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The effect of the solvent on the film-forming parameters of hydroxypropyl-cellulose

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Abstract

In pharmaceutical technology, film-forming agents are often applied in solution during the preparation of solid dosage forms. A wide range of polymers have already been examined, but many of the effects of the applied solvent on the properties of the film are still not fully known. The study of these phenomena might be of great help in the preparation of better films. In the present study, the frequently used polymer hydroxypropyl-cellulose was examined in water and ethanol. The latter solvent exhibits better wetting properties for this polymer. It was found that the use of ethanol enhanced the processibility because of the easier atomization and the shorter drying period. Properties characteristic of the chemical nature (wetting, surface free energy and thermal properties) and the physical behaviour (deformation process) of the poured films were studied. Relevant differences were detected only in the mechanical parameters. The sizes of the free volume holes in the differently prepared polymers were also determined, but this parameter proved irrelevant as concerns alterations of the breaking process. The explanation of the differences processibility of the films might be the different strengths of binding between the macromolecular chains. This phenomenon can also explain the different degrees of hydration of the polymer and the changes in the drying process.

Keywords: HPC; Investigation of solutions; Deformation process; Polymer film; Solvent

1. Introduction

Film-forming polymers are widely used in the formulation of solid dosage forms. These materials are mainly used as coating substances (Cole, 1995) and as binder agents for granulation (Planinšek et al., 2000; Sinha and Kumria, 2002; Prabakaran et al., 2003). The solubility, digestibility and mechanical behaviour of the films formed must be adequate for the objective of their application (Schulze Nahrup et al., 2004; Lafferty et al., 2002; Leong et al., 2002; Fulzele et al., 2002). The films are formed from dispersions of polymers, or

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most simply from solutions of macromolecular film-forming materials (Cole, 1995). The type of solvent can be a very important parameter during the formulation. Mainly aqueous solutions are used because they are environmentally more suitable and cheaper than other solutions. However, an aqueous system cannot be applied in all situations, e.g. a water-sensitive material, effervescent tablets, floating tablets, etc. In these cases, an organic solution (especially in ethanol) is applied (Krögel and Bodmeier, 1999; Bühler, 2001). The polymers (e.g. PVP derivatives and cellulose esters) utilized in inorganic and organic solutions are the same (Bühler, 2001; Pearnchob et al., 2004; Bauer et al., 1988). There are no comparative studies in the literature that deal with the role of the solvent on the behaviour of the resulting films, and consequently on the properties of solid dosage forms containing films.

The main objective of this paper is a comparison of the properties of the films formed from solutions of polymer in different solvents. A polymer was chosen as model which displays excellent solubility in water and in many polar organic solvents: hydroxypropylcellulose (HPC), which is widely employed for film coatings and as a binder for the preparation of granules (Jian-Hwa Guo et al., 1998; Rowe et al., 2003). Water (a polar solvent) and ethanol (a semipolar solvent), the most commonly used solvents, were applied in our work. In the practice of the pharmaceutical industry, however, there is currently to a tendency to eliminate ethanol from coating or granulating fluids because of environmental problems. Accordingly, the aim of our study was to examine how this change influences the film-forming or the properties of the resulting film.

The wetting properties and uptake of the solvent were followed, these parameters relating to the hydration of the polymer in the solvent. The processibility of the solution, which is a very important feature was examined. The viscosity of the fluid is a highly significant parameter because the coating or granulating fluid is mainly processed by atomization. The film-forming time and the minimum film-forming temperature (MFT) are further relevant properties. It is recommended to work at a temperature about 10 °C above the MFT (Bauer et al., 1988). This temperature ensures a smooth, even film. The thickness, wetting, surface free energy, deformation and thermoanalytical parameters of films were compared. The phenomena possibly responsible for the differences experienced were studied. Free volumes were measured by determination of the lifetime of ortho-positronium, a method very often used for polymers (Terashima et al., 2003; Kilburn et al., 2002; Hiemenz, 1984; Süvegh et al., 1999).

2. Materials and methods

2.1. Materials

HPC (Klucel LF, Herkules Inc.) was used as film-forming agent. Klucel LF is a low molecular weight (Mw ≈ 95000) and low viscosity grade of HPC. The moles of substitution of the polymer applied was 3.8. In a previous study, a 10% aqueous solution of this polymer proved a very effective binder material for granules (Deák et al., 1999). The tablets prepared with a high active agent content from these granules exhibited very good mechanical properties. Ten percent aqueous and ethanolic solutions of HPC were prepared. Five milliliters of each solution was poured into a Petri dish with a diameter of 7.5 cm. This solution was then dried on an even surface at 25 ± 2 °C and 50 ± 5% RH. The fresh films were stored in a desiccator (25 ± 2 °C) for 1 day before they were examined. The stored films were kept over silica gel in the same desiccator for 1 month.

2.2. Investigation of solutions

A Brookfield LVDV-II viscosimeter (Brookfield Engineering Laboratories Inc.) was used for the determination of the viscosity of the solutions at 20 °C.

An MFT bar apparatus (Rhopoint Instrumentation Ltd.) was applied to determine the MFT and the film-forming time of a 75 μm-thick layer of solution at different temperatures. The method of evaluation of the film forming time with this apparatus was not previously been reported in the literature. Six parallel measurements were performed.

2.3. Uptake of solvent

A number of studies have demonstrated that there is a connection between this parameter and the hydration of polymers (Ebube et al., 2000; Roy and Rohera, 2002; Munday and Cox, 2000). An Enslin apparatus with a glass filter and a pipette with an accuracy of 0.01 ml

were used to determine the solvent uptake (ethanol and water) of Klucel LF powder. The quantity of fluid was controlled every 10 s. Five parallel experiments were performed.

2.4. Film thickness

Film thickness was measured with a screw micrometer with an accuracy of 0.001 mm (Mitutoyo) at the middle of the 20 specimens.

2.5. Wetting properties

An optical contact angle measuring device (Data-Physics Instruments GmbH) was utilized to determine the wetting properties of the samples (powders and films). An automatic syringe was used for the dropping, and circle fitting was applied to determine the contact angle. The Wu equation was used for the calculation of surface free energy (Wu, 1971).

Compacts of the powder (150 mg) were prepared in a highly polished stainless steel punch and die assembly (13 mm diameter) in a Specac (Specac Inc., Graseby, England) hydraulic press with a 10-s dwell time, at a pressure of 6×10^8 Pa. The compacted powders were stored for 24 h in a desiccator (<20% RH/room temperature) and were examined with the two solvents (water and ethanol).

The films were fixed horizontally in a special sample holder. The test liquids with known surface tension were diiodomethane ($\gamma^d = 50.8$ mN/m, $\gamma^p = 0$ mN/m) and glycerol ($\gamma^d = 32.0$ mN/m, $\gamma^p = 31.70$ mN/m) (Oh and Luner, 1999). Twenty parallel measurements were performed.

2.6. Deformation process

The deformation processes of films can also be examined. The film must be suitably elastic, so that no injury occurs during the subsequent processes. The strength tester and the software were developed in our institute. The aim of our developmental work is to facilitate the investigation of polymers applied in solid dosage forms. This device contains a special specimen holder (20 mm in diameter) and a hemisphere stamp with 201 mm^2 surface and is connected to a computer via an interface; thus, not only can the ultimate deformation force be measured, but the process (force-time, force-displacement curves) can be followed. The round specimen is located horizontally and the stamp moves vertically.

Measuring range was 0–200 N, the speed of stamp was 20 mm/min, the output was 0–5 V, the sensitivity was $\pm 0.5\% \pm 0.1$ digit. The sensor was UNICELL force measuring equipment (MIKI), which was calibrated with C9B 20 kN cell.

Twenty parallel measurements were performed.

2.7. Positron lifetime measurements

The positron source applied for the measurements was made of carrier-free ^{22}NaCl with an activity of 4×10^5 Bq, sealed between two very thin (5 μm) titanium foils. The source was then placed between two cast HPC films.

Positron lifetime spectra were recorded by a conventional fast–fast coincidence system. The system was constructed from standard ORTEC electronic units, while the detectors were made from BaF_2 scintillator crystals and XP2020Q photomultipliers. The time resolution of the system was about 200 ps.

2.8. Thermoanalytical measurements

The DSC examinations of the free films were performed with a Mettler-Toledo DSC 821e (Mettler-Toledo GmbH, Switzerland) instrument. A modulated temperature technique (ADSC) was utilized, the start-temperature was 160 °C, the end-temperature was 240 °C and the sinusoid heating method involved 60 periods with a period of 0.8 min. 10 ± 1 mg of material was taken for each measurement. An argon atmosphere and aluminium pans (40 μl) were used. DSC curves were studied with STAR^e Software. Three parallel measurements were performed.

3. Results

The investigations of the solutions were performed to determine the processibility of the fluids. The viscosity of the ethanolic solution was lower; the atomization of this fluid is therefore easier, a lower atomizing pressure being necessary to produce small droplets of liquid (Table 1). It can be seen from the results of the determination of MFT that this parameter was lower than 0 °C

Table 1
Properties of HPC solutions

	Aqueous solution	Ethanolic solution
η (dPas)	8.2	7.0
MFT (°C)	<0	<0
Film forming time (s)		
25 °C	840.6 (S.D. = 33.1)	123.7 (S.D. = 5.4)
30 °C	452.2 (S.D. = 11.2)	80.2 (S.D. = 5.1)
35 °C	284.4 (S.D. = 13.0)	58.0 (S.D. = 5.8)
40 °C	191 (S.D. = 14.4)	40.7 (S.D. = 6.7)
45 °C	130.4 (S.D. = 9.2)	25.0 (S.D. = 3.8)
50 °C	95.2 (S.D. = 8.0)	15.2 (S.D. = 1.2)
55 °C	62.6 (S.D. = 11.3)	12.7 (S.D. = 1.8)
60 °C	34.4 (S.D. = 18.6)	7.3 (S.D. = 0.5)

for both films. Accordingly the temperatures at which the coating and granulation were generally performed (25–60 °C) are appropriate for the production of a uniform film. There was a significant difference ($p < 0.05$) in the film-forming time. At every temperature, for the ethanolic solution a shorter time was observed. There were significant differences in the characteristics of the drying curves of the different solutions. The best fitting was the exponential for both curves ($R^2 = 0.9949$ for the alcoholic solution, and $R^2 = 0.9924$ for the aqueous solution, respectively), but the equations were very different:

$y = 916.77 \exp(-0.0798x)$ for the ethanolic solution;
$y = 6258.51 \exp(-0.0855x)$ for the aqueous solution.

The uptake of solvent by HPC was significantly different for ethanol and water (Table 2). The uptake of Klucel LF powder was substantially higher for the ethanol test fluid. There was a significant difference in the speed of uptake of the solvent. After 30 s, 62.65% (S.D. = 9.19) of the maximum value could be detected in water, while 99.94% (S.D. = 2.84) of the maximum amount of uptaken solvent could be measured in ethanol. Similarly, there was a difference in the contact angle of the solvent on the surface of the compacted powder. The smaller angle (Θ) for ethanol

Table 2
The wetting properties of HPC

	Water	Ethanol
$\Theta_{solvent}$ (°)	59.58 (S.D. = 0.80)	26.5 (S.D. = 0.86)
Enslin number (ml/g)	0.309 (S.D. = 0.099)	0.732 (S.D. = 0.097)

Table 3
Wetting parameters of films

	Films prepared from aqueous solution	Films prepared from ethanolic solution
$\Theta_{glycerol}$ (°)	71.28 (S.D. = 0.76)	71.21 (S.D. = 0.82)
$\Theta_{diiodomet.}$ (°)	41.22 (S.D. = 0.61)	43.73 (S.D. = 0.84)
γ^p (mN/m)	39.60	38.42
γ^d (mN/m)	3.73	4.05
γ^{tot} (mN/m)	43.33	42.40
Polarity (%)	91.39	90.61

was an indication of the better wetting properties. These differences can denote changes in degree of hydration of the polymer in the solvent with varying polarity. The differing extent of hydration of the film-forming agent can influence the arrangement of the polymer chain, which can affect the parameters of the film after the drying.

There was no significant difference between the film thicknesses (ethanolic: 100.6 ± 16 μm; aqueous: 98.8 ± 22.6 μm). A slight difference was detected for the contact angle of diiodomethane on the surface of the films, and therefore in the surface free energy and in the polarity (Table 3). The wettings of the samples with the polar glycerol were similar, so the dissolution of the films in polar media (e.g. digestive fluids) was not influenced by the solvent.

The two films exhibited deformation curves with similar shapes. They demonstrated very elastic behaviour (Figs. 1 and 2). Each curve can be divided into three parts: a very short elastic period with a small slope, a visco–elastic segment (it is parallel to the x-axis), and a long elastic segment, continuing on to the deformation point. However, there were significant differences ($p < 0.05$) in the force and work of breaking (Table 4). A higher force was necessary to a break a film of the same thickness prepared from ethanolic solution. There was also a difference between the times of deformation, but this was not significant.

Table 4
Deformation parameters of films

	Film prepared from aqueous solution	Film prepared from ethanolic solution
Force (N)	24.13 (S.D. = 3.35)	30.03 (S.D. = 3.79)
Work (mJ)	140.1 (S.D. = 21.1)	186.0 (S.D. = 30.5)
Time (ms)	17435 (S.D. = 1153)	18579 (S.D. = 2043)

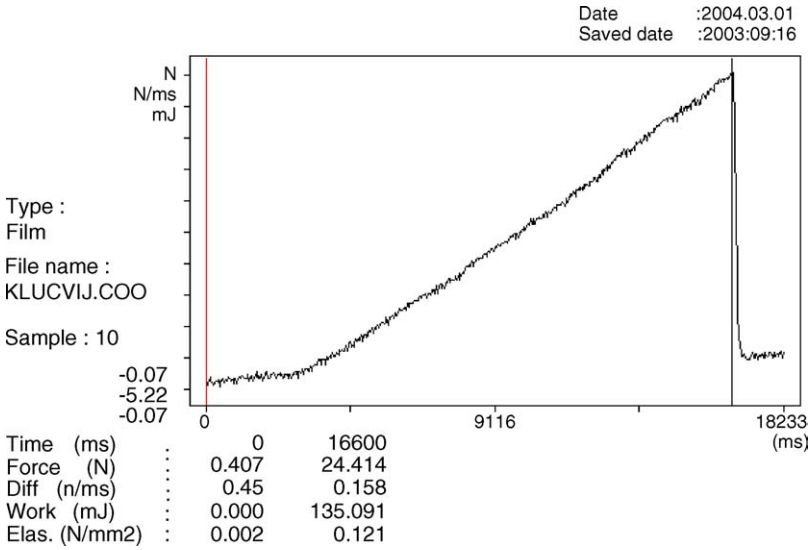

Fig. 1. Deformation of film prepared from aqueous solution.

At this point, the question arose as to that what structural parameter causes this change in the mechanical behaviour. Important pharmaceutical phenomena in polymers used to formulate solid dosage forms can often be explained by determining the size of the free volume holes of the polymer (Süvegh and Zelkó, 2002). Unfortunately, this parameter was not informative in this case. There was no significant difference in the lifetime of the o-Ps (Table 5). Hence, it can be stated that the size of the free volume holes in the differently prepared polymers was not the cause of the alteration in the deformation of the films.

Since it is well known that there is a connection between the free volume and the temperature of the glass transition, thermoanalytical measurements can be useful to support the results of the previous studies. A

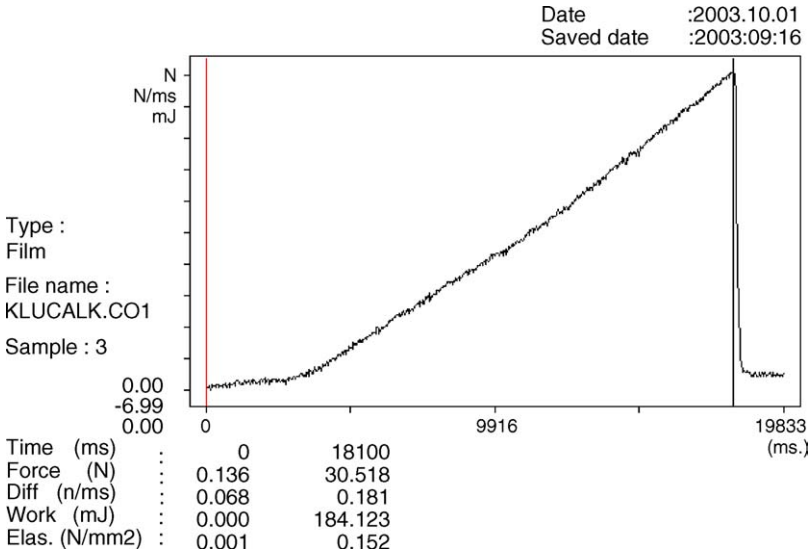

Fig. 2. Deformation of film prepared from ethanolic solution.

Table 5
The o-Ps lifetime of films

	Films prepared from aqueous solution	Films prepared from ethanolic solution
τ_3 (ps)	1940 (S.D. = 8)	1940 (S.D. = 8)
Intensity (%)	19.2 (S.D. = 0.1)	20.0 (S.D. = 0.1)

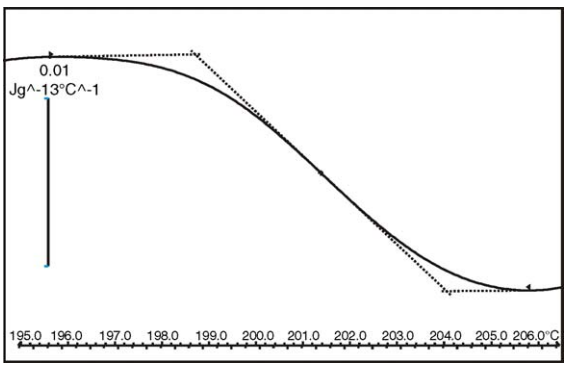

Fig. 3. ADSC curve of film prepared from aqueous solution.

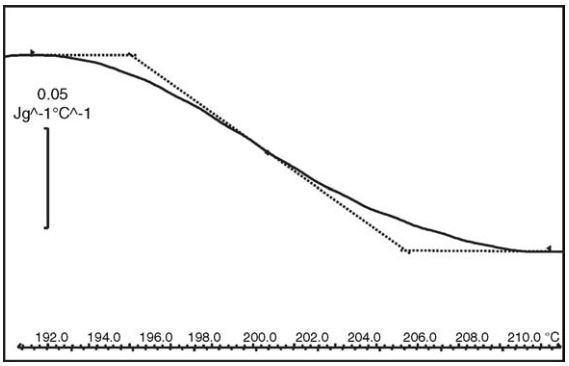

Fig. 4. ADSC curve of film prepared from ethanolic solution.

significant ($p < 0.05$) difference in thermal behaviour between the films prepared from the different solutions could not be detected by ADSC methods. There was a baseline shift of the curve at about 200 °C (ethanolic: 200.8 ± 0.7 °C; aqueous: 200.5 ± 0.7 °C) (Figs. 3 and 4).

4. Conclusion

It can be stated from the results that the viscosity of ethanolic fluid is lower, the film forming from solution of HPC in ethanol is quicker and thus the drying time is shorter. There was no relevant difference in wetting, surface free energy or thermal behaviour between the films. This was confirmed by the similar chemical properties of the film-forming agent. The elastic behaviour of the films did not change, but there was a significant difference between the deformation parameters of the films. This can be explained by the variation in the inner structure of the films. Different types of solvents (polar water and semipolar alcohol) were used, which can influence the hydration and hence the arrangement of the macromolecules. Different types of binding with differing intensity can therefore be applied during the drying, the speeds of this also differing.

Finally, it can be concluded that the properties of films, and hence the solid dosage forms containing these macromolecular films, are influenced by the solvents of HPC solutions.

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