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In-process Rheometry as a PAT tool for Hot Melt Extrusion

A L Kelly^{1*}, T Gough¹, M Isreb¹, R Dhumal¹, J W Jones², S Nicholson², A B Dennis²,
A Paradkar¹

¹ Centre for Pharmaceutical Engineering Science, University of Bradford, UK, BD7 1DP

² Bristol-Myers Squibb Research & Development, Reeds Lane, Moreton, UK, CH46 1QW

*Corresponding Author:

Dr Adrian Kelly

Centre for Pharmaceutical Engineering Science,

University of Bradford, BD7 1DP, UK

Tel: 00 44 1274 234532

Email: A.L.Kelly@Bradford.ac.uk

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Abstract

Real time measurement of melt rheology has been investigated as a Process Analytical Technology (PAT) to monitor hot melt extrusion of an Active Pharmaceutical Ingredient (API) in a polymer matrix. A developmental API was melt mixed with a commercial copolymer using a heated twin screw extruder at different API loadings and set temperatures. The extruder was equipped with an instrumented rheological slit die which incorporated three pressure transducers flush mounted to the die surface. Pressure drop measurements within the die at a range of extrusion throughputs were used to calculate rheological parameters such as shear viscosity and exit pressure, related to shear and elastic melt flow properties respectively. Results showed that the melt exhibited shear thinning behavior whereby viscosity decreased with increasing flow rate. Increase in drug loading and set extrusion temperature resulted in a reduction in melt viscosity. Shear viscosity and exit pressure measurements were found to be sensitive to API loading. These findings suggest that this technique could be used as a simple tool to measure material attributes in-line, to build better overall process understanding for hot melt extrusion.

Introduction

Hot Melt Extrusion (HME) is a continuous manufacturing process which is increasingly being used to generate amorphous solid dispersions or solutions of poorly soluble Active Pharmaceutical Ingredients (APIs) in polymer matrices^{1,2}. Typically HME renders the drug amorphous, a state which can significantly enhance both drug kinetic solubility and bioavailability. The application of HME for manufacture of pharmaceuticals has been widely reported including pellets³, sustained release tablets^{4,5} implants⁶ and transdermal films⁷. A number of comprehensive reviews of the pharmaceutical HME process are available^{1,9,10}.

In the hot melt extrusion process the API, polymer and other excipients are conveyed along a heated barrel by two closely intermeshing screws. Temperature, residence time and mixing intensity of the process can be varied by tailoring extruder screw configuration and by adjusting process parameters such as throughput and screw rotation speed. Within the process the API and carriers experience significantly high temperatures and levels of shear deformation, which serve to melt the polymer and dissolve or disperse the API within the matrix.

There exists a drive within the pharmaceutical industry to adopt real-time measurements for continuous processes to enhance process understanding and product quality, as part of a wider Quality by Design (QbD) approach. This has been exemplified by publication of the US Food and Drug Administration (FDA) code of practice for Process Analytical Technology¹⁰. Within the extrusion process, primary process variables such as temperature and pressure in the die can be readily monitored to provide an indication of process stability (i.e. homogeneity of throughput). Motor torque and material throughput can also be recorded and used to give an indication of specific energy input to the melt, which is related to the temperature, material properties and degree of filling in the extruder screw channels. However, these basic process measurements give little direct indication of the consistency or rheology of the extrudate. Thus there is a need to develop suitable real-time characterization techniques capable of providing such information to shed light on the likely real-time effects of torque, temperature, API loading and its interaction with the polymer matrix. Simulation can be used to help to understand and predict the behavior of materials within the process although due to the highly complex three dimensional nature of twin screw extrusion flow, no fully-resolved first principle simulations have been reported. Recent progress in HME simulation has been made using finite element method (FEM)¹¹, finite volume method (FVM)¹² and smoothed particle hydrodynamics (SPH)¹³.

Spectroscopic techniques such as Raman and near infra-red (NIR) have been applied to hot melt extrusion to monitor drug concentration or specific drug-polymer molecular interactions¹⁴⁻¹⁷.

However, such equipment does not provide rheological insight into process stability. The aim of this work was to investigate the use of rheometry as a complimentary, low cost real-time measurement technique for HME.

Rheology is the study of flow and deformation and is widely applied to polymers and other soft solids such as gels and personal care products¹⁸⁻¹⁹. Flow behavior can be measured by applying a deformation to a sample of material and measuring the response; polymers are complex viscoelastic materials whose flow properties depend upon temperature, applied strain rate and time. Rheology can be used for a number of applications; as a quality control tool, to predict how materials will flow inside a process, to understand the interaction between blends or compounds or to measure temperature stability. Typically, polymer melt rheology is measured using rotational or capillary rheometry techniques. In the former, molten polymer is held at temperature between two plates and an oscillatory deformation is applied. The response of the polymer to deformation at a range of frequencies describes its flow behavior; additionally the viscous and elastic components of flow can be separated and used to provide information about the structure of the material. Capillary rheometry is a pressure driven technique which mimics the flow of polymer through an extruder die. Molten polymer is forced at known volumetric flow rate through a capillary die of fixed geometry. Measurement of the pressure drop across this die at a range of flow rates allows calculation of rheological properties such as viscosity. Capillary rheometry has the advantage that it measures flow at real process conditions and therefore provides a good indication of how a material will behave in the process.

Rheology has been used to characterize pharmaceutical solid dispersions and solutions, although only a relatively small number of studies have been reported. Capillary rheometry has been used to investigate the effect of molecular weight of hydroxy propyl cellulose (HPC) on flow behavior²⁰. A similar study was reported on the rheological behavior of lactose filled polyethylene glycol²¹. The effect of lamivudine, zidovudine and plasticizers on the rheological behavior of ethyl cellulose, using oscillatory rheometry as a pre-formulation tool for hot melt extrusion was reported²². Other workers have also used oscillatory rheometry as a pre-formulation tool^{23,24}. Capillary and oscillatory rheometry were used as complementary tools to investigate the properties of acetaminophen in a polyethylene oxide matrix for hot melt extrusion²⁵. The rheological data were used to determine optimum extrusion process conditions and also to measure miscibility of the API in the polymer.

Real-time assessment of rheology within the extrusion process can be achieved by measurement of pressure drop inside an instrumented extruder die. In-line or in-process measurement are terms typically used to describe measurements made on material inside the main process stream, rather than

on a sample stream abstracted from the main flow (on-line). A range of in-line rheological techniques have been reported for polymer extrusion to enhance process control or process understanding. The rheological properties of several grades of high density polyethylene were measured using a slit rheometer attached to a single screw extruder²⁶. The design incorporated an aluminum slot section with three pressure transducers mounted flush to the slot wall. Measurement of wall stress was used to determine rheological properties of the melts (at shear strain rates of up to 300 s^{-1}) from the slope of axial pressure profiles and melt elasticity from the predicted exit pressures. The study found good correlation with results from an off-line capillary rheometer. Similar work was performed using a slit die viscometer incorporating four pressure transducers²⁷. The die was fed with polymer from a single screw extruder followed by a gear pump to further stabilize flow. Results indicated a lower viscosity in the melt compared to that from a laboratory capillary rheometer. Other workers have sought to increase the range of shear rates examined by developing a novel in-line rheometer based on the flow of polymer through a wedge shaped profile²⁸. This had the effect of increasing the shear strain rate along the length of the slit, although the convergence of the flow channel meant that flow was not viscometric and therefore both viscous and elastic effects were observed. The use of several pressure transducers allowed apparent viscosity determination over a broad range of shear rates ($10\text{-}1000\text{ s}^{-1}$) to measure polypropylenes with different molecular weights. In-line rheological slit dies have also been used in twin screw extrusion, both for monitoring reactive extrusion processes such as cross-linking of polyethylene²⁹ and for incorporation of additives such as the flame retardant magnesium hydroxide into a polyethylene³⁰. Recently a slit die rheometer was reported consisting of multiple steps, used for monitoring extrusion of thermoplastic starches³¹. Three different heights within the slit allowed viscosity at three shear strain rates to be calculated at a single extruder throughput. In the current work a slit die rheometer has been evaluated as a tool to investigate rheological behavior during extrusion, offering a unique insight into API, polymer process interactions and their impact on output material rheology. Results are presented for a blend comprising a commercial polymer and a developmental API extruded at a range of process conditions including various mass ratios and temperatures.

Materials and Methods

Materials

Polyvinylpyrrolidone-vinylacetate (PVP-VA) copolymer (Kollidon® VA 64) was procured (BASF, Germany) in powder form. A development API was provided by Bristol-Myers Squibb in powder form, having particle size $d_{10}=12.0\ \mu\text{m}$, $d_{50} = 96.3\ \mu\text{m}$, $d_{90} = 257.2$, $d(3,2) 24.5\ \mu\text{m}$ and $d(4,3) 118.3\ \mu\text{m}$ as measured by a Malvern Mastersizer 2000 (5g sample, 0.3 MPa dispersion pressure, 3 replicates). API loadings of between 10, 20, 30 and 40% w/w were investigated in addition to the pure polymer.

Thermal Analysis

Thermo-gravimetric analysis (TGA) was carried out using a Q500 TGA (TA Instruments, UK) to determine the moisture content and the decomposition temperature of the base materials. Samples (weighing 5 ± 1 mg) were analyzed at a heating rate of $10\ ^\circ\text{C}/\text{min}$ under a nitrogen atmosphere. The temperature range used was $30 - 600\ ^\circ\text{C}$ and the gas flow was set to $20\ \text{ml}/\text{min}$. All measurements were carried out in duplicate and the data were analyzed using Universal Analysis 2000 v.4.3A software (TA Instruments, UK). Differential scanning calorimetry (DSC) was performed using a Q2000 DSC (TA Instruments, UK). Samples of the polymer, drug, polymer:drug physical mixtures and extrudates were enclosed in an aluminum pan and sealed with a pin-holed lid allowing evaporation of moisture. A heat/cool/heat cycle was carried out for all the samples at rates of $10\ ^\circ\text{C}/\text{min}$. Samples were heated to $190\ ^\circ\text{C}$, cooled to $0\ ^\circ\text{C}$ and then re-heated to $190\ ^\circ\text{C}$. The melting point was recorded at the top of the peak during the first heating stage, while the glass transition temperature (T_g) was calculated at onset, inflection and endpoint of the transition during the reheating step.

Rheological Analysis

Off-line rheological testing was carried out using a Physica MCR 501 rotational rheometer (Anton Paar, Austria) with parallel plate geometry of diameter $25\ \text{mm}$. The gap between the two plates was set to $1\ \text{mm}$ for all tests. Frequency sweeps were performed at a constant strain of 3%, this value having been determined to be within the linear viscoelastic range by preceding strain amplitude tests. The angular frequency range tested was $0.1 - 100\ \text{s}^{-1}$. Physical mixtures of API loadings 0, 10, 20, 30 and 40 % w/w with PVP-VA were characterized at temperatures of 120, 130, 140, 150 and $160\ ^\circ\text{C}$.

Hot Melt Extrusion

Extrusion was performed using a co-rotating twin screw pharmaceutical grade extruder (Pharmalab, Thermo Scientific, UK) with screw diameter $16\ \text{mm}$ and a screw length to diameter ratio of 40:1. The

extruder barrel comprised 10 separately temperature controlled zones. Material feeding was achieved using a gravimetric twin screw feeder (Mini-twin, Brabender, Germany). The extruder was fitted with a rheological slit die (in-house design, University of Bradford) consisting of a temperature controlled adaptor and slit-die block. The slit die was 1.5 x 15 x 90 mm long. Three pressure transducers (Dynisco PT435) with a full scale deflection of 10.3 MPa were flush mounted at the surface of the slit and monitored at a frequency of 1 Hz using software programmed in-house (LabView, National Instruments). A schematic diagram and photograph of the rheological slit die are shown in Figure 1.

Experiments were performed to measure the viscosity of polymer-drug formulations during extrusion at drug loadings of 0, 10, 20, 30 and 40 % w/w. Three set extruder temperatures were used in each case: labelled as T120, T140 and T160 and detailed in table 1. At each set temperature, the three pressure transducers used in the rheological die were calibrated to minimize any temperature-related signal drift. Calibration was performed electronically using internal shunt resistors designed to provide an output signal representative of 80% of full scale.

Polymer and API were blended in a Turbula mixer for 15 minutes in predefined weight ratios prior to extrusion. The powder blend or the polymer alone was fed into the extruder at each specified feed rate using a gravimetric twin-screw feeder. The extruder was run continuously at a set screw rotation speed of 50 rpm and pressure readings within the slit die rheometer were monitored at a frequency of 1 Hz. At each set throughput, the process was allowed a 15 minute stabilization period before pressure measurements were recorded, for a representative period of around 10 minutes. At each API loading and set temperature, a range of throughputs between 0.2 and 0.6 kg/hr were used to provide a range of shear strain rates over which the rheological properties could be investigated. Measured pressure data were subsequently analyzed and mean values taken over a suitably stable period. A linear fit was then applied and pressure drop along the slit length (ΔP) and predicted pressure at the exit of the die (P_{exit}) were calculated.

From the measured pressures and throughputs, viscosity was calculated using the following Equations³²:

$$\text{Apparent Wall shear rate, } \dot{\gamma}_{app} (s^{-1}) = \frac{6Q}{WH^2} \quad (1)$$

Where Q = volumetric throughput, W = slit width and H = slit height

$$\text{Wall Shear Stress, } \tau_{wall} (Pa) = \frac{H\Delta P}{2L} \quad (2)$$

Where ΔP = pressure drop and L = slit length

$$\text{Shear Viscosity, } \eta \text{ (Pa. s)} = \frac{\tau_{wall}}{\dot{\gamma}_{app}} \quad (3)$$

Results and Discussion

DSC thermograms of the pure API, polymer and physical mixtures are shown in Figure 2. A melting endotherm was detected for the API in the region of 158 to 162°C. The pure polymer exhibited a broad glass transition starting at 108°C. On first heating (during annealing), physical mixtures showed both the glass transition of the polymer and melting endotherm of the API. However, on second heating, as shown in Figure 2 melting of the API was not observed in the physical mixtures, but increased loading of API caused the glass transition to shift to lower temperatures. This indicated that the API was readily miscible within the polymer matrix in the molten state, and that the API had a plasticising effect. The transition region was also observed to broaden with increasing drug loading. This plasticisation can affect the melt processing behaviour of the polymer during melt extrusion, resulting in a viscosity reduction.

Results from off-line oscillatory rheometry are displayed in Figure 3, for pure polymer and physical mixtures at a set test temperature of 150°C. These results show the frequency dependence of melt viscosity. All materials demonstrated a shear thinning behavior, whereby increasing rate caused viscosity to decrease. Shear thinning behavior is typical of thermoplastic polymers and allows polymers to be forced through narrow dies or into thin walled mold cavities at high flow rates. Increasing shear strain deformation breaks entanglements between polymer molecules, thus reducing resistance to flow. The API was found to cause a significant plasticization effect on polymer viscosity. Viscosity of the pure polymer at low frequency (0.1s^{-1}) was close to 100,000 Pa.s. This reduced with increasing API loading to 3,000 Pa.s at 40 % w/w. The effect of set temperature and API loading is summarized in Figure 4, at a constant angular frequency of 50 s^{-1} . This shows that both increasing temperature and increasing drug loading caused the melt viscosity to decrease. The highest measured viscosity (over 10^6 Pa.s) for pure polymer at 120°C was reduced to 115,000 Pa.s at the same temperature at 40 % w/w API. Viscosity of pure polymer reduced to 6,000 Pa.s when temperature was increased to 160°C. Increasing temperature provides the polymer molecules with greater mobility allowing them to flow more freely whereas plasticizers act to reduce the internal resistance of the polymer melt by effectively lubricating the flow of polymeric chains. Attaining a suitable polymer viscosity is important in melt processes such as extrusion.

Extrusion experiments were performed at a range of drug loadings (0 – 40 % w/w API), temperatures (120, 140 and 160°C) and throughputs (200 – 800 g/hr). Different throughputs were used in order to provide a range of shear strain rates, thus allowing the rate dependence of the material's rheology to

be investigated. It was not possible to examine the full matrix of drug loadings and set temperatures due to process limitations; at low set temperatures and low drug loadings, excessively high torque was generated on the extruder screws; conversely at high temperature and high drug loadings the extruded material had insufficient melt strength to handle. A summary of the experiments performed is shown in table 2, detailing feed rates achieved and limitations encountered.

Figure 5 shows measured average pressure drop at each of the three locations in the rheological die, for 20 % w/w API at 160°C at a range of set throughputs. At each throughput a linear fit was applied to the pressure drop and used in Equation (2) to calculate wall shear stress. Pressure in the die increased with increase in extruder throughput. Shear viscosity values, calculated using Equations (1) to (3) are shown in Figure 6 for each API loading at a set extrusion temperature of 140°C. For each material, a shear thinning effect was observed, in agreement with the off-line rheometry results previously shown in Figure 3. The plasticization effect of the API was also clearly observed, with shear viscosity decreasing from 1150 Pa.s at 20 % w/w API to 233 Pa.s at 40 % w/w API at an apparent shear strain rate of 15 s⁻¹.

In-process rheometry is also useful for real-time monitoring of melt viscosity during extrusion at a constant throughput. Figure 7 shows three overlaid plots of viscosity measured during extrusion at 140°C with 20, 30 and 40% w/w API loading. A clear discrimination between measured viscosity at the three drug loadings was apparent, although fluctuation in viscosity values was also observed in each case. Such measurements can be used as a quality control indicator, using statistical process control and trending analysis to detect deviations from the desired set point.

Shear and complex viscosities measured during extrusion and using oscillatory rheometry are compared at 140°C for 20% w/w API in Figure 8. It is clear that the whilst the gradient of shear thinning behavior observed from both techniques was comparable, there was a significant difference between the two sets of measurements, viscosity measured in-line being more than an order of magnitude lower than complex viscosity measured off-line. This is an important observation and warrants discussion as to whether the discrepancy resulted from differences between the measurement techniques or from the consistency of the polymer and API being measured. In polymer rheology, the Cox-Merz rule³³ is an empirical relationship which states that for many polymeric systems the steady state shear viscosity plotted against shear rate corresponds closely to the complex viscosity plotted against angular frequency, allowing pressure driven flow and oscillatory deformation to be compared directly. The rule has been studied in detail³⁴ and found to hold for most polymer melts, although it may not hold for more complex binary and tertiary mixtures or for polymers which exhibit thermal

sensitivity. This may explain partially the observed differences in viscosity measured here, with the polymer and API mixture exhibiting a more complex rheology than a pure polymer, with the API acting as a plasticizer and possibly lubricating the flow within the extruder die. However, it is also likely that the thermal history of the material at the point of measurement also had an effect on the measured viscosity. For example, the polymer and API mixture tested in the oscillatory rheometer was prepared for testing by heating the powdered mixture statically between two parallel plates. Inconsistencies and problems such as cavitation and bubbles have been reported to result from this method³⁵. In contrast the material measured in-line at the extruder die had been extensively mixed and sheared throughout the extrusion process prior to measurement. It appears likely that this exposure to high temperature and mixing had an effect on the consistency of the flow properties of the compound, increasing the level of plasticization and mixing. This area warrants further investigation in order to get a better understanding of rheology of such API-polymer dispersions change during and after the twin screw extrusion process.

By extrapolation of the measured pressures along the length of the rheological die it was also possible to calculate the exit pressure drop. This has been used in rheometry to provide an indication of the elastic component of flow³⁶. Figure 9 shows calculated exit pressures during extrusion at 160°C for 10, 20 and 30 % w/w API. Exit pressure was found to increase with increasing shear rate in each case. These measurements displayed a clear discrimination between drug loadings not only in magnitude of exit pressure drop but also in the rate of increase with shear rate. This indicates that the elastic component of flow may be more sensitive than shear viscosity to small changes in materials properties for the polymeric solid solution studied here. Linear fits were applied to the exit pressure versus shear rate data for set temperatures of 140 and 160°C, as shown in table 3. Both gradient and intercept were found to decrease with increasing temperature and increasing drug loading. These results suggest that the exit pressure could be a useful complementary variable to shear viscosity to monitor during HME.

Overall, the in-process rheological measurements provided useful data relating to the consistency of the extrudate, reflecting the influence of API loading, polymer and set extrusion conditions. This method is non-intrusive to the melt flow, low cost, relatively simple, and provides a real-time indication of the status of the HME process. Rheometry could be used either as a quality control tool during HME (i.e. continuous monitoring at constant process conditions) or as a development tool during set-up of a new HME process, for example to monitor process dynamics during start-up, the effect of step changes, to provide an indication of API miscibility, or viscosity related factors for API thermal degradation.

Conclusions

An instrumented slit die rheometer designed to fit a pharmaceutical grade twin screw extruder has been developed and used to monitor hot melt extrusion of a development API within a copolymer matrix. Results showed that the compound displayed shear thinning behavior in the mixtures tested and that shear viscosity decreased with increase in API loading, reflecting miscibility of the API within the polymer matrix. Viscosity and die exit pressure were found to be heavily dependent upon both API loading and set temperature, with exit pressure being more sensitive to API loading. The results demonstrate that in-line rheometry is a useful non-intrusive real-time technique, which could readily be applied as a PAT tool to deepen knowledge of hot melt extrusion of pharmaceutical systems.

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Declaration of Interest

None.

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Code	Die	Zone	Zone	Zone	Zone	Zone	Zone	Zone	Zone	Zone	Zone
		10	9	8	7	6	5	4	3	2	1
T160	160	160	160	160	150	140	110	80	35	20	10
T140	140	140	140	140	130	110	100	80	35	20	10
T120	120	120	120	120	110	100	90	80	35	20	10

Table 1: Set temperature (°C) profiles along the extruder barrel from die face to zones decreasing in number towards the feed throat

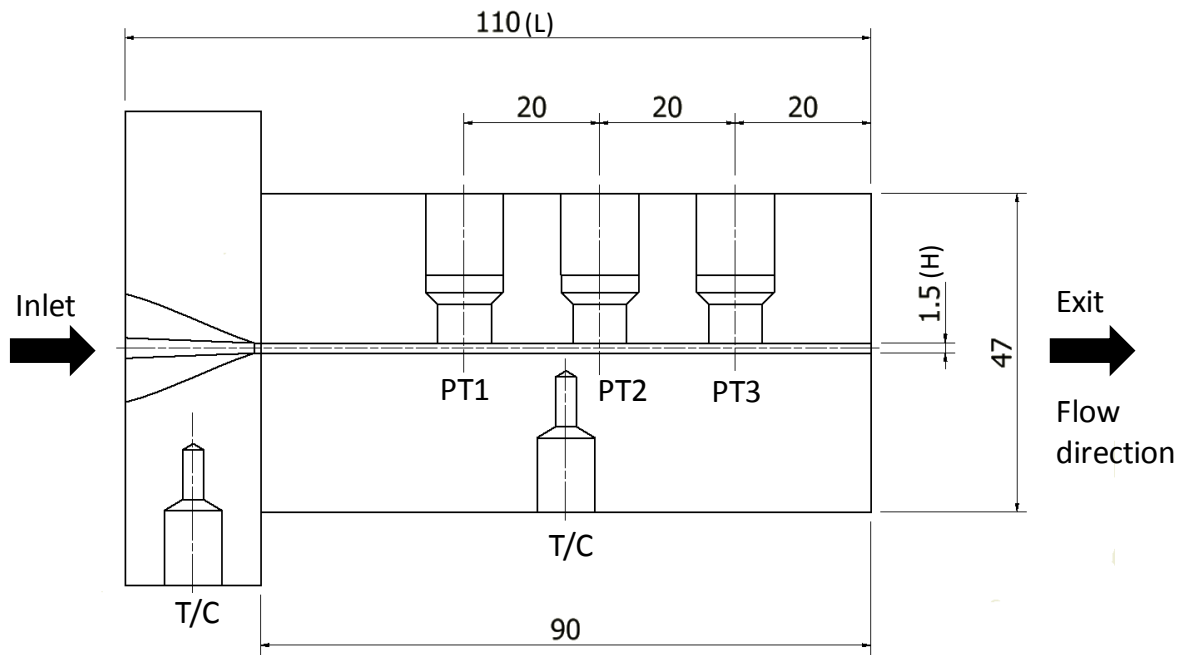
	120°C	140°C	160°C
0% API	■	■	200-350
10% API	■	200	200-350
20% API	■	250-400	250-500
30% API	■	300-800	200-600
40% API	200-300	250-800	□

■ = over pressure / over torque, □ = melt strength too low

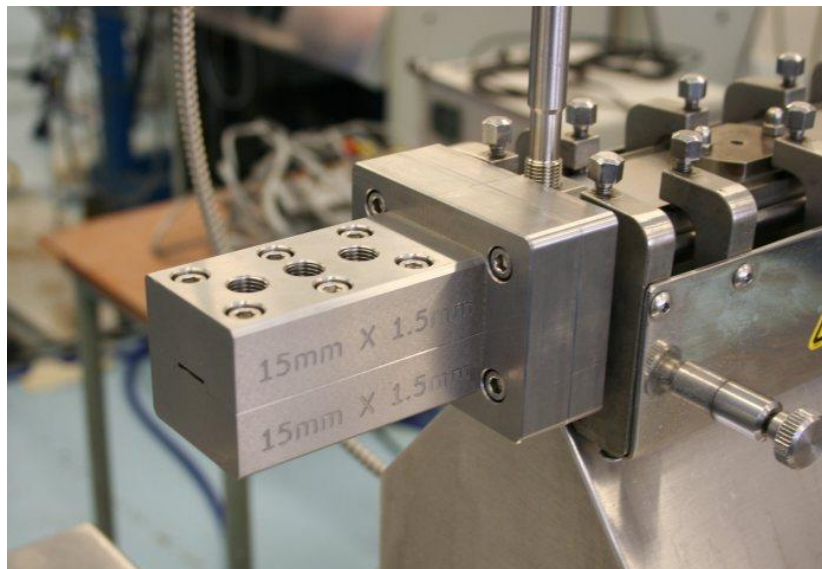
Table 2: Range extruder throughputs (g/hr) achieved and related process constraints

Set temperature (°C)	API loading (% w/w)	Gradient (x10 ⁻³ MPa.s)	Intercept (MPa)
140	10	13.9	0.204
140	20	4.8	0.176
140	30	1.8	0.100
160	10	1.3	0.098
160	20	0.8	0.088
160	30	0.5	0.075

Table 3 – Gradient and intercept of predicted exit pressure vs. shear strain rate at 140 and 160°C,
from linear fits



(a) Schematic representation of die cross-section, dimensions in mm
 (T/C denotes thermocouple locations; PT denotes pressure transducer locations)



(b) Attached to the Pharmalab extruder (without heater bands and sensors)

Figure 1 Rheological extruder die

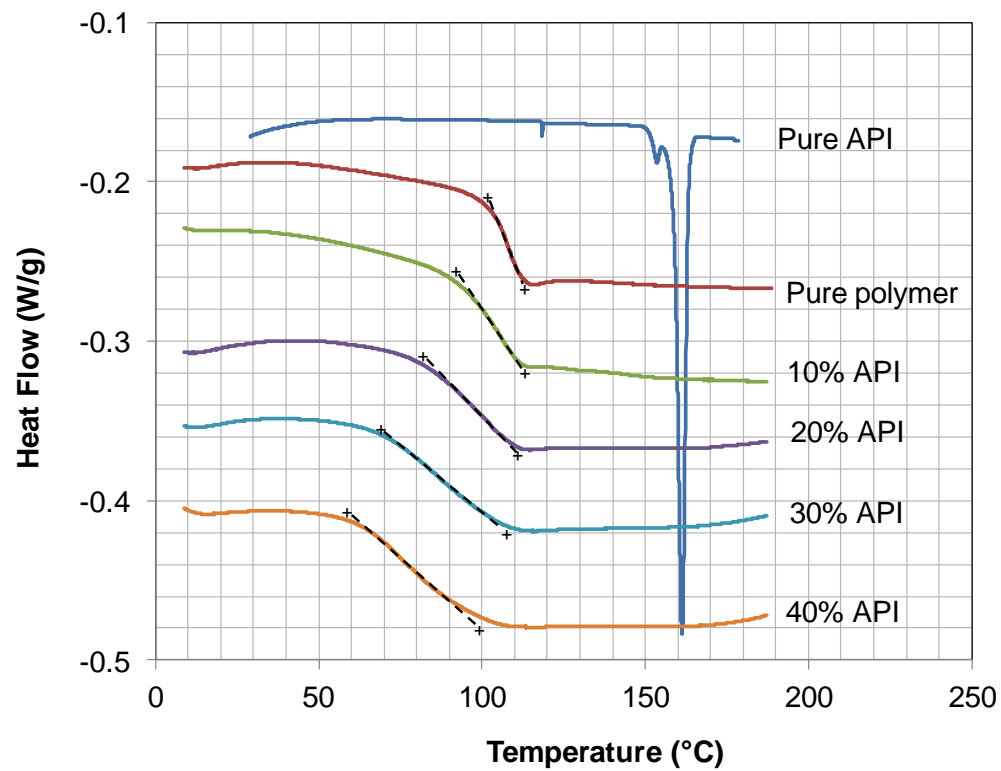


Figure 2 DSC thermograms showing initial heating of pure API and polymer; and second heating of physical mixtures (exotherm up, dashed lines indicate glass transition)

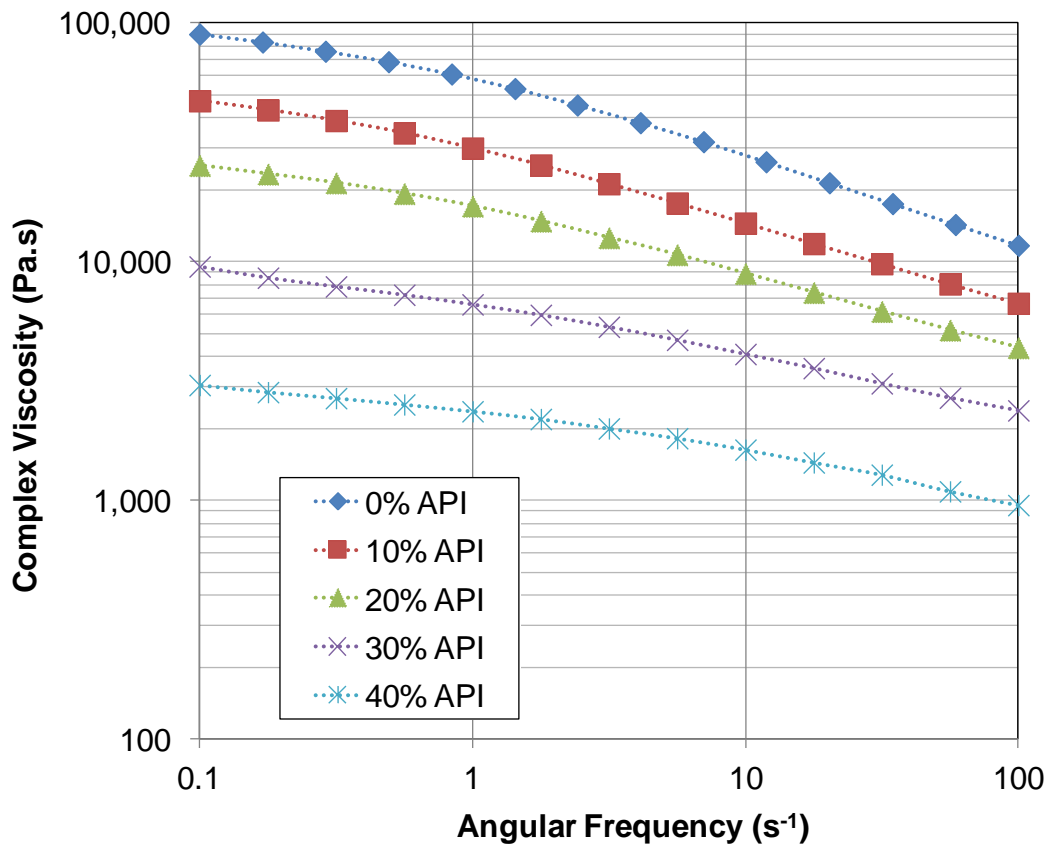


Figure 3 Effect of API loading on complex viscosity at 150°C;
measured by parallel plate oscillatory rheometry

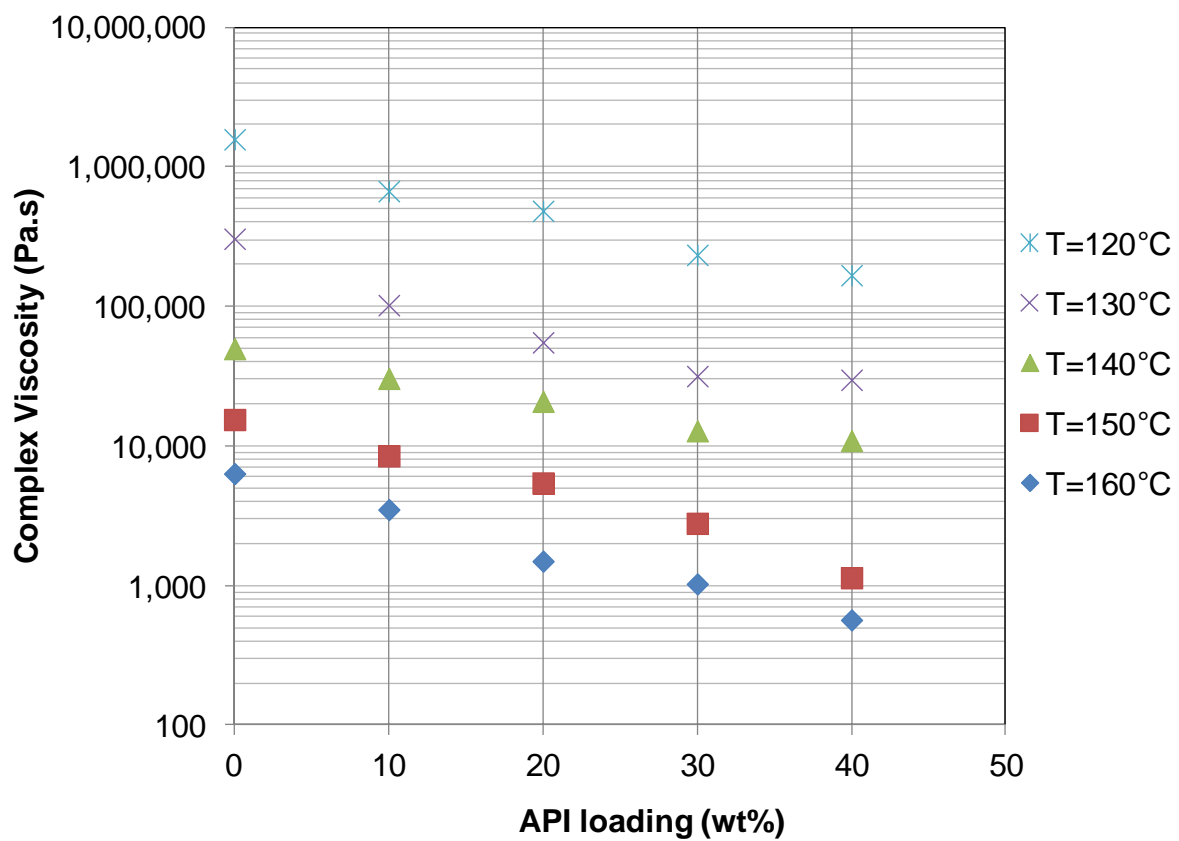


Figure 4 Effect of drug loading and temperature on complex viscosity at a constant angular frequency of 50s^{-1} ; as measured by oscillatory parallel plate rheometry

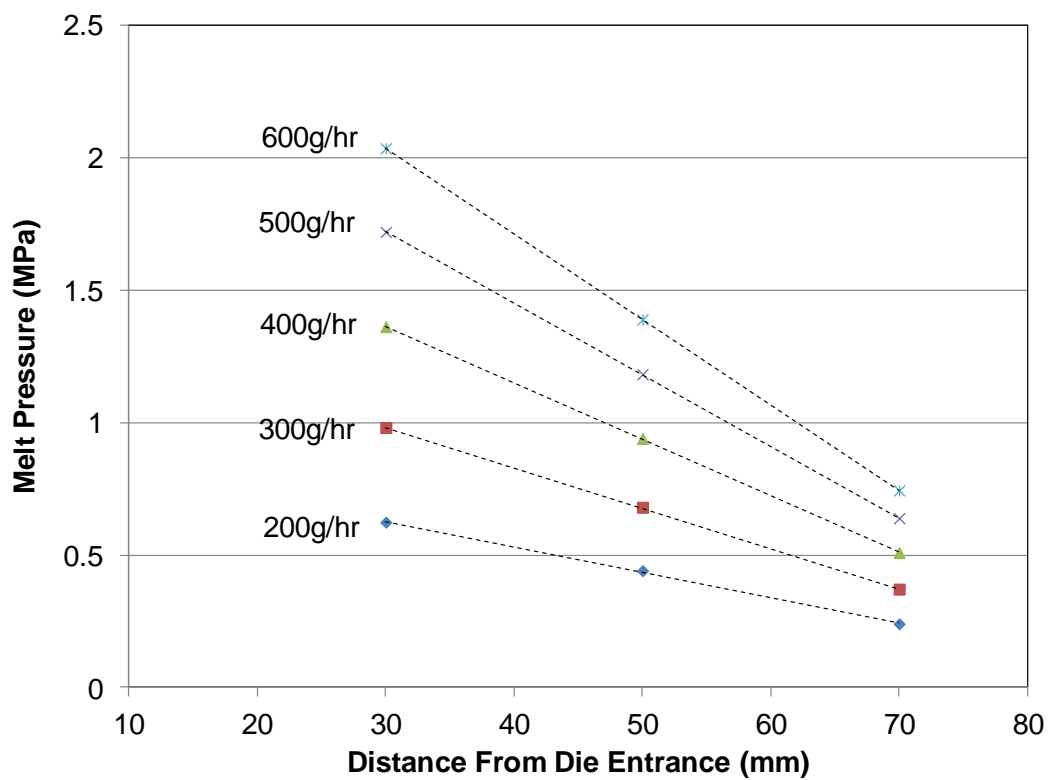


Figure 5 Measured in-line rheometer pressure drop; 20% API, 160°C

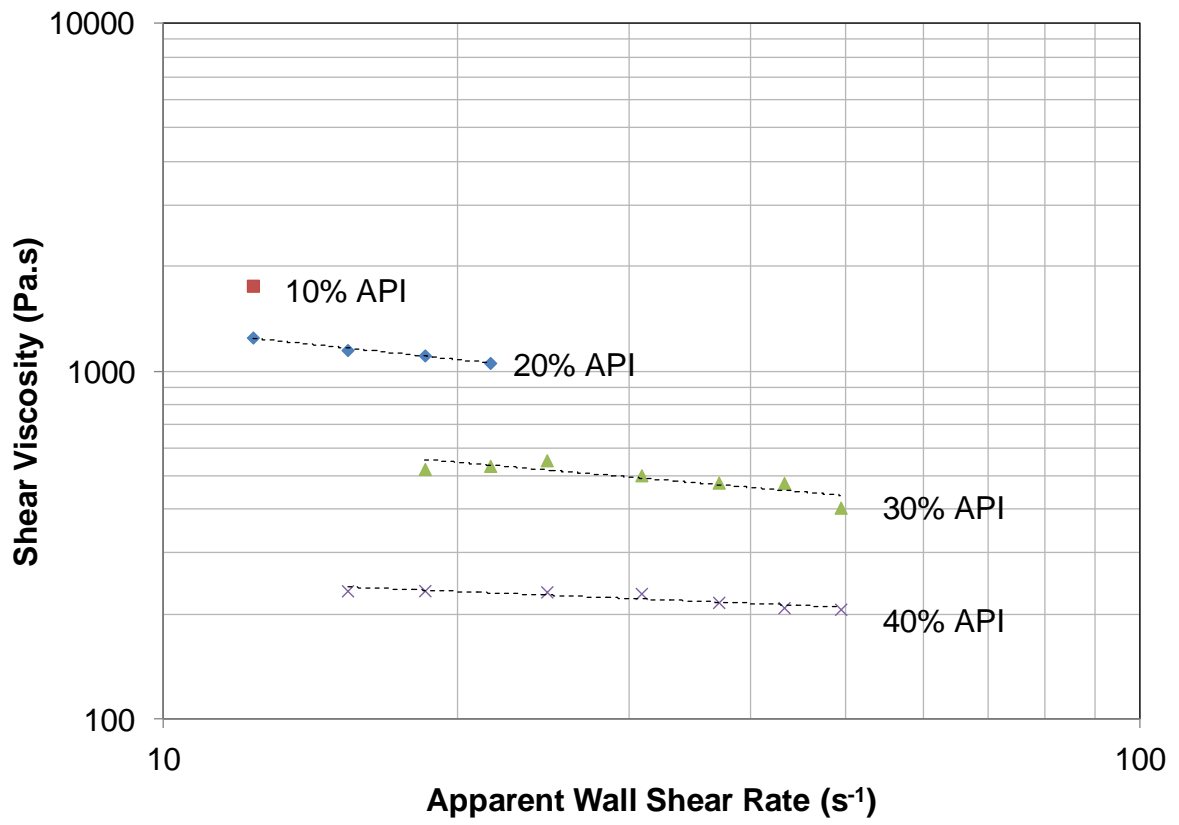


Figure 6 Effect of drug loading on measured shear viscosity during extrusion at 140°C

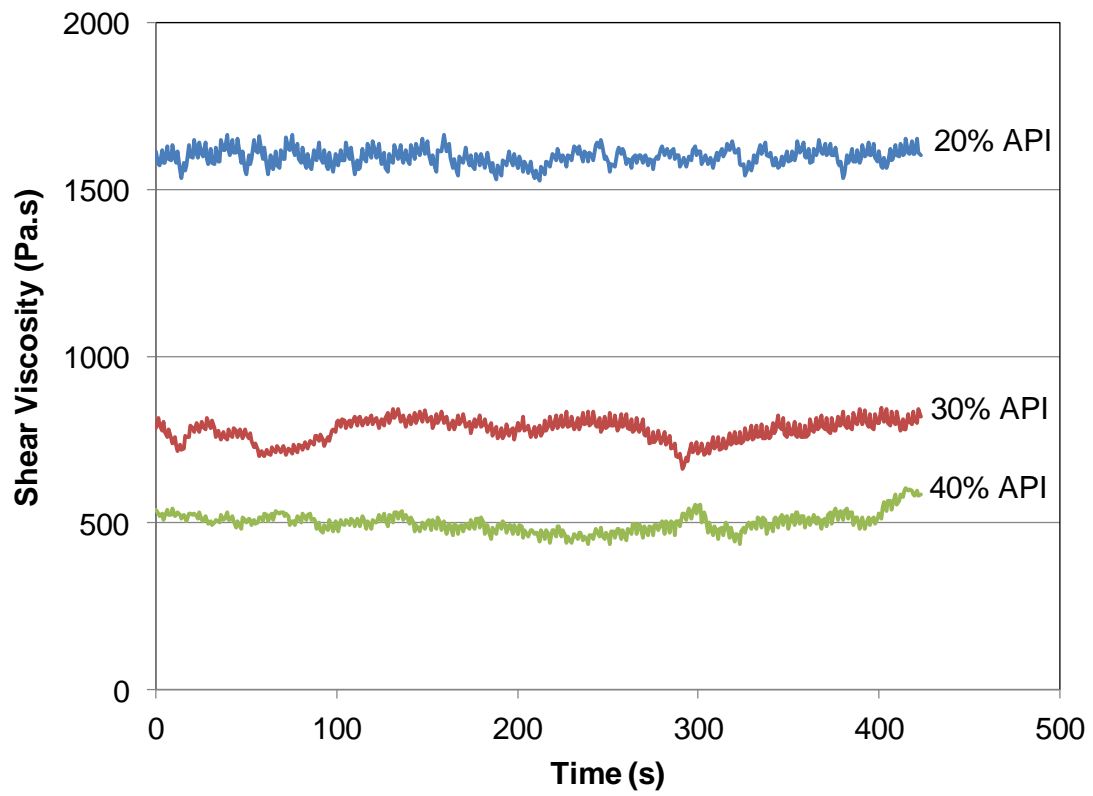


Figure 7 Measured viscosity during extrusion; effect of drug loading at 140°C

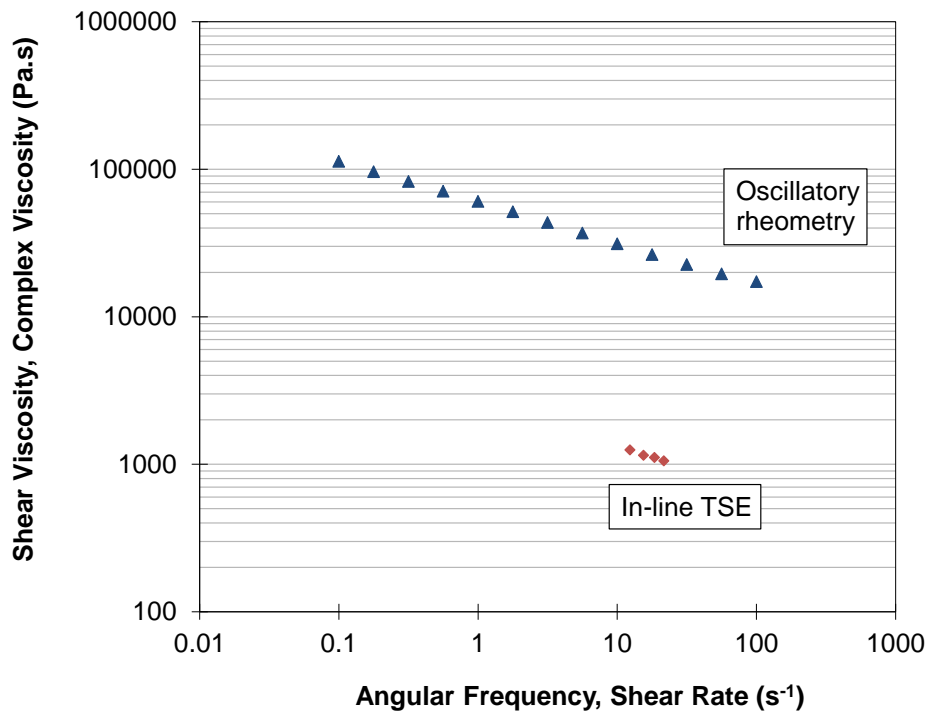


Figure 8 Comparison of in-line shear viscosity and off-line complex viscosity;
 20% w/w API at a set temperature of 140°C

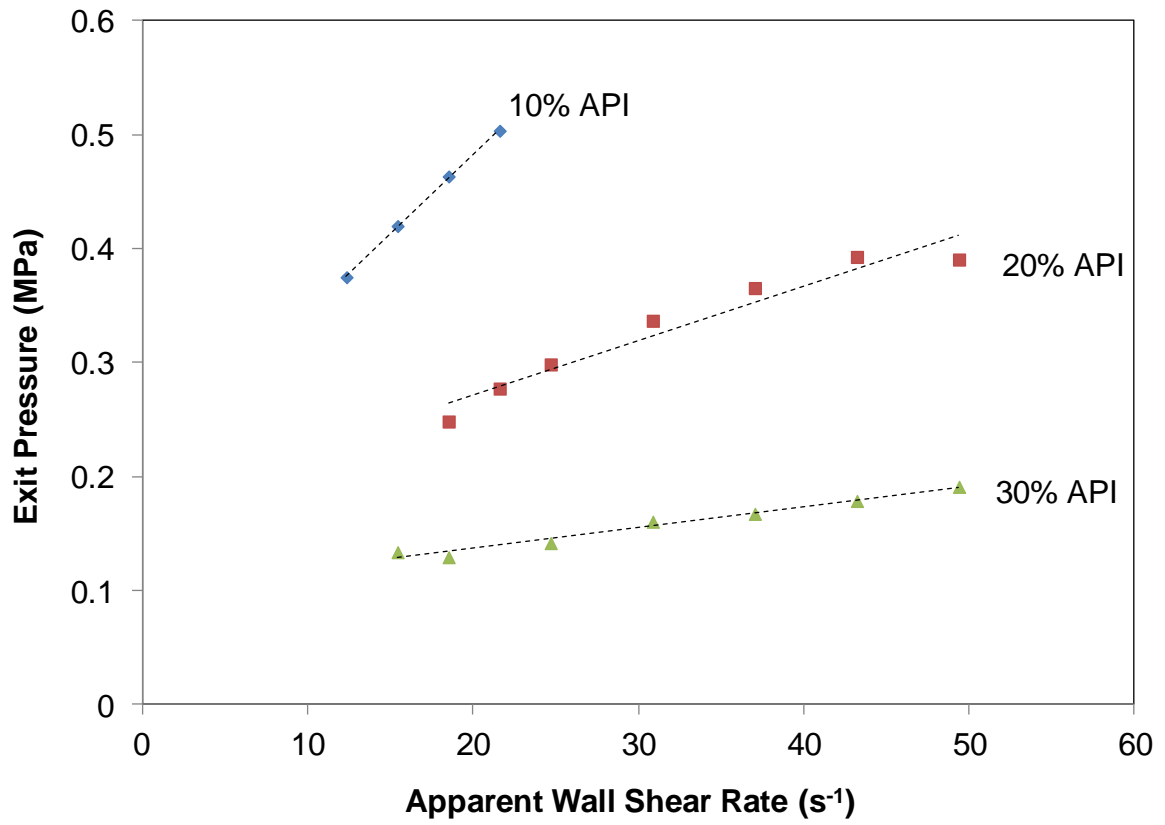


Figure 9 Effect of drug loading on exit pressure during extrusion at 160°C