not available
2	34.07	28.19	1.208	Not available
3	21.89	4.07	5.378	Not available
4	37.07	2.04	18.171	Not available
5	0.66	29.71	0.022	83.71
6	32.30	109.56	0.294	79.52
7	3.16	53.96	0.058	82.74
8	22.53	97.59	0.230	79.20
9	34.69	111.27	0.311	82.20
10	20.89	52.26	0.399	79.83
11	0.0	13.94	0.000	92.25
12	36.67	87.41	0.419	81.61
13	20.54	46.26	0.444	86.64
14	0.0	66.94	0.000	95.51
15	34.73	30.58	1.135	60.62
16	13.58	98.16	0.138	66.53
Mean	20.15	52.68	1.818	80.86
Median	20.81	55.28	1.877	81.90
S.D.	19.98	56.98	1.918	9.59
CV (%)	99.1	108.2	105.508	11,86

[a] Excipient: 125 mg Hypromellose.
[b] Isopto-Pilocarpin 1%, Alcon-Thilo, D-Freiburg.
[c] A_L, normalized area under the effect–time profiles after administration of lyophilisates.
[d] A_D, normalized area under the effect–time profiles after administration of conventional eye drops.
[e] Fraction of nominal dose recovered from carrier strip after administration.

Table 3
Areas under effect–time profiles of mydriatic pupil reaction after administration of a nominal dose of 0.15 mg tropicamide in OLCS and conventional eye drops[a]

Subject	A_L (min)[bd]	A_D (min)[c]	A_L/A_D	Subject	A_L (min)[be]	A_D (min)[c]	A_L/A_D
1	2.60	17.56	0.148	9	13.72	24.81	0.553
2	8.90	53.50	0.166	10	30.30	37.96	0.798
3	19.66	46.33	0.424	11	40.96	8.64	4.740
4	7.72	40.50	0.191	12	15.20	34.71	0.438
5	20.46	67.52	0.303	13	58.12	50.38	1.154
6	49.02	28.79	1.703	14	43.99	30.12	1.460
7	3.59	28.85	0.124	15	43.88	27.56	1.592
8	0.02	30.43	0.001	16	26.64	12.30	2.166
				17	39.01	36.85	1.059
				18	20.56	54.35	0.378
Mean	14.00	39.19	0.383	Mean	33.24	31.77	1.434
Median	8.31	35.47	0.178	Median	34.66	32.42	1.106
S.D.	16.03	16.12	0.548	S.D.	13.64	13.83	1.225
CV (%)	114.55	41,15	143.250	CV (%)	41.03	43.52	85.421

[a] Mydriaticum Stulln® UD 0.5%, Pharma Stulln, D-Stulln.
[b] A_L, normalized area under the effect–time profiles after administration of lyophilisates.
[d] Excipient: 0.25 mg Hypromellose E 50.
[c] A_D, normalized area under the effect–time profiles after administration of conventional eye drops.
[e] Excipients: 0.125 mg sodium hyaluronate + 0.25 mg Mannitol.

3.5. Relationship between freezing conditions and adhesion force in fluorescein-OLCS

The freezing rate can be controlled within wide margins by the onset time and the rate of evacuation. A slow freezing rate is achieved if the vacuum valve remains closed after introduction of the loaded lyophilisate carrier and closure of the chamber. In this case, the valve is opened after completion of freezing at a pressure slightly above the atmospheric level. As long as the chamber is open, it is gently flushed by a stream of sterile and dry nitrogen gas at ambient temperature in order to prevent freezing of atmospheric moisture on the condenser. When the gas flow stops as soon as the chamber is closed, the mean temperature of nitrogen in the chamber drops as the temperature gradient between the walls of the chamber, which are close to room temperature, and the cold condensor surface flattens. The solution freezes when the temperature in the surrounding gas falls below the supercooling limit. It was observed that under these conditions the first ice crystals form at the bottom of the drop and that the freezing front moves up. Solutes are visibly concentrated at the tip of the drop, which becomes slightly pointed.

At the other extreme, the freezing rate is maximized when the vacuum valve is opened wide immediately after the drying chamber is closed. As the pressure drops, water evaporates quickly from the exposed surface of the drop and cools it below the temperature at which ice forms spontaneously. Under flash-freezing conditions the ice front advances rapidly from the exposed surface of the drop downwards, and there are no signs of freeze concentration. The risk of frothing upon rapid evacuation can be controlled by careful de-gassing of the solution prior to freezing.

The pore structure of the lyophilisate, the pattern of residues on the carrier surface after administration, which is particularly visible if the lyophilisate is colored, and the adhesion force depend on the freezing rate. The latter does not correspond to any simple kinetic model and is determined by the setting of a needle valve. A slow drying rate means nominal gas flow rates between 5 and 10 mbar l/s, intermediate flow rates range from 20 to 50 mbar l/s and fast rates settings above 80 mbar l/s. If the drop is frozen slowly, there are usually only slight traces of

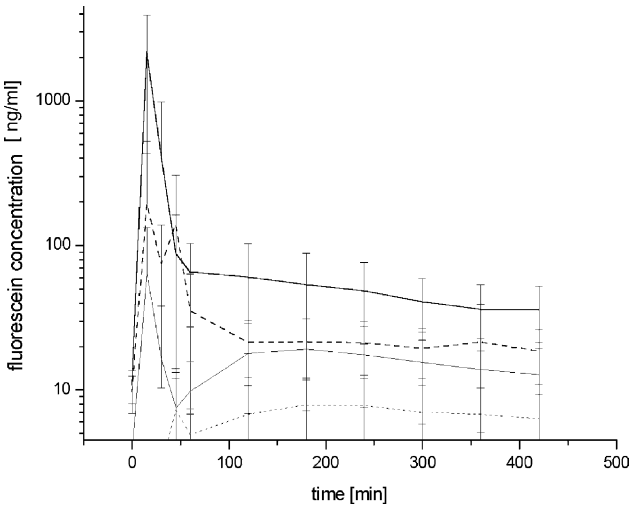

Fig. 7. Fluorescein concentration profiles in the cornea (fat lines) and anterior chamber (light lines) after administration of 1 × 68 μg fluorescein OLCS at 0 min (solid lines) and three drops containing 68 μg fluorescein at 0, 15 and 30 min (dashed lines). Mean and S.D. ($n = 20$).

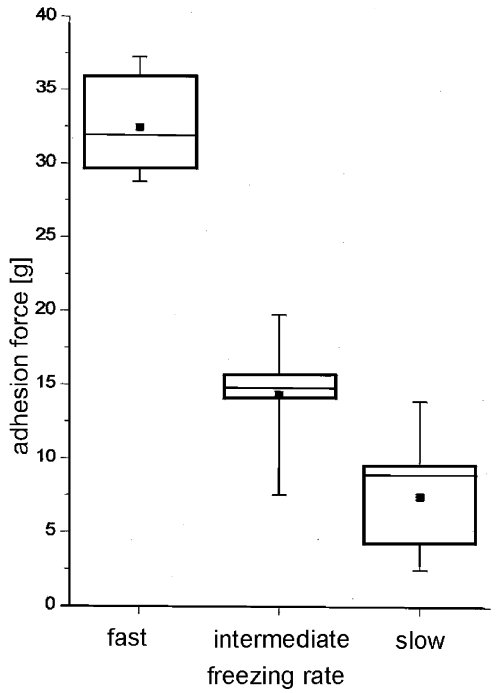

Fig. 8. Correlation between freezing rate and adhesion force. Mean, median, interquartile range and range ($n = 6$).

lyophilisate on the carrier surface, which are primarily located at the circumference and center of the drop, and the adhesion force is low. If freezing is fast, the whole contact surface is covered with an irregular network of polymer foam, and the adhesion is much stronger. The correlation between freezing rate and adhesion force in OLCS containing fluorescein and Hypromellose is given in Fig. 8 [16].

An intermediate freezing rate leading to adhesion forces between 10 and 15 g appears to be optimal.

4. Discussion

A water-free single-dose ophthalmic dosage form making use of the tear fluid as its solvent is insensitive to microbial contamination and chemically more stable than an aqueous solution. Besides, the precision of dosing is increased and the risk of systemic side effects reduced. In an early study on placebo OLCS it has been shown that Hypromellose lyophilisates are well tolerated, and similar results were obtained later with lyophilisates containing pilocarpine, tropicamide and fluorescein. Besides the topical administration of pharmacologically active agents to the eye, similar systems could be used to deliver drugs precisely to other sites, e.g. hemostyptic or nerve-blocking agents during surgery.

For OLCS, the adhesion force between the lyophilisate and its carrier surface and a sufficient resistance to compression and adequate dissolution rate without excessive rigidity are characteristics determining the ease and reproducibility of administration and hence the biopharmaceutical quality of the dosage form. There are several possibilities to control these parameters, e.g. the choice and concentrations of excipients and the material and the structure of the carrier surface, but it appears that the degree of control of freezing and drying conditions is the dominating factor. In batch-oriented freeze dryers, where a larger scale offers economic advantages, the homogeneity of conditions is inversely related to the size of the drying chamber. This is tolerable for goods, where precise control is not essential, but not for sensitive materials or dosage forms like the OLCS. The solution to the problem at hand was to move against the prevailing trend towards bigger and more expensive machinery and develop a mini-freeze dryer, which accepts only one unit at a time. Besides precise control of pressure and temperature, the drying goods can be heated directly by infrared or microwave radiation and since the gas in the chamber is no longer required for the transfer of thermal energy, the drying rate can be increased further by operating the system at a gas pressure as low as 0.02 mbar. Besides the internal temperature of the drops, which is measured by an embedded mini-thermocouple, the surface temperature can be measured non-invasively by an external infrared sensor.

In spite of the dramatic reduction in process cycle time, the production capacity of any single drying chamber will hardly exceed 72 OLCS within 24 h even if loading and unloading are automated. For production on a larger scale, an array of chambers would have to be operated simultaneously, preferably in an isolator. With automatic sequential loading and unloading, the conventional batch-oriented lyophilization process can be converted into a quasi-continuous operation. It is, however, unlikely that the throughput of such an array could ever match the capacity of current large production units. On the other hand, the new method has clear advantages with respect to process development and validation, the processing of very sensitive substances under closely controlled conditions, and the flexible and rapid manufacture of limited quantities of lyophilisates from expensive starting materials. Another interesting aspect is that the conditions optimized in a single cell can be applied directly to any number of cells operating in parallel so that upscaling is not necessary. The number of units produced is directly proportional to the number of cells available and the length of the production run.

The principle of single-unit rapid lyophilization is also applicable to the production of injectable lyophilisates. A laboratory prototype is being tested.

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