Interaction Studies of Tretinoin with Microspheres in Tretinoin Topical Gel

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Abstract
BACKGROUND: Microparticle delivery systems such as porous microspheres have been used for more than two decades for the topical delivery of tretinoin. Due to the porous surface and correspondingly large surface area of microspheres, a relatively large amount of tretinoin can be loaded onto the microspheres. Our previous study showed that physicochemical properties, such as the particle size and drug loading of the microspheres, affected tretinoin release from the particles. However, the mechanism and kinetics of tretinoin release from microspheres are not well understood. PURPOSE: The purpose of this study is to elucidate the potential interactions between tretinoin and the microspheres, which provides insights into the mechanism(s) controlling the release of tretinoin from the microspheres. METHODOLOGY: Tretinoin was loaded onto Micropumps® 5640, a commercial microspheres product, at a loading efficiency of 0.5%, 1% and 2% w/w. Blank Micropumps® 5640, drug-loaded microspheres, and microspheres that were separated from marketed (tretinoin) topical gel, 0.1% were studied by X-ray diffraction (XRD), differential scanning calorimetry (DSC) and Fourier transformed infrared (FTIR) spectroscopy. Raw and processed tretinoin powder, and physical mixtures (PM) of tretinoin and blank microspheres at 1%, 2% and 50% w/w, were tested and compared. Powder XRD patterns were recorded using an X-Ma� the 2θ ranges 3–140. DSC thermograms were collected using a DSC/TGA instrument at a heating rate of 10°C/min up to 300°C. FTIR spectra were collected using FTIR spectra over the range 4000–500 cm⁻¹ with an attenuated total reflectance (ATR)ay diffractometer at a voltage of 25 kV and a current of 30 diamond accessory.

Materials and Methods
Tretinoin was loaded onto Micropumps® 5640, a commercially available microspheres product, at a loading efficiency of 0.5%, 1% and 2% w/w. Blank Micropumps® 5640, drug-loaded microspheres, and microspheres that were separated from marketed (tretinoin) topical gel, 0.1% were studied by X-ray diffraction (XRD), differential scanning calorimetry (DSC) and Fourier transformed infrared (FTIR) spectroscopy. Raw and processed tretinoin powder, and physical mixtures (PM) of tretinoin and blank microspheres at 1%, 2% and 50% w/w, were tested and compared. Powder XRD patterns were recorded using an X-Ma� the 2θ ranges 3–140. DSC thermograms were collected using a DSC/TGA instrument at a heating rate of 10°C/min up to 300°C. FTIR spectra were collected using FTIR spectra over the range 4000–500 cm⁻¹ with an attenuated total reflectance (ATR)ay diffractometer at a voltage of 25 kV and a current of 30 diamond accessory.

Results and Discussion

Differential Scanning Calorimetry

The thermograms of raw and processed tretinoin, and the 50% PM, showed two distinctive endothermic peaks of tretinoin: the sharp and strong endotherm near 183°C due to the melting process of tretinoin and the weak endothermic transition near 148°C due to a phase transition from monoclinic to triclinic form of tretinoin from the drug product, and the inhouse 0.5% and 1% w/w drug-loaded microspheres. The FTIR spectra showed a strong and broad stretch of the hydroxyl group at 3200–3200 cm⁻¹ for tretinoin, and a strong stretching vibration of the carbonyl group at 1700–1710 cm⁻¹ for blank microspheres. The characteristic bands observed with microspheres disappeared, and the hydroxyl band of tretinoin shifted by 8–12 cm⁻¹, for drug-loaded microspheres and separated microspheres, indicating that there was a molecular interaction between tretinoin and the polymeric matrix of the microspheres, via hydrogen bonding.

Conclusion

Data indicated that tretinoin was molecularly dispersed within the pore structure of the microspheres and interacted with the acrylate matrix of microspheres through hydrogen bonding. The study suggested that the release of tretinoin from the microspheres may involve the dissociation of the hydrogen bonds between tretinoin and the acrylate polymer, before tretinoin diffuses out from the pores of microspheres.

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Introduction
The study focuses on elucidating the potential interactions between tretinoin and microspheres, which provides insights into the mechanism(s) controlling the release of tretinoin from microspheres. These insights would help identify what aspects of tretinoin microspheres may be critical to control the performance of the topical microsphere gel product.

Tretinoin crystal habit and polymorphic forms

Figure 1. Polarized light optical images of raw (A), processed (B) tretinoin, and inhouse 2% w/w drug-loaded microspheres (C) 0.1%.

- Two polymorphic forms of tretinoin have been reported in the literature, monoclinic (I) and triclinic (II) forms.
- The monoclinic form (I) can be converted to the thermodynamically stable triclinic form (II) at a high transition temperature (above 136.6°C).
- There was no evidence of the formation of any triclinic form (II), and no evidence of tretinoin crystalization among the microspheres, or on microsphere surfaces.
- This result may indicate that tretinoin is precipitating in an amorphous or molecular state within the pore structure of the microparticles.

Comparison of FTIR spectra of raw and processed tretinoin powder, blank microspheres, 1%, 2% and 50% w/w physical mixtures of tretinoin and triclinic and monoclinic forms of tretinoin, and separated microspheres from the marketed product, and the inhouse 0.5% and 1% w/w drug-loaded microspheres.

- The FTIR spectra showed a strong and broad stretch of the hydroxyl group at 3200–3200 cm⁻¹ for tretinoin, and a strong stretching vibration of the carbonyl group at 1700–1710 cm⁻¹ for blank microspheres. The characteristic bands observed with microspheres disappeared, and the hydroxyl band of tretinoin shifted by 8–12 cm⁻¹, for drug-loaded microspheres and separated microspheres, indicating that tretinoin may be present in the microspheres in an amorphous state.

Powder X-ray diffraction

Figure 2. DSC thermograms of raw and processed tretinoin powder, blank microspheres, 1%, 2% and 50% w/w physical mixtures of tretinoin and blank microspheres, separated microspheres from the marketed product, and the inhouse 0.5% and 1% w/w drug-loaded microspheres.

- The thermograms of raw and processed tretinoin, and the 50% PM, showed two distinctive endothermic peaks of tretinoin: the sharp and strong endotherm near 183°C due to the melting process of tretinoin and the weak endothermic transition near 148°C due to a phase transition from monoclinic to triclinic form of tretinoin from the drug product, and the inhouse 0.5% and 1% w/w drug-loaded microspheres.

- The endothermic peaks were not found for 0.5%, 1%, and 2% drug-loaded microspheres or for separated microspheres, indicating that tretinoin may be present in the microspheres in an amorphous state.