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THE EFFECT OF STORAGE ON THE BEHAVIOUR OF EUDRAGIT NE FREE FILM

J. Bajdik[1], *K. Pintye-Hódi*[1*], *G. Regdon Jr.*[1], *P. Fazekas*[2], *P. Szabó-Révész*[1] *and I. Erős*[1]

[1]Department of Pharmaceutical Technology, University of Szeged, Eötvös str. 6, H-6720 Szeged, Hungary
[2]Egis Pharmaceuticals, Lacta Factory, P.O. Box 54, H-9901 Körmend, Hungary

Abstract

Eudragit NE 30 D aqueous dispersion is a commonly used coating material, which contains methacrylate copolymers as film-forming agent and nonoxynol 100 as an endogenous emulsifier. The dissolution of the active ingredient from Eudragit NE-coated samples during storage is known to undergo a change. The crystallization of the emulsifier agent can play an important role in this. This polymer is not soluble in the gastrointestinal tract, but is permeable. Various parameters can influence the permeability of this film, e.g. via the tensile properties of the film. Change in the film thickness can cause the stretching of the film on a solid surface. Alterations in this physical parameter of the film were measured and the effects of different storage conditions were evaluated. The free film was prepared by spraying onto teflon. The crystallization of nonoxynol was followed via the changes in the DSC curve of the free film. A relationship was found between the film thickness and the crystallization of nonoxynol. It was established that the different storage conditions influence these changes. The temperature and the air humidity are important in this phenomenon. Lengthening of the storage time increased the difference in film thickness and crystallisation of emulsifier.

Keywords: crystallisation, Eudragit NE 30 D, film thickness, nonoxynol 100, storage

Introduction

Film coatings are very popular in the pharmaceutical technology, and are applied during the formulation of solid dosage forms. This is a widespread method for protection, retardation and identification. Gastric-soluble polymers are used to protect ingredients from light, moisture and oxygen during storage and from heat transfer during processing [1] to identify the products or increase the flowability and the processibility of the samples [2]. Intestine-soluble polymers can be used to achieve a local effect and can provide protection of the active ingredient *vs.* the acidic medium and protection of the stomach *vs.* the mucosa-irritating effect. The permeable polymers are insoluble throughout the entire gastrointestinal tract, but swell in the fluids. In the swollen form, these polymers are permeable to water and dissolved ingredients [3].

* Author for correspondence: E-mail: hodi@pharma.szote.u-szeged.hu

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Akadémiai Kiadó, Budapest

Different types of acrylic polymers can be used for different purposes; their chemical structures determine the solubility of these polymers [4]. Eudragit NE is a commonly used coating material which contains an acrylic polymer. Methacrylic ester copolymers are not soluble in the physiological pH range, but are permeable. These materials can be used for the preparation of matrix tablets, controlled-release buccal patches, controlled-release floating pellets, topical delivery systems and combination colonic drug delivery systems [5–9]. The stability of such coating materials under very different circumstances therefore is very important.

The chemical and physical stability of polymethacrylate polymer and coated materials was evaluated earlier [10]. The ageing of Eudragit NE film-coated samples and so the change in the dissolution of the active ingredient from Eudragit NE-coated samples are known from literature [11, 12], but other examinations of the free film (e.g. studies of mechanical properties, microscopic studies, and thermal analysis) are also important [13–15].

Changes in the physical parameters of film can influence the permeability of the film and therefore the liberation of the active agent, which in turn can influence the bioavailability. Changes in thickness of the film on a solid rigid surface during storage can indicate various problems. It is known that the film prepared from Eudragit NE is very elastic [16, 17]: the film does not crack, but stretches, and its structure is modified. The changes in the tensile properties can cause changes in the permeability of the film [18].

Eudragit NE 30 D contains 28.5–31.5% dry matter (poly (ethyl acrylate, methyl methacrylate) 2:1) and approximately 1.5% Nonoxynol 100 as emulsifier. Nonoxynol 100 is a water-soluble, off-white solid with a melting point of 58–59°C. It is known that this endogenous surfactant can crystallize during storage, which can alter the dissolution profile of the active agent: the crystallization of the emulsifier increases the number of holes on surface of film [19].

In this study, films were prepared from Eudragit NE 30 D without any additives, since they may change various properties of films [20]. The dispersion was sprayed onto a rotating teflon surface. The thickness and the thermoanalytical properties of the free film stored under different circumstances were examined. The relationships between these parameters were evaluated. The aim of the study was to investigate the background of stability problems of Eudragit NE films.

Methods

Preparation of free film

The free film was made by the spraying of Eudragit NE 30 D (Rhöm Pharma GmbH Chemische Fabrik, Germany) onto a rotating teflon surface. The teflon surface was stuck on the bottom of a conventional coating pan (Dragex-1, Jørgen Jørgensen, Copenhagen, Denmark).

Parameters: rotating speed of pan: 30 rpm, drying temperature: 30±2°C, atomizing pressure: 0.8 bar, liquid flow rate: 3 mL min^{-1}, nozzle size: 0.8 mm, distance of teflon surface from the nozzle: 30 cm.

Films 0.30±0.05 mm thick were prepared.

Investigation of films

The relative changes in thickness of the films were checked regularly. The bases of comparison were the properties of the film 1 day (25±3°C/50±5% relative humidity (RH)) after preparation. A Mitutoyo screw micrometer was used for the determination of thickness with an accuracy of 0.001 mm. For every condition, 10 films were used for each experiment. All the films were stored in closed desiccator and thermostat (Hereaus Instruments, Hanau, Germany).

Storage circumstances:

40±2°C/75±5% RH

25±2°C/60±5% RH

Ambient (25±3°C)/RH<35%

The first two of these conditions accord to the guidelines of the International Conference on Harmonisation (ICH). These conditions are often used for stability tests [21, 22]. The third condition simulates the conditions for the storage of a solid dosage form in a well-closed, silica-filled container.

Thermoanalytical measurements

The thermoanalytical examinations of the free films were carried out with a Mettler-Toledo DSC 821e instrument. The start temperature was –30°C, the end temperature was 100°C, the applied heating rate was 5°C min^{-1}. The minimum film forming temperature of this polymer is at about 5°C and the glass temperature at about –8°C therefore the start temperature was below this temperatures [23]. The first heating curves were recorded. Argon and nitrogen atmospheres were used. 10±1 mg sample was measured into aluminium pans (40 μL). The peak areas were evaluated with STAR^e Software. Three parallel examinations were made in every case.

Results and discussion

It can be seen from Table 1, that the thickness of the films changed during storage. The alteration in thickness for the films stored at 40°C/75% RH was significantly differed from the other two cases. A slight reduction can be detected for films stored at 40°C and a significant increase in film thickness was for films stored at 25°C. Lengthening of the storage time increased the relative change in film thickness for both films stored at 25°C. The difference in film thickness after 4 weeks for these two samples was significant ($p<0.05$).

The thermoanalytical experiments were used to determine the reason for this change in thickness. It can be seen from the DSC curve of the fresh film that there is

an endothermic peak at 55.6°C (*SD*=0.1) with ΔH=0.52 J g^{-1} (*SD*=0.09) (Fig. 1) since this endothermic peak appeared around the melting point of nonoxynol. The crystalline nature of this emulsifier in coating film is known from the literature [19]. This peak can therefore can be explained by the presence of nonoxynol crystals in the film. No other characteristic changes on the other part of the curve can be seen. Similar curves can be detected for the stored samples. Therefore the curves between 20 and 90°C are performed for the stored samples.

Table 1 Relative change in thickness of films during storage

Storage time	Relative change in thickness of film/%		
	40°C/75% RH	25°C/60% RH	25°C/<35% RH
1 week	–1.48 *SD*=3.87	0.45 *SD*=1.10	0.61 *SD*=3.26
2 weeks	–2.41 *SD*=2.39	1.67 *SD*=2.81	5.66 *SD*=2.24
4 weeks	–2.48 *SD*=3.33	13.28 *SD*=4.83	18.83 *SD*=5.87

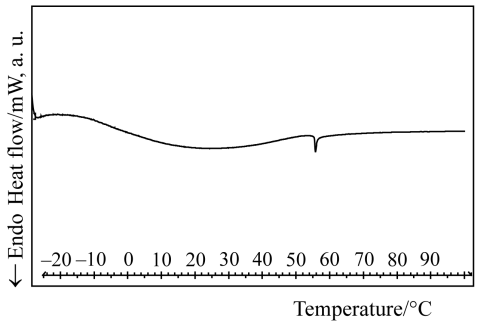

Fig. 1 DSC curve of fresh film

The DSC curves of the stored samples also exhibited the endothermic peak at about 55°C indicating the presence of crystalline nonoxynol (Figs 2–4). The films stored at 25°C (60% RH and <35% RH) gave similar curves, containing an endothermic peak. The films stored at 40°C/75% RH yielded curves with different shapes. There are two peaks at about this temperature. The first one was evaluated. The peaks can be separated by a deconvolution program. The different shapes of the DSC curves of samples stored at different circumstances (temperatures and relative humidity) point to different changes in the structure. It will be supported in a following study.

Lengthening of the storage time increased the peaks under every condition. The temperatures of the endothermic peaks are listed in Table 2. It can be seen that, for the films stored at 40°C/75% RH the peak appeared at slightly higher temperature compared to the other two films. The peak temperatures for films stored at 25°C (both cir-

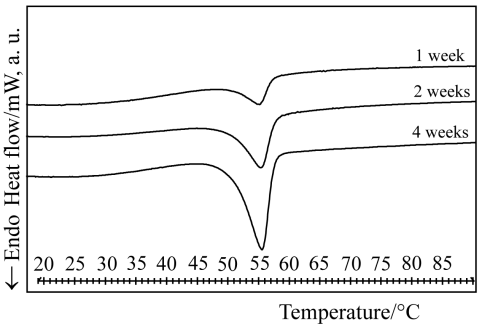

Fig. 2 DSC curves of films stored at 25°C/60% RH

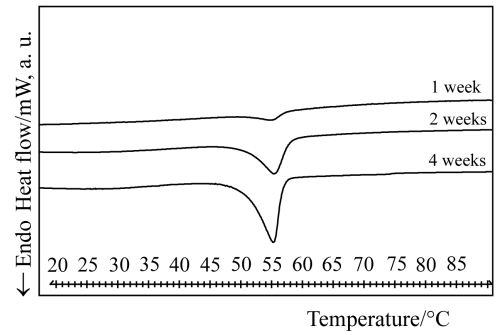

Fig. 3 DSC curves of film stored at room temperature/<35% RH

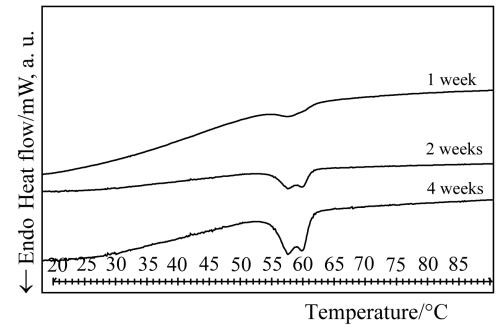

Fig. 4 DSC curves of films stored at 40°C/75% RH

cumstances) did not differ from peak temperature of fresh film. The time of storing did not influence the peak temperature significantly (Table 2).

It can be seen that the endothermic peaks differed for different films. The highest area under curve (AUC) was observed for the film stored at room temperature and low RH (Table 3). Since the enthalpy values show a gradual increase as a function of storing time under every condition, it refers also to the continuous increase of the crystallised part of the emulsifier within the samples.

Table 2 Temperatures of endothermic peaks of sample during storage

Storage time	Temperatures of endothermic peaks/°C		
	40°C/75% RH	25°C/60% RH	25°C/<35% RH
1 week	57.7 *SD*=0.8	55.1 *SD*=0.1	54.9 *SD*=0.1
2 weeks	57.4 *SD*=0.1	55.3 *SD*=0.1	55.3 *SD*=0.1
4 weeks	57.6 *SD*=0.1	55.6 *SD*=0.3	55.3 *SD*=0.3

Table 3 The enthalpy of endothermic peaks during storage

Storage time	Enthalpy of endothermic peaks/J g^{-1}		
	40°C/75% RH	25°C/60% RH	25°C/<35% RH
Fresh time	0.52 *SD*=0.09	0.52 *SD*=0.09	0.52 *SD*=0.09
1 week	0.42 *SD*=0.24	2.02 *SD*=0.20	1.32 *SD*=0.24
2 weeks	1.25 *SD*=0.29	4.91 *SD*=0.32	6.16 *SD*=0.31
4 weeks	2.28 *SD*=0.33	8.15 *SD*=0.22	8.99 *SD*=0.42

By the evaluation of the data obtained, it can be concluded that a higher extent of change in the crystallinity of nonoxynol can be seen in the films stored at 25°C, especially at lower RH. Therefore, it can be stated that the RH also plays an important role. This finding is in a good agreement with literature data, as it was pointed out by Lin *et al*. [19].

Conclusions

It has been established that the film thickness increases during storage at lower temperature and lengthening of the storage time enhances this difference. A lower temperature causes a higher crystallization of the emulsifier agent, but lengthening of the storage time increases the crystallization under every condition. It can be seen from our results that there is a relationship between the film thickness and the crystallization of nonoxynol. The crystals can indicate a change in the structure of the film and hence the thickness of the film varies. An alteration in this parameter can cause a change in the tensile properties of the film on the solid surface and can change the permeability of the film, which can influence the dissolution of the active ingredient from the coated dosage form. The problem of dissolution is well known from the literature and it was supported by dissolution test [11, 12]. It can be stated that the stor-

age circumstances of dosage forms (pellets, tablets and capsules etc.) coated with Eudragit NE 30 D can influence the bioavailability. A well-closing package (e.g. blister) is advisable for the packing of solid dosage forms coated with Eudragit NE 30 D, which reduces the effects of varying storage conditions.

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