Effect of Pore Former on the Properties of Casted Film Prepared from Blends of Eudragit® NE 30 D and Eudragit® L 30 D-55

Xiangrong ZHANG,* Yanjiao WANG, Jing WANG, Yan WANG, and Sanming LI

Department of Pharmaceutics, Shenyang Pharmaceutical University; Shenyang 110016, P.R. China.
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The casted films of aqueous dispersions of Eudragit® NE30 D and Eudragit® L30 D-55 containing pore former were prepared. The study investigated the influence of pore former on basic model drug clarithromycin release, water uptake and water vapor permeability from casted film prepared from the blends of neutral polymer dispersion of Eudragit® NE30 D and enteric polymer dispersion of Eudragit® L30 D-55. This study was concluded that pore former hydroxypropyl methyl cellulose, lactose, polyethylene glycol (PEG) and polyvinyl pyrrolidon (PVP) was released at the beginning of the release process, the rate and extent of water uptake of the polymeric films were much higher in phosphate buffer pH 6.8 than in pH 5.0 and the concentration of pore former have a significant influence on the permeability to water vapour.

Key words blended film; Eudragit® L30 D-55; Eudragit® NE30 D; pore former

The polymeric coating materials may be in a form of solution in organic solvent or water, or in a form of aqueous dispersion. Recently, aqueous polymeric dispersions have gained popularity and are replacing solvent-based systems due to their lower toxicity level and environment friendly standpoint. Acrylate polymers and their derivatives such as Eudragit® NE30 D and Eudragit® L30 D-55 (Rohm Phama, Germany) in a form of aqueous dispersion are widely used in the pharmaceutical industry as dosage excipients or coating materials. Formulation with this kind of polymers has been applied to dosage form for controlled release in oral drug delivery as well as in transdermal therapeutic system.[1—3] Many copolymers of acrylic and methacrylic acid or ester with various function groups have been developed to fulfill various formulation requirements. However, each polymer has specific physicochemical properties, and it is often difficult to obtain a particular, desired release profile which is adapted to the pharmacokinetic/pharmacodynamic characteristics of the drug. Two different acrylate polymers have been suggested to adjust the drug permeability in controlled release application. In particular the anioic acrylic with graded solubility in the pH range 5.5—7.0 (Eudragit® 30 D-55, Eudragit® L100, and Eudragit® S100) can be mixed in proper proportions with the neutral acrylic polymer (Eudragit® NE30 D). The permeability of films obtained from these blends increases at intestinal pH as a function of the content of anionic enterosoluble polymers. Such coating could be especially useful for drugs which show reduced solubility and dissolution rate at intestinal pH values. The choice of Eudragit® L30 D-55 is imperative in this case in order to offset the decrease of the drug dissolution rate as soon as the form enters the proximal portion of the small intestine. The character makes the blended film promising materials for the coating of oral dosage forms and to obtain pH-independent drug delivery form.[4—7]

Studies undertaken are to improve drug permeability through formation of pores using hydrophilic additives. Hydrophilic additives increase the permeability of hydrophobic films by several mechanisms. For example, polyethylene glycol can dissolve or erode in the release medium and thus create pores in the film. All the water-soluble polymers are potential polymeric film modifier for achieving improved drug release.

Clarithromycin (CLA) as a poorly soluble weak base belongs to class II with a low solubility in water, pH-dependent solubility. The solubility of CLA in phosphate buffer solution of pH 4 and pH 7 are 20.0 mg/ml and 0.5 mg/ml, respectively.[8]

The major objective of the present study was to get insight into the effect of pore former in the process of blend Eudragit® L30 D-55 with Eudragit® NE30 D free film, drug release from the free film, the transmission of water and water uptake studies of the free films in the mediums with various pH. Hence, information about properties of the drug diffuse from the blended free film containing hydroxypropyl methylcellulose (HPMC), polyethylene glycol (PEG), polyvinyl pyrrolidone (PVP), and lactose may be useful for interpretation of release characteristic of this type of drug delivery systems coated with the blended film.

Experimental

Materials Clarithromycin was purchased from Zhejiang Huangyan Biological Product Company (batch 021208, 947 μg/mg). Hydroxypropyl methyl cellulose (HPMC) (Methocel E5, 5 mPa·s, 2% aqueous solution at 20 °C) was supplied by Colocron Coating Technology Limited (Shanghai, China). Methacrylic acid copolymers (Eudragit® L30D-55, Eudragit® L100, Eudragit® S100, Eudragit® RL30D) were supplied by Röhm GmbH Chemische Fabrik, Darmmmstadt, Germany. Polyvinyl pyrrolidone (PVP K30, molecular weight 3400—4200) was supplied by America ISP group. Polyethylene glycol (PEG 4000, molecular weight 3400—4200) was supplied by Shenyang Chemical Reagent (China) and lactose was supplied by Shanghai Reagent Factory No. 2 (China). Methanol was of HPLC grade. All other chemicals were of analytical-grade and were used without further purification, and deionized double-distilled water was used throughout the study.

Preparation of Thin, Polymeric Films The aqueous dispersions of Eudragit® NE30 D and Eudragit® L30 D-55 were diluted with identical volume of purified water respectively. Blend two diluted dispersions in a small beaker. The composite polymeric dispersion then was stirred using a magnetic stirrer for 2 h, and allowed to stand for 30 min. In order to gain high drug transmission, water soluble polymers, namely HPMC, PEG 4000, PVP K30, or lactose was added as pore formers into the blended dispersion to obtain the polymer dispersions with 10% (w/w) weigh gain (based on the polymer mass). Therefore three formulations containing the same amount of acrylic polymer and 10% pore former respectively (related to the acrylic polymer) were evaluated. Aqueous dispersions under gentle stirring, then all the components of the coating dispersions were blended and the stirring was continued for 1 h before casting in a Teflon mould. The subsequent ageing process was standardized as follows: 1 d at 50 °C, and 1 d at room tempera-

* To whom correspondence should be addressed. e-mail: zhangxr@vip.sina.com

ture. Then, the film was dried in a vacuum desiccator for an additional 10 h to decrease the level of moisture that was absorbed during the preparation. The amount of solution used for preparing the films was quantified, so that the resulting film thickness was definite. The thickness of the film was measured using a micrometer. The films prepared in this way are completely transparent and flexible. The thickness of the film was measured using a micrometer. Only films that were free from visually evident imperfections, such as cracks or presence of air cavities, were used for subsequent tests.

Permeability Study-Diffusion of Clarithromycin Sample analysis was performed by HPLC-UV method at 210 nm and using a mobile phase that consisted of 65% methanol and 35% (v/v) 0.05 M monobasic sodium phosphate buffer. The pH was adjusted to 4.0 using orthophosphoric acid. Method linearity was established for the range of concentrations 25—1000 μg/ml with a regression factor of 0.9994. The method was proved to be sensitive and specific.

Drug permeation through thin, polymeric films was measured using side-by-side diffusion cells which were placed in horizontal shaker at 37 °C with an effective diffusion area of 4.59 cm^2. The polymeric films were clamped between two well-stirred compartments of equal volume (5 ml). A saturated clarithromycin solution was used as a donor solution.

The permeability of clarithromycin through the blended polymer films: the donor and acceptor compartments were both composed of phosphate buffer pH 6.0 and stirred continuously with a magnetic stirrer. Aliquots of 500 μl were taken from the receptor cells and replaced with fresh medium at predetermined time intervals. The films were tightly fixed to assure constant surface areas exposed to the media. All experiments were performed in triplicates for 8 h.

When the stationary state was achieved, the permeability coefficient (P, cm^2/s) of the studied drug was obtained by the following formula:

$$P=(dQ\times h)/(dt\times A\times C_d) \quad (1)$$

where Q is the amount permeated at time t, h is the film thickness, A is the film area of diffusion, and C_d is the donor concentration of drug. The mass transfer boundary layer resistance near the film surface was estimated to be negligible. Three parallel measurements were performed in each case.

Water Uptake Studies of Thin, Polymeric Films Thin, polymeric films containing 10% PEG 4000 were cut into pieces of 2 cm×2 cm, which were weighed and immersed in 250 ml plastic containers filled with 200 ml pre-heated release medium of acetate buffer pH 5.0, phosphate buffer pH 6.0, 6.8, followed by horizontal shaking for 8 h. To avoid film folding and floating during the experiment, the film were fixed within the plastic containers. At pre-determined time intervals, samples were withdrawn, accurately weighed [wet weight (t)] and dried to constant weight at 50 °C [dry weight (t)]. The water content (%) and dry film mass (%) at time t were calculated as follows:

$$\text{water content (\%)}\,(t)=\frac{\text{wet weight}\,(t)-\text{dry weight}\,(t)}{\text{dry weight}\,(t)}\cdot 100\% \quad (2)$$

$$\text{dry film mass (\%)}\,(t)=\frac{\text{dry weight}\,(t)}{\text{dry weight}\,(0)}\cdot 100\% \quad (3)$$

Determination of Water Vapor Permeability of Films The water vapor permeability of the films was determined using the desiccant method.[9,10] Briefly, films of a known thickness were fixed with glue over the vials (5 cm depth and 1.8 cm inner diameter) containing silica gel as a desiccant. The assembled weight of each vial was accurately weighed and placed into the a chamber containing saturated sodium chloride solution at a relative humidity of 75% stored at room temperature (21 °C). The weight gain of the vial and was recorded periodically to determine the amount of vapor movement through the film into the desiccant. Permeability (P) was calculated by the following equation:

$$P=\frac{Q\times d}{A\times T\times S\times(R1-R2)} \quad (4)$$

where Q is the amount of water vapor absorbed (mg) at time t (h); d is the film thickness (cm); A is the test area (cm^2); S is saturated water vapor pressure at test temperature (Pa); $R1$ is the relative humidity in the chamber (equal to 75% in this study) and $R2$ is the relative humidity inside the vial (equal to 0% in this study). Studies of various concentration of pore former including PVP K30, HPMC and PEG 4000 were performed in the experiment.

Results and Discussion

***In Vitro* Drug Release and Diffusion Cell Studies** The film was permeable to model drugs due to micro-pores in the system, which was formed after leaching of the hydrophilic excipients of the dispersion. The permeation coefficients for the film containing different core former were 1.39×10^{-7} cm^2/s, 1.45×10^{-7} cm^2/s, 1.52×10^{-7} cm^2/s, 1.40×10^{-7} cm^2/s for PVP K30, PEG 4000, lactose, and HPMC. Figure 1 showed the drug permeability through free film with different pore former in phosphate buffer pH 6.0. Lactose showed the best permeability but there were no much difference among the different pore formers. This phenomenon can be explained by the higher porosity and permeability of these films at higher pH. The hydration of the hydrophilic polymer and leaching from the film caused the lag times about 2 h. The blended free film containing PEG 4000 was used as studies about water uptake studies because the film is flexibility instead of the brittleness of other blended film especially containing lactose.

Weight Loss and Water Uptake Studies of the Free Films Figure 2 shows the water content of free blended films containing 10% PEG 4000 in various buffers after swelling in acetate buffer pH 5.0, phosphate buffer pH 6.0 and pH 6.8, respectively. The rate and extent of water uptake of the polymeric films were much higher in phosphate buffer pH 6.8 than in pH 5.0. This is probably due to the greater hydrophilicity of Eudragit® L30 D-55 at higher pH, partial leaching of the enteric polymer out of the system, and /or due to electrostatic repulsion effects. Being a poly-acid, Eudragit® L30 D-55 is not charged under pH 5.5, but negatively charged in phosphate buffer pH 6.8. The electrostatic repulsion of the negative charges at high pH leads to increased distances between the macromolecules and to facilitated water imbibitions. The permeability of a polymeric system for a drug strongly depends on its water content. With in-

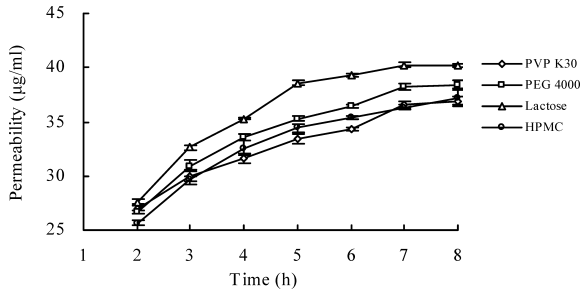

Fig. 1. Drug Permeability through Free Films with Various Pore Former at pH 6.0 (n=3, Mean±S.D.)

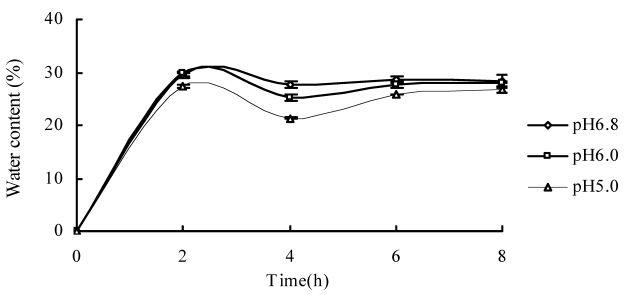

Fig. 2. Water Content of Free Blended Films Containing 10% PEG 4000 in Various Buffers after Swelling (n=3, Mean±S.D.)

creasing relative amount of water the mobility of the macromolecules increase and thus, the free volume available for diffusion increase.

Water Vapor Permeability through the Film The water vapor permeability (WVP) of the polymer film is critical to the drug dissolution profiles; it determines both the onset of the drug release and release rates of the drug products. Table 1 shows that the amount of water vapor absorbed (Q) did not decrease as the increase of the film thickness, it is nearly invariable. When Q is fixed, the thicker the film is, the bigger the permeability (P) grows. This is because that the film has two layers: the compact layer and the loose layer. The compact layer that contacts with the air is rate limiting step of permeability. The films formed in the same condition have identical compact layers, though the film thicknesses are different. The loose layer has little effect on film permeability. Therefore, Q is only impacted by the compact layer and has no relations to the film thickness.

It was concluded from this study that the concentration of pore former have a significant influence on the permeability to water vapor. Figure 3 shows that in relation to the WVP, an increase in the PEG 4000 concentration increased this property. PEG 4000 is a water-soluble, so it easily penetrates the film structure and since it has a hydroxyl group on each carbon, this renders the films very hydrophilic, favoring more water absorbing into the polymer and increasing the WVP through the specimens. Another explanation is that with the addition of PEG 4000, the network may become less dense because of an increase in the mobility of the polymeric chains and in the free volume between the chains, causing the polymer network to relax. The consequences of the plasticizing action of PEG 4000 are favorable to the adsorption and absorption of water molecules to the film, so the WVP is substantially increased.

Table 1. Permeability (P) among Different Film Thickness ($P/10^{-6}$ $mg \cdot Pa^{-1} \cdot cm^{-1} \cdot h^{-1}$)

d (cm)	Q (mg/h)	P	Equation of permeability	(r^2)
0.0030	1.24	1.39	$Q=1.3337T+0.577$	0.9995
0.0038	1.18	1.56	$Q=1.1805T+0.0581$	0.9999
0.0050	1.21	1.78	$Q=1.0221T+0.1824$	0.9998

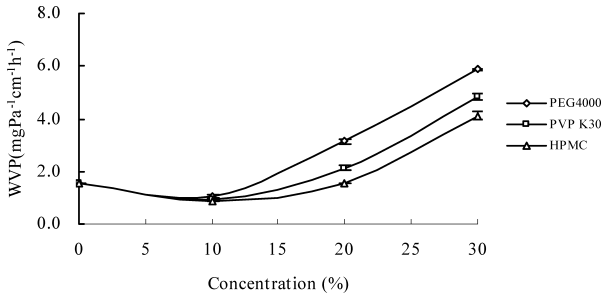

Fig. 3. Influence of Pore Former Concentration on Water Vapor Permeability through the Blended Free Film ($n=3$, Mean±S.D.)

Conclusions

The use of blends of neutral polymer dispersion of Eudragit® NE30 D and enteric polymer dispersion of Eudragit® L30 D-55 containing pore former is an effect tool to provide a large range of basic drug release at high pH. The strongly increased permeability for hydrophilic polymers might be explained by an increase in porosity of the film. Pore former is highly soluble in aqueous medium and is rapidly extracted from the film. As a consequence, small pores are created which clarithromycin molecules can permeate through. It was concluded from this study that the concentration of pore former have a significant influence on the permeability to water vapour. On the whole, although free film studies do not always provide an exact replica of the performance of coated products. Furthermore, free film studies offer method for rapid screening potential formulations.

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