Preparation, Physical Characterization and Solubility-Dissolution Testing of Loratadine Hot Melt Extrudates Prepared with Copovidone on a Laboratory Mixing Extruder

K. Tsinman[1], O. Tsinman[1], M. Rahman[2], M. Keshtmand[2], J. Lester[2], and M. Caslow[3] ktsinman@pion-inc.com

[1]Pion Inc., 10 Cook Street, Billerica, MA 01821, USA; [2]Ashland Specialty Ingredients. Wilmington, DE 19894-0001, USA; [3]Dynisco Plastics, 38 Forge Parkway, Franklin, MA 02038, USA

INTRODUCTION

Solid dispersion technology is used to create amorphous forms of active pharmaceutical ingredients (APIs) with enhanced solubility leading to increased bioavailability. The goal of this study was to prepare and test hot melt extrudates of a poorly soluble compound (Loratadine) with copovidone (Plasdone™ S-630) at 30% and 40% drug loading using a bench-top Dynisco laboratory mixing extruder (LME) at various temperatures. Dissolution behavior and solubility enhancement was tested using a small-volume *in situ* UV dissolution apparatus the µDISS Profiler™ (Pion Inc.) to collect concentration-time profiles in biorelevant media (e.g., FaSSIF and FeSSIF).

MATERIALS AND METHODS

Loratadine USP (MW 382.9 Da, a weak base with a calculated pK_a of 4.7) is manufactured by Dolphin, Inc. Plasdone S-630 copovidone is manufactured by Ashland Specialty Ingredients (ASI) and is USP, Ph.Eur., and JPE compliant. It has been established that stable solid dispersions can be prepared through hot melt extrusion[1]. The Dynisco LME (Figure 1) was used to prepare solid dispersion of Loratadine (SDL) with Plasdone S-630 copovidone at 30% or 40% API loading at various temperatures (120° C – 180° C). The LME was chosen for its ability to operate with very small amounts of material, promoting a quick and economical solution for preparing samples. A unique, screwless design and adjustable header allows for various levels of user defined mixing.

Figure 1. Dynisco bench top laboratory mixing extruder (LME) used in the study.

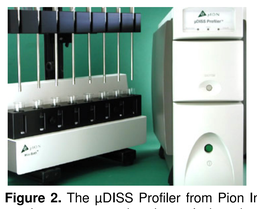

Figure 2. The µDISS Profiler from Pion Inc monitors concentration in real time in 8 temperature controlled channels using only 1 – 20 mL of dissolution media.

The solubility-pH profile in aqueous buffer was measured by the µSOL Evolution instrument (Pion Inc.) using a miniaturized shake-flask method[2]. Dissolution behavior and solubility enhancement in FaSSIF were assessed by the µDISS Profiler (Figure 2).

RESULTS AND DISCUSSION

Physical Characterization of Hot Melt Extrudate Powders

SDL samples were analyzed by x-ray powder diffraction (XRPD) and polarized light microscopy (PLM) for amorphous content. LME samples prepared at various temperatures at both drug loads were found to be amorphous; XRPD profiles are provided in Figures 3 and 4.

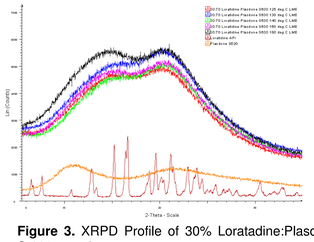

Figure 3. XRPD Profile of 30% Loratadine:Plasdone S-630 samples.

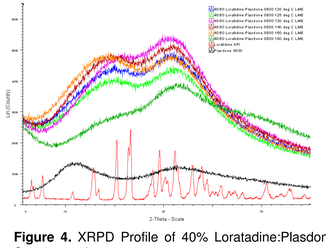

Figure 4. XRPD Profile of 40% Loratadine:Plasdone S-630 samples.

Solubility-pH Profile of Loratadine USP and its Hot Melt Extrudates

Solubility of Loratadine USP and its amorphous dispersions with Plasdone S-630 copovidone was first measured in universal aqueous buffer (Prisma HT, Pion Inc.) at different pH values. Intrinsic solubility (solubility of uncharged species, pH >> pK_a^{APP}) of Loratadine was determined to be 0.78±0.14 µg/mL. The slope of the solubility-pH profile was consistent with a model that takes into account cationic aggregation[3]. Intrinsic solubility of SDL products (5.2±1.2 µg/mL) was higher than that of Loratadine powder and did not show any significant dependency on the load or temperature of preparation. Solubility in the ionizable region (pH < pK_a^{APP}) was comparable between Loratadine and the various SDL products. Figure 5 shows the logarithm of solubility versus pH profiles for Loratadine and one of the SDL extrudates.

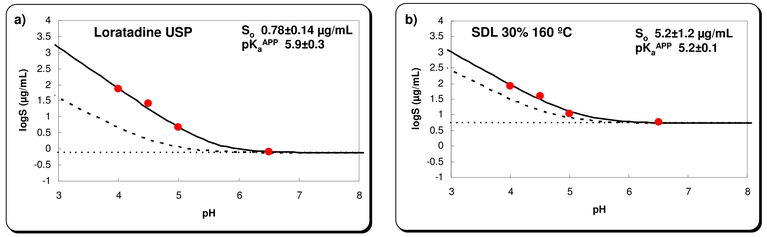

Figure 5. Logarithm solubility (µg/mL) versus pH profiles for Loratadine (a) and SDL dispersion prepared under 160° C with 30% Loratadine load (b). Red dots are experimentally measured values; the solid line is a fitting to a model that takes into account both ionization and aggregation phenomena[3]; the dashed curves are based on the Henderson-Hasselbalch equation using the predicted pK_a value of 4.7; the dotted lines indicate the logarithm of the intrinsic solubility.

In Situ Concentration Monitoring of Loratadine and SDL in FaSSIF

µDISS Profiler instrument was used to monitor in real time the dissolution/precipitation behavior of Loratadine and SDL products in FaSSIF. Figure 6 demonstrates dissolution of Loratadine in FaSSIF. Equilibrium was reached after 1 hour of dissolution indicating solubility more than 20 times higher in FaSSIF than in corresponding aqueous buffer at pH 6.5.

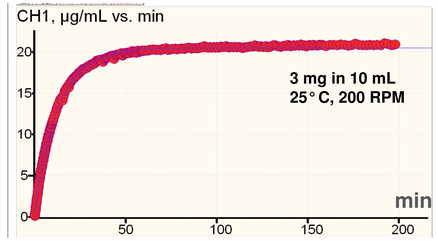

Figure 6. Dissolution (µg/mL versus minutes) of Loratadine in FaSSIF.

Table 1. Parameters (average from 2 replicates) estimated from the dissolution curve analysis.

Parameter	Value
Solubility	19.3 ± 1.8 µg/mL
IDR[4]	0.35 ± 0.01 µg cm^{-2} min^{-1}
Effective Area	4.4 ± 0.6 cm^2 mg^{-1}
Spherical Particle Radius	5.3 ± 0.7 µm
Effective Diffusion Layer Thickness	3.6 ± 0.4 µm

Analysis of the dissolution curve (blue line on Figure 6) allowed estimation of additional characteristics (Table 1) and predicting Loratadine disk intrinsic dissolution rate (IDR) in FaSSIF at 200 RPM rotation speed from the powder dissolution experiment[4,5].
SDL products showed different dissolution behavior compared to crystalline Loratadine powder. Majority of extrudates reached supersaturation followed by a slight decrease in concentration as seen in Figure 7 and 8.
Kinetic solubility of all studied SDLs showed up to a 2 fold higher solubility than crystalline Loratadine, regardless of preparation temperature.

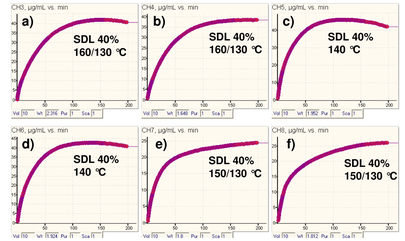

Figure 7. Concentration profiles in FaSSIF (µg/mL versus minutes) of SDL with 40% API load prepared under different temperature conditions. Data collected at 25°C and 200 RPM stirring.

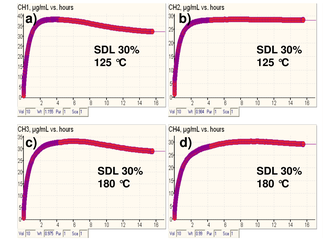

Figure 8. Same as Figure 7, but for SDL with 30% API load and time scale (X-axis) in hours.

In general, the 40% drug load samples in Plasdone S-630 copovidone produced higher kinetic solubility (~40 µg/mL) after 2 hours of dissolution than the 30% drug load samples in Plasdone S-630 copovidone (~30 µg/mL).

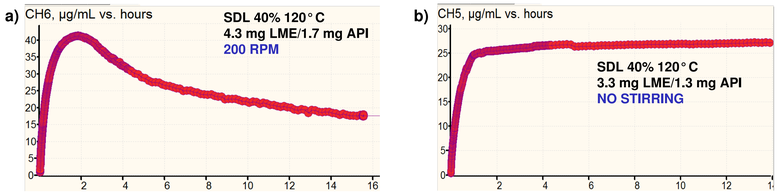

Figure 9. Dissolution/precipitation profile (µg/mL versus hours) for SDL 40% 120° C in FaSSIF in case of vigorous stirring conditions (a) and with no stirring (b). Similar results were observed for SDL 40% 160° C.

It was discovered that supersaturation phenomenon for dispersions is strongly influenced by mixing conditions. The same SDL reached supersaturation with follow up precipitation under vigorous mixing conditions (Figure 9, a) while it was continuously dissolving when no mixing was applied (Figure 9, b)

CONCLUSION

Prolonged supersaturation of Loratadine hot melt extrudates with Plasdone S-630 copovidone indicated a potential for higher bioavailability of Loratadine from such formulations.

Plasdone S-630 copovidone processed very easily through the Dynisco LME and was a suitable polymer for preparing amorphous solid dispersions of Loratadine.

The combination of a bench-top Dynisco LME and the µDISS Profiler enables a fast and effective way of selecting an appropriate formulation strategy for enhancing the bioavailability of poorly soluble compounds.

The ability of monitoring concentration *in situ* makes the µDISS Profiler the tool of choice for studying supersaturation phenomena in biorelevant dissolution media.

REFERENCES

1. Leuner, C., Dressman, J. Improving Drug Solubility for Oral Delivery using Solid Dispersions. Eur. J. Pharm. Biopharm., 2000, 50(1), 47-60. Review.
2. Kerns E.H., Di L. Automation in Pharmaceutical Profiling. JALA **2005**, *10*, 114-123.
3. Avdeef A., Bendels S., Tsinman O., Tsinman K., and Kansy M. Solubility-Excipient Classification Gradient Maps. *Pharm. Res.*, **2007**, *24*, 530-545.
4. Fagerberg J. H., et. al. Dissolution Rate and Apparent Solubility of Poorly Soluble Drugs in Biorelevant Dissolution Media. *Mol. Pharm.* **2010**, 7 (5), 1419-1430.
5. Avdeef A., Tsinman K., Tsinman O., Sun N., and Voloboy D. Miniaturization of Powder Dissolution Measurement and Estimation of Particle Size. *Chem. Biodev.* **2009**, 6 (11), 1796-1811.