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Note

Evaluation of films used in development of a novel controlled-release system for gastric retention

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Abstract

A novel gastric retention system was developed consisting of a tablet coated with a porous membrane. The membrane consisted of aqueous dispersions of methyl methacrylate copolymers, plasticizers, anti tacking and anti foaming agents. This article presents research work performed in order to characterize these membranes. The films were cast on glass plates coated with teflon. The films were dried at 30°C in a vacuum oven. The three main properties studied on these films were as follows: (1) Transport of drugs across the membrane; (2) mechanical properties; (3) thermo-mechanical properties. These properties were studied to produce a film having the desired characteristics for drug release and mechanical strength. It was observed that the permeability of the drug decreased slightly with increase in the Eudragit® NE 30D concentration. This result correlated well with dissolution rate constants of tablets at 15% coating level. The thermo-mechanical studies helped to understand the results from permeability studies. Based on mechanical properties, a 70:30 ratio of Eudragit® RL 30D and NE 30D was found to be optimum. The study has shown that the evaluation of films will be helpful in providing guidelines in selecting the membrane for the gastric retention system. © 1997 Elsevier Science B.V.

Keywords: Drug diffusion; Mechanical properties of films; Thermomechanical properties of films; Gastric retention system

1. Introduction

Films have been applied to pharmaceutical dosage forms for many decades. They are applied to render protection against the environment, to improve appearance, to mask undesirable taste or odor and to control drug release. Today, films

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have earned an important place in controlled release drug delivery systems. Many of these systems are tablets or capsules (a matrix) covered with a film that helps in achieving the controlled release of a drug. Studies conducted on films or membranes help in understanding some important criteria, such as drug release from a system. Often, tablets coated with a film behave differently from the film itself. However, there is no doubt that studies conducted on films help in understanding the behavior of tablets coated with these films. Various properties such as drug release, dry and wet strengths, effect of plasticizers and adhesion to tablet surfaces have been studied in detail (Béchard et al., 1995; Bodmeier and Paeratakul, 1990, 1993; Heinämäki et al., 1994; Lehtola et al., 1995; Okutgen et al., 1995; Rowe, 1978).

This paper reports an investigation performed on films to study drug diffusion, mechanical properties such as elongation and tensile strength and thermo mechanical properties of the films. The objective was to deduce the optimum composition of the film with respect to desired drug release characteristics, as well as elongation and tensile strength. Another objective was to find a possible correlation between these results and the results obtained from studies conducted on the tablets coated with these films for the gastric retention system, as described in our earlier investigation (Deshpande et al., 1997).

2. Materials and methods

The films were cast from the coating solutions used to coat the tablets. The coating solutions consisted of aqueous dispersions of polymers, plasticizer, talc and anti foaming agent. The polymers used were methacrylate co-polymers. Among various such copolymers available, Eudragits® marketed by Rohm Pharma Tech, MA, were used. Eudragit® RL 30D was used for its porosity whereas Eudragit® NE 30D was used for its elastic properties. Aqueous dispersions of Eudragit® RL 30D and Eudragit® NE 30D were mixed in different proportions such as 60:40, 70:30 and 80:20, respectively. Tri ethyl citrate (TEC) from Morflex, NC, was incorporated as a plasticizer (30.0% w/w of Eudragit® RL 30D). Talc (Ashland Chemical, OH) was added to avoid tackiness (5.0% w/w of Eudragit® RL 30D and NE 30D). Simethicone (OSI Specialities, WV) acted as an anti foaming agent (1.0% w/w of Eudragit® RL 30D and NE 30D). During tablet coating, it was necessary to maintain the temperature around 30°C in order to avoid tackiness. Therefore, the films were also dried at 30°C in vacuum oven and were stored under vacuum after drying. Films were cast on glass plates covered with teflon. Films of around 200 μm thickness were prepared. This thickness closely resembled that of the films from the coated tablets. Various properties such as diffusion of the drug through these films, tensile strength and glass transition temperature were studied on these films. For all experiments, six replicates were performed.

2.1. Drug diffusion

Diffusion cells made of glass were used for this experiment. Two glass diffusion cells were placed horizontally beside each other. Film was placed between these two cells. Into one cell was placed 100 ml of a drug suspension and into another cell was placed 100 ml of simulated gastric fluid (pH 1.2), prepared according to the procedure given in US Pharmacopea XXII. Water was circulated around these cells to maintain the temperature at 37°C. The concentration of drug (chlorpheniramine maleate; CPM) diffused in the cell containing simulated gastric fluid was measured over time using a spectrophotometer with an ultraviolet light source at a wavelength of 274 nm.

2.2. Mechanical properties

A tensiometer (Instron, MA, model #4301) was used to study the elongation and load required to break the films. However, the instrument was not equipped to control the temperature and humidity. Therefore, studies were conducted at room temperature. The maximum load of this instrument was 20 lb. The film dimensions were 1 in. $\times$ 4 in. $\times$ about 200 μm (width $\times$ length $\times$ thickness). The film was held between two tongs and pulled from the top at the rate of 0.5 in./min.

Table 1
Effect of different concentrations of Eudragit® RL 30D and NE 30D on various film properties

Eudragit® RL 30D concentration (w/w)	Eudragit® NE 30D concentration (w/w)	Permeability coefficient (ml/min·cm^2)	Dissolution rate constant (/min)	Load at break (g)	Elongation at break (cm)
80	20	0.160 ± 0.003	$0.006 \pm 6.0 \times 10^{-4}$	181.9 (2.3)	2.66 (0.03)
70	30	0.158 ± 0.004	$0.005 \pm 5.5 \times 10^{-4}$	327.5 (0.9)	4.11 (0.13)
60	40	0.147 ± 0.0035	$0.004 \pm 5.5 \times 10^{-4}$	563.8 (3.6)	4.55 (0.10)

Film thickness, 200 μm. Drug diffusion studied by using diffusion cells filled with 100 ml of saturated drug suspension at 37°C. Dissolution rate constants are from tablets with a 15% coating level. SD values are shown in parentheses.

Load and elongation were measured when the films broke.

2.3. Thermo mechanical analysis

A thermo mechanical analyzer (Seiko Instruments, CA, model # 120C) was used for this purpose and in addition, a penetration probe was used. A small part of the film was placed below the penetration probe, which was placed in such a way as to touch the film. The films were then heated from -45 to 150°C at rate of 10°C per minute to establish the glass transition temperature of the films.

3. Results and discussion

The effect of different ratios of Eudragit® RL 30 and Eudragit® NE 30D membranes on the passage of CPM across the membranes, as determined from the saturated suspension in the horizontal diffusion cells, is shown in Table 1. The data showed, that with increase in the concentration (20–40%) of Eudragit® NE 30D in the Eudragit® RL 30D:Eudragit® NE 30D membrane, there was only a slight decrease in the diffusion of CPM across the membrane. Eudragit® NE 30D is more hydrophobic compared to Eudragit® RL 30D and therefore, a remarkable decrease in the permeability of the films should have occurred with the increase in the Eudragit® NE 30D concentration. The data from the thermomechanical analysis provided the explanation for these results. The glass transition temperature (Tg) from the thermomechanical studies as a function of Eudragit® NE 30D concentration is shown in Fig. 1. The data clearly shows that as the concentration of Eudragit® NE 30D increases, so does the hydrophobicity, but overall permeability is also increased due to the lowering of the Tg. It is known that the Tg influences many physical properties such as viscosity, elasticity and permeability of coating polymers. Permeability of membranes can be increased by lowering their glass transition temperature. Therefore, a decrease in the Tg and

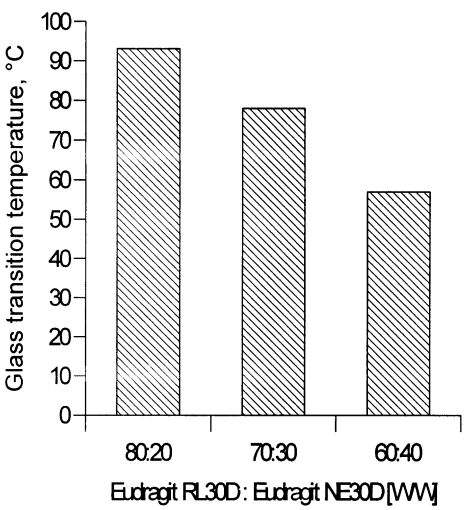

Fig. 1. Effect of different ratios of Eudragit® RL 30D and NE 30D on glass transition temperatures in 200 μm thick films.

an increase in the hydrophobicity of the membranes due to the increase in the Eudragit® NE 30D concentration have normalized the overall permeability of the membranes. The data in Table 1 indicates that there was good correlation between the dissolution rate constants from the tablets coated at 15% coating level and the permeability of the films 200 μm thick.

The effect of different ratios of Eudragit® RL 30D and Eudragit® NE 30D membranes on the mechanical properties of the films is also shown in Table 1. The data demonstrated that with increase in the concentration (20–40%) of Eudragit® NE 30D in the Eudragit® RL 30D:Eudragit® NE 30D membrane, elongation of the films was improved. The load required to break the films also increased with Eudragit® NE 30D concentration. Eudragit® NE 30D is more elastic than Eudragit® RL 30D and thus improves the mechanical properties of the films. The optimum ratio of Eudragit® RL 30D and Eudragit® NE 30D in films for coating tablets was found to be 70:30, as this combination had enough elasticity to withstand the pressure of expansion and at the same time is not so highly elastic that it will not break at the end of the release. These films also controlled drug release to the desired level. The data shows that the study of mechanical properties of films is helpful in establishing the optimum coating solution for the tablets.

4. Conclusion

The data on film permeability, tensile strength and thermomechanical properties have provided insight into the selection of a membrane for the controlled release of a drug. Permeability studies indicated that the permeability of the drug will slightly decrease with increase in the Eudragit® NE 30D concentration. A similar trend was observed in the dissolution rate constants as shown in Table 1. The dissolution rate constant at a 15% coating level slightly decreased with increase in the concentration of Eudragit® NE 30D, from 20 to 40%. The TMA data helped to explain why permeability did not drastically decrease with increase in the concentration of Eudragit® NE 30D. The data of the elongation and load required to break the films helped to explain the basis of the selection of a 70:30 ratio of Eudragit® RL 30D and Eudragit® NE 30D.

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