ANALYTICAL TOOLS & TECHNIQUES IN HOT MELT EXTRUSION

CASE STUDY ON PROCESS SCALE UP

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INTRODUCTION

Hot melt extrusion has been widely used as a processing method for many purposes, including formation of a solid molecular dispersion to increase the bioavailability of poorly soluble drugs[1]. Analytical tools and techniques can greatly reduce time and improve success rates in development of hot melt extrusion formulations.

In the scale-up phase, analytical characterization techniques ensure similar solubility enhancement occurs on larger extrusion equipment as with the lab scale equipment used for formulation development.

Analytical Techniques for HME Process Scale-up

Formulation development using hot melt extrusion is generally performed using small, laboratory equipment. Scale up of these developed formulations by achieving similar properties of the dosage forms is always a challenge in pharmaceutical industry. There is limited information available in the literature for scale up of solubility enhanced formulations prepared by melt extrusion processing. Analytical characterization and techniques are critical in the scale up of these melt extruded solid dispersions in order to ensure similar products are produced, specifically in obtaining similar solubility enhancing effect.

When attempting to achieve similar solubility for a formulation on a large extruder to that of the lab scale, the first step is to match process energies between the extruders, both mechanical and thermal. Mechanical energy influences the degree of mixing achieved in the process and thermal energy determines the amount of heat the formulation experiences in the process. Matching energy input of the extruders ensures good mixing without degrading the formulation. Computer aided process simulation is used to match energies between the small and large extruder. This requires thermodynamic and rheological characterization of the formulation. The simulation provides an initial screw design and process conditions for the larger extruder that provides similar mechanical and thermal energies to the small extruder.

Once initial a screw design and process conditions are established for the large extruder, extrusion trials provide samples that can be analytically characterized and compared to the original samples. Iterative trials to fine tune process conditions may be required to achieve optimal results.

Process Scale Up Case

A stable, solid dispersion of EUDRAGIT® E/Nifedipine and EUDRAGIT® NE 30 D formulation was required to be scaled up from an 18mm twin screw extruder to a 27mm twin screw extruder. Consistent physical and chemical properties of the scaled up solid dispersion were required.

Different drug loadings (10, 20 and 30% Nifedipine) were extruded with EUDRAGIT® E PO/ NE 30D (90%:10% dry polymer). EUDRAGIT® E PO and EUDRAGIT® NE 30D were extruded in a first step to prepare a preblend and cut into granules. Nifedipine and the granular polymer blend were fed with separate doses into either an 18mm or 27mm co rotating twin-screw extruder (Leistritz, Nuremberg, Germany).

Scale-up parameters were calculated with software to determine all important parameters. Scale up parameters on the 27mm extruder were based on the process parameters from the 18mm extruder. Screw configuration in both extruders consisted of conveying and mixing elements. The screw speed of the 18mm was set to 140rpm. Based on the mass throughput, the output of the 27mm extruder was calculated to be 100rpm. Screw configuration on both extruders were similar. The melt was cooled as a strand on a conveying belt and subsequently cut into cylindrical granules. The granules were milled prior to analysis.

Visually, the extrudates were completely transparent, indicating a transformation of crystalline Nifedipine into an amorphous state. XRPD analyses for extrudates were performed on an X'Pert Pro (PANalytical) using an X'Celerator as detector. The instrument is equipped with a Cu tube as X-ray source. Each diffractogram was recorded between 4°-74°C (28). Crystallinity was not observed.

Dissolution testing was performed using a USP apparatus II in 900ml 0.1N HCl pH 1.2, 100rpm. Samples equivalent to 45mg nifedipine were analyzed.

The extrudates were stored in HDPE bottles at 40°C/75 % relative humidity. Formulations prepared with 10 and 20% drug loading were stable over 3 months. The formulation containing 30% drug loading demonstrated a decrease in dissolution rate of 20-25%.

Initially, a faster release rate of the extrudates prepared with the 27mm extruder was observed. The faster release rate was due to the differences in granule particle size. The granules from the 27mm extruder were smaller than the granules prepared with the 18 mm. The formulation with 20% drug loading demonstrated a slight re-crystallization after dissolution testing. This observation can be attributed to small crystals present in the extrudate that could not be detected by XRPD, seeding re-crystallization.

Conclusion.
XRPD and dissolutions studies were used to confirm formulations with EUDRAGIT® E /NE 30D containing different loadings of Nifedipine demonstrated an increase in solubility and a stabilized dissolution profile. 10% and 20% drug loading were stable up to 3 months at accelerated conditions. Trials on the 18mm and 27mm extruder led to similar dissolution behavior of nifedipine from the extrudates. This study demonstrated that scale up of a solubility enhanced formulation containing EUDRAGIT® from an 18mm to a 27mm extruder could successfully be performed.

Figures

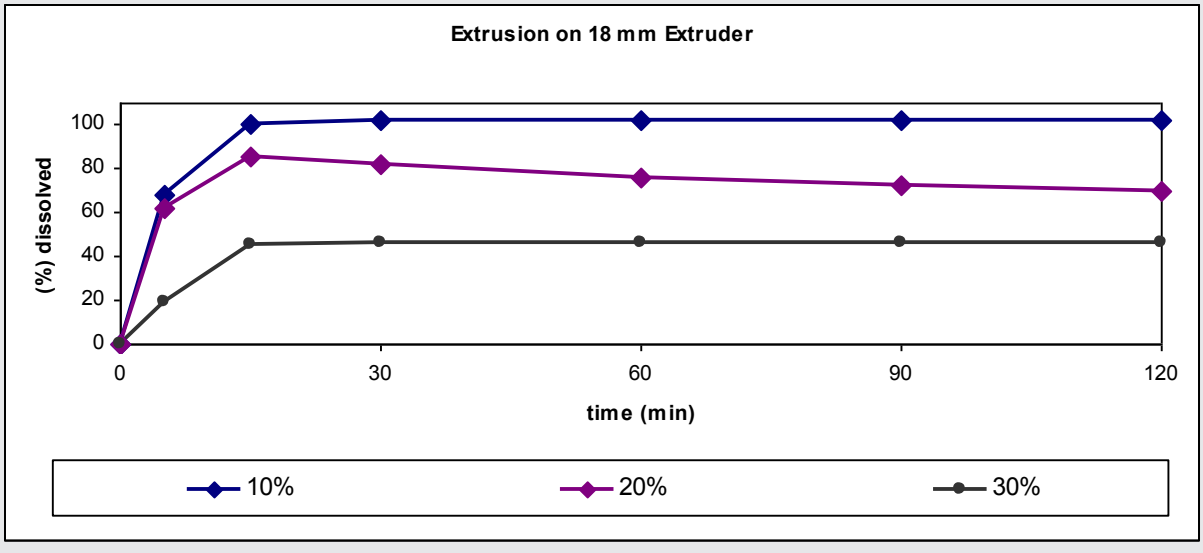

Figure 4: Dissolution results of different drug loadings on 18 mm extruder

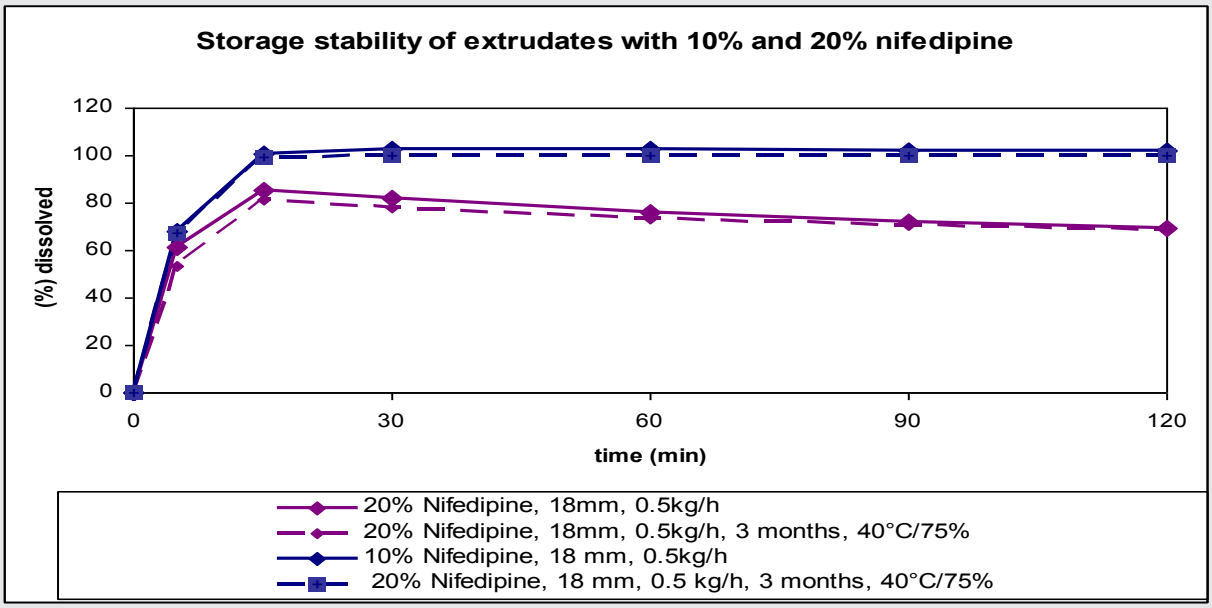

Figure 5: Storage stability of extrudates

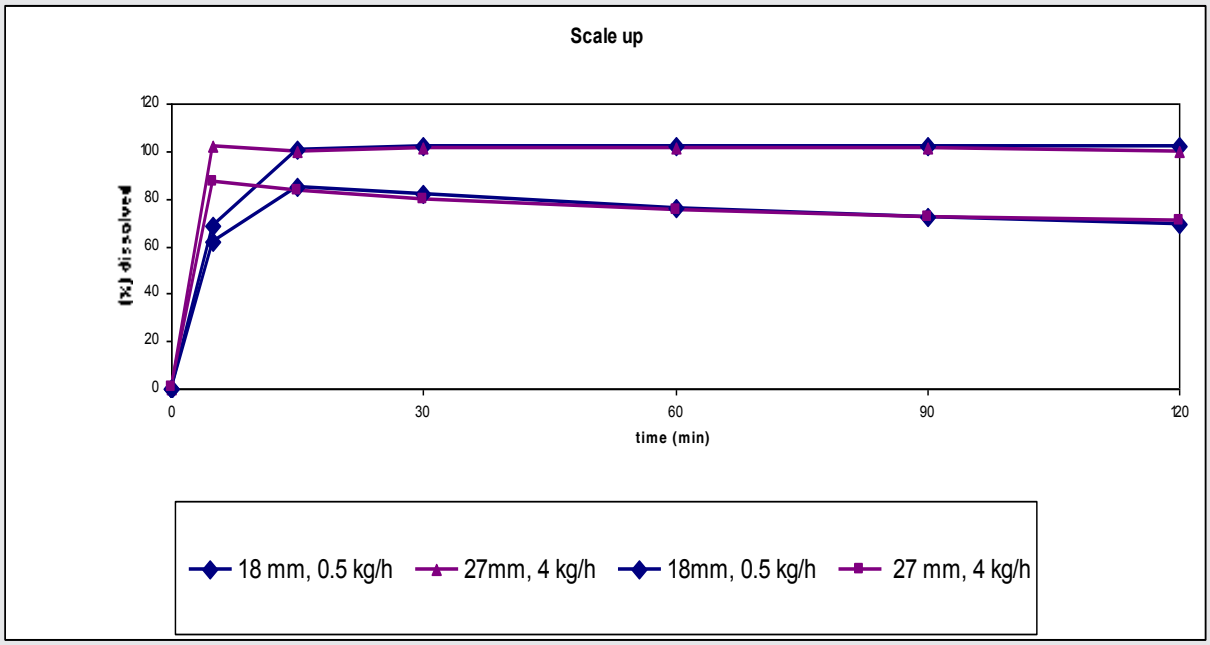

Figure 6: Comparison of extrudates with 10 and 20% nifedipine prepared on 18mm and 27mm extruder

REFERENCES

1. MM Crowley, F Zhang, MA Repka, S Thumma, SB Upadhye, SK Battu, J McGinity, C Martin (2007) Pharmaceutical Applications of Hot-Melt Extrusion: Part I. Drug Development and Industrial Pharmacy 33: 909-926

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Tony Listro is Vice President, Technology and Site Lead of Sever Pharma Solutions Putnam, CT. Tony is an expert in the areas of polymer materials and polymer processing. He has worked on blending active pharmaceutical ingredients with polymers for various drug delivery applications including oral and implantable dosage forms for more than 15 years. Tony holds both a BS and MS in Plastics Engineering from the University of Massachusetts in Lowell, MA, and an MBA from the University of Massachusetts in Amherst, MA. He holds 2 issued US patents and has authored and/or co-authored 20 publications. Tony is a member of the Society of Plastics Engineers, Controlled Release Society, and AAPS.

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Dr. Crowley has worked in the field of drug delivery and pharmaceutical research for more than 19 years and has previously been employed in senior management roles with PharmaForm, Monsanto Company, Warner-Jenkinson Company and Mission Pharmacal. Dr. Crowley received his B.S. degree in Chemistry from the University of Missouri at St. Louis, an M.A. in Organic Chemistry from Washington University and a Ph.D. in Pharmaceutics from The University of Texas at Austin where he studied under Professor James McGinity. His research interests include physical pharmacy and pharmaceutical technology focused on novel drug delivery.

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