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Aqueous colloidal polymer dispersions of biodegradable DL-lactide/glycolide copolymer as basis for latex films: a new approach for the development of biodegradable depot systems

Andreas Schade [1], Toshiyuki Niwa, Hirofumi Takeuchi, Tomoaki Hino, Yoshiaki Kawashima *

Department of Pharmaceutical Engineering, Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502, Japan

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Abstract

While biodegradable polymers are usually used for the preparation of drug-loaded nanoparticles, we studied the application of biodegradable polymers in the form of aqueous colloidal polymer dispersions for the preparation of latex films. We consider biodegradable latex films as a new interesting approach for the development of pharmaceutical preparations such as the coating of core materials for subcutaneous application. Aqueous colloidal dispersions of the biodegradable DL-lactide/glycolide copolymer (PLGA) were prepared by a spontaneous emulsification solvent diffusion method. Drying of the aqueous colloidal polymer dispersions led to the formation of PLGA latex films. The properties of these PLGA films and the influence of plasticizers were investigated using thermomechanical analysis (TMA) and differential scanning calorimetry (DSC). It was found that polyethylene glycol 1500 (PEG 1500) and triethyl citrate had a good plasticizing effect, decreasing significantly the glass transition temperature (T_g) of the PLGA latex films. The T_g value determined via TMA was higher than that with DSC measurement. It was suggested that DSC might be useful to detect the mobility of plasticizer molecules, whereas TMA could be helpful in detecting the changes in the mechanical properties of films induced by heat. Further, it was found that the amount of residual organic solvent in the present PLGA latex films was below the sensitivity of the assay (gas chromatography).

Keywords: DL-Lactide/glycolide copolymer; Aqueous colloidal polymer dispersion; Biodegradation; Latex film; Plasticizer; Depot system; Nanosphere

1. Introduction

During the past two decades controlled release systems have received increasing attention. However, despite much research activity, the progress

* Corresponding author. Tel. 81-582-37-3931; Fax 81-582-37-5979.

[1] Present address : Hoffmann-La Roche Ltd, POMF-PS, CH-4002, Basel, Switzerland.

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toward safe and effective depot systems has been slow.

Due to problems of safety and effectivity, particular attention has recently been paid to the development of injectable formulations on the basis of biodegradable polymers. Such systems offer important advantages: they are easy to administer, able to release their drug content over a long period of time (some weeks or even longer) and there is no need to remove the spent devices surgically.

The following biodegradable polymers are considered suitable for parenteral depot systems: polylactic acid (PLA), polyglycolic acid (PGA), and DL-lactide/glycolide copolymer (PLGA) as well as polyhydroxybutyrate (PHB) and polycaprolactone (PCL) (Aftabrouchard and Doelker, 1992). Using these biodegradable polymers, significant progress has been made during the last 5 years, leading to the introduction of two new depot systems onto the market: Sandoz Co. introduced Parlodel, containing bromocriptine (Kissel et al., 1991) and Takeda Co. Lupron Depot, containing leuprolide acetate (Ogawa et al., 1988).

We attempted to devise a new approach to the development of biodegradable depot systems: instead of employing biodegradable polymers to prepare drug-loaded nanoparticles, we studied the use of aqueous colloidal dispersions of a biodegradable polymer (PLGA) to prepare films as a basis for depot systems. In this paper, we describe the preparation of aqueous colloidal PLGA dispersions, the properties of PLGA latex films made of colloidal dispersions and the influence of plasticizers and discuss possible future applications.

2. Materials and methods

2.1. Materials

DL-Lactide/glycolide copolymer (henceforth referred to as PLGA) with an average molecular weight of 46772 and with a copolymer ratio of DL-lactide to glycolide of 85:15 was supplied by Du Pont Co., Ltd, USA. The following materials were also used as received: polyvinyl alcohol (PVA-217, Kuraray Co., Ltd, Tokyo, Japan), polyethylene glycol 1500 (PEG 1500, Kishida Chemical Co., Ltd, Osaka, Japan), polyethylene glycol 4000 (PEG 4000, Kishida Chemical Co.), polyethylene glycol 6000 (PEG 6000, Nihon Yushi Co., Ltd, Tokyo, Japan), triethyl citrate SC-60 (Pfizer Co., Ltd, Tokyo, Japan), propylene glycol (Kishida Chemical Co.), and citric acid (Kishida Chemical Co.).

2.2. Preparation of aqueous colloidal dispersions of PLGA

In recent years, several authors have developed different techniques for the preparation of aqueous colloidal dispersion of PLGA (Allemann et al., 1993). One such method is a precipitation technique, including the 'emulsion-solvent diffusion technique' developed by Niwa and coworkers (Kawashima et al., 1989; Niwa et al., 1993), which was used in a modified form. The main modifications to the above-mentioned technique are that the amount of PLGA was much greater (6 g instead of 120 mg) and no drug was used.

PLGA (6 g) was dissolved in a mixture of 800 ml acetone and 25 ml dichloromethane. The resultant organic solution was added to 600 ml of an aqueous PVA solution (2%, w/v), with continuous stirring with a common magnetic stirrer (Model BHR-2, Toyo Seisakusho Co., Japan) under reduced pressure. The speed of addition of the organic solution was 0.8 g/min. After the end of liquid addition, stirring of the dispersion under reduced pressure was continued for a further 6 h in order to remove the organic solvents. During evaporation of the organic solvents from the dispersed droplets of the organic PLGA solution, the droplets were solidified in the aqueous solution; these solidified PLGA droplets are designated nanospheres (Niwa et al., 1993). After completion of evaporation, the dispersion was filtered through a 300 mesh sieve to remove aggregated PLGA particles. The dispersed PLGA nanospheres were sedimentated by ultracentrifugation ($156200 \times g$ for 1 h; CP-56 G, Hitachi Koki Co., Tokyo).

To clean the resultant PLGA nanospheres, the aqueous supernatant was removed. The sedimented nanospheres were redispersed in 400 ml

distilled water under stirring for 2 h and then sedimented as above by ultracentrifugation. Once again the nanospheres were cleaned by redispersion in 400 ml distilled water and sedimentation by ultracentrifugation. The supernatant was removed and the sedimented PLGA nanospheres were redispersed in a small volume of distilled water by stirring.

Depending on the amount of PLGA necessary for the experiment (more than 6 g PLGA often being required), the entire preparation procedure was carried out several times. The resultant colloidal PLGA dispersions were collected, sieved through a 300 mesh sieve and stored at 4°C. The PLGA content of the latex dispersion was calculated by measuring the dry weight of a representative sample after vacuum evaporation of the water. The final aqueous colloidal PLGA dispersion was diluted to the desired concentration and was ready to be used. The scheme of the preparation procedure is shown in Fig. 1.

2.3. Analysis of the aqueous colloidal PLGA dispersion

The average particle size of the PLGA nanospheres in the resultant aqueous colloidal polymer dispersion was measured by means of a laser particle analyzer (LPA 3100, Otsuka Electronics Co., Ltd, Osaka, Japan) and a photon correlator (LPA 300, Otsuka Electronics Co.), using a dynamic light scattering method. The recovery of PLGA finally found as nanospheres in the aqueous PLGA latex dispersion was assessed by vacuum drying of a representative sample. PLGA recovery was calculated based on the ratio of the weight of the nanospheres (after vacuum drying) to that of the starting PLGA polymer. The topography of nanospheres obtained by drying diluted suspension under room temperature was observed by means of a scanning electron microscope (JSM-T330A, Nihon Denshi Co., Ltd, Japan).

2.4. Preparation of PLGA latex films

In order to study the properties of PLGA films made of aqueous colloidal PLGA dispersions, film formation had to be carried out under reproducible conditions. To this end, the following film preparation method was used: 5.0 ml of a colloidal PLGA dispersion (containing 13% PLGA) was dropped on a Teflon film, stuck to a horizontal glass plate to achieve a very smooth surface. A constant surface and thickness of the film was achieved by surrounding the Teflon tape by a

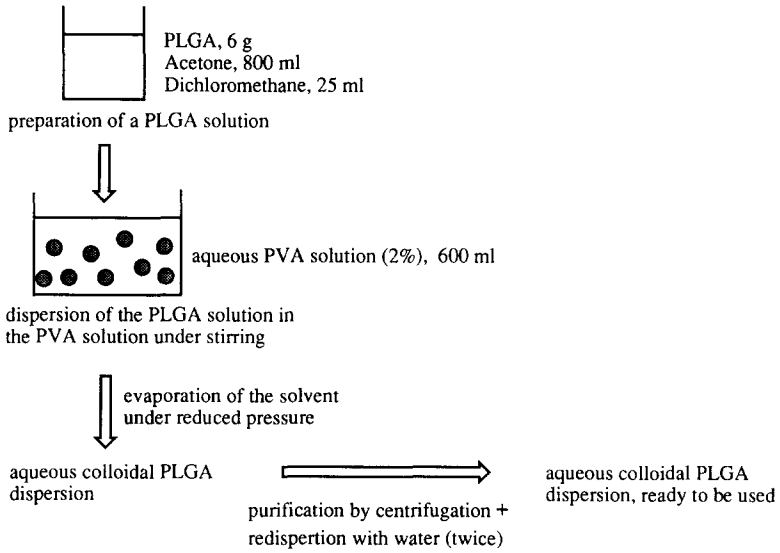

Fig. 1. Scheme of the preparation procedure of aqueous colloidal PLGA dispersions.

metallic frame. The frame had a square shape and an inner size of 4.7 × 4.7 cm, thus leading to the formation of films with a surface of 22.09 cm^2. If not otherwise stated, the drying of the films was carried out at 25°C in a desiccator for 3 days.

In order to obtain PLGA films with better mechanical and pharmaceutical properties, various plasticizers were added to the colloidal PLGA dispersion on a weight basis in percent (weight of the plasticizer/weight of the PLGA nanospheres) to the stock colloidal PLGA dispersion, and latex films were prepared as described above.

2.5. Differential scanning calorimetry (DSC)

To exclude the influence of the DSC calorimeter, two different DSC instruments were used for the examination of each sample: (1) a DSC SSC/560 (Daini Seikosha, Tokyo, Japan) and (2) a DSC 200 (Seiko Instruments Inc., Tokyo, Japan). Calibration was conducted with indium (m.p. 156.5°C) used as a standard reference. Since the glass transition temperatures of PLGA films never showed differences more than 2°C between both DSC instruments, both were considered as reliable and the average value of both instruments was used. Samples of the films (1.8–2.1 mg), prepared as described above, were placed in open or sealed aluminium pans, respectively. The samples were program-heated at a rate of 10°C/min from −30 to 200°C under a nitrogen gas purge. The films were not preheated as the glass transition temperature was difficult to detect after preheating.

2.6. Thermomechanical analysis (TMA)

A latex PLGA film specimen with thickness in the range of 0.2–0.25 mm, prepared as described above, was mounted in the probe and sample tube of a Seiko model TMA/SS 100 thermomechanical analyzer (Seiko Instruments Inc., Tokyo, Japan). The apparatus was operated in the penetration mode under an applied load of 2 g, while continuously heating from −20 to 250°C at a rate of 5°C/min. The films were not preheated. The onset point of T_g was determined using the standard program supplied by Seiko Instruments. All the DSC and TMA measurements were made at least in duplicat. The mean deviation did not exceed 2°C in any instance.

2.7. Gas chromatography (GC)

Aqueous based PLGA films were prepared as described above by dropping an aqueous PLGA dispersion onto a Teflon tape. For drying, a convection oven (KCV-4D, Advantec Toyo Co., Ltd, Japan) at 60°C was used. Organic based PLGA films were prepared identically by dropping 5.0 ml of a PLGA solution in acetone (13%, w/v) onto the Teflon tape, and drying as for the aqueous films.

An accurately weighed probe (10–25 mg) of the PLGA film was filled in a 10 ml vial. 3.0 ml *N,N*-dimethylformamide and 0.5 ml ethyl acetate, as internal standard, were filled in the vial which was capped with a rubber and an aluminium seal ring (Shimadzu Co., Kyoto, Japan). After heating the vial to 95°C for 10 min to dissolve the films, the vials were kept at 60°C for 30 min. The air above the solution was analysed with a gas chromatograph GC-14A (Shimadzu Co., Ltd, Kyoto, Japan), equipped with an FID detector. The amount of acetone was calculated on the basis of the area response in relation to the internal standard (ethyl acetate). Analysis of standards in the concentration range of 50 ng to 2000 μg acetone showed excellent linearity ($r = 0.999$) for amounts of acetone down to 250 ng.

3. Results and discussion

3.1. Properties of the aqueous colloidal PLGA dispersion

The recovery of the PLGA in aqueous colloidal PLGA dispersions prepared according to the above preparation method was investigated using vacuum drying. The recovery of the PLGA was 40%. This result indicates that the degree of recovery was poorer than in the preparation procedure for smaller amounts of PLGA (Niwa et al., 1993), where over 75% recovery was achieved.

The loss during recovery is due mainly to the fact that less PVA solution and less acetone is used. Nevertheless, the recovery is still within a reasonable range and a greater recovery can be expected by catering to the scale-up effect.

The average particle size of the PLGA nanospheres (mean diameter) of the dispersion was 355 nm (SD: 21 nm). The particle size of the PLGA nanospheres did not change during storage for 10 days at 4°C. While PLGA nanospheres are usually produced by using a stirrer at a high rate of revolution, in our preparation procedure a common magnetic stirrer was sufficient. Because the magnetic stirrer has several advantages compared to high speed stirrers, such as no warming up of the solution, reduced electrical power consumption and the possibility to work in a closed system, which can also be used for a sterile production, this is an interesting point for the preparation of nanospheres. Nevertheless, the particle size of the resultant PLGA nanospheres (355 nm) is rather small, thus providing a good colloidal dispersion, which can also be stored for a number of days. Therefore, this preparation procedure can be considered as an interesting alternative to existing methods for nanoparticle preparation.

3.2. Influence of various plasticizers on PLGA latex films

It was found that when the aqueous suspensions of nanospheres were dried at room temperature, the dried nanospheres formed a porous latex film due to the fusion of each particle as shown in Fig. 2. This finding inspired us to improve the film property with the aid of a plasticizer and to establish an aqueous based dispersion system to produce a biodegradable latex film. In order to investigate the properties of aqueous based PLGA films and to study the influence of plasticizers, DSC was used. In order to examine the reliability and reproducibility of the DSC measurement, the glass transition temperature of PLGA films made of an aqueous colloidal PLGA dispersion was investigated and was found to be 48.7°C, with a standard deviation of 1.7°C ($n = 10$). This value corresponds with that given by the supplier for pure PLGA, thus demonstrating good reliability and reproducibility of the DSC measurement of PLGA films.

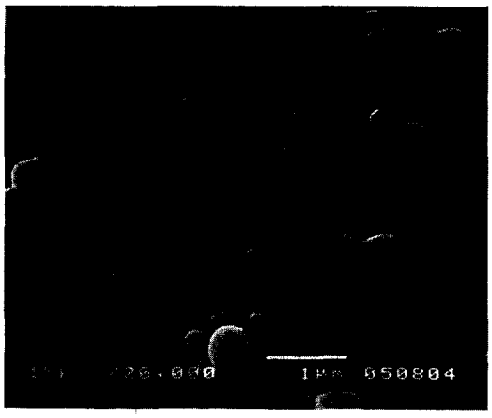

Fig. 2. Scanning electron microphotograph of PLGA nanospheres dried at room temperature.

Table 1
Influence of plasticizers on the glass transition temperature (T_g) of PLGA films made of aqueous colloidal PLGA dispersions; measured by DSC

Plasticizer	Concentration (%)	Glass transition temperature (°C)
No plasticizer	0	48.7
Citric acid	15	49.0
Urea	15	47.0
Propylene glycol	15	46.5
PEG 6000	15	48.1
PEG 4500	15	49.5
PEG 1500	15	25.6
Triethyl citrate	15	18.6

To study the effect of plasticizers on the PLGA latex films, various plasticizers were added to the PLGA latex dispersion. Only plasticizers which are considered to be of relatively low toxicity were used in this experiment.

In the DSC charts the glass transition temperature was found to be the only endothermic point. The influence of various plasticizers on the properties of the PLGA latex film was therefore compared by measuring the glass transition temperature (T_g) of the PLGA films (Table 1), whereby a decrease in the glass transition temperature is, according to the literature, regarded as a sign of an improvement in the film properties (McGinity, 1989a). The results of DSC measurement (Table 1) show that most of these plasticizers have only a

slight effect, if any, on the glass transition temperature of aqueous based PLGA films. Only PEG 1500 and triethyl citrate exerted a significant influence on the glass transition temperature.

The fact that citric acid and urea, which are strong plasticizers for aqueous HPMC and PVA films (Okhamafe and York, 1988), have no significant effect on PLGA latex films is assumed to be due to the high hydrophilicity of the two plasticizers, which are highly water-soluble. While HPMC and PVA are hydrophilic and water-soluble, PLGA is lipophilic and not water-soluble. Theoretically speaking, the suitability of a plasticizer for a polymer can be determined by the miscibility based on the solubility parameters of the polymer and the plasticizer. If the solubility parameters of the polymer and the plasticizer are known, the enthalpy of the mixture can be determined. The enthalpy of the mixture is dependent on the relative solubility parameters and the best theoretical case is a binary mixture in all proportions (McGinity, 1989b). While such theoretical constructs may have only limited application for the exact prediction of the properties of a plasticizer for a given polymer, they can provide a good tool for understanding the influence of plasticizers. Taking into account these considerations, it is quite reasonable that the highly water-soluble plasticizers citric acid and urea, and also propylene glycol, showed no significant plasticizing influence on the water-insoluble polymer PLGA.

The different influences of the various PEGs could be attributed to several factors. PEG 6000 and PEG 4500 have a higher molecular weight than PEG 1500. The molar concentration, which is mainly related to the plasticizer effect, of PEG 1500 is much greater than that of PEG 4500 and PEG 6000 of the same weight concentration (15%). Another point is that the melting point of PEG 1500 is significantly lower that of the other two PEGs. The melting point of a plasticizer influences its temperature-dependent mobility in the film and the efficiency of the plasticizer. Furthermore, the molecular size of the PEGs may have an effect. PEG 1500 molecules are smaller and may therefore have a greater mobility between the polymer chains of the PLGA. The interposition of PEG 1500 molecules between adjacent PLGA chains might influence the intermolecular interaction and hence laed to a fall in the glass transition temperature.

Since triethyl citrate is considered as questionable for parenteral use, attention was mainly paid to the less problematic PEG 1500 in our experiments. Although PEG 1500 has thus far been widely used only for external and oral preparations, polyethylene glycols have also been recently under investigation for parenteral applications (Martindale, 1993) due to their relatively low toxicity.

3.3. *Influence of PEG 1500 on PLGA latex films*

The influence of the concentration of PEG 1500 on the properties of PLGA films was studied in order to determine the PEG concentration which reduces the glass transition temperature significantly at a reasonable low concentration. PLGA films containing different PEG 1500 concentrations were prepared as described above. The influence of the PEG 1500 concentration on the glass transition temperature (T_g) measured by DSC is depicted in Fig. 3. The glass transition temperature of the PLGA films decreases sharply with increasing PEG 1500 concentration, when the PEG concentration is below 10 wt%. On increasing the PEG concentrations above 10 wt%, the decrease in the glass transition temperature is less sharp.

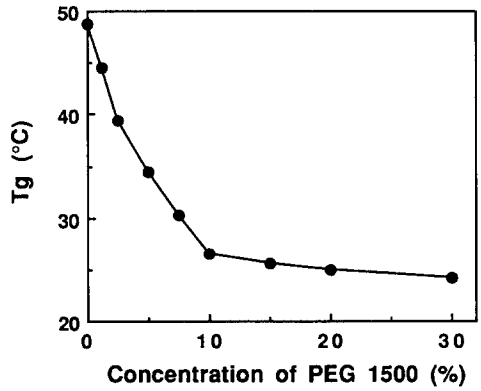

Fig. 3. Influence of PEG 1500 concentration on the glass transition temperature (T_g) of PLGA films made of aqueous colloidal PLGA dispersions; measured by DSC.

This decrease in the glass transition temperature or in the softening point of a film in relationship to the concentration of a plasticizer over a limited concentration range is a well-known phenomenon and an empirical relationship (Eq. 1) which expresses the softening point as a function of the mole fraction of the additive was proposed (Okhamafe and York, 1988):

$$T_s = T_0 \cdot e^{-kn} \quad (1)$$

where T_s (in °C) is the softening point of a film containing an additive, T_0 denotes the softening point of the film without an additive, n is the mole fraction of the additive and k represents the softening point depression coefficient. In a plot of ln T_s vs n, k can be evaluated as the slope of the linear portion of the plot. The higher the value of k, the greater the plasticizer efficiency is. The data for the glass transition temperature measured by DSC as shown in Fig. 3 have been replotted in the above manner in Fig. 4. The compatibility limit of the plot was 10 wt%, which is similar to that reported in the literature (Okhamafe and York, 1988). Above the compatibility limit of the plot, the curve does not follow the empirical relationship of Eq. 1, due to a kind of saturation effect. The slope k and the regression coefficient of the initial linear portion of the plot were calculated, and k was found to be 0.063, indicating a significant plasticizing effect of PEG 1500 for PLGA latex films, while the regression coefficient of this plot was 0.990.

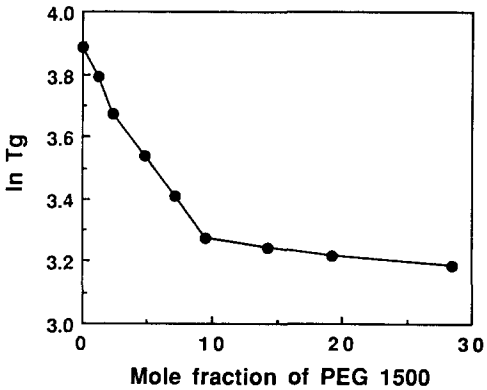

Fig. 4. Influence of mole fraction of PEG 1500 on the glass transition temperature (T_g) of PLGA films made of aqueous colloidal PLGA dispersions; measured by DSC.

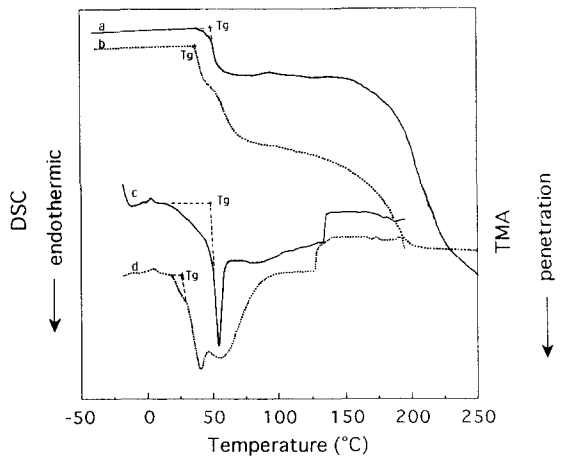

Fig. 5. Comparison between the TMA and DSC charts of PLGA latex film: (a) TMA chart of a pure PLGA film; (b) TMA chart of a PLGA film containing 30% PEG 1500; (c) DSC chart of a pure PLGA film; (d) DSC chart of a PLGA film containing 30% PEG 1500.

3.4. Comparison between DSC and TMA analysis of PLGA latex films

In order to examine the influence of the PEG 1500 concentration on the thermomechanical properties of PLGA latex films, PLGA films containing different PEG amounts, were investigated using thermomechanical analysis (TMA), and the results were compared to those of the DSC measurements. In Fig. 5, a comparison between the TMA charts of a pure PLGA film and a PLGA film containing 30% PEG 1500, and the DSC charts of the same films is shown. Fig. 5 demonstrates that the glass transition temperature of a pure PLGA film occurs at nearly the same temperature in both the DSC and TMA charts (DSC, 48.7°C; TMA, 48.5°C). However, PLGA films containing 30% PEG show a different behaviour between the DSC and TMA charts: the T_g value in the DSC chart is lower than that in the TMA chart (DSC, 24.2°C; TMA, 36.8°C).

This difference between TMA and DSC data is not surprising and was also found by other researchers for aqueous HPMC and PVA films (Okhamafe and York, 1988), where generally the TMA data for the glass transition temperature were greater than the corresponding DSC data. An explanation of this difference may be that

DSC is more sensitive to the thermal events caused by the plasticizer. The plasticizer molecule is significantly smaller than the polymer and is able to move more freely than the polymer. This may be the reason why the plasticizer can be activated with a lower thermal energy to result in an endothermic effect in the DSC charts than in the corresponding TMA charts. On the other hand, TMA analyzes the penetration in the film, i.e., it is dependent on the macrostructure of the film. Because the softening of the film is strongly influenced by the mobility of the polymer molecules, TMA may be more suitable for detecting the actual change in film dimensions than DSC.

In the TMA charts a previously unknown softening point between 130 and 170°C was found, which decreased with increasing plasticizer concentration. Since this softening point also appeared in the charts of the pure PLGA latex films, it must have been caused by PLGA. High temperature transitions of polymers are generally ascribed to a sharp increase in polymer chain mobility, due to the disruption of intra- and inter-chain interactions. This leads to a loss in the compact structure of the film, observed as softening of the film in the TMA analysis.

Furthermore, a previously unknown exothermic increase between 125 and 140°C was observed in the DSC charts, which is caused by PLGA and is only slightly influenced by the plasticizer. This exothermic increase in the DSC charts is due to a sudden change in the thermal energy of the polymer caused by reordering of the polymer chain, but cannot yet be fully explained.

3.5. Influence of PEG 1500 on the thermomechanical film properties

The relationship between the thermomechanical properties of the aqueous based PLGA films and PEG 1500 concentration was studied by TMA measurements. For a comparison of the thermomechanical properties, the glass transition temperature, which is easier to monitor and to explain than the high temperature transition in the TMA charts, was used as the basis (Fig. 6). Similarly to the DSC measurements, the glass transition temperature (T_g) decreases with increasing PEG concentration. However, the TMA data for the glass transition temperature suggest a less significant influence of low PEG 1500 concentrations (below 15%) on the glass transition temperature than that seen in the DSC data (Fig. 3 and 6). This phenomenon is assumed to be due to the different measuring procedures employed, as explained above.

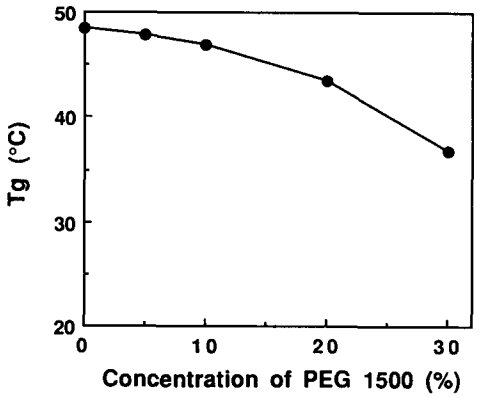

Fig. 6. Influence of PEG 1500 concentration on the glass transition temperature (T_g) of PLGA films made of aqueous colloidal PLGA dispersions; measured by TMA.

Via both analysis methods, DSC and TMA, PEG 1500 was found to reduce the glass transition temperature of PLGA latex films significantly and may be regarded as a suitable plasticizer for such latex films.

3.6. Residual organic solvents in the PLGA films

The present authors are aware that a large amount of organic solvents (mainly acetone) is used in the preparation procedure. This means that the aqueous colloidal polymer dispersion and the resulting films may also contain a certain amount of organic solvents. To judge the toxicity of the residual organic solvents in the film, the residual amount of acetone in the PLGA latex film was determined. The amount of PVA which may also be contained in small quantities in the PLGA latex films was not investigated in this paper.

For comparison, the amount of acetone found in PLGA films made of a PLGA solution in acetone was also examined. Both films were pre-

Table 2
Residual amounts of acetone in PLGA latex films

Drying time (h)	Acetone based PLGA film	Aqueous based PLGA film
3	0.75%	not detectable
6	0.40%	not detectable
24	0.33%	not detectable

pared and dried under the same conditions. Analysis of the residual organic solvents was carried out by gas chromatography. As it was assumed that a longer drying time would reduce the amount of organic solvents in the PLGA films, the influence of the drying time was also studied (Table 2).

While the residual amount of acetone in the acetone based PLGA films was quite high and could not be reduced significantly by longer drying time, the residual amount of acetone in the aqueous based PLGA films was below the sensitivity of the assay (250 ng), which corresponds to 10 ppm, i.e., orders of magnitudes below the acetone content of the organic films. These findings are not surprising: although acetone is used for the preparation of the aqueous colloidal PLGA dispersion, nearly all the acetone is removed after the formation of the PLGA nanospheres by 6 h evaporation of the dispersion. Therefore, at the beginning of the drying of the films, the aqueous PLGA dispersion already contains nearly no acetone, while the PLGA solution contains pure acetone, which is very difficult to remove. These results indicate that the residual amount of acetone found in the PLGA latex films is very low and should not be of toxicological importance.

4. Conclusions

Biodegradable latex films have been prepared using aqueous colloidal PLGA dispersions. Suitable plasticizers for such biodegradable latex films have been found using DSC and TMA analysis. The use of biodegradable latex films for pharmaceutical applications such as the preparation of solid dispersions by spray drying or coating of core materials may provide interesting new possibilities to develop parenteral depot systems.

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