The Mechanism of Improvement of Film Solubility: Design and Evaluation of Film Forming System with Terbinafine as a Model Drug

Jing Zhang

Guangdong Pharmaceutical University

bohong lu

Guangdong Pharmaceutical University

Qiuyan Ma

Guangdong Pharmaceutical University

Shelke Om

Bright Future Pharmaceutical Laboratories Limited

William Wu

Bright Future Pharmaceutical Laboratories Limited

huaqing lin (✉ huaqing_@163.net)

Guangdong Pharmaceutical University <https://orcid.org/0000-0003-2915-8672>

Research Article

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Abstract

Purpose: Film forming system (FFS) combines the advantages of patch and gel, it is expected to replace small doses of topical administration in the future. This work targets the design and evaluation of HPC-acrylic FFS with different excipients in appearance, rheology and in vitro properties. Also, the reason of improving the solubility of terbinafine film was illustrated by melting enthalpy thermo analysis.

Methods: In this work, we prepared 8 HPC-acrylic FFS samples with different excipients, and characterized the film forming solutions and films in appearance, rheological properties, drug crystallization and in vitro performance. Then used melting enthalpy thermo-analysis to explain the mechanism of improvement of film solubility.

Results: According to appearance evaluation, the samples which had a small amount of plasticizer could achieve an uniform surface morphology. The XRD and DSC demonstrated HPC could maintain drug amorphous in films. Based on oscillation frequency sweep, short chain plasticizer tributyl citrate (TBC) leading to strong entanglement and hydrogen bonding among the molecules. In vitro release test showed FP1 had favorable release. And the melting enthalpy thermo-analysis explained why FP1 had favorable release.

Conclusions: HPC acted as an effective crystallization inhibitor. TBC could lead stronger intermolecular hydrogen bonds. The poloxamer had favorite miscibility with HPC-acrylic FFS. The combination of MCT and poloxamer with HPC resulted in a high Terbinafine solubility.

1. Introduction

The study of film forming systems (FFS) allows the therapy to be adapted to the patient or application requirements. The conventional topical preparations, such as ointment and cream, can be easily wiped off by clothes, which leads to a poor treatment effect due to the improper dosing. The need of the repeated application of the topical preparation generates a series of issues associated with the patient compliance. Although the patches can be effectively retained on the skin, their disadvantages, such as prevent skin from sweating, cause allergy, or obviously visual, that cannot be ignored in surface application [1, 2]. FFS can provide an effective drug concentration, along with an invisible cosmetic appearance, thus, prolonging the maintenance time on the skin. It reduces the dosing frequency and improves the patient compliance [3]. FFS contain three main components - drug, film forming polymer and volatile solvent. FFS can replace the small dosage topical preparation by combining the advantages of gels and patches [4].

In order to achieve the rapid film formation after application, the volatile solvent system with a high concentration is required. After evaporation of the volatile solvent, the drug concentration in the residual film increases and even reaches the super-saturation state. The observed enhancement in the drug saturation and thermodynamic activity can result in an improved driving force for the drug delivery across the skin, which rises in a proportional manner as the drug saturation degree in the residual formulation

after evaporation [5, 6]. Because of such a metastable state, the drug is thermodynamically unstable [7]. A few polymers are known to act as the crystallization inhibitors, preventing the crystallization and enhancing the drug flux, even after the solvent has been completely evaporated. The examples of the crystallization inhibitor polymers include polyvinyl pyrrolidone, polyethylene glycol and hydroxyl propyl methyl cellulose [8].

Many film forming agents which can form a stable film structure in the aqueous solution, but they may not form a stable film in the alcohol system. Hydroxypropyl cellulose (HPC) possesses low toxicity and optimal film-forming properties, and it swells in ethanol to form a gel-like solution. Furthermore, the pure HPC films do not demonstrate an excellent water barrier due to the presence of a large number of hydrophilic groups [9], which can cause the films to break and fall off during sweating. Owing to the excellent compatibility of acrylates/octylacrylamide copolymer (ACOA) and HPC, the incorporation of ACOA in the system as a hydrophobic film forming component can improve the water and wearing resistance. It indicates that a favorable pharmaceutical blend film can be developed by combining these polymers. Carbomer and poloxamer are usually used in hydrogels, but now they are introduced to non-aqueous solution. However, neither carbomer nor poloxamer possesses an independent film-forming capacity. So the HPC matrix as a vehicle to maintain a stable polymer system.

Usually, plasticizers are used to enhance the flexibility and adhesion of the films by reducing the glass transition temperature (T_g) of the film forming polymer. plasticizers can improve the drug release performance by enhancing the polymer free volume and mobility of the polymer chains [10-12]. Furthermore, it not only weakens the intermolecular forces among the polymer chains [13], but also leads to the formation of the hydrogen bonds with polymer chains [14]. In this study, medium-chain triglycerides (MCT) and tributyl citrate (TBC) were chosen as plasticizers owing to their satisfactory safety.

Terbinafine is an antifungal materials and inhibits the ergosterol synthesis in cytoderm by inhibiting the squalene epoxidase. Terbinafine displays a strong affinity with stratum corneum (SC), and Terbinafine can form a reservoir in SC [15]. In this study, FFS was used for the treatment of superficial cutaneous fungal infections (SCFIs). The penetration enhancer was not included in the formulation owing to the high drug penetration in the skin would make it difficult to maintain a drug reservoir in SC [16]. In addition, it was vital to prevent the side effects by avoiding the systemic circulation of the drug.

During the formation of a solid film, the dynamic nature of the solvent evaporation process makes it challenging to fully understand the role of each component and their impact on the final product. The rheological analysis is sensitive to the changes in the molecular structure, it can provide an understanding of the impact of the excipients changes on the topical preparation. The viscoelasticity can reflect the changes in the molecular interactions, thus, allowing the effective characterization of the film [17]. Moreover, the skin sensation is an important in topical preparation. The polymer system can influence the sensorial parameters by modifying the final texture [18]. In this way, the subjective feeling can be expressed and compared with objective physical parameters.

In the first part this work targets the design and evaluation of HPC-acrylic FFS in appearance, rheology, in vitro properties. The second half is to demonstrate both the feasibility and the practicability of applying melting enthalpy thermo-analysis in drug-film solubility determination. This method used to explain the mechanism of improvement of film solubility. It is a functional tool but it has rarely used in mechanism demonstration. This study provides new strategies for the development and evaluation of a new topical preparation, which may facilitate to replace a part of defective traditional topical preparations.

2. Materials And Methods

2.1 Materials

Hydroxypropyl cellulose (HPC, molecular weight: 8.5×10^5 Da, 25 °C Brookfield viscosity of 2% concentration in water: 4000~6500 mPa·s, fine particle size) purchased from Ashland Industries Europe GmbH (Nanjing, China). Acrylates/octylacrylamide copolymer (ACOA) used as hydrophobic film forming polymers purchased from Nouryon Chemicals Co., Ltd (Boxing, China). Poloxamer 124 and Carbomer 980 used as co-film forming material. Poloxamer 124 was kindly provided by BASF SE (Guangzhou, China). Carbomer 980 was purchased from Lubrizol Corporation (Guangzhou, China). Medium-chain triglycerides (MCT) and tributyl citrate (TBC) used as plasticizers were purchased from IOI Oleo GmbH (Hamburg, Germany) and Shanghai Aladdin Bio-Chem Technology Co., LTD (Shanghai, China), respectively. Terbinafine hydrochloride (TH) purchased from Qilu Antibiotics Pharmaceutical Co., Ltd (Linyi, China). 96% Ethanol was purchased from Hayman Group, Kimia, UK. The commercial product (Lamisil once® Cutaneous solution) was purchased from GlaxoSmithKline PLC (Basel, Switzerland). All other chemicals were used without any further purification.

2.2 Preparation of film forming solution

TH was dissolved in 96% ethanol to achieve a clear solution, followed by the addition of ACOA. The film-forming solutions were prepared by dispersing the HPC in the lipophilic plasticizers. The HPC dispersions were added to the earlier formed solution of TH and ACOA in 96% ethanol at a concentration of 1.125% (w/w) (equivalent to 1.0% (w/w) Terbinafine). The contents were stirred until a clear solution was obtained, and the film forming solution was kept in dark overnight. In the formulations without MCT, HPC was swollen in ethanol for more than 12 h until no insoluble white HPC particles were observed. It was followed by the addition of 96% ethanol solution with TH and ACOA. The contents were stirred until a clear solution was obtained. The compositions of the formulations are presented in Table 1.

Table 1 Composition of film forming system

Materials w/w [%]	FMP1	FMP2	FMC1	FMC2	FC1	FC2	FP1	FP2
TH	1.125	1.125	1.125	1.125	1.125	1.125	1.125	1.125
MCT	3.000	3.000	3.000	3.000	-	-	-	-
ACOA	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
HPC	2.000	2.000	2.000	2.000	2.000	2.000	2.000	2.000
TBC	1.000	-	1.000	-	1.000	-	1.000	-
Polxamer 124	1.000	1.000	-	-	-	-	1.000	1.000
Carbomer 980	-	-	1.000	1.000	1.000	1.000	-	-
96% Ethanol	QS to 100%							

Note: Naming rule: M = MCT, C = Carbomer, P = Poloxamer, 1 = With TBC, 2=Without TBC.

2.3 Chromatographic equipment and conditions

Quantitative analysis of Terbinafine was performed using Waters Alliance W2690/5 high-performance liquid chromatography with Waters W2998 PDA detector and Shimadzu, Inertsil ODS-2 column (5 μm , 3.0 $\times$ 150 mm). The detection method of Terbianfine was based on the Chinese pharmacopoeia [19]. The retention time of Terbinafine under these conditions was approximately 15 min. The HPLC procedure was validated for linearity, precision and accuracy. The produced calibration curve $A = 40115.8c - 10716.7$ was linear over the concentration range 2~1000 $\mu\text{g}\cdot\text{mL}^{-1}$, with a coefficient of determination (r^2) of 0.9999. The intra-and inter-day precision (% RSD) for the three standards representing the high, medium and low drug concentrations ranged from 0.22% to 0.66% and 0.86% to 1.59% respectively. The accuracy of the three concentrations ranged between 98.76% and 98.98% (RSD=0.10%).

2.4 Scanning electron microscopy

The films were observed by using scanning electron microscope (Helios Nanolab 600i, FEI, USA). The surface of the films was sputtered with a thin gold coating. The analysis was performed at an accelerating voltage of 5 kV, and the images were acquired at magnifications of 5000 $\times$.

2.5 Rheological properties

2.5.1 Steady shear measurement

The steady shear properties were evaluated using a rotational rheometer (MARS 40, Haake Ltd., Hamburg, Germany) at 25 °C with a cone-plate geometry of 60 mm diameter. The cone angle and gap were set at 1° and 1.00 mm, respectively. The shear rate was varied from 0.001 to 100 s⁻¹ to evaluate the viscous behavior of the sample, and the associated data was fitted to the following power law equation:

$$\tau = K\dot{\gamma}^n \quad (1)$$

where τ is the shear stress (Pa), K is the consistency index (Pa s), $\dot{\gamma}$ is the shear rate (s⁻¹), and n is the flow index.

2.5.2 Dynamic viscoelasticity measurement

The dynamic rheological analysis was performed using the same conditions as the steady shear analysis. The shear stress was varied from 0.01 to 2000 Pa at a frequency of 5.00 Hz to evaluate the linear viscoelastic zone (LVR).

2.5.3 Oscillation frequency sweep

The oscillation frequency sweep was performed by using the same conditions. The shear stress in LVR was set as 10 Pa, and the frequency ranged from 0.10 to 20 Hz. The change in the storage and the loss moduli were subsequently recorded.

2.6 Differential scanning calorimetry

The thermal properties of the films were measured by using a differential scanning calorimeter (TA Q100-DSC, TA instruments, UK) under nitrogen atmosphere. The film samples (5 mg) were placed in the aluminum pans, followed by sealing of the pans. The samples were heated in the temperature range 25 °C to 300 °C using a heating rate of 10 °C/min.

2.7 X-ray diffraction

The crystal structure of the pure TH powder, physical mixture of TH and HPC, TH and HPC films and blend films were characterized by using an X-ray diffractometer (SmartLab 9 kW, Rigaku, Japan) equipped with Cu K α radiation ($\lambda = 0.1542$ nm). The samples were scanned in the 2θ range from 1.5° to 20° using a scanning rate of 2° min⁻¹.

2.8 *In vitro* release test

The experiments were conducted using Vertical Diffusion Cell (RermeGear V6-Ca-01, USA) with a Nylon membrane (JINTENG[®] TJMF25 Nylon membrane, 0.45 μm) at a constant stirring speed at 600 rpm. The receptor medium based on methyl alcohol and water (30:70) was added, and the water bath temperature was set to $32\pm 1^\circ\text{C}$. Subsequently, 300 mg FFS was added on the membrane soaked prior for 30 min in the medium for equilibration. A period of 180 min was provided to achieve the film formation. The cells were occluded with Parafilm[®] throughout the analysis to prevent the evaporation of the medium. 1 mL receptor cells samples were withdrawn after 1, 2, 4, 6 and 8 h and replenished with the same amount of the medium.

2.9 Statistical analysis

The samples were tested at least in triplicate, and the results were presented as mean $\pm$ standard deviation. The statistical analyses were performed using the Origin 2018 95C software (OriginLab Corporation, Northampton, MA, USA). Two-way ANOVA ($p < 0.05$) was used to compare the statistical differences in the obtained values.

3. Results And Discussion

3.1 Appearance of FFS and films

Supplemental Fig. 1 demonstrates the appearance of the different FFS. The poloxamer FFS was observed to be a transparent and uniform gel-like solution, whereas the carbomer FFS was an off-white gel-like solution. For 0.5 g film forming solution applied on the forearm skin, the formed thin and invisible film dried within 3 min.

3.2 Scanning electron microscopy

Some formulations couldn't get integrated films in drying process. Like FMC1 and FMC2, the separated two-phase structure generated cracks on the film surface, and the FC1 films exhibited cracks and did not form an integrated structure (Supplemental Fig. 2). This phenomenon could be interpreted as the carbomer-HPC FFS had a poor miscibility with the lipophilic plasticizer.

As shown in Fig. 1, the surface of the original HPC-ACOA blend film demonstrated a few cracks, which indicated that the original blend film was not ideal as a drug carrier. Similarly, FC2 and FP2 also displayed cracks and a certain extent of breakage, while FP1 presented a smooth morphology with uniform texture. It revealed that a small amount of plasticizer was necessary to achieve the uniform surface morphology.

When the MCT was gradually added to poloxamer FFS, The the SEM images of FMP1 and FMP2 revealed the soft MCT inclusions surrounded by the rigid polymer framework. The inclusions also led to the formation of inter-connected holes. Such drug-carrying films may be beneficial for buccal mucosa and

oral delivery. As the saliva and gastric juice enter the holes, it can promote the polymer framework swelling and drug dissolution. It is feasible to control the rate of drug release by controlling the number of holes, which has a positive correlation with the plasticizer content.

3.3 Rheological properties

3.3.1 Steady shear measurement

As shown in Fig. 2a and 2b, viscosity decreased rapidly on increasing the shear rate. The high shear rates simulates the activity of applying samples on the skin. Based on the power law fitting, the parameters n and K are presented in Supplemental Table 1. All film forming solutions exhibited a high correlation coefficient ($R^2 > 0.98$). The film forming solutions with $n < 1$ revealed a shear thinning behavior representing the non-Newtonian pseudo-plastic fluids. It represents an ideal property of topical semisolid systems, as the low viscosity system is more conducive to achieve the uniform paint and subsequent application.

3.3.2 Dynamic viscoelasticity measurement

The storage (G') and loss (G'') moduli of the sample are presented in Fig. 3a and 3b. As the stress was increased, the storage and loss moduli curves ran nearly parallel to each other. This was followed by a rapid decline in G' , generating a crossover point with G'' . The crossover point indicated the irreversible damage in the internal structure of FFS. The parallel range is also termed as the linear viscoelastic range (LVR).

In practice, G' values in LVR represent the stiffness of the sample or gel strength. The poloxamer FFS exhibited a reduction in the G' values after the incorporation of MCT in the formulations (Fig. 3a). FMP1 and FMP2 demonstrated lower G' values as compared to FP1 and FP2 (Supplemental Table 1). Another lipophilic plasticizer TBC was also evaluated in this work. As shown in Fig. 3a, an increment in the amount of the lipophilic plasticizer (both MCT and TBC) was inversely proportional to the stiffness and strength of FFS ($P < 0.05$).

However, the inverse relation was not evident in the carbomer FFS. As observed in Fig. 3b and Supplemental Table 1, the G' values and lipophilic plasticizer did not exhibit any significant relation. Except for FC1 demonstrating the highest G' values ($P < 0.05$), other changes in the carbomer formulation did not significantly impact the G' values ($P > 0.05$).

The yield stress values (Supplemental Table 1) of the samples between 10 and 100 Pa indicated that a minimal force could initiate the flow (1-10 mN force over 1 cm² area), which confirmed the easy application of the developed formulations on the skin [20].

3.3.3 Oscillation frequency sweep

Oscillation frequency sweep was used to determine the system response to the impact or gradual loading forces. Fig. 4a and 4b demonstrate the changes in G' and G'' as a function of frequency. G'' was higher than G' at low frequency values, which indicating the viscous characteristic of the system. At high frequency values, G' was higher than G'' , revealing the elastic characteristic.

A large number of literature studies [17, 21, 22] have explained the observed changes: at low frequency values, the polymer molecular chains have sufficient time to relax and disentangle, thus, rendering the viscous fluid characteristic. However, on enhancing the frequency (the high frequency acting more like a strike on the system), the short periodic oscillation does not provide sufficient time to the entangled molecular chains to relax. These entanglements, thus, play the role of the three-dimensional (3D) network of the temporary junction. Although the entanglement of the polymer chains can be regarded as the temporary 3D structure at high frequency, G' and G'' show frequency dependency, suggesting that HPC in FFS is present as a polymer solution rather than a network structure [17, 23].

Classified curves by MCT, then respectively compared the samples with or without TBC. Both G' and G'' were observed to increase for the system with TBC, and the crossover point moved towards the low frequency values, representing a strong entanglement and hydrogen bonding among the molecules. This confirmed that the short chain plasticizer TBC was more likely to be inserted in the incompletely swollen polymer chains, so that exposed carboxyl groups on the stretched chains to form a large number of strong intermolecular hydrogen bonds

3.4 Differential scanning calorimetry

As shown in Fig. 5a, the TH drug powder demonstrated two characteristic endothermic peaks in the DSC pattern: one of the peaks was attributed to TH, while the other peak was related to its homeopathic isomers. However, these characteristic heat-absorption peaks were observed to disappear in the physical mixture. The observed phenomenon is due to the reason that a drug was physically mixed with an amorphous polymer it can dissolved in, the amorphous polymer initially absorbs the heat to form a glassy structure. On further heating to the drug melting temperature, the drug dissolves in the glassy polymer, resulting in the reduced melting enthalpy. This phenomenon can be used to determine the drug solubility in polymers [6]. The disappearance of peaks was also observed in the films indicating the crystal transformation in FFS. Overall, the crystal transformation to the amorphous structure is conducive for the drug entry in SC.

3.5 X-ray diffraction

XRD analysis was performed to verify the crystal structure of TH in the physical mixture. As shown in Fig. 5b, the pure TH powder and physical mixture exhibited sharp diffraction peaks, especially at $2\theta = 5.98^\circ$.

This indicated that the crystal structure still existed in the mixture at room temperature. The characteristic peaks were observed to disappear or broaden in the films. It suggested that the transformation of the Terbinafine crystal occurred in the films due to the hydrogen bonding interactions, which was consistent with the findings from DSC. Combining the DSC and XRD results also revealed that HPC maintained TH in the amorphous form during the solvent volatilization. HPC act as an ideal crystallization inhibitor.

3.6 *In-Vitro* release test

As shown in Fig. 6, the formulations exhibited a significantly higher extent of release than the commercial product ($P < 0.05$), indicating the formation of a higher drug reservoir formed in SC. The high lipophilicity of TH makes it difficult to pass through the hydrophilic dermis in the absence of a penetration enhancer, thus, a high concentration of the drug reservoir does not enhance the risk of the side effects. Two features can be clearly noted from Fig. 6. Firstly, TBC occupied a content of 10.9%~16% in the dried films, however, it did not significantly influence the released amount ($P > 0.05$). Secondly, a high amount of MCT (3 times higher than TBC) added in the carbomer-films (FMC1 and FMC2) significantly enhanced the drug release rate than FC1 and FC2 ($P < 0.05$), which was consistent with the plasticizer effect mentioned earlier. In contrast, poloxamer improved the initial release and release rate, however, the presence of MCT in the poloxamer-film reduced the extent of release. A probable reason is that the solubility of Terbinafine may be enhanced due to the combination of MCT and poloxamer. This corresponds to a decrease in the drug saturation and thermodynamic activity, thus, reducing the drug delivery. The release curves were fitted with the first-order, zero-order and Higuchi functions respectively. As per Supplemental Table 2, the formulations mainly followed the first-order release behavior.

3.7 Thermo-analysis of release behavior

It is important to analyze the observed decrease in the drug release on adding MCT in the poloxamer FFS. In order to explore if the observed decrease in the drug release was related to the improvement in the drug solubility, the TH+HPC+P physical mixtures were prepared using different mixing ratios. DSC analysis was performed to ascertain the solubility of TH in HPC. The solubility was re-measured after adding MCT. The principle is that the drug dissolves in the glassy polymer during melting, a reduction in the melting enthalpy can be observed. This reduction should linearly related to the drug fraction. In case the weight fraction of the drug exceeds the maximum solubility level within the polymer, a fraction of the drug is no longer dissolved in the polymer, and the linear relationship with the melting enthalpy may change.

As shown in Fig. 7a, the glass transition temperature of HPC was $\sim 55^\circ\text{C}$, and the glass transition curve was noted to flatten after adding MCT (Fig. 7b). This could be attributed to the molecular interactions in the HPC-poloxamer-MCT system.

As shown in Fig. 7a and 7b, compared to the TH+HPC+P mixture, the reduction in the TH melting peak was deeper in the mixture with MCT. Especially for the 40:60 mixtures, the TH+HPC+P+MCT mixture

exhibited a small TH melting peak, while the melting peak was obvious in the TH+HPC+P system. This indicated that TH had a superior solubility in the HPC+P+MCT mixture.

Fig. 8 present the melting enthalpy variation observed in each mixture. For the TH+HPC+P mixture (Fig. 8), the changes of melting enthalpy could be divided into two linear stages of drug loading. The first stage occurred for the drug loading between 40 to 70%, while the second was noted from 70 to 90%. The solubility obtained by the linear regression analysis was 71.81% w/w. Similarly, the TH solubility in the HPC+P+MCT mixture was 80.90% w/w.

These findings qualitatively and quantitatively verified that the addition of poloxamer and MCT to HPC resulted in an enhanced TH solubility. These also explained the reduction in the drug release on incorporating MCT to the poloxamer FFS: the enhanced solubility led to a reduction in the super-saturation driving force.

4. Conclusion

This work provide strategies for the design and development of new topical preparations that can replace a part of defective traditional topical preparations, and explains the influence of excipients on drug-film solubility. The different excipients effect in appearance, rheology, *in vitro* properties in HPC-acrylate blend FFS has been demonstrated. HPC acted as an effective crystallization inhibitor to maintain drug amorphous in films. the poloxamer had favorite miscibility with HPC-acrylic FFS. But carbomer FFS was noted to be immiscible with the plasticizer, and its appearance and release behavior were unsatisfactory. FP1 was confirmed to be the potential formulation because of uniform film appearance as well as high drug release and satisfactory rheological performance. The drug-film solubility could be effectively characterized by thermos-analysis. The combination of MCT and poloxamer with HPC resulted in a high Terbinafine solubility All the formulations exhibited their easy application and uniform paint-forming ability.

Declarations

Research involving humans and animals participants

No animal or human studies were carried out by the authors for this article.

Competing interests

The authors declare no competing interests regarding the publication of this paper.

Author information

Affiliations

Department of Pharmacy, Guangdong Pharmaceutical University, Guangzhou, 510000, China

Jing Zhang, Bohong Lu, Qiuyan Ma, Huaqing Lin

Bright Future Pharmaceutical Laboratories Limited, Yuen Long, New Territories, Hong Kong

Om Shelke, Tao Wu

Contributions

All authors discussed the results and contributed to the final manuscript.

Corresponding author

Correspondence to Huaqing Lin

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Data availability

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

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Figures

Figure 1

SEM images of different films

Figure 2

Viscosity behavior curve at 25°C.

Figure 3

Changes of storage (G') and loss (G'') modulus under increasing shear stress at 25°C.

Figure 4

Changes of G' and G'' under frequency sweep at 25°C. The colored vertical lines indicate the crossover point of the corresponding curve.

Figure 5

a) DSC profiles of Terbinafine and films. b) XRD profiles of Terbinafine and films.

Figure 6

The drug release profiles of Terbinafine film forming system

Figure 7

Representative DSC curves showing the TH melting transition for HPC+P physical mixtures (a) and HPC+P+MCT physical mixtures (b) in varying proportions.

Figure 8

The melting enthalpy curve for HPC+P physical mixtures and HPC+P+MCT physical mixtures in varying proportions.

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