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 Microsponges® 5640, a commercial microspheres product, at a loading efficiency of 0.5%, 1% and 2% w/w. The in-house prepared drug-loaded microspheres, and microspheres that were separated from Retin-A® Micro (tretinoin) topical gel, 0.1% were studied by Microscopy, X-ray diffraction (XRD), differential scanning calorimetry (DSC) and Fourier transformed infrared (FTIR) spectroscopy. RESULTS: The XRD diffractograms of raw and processed tretinoin exhibited a series of intense sharp peaks, which disappeared in the drug-loaded microspheres and the separated microspheres. The FTIR spectra showed a strong and broad stretch of the hydroxyl group at 2800-3200 cm^{-1} for tretinoin, and a strong stretching vibration of the carbonyl group at 1790–1710 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: Tretinoin presented in an amorphous dispersion state within the microspheres in Retin-A® micro gel, 0.1%, and when tretinoin was loaded into Microsponges® 5640. It was molecularly dispersed within the pore 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.

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.

Materials and Methods

Tretinoin was loaded onto Microsponges® 5640, a commercially available microspheres product, at a loading efficiency of 0.5%, 1% and 2% w/w. Blank Microsponges® 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-rmA over 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.

❑ Tretinoin crystal habit and polymorphic forms

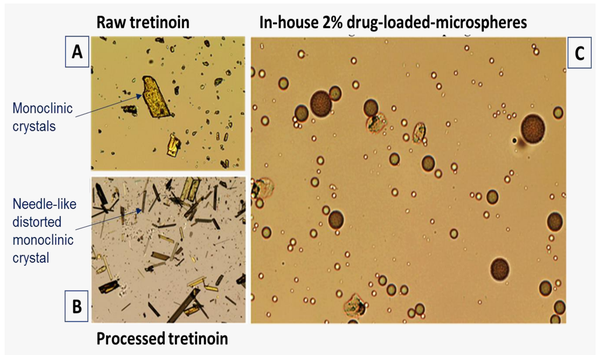

Figure 1. Polarized light optical images of raw (A), processed (B) tretinoin, and inhouse 2% w/w drug-loaded- microspheres (C).

- 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 crystallization 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.

Results and Discussion

❑ Differential Scanning Calorimetry

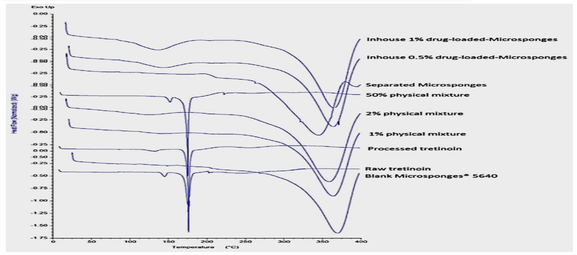

Figure 2: DSC thermograms of raw and processed tretinoin powder, blank microspheres, 1%, 2% and 50% w/w physical mixtures of tretinoin and blank microspheres, separated microspheres from the marketed product, and the inhouse 0.5% and 1% w/w drug-loaded- microspheres.

- 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 endodermic transition near 148°C due to a phase transition from monoclinic to triclinic form of tretinoin.
- 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.

❑ Powder X-ray diffraction

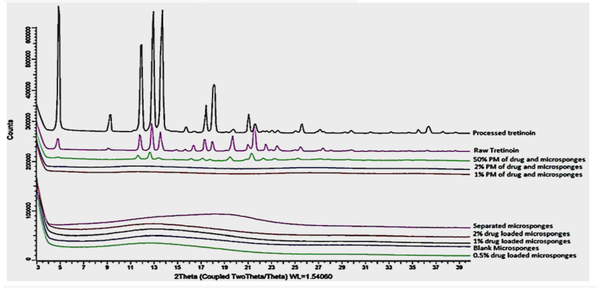

Figure 3. XRD diffractograms of raw and processed tretinoin powder, blank microspheres, 1%, 2% and 50% w/w PM of tretinoin and blank microspheres, separated microspheres from the marketed product, and the inhouse 0.5%, 1%, and 2% w/w drug-loaded-microspheres.

- The XRD diffractograms of raw and processed tretinoin exhibited a series of intense sharp peaks, which disappeared in the 0.5%, 1%, and 2% drug-loaded microspheres and the separated microspheres
- XRD data indicated that either tretinoin exists in an amorphous state in the microspheres or the XRD method is not sensitive enough to detect tretinoin crystallinity.

❑ Fourier-transform infrared spectroscopy

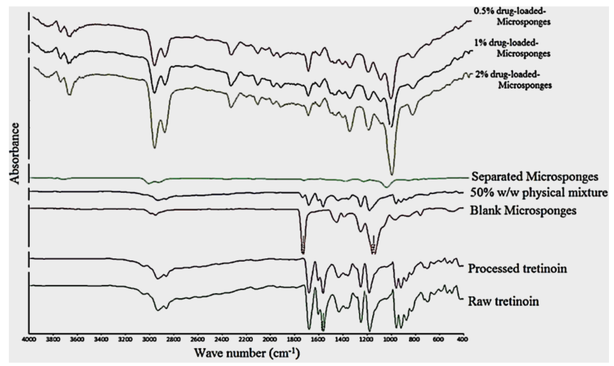

Figure 4. FTIR spectra of raw and processed tretinoin powder, blank microspheres, 50% w/w physical mixtures of tretinoin and blank microspheres, separated microspheres from the marketed product, and the in-house 0.5%, 1% and 2% w/w drug-loaded microspheres.

FTIR spectra showed a strong and broad stretch of the hydroxyl group at 2800-3200 cm^{-1} for tretinoin, and a strong stretching vibration of the carbonyl group at 1790–1710 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 0.5%, 1% and 2% drug-loaded microspheres and separated microspheres. These changes in the FTIR characteristics indicated that there was a molecular interaction between tretinoin and the polymeric matrix of the microspheres, and that the interactions are through 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.

ACKNOWLEDGMENT & DISCLAIMER

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