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# Preparation and characterization of a novel aqueous dispersion for enteric coating of pantoprazole sodium pellets

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The purpose of this work was to investigate a novel aqueous dispersion (Eudragit® L100-55) for enteric coating of drugs. Three different casting solutions, Eudragit® L100-55 aqueous dispersion, Eudragit® L100-55 organic solution, and Eudragit® L30D-55 aqueous dispersion, were used to prepare free films by the casting method. Drug-loaded pellets, prepared by the extrusion-spheronization method, were coated with one of these three coating solutions using the fluidized-bed spray coating technology. Properties of the free films were thoroughly investigated. Films formed by Eudragit® L100-55 aqueous dispersions showed similar properties to those formed by Eudragit® L100-55 organic solution regarding thermodynamic properties, moisture permeability, solubility and acid tolerance ability. Furthermore, the performance of the novel film was better than that formed by Eudragit® L30D-55 aqueous dispersion. Among the three enteric coating solutions, Eudragit® L100-55 aqueous dispersion will be a promising aqueous dispersion for enteric coating and can be used in the development of enteric-coated preparations.

*Keywords:* aqueous dispersion, Eudragit® L100-55, Eudragit® L30D-55, free films, enteric-coated pellets, acid tolerance ability

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Enteric coating materials are generally non-toxic, chemically inert, and relatively stable; they do not react with the drug and can be dissolved or uniformly dispersed in a certain medium. These enteric coating materials usually have excellent wet insulation, protect from light and have airtight effects (1–3). The enteric-coated products currently available on the market are organic polymer solutions (Eudragit® L100-55) and aqueous polymer dispersions (Eudragit® L30D-55). Eudragit® L100-55 and Eudragit® L30D-55 are both methylacrylic acid and ethyl acrylate (1:1) copolymers. Eudragit® L100-55 organic polymer solutions are prepared by the spray drying method at low temperature. Eudragit® L30D-55 aqueous polymer dispersions are prepared by the emulsion polymerization method without addition of other excipients. It is necessary to add a plasticizer to the dispersion during the

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coating process (4). Mechanisms of film formation of aqueous dispersions and organic solutions are different (5–8). With evaporation of the solvent, polymers in the organic solution condense and polymer chains interdiffuse, resulting in alteration from a solution to a gel and finally a film (9). Polymers in this film are highly permeable, making the film structure very compact and difficult for water to penetrate (5). However, due to high viscosity, it is difficult to use organic polymer solutions for enteric coating applications, especially for coating pellets. Moreover, the drawbacks of organic polymer solutions, such as high toxicity, volatility, flammability and explosivity, as well as expensiveness and potential environmental pollution, also make them unsuitable for enteric coating (10, 11).

The aqueous polymer dispersion, with water as dispersion medium, is a complex system where the polymer is dispersed in water in the form of solid or semi-solid spherical particles with a particle size of ~10–1 μm (5). This solution has become the mainstream of coating techniques owing to its low toxicity, low viscosity, low coating time, *etc.* (12). Since polymer molecules and plasticizer molecules aggregate to form solid or semi-solid spherical particles, respectively, the polymers cannot interdiffuse, leading to a less dense film than that formed by organic polymer solutions. Consequently, some properties, such as permeability, are not as good as that seen in films formed by organic polymer solutions.

To overcome the shortcomings of these two films, a novel aqueous dispersion for enteric coating was prepared. Different from the current commercially available aqueous dispersion (Eudragit® L30D-55), this novel aqueous dispersion was prepared by first adding the plasticizer to the colloidal material to make the plasticizer and the polymer mix with each other in the organic solvent and then preparing them to form an aqueous dispersion. In this study, plasticizer or other required additives were added to the polymer, which was dissolved in an organic solvent, and then the organic solvent was evaporated after the addition of water to obtain the aqueous dispersion: Eudragit® L100-55 aqueous dispersion. This casting method was employed to prepare free films using three different casting solutions (13, 14): Eudragit® L100-55 aqueous dispersion, Eudragit® L100-55 organic solution, and Eudragit® L30D-55 aqueous dispersion. Properties of these free films were thoroughly investigated, including the glass transition temperature ($T_g$), tensile properties, moisture-permeability, and solubility in different dissolution media.

Pantoprazole sodium (PAZ-Na) is a weakly basic drug, only stable in an alkaline environment. High acidity in the stomach poses a great challenge to the development of PAZ-Na as an orally administered drug. In our study, we applied this novel aqueous dispersion for the enteric coating of PAZ-Na pellets (obtained by the extrusion-spheronization method). First, drug-loaded pellets were overlaid by hydroxyl propyl methyl cellulose (HPMC) as an isolated layer *via* the fluidized-bed spray coating technology. Then, using the same method, PAZ-Na loaded enteric-coated pallets were prepared using three different enteric coating materials. The acid tolerance ability and drug release properties of these enteric-coated pallets were investigated to promote the development of enteric-coated formulations.

## EXPERIMENTAL

### *Materials*

Eudragit® L100-55 and Eudragit® L30D-55 were supplied by Evonik Degussa (Shanghai, China) Co., Ltd. PAZ-Na was obtained from Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd. HPMC-E3 was obtained from Samsung Fine Chemicals Co. Ltd. Triethyl

citrate (TEC) was purchased from Bengbu Fengyuan Pharmaceutical Technology Development Co., Ltd. All other reagents were of analytical grade or better. Mannitol was supplied by Guangxi Nanning Chemical Pharmaceutical Co., Ltd. Microcrystalline cellulose PH101 (MCC PH101) was supplied by J. Rottenmaier & Sohne GmbH. Co., Ltd. Titanium dioxide was supplied by Shanghai Jianghu Titanium Chemical Manufacturer Co., Ltd. Talcum was supplied by Guangxi Longsheng Huamei Talc Development Co., Ltd.

## METHODS

### *Preparation of aqueous dispersion for enteric coating*

Putting Eudragit® L100-55 directly in water generates an unstable solution with big particles. We thus improved the method of preparation as follows. First, Eudragit® L100-55 (10 g) was dissolved in 21 g of alcohol. After that, an appropriate amount (1 or 2 g) of plasticizer (triethyl citrate, TEC) was added. Under magnetic stirring, 3.3 g of sodium hydroxide solution (1 mol $L^{-1}$) and 42 g of water were added and stirred for a further 20 min. Alcohol was evaporated by rotary steaming to form the Eudragit® L100-55 aqueous dispersion. Ethanol concentration was controlled by gas chromatography detection in the Eudragit® L100-55 aqueous dispersion so as to be under 0.5 %.

### *Preparation of films*

Preparation of the Eudragit® L30D-55 aqueous dispersion film and Eudragit® L00-55 aqueous dispersion film: to generate Eudragit® L30D-55 or Eudragit® L-55 (30 g) aqueous dispersions, predetermined amounts (3 and 6 g, respectively) of TEC were added. Water was then added until the polymer content reached 15 %, and this solution was stirred for 20 min. Preparation of the Eudragit® L00-55 organic dispersion film: 10 g of Eudragit® L100-55 powder was first dissolved in 60 g of alcohol, a predetermined amount of TEC was then added, and the solution was stirred for 20 min. It was then poured into horizontal rectangular boxes to form tight, uniform, thin films by drying at 40 °C in a thermostatic drum wind drying oven (DHG-9145A, Yiheng Technology Co, China). The films, along with the boxes, were translocated to a desiccator with 92.5 % relative humidity (RH) and maintained at room temperature for 10 h. Due to softening *via* moisture absorption, intact films were easily achieved. These films were cut into appropriate shapes, re-dried for 24 h at 40 °C, and then preserved in a desiccator set at 43 % relative humidity.

Films with folds, cracks, and/or spots were discarded. Film thickness of different parts was measured with a Vernier caliper, and those with relative standard deviation (RSD) beyond 15 % were discarded.

### *Characterization of films*

*Detection of glass transition temperature.* – $T_g$ measurements were performed using a Q200 differential scanning calorimeter (DSC, TA, USA) equipped with a refrigerated cooling system (12, 15). Free films (approximately 8–10 mg, dried to constant weight, accurately weighed) were placed in hermetically sealed aluminum pans. After equilibration at –40 °C for 2 min, the pans were heated to 80 °C at a heating rate of 10 °C/min. The $T_g$ values reported represent the intermediate values of the heat transformation process.

*Investigation of tensile properties*. – Mechanical properties of the free films were measured by a tensile test (16). The films were cut into 9 × 1.5 cm rectangles and then cut into dumb-bell shapes with an intermediate test section width of 4 mm and effective length of 50 mm ($n = 5$). Both ends of the cut film were clipped on a tensile testing machine. A universal materials testing (Zwick/Roell Z020, ZWICK, Germany) machine was employed to test the tensile properties at a drawing speed of 4 mm $min^{-1}$, and the force-displacement curve was recorded. Mechanical parameters were calculated using the following equations:

$$\sigma = F / (h \times b)$$
$$\varepsilon = (L_1 - L_0)/L_0 \times 100\ \%$$
$$E = k / (h \times b)$$

where $\sigma$ (MPa) is tensile strength, $F$ (N) is rupturing load, $h$ (mm) is film thickness, $b$ (mm) is the thin film width, $\varepsilon$ (%) is the extension rate at fracture, $L_1$ (mm) is the extended length of the film at breakage, $L_0$ (mm) is the initial length of the film, $E$ (MPa) is the elasticity modulus, and $k$ is the slope coefficient of the elastic deformation zone.

*Moisture permeability test*. – Moisture permeability of the film was tested by the glass method. In brief, silica gel self-indicator, which was used as a drier, was loaded into a weighing disk ($\Phi$ 4.6 cm). The free film (0.3 mm in thickness) was sealed in the bottle of the weighing disk using mucilage. The film-sealed weighing disk was maintained at 40 °C with 92.5 % relative humidity after accurate weighing. At predetermined times (12, 24, 36, 48, 60 and 72 h), the weighing disk along with the sealed film were weighed, and the related parameters of moisture permeability were calculated using the following equations (17, 18):

$$Q = (K \times \Delta P \times A \times t) / h$$
$$P = \varphi\ P_0$$

where $Q$ (g) is the amount of water vapor transmission, $K$ (mg /Pa × cm × h) is the coefficient of moisture permeability, $\Delta P$ (kPa) is the difference in water vapor pressure between both sides of the film, $A$ ($m^2$) is the moisture permeable area, $h$ (mm) is film thickness, $t$ (h) is the time of water vapor transmission, $P$ (kPa) is the saturated vapor pressure of water in the air, $\varphi$ (%) is relative humidity of the air, and $P_0$ (kPa) is the saturated vapor pressure of water. The $k$ value was calculated from the slope of the plot of $Q$ *vs.* $t$.

*Dry mass loss studies*. – Loss of the dry mass of free films was evaluated by detecting the weight loss after drying (5, 19). The film was cut into 3 × 1.5 cm rectangles and then tested according to the first dissolution test method of the Chinese Pharmacopoeia II (2010 edition, appendix XC). The solubility experiment was performed at 37 ± 0.5 °C using an intelligent drug dissolution tester (RCZ-8A, Tianjin University Instrument Factory, China). Then, 500 mL of 0.1 mol $L^{-1}$ hydrochloric acid or phosphate buffered saline (PBS, pH 6.0 or 6.8) was selected as dissolution medium, and the rotation speed was set at 100 rpm. The film was accurately weighed and then put into medium. At predetermined times, wet weight and dry weight (dry weight being defined as having a constant weight at 40 °C for 24 h) were accurately measured. The related parameters were calculated using the following equations:

$$A = (m_2 - m_1) / m_0 \times 100\ \%$$
$$L = (m_0 - m_1) / m_0 \times 100\ \%$$

where $A$ (%) is the amount of water absorption, $L$ (%) is the loss of dry mass, $m_0$ (g) is the initial dry mass of the film, and $m_1$ and $m_2$ (g) are the dry mass and wet mass of the film at predetermined times, respectively.

*Observation of aqueous dispersion by transmission electron microscopy.* – A few drops of Eudragit® L100-55 aqueous dispersions (0.1 mg mL$^{-1}$) and Eudragit® L30D-55 aqueous dispersion (0.1 mg mL$^{-1}$) were placed on copper grids. Then, the samples were dyed with 2 % phosphotungstic acid. After natural drying, the sample was observed by transmission electron microscopy.

## *Preparation of PAZ-Na-loaded delayed-release pellets*

*Preparation of PAZ-Na-loaded pellets.* – PAZ-Na is a weakly basic drug, which is only stable in an alkaline environment. We used sodium carbonate in PAZ-Na loaded pellets as a stabilizer to prevent PAZ-Na degradation. According to the formulation, microcrystalline cellulose (MCC), mannitol, sodium carbonate and PAZ-Na were weighed and blended. Soft material was made *via* adding water as an adhesive. Drug-loaded pellets were prepared by the extrusion-spheronization method (20) using an extrusion-spheronization machine (Mini, Shenzhen Xinyite Science and Technology Co. Ltd, China). The extrusion speed was 50 rpm, spheronization speed was 30 rpm and spheronization time was 3 min. Freshly prepared pellets were dried at 40 °C for 2 h. After being sieved, the PAZ-Na-loaded pellets with particles sized between 20 to 24 mesh were selected for further study.

## *Coating of PAZ-Na-loaded pellets*

Since enteric coating material is weakly acidic, and the PAZ-Na-loaded pellets are weakly basic, we added an isolating layer between them in order to enhance the stability and the acid tolerance properties of the enteric-coated pellets. The PAZ-Na-loaded pellets were coated with 4 % hydroxylpropylmethylcellulose (HPMC) as an isolating layer *via* the fluidized-bed spray coating technology using a fluidized bed (Mini-DPL, Chongqing Jinggong Pharmaceutical Machinery Co., Ltd, China). The material temperature, jet pressure, and blast frequency were set at 35 °C, 0.1~ 0.2 MPa and 25 ~ 30 Hz, respectively, during the isolated layer coating. TEC and talc powder were added under continuous stirring to Eudragit® L30D-55 aqueous dispersion, Eudragit® L100-55 ethanol solution and Eudragit® L100-55 aqueous dispersion to obtain three kinds of uniform enteric-coated dispersions. The material temperature, jet pressure, and blast frequency were set at 30 °C, 0.1~0.2 MPa, and 25~30 Hz during the entire enteric coating process. Freshly prepared enteric-coated pellets were dried at 40 °C for 2 h.

## *Acid tolerance of PAZ-Na-loaded delayed-release pellets*

The acid tolerance ability test was performed according to the first dissolution test method of the Chinese Pharmacopoeia II (edition 2010, appendix XC), which was similar to the USP dissolution method I. This experiment was performed at 37 ± 0.5 °C using an RCZ-8A dissolution apparatus. Briefly, 900 mL of 0.1 mol mL$^{-1}$ hydrochloric acid was selected as dissolution medium, and the rotating speed was set at 100 rpm. Six capsules were placed in the basket and put in the dissolution medium at the same time. Two hours later,

PAZ-Na-loaded delayed-release pellets were washed with water until the washing had neutral pH. After that, the drug loaded pellets were moved to a flask (50 mL) containing 0.001 mol $L^{-1}$ sodium hydroxide. Ultrasonic processing for 15 min was used to dissolve the drug, and then the final volumes were obtained. After proper dilution, the absorbance of the testing solution was measured by UV spectrophotometry (UV-1810, Purkinje, Beijing, China) at $\lambda$ = 288 nm wavelength according to the Chinese Pharmacopoeia II. The remaining quantity of the drug was also determined using high-performance liquid chromatography (HPLC, Agilent1100, USA).

### *Drug release test*

The drug release test was conducted according to the first dissolution test method of the Chinese Pharmacopoeia II (2010 edition, appendix XD). The experiment was performed at 37 ± 0.5 °C using an RCZ-8A dissolution apparatus. Then, 900 mL of 0.1 mol $L^{-1}$ hydrochloric acid and PBS (pH 6.8) was selected as dissolution medium, and the rotation speed was set at 100 rpm. The drug release test was conducted in the 0.1 mol $L^{-1}$ hydrochloric acid first for 2 hours, and then the pellets were transferred to PBS (pH 6.8) to continue the test. At different time intervals (5, 10, 20, 30, 45, and 60 min), 4 mL samples were withdrawn and replaced by fresh medium. After filtration with a 0.45 μm microporous membrane, the samples were analyzed at 288 nm using UV spectrophotometry (UV-1810, Purkinje, Beijing, China). The corresponding drug concentration and cumulative drug-release percentage were calculated by a standard curve.

## RESULTS AND DISCUSSION

### *Determination of glass transition temperature by DSC*

Since the glass transition temperature of Eudragit® L30-D and Eudragit® L100-55 is approximately 110 °C, plasticizers are added during the coating process to reduce the glass transition temperature of the material and adjust film toughness (4, 21). Increasing the dosage of the plasticizer in the coating material increases both the plasticity and permeability of the polymer material. In general, the amount of plasticizer in enteric material is approximately 5 to 20 % according to the characteristics of the material itself during the coating process. Considering that the enteric coating film requires sufficient resistance to acidic liquid, the amount of the plasticizer finally selected was 10 % of the enteric material.

As displayed in Fig. 1, at the same concentration of TEC, the $T_g$ value of the film prepared with the Eudragit® L30D-55 aqueous dispersion was the highest. Furthermore, the Eudragit® L100-55 aqueous dispersions were higher than the Eudragit® L100-55 organic solution. The reason for this phenomenon was that the contact area of the plasticizer and the polymer in the aqueous dispersion was smaller than that in the organic solution. Thus, the effect of the plasticizer on decreasing $T_g$ and improving the toughness of the film in aqueous dispersion was not adequately revealed. The $T_g$ value of the film prepared by Eudragit® L100-55 aqueous dispersions fell in between the other two enteric coating solutions, further indicating that the plasticizer and the polymer in this novel aqueous dispersion interfused better than in the Eudragit® L30D-55 aqueous dispersion.

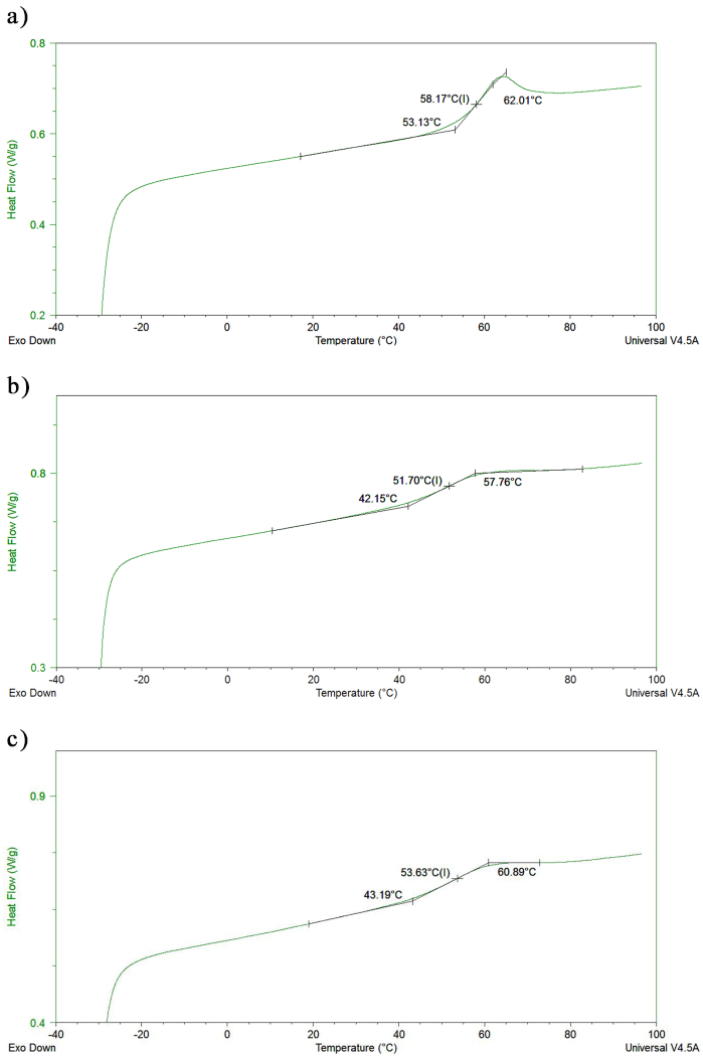


Fig. 1. Differential scanning calorimetery profile of: a) L30D-55 aqueous dispersion film, b) L100-55 organic film, c) L100-55 aqueous dispersion film; TEC content is 10 %.

## *Tensile properties of the films*

To evaluate their physical and chemical properties, films were prepared by the cast method. To investigate the tensile properties of the film, tensile strength (MPa), elongation (%) and elastic modulus (MPa) were determined (22, 23). The larger were the values for tensile strength, extension at fracture and elastic modulus, the better were expected to be the properties of wear-resistance, flexibility of membrane material, and elastic deformation

*Table I. Tensile property analysis data of the films containing 20 % TEC measured by a universal material testing machine*[a]

| Film-forming material | $\sigma$ (MPa) | $\varepsilon$ (%) | $E$ (MPa) |
|---|---|---|---|
| L100-55 aqueous dispersion | 11.57 ± 0.10 | 65.75 ± 17.64 | 563.75 ± 29.35 |
| L100-55 organic solution | 5.6 ± 0.56** | 113.32 ± 32.26* | 235.40 ± 47.64** |
| L30D-55 aqueous dispersion | 8.17 ± 0.93** | 97.88 ± 19.03* | 392.2 ± 63.86** |

[a] mean ± S.D., $n = 5$, *$p < 0.05$, **$p < 0.01$

stress. Addition of a plasticizer can significantly change the coating film mechanical properties and increase the toughness of the film (24).

The film formed by Eudragit® L30D-55 aqueous dispersion is a fragilely rigid membrane. The film formed by adding 10 % TEC was too brittle to be stretched. Thus, 20 % TEC was added to perform tensile tests for these three types of films.

As illustrated in Table I, with 20 % of TEC, the mechanical properties of the three films were changed. Different polymer solutions (aqueous dispersions and organic solutions) led to different mechanisms of film formation (5, 23).

The tensile strength value of the film formed by the Eudragit® L100-55 aqueous dispersion was higher than that of the other two films, and there were significant differences between these results ($p < 0.01$), indicating that the wear-resisting properties and rigidity of this film were better than of the other two films. Elasticity modulus is an indicator that can measure the resistance of the material to elastic deformation. The higher it is, the more stress is needed to initiate elastic deformation. The elasticity modulus values of the film formed by the Eudragit® L100-55 aqueous dispersion were higher than those of the other two films, indicating that the elastic deformation of this film was smaller under the same stress. The extension rate at fracture of the film formed by the Eudragit® L100-55 aqueous dispersion was the lowest, indicating that the toughness of the film was weaker than that of the other two films. Experimental results showed that the properties of the free films produced by different polymer dispersions were different (23).

### *Moisture permeability of the films*

A higher coefficient of moisture permeability indicates higher moisture permeability of a given film. Many properties of the polymer determine the moisture permeability of the film, such as the flexibility of the polymer chain, its crystallinity, the degree of crosslinking, *etc.* Greater rigidity of the polymer chain and a higher degree of crystallinity or degree of crosslinking make it more difficult for water molecules to pass through the film. As shown in Fig. 2, the moisture permeability of the film grew with incremental increases in the plasticizer, indicating that the features of the film changed with plasticizer addition, such as decreasing the interaction between polymer chains, increasing the freedom of movement of polymer chains and increasing the number of membrane pores and the size of membrane pores.

With the same concentration of plasticizer, the coefficient of moisture permeability of the film prepared by the Eudragit® L30D-55 aqueous dispersion was significantly higher

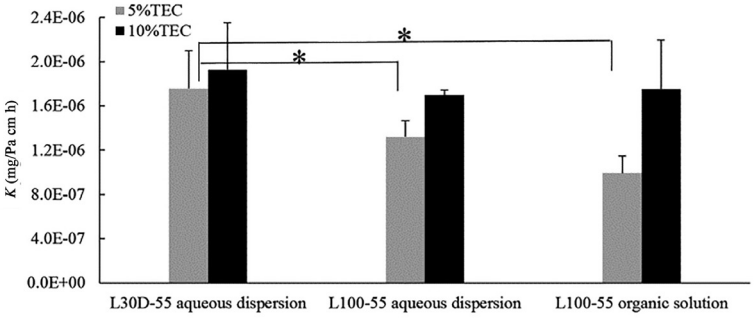


Fig. 2. Coefficient of moisture permeability of films. Data are shown as mean ± SD ($n = 3$, $^*p < 0.05$).

than that of the other two films ($p < 0.05$), while the films formed by the Eudragit® L100-55 aqueous dispersion or Eudragit® L100-55 organic solution had similar *K* values, which demonstrated that the moisture permeability of the film was affected by the method of film preparation. The film prepared by the Eudragit® L30D-55 aqueous dispersion was more moisture permeable than that formed by the Eudragit® L100-55 aqueous dispersion or Eudragit® L100-55 organic solution. This may be because the interfusion of the polymer chain in the film formed by the Eudragit® L30D-55 aqueous dispersion was not tight enough to form a compact membrane, resulting in larger membrane pores and thus higher moisture permeability. The film formed by the Eudragit® L100-55 aqueous dispersion was similar to that formed by the Eudragit® L100-55 organic solution and better than that formed by the Eudragit® L30D-55 aqueous dispersion, indicating that the compactness of the film formed by the Eudragit® L100-55 aqueous dispersion was better than that formed by the Eudragit® L30D-55 aqueous dispersion.

### *Solubility of the films*

As shown in Fig. 3, the solubility of the three types of films was similar in phosphate buffered saline (PBS, pH 6.0 or 6.8). In 0.1 mol $L^{-1}$ hydrochloric acid solution, the mass loss after drying of the enteric-coated film prepared by the novel method in this study was similar to that formed by the Eudragit® L100-55 organic solution, and significantly smaller than that of the Eudragit® L30D-55 aqueous dispersion.

### *Transmission electron microscopy observation of aqueous dispersion*

Droplet morphology of Eudragit® L100-55 aqueous dispersions and Eudragit® L30D-55 aqueous dispersion with 10 % TEC was observed by transmission electron microscopy. As displayed in Fig. 4, the droplet size of these two dispersions was similar, indicating that the Eudragit® L100-55 aqueous dispersion had a similar degree of mixing to that of the Eudragit® L30D-55 aqueous dispersion.

### *Acid tolerance ability and drug-release properties of PAZ-Na-loaded enteric-coated pellets*

As shown in Table II, the drug loss decreased with increasing coating weight, indicating that enteric coating can play an important role in protecting the drug from degradation

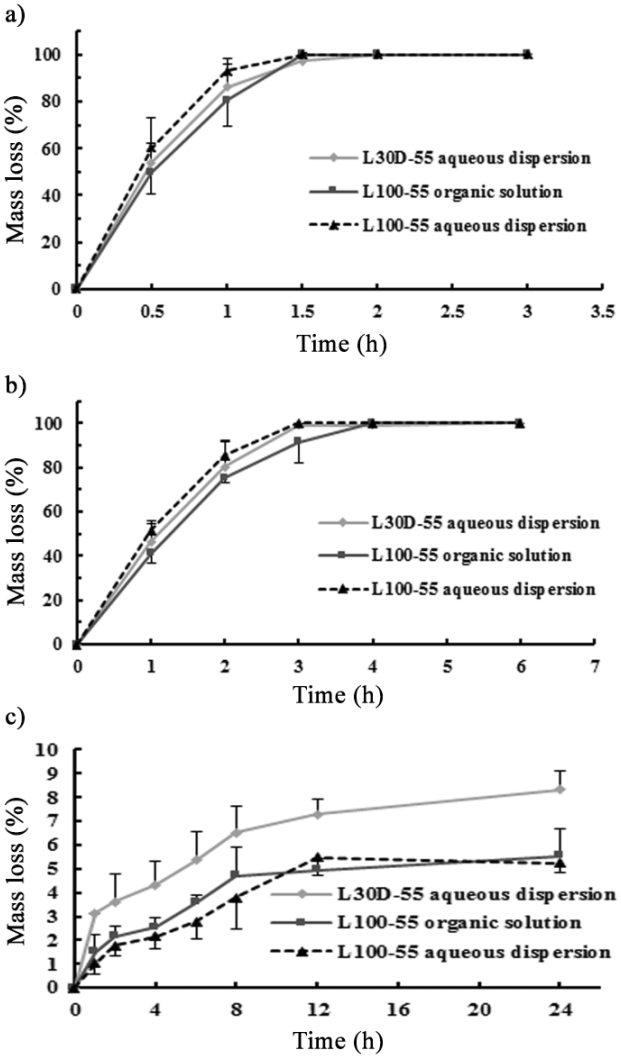


Fig. 3. Mass loss after the drying of enteric-coated films in pH: a) 6.8, b) pH 6.0 and c) pH 1.0. Data are shown as mean ± SD ($n$ = 3).

by hydrochloric acid. For a given coating weight increment, the remaining drug content in pellets coated with the Eudragit® L30D-55 aqueous dispersion was lower than that coated with the Eudragit® L100-55 aqueous dispersions and the Eudragit® L100-55 organic solution after a 2 h dissolution test in 0.1 mol $L^{-1}$ hydrochloric acid solution. With the same coating weight increment (12 %), the drug loss of pellets coated with the Eudragit® L100-55 organic solution or the Eudragit® L100-55 aqueous dispersions were both lower than 10 % in the acid tolerance ability test. In contrast, the drug loss of pellets coated with the Eu-

*Table II. The amount of PAZ-Na loaded in the pellets after 2 h of acid tolerance ability test with 9 % coating mass increment and 12 % coating mass increment*[a]

| Coating mass increment (%) | L30D-55 aqueous dispersion (%) | L100-55 organic solution (%) | L100-55 aqueous dispersion (%) |
|---|---|---|---|
| 9 | 76.19 ± 1.25 | 86.52 ± 4.72** | 85.19 ± 5.57** |
| 12 | 88.86 ± 2.81 | 94.51 ± 1.80** | 93.78 ± 1.58** |

[a] Mean ± SD, $n = 6$, $^{**}p < 0.01$

dragit® L30D-55 aqueous dispersion was more than 10 %, and there were significant differences between the results ($p < 0.01$). These results indicate that the acid tolerance ability of the films prepared by the Eudragit® L100-55 organic solution and the Eudragit® L100-55 aqueous dispersions was better than that prepared by the Eudragit® L30D-55 aqueous dispersion. Consequently, the acid tolerance requirement for enteric-coated drugs can be achieved with a lower coating weight using these two enteric coating solutions, and thus the materials and time used for enteric coating will be decreased.

*Drug release properties of PAZ-Na-loaded enteric-coated pellets*

When preparations are coated with enteric material, the weight increment of the material is generally controlled so as to be above 8 % (4). To ensure adequate isolation performance, the pellets coated with 9 and 20 % mass increment were selected for further study. The drug-loaded pellets that were overlaid with an isolation layer were coated with the Eudragit® L30D-55 aqueous dispersion, the Eudragit® L100-55 aqueous dispersions or the Eudragit® L100-55 organic solution. The drug-releasing properties of these enteric-coated pellets at different coating weight increments were investigated, and the results are shown in Figs. 5 and 6. This experiment analyzed how much drug was released from the pellets

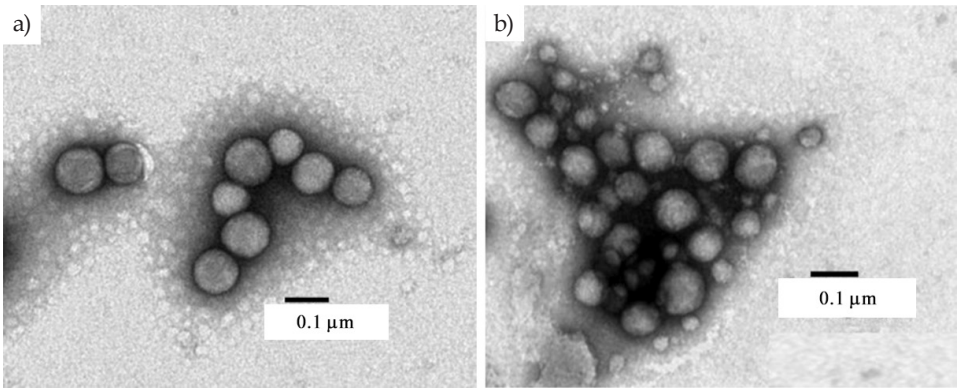


Fig. 4. Transmission electron microscopy images of the films formed by: a) Eudragit® L30D-55 aqueous dispersion and b) Eudragit® L100-55 aqueous dispersion.

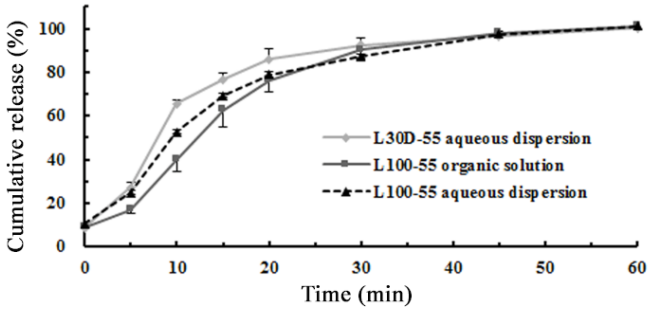


Fig. 5. *In vitro* release profiles of PAZ-Na from the films formed by Eudragit® L100-55 aqueous dispersion with 9.42 % coating weight increment (▲), Eudragit® L30D-55 aqueous dispersion with 9.34 % coating weight increment (◆) and Eudragit® L100-55 organic solution with 9.84 % coating mass increment (■) according to the first dissolution test method of Chinese Pharmacopoeia II (2010 edition, appendix XD). Data are shown as mean ± SD ($n$ = 3).

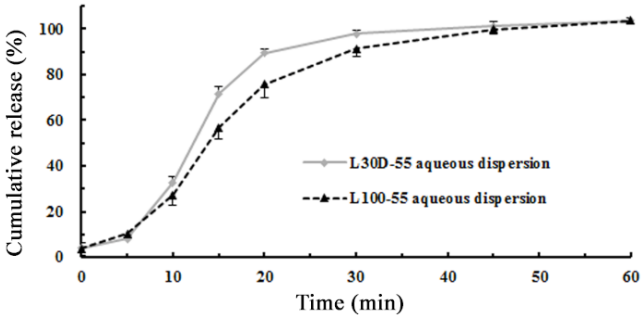


Fig. 6. *In vitro* release profiles of PAZ-Na from the films formed by Eudragit® L100-55 aqueous dispersion with 20.05 % coating weight increment (▲), Eudragit® L30D-55 aqueous dispersion with 19.6 % coating mass increment (◆) according to the first dissolution test method of Chinese Pharmacopoeia II (2010 edition, appendix XD).

in the phosphate buffered saline (pH 6.8) after standing in 0.1 mol $L^{-1}$ hydrochloric acid solution for 2 hours. It can be seen from the results that the three different enteric-coated pellets were completely released within 60 minutes, which meets the requirements of the Chinese Pharmacopoeia for the dissolution of enteric preparations. Release behaviors of the drug from the different pellets with a coating weight increment of 9 % were observed, and the cumulative release (%)-time (min) line chart is displayed in Fig. 5. Drugs in the pellets coated with a 95 % ethanol solution of Eudragit® L100-55 exhibited the slowest release. In contrast, the pellets coated with the Eudragit® L30D-55 aqueous dispersion exhibited the fastest drug release. Fig. 6 shows the time-dependent drug release of the pellets coated with these three types of enteric coating solutions at a 20 % mass increment. The results indicate that increasing the coating weight results in decreased release of the drug from the pellets. The effect of increased coating mass on drug release was similar, both at

9 or 20 %, for the three compounds. There is no release profile of the pellets coated with the Eudragit® L100-55 organic solution at the coating weight increment of 20 % in Fig. 6 because the adhesion was too severe to complete the coating process at this coating mass.

## CONCLUSIONS

In the organic solvent coating process for enteric material, the polymer material and the plasticizer are both dissolved in ethanol. With solvent evaporation, plasticizer molecules can be uniformly inserted between the polymer chains of the film-forming material, which results in high homogeneity and compactness of enteric films. When pellets coated with the commercially available L30D-55 aqueous dispersion, polymer molecules and plasticizer molecules aggregate and form solid or semi-solid spherical particles during the process. Therefore, most of the plasticizer is distributed between the particles of the enteric material, and a small amount of plasticizer molecule is inserted into the interface of the enteric material particles by diffusion. Consequently, the resulting homogeneity and compactness are not as good as in films formed by organic polymer solutions. In this paper, the plasticizer is first dissolved and mixed with the enteric material and then dispersed in water to form an aqueous dispersion. Plasticizer molecules can thus be uniformly inserted between the polymer chains of the enteric material, and with the evaporation of the solvent, the resulting enteric film formed is similar to the organic solvent coating.

In the present study, a novel Eudragit® L100-55 aqueous dispersion was prepared by first adding the plasticizer to the enteric coating materials to form enteric coating aqueous dispersions. With the same concentration of plasticizer, the free film formed by this novel enteric coating aqueous dispersions had lower glass transition temperature and lower moisture permeability compared to the film formed by the Eudragit® L30D-55 aqueous dispersion. In addition, the dry mass loss of the film formed by the Eudragit® L100-55 aqueous dispersion was lower than that formed by the Eudragit® L30D-55 aqueous dispersion in 0.1 mol $L^{-1}$ hydrochloric acid solution within the same time intervals, indicating that the acid tolerance ability of this novel film was better than that formed by the Eudragit® L30D-55 aqueous dispersion. Our findings demonstrated that this novel film had similar properties to the film formed by the Eudragit® L100-55 organic solution in terms of thermodynamic properties, moisture permeability, dry mass loss, acid tolerance ability, *etc*., and the performance of this novel film was better than of that formed by the Eudragit® L30D-55 aqueous dispersion. During the coating process, the viscosity of the Eudragit® L100-55 aqueous dispersion was lower than that of the Eudragit® L100-55 organic solution. Similarly to the Eudragit® L30D-55 aqueous dispersion, the time of the coating process using this novel enteric coating aqueous dispersion can be greatly shortened. In addition, using the available industry-specific equipment, we could apply our coating material to industrial-scale production, which would be a promising approach for enteric coating.

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