SOLUPLUS® FOR MODIFYING THE RELEASE OF HIGHLY WATER SOLUBLE APIs

Kaisa Naelapää, Johan Peter Boetker, Anette Müllertz, Thomas Rades, Jukka Rantanen, Daniel Bar-Shalom

Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

Correspondence: kn@farma.ku.dk

ABSTRACT:

Well established techniques for increasing the solubility of poorly water soluble APIs are available. However, formulating highly water soluble APIs into dosage forms exhibiting modified release profiles is also gaining interest. In this work a novel approach where Soluplus® is used as a dissolution modifying agent for highly water soluble APIs is introduced.

Acetaminophen (APAP) and guaifenesin (GF) were used as water soluble model APIs. 95:5 (w/w) and 90:10 (w/w) ratios of respective API and Soluplus® were either physically mixed (PM) or melted together on a hot plate. Melts and PMs were investigated using DSC and XRPD and compacts were submitted to dissolution studies.

In case of APAP:Soluplus® a single melting event with an onset similar to pure APAP was determined by DSC. The XRPD diffractogram of molten material exhibited an amorphous halo, however further processing caused the material to crystallize. The compacts made of ground molten materials had a similar release profile and showed a slower release compared to compacts prepared from PMs.

When GF:Soluplus® melts were submitted to DSC a single melting event occurred. The onset of this event did not match with the melting event of pure GF. The XRPD diffractogram of the molten samples revealed that a new polymorphic form of GF had crystallized. GF:Soluplus® compacts made of molten material revealed faster release of GF compared to compacts made of PMs.

Using Soluplus® as a dissolution modifying agent enables tailoring of the release of the API. In this work the release of two water soluble APIs was modified by two different methods. Furthermore, presence of a new previously not identified polymorphic form of GF was identified. This is underpinning the need for careful preformulation of unstable formulations where the possibility for recrystallization of high-energy polymorphic form exists.

Keywords: solid dispersion, Soluplus®, polymorphism, water soluble APIs, modified release

1. INTRODUCTION:

According to the Biopharmaceutics Classification System (BCS) APIs are divided into four classes of which Classes II, III and IV suffer from solubility or/and permeability problems [1]. Currently the pharmaceutical industry is mainly dealing with poorly water soluble drugs, Class II and IV drugs respectively, in terms of increasing solubility/dissolution rate with the aim to enhance the bioavailability. Bioavailability problems are not encountered with Class I drugs, however, the pharmacokinetic profile may not be optimal as rapid increase and decrease of drug concentration in blood plasma level occurs. This is not advantageous with some Class I drugs as therapeutic action lasting for longer time periods might be desired.

Several formulation approaches and manufacturing techniques to overcome the different problems associated with poor water soluble APIs have been introduced. Solutions for dealing with the poor solubility issue of Class II drugs include amorphisation, complex formation, solid dispersions, use of solubilizers, etc [2-5]. In case of Class I drugs, it might be necessary to reduce the dissolution rate and one option is to work with polymer based formulations.

The most common approach to improve the solubility of poor water soluble drugs is formulation of solid dispersions [6;7]. Typically, these consist of at least two different components: hydrophilic matrix (polymer) and hydrophobic drug. In general, solid dispersions are prepared by heating the polymer to or above its glass transition temperature followed by the dissolution of the drug in the polymer (often at a high polymer to drug ratio). A wide variety of polymers is available for formulation of solid dispersions. Recently, the graft copolymer Soluplus® (polyvinyl caprolactame – polyvinyl acetate – polyvinyl glycol) was launched by BASF. Soluplus® is recommended for solubilizing poorly soluble APIs due to the polymer's amphiphilic nature [8].

The aim of this work is to introduce a new method for preparation of solid dispersions containing water soluble drugs, acetaminophen (APAP, Class I) [9] and guaifenesin (GF), in order to obtain sustained drug dissolution. The new technique involves the dissolution or dispersion of a polymer in a drug matrix, which can be either in amorphous or crystalline state (high API to polymer ratio). Furthermore, in this work a new application for Soluplus® as a dissolution modifying agent for freely water soluble drugs is suggested. Additionally, physicochemical characterization of API:polymer mixtures is reported.

2. MATERIALS AND METHODS

2.1. MATERIALS

Acetaminophen (APAP) and guaifenesin (GF) were obtained from Sigma Aldrich (St. Louis, MO, USA). BASF SE (Ludwigshafen, Germany) kindly provided the Soluplus®.

2.2. METHODS

2.2.1. Preparation of melts

The API and Soluplus® were mixed together in ratios 95:5 or 90:10 using the geometrical dilution principle. The mixtures were heated on a hot plate up to 180°C in case of APAP and 110°C for GF until a homogenous molten sample was obtained. Then the molten material was allowed to cool and was crushed in mortar in order to obtain powdered material.

2.2.2. Preparation of compacts

Compacts containing 200 mg of API were prepared using a hydraulic press and modified tablet press tooling (non-vevel, 5 mm). Compaction pressure was 3.5 tons for five minutes in case of both GF and APAP compacts made of molten material. Compacts of physical mixtures (PMs) of the APIs and Soluplus® were also prepared. However, compacts of PM of APAP:Soluplus® were prepared by using lower compaction pressure, 2 tons for three minutes for 95:5 APAP:Soluplus® PM and one minute for 90:10 APAP:Soluplus® PM. The compaction pressure was adjusted in order to obtain coherent compacts.

2.2.3. X-ray powder diffraction (XRPD)

A PANalytical X'Pert Pro MPD θ/θ X-ray diffractometer (PANalytical B.V., Almelo, The Netherlands) equipped with a PIXcel detector was used to determine X-ray diffractorgrams. A continuous 2θ scan was performed in a range of 2° - 40° using CuK_α radiation (λ=1.5406 Å) with a step size of 0.0260° 2θ. The operating current and voltage were 40 mA and 45 kV. Data were collected using X'Pert Data Collector, version 2.2., and were analyzed with X'Pert High Score Plus, version 2.2.4 (PANalytical B.V., Almelo, The Netherlands).

2.2.4. Differential Scanning Calorimetry (DSC)

A Perkin Elmer calorimeter (DSC 7, Norwich, CT, USA) was used for DSC measurements. The instrument was controlled by Pyris software, version 7.0.0.0110. The temperature axis and heat flow of the equipment were calibrated using indium. Samples (n=3) were analyzed in sealed sample pans using 40 µl pans and 50 µl lids with pin holes. Measurements were carried out at 10 °K/min with nitrogen flow of 20 ml/min in triplicates.

2.2.5. Dissolution tests

For dissolution studies the prepared compacts (n=3) were placed into dissolution vessels which contained 900 ml of demineralised water at 37°C and the rotation speed was 50 rpm (Erweka DT 70, Erweka GmbH, Heusenstamm, Germany). Samples of 2.5 ml (replaced) were collected every 5 minutes for the first 45 minutes and final sample at 60 minutes. Withdrawn samples were diluted and measured by using a UV-Vis spectrophotometer (Evolution 300, Thermo Fisher Scientific, Waltham, MA, USA) at the wavelengths of 274 nm and 243 nm.

3. RESULTS AND DISCUSSION

3.1.1. X-Ray Powder Diffraction (XRPD)

XRPD analysis was performed on the 95:5 and 90:10 APAP:Soluplus® and GF:Soluplus® molten samples as well as on the physical mixtures. The diffractograms of APAP:Soluplus® molten materials revealed that the material was amorphous after preparation. However, when the material was ground in a mortar with a pestle recrystallisation of APAP occurred. XRPD analysis revealed that APAP recrystallized as the initial polymorphic form (figure 1A).

The XRPD diffractograms of the molten GF:Soluplus® samples are presented in figure 1B. Interestingly, the GF present in the molten samples recrystallized into another polymorphic form of GF that has not been identified earlier. It has not been possible for the authors to find any literature describing the new polymorphic form of GF.

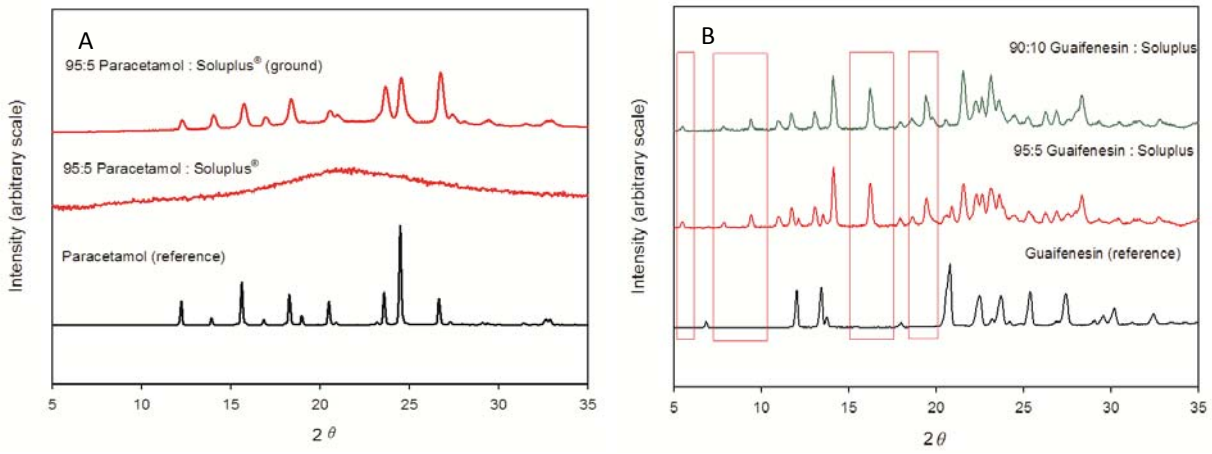

Figure 1. X-ray diffractograms of (A) APAP:Soluplus® 95:5 melt (red) and pure APAP (black); (B) GF:Soluplus® melts, 95:5 (red), 90:10 (green), and pure GF (black).

3.1.2. Differential Scanning Calorimeter (DSC)

The APAP and Soluplus® melts, 95:5 and 90:10, were submitted to thermal analysis using DSC. A single melting event having an onset at 168°C and a peak maximum at 169°C was observed. The pure APAP exhibited a similar melting event (figure 2A).

The GF and Soluplus® melts, 95:5 and 90:10, were also analyzed with DSC. In case of GF and Soluplus® melts a deviating melting event compared to pure GF was observed. The melting event of GF:Soluplus® melts had the onset at 65°C and a peak maximum at 72°C, which differed from the melting event of pure GF by 10°C (figure 2B).

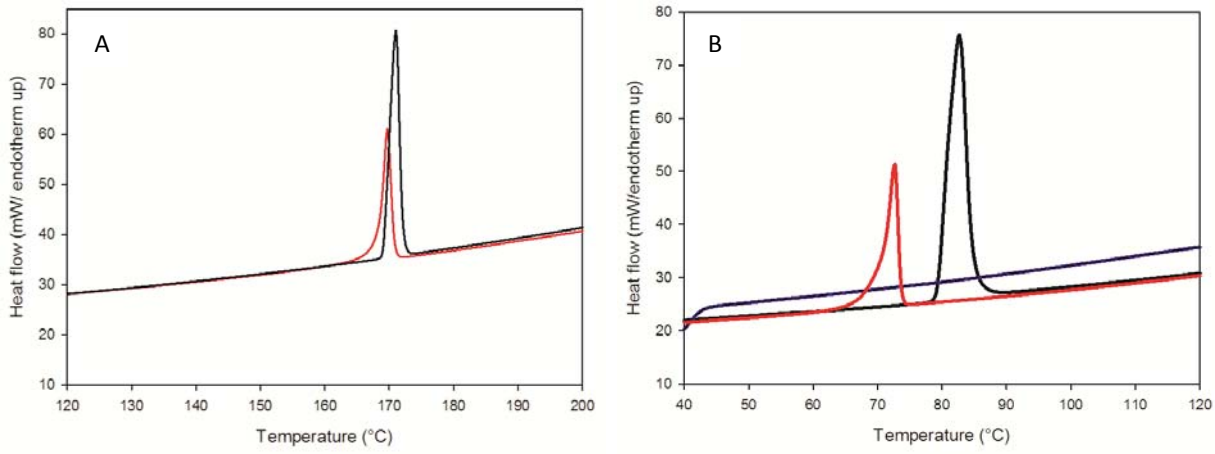

Figure 2. DSC thermograms of (A) APAP (black) and APAP: Soluplus® 95:5 melt (red); (B) GF (black), Soluplus® (blue) and GF:Soluplus® 95:5 melt (red).

3.1.3. Dissolution tests

In order to study the effect of Soluplus® on the release behaviour of the APIs dissolution studies were conducted. Compacts prepared from molten, cooled and ground material, as well as of PMs were investigated.

The compacts made of APAP:Soluplus® molten materials at drug to polymer ratios of 95:5 and 90:10 (w/w), showed similar release profiles and the release was slower compared to the compacts prepared of PMs. Additionally, the release of APAP from 90:10 APAP:Soluplus® PM compacts was faster compared to the compacts prepared from 95:5 APAP:Soluplus® PM (figure 3A).

In case of GF:Soluplus® mixtures a different effect of Soluplus® on the dissolution behaviour was observed. The compacts made from molten material, at drug to polymer ratios of 90:10 and 95:5 (w/w), showed an increased release of GF when compared to the compacts made from PMs (figure 3B). An overall deviating dissolution performance between GF:Soluplus® and APAP:Soluplus® compacts was observed. The compacts containing APAP:Soluplus® showed that melting of APAP and Soluplus® together will most efficiently sustain the release of APAP. Furthermore, the concentration of Soluplus® did not have an influence on the release of APAP. In contrast, the compacts made of GF:Soluplus® showed that physical mixing of GF and Soluplus® together is a more suitable technique for obtaining a decreased release rate of GF.

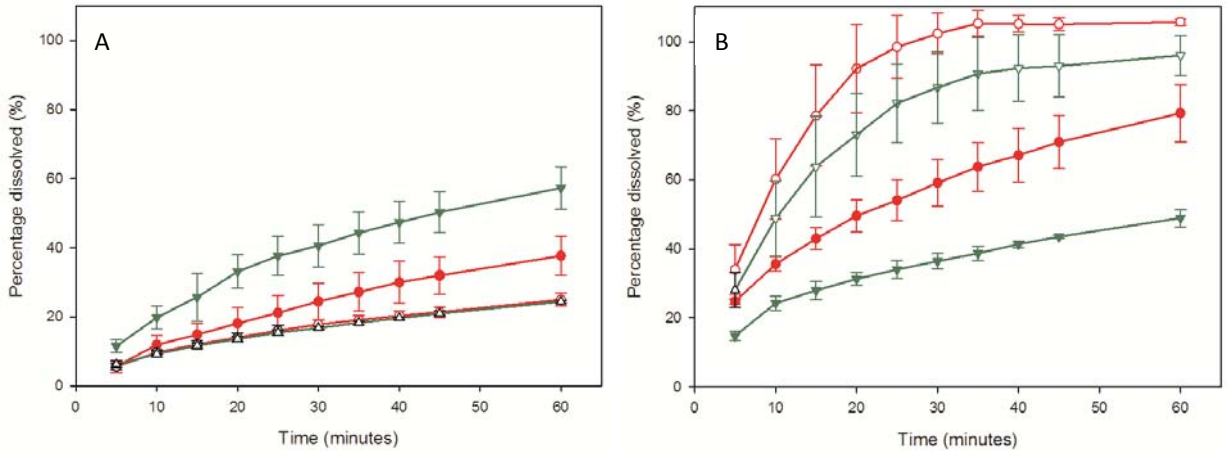

Figure 3. Dissolution profiles of compacts made of 95:5 (red) and 90:10 (green) molten material (open symbols) and physical mixtures (PMs) (closed symbols); (A) APAP:Soluplus®; (B) GF:Soluplus®.

4. CONCLUSIONS

The preliminary conclusion from this study is that addition of small amounts of Soluplus® enables to tailor the release profile of water soluble APIs. In this study two different preparation methods were investigated: melting and mixing of the water soluble API together with Soluplus®. Both techniques were able to modify the release behaviour of the model APIs, APAP and GF. The modification of the dissolution behaviour was mainly controlled by the method used to incorporate Soluplus®. Further investigations are needed to confirm whether the variability in the dissolution performance is drug structure dependent.

Additionally, a new, previously not identified polymorphic form of GF was obtained after GF was melted together with Soluplus®.

This study reveals that Soluplus® can also be used to obtain sustained release of water soluble APIs in addition to being used as solubilizer in case of poorly water soluble drugs.

5. REFERENCES

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