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Preparation and stability investigation of tamsulosin hydrochloride sustained release pellets containing acrylic resin polymers with two different techniques

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ABSTRACT

The objective of this study was to prepare tamsulosin hydrochloride-sustained release (TSH-SR) pellets which showed good release stability with frame-controlled method. TSH was added to Eudragit®NE30D and Eudragit®L30D-55 polymers to form drug-loaded inner core. Afterwards, enteric Eudragit®L30D-55 polymer was modified on the surface of it to the final product. Dissolution studies showed that TSH-SR pellets were more stable during the coating process, different curing temperatures and storage conditions compared with TSH pellets produced by film-controlled technique. Appearances and glass transition temperatures (Tgs) of free films and surface morphologies observed by scanning electron microscopy (SEM) of blank sustained release pellets prepared by different ratios of Eudragit®NE30D and Eudragit®L30D-55 further indicated that temperature and relative humidity (RH) were the key factors when Eudragit®NE30D blended with Eudragit®L30D-55 were applied to sustained/controlled release preparations. In addition, SEM identified the surface morphologies of TSH-SR pellets before and after dissolution, which showed intact surface structure and great correlation with release curve respectively.

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1. Introduction

TSH has an excellent effect in the process of treating lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUPS/BPH) in clinical trials [1]. As patients on treatment with LUTS/BPH are men aged in their mid-sixties [2]. Some adverse effects, such as asthenia, dizziness and orthostatic hypotension [3]should be avoided by formulating it into sustained/controlled release preparation. At the same time, it could improve the symptom of urination disorder therefore reducing the times patients get up during night. Up to now, literatures have reported that tamsulosin hydrochloride sustained/controlled release pellets were successfully prepared by different techniques and coating materials.

Min-Soo Kim [4] described tamsulosin hydrochloride controlled release (TSH-CR) pellets which were prepared using ethylcellulose aqueous dispersion (Surelease®) and sodium alginate. Controlled drug release pattern might be attributed to the nature of sodium alginate which is soluble at neutral pH but swells below pH 3.When dissolution media (at first in simulated gastric fluid and then intestinal) penetrated into substrates containing sodium alginate, it at first swelled and then dissolved, producing osmotic pressure to assist TSH diffuse out of film formed by Surelease®.

Xiong Zhang [5] depicted TSH-CR pellets consisted of two different coated pellets mixed by a certain ratio, Eudragit®NE30D and Eudragit®L30D-55 were used as the coating materials respectively to achieve two different release rhythms. The author aimed to prepare TSH-CR pellets mixing two different formulations instead of coating materials.

Atsushi Maeda [6] prepared microparticles intended for orally disintegrating tablets using ethylcellulose aqueous dispersion (Aquacoat®) and Eudragit®NE30D in single step coating. However, it only considered release in simulated intestinal fluid.

Jing min Wang [7] developed TSH-SR pellets by two-layered films. Inner film consisted of Eudragit®NE30D and Eudragit®L30D-55 mixed by a certain ratio, outer enteric film was Eudragit®L30D-55.

According to the above coating materials used for preparing TSH sustained/controlled release pellets, aqueous dispersions composed of latex particles were mentioned. Utilizing aqueous dispersions for solid dosage forms coating provides various advantages, such as reducing toxicity and lessening environmental concerns [8]. However, in the course of film formation, latex particles do not experience absolute coalescence in a short time. This change is not obviously seen until a period of time [9]. As a result, mechanical properties of film might vary thereby altering release behavior of formulation in the long-term storage. Investigations above did not refer to the release stabilities of their final products. Yet from the process of film formation, it was inferred that the formulation prepared with aqueous dispersions might be invalid in the long run. Therefore, investigating and solving the issue of the release stability of sustained/controlled release formulations using aqueous dispersions was of great significance.

In the present study, TSH-SR pellets were prepared by frame-controlled technique. TSH was added to Eudragit®NE30D and Eudragit®L30D-55 polymers to form drug-loaded inner core. Afterwards, enteric Eudragit®L30D-55 polymer was modified on the surface to become the final product. Fluidized bed coater was employed to coat the TSH-containing sustained release and enteric films. It was found that not only did it reach the release behavior similar with Harnual®, but also identified better release stability in comparison with TSH film-controlled pellets in the process of coating, curing and storage. Then we designed and prepared free films and blank sustained release pellets containing different ratios of Eudragit®NE30D and Eudragit®L30D-55 polymers in order to further verify factors affecting the formation and mechanical properties of film. Additionally, drug release mechanism of TSH-SR pellets was proved by observing surface morphology of it after dissolution.

2. Materials and methods

2.1. Materials

TSH (99.8% purity) was purchased from Zhejiang Jinhua Pharmaceutical Co. Ltd. (Zhejiang, China), Microcrystalline cellulose (MCC) (WJ-101) and hydroxypropyl methylcellulose-E5 (HPMC-E5) were purchased from Shanhe Pharmaceutical Co. Ltd. (Anhui, China), methacrylic acid copolymers (Eudragit®NE30D and Eudragit®L30D55) were kindly provided by Degussa (Esson, Germany), TSH controlled-release brand capsule (Harnal, 0.2 mg, Yamanouchi Pharmaceutical Co. Ltd. Japan). All organic solvents were of high-performance liquid chromatography (HPLC) grade. All other chemicals were of analytical grade.

2.2. Methods

2.2.1. Preparation of MCC blank pellets

Microcrystalline cellulose (MCC) worked as framework and dry blinder of the blank pellets, while redistilled water was wet blinder. Centrifugal granulator was employed to successfully prepare it by powder coating technique. Wet granules were put into 40 °C oven for 6 h. At last, sieving pellets through 40–50 mesh screen.

2.2.2. Preparation of TSH-SR pellets

Four hundred grams of MCC blank pellets were further coated with sustained release film consisted of TSH and enteric film. The dispersions used to perform inner TSH-containing film were comprised of Eudragit®NE30D and Eudragit®L30D-55. Talc (at 50% of Eudragit®NE30D dry polymer weight) homogenized with purified water for 10 min was added to the Eudragit®NE30D. Then Eudragit®L30D-55 previously plasticized with 20% triethyl citrate (TEC) based on dry polymer weight was added to the Eudragit®NE30D dispersion. Finally, TSH with proper amount of purified water was added to the above dispersion. The processing parameters of fluidized bed coater listed in Table 1 were used in the process of coating until the desired theoretical weight gain. After coating, pellets were dried at 40 °C for 24 h. Then outer enteric film composed of Eudragit®L30D-55 plasticized with 20% TEC based on dry polymer weight at proper weight gain was coated. The final product was dried at 40 °C for 2 h.

2.2.3. Preparation of TSH film-controlled pellets

Three hundred eighty grams of MCC blank pellets were placed in centrifugal granulator. TSH was dissolved in 400 ml puri-

Table 1 – The coating process parameters of fluidized bed coater.

Coating technique	Bottom spray
Air source pressure	5.0 bar
Atomization pressure	1.8 bar
Inlet temperature	25 °C
Outlet temperature	20 °C
Air flow	55–60m³/h
Spray rate	6 ml/min

fied water containing 0.4% (m/m) HPMC-E5, which was sprayed on the surface of MCC blank pellets as drug-solution. Appropriate MCC powders were added now and then in order to avoid pellets sticking each other. The final product was dried at 40 °C for 6 h. After desiccation, 400 g drug-containing pellets were further coated with Eudragit®NE30D and Eudragit®L30D-55 polymers at the optimized 22:1 ratio. The method preparing polymer dispersions and coating process parameters were the same as TSH-SR pellets except for not adding TSH-solution and had no enteric film at last.

2.2.4. *Dissolution study of the TSH-SR and TSH film-controlled pellets*

In vitro drug dissolution test was performed using USP XXVII Type 2 dissolution apparatus (paddles method). Dissolution studies were performed in 500 ml of a step function pH media. Including the simulated gastric fluid (SGF) containing 0.003% (w/w) polysorbate 80 (pH 1.2) and simulated intestinal fluid (pH 7.2), after starting the test 2 h, withdrawing 10.0 ml of the solution under test. Draining the SGF with the help of a 100-mesh screen and rinsing the screen while adding the pH 7.2 buffer which was previously warmed. At each predetermined time point, 10.0 ml of the solution was withdrawn and replaced by the same volume of fresh solution until 4 h (in pH 7.2 buffer). All the sample solutions were filtered through 0.22 mm filtration film and analyzed by HPLC [7].

2.2.5. *Preparation of Eudragit®NE30D and Eudragit®L30D-55 free films*

Eudragit®L30D-55 plasticized with 20% TEC (based on dry polymer weight) was added to Eudragit®NE30D which was diluted with an equal volume of purified water. The ratios of Eudragit®NE30D and Eudragit®L30D-55 were 5:1, 10:1 and 20:1 respectively. Blend dispersions were stirred for 1 h and casted on round watch glass (diameter: 12 cm, total dispersion weight: 20 g), then dried at 40 °C for 24 h. Thickness of the dry film was approximately 300 μm.

2.2.6. *Preparation of Eudragit®NE30D and Eudragit®L30D-55 MCC blank sustained release pellets*

Eudragit®NE30D was not diluted with an equal volume of distilled water but Talc (at 50% of Eudragit®NE30D dry polymer weight) aqueous dispersion in 2.2.5. Then it was sprayed on the MCC blank pellets employing fluidized bed coater at an appropriate weight gain, dried at 40 °C for 24 h.

2.2.7. *Stability analysis*

TSH-SR pellets were investigated in different coating weight gains, relative humidity, curing time and temperatures compared with TSH film-controlled pellets. Then cured TSH-SR and TSH film-controlled pellets were stored at 40 °C/0% RH for 90 d and 25 °C (29%, 51%, 75%, 84% and 92.5% RH) for 30 d. At last, observing the dissolution curves in different conditions. Different ratios of Eudragit®NE30D and Eudragit®L30D-55 free films and MCC blank sustained release pellets were stored at 40, 60 °C/0% RH and 25 °C/ 75, 92.5% RH for 10 and 30 d respectively. Appearances and Tgs of free films and surface morphologies of blank sustained release pellets were observed and measured in different conditions.

2.2.8. *Thermal analysis of free films*

Thermal analysis was determined on film samples using a modulated differential scanning calorimeter. Three milligram free films were accurately weighed into aluminum pans and then sealed. At first, the samples under a nitrogen atmosphere were cooled to –40 °C, then they were heated at a constant rate of 3 °C/min up to 100 °C. The glass transition temperature (Tg) was recorded as the midpoint of the transition that appeared in the reversible heat flow.

2.2.9. *Scanning electron microscopy*

To evaluate the surface of the coated polymer film, images of scanning electron microscopy were achieved from TSH-SR pellets before and after dissolution for further analyzing the drug release mechanism. In addition, surface morphologies of Eudragit®NE30D and Eudragit®L30D-55 MCC blank sustained release pellets after 6 h dissolution in different conditions were observed.

3. Results and discussions

3.1. *Ratio of Eudragit®NE30D and Eudragit®L30D55 of TSH-containing film*

Three ratios of Eudragit®NE30D and Eudragit®L30D55 (18:1, 12:1 and 8:1) were emphasized in the present study. As shown in Fig. 1, during 2 h in SGF, the release rates were almost consistent under the circumstance of the same weight gain. However, when the dissolution media was replaced with pH 7.2 buffer, three ratios had significant differences. It is because both Eudragit®NE30D and Eudragit®L30D55 are insoluble in acid environment. TSH could depend chiefly on the particle–particle interval release. Whereas in pH 7.2 buffer, Eudragit®L30D55 is able to leach out from the film and form a porous structure which could increase the mobility of it, therefore fast release tendency was seen during 2–3 h. However, during 4–6 h, TSH exhibited a delayed release profile, indicating the left TSH had difficulty in rupturing from block formed by the inner polymer film. In a word, the drug release tendency was initially ascendant but subsequently plateaued. Compared with release curves of three ratios, it was found that the ratio of 12:1 had potential ability for reaching the similar release with Harnual®.

3.2. *Weight gain of Eudragit®L30D55 of outer enteric film*

The outer enteric film aimed at decreasing the release trend entirely. It was because both 2 and 3 h release rate of inner

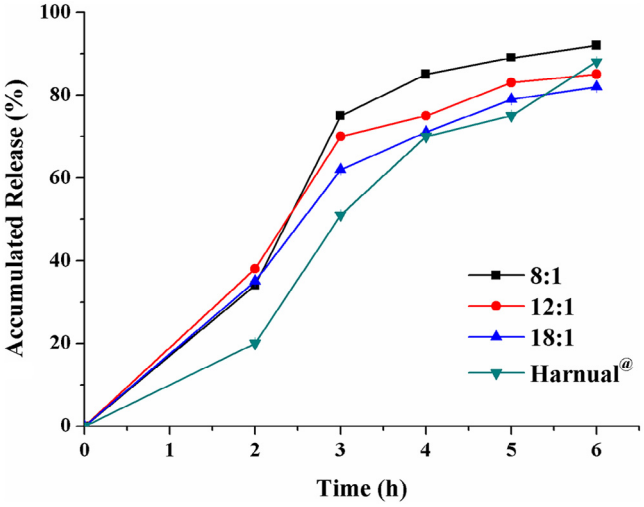

Fig. 1 – Release profiles of different ratios of Eudragit®NE30D and Eudragit®L30D55 of TSH-containing films and Harnual®. (Mean ± SD, n = 3).

TSH-containing film were relatively faster compared with Harnual®. Three coating levels of the outer films were tried to reach the ideal profiles. Fig. 2 showed that at 0.6% weight gain, the only decrease of 2 h release rate was probably because of the lower thickness of enteric film, making it ruptured rapidly in pH 7.2 buffer. While at 2%, except for 2 h, other time points also had different degree of decrease. The explanation might be the fact that TSH is a kind of weak base salt. During 2 h in SGF, with water penetrating into the intact enteric film, it was hydrolyzed and released hydrogen ion to keep an acid environment thus hindering Eudragit®L30D55 dissolved in pH 7.2 buffer. At 3%, it had a similar release behavior with 2%.Thus we decided that the weight gain of the outer enteric film was 2–3% finally.

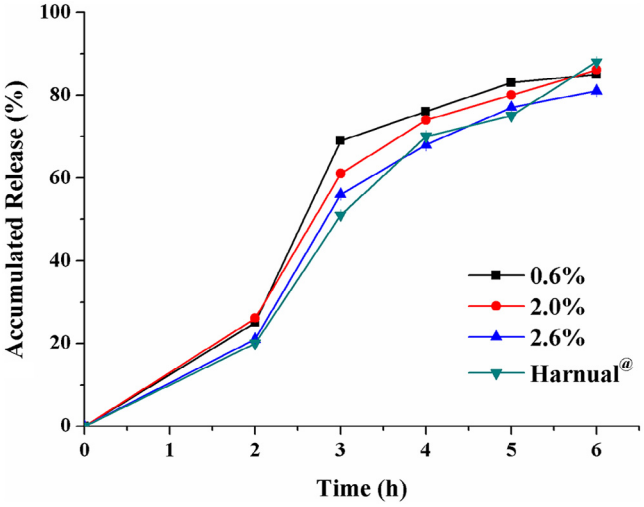

Fig. 2 – Release profiles of weight gains of Eudragit®L30D55 of outer enteric film and Harnual®. (Mean ± SD, n = 3).

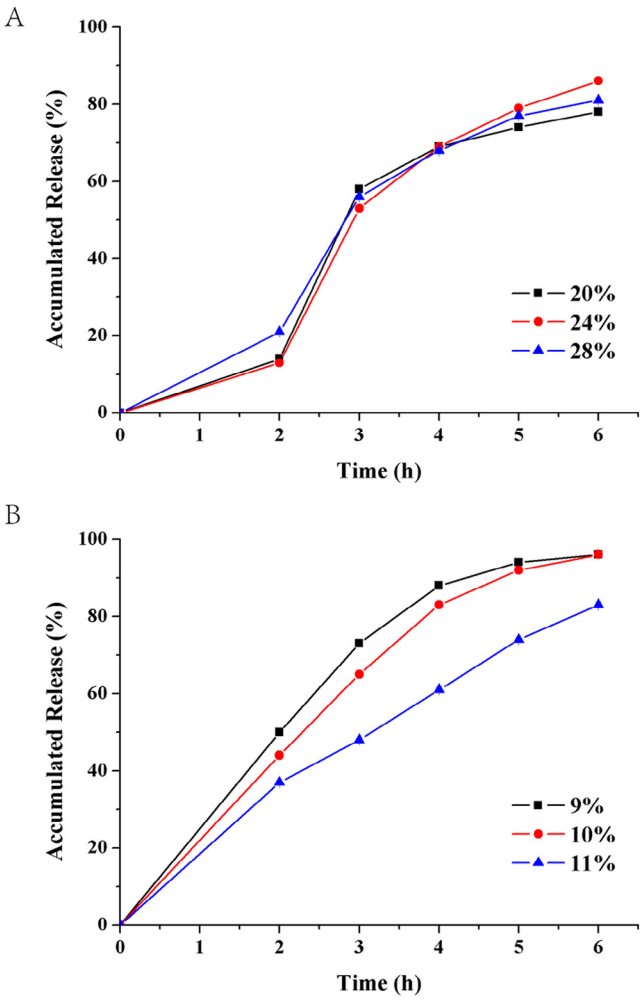

Fig. 3 – Release profiles of different weight gains of A: TSH-SR pellets and B: TSH film-controlled pellets. (Mean ± SD, n = 3).

3.3. *Stability analysis of TSH-SR and TSH film-controlled pellets*

3.3.1. *In different coating, curing condition*

Fig. 3A and 3B, Fig. 4A and 4B showed that TSH-SR pellets had a wide range in coating weight gain and relative humidity in the process of coating compared with TSH film-controlled pellets respectively. The final release profiles were found to be little changed in 20–28% coating weight and 40–60% relative humidity range unlike film-controlled pellets which were almost significantly changed in 9–11% coating weight and 50–60% relative humidity, demonstrating TSH-SR pellets were more stable in the coating process. In addition, release profiles of TSH-SR pellets were not dramatically changed at 40, 60 °C in a range of 4–24 h respectively while decreased at 60 °C in comparison with 40 °C as Fig. 5A and 5B showed. However, Fig. 6A and 6B revealed TSH film-controlled pellets were notably decreased not only in a range of 40–60 °C, but also 0–24 h, making it clear that release profiles could be altered with different curing temperature and time and TSH-SR pellets were more stable in the curing process than TSH film-controlled pellets.

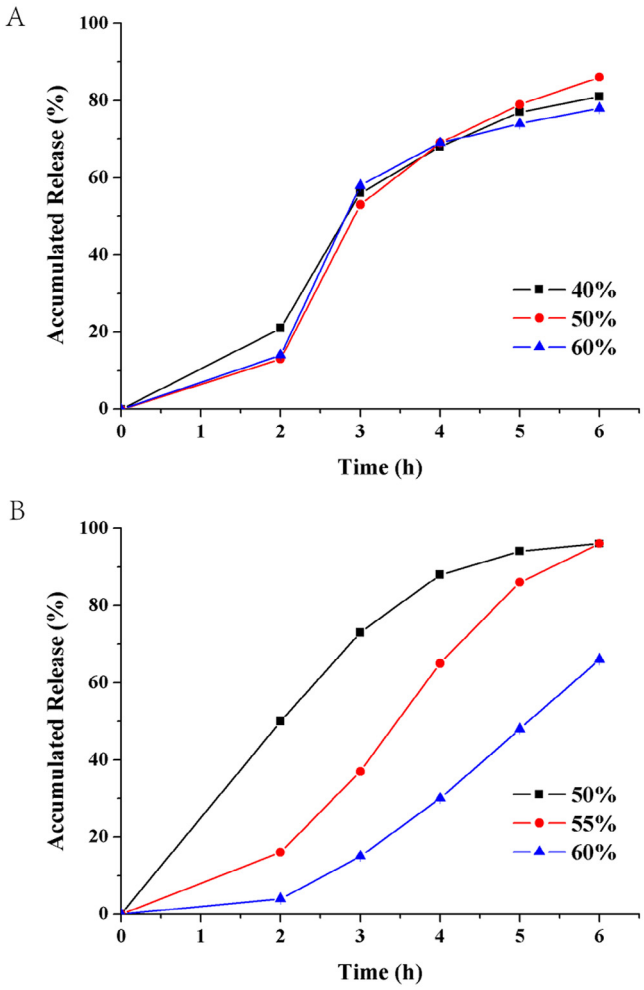

Fig. 4 – Release profiles of different relative humidity in coating process of A: TSH-SR pellets and B: TSH film-controlled pellets. (Mean ± SD, n = 3).

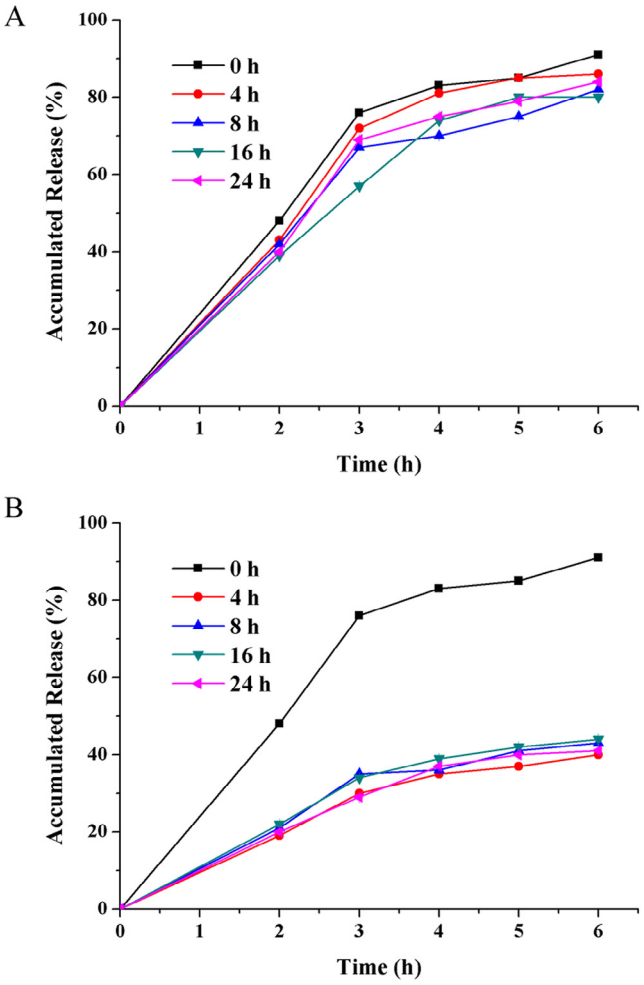

Fig. 5 – Release profiles of different curing time points of TSH-SR pellets at A: 40 °C and B: 60 °C. (Mean ± SD, n = 3).

3.3.2. *In accelerated temperature condition*

Latex particles of aqueous dispersions are not able to go through absolute coalescence at a time. The process of coalescence is divided into two stages. During the first stage, water evaporates at a constant rate and latex particles concentrate at the surface of substrate. As a result, transparent film forms. Then outer latex particles contacting with each other irreversibly become deformed by evaporation of water at a reduced rate [10]. The second stage comes during the curing time, inner rather than outer particles gradually begin gathering and amalgamating with water of inter-particle diffusing through the continuous outer film thereby forming entirely homogeneous film and gaining mechanical properties. This final stage can last for a long time after initial film forms. Therefore with coalescence going on, free volume of the polymer decreases [11]. Changes in mechanical properties and dissolution behaviors of the formulation were found.

In the present study, 40 °C was chose as a factor to investigate stability for the reason that elevating temperature of storage could accelerate the coalescence rate of latex particles, thus the release stability of the sustained/controlled release formulations could be initially verified. Fig. 7A and 7B showed the results that TSH-SR pellets were considered stable from the dissolution profiles during 90 d. It was probably because water-soluble TSH acted as a hydrophilic pore-producer in Eudragit®NE30D and Eudragit®L30D55 polymers film which was water-insoluble in simulated gastric fluids at first, then TSH and Eudragit®L30D55 both acted as pore-producers in simulated intestinal fluids. Assuming TSH and polymers as a whole, then Fick's law could be applied to discuss why the TSH-SR pellets were able to stabilize during 90 d.

$$Q = \frac{DS(C_s - C)t}{h} \quad (1)$$

Where Q is the quantity of drug release in time t, h is the film thickness, C_s is the concentration in preparation, C is the concentration of drug in the dissolution media, D is the diffusion coefficient of the drug and S is the area of formulation. The diffusion coefficient, D has been modified to account for the recognized film structure by Iyer [12].

$$D = \frac{D_w e}{\tau} \quad (2)$$

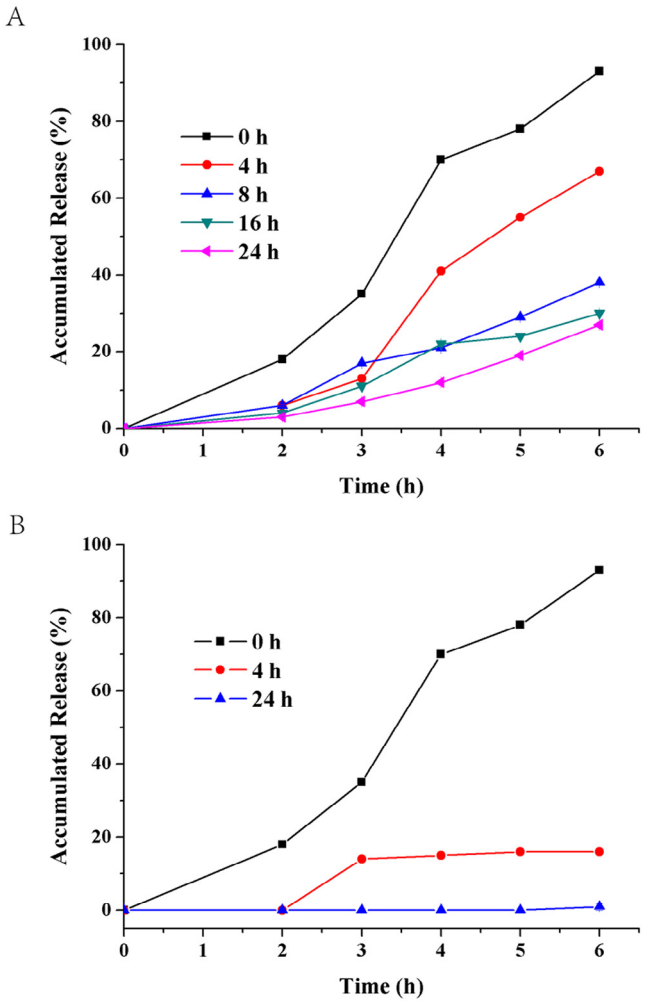

Fig. 6 – Release profiles of different curing time points of TSH film-controlled pellets at A: 40 °C and B: 60 °C. (Mean ± SD, n = 3).

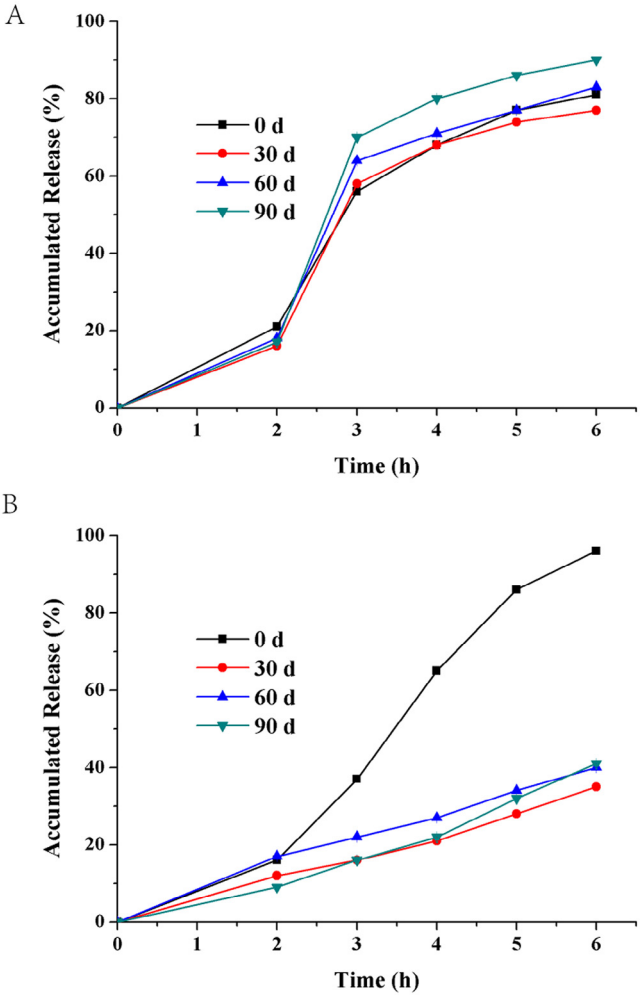

Fig. 7 – Release profiles of different time points at 40 °C/0% RH of A: TSH-SR pellets and B: TSH film-controlled pellets. (Mean ± SD, n = 3).

Where D_w is the diffusion coefficient in the medium, e is the porosity factor and τis the tortuosity factor. When proceeding in the final stage of film formation, coalescence decreased porosity factor and then altered drug diffusion coefficient and release behavior. However, TSH formed a water-soluble phase around the insoluble polymer, hindering further coalescence of latex paticles.TSH film-controlled pellets did not possess such a structure that diffusion coefficient of drug decreased subsequently leading to a significantly decrease of release rate.

3.3.3. *In different storage relative humidity condition*

Water in the air can act as a plasticizer [13], the addition of plasticizer to the polymer has great advantages, such as Tg decrease, elongation increase, making the polymer more flexible and soft in the process of coating [14]. The final product usually has an intact structure and the polymer film is continuous so that burst release can be avoided [8]. Nevertheless, the type and quantity of plasticizers are able to affect both the slope and shape of release curves [15]. The aim of investigating release behavior of TSH-SR pellets in different relative humidity conditions was to verify whether the formulation had a resistance ability to relative humidity or not. The results in Fig. 8A revealed that drug release rate of TSH-SR pellets decreased except for in 29% relative humidity while Fig. 8B showed that TSH film-controlled pellets decreased even in 29% relative humidity in comparison. It was inferred that film possibly formed a structure which was not similar to the accelerated condition, such a flexible and soft film made the media had difficulty in penetrating into both outer and inner film. When water came across the polymer film, it occupied the space of particle–particle chains to weaken interaction. The diffusion coefficient remained decreased though TSH was added to two polymers. From the results above, relative humidity was still not neglected in storage and would be a tough problem to be solved.

3.4. *Appearance and Tg of Eudragit®NE30D and Eudragit®L30D-55 free film*

Film containing two kinds of polymers was usually more complex than single polymer. As two kinds of polymers having different properties might lead to incompatibility in the course of mixture, coating and storage. As a result, characters of free

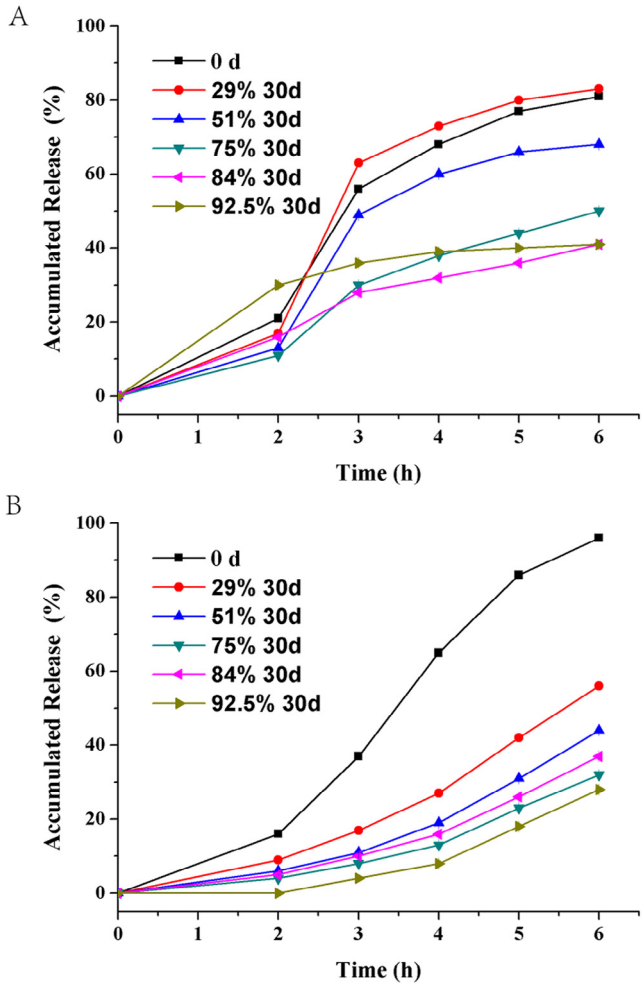

Fig. 8 – Release profiles of different relative humidity for 30 d of A: TSH-SR pellets and B: TSH film-controlled pellets. (Mean ± SD, n = 3).

Table 2 – Appearances and glass transition temperatures of films made of different ratios of Eudragit®NE30D and Eudragit®L30D-55 polymers.

Ratio	Condition	Appearance	Tg(°C)
5:1	0 d	Translucent, not smooth	17.0
	40 °C, 10 d	Translucent, not smooth and tough	-
	60 °C, 10 d	Translucent, not smooth and tough	-
	75% RH, 10 d	Translucent, incompatible and soft	12.5
	92.5% RH, 10 d	Translucent, incompatible and soft	12.0
10:1	0 d	Translucent, smooth	11.0
	40 °C, 10 d	Translucent, smooth and tough	-
	60 °C, 10 d	Translucent, smooth and tough	-
	75% RH, 10 d	Translucent, incompatible and soft	7.0
	92.5% RH, 10 d	Translucent, incompatible and soft	6.0
20:1	0 d	Transparent, smooth	3.0
	40 °C, 10 d	Transparent, smooth and tough	-
	60 °C, 10 d	Transparent, smooth and tough	-
	75% RH, 10 d	Transparent, smooth and soft	1.0
	92.5% RH, 10 d	Transparent, smooth and soft	–2.5

film and dissolution profiles of solid formulation altered [8]. We considered it essential in studying film containing two polymers in appearance and affecting factors which might produce potential decrease in release rate. In view of factors in the course of coating, curing and storage, temperature and relative humidity were chose for investigating the free film. Weijia Zheng had identified that Eudragit®NE30D and Eudragit®L30D-55 were compatible at ratio more than 4:1 [16]. We designed three ratios (5:1, 10:1 and 20:1) within the limit of compatibility meeting sustained/controlled release kinetics of Eudragit®NE30D and Eudragit®L30D-55 films at 40, 60 °C/0% RH and 25° C/75, 92.5% RH. Tg is a significant parameter in the process of coating and storage of the sustained/controlled release formulations, representing the chain mobility of the polymer [17]. Generally, with the decrease of Tg, polymer exhibits better flexibility. The aim of adding plasticizer to some coating polymers is to decrease Tg thus resulting in a compacted film .Appearances and Tgs of free films were listed in Table 2. With the increase of the

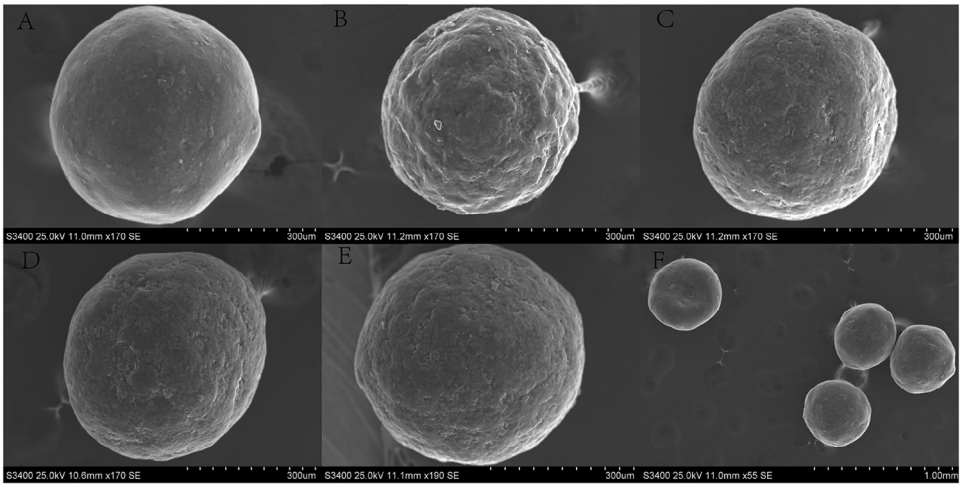

Fig. 9 – Images of surface morphology of TSH-SR pellets before and after dissolution (A: before dissolution, B: after dissolution 2 h, C: after dissolution 3 h, D: after dissolution 4 h, E: after dissolution 6 h, F: before dissolution in general).

ratio of two polymers, film was from translucent to transparent in appearance, and decrease in Tg. In addition, at 40 and 60 °C, films became tough while in 75 and 92.5% RH, films were flexible and Tgs decreased. It was signed that Eudragit®NE30D and Eudragit®L30D-55 aqueous dispersions were easily affected by temperature and relative humidity in a wide range. Variations in appearance and Tg in a sense symbolized transformation in mechanical characters. Temperature made film smooth and dense, moisture interposed itself between polymer chains to make the film more flexible. Therefore the release rate was delayed either by temperature or moisture finally.

3.5. *Scanning electron microscopy analysis*

From Fig. 9, we might come to conclude and discuss as follows. The surface of TSH-SR pellets was intact and smooth before dissolution, indicating that the final formulation by optimized processing parameters was successfully prepared. While after dissolution 2 h, it seemed that irregularities and pores were on the surface of TSH-SR pellets. It was concluded that the plasticizer was exuded into water thus forming such a surface morphology. At 3, 4 and 6 h, fragments appeared and the surface seemed to be flat compared with 2 h. It was because during 2–3 h, Eudragit®L30D-55 began to dissolute gradually. In the process of 3–6 h dissolution, surface morphology seemed to remain similar therefore diffusion was concluded as the main release mechanism in later stage. More coating weight gain might be the reason to explain the structure on the surface of TSH-SR pellets after dissolution 3 h, developing correlations with the shape of release curves. Especially in later stages, delayed drug release tendency was well-explained, as firm penetration barriers made drug less possible to leap over from the film.

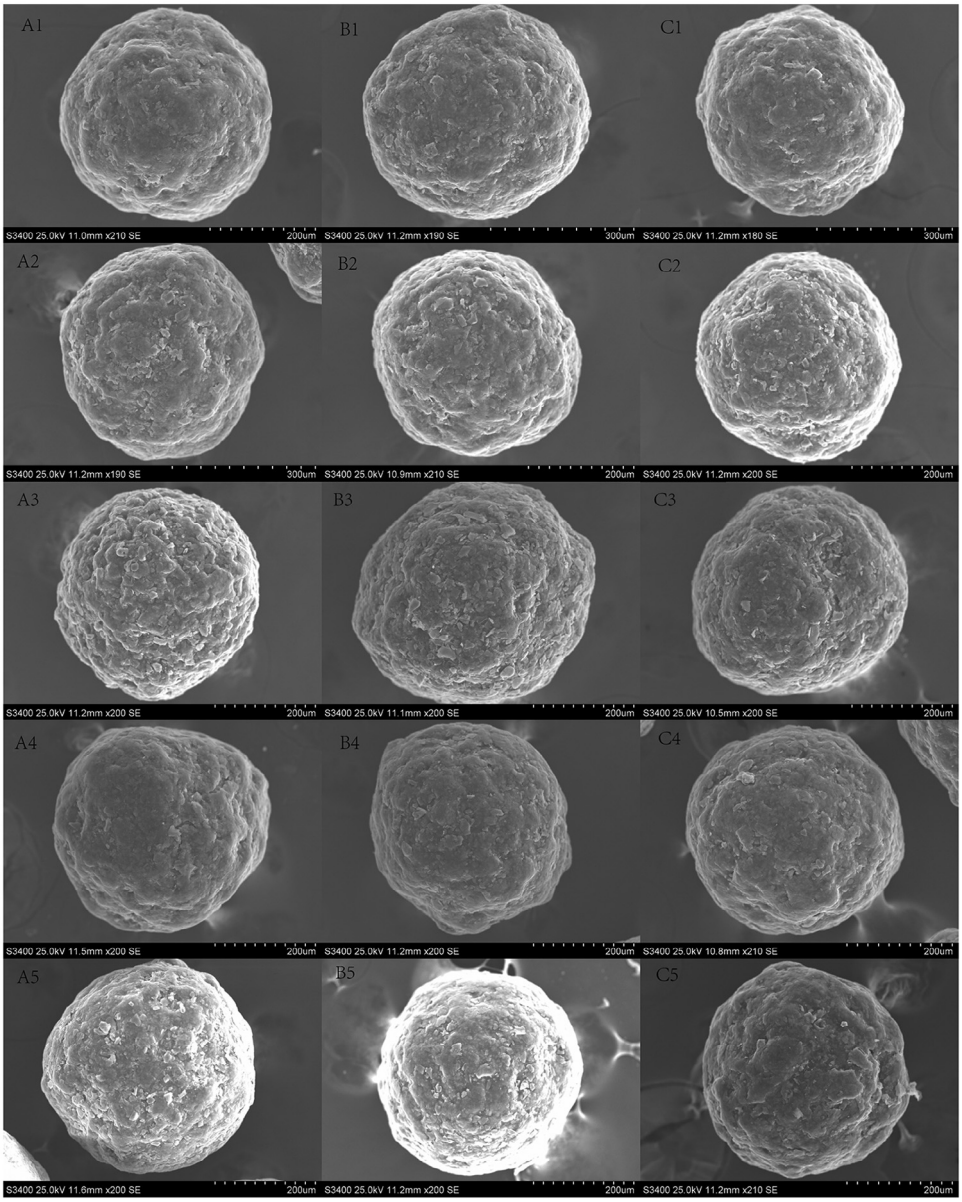

Fig. 10 – Images of surface morphology of different ratios (A: 5:1, B: 10:1 and C: 20:1) of Eudragit®NE30D and Eudragit®L30D55 MCC-blank pellets in different conditions after dissolution. (1: 0 d, 2: 40 °C for 30 d, 3: 60 °C for 30 d, 4: 75% RH for 30 d, 5: 92.5% RH for 30 d).

Similar patterns were found from the surface images of different ratios of Eudragit®NE30D and Eudragit®L30D-55 MCC blank sustained release pellets after dissolution in different storage conditions. As shown in Fig. 10, with the temperature and relative humidity increasing, not only the left fragments on the surface of sustained release pellets increased, but also became gathering together at the same ratio of Eudragit®NE30D blended with Eudragit®L30D55, indicating that the release profiles might be changed of formulations coated with Eudragit®NE30D blended with Eudragit®L30D55 from 5:1 to 20:1 ratio range. Compared with the surface of pellets at 40, 60 °C/0% RH, it was more flat at 25 °C/75, 92.5% RH at the same ratio thereby indicating that the structure of film was not similar in different affecting factors. Conclusions were made from micro-morphology view and consistent with appearances and Tgs of free films above.

4. Conclusion

TSH-SR pellets were successfully prepared similar with Harnual®. Of outmost significance, the formulation was relatively insensitive of temperature and relative humidity which showed better advantage in the process of coating and long-term storage compared with film-controlled formulations utilizing Eudragit®NE30D and Eudragit®L30D-55 aqueous dispersions if kept in a adequate lower relative humidity condition. Adding main drug (TSH) to polymer film might also be a method to increase release stability of the formulation. From the results of appearances and Tgs of free films and surface morphologies of blank sustained release pellets produced by Eudragit®NE30D and Eudragit®L30D-55, care should be taken when utilizing Eudragit®NE30D and Eudragit®L30D-55 polymers in the process of coating. Strategies must be developed in the future to improve the issue of poor release stability of the aqueous dispersion coating. The study would make suggestions to other researchers investigating sustained/controlled release preparations utilizing Eudragit®NE30D blended with Eudragit®L30D-55 in coating.

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