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Evaluation of the Physical Stability and Drug Release of Mefenamic Acid Amorphous Solid Dispersions in Topical Administration

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Abstract

Mefenamic acid (MFA) has been used as a pain reliever for a long time. However, as a Biopharmaceutics Classification System II drug, the low solubility remains a major issue. Recently an article has featured the efforts in generating amorphous solid dispersions of MFA for topical administration. Despite the novelty and some successful results from the polyvinylpyrrolidone dispersions, there are a few key points that are worth a thorough discussion, including the experimental methodology for the characterization, evaluation of the physical stability, and data interpretation for the drug release.

Keywords: Drug delivery system; Carrier; Mefenamic acid; Amorphous solid dispersion; Topical administration

Introduction

Mefenamic acid (MFA) has been used as a pain reliever for a long time [1]. Due to its low solubility and high permeability, MFA is classified as Biopharmaceutics Classification System II drug. Amorphous solid dispersion has been a well-established approach to improve drug solubility [2]. The glassy state enhances the dissolution of the compound while the long polymer chains wrap and separate the active pharmaceutical ingredient (API) molecules, quite often, at the nano-level, to stabilize the system by preventing them from crystallization. A study of amorphous solid dispersions of MFA was recently published entitled *Formulation, Characterization, and In Vitro Evaluation of Transdermal Patches for Inhibiting Crystallization of Mefenamic Acid*. [3]. This work presented the novelty and research significance of the physical stability of MFA solid amorphous dispersions in topical administration. We appreciate the efforts of improving the efficacy and applicability of MFA in this work. However, the results of this study still leave some questions regarding the appropriate methods to evaluate the physical stability and drug release of MFA in topical administration. We believe some of the approaches and results are worth a thorough discussion.

Review of Study

In the article, Suksaeree et al. [3] did not directly point it out, while the formulations generated are amorphous solid dispersions. Although there have been a few studies on MFA dispersions [4-6], this paper is the first to employ the polyvinylpyrrolidone (PVP K30 and K90) in the formulations. However, the objectives of this paper might be elusive. MFA is readily available as a crystalline material, which was included as the starting material in the experiments. PVP were successfully employed to generate amorphous dispersions of MFA based on the x-ray diffraction (XRD) results [3]. This study, however, does not present a clear investigation on the resistance of crystallization of MFA dispersions. First of all, the interpretation of the melting points [3] is problematic. It is well known that for amorphous materials, there are no well-defined melting points and therefore, it is ambiguous to study and compare the melting of the dispersions with crystalline MFA based on the differential scanning calorimetry (DSC) results, as DSC is not as informative as the modulated DSC (mDSC) regarding the thermal events of amorphous materials. Instead, it is more meaningful to employ mDSC to study the glass transition of the dispersions with the amorphous MFA as the control. While amorphous materials favor a high glass transition temperature (T_g) for a decent physical stability, the goal is that the dispersions would have significantly higher T_g than the pure amorphous MFA.

With respect to the physical stability in applications, it is crucial to study the physical stability of MFA at two conditions: 1) storage and transportation; 2) topical administration. The studies on physical stability can be found in the literatures employing long-term [7] or more approachably, short-term methods [2]. An example is provided in Table 1 as a direct study on the physical stability evaluation. The physical stability can be quantitatively assessed based on the survival (remain amorphous) of the dispersions after undergoing two separate experimental conditions.

The drug release study is important and essential. However, the authors chose an experimental design that was more relevant for oral administration (37°C instead of 32°C). Standard test configurations simulating transdermal delivery are available using USP Apparatus 5 – Paddle over Disk (32°C) (paddle and vessel similar to Apparatus 2 with a stainless steel disk assembly to hold the transdermal on the bottom of vessel), or diffusion cells with membranes [8-10]. In addition, the drug release data themselves [3]) are also limited since only the results within first 8 hours are provided. Noticing that the cumulative release is still increasing at the time of 8 hours, the release trends after this time frame are still nontrivial. A more robust study is to continuously monitor the drug release for up to 24 hours or when a plateau in the release curve is reached. More importantly, as the authors described in the Introduction section that MFA has a short elimination half-life time of 2 hours. In this case, a sustained release is more desirable than a fast release and hence based on [3], the dispersions do not present preferred release profiles as compared with the pure MFA.

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Application relevance	Targeted environment	Experimental conditions	Characterization
Storage and transportation	Elevated temperature and relative humidity	Formulations exposed to >35°C and >80% RH for 7 days or longer	XRD for the post-stress formulations
Topical administration	USP Dissolution Apparatus	Samples subject to dissolution testing for different times (0.5~24 hours)[a]	XRD for the post-dissolution patch

[a]The sample size should be sufficiently large to make sure not all solids are dissolved into the medium.

Table 1: Methods to identify the physical stability (resistance to crystallization).

Conclusion

In the recently published article on MFA amorphous solid dispersions, the methods and results are thoroughly discussed in this communication. It is believed that the characterization methods may be revised to be more suitable for a comparison between amorphous dispersions and the pure amorphous MFA. Well-designed stress studies are also necessary to validate the physical (and/or chemical) stability of the dispersions. Most importantly, the investigation on drug release could be performed in the apparatus that is more suitable for topical applications in a long-term release.

References

1. Shirvani MA, Motahari-Tabari N, Alipour A (2015) The effect of mefenamic acid and ginger on pain relief in primary dysmenorrhea: a randomized clinical trial. Archives of Gynecology and Obstetrics 291: 5.
2. Cao Y, Teng J, Selbo J (2017) Amorphous Solid Dispersion of Epigallocatechin Gallate for Enhanced Physical Stability and Controlled Release. Pharmaceuticals 10: 17.
3. Suksaeree J, Siripornpinyo P, Chaiprasit S (2017) Formulation, Characterization, and In Vitro Evaluation of Transdermal Patches for Inhibiting Crystallization of Mefenamic Acid. Journal of Drug Delivery.
4. Kojima T, Higashi K, Suzuki T, Tomono K, Moribe K, et al. (2012) Stabilization of a Supersaturated Solution of Mefenamic Acid from a Solid Dispersion with EUDRAGIT® EPO. Pharmaceutical Research 29: 15.
5. Fang L, Numajiri S, Kobayashi D, Ueda H, Nakayama K, et al. (2004) Physicochemical and crystallographic characterization of mefenamic acid complexes with alkanolamines. Journal of Pharmaceutical Sciences 93: 11.
6. Andrews GP, Zhai H, Tipping S, Jones DS (2009) Characterisation of the thermal, spectroscopic and drug dissolution properties of mefenamic acid and polyoxyethylene–polyoxypropylene solid dispersions. Journal of Pharmaceutical Sciences 98: 12.
7. Nurzyńska K, Booth J, Roberts CJ, McCabe J, Dryden I, et al. (2015) Long-Term Amorphous Drug Stability Predictions Using Easily Calculated, Predicted, and Measured Parameters. Mol Pharmaceutics 12: 10.
8. Salerno C, Carlucci AM, Bregni C (2010) Study of In Vitro Drug Release and Percutaneous Absorption of Fluconazole from Topical Dosage Forms. AAPS PharmSciTech 11: 8.
9. Souto EB, Wissing SA, Barbosa CM, Müller RH (2004) Development of a controlled release formulation based on SLN and NLC for topical clotrimazole delivery. International Journal of Pharmaceutics 278: 7.
10. Ruela ALM, Perissinato AG, Lino MEdS, Mudrik PS, Pereira GR (2016) Evaluation of skin absorption of drugs from topical and transdermal formulations. Braz J Pharm Sci 52: 18.