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Changes in Molecular Weight of Polyacrylate, Ph. Eur., Induced by Temperature, Light, and Time

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ABSTRACT

Drug release profiles of formulations coated with polyacrylate, Ph. Eur. (Eudragit® NE30D), may change upon their storage conditions. These drug release changes are investigated by determining the changes in intrinsic viscosity and molecular weight of the polymer induced by temperature, light, and time. Free polyacrylate polymer was obtained by dip casting. The polymer was exposed either for 1 year to temperatures in the range of 5°C to 61°C to check the thermal stability, or for 24 hr to an intensive light source to check light stability. Results show an increase in intrinsic viscosity and an increase in molecular weight of the polymer with increasing temperature and time, indicating an ongoing polymerization of polyacrylate. After light exposure, the intrinsic viscosity as well as the molecular weight of the polymer decreased, indicating a depolymerization of polyacrylate.

INTRODUCTION

Pharmaceutical formulations are often coated, e.g., to modify drug release (enteric or sustained-release coatings), to mask the taste, or to improve the stability of a product.

After coating, stability studies are carried out on the drug formulations in order to detect any changes in drug release profiles or decomposition of the drug. It turned out that drug release profiles of film-coated formulations can change in time (1-3). This phenomenon is known as aging of the coating material. Chowhan (2) investigated the release of ticlopidine·HCl tablets coated with various polymers. In general, after storage at 23°C or 37°C at 95% relative humidity, a decrease in dissolution rate was found in time, sometimes after an initial increase. Murthy et al. (3) described the effect of storage on the release of procainamide·HCl tablets coated with Aquateric® (aqueous cellulose acetate phthalate dispersion). The drug release rate decreased enormously after storage for 3 months at room temperature. A decrease in drug release rate was also observed with pro-

cainamide·HCl tablets coated with Coateric® (aqueous polyvinyl acetate phthalate dispersion) after storage for 9 months at room temperature. Polymer properties can be influenced by temperature and humidity as well as by additives and light (4–6). From the paint industry it has been known for a long time that polymer properties can change after exposure to light (7). The same phenomenon has been described for film-coated drug formulations. Thoma et al. (8) observed an increase in drug release rate after exposing Eudragit-RS–dibutylphthalate-coated pellets to diffuse daylight at room temperature over 30 months.

Changes in polymer structure are reflected by a change in the intrinsic viscosity of polymer solutions (9). Furthermore, changes in the molecular weight of polymers can be detected by gel permeation chromatography.

The aim of the present study was to detect changes in polymer structure of free polyacrylate polymer after thermal and light stress by using viscosity measurements and gel permeation chromatography (GPC).

EXPERIMENTAL SECTION

Materials

- Polyacrylate Ph. Eur.: poly(ethyl acrylate:methyl methacrylate) = 2:1, Eudragit NE30D; Röhm Pharma GmbH, Weiterstadt, Germany. Five different batches, referred to as batch numbers 1 to 5.
- Nitroethane: Aldrich Chemie, Steinheim, Germany.
- Tetrahydrofurane (THF) purified; technical THF is filtered under vacuum through a Fluoropore membrane of 0.5 μm after contact for 24 hr with molecular sieves of 4 Å porosity previously heated for 24 hr at 180°C under vacuum.
- Polystyrene: Waters calibration standards with molecular weights: 2025, 3550, 10,000, 19,750, 50,000, 97,200, 171,000, 402,000, 830,000, and 2,050,000 Da.
- Dried silicagel: J. T. Baker B.V., Deventer, The Netherlands.

Methods

Preparation of Free Polyacrylate Polymer

Free polyacrylate polymer was obtained [using a modification of the casting process as described by Okhamafe and York (10)] by a continuously dipping–drying process as shown in Fig. 1.

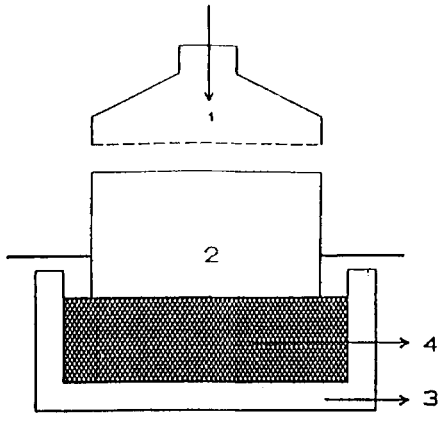

Figure 1. The dip-cast process. 1 = drying air; 2 = rotating glass drum; 3 = jacket (temperature controlled); 4 = polyacrylate dispersion.

The glass drum rotated in the polyacrylate dispersion. During every rotation a thin film was built up and dried before the next dip, to create finally free polymer.

After dip casting, the polymer was easily removed from the glass surface. The rotational speed of the drum was 0.33 rpm. The outer diameter of the drum was 20 cm.

The temperature of the dispersion was between 5°C and 8°C. The temperature of the drying air was between 40°C and 45°C.

Viscosity Measurements

Samples of the polymer were dissolved in nitroethane in a concentration range of 0.4 to 1.5 g/100 ml solution. The solutions were stirred for 18 hr at room temperature to complete dissolution.

The viscosity of the solutions was determined at 25°C using the measuring system O-1383 of the RHEOMAT 30 rotation viscometer (Contraves—Zürich, Switzerland) using shear rates between 213 sec^{-1} and 534 sec^{-1}.

Gel Permeation Chromatography

The molecular weight distribution curve of the polymer was determined by GPC. The following GPC conditions were used:

Column	Shodex 50 cm length, type A80M (SHOWADENKO; catalog number 34134)
Column temperature	25°C

Solvent	THF, purified
Flow	1 ml/min
Concentration	2 g/l solution
Injection volume	50 µl
Detection	differential refractional index (DRI)
Calibration	Polystyrene standards

It is noted that molecular weight is given in polystyrene equivalents expressed in daltons (Da) and not in absolute terms.

Storage Conditions

To study the thermal stability, the polymer was stored in glass containers. The containers were covered with a nylon NYBOLT filter tissue PA 30/17 (Schweizerische Seidengaze Fabrik AG—Zürich, Switzerland) and put in dessicators filled with dried silica gel.

The containers were stored in the dark at temperatures of 5°C, 21°C, 41°C, and 61°C, respectively. Samples were taken after a storage time of 4, 12, 26, and 52 weeks.

To study the light stability, the polymer was put on open glass dishes (20 cm diameter). The dishes were put into a Suntest apparatus (Original HANAU Quarzlampen GmbH—Hanau, Germany) for 24 hr using a xenon lamp with an intensity of 830 W/m^2 and a wavelength between 300 and 830 nm.

RESULTS AND DISCUSSION

Intrinsic Viscosity

Free polyacrylate polymer was dissolved in nitroethane and shear curves were measured. From these curves the viscosity of the solution was calculated.

The viscosities η obtained for various concentrations C of polymer were used to calculate the reduced viscosity, η_{red} [Eq. (1)]. The linear relation between η_{red} and concentration C, as proposed by Huggins (11), [Eq. (2)], was used to calculate the intrinsic viscosity [η]:

$$\eta_{red} = (\eta/\eta_{0-1})/C \quad (1)$$

$$\eta_{red} = k \cdot [\eta]^2 \cdot C + [\eta] \quad (2)$$

In Eq. (1), η_0 is the viscosity of the solvent. In Eq. (2), k is a constant for a given polymer–solvent system and a given temperature, the intrinsic viscosity [η] is the extrapolated value of η_{red} as C becomes zero. The intrinsic viscosity of unstored polymer was calculated and the results for five batches are shown in Table 1. Free polymer was stored for 1 year at different temperatures. During this storage period, samples were taken after 4, 12, 26, and 52 weeks. The reduced viscosities were determined and the values of the intrinsic viscosity were calculated using Eq. (2).

The results of the intrinsic viscosity determinations for the five batches of polyacrylate polymer after 1-year storage at 5°C, 21°C, 41°C, and 61°C are shown in Table 1. The mean results of the intrinsic viscosity for five batches of polyacrylate polymer after temperature stress during 1 year are shown in Fig. 2.

The results in Table 1 show that there are differences in the intrinsic viscosity of unstored polymer. The intrinsic viscosity is related to the molecular weight of polymers. Rowe (12) showed the influence of the molecular weight of polymers on drug release rates. The differences in intrinsic viscosity of unstored polyacrylate polymer may account for differences in drug release rate from formulations coated with this material.

Table 1

Intrinsic Viscosity of Polyacrylate Before and After Temperature Stress During 1 Year at Different Temperatures

Batch No.	Intrinsic Viscosity (dl/g) after 52 Weeks at Various Temperatures				
	Unstored	5°C	21°C	41°C	61°C
1	1.54	1.93	1.95	2.38	Insoluble
2	1.80	1.84	1.80	2.50	Insoluble
3	1.60	1.88	1.79	2.15	Insoluble
4	1.92	1.84	1.98	2.20	Insoluble
5	1.71	1.85	2.06	2.12	Insoluble
Mean	1.71	1.87	1.92	2.27	NA
SD	0.14	0.03	0.11	0.15	NA

Note: NA = not applicable; *SD* = standard deviation (n = 5) of [η].

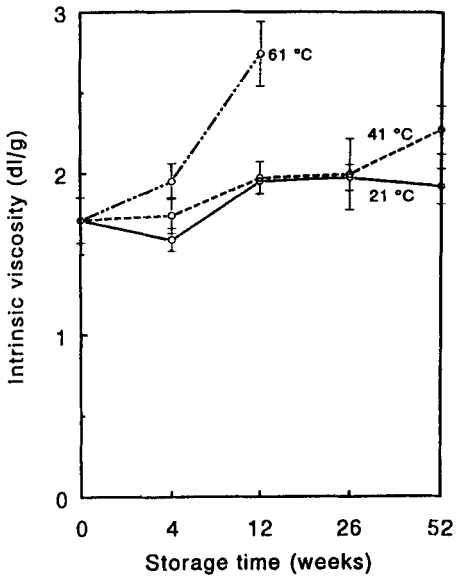

Figure 2. Effect of storage time on the intrinsic viscosity of polyacrylate polymer at different temperatures.

After a storage period of 1 year, it is found that the intrinsic viscosity increases with an increasing temperature up to 41°C. After a storage period of 12 weeks at a storage temperature of 61°C, the polymer became insoluble. The mean intrinsic viscosity had reached a value of 2.74 dl/g.

From Fig. 2, it is clear that the mean intrinsic viscosity after a temperature stress of 41°C increases with storage time. At temperatures above 41°C, the intrinsic viscosity increased sharply with storage time, as mentioned above. At temperatures below 41°C it was found that the changes in intrinsic viscosity after storage time of 52 weeks was in the same range as for 12 weeks at 41°C. Hence, it is concluded that at temperatures up to 21°C, relatively small changes in the polymer structure are found. At 41°C, changes in the polymer structure are ongoing in time, whereas at 61°C a fast change leads to a much more dramatic change in polymer structure.

Since the intrinsic viscosity increases, it is concluded that the polymer chain length increases, pointing to ongoing polymerization under thermal stress.

Polyacrylate polymer was exposed to light during 24 hr in a SUN-test apparatus. After exposure, samples were taken and the reduced viscosities were calculated. The intrinsic viscosities calculated from these results are shown in Table 2.

Table 2

Intrinsic Viscosity of Unstored and Light-Stressed Polyacrylate Polymer

Batch No.	Intrinsic Viscosity (dl/g)	
	Unstored	Light Stressed
1	1.54	1.51
2	1.80	1.51
3	1.60	1.55
4	1.92	1.48
5	1.71	1.46
Mean	1.71	1.50
SD	0.14	0.03

Note: *SD* = standard deviation (n = 5) of [η].

The results in Table 2 show that an exposure to light during 24 hr causes a decrease of the intrinsic viscosity of polyacrylate polymer. The initial differences in the intrinsic viscosities of the five batches seem to disappear after light stress, indicating that possible initial differences in the polymer structure are eliminated.

Molecular Weight (Distribution)

Polyacrylate polymer was dissolved in THF, and gel permeation chromatography (GPC) was carried out to obtain the molecular weight distribution. A representive GPC chromatogram of unstored polymer is shown in Fig. 3.

From Fig. 3 it is clear that the polyacrylate polymer possesses peaks at about 3500 Da and at about 600,000 Da. From the chromatogram shown in Fig. 3, the weight-average molecular weight M_w is calculated.

After exposing the polymer to different temperatures, samples were taken to determine changes in molecular weight distribution of stressed polymer.

The results in M_w of unstressed and temperature-stressed polymer during 52 weeks are given in Table 3. The mean results of the weight-average molecular weight for five batches polyacrylate polymer before and after temperature stress during 1 year are given in Fig. 4.

As can be seen from Table 3, some variations are found in M_w between the five batches of unstored polyacrylate polymer. These differences can cause differences in drug release rates.

After a storage period of 52 weeks, an increasing M_w with temperature is observed. After a temperature stress of 61°C, the polyacrylate polymer became partly in-

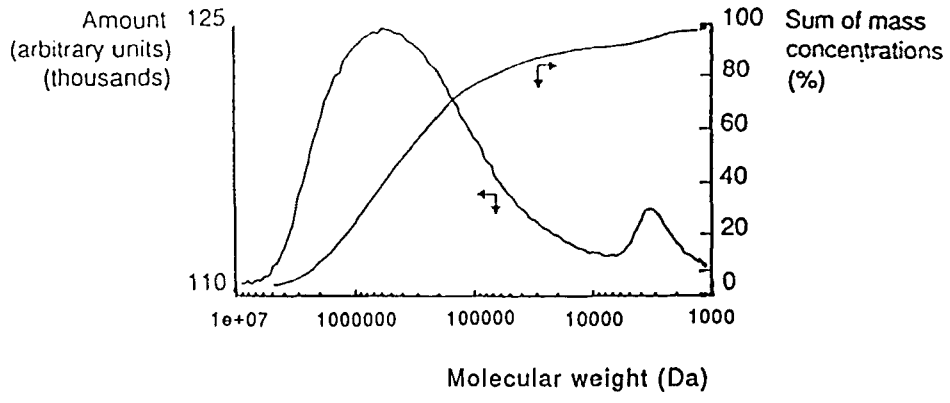

Figure 3. Gel permeation chromatography curve of unstored polyacrylate polymer. Left y axis: frequency of distribution curve; right y axis: cumulative distribution curve.

soluble after a storage period of 12 weeks, as shown in Fig. 4. It is concluded that changes in polymer structure take place to the same level independent of the storage temperature up to 41°C.

With respect to the influence of the storage time on M_w, it can be seen from Fig. 4 that M_w increases with storage time. At elevated temperatures, the increasing effect is accelerated in such a way that the polymer becomes partly insoluble after a storage period of 12 weeks. Identical results were obtained from the intrinsic viscosities.

From the changes in M_w it is concluded that temperature stress induces a further polymerization of polyacrylate. The rate of this polymerization process becomes more pronounced at higher temperatures. This conclusion is in accordance with the changes in intrinsic viscosity induced by temperature stress.

Polyacrylate polymer was exposed during 24 hr to a light source. In Table 4, the results of the weight-average molecular weight for five batches of polyacrylate before and after light stress are given.

From Table 4, it is clear that the weight-average molecular weight decreases after light stress. This is in accordance with the observed decrease in intrinsic viscosity of the light-stressed polymer. It is concluded from these results that light induces a depolymerization of the polymer chain to create chains with smaller molecular mass.

CONCLUSIONS

As shown in this study, a considerable effect on the intrinsic viscosity and molecular weight of the polymer was found at temperatures above 41°C. Both viscosity

Table 3

Effect of Temperature on M_w *of Poly Acrylate Polymer After a Storage Period of 1 Year*

Batch No.	M_w (E3 Da) After a Storage Period of 52 Weeks at Different Temperatures				
	Unstored	5°C	21°C	41°C	61°C
1	625	897	858	930	Insoluble
2	639	907	848	945	Insoluble
3	677	892	864	952	Insoluble
4	546	853	862	934	Insoluble
5	576	829	904	885	Insoluble
Mean	613	876	867	929	NA
SD	52	30	19	23	NA

Note: *SD* = standard deviation (n = 5) of M_w; NA = not applicable.

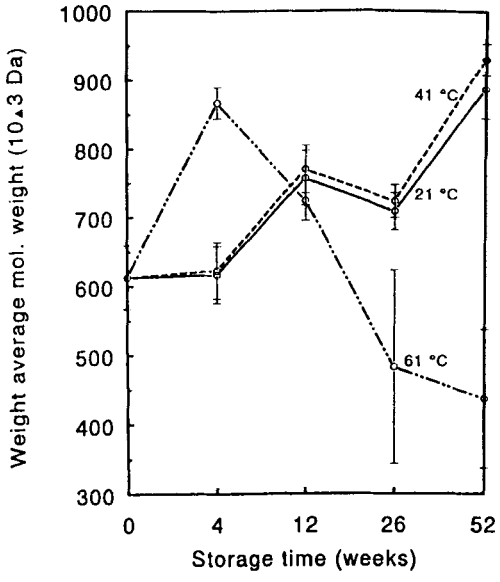

Figure 4. Effect of storage time on weight-average molecular weight of polyacrylate at different temperatures.

and molecular weight of polyacrylate, Ph. Eur., increased, caused by an increase in storage temperature and storage time. After a storage period of 12 weeks at 61°C, the polymer was insoluble, so no viscosity and GPC results are available.

Light stress during 24 hr caused decreases in intrinsic viscosity and in molecular weight of polyacrylate, Ph. Eur.

The results show that the drug release from formulations prepared with polyacrylate are influenced by the storage conditions induced by the changes in polymer structure. However, the results can only partly explain the changes in drug release from water-based preparation formulations as described in the literature. Other factors, such as humidity and interactions between coating and core material, can also contribute to changes in release profiles.

Table 4

Effect of Light Exposure on M_w

Batch No.	Weight-Average Molecular Weight (E3 Da)	
	Unstressed	Light Stressed
1	625	465
2	639	441
3	677	437
4	546	382
5	576	407
Mean	613	426
SD	52	29

Note: *SD* = standard deviation (n = 5) of M_w.

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