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A simple strategy for washing a recrystallized drug from viscous and non-volatile solvents prior to XRD study: A technical note

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Summary

Aim: obtaining a dried powder residual from a viscous and non-volatile solvents is impossible. Thus, their analysis by using the methods required for the dried form of materials has always been a problem. In the current technical note, our aim was to offer a simple method for this issue. **Results:** the proposed method was based on washing of the viscous residuals with a volatile solvent and their drying in the ambient conditions. For this purpose, we have provided sufficient data on some drugs in the selected viscous and non-volatile solvents to support our claim.

Keywords: Crystal structure, viscose solvents, non-volatile solvents.

Resumen

Una estrategia simple para lavar un fármaco recristalizado de solventes viscosos y no volátiles antes del estudio DRX: una nota técnica

Objetivo: es casi imposible obtener un residuo de polvo seco a partir de disolventes viscosos y no volátiles. Por lo tanto, su análisis mediante el uso de los métodos nece-

sarios para la forma seca de los materiales siempre ha sido un problema. En esta nota técnica nuestro objetivo es ofrecer un método simple para este problema. **Resultados:** el método propuesto se basa en el lavado de los residuos viscosos con un solvente volátil y su secado en condiciones ambientales. Para este propósito, hemos proporcionado datos suficientes sobre algunos fármacos en los solventes viscosos y no volátiles seleccionados para respaldar nuestra afirmación.

Palabras clave: Estructura cristalina, disolventes viscosos, disolventes no volátiles.

Resumo

Uma estratégia simples para lavar uma droga recristalizada de solventes viscosos e não voláteis antes do estudo DRX: uma nota técnica

Objetivo: a obtenção de um resíduo de pó seco a partir de solventes viscosos e não voláteis é impossível. Assim, sua análise usando os métodos necessários para a forma seca dos materiais sempre foi um problema. Na presente nota técnica, nosso objetivo é oferecer um método simples para essa questão. **Resultados:** o método proposto baseia-se na lavagem dos resíduos viscosos com um solvente volátil e sua secagem em condições ambientais. Para este propósito, fornecemos dados suficientes sobre algumas drogas nos solventes viscosos e não voláteis selecionados para apoiar nossa afirmação.

Palavras-chave: Estrutura cristalina, solventes de viscose, solventes não voláteis.

INTRODUCTION

There are three forms of crystal types for pharmaceutical solids including polymorphic, hydrate/solvate and amorphous forms [1]. Polymorphs are defined as the substance crystallization in different crystal packing arrangements [2]. Hydrate/solvate is defined as the incorporation of water/solvent in the crystal lattice and amorphous is defined as a solid with no crystallinity and no specific arrangement [3]. Controlling the crystal form of the drug substances is a very important issue, as it can affect their bioavailability and stability [4, 5]. Therefore, in the new drug application, the information on solid state properties is highly demanded by the regularities [6]. For obtaining this information, the solid substance must be characterized using some methods such as X-ray powder diffraction (XRD), differential scanning calorimetry (DSC), elemental analysis,

etc. However, for most of these analysis methods, the required form of the substance is dried solid form. This can be considered a limitation when the recrystallization is carried out from a viscous and non-volatile solvent for our investigations. Because the pharmaceutical solids form a viscous substance that cannot be dried under any conditions, their analysis and controlling their crystallinity in these solvents are not possible. In the current technical note, a simple and practical technique to aid recrystallization and analysis of drug residuals from the viscous and non-volatile solvents, is reported.

Technique

Because this technique is almost applicable in solubility studies, we describe it based on the shake-flask method. The investigated drug was dispensed in excess amounts into the vessels containing viscous solvents and incubated to reach equilibrium. After centrifugation, the drug residuals were separated and washed with a volatile solvent several times until a homogenous suspension was formed without any signs of particles sticking together. The suspension was poured into a plate and was placed at room temperature until washing solvent was evaporated and left a dry powder.

Results and discussion

XRD analysis is one of most important analytical technique for studying the crystalline phase in solubility investigations. The main limitation of this technique is that the acceptable drug sample form for analysis must be a dried solid powder. Whereas, most of the commonly used solvents in the pharmaceutical industry such as *N*-methyl-2-pyrrolidone (NMP), Carbitol®, polyethylene glycols (PEGs), or propylene glycol (PG) are viscous and non-volatile. Thus, the dispensed drug powder into these solvents is turned into a viscous mixture that cannot be analyzed. In the current work and in order to show the efficiency of the proposed technique, we chose some drugs as the model drugs and some solvents as the viscous solvents. Two drugs in base form (lamotrigine and mesalazine) and two drugs in salt form (nicotinamide and losartan potassium) were chosen. We selected four non-volatile and viscous solvents as the model solvents including PEG 400, PG, NMP and choline chloride (ChCl)/PG deep eutectic solvent (DES) which was synthesized according to a reference [7]. As it has been explained in the previous section, we provided a residual of each drug powder in each mentioned viscous solvent. It was found that when the viscous residuals were washed with a volatile solvent such as ethanol, they can be easily dried in the ambient condition to give a dried solid powder that can be analyzed with XRD instrument. The XRD pattern for all investigated pharmaceuticals were recorded and given in Figures 1 and 2. As can be seen, the XRD patterns of raw pharmaceuticals

were similar to the equilibrated ones in the investigated solvents for each studied drug demonstrating their crystalline forms did not transform to amorphous or polymorphic form after saturation equilibrium in the viscous solvents and during the washing time. These results showed that the claim of washing with ethanol as a volatile solvent can be an effective method for compensation of limitation for providing XRD pattern in the viscose solvents. It should be said that in the initial studies, we used acetone either as a volatile solvent for washing, however, in some cases we observed the different XRD patterns in comparison with raw materials. As the same patterns were observed in washing with ethanol, it can be concluded that these phase changes in washing with acetone can be related to the conversion of pharmaceuticals to amorphous or polymorphic forms in the acetone. However, we do not guarantee that for other existing drugs, these polymorphic changes cannot be happen when washing with ethanol.

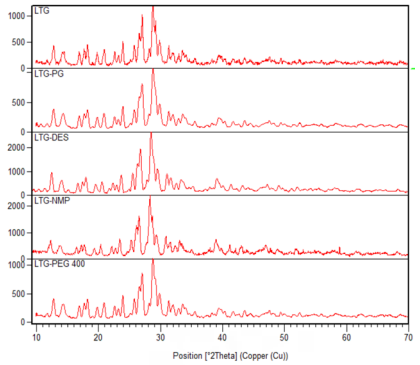

Figure 1A

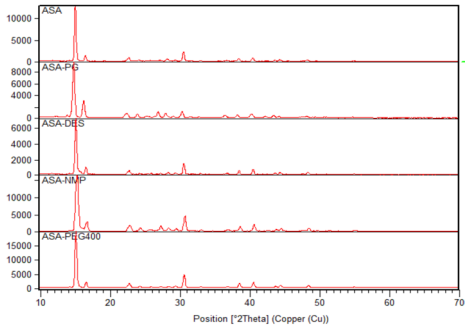

Figure 1 B

Figure 1. XRD pattern of lamotrigine (LTG) (A) and mesalazine (B) as base model' drugs in some viscous and non-volatile solvents.

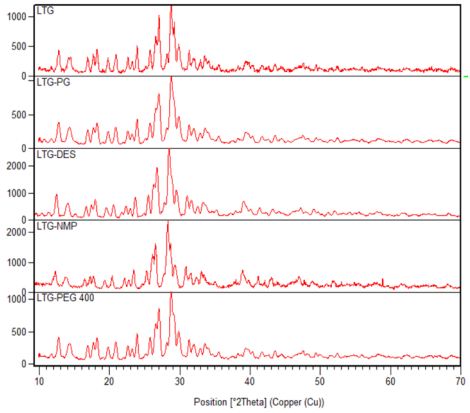

Figure 2A

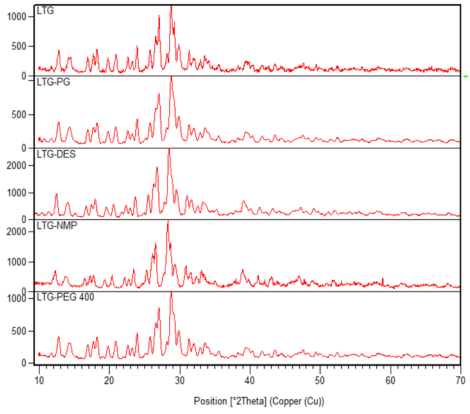

Figure 2B

Figure 2. XRD pattern of nicotinamide (NA, A) and losartan potassium (LP, B) as salt form model' drugs in some viscous and non-volatile solvents.

Conclusion

In this technical note, a fast technique has been proposed for washing the drug residuals equilibrated in some non-volatile and viscous solvents to reach a dried powder that can be easily analyzed by XRD. Although it is impossible we can test this method for all drugs, it is clear that in the investigated drug models and the viscous-non-volatile model solvents, with ethanol as washing solvent we reached satisfactory results that confirm the applicability of this technique.

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Credit authorship contribution statement

Elaheh Rahimpour: Investigation, Writing - original draft. Abolghasem Jouyban: Supervision, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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