Impact of Extrusion Process Parameters on Drug Recovery and Dissolution Performance of Solid Dispersions of Ritonavir and AFFINISOL™ HPMC HME

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Introduction

Hot melt extrusion (HME) is a versatile, continuous and solvent free process technology that has gained significant popularity in the pharmaceutical industry in recent years. The high number of poorly soluble drugs in both development pipelines and commercial products [1] has directed formulators to utilize HME for the manufacture of amorphous solid dispersions (ASDs) [2]; the high energy state of the amorphous active and stabilizing properties of the polymeric excipients can provide significant increases in apparent solubility without sacrificing permeability potentially resulting in great improvements in bioavailability [3].

Hydroxypropyl methylcellulose (HPMC) is an amorphous, water soluble polymer used broadly in pharmaceutics in both immediate-release and controlled-release applications. Though HPMC has been shown to be highly successful at inhibiting recrystallization and increasing bioavailability [4] when utilized as the polymeric stabilizer in ASDs, it has been disadvantaged in hot melt extrusion due to a high glass transition temperature (T_g) , high melt viscosity and significant color change at elevated temperatures [5] requiring unique formulation to overcome the processing difficulties [6]. Recently, The Dow Chemical Company introduced a new grade of HPMC, AFFINISOL™ HPMC HME, designed for hot melt extrusion with a notably lower T_g, reduced melt viscosity, and reduced color change at elevated temperatures [7]. AFFINISOL™ HPMC HME has demonstrated the ability to be successfully processed at a wide range of processing conditions into binary solid dispersions with the resulting formulations providing increased solubility of the model compounds [8].

Ritonavir (RTV) (Figure 1) is a poorly soluble drug used in the treatment of HIV-infection. Previous studies have confirmed that RTV formulated into an ASD can greatly improve the drug's solubility [9] and a commercial ASD is currently available [6]. However, RTV displays thermal instability above its melt temperature making formulation by extrusion challenging.

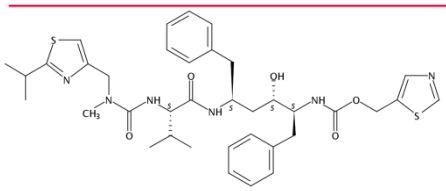

Figure 1 – Chemical structure of ritonavir

In HME formulation, it may be necessary to include additives that enable process temperature reductions to ensure the stability of each component during extrusion. However, this can create undesirable formulation complexity and such additives may not be required if the operating design space is adequately explored. Thus, it is important to understand the impact of key process variables on drug degradation and product performance to fully optimize a system and ensure robust production. The primary variables controlled by the operator include barrel temperature, which will dominate the extent of thermal exposure the active experiences, screw speed, which changes the residence time distribution and can generate viscous/frictional heating, and feed rate, which will dictate the residence time of the material within a twin screw extruder. In the present study, solid dispersions of RTV and AFFINISOL™ HPMC HME 15LV (AFF) were prepared by HME. The impact of process variables (screw speed, feed rate and temperature) on drug degradation as well as drug release rate were explored using a factor screening Design of Experiments (DOE).

Materials

Ritonavir was purchased from Indo Overseas Trading Agencies-India. AFFINISOL™ HPMC HME 15LV was obtained from The Dow Chemical Company (Midland, MI). Acetonitrile, potassium dihyrogen orthophosphate, methanol and acetonitrile used in the study were Analytical grades procured from Orion Scientific Suppliers Pvt. Ltd. (Mumbai, India)

Methods

Hot melt extrusion:

The formulation was held constant comprising 33% RTV blended with 66% AFF. All extrusions were performed on a Thermo Fisher Pharma 11 (Thermo Fisher -Germany) twin screw extruder and the formulations were fed into the extruder via a gravimetric feeder. The screw kneading elements used have 30°, 60° & 90° configurations. Process variables were adjusted according to the Design of Experiments outlined below. The obtained extrudates were ground and sieved through a16 mesh sieve.

Design of Experiments (DOE)

The drug polymer blends were extruded at different processing conditions exploring the variables of feed rate, screw speed and temperature. The factor screening DOE used for the study was designed using JMP software. The order of the trials was randomized but for clarity herein runs have been reordered by temperature in Table 1.

Table 1: Design of experiment parameters used in HME

B.No.	Temperature (ºC)	Screw Speed (RPM)	Feed Rate (g/h)
1	130	100	100
2	130	100	250
3	130	300	250
4	130	300	100
5 (3X repeat)	150	200	185
6	170	100	100
7	170	100	250
8	170	300	250

Differential Scanning Calorimetry (DSC):

DSC (TQ2000, TA Instrument) was used to study the thermal behavior of RTV and the extrudates. The DSC experiments were run in dry nitrogen atmosphere at flow rate of 50 mL/min. The samples were weighed into an aluminum pan, crimped and heated at a ramp rate of 10 °C/min from 25 °C to 225 °C. A temperature modulation of 0.5 °C with a frequency of 40 seconds was applied. Data analysis was performed in TA Instruments Universal Analysis.

Powder X-ray Diffraction

X-ray diffraction was performed on PANalytical - Empyrean (Netherlands) X-Ray diffractometer. The X-ray was applied at a voltage of 40 kV and a current intensity of 20 mA. The samples were analyzed over a 2θ range of 5°–50° with a step size of 0.002^0.The samples were placed in a zero background sample holder and incorporated on a spinner stage.

High Performance Liquid Chromatography

The RTV drug content of the extrudates was evaluated using HPLC (Agilent 1260). The mobile phase was composed of acetonitrile and phosphate buffer (adjusted to pH of 4.0) in ratio of 55:45 at flow rate of 1 mL/min. The column used was an Eclipse plus C8 4.6 x 150 mm, 5 µm and detection of RTV was determined at 246 nm.

Dissolution studies

In vitro dissolution studies were conducted in USP dissolution apparatus II (Electrolab, India) maintaining sink conditions to determine if processing conditions impacted drug release rate. A quantity equivalent to 100 mg of ritonavir from extruded samples was weighed and filled into hard gelatin capsules. Dissolution of RTV from the capsules was performed in triplicate in 0.1 N HCl with the temperature maintained 37 °C at a paddle speed of 75 RPM. The samples were collected at time points of 10, 20, 30, 45, 60 and 120 minutes and analyzed by HPLC after filtering the samples through a 0.45um PVDF filter.

Results and Discussion

Hot Melt extrusion

Ritonavir and AFFINISOL™ HPMC HME 15cP were successfully extruded at all conditions of the DOE confirming the broad processing window of AFF previously observed [8]. No processing challenges were observed during the trials despite the low processing temperature and high feed rate of some runs. This suggests RTV has a plasticizing effect on the polymer upon mixing.

When extruded at temperatures of 130 °C, 150 °C and 170 °C the extrudates were clear and transparent which indicated homogenous mixing and amorphization of the drug with AFF. The color of the extrudates was dependent upon the processing temperatures and feed rate. For example, the extrudate obtained at 130 °C, 250 g/hr at 100 rpm (B.No. 2) was light

yellow compared to extrudate obtained at 170 °C, 100 g/h at 100 rpm (B.No.6) which was comparatively yellow in color (Figure 2). This is due to synergistic effects of high temperature and longer residence time of B. No. 6 inside the extruder. The difference in color does not impact the release rate from the resulting ASD as will be discussed below.

Figure 2 – Extrudate images of B.No. 2 (left) and B.No. 6 (right)

Differential Scanning Calorimetry:

The DSC thermogram of pure RTV showed a sharp endothermic peak at 122.12 °C attributed to melting of the crystalline drug (data not shown) whereas the DOE extrudates showed no endothermic or exothermic events indicating the extrudates were rendered amorphous. Example DSC thermograms of batches 2 and 6 are shown in Figure 3a and 3b, respectively. It can be seen that even at the low processing temperature and short residence time a successful amorphous system was obtained (Figure 3a).

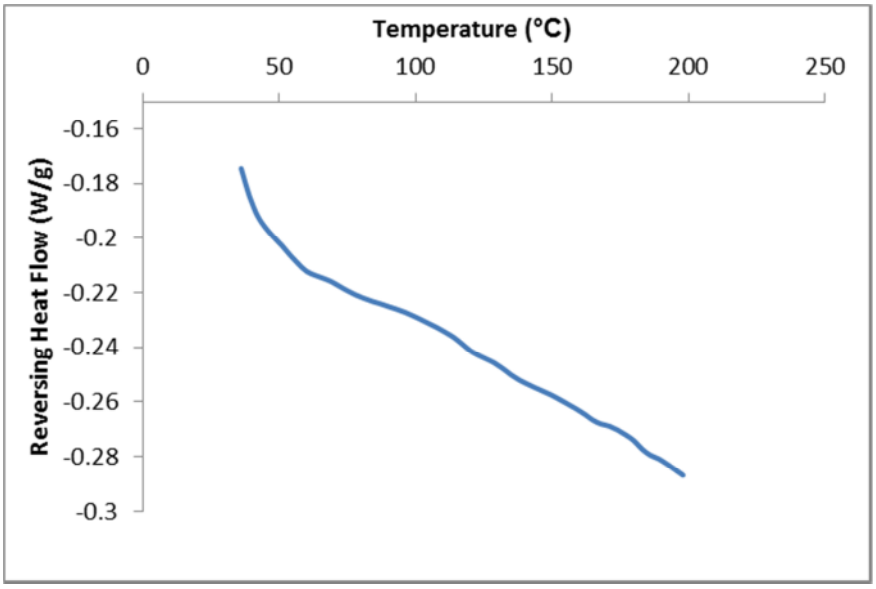

Figure 3a: DSC thermogram of B.NO.2

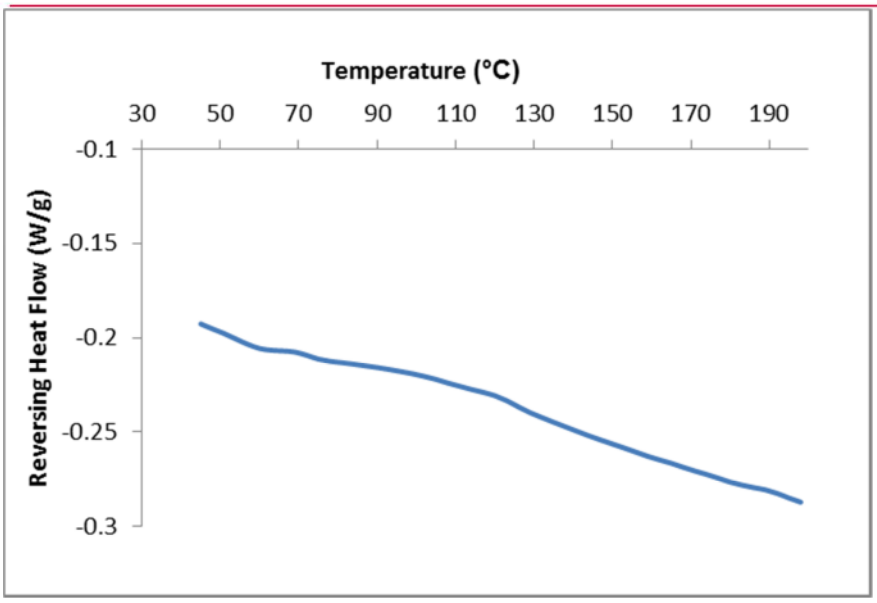

Figure 3b: DSC thermogram of B.NO. 6

The T_g of pure amorphous RTV is 45 °C to 49 °C (onset to endpoint; Patent EP1418174B1); this event was not observed in any DOE batch indicating the absence of drug rich domains. The predicted glass transition temperature of the 1:2 RTV:AFF formulation is approximately 84 °C as calculated using the Gordon-Taylor equation however, the DOE batches each display a T_g at 73.9 °C as seen in Figures 3a and 3b. This negative deviation from the predicted value is attributed weak RTV:AFF interactions resulting in a positive entropy of mixing [10]. Despite this negative deviation from the predicted value, the single observed T_g indicates good miscibility between the two components.

Powder X-ray Diffraction

The XRD diffractogram of pure RTV showed characteristic crystalline peaks between 2θ of 5°- 45°. However, the extruded samples did not show crystalline peaks in this range and displayed only an amorphous halo. This was true for all conditions of the DOE, including the low temperature conditions, confirming that processing parameters did not impact the amorphous nature of the extrudates in good agreement with the DSC data. The XRD of batches 2 and 6 are shown in Figure 4 as examples. The amorphicity of the low temperature samples also demonstrates a strong capability of the polymer to solubilize the drug into the polymeric matrix. The minor peaks in the extrudates at approximately 32° and 45 °are due to

residual sodium chloride present in HPMC following manufacture.

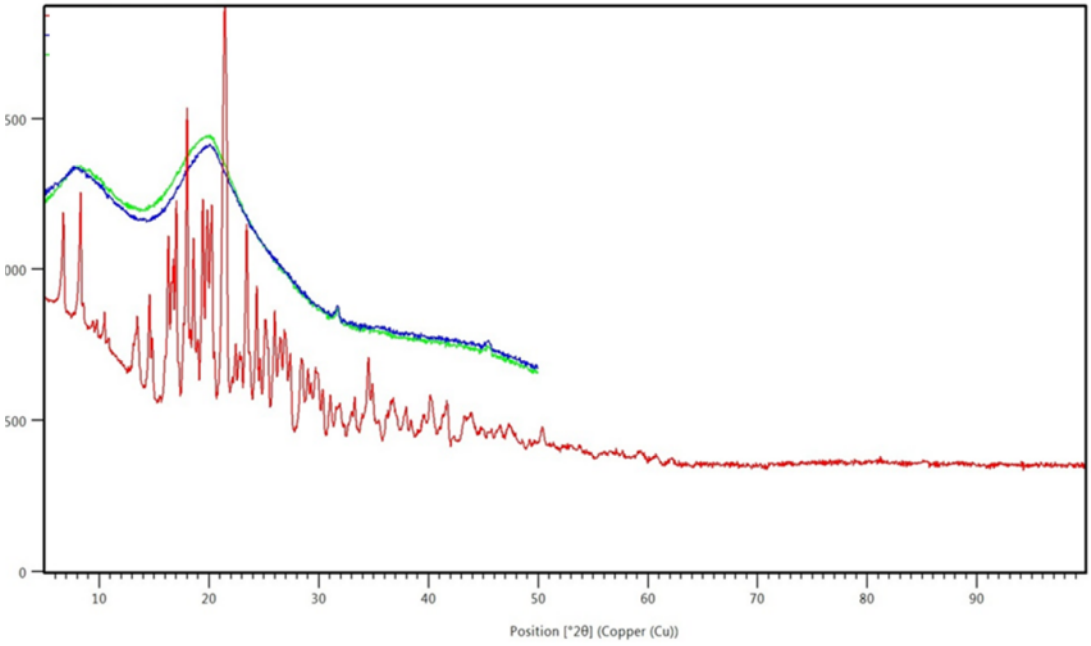

Figure 4 – X-ray diffraction patterns of: unprocessed RTV (red), and DOE Batches 2 (green) and 6 (blue)

Drug Content:

The RTV content was determined by HPLC for all extruded batches of the DOE to understand the impact of processing conditions on drug stability. The drug recovery values of the DOE batches are shown in Table 2, primary impurities were not quantified. The results showed that RTV degradation occurred as temperature increases from 130 °C to 170 °C. This result was expected due to the known thermal instability of RTV. Fitting the data confirmed that temperature, screw speed and feed rate all have a statistically significant impact on drug degradation ($p < 0.05$) with a rank order of temperature > feed rate > screw speed. Thus, it was observed that at the most aggressive DOE conditions utilizing the maximum screw speed (300 RPM), longest residence time (100 g/h), and highest temperature (170 °C), RTV showed the greatest degradation (>20%) while the extrudates obtained at the least aggressive DOE conditions at 130 °C, feed rate of 250 g/h at speed of 100 RPM resulted in the least degradation (~1%). For a drug with process sensitivity challenges such as RTV, the ability of AFFINISOL™ HPMC HME to be extruded over a broad temperature range allows selection of acceptable extrusion conditions to reduce or eliminate drug degradation.

Table 2 – RTV recovery from DOE batches

B.No.	Temperature (°C)	Screw Speed (RPM)	Feed Rate (g/h)	Drug Recovery (%)
1	130	100	100	96
2	130	100	250	99
3	130	300	250	94
4	130	300	100	91
5	150	200	185	91
5(2)	150	200	185	91.5
5(3)	150	200	185	92
6	170	100	100	82
7	170	100	250	88
8	170	300	250	84

Dissolution studies

Ritonavir release profiles of extruded DOE batches are shown in Figure 5. Due to the impact of processing conditions on drug degradation, differences in dissolution profiles were observed. For example, the extrudate obtained at 130 °C, feed rate of 250 g/h at 100 RPM showed ~ 70% release in 60 min in 0.1 N HCl whereas the extrudate prepared at 170 °C, 100 g/h feed rate and 100 RPM screw speed showed approximately 55% drug release in 60 min. Indeed, f2 analysis confirmed the dissolution profiles batches 6 and 8 were dissimilar to batches 1-5 ($f2 < 50$). Despite these differences, all ASDs displayed significantly faster dissolution compared to the physical mixture demonstrating the ability of the polymer to improve the dissolution rate of the poorly soluble compound.

By adjusting for the analyzed drug content of each sample it is possible to understand if the dissolution rate is different among the batches due to changes in the polymer following HME. It can be seen (Figure 6) that when adjusting for drug degradation, the dissolution profiles for all process conditions are similar (f2 > 50 for all comparisons). This confirms that the initially observed differences in dissolution were due to changes in the API content, and not due to changes in the polymer as a function of processing conditions.

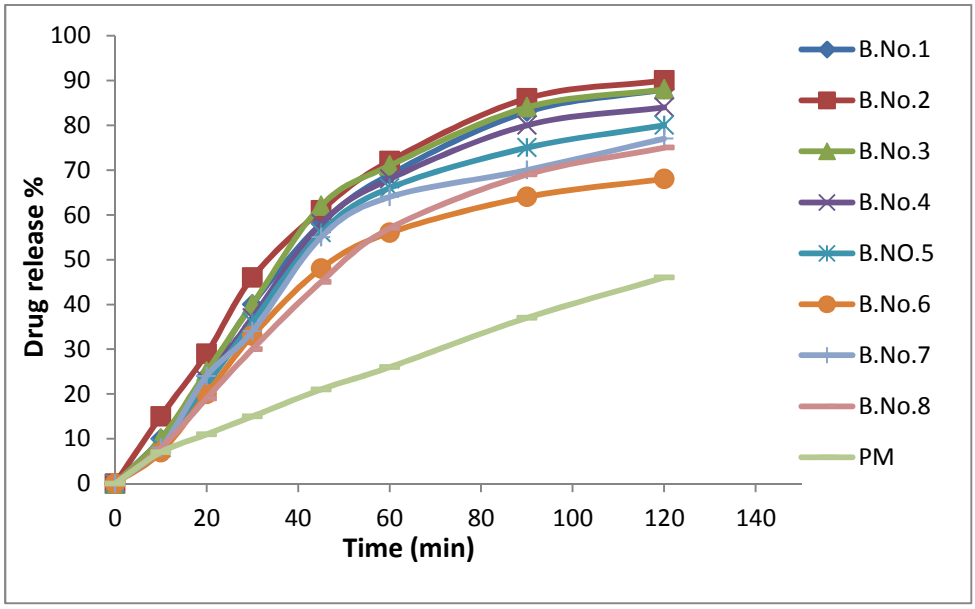

Figure 5: USP 2 Dissolution profiles of DOE batches and non-extruded physical mixture (PM)

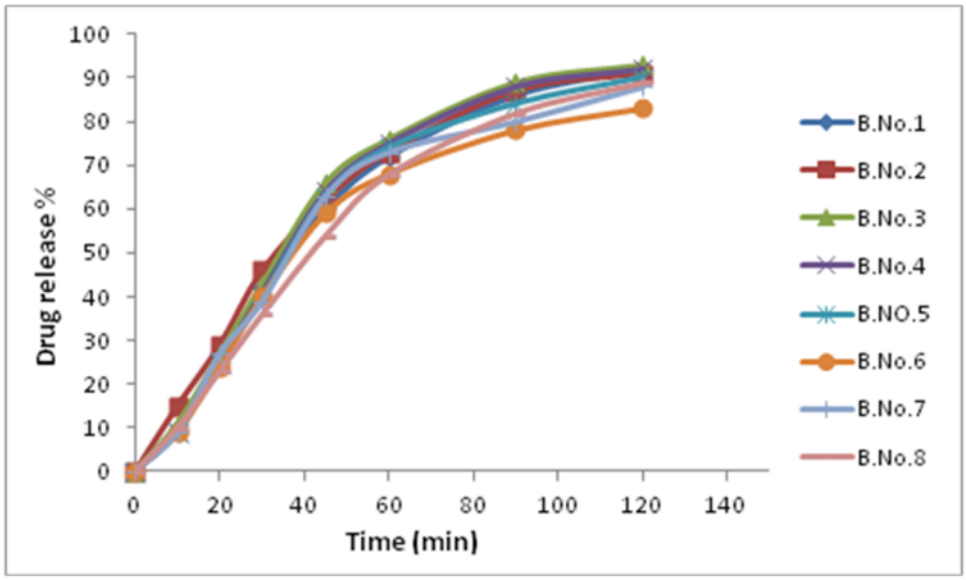

Figure 6: Dissolution profile of DOE batches with Potency adjusted values

Conclusions

The process conditions of temperature, screw speed and feed rate significantly impacted drug degradation for the poorly soluble compound ritonavir. The observed change in dissolution behavior is due to drug degradation and not changes to the polymer. The broad processing window of AFFINISOL™ HPMC HME allows exploration of the process parameter design space to study and minimize drug degradation for compounds with sensitivities such as RTV.

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