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The kinetics of drug dissolution in polymers during hot-melt extrusion

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ABSTRACT

THE KINETICS OF DRUG DISSOLUTION IN POLYMERS DURING HOT-MELT EXTRUSION

by
Huayang Fang

Extrusion has been a most important and widely used continuous process in polymer processing for over one hundred and fifty years. However, it has only been recently applied and adopted by the pharmaceutical industry to prepare solid oral dosage formulations with increased bioavailability for the poorly-water soluble drugs and controlled release characteristics for the water-soluble drugs. In pharmaceutical Hot-melt extrusion poorly water soluble drug particulates are mixed with water soluble polymer excipient particulates and fed in the extruder, where the polymer is melted, after which the drug particulates begin to dissolve into the polymer melt. Extrusion-generated mixing accelerates dissolution process. One issue concerning the pharmaceutical industry is the degradation of drugs when they are exposed to relatively high temperatures of the extrusion process (usually 100℃ above ambient). In order to keep drugs from thermally degrading and at the same time achieving complete dissolution, the dissolution kinetics of drugs (APIs) must be specified for any given excipient/API pair, and a variety of extrusion conditions. In this work the Brabender Batch Mixer is utilized to determine such kinetic data at different concentrations and temperatures by connecting the exponential torque decay after the introduction of the API to the API dissolution. The time to complete the decay is then associated with the average residence time needed for complete dissolution.

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by
Huayang Fang

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APPROVAL PAGE

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I dedicate this thesis to my beloved family.

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LIST OF SYMBOLS

t_D	Characteristic Diffusion Time
L	Phase Droplet or ligament Radius
m	Mass
t	Time/Residence Time
C	Concentration
D	Diffusivity
h	Thickness
Tm	Melting Temperature
Tg	Glass Transition Temperature
T	Temperature
μ_s	Viscosity of Suspension of Spherical Particles in Newtonian Liquids
μ_f	Viscosity of Newtonian Fluid
Ø/Øm	Particulate Volume Fraction in Polymer
y	Torque
N	Pre-exponential Number
k	Reaction constant
R^2	The Plotting Fitted Values
Ea	Activation Energy
R	Gas Constant

LIST OF SYMBOLS
(Continued)

AV	Average Value
SD	Standard Deviation
SE	Standard Error

CHAPTER 1

INTRODUCTION

1.1 Objective

Plastics Extrusion has been used in polymer processing for decades; However, it has only been recently adopted by the pharmaceutical industry to prepare solid oral dosage formulations with increased bioavailability for the poorly-water soluble drugs and controlled release characteristics for the water-soluble drugs (Maniruzzaman, Boateng et al. 2012). In the case of poorly water-soluble drugs, bioavailability enhancement is achieved through amorphization of the crystalline drug, by dissolving it into water-soluble, hydrophilic polymers, thus forming what is known as a solid solution. Specific intermolecular bonds with, and steric hindrance effects by the polymer chain prevent the drug from re-crystallizing. Although the extrusion process during the production of solid solutions typically takes place below the melting point of the drug, the potential of thermal degradation of the API still exist and is in fact a major concern preventing the universal applicability of the HME technique as a pharmaceutical manufacturing method. To achieve total dissolution of the API in the formulation while minimizing its potential thermal degradation, the dissolution kinetics of the API into the excipient must be known. In this work, we determine the dissolution kinetics of a model API into a polymeric excipient we by carrying out melt-mixing experiments using the Brabender Batch Mixer.

1.2 Background Information

1.2.1 Hot-melt Extrusion

Conventional extrusion was first invented for at the end of the eighteenth century (James et al., 2004). Since then, it has been used in the plastic, rubber, and food manufacturing industry to produce stuffs such as pipes, sheets, and bags. Hot-Melt Extrusion has emerged as a novel processing technology in developing molecular dispersions (solid solutions) of poorly water-soluble active pharmaceutical ingredients (APIs) into various hydrophilic polymer matrices. The Hot-melt extrusion technology has proven to be a robust method of producing numerous drug delivery systems and therefore it has been found to be useful in pharmaceutical industry as well (Andrews, 2010).(Crowley, 2007). HME involves the compaction and conversion of blends from a powder or a granular mix into a product of uniform shape (Breitenbach, 2002). During this process, polymer are melted and formed into products having different shapes and sizes such as plastic tablets, capsules, films, and implants for drug delivery. The extrusion process can be broken down to the following general process sections (Chokshi et al., 2004):

(1) Feeding of the extruder by hopper;

(2) Mixing, grinding, reducing the particle size, and kneading;

(3) Flow through the die;

(4) Extrusion from the die and further downstream processing.

Processing by HME can improve the bioavailability of the poorly water-soluble active pharmaceutical ingredients by dissolving them into water-soluble polymers. At the same time, oral dosages with controlled release characteristics can be produced by dispersing water-soluble APIs into water-insoluble polymers. The elementary steps of this process are identical to the ones involved in conventional plastics melt compounding by extrusion:

(1) Feeding particulates; (2) melting; (3) dispersive and distributive mixing; (4) devolatilization and stripping; (5) pressurization and pumping. However, for pharmaceutical hot-melt extrusion, the *API dissolution* is an additional and very important elementary step, along with melting of the polymeric excipient that precedes it, and mixing which accelerates the dissolution process. In the case of solid solutions, the drug's (API) dissolution is an additional and very important elementary step, along with melting of the polymeric excipient that precedes it, and mixing which accelerates the dissolution process.

HME provides several advantages over traditional available pharmaceutical processing techniques such as (1) Increased solubility and bioavailability of water-insoluble compounds; (2) solvent free process; (3) economical process with reduced production time, fewer processing steps, and a continuous operation; (4) capabilities of sustained, modified, and targeted release; (5) better content uniformity in products; (6) no needs for the compressibility of active ingredients; (7) uniform dispersion of fine particles; (8) good stability at changing pH and moisture levels and safe application in humans; (9) reduced number of unit operations and production of a wide range of performance dosage forms; (10) a range of screw geometries (McGnity et al., 2004).(Jones et al., 2008).(Grunhagen et al., 1995).(Singhal et al., 2011). However, the HME also have disadvantages as well. The main drawbacks of HME include thermal process (drug/polymer stability), use of high flow properties of polymers, and excipients required and not suitable for relatively high heat sensitive molecules such as microbial species and proteins (Grunhagen et al., 1995). (Singhal et al., 2011).

As mentioned above, the thermal degradation of drugs (API) is one of the major concern in pharmaceutical HME process. Producing an extrudate that contains a molecularly disolved API and at the same time not overexposing the API to high processing temperature for long time is one of the major objectives during the extrusion of solid solutions. To achieve the balance between complete dissolution of API and minimal thermal degradation of the API, the dissolution kinetics of the API particulates inside the molten polymeric matrix during extrusion must be known. Melting of the polymeric excipient, dispersive/distributive mixing, and API dissolution can occur simultaneously during extrusion. Therefore to determine the dissolution kinetics of API, the above phenomena must be isolated from each other. One way to achieving this is by exploiting the effect of polymer melting, dispersion/ distribution of API particulates and API dissolution on the melt viscosity of the polymer matrix: Melt viscosity decreases with heat. Addition of particulates in molten polymers increases the melt viscosity. Dissolution of an API into molten polymers generally decreases viscosity of virtue of plasticization.

In this work we determine the dissolution kinetics of Acetaminophen into Eudragit EPO by performing batch melt-mixing experiments using a specific addition protocol: We first melt-mix the polymer and allow it to reach steady state, then add the crystalline API quickly and in small quantities. In this way we minimize the effect of dispersion and distribution that occurs prior to and during the dissolution of the API. Following the addition of the API to the molten polymer, the dissolution kinetics are then determined from the drop in the torque of the processed formulation by virtue of the API plasticization of the polymer.

1.3 Distributive Mixing and Dispersive Mixing

Generally, the mixing processes in single or twin screw extruders is induced by laminar flow and is generally categorized into two types: dispersive mixing and distributive mixing. Dispersive mixing refers to the process involving the particle size reduction of particulate cohesive components such as fillers, polymer gels, or liquid droplets. Distributive mixing refers to expanding and stretching the interfacial area between the components lacking a cohesive force in between and distributing them uniformly throughout the volume of the molten polymer. Dispersive mixing is mainly controlled by the laminar shear or extensional forces and distributive mixing is mainly controlled only by the flow-generated strains and does not require high stresses. According to the definitions, the mixing of miscible liquids is regarded as distributive mixing, and mixing of hard solid agglomerates, immiscible liquids, and soft agglomerates is regarded as dispersive mixing (Tadmor, Gogos, 2006). The dispersive and distributive mixing of solid agglomerates is schematically shown in Figure 1.1.

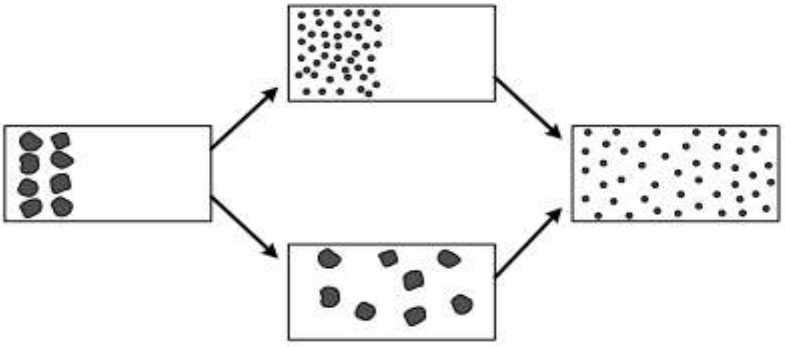


Figure 1.1 Dispersive mixing and distributive mixing of solid agglomerates and immiscible liquid droplets (Tasmor and Gogos, 2006).

Source: Z. Tadmor, C. G. Gogos (2006). *Principles of Polymer Processing,* John Wily & Sons, Inc. Hoboken, NJ, USA.

1.4 Dissolution of API Particles in Polymeric Melt

The dissolution of API within the polymer largely depends on their physicochemical properties. Good blended dispersions require miscibility between the drug and polymer (Marsac, 2009). In practice, the majority of drug/polymer systems cannot fully miscibility, they may likely to show only partial miscibility. This means that there exists a certain thermodynamic solubility of drugs in polymer matrixes. HME can be carried out in two distinctly different conditions, referred to here as Case I and Case II:

Case I: The processing temperature is above the melting temperature for a semi-crystalline polymer, or the softening temperature for an amorphous polymer, (T_g + 50 ~ 100 ºC) but below the melting point of a drug.

Case II: The processing temperature is above both the melting temperature and the softening temperature of semi-crystalline or amorphous polymers, respectively, and above the melting point of a drug. It is important to be noted that processing temperature should be the melt temperature instead of the set temperature of the processing equipment.

It should also be noted that the glass transition temperature of an amorphous polymer or the melting temperature of a semi-crystalline polymer may decreased if incorporation of the API (Crowley et al., 2007).

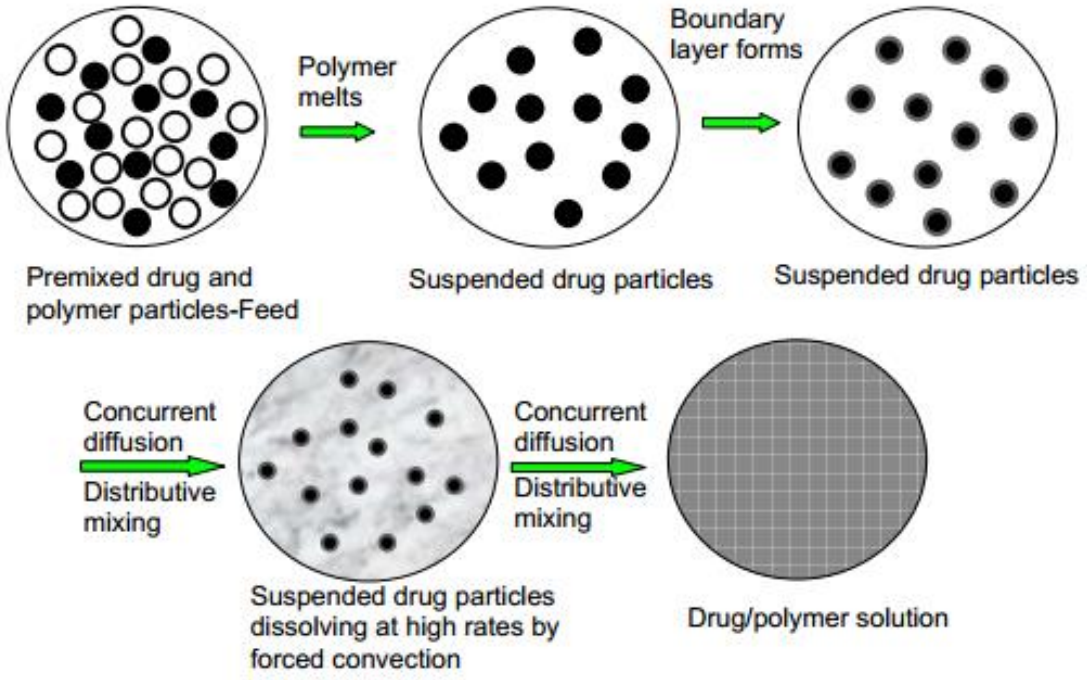


Figure 1.2 Schematic representation of the morphological changes of the drug and polymer system in the solution formation process for Case I.

Source: C.G. Gogos, H. Liu, P. Wang, in: Douroumis, *"Hot-Melt Extrusion: Pharmaceutical Applications,"* Wiley: Chichester, UK, 2012.

Case I provides a viable method to circumvent the thermal degradation issues. In Case I, the drug is processed below its melting point and mixed with a polymer melt, then the solid drug particles gradually dissolve into the polymer excipient melt. And this process should be able to provide a desirable polymer-drug solid dispersion or solid solution. During the HME process, the solid API act as a solute and the polymeric melt

act as a solvent. In addition, the dissolution rate and solubility of the API in the polymer will increase with higher temperature.

The dissolution process of the drug in the polymer melt is schematically shown in Figure 1.2. Firstly, the drug particles (black) and polymer particles (white) are fed into the batch mixer or an extruder. Then, the polymer particles start melting due to the conductive heat from the mixer or extruder barrel and frictional and plastic energy dissipation. These two phenomena result in a process charge state that the solid drug particles are suspended in a continuous polymer melt matrix. Then the polymer molecules start to heat up the API particles and create a mass transfer boundary layer. This layer shall be continuously wiped away and replaced with fresh polymer melt nearby. The drug molecules diffuse into the polymer melt through the boundary layer, and the size of the suspended drug particles will continue to decrease as the diffusion goes. Finally, a homogeneous *solution* will be formed.

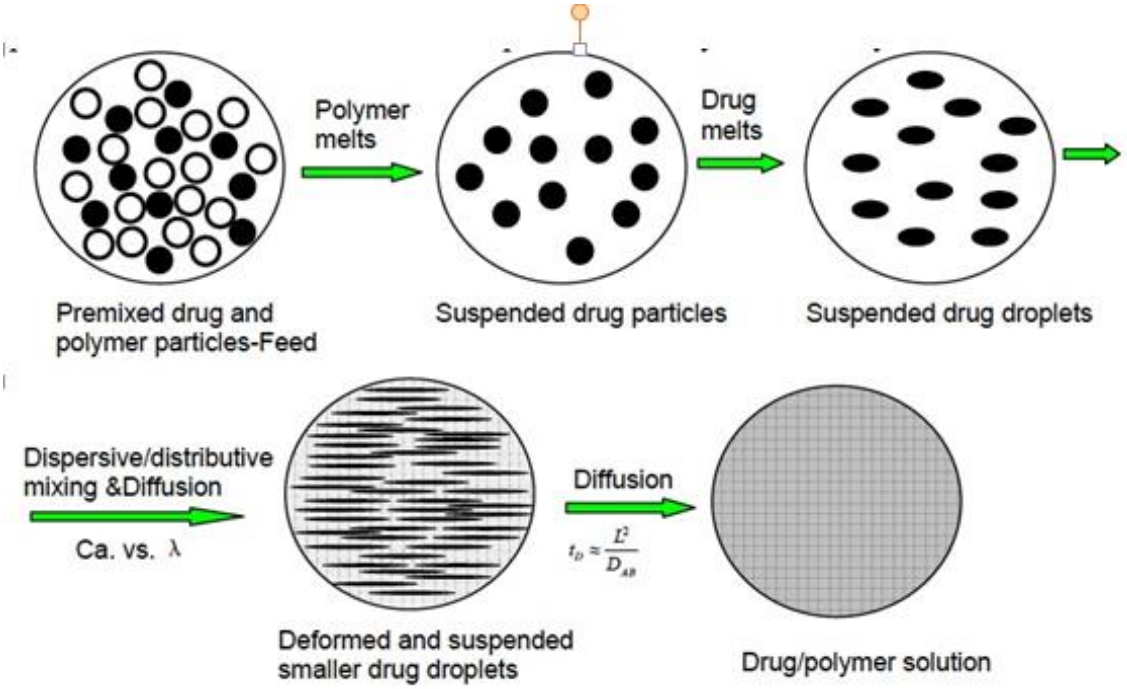


Figure 1.3 Schematic representation of the morphological changes of the drug and polymer system in the solution formation process for Case II.

Source: C.G. Gogos, H. Liu, P. Wang, in: Douroumis, *"Hot-Melt Extrusion: Pharmaceutical Applications,"* Wiley: Chichester, UK, 2012

Case II, on the other hand, involves miscible or partially miscible liquid-liquid mixing because both the polymer and drug will be melted. As shown in Figure 1.3, the drug (black) and polymer (white) particles are fed into an extruder and processed by the screw elements. Due to the heat transfer from the extruder barrel or a batch mixer, and frictional and plastic dissipation, the polymer particles will melt first. During or after the melting of the polymer, the drug particles will melt to droplets and be deformed by the mixing flows generated by the screws. The droplets will be deformed along the shear direction and blurred the contacting surface between the drug and polymer. As this process goes on and with diffusion continuously being carried on, we will finally get a homogeneous drug – polymer solution.

In both cases discussed above between either the dissolving API particles or the

drug droplets and the molten polymer, the diffusion will happened. The "characteristic diffusion time" t_D is proportional to the square of the API phase droplet or ligament radius L or the thin dimension D_{AB} of a sheet Equation 1.1.

$$t_D = \frac{L^2}{D_{AB}} \tag{1.1}$$

During the HME process, the relationship between the rate of dissolution of drug particles in molten polymer excipients, dm/dt, and the solubility, C_S, is described by the Noyes-Whitney as follows:

$$\frac{dm}{dt} = \frac{D \times A \times (C_s - C)}{h \times V} \tag{1.2}$$

where m = mass (mol), t = time (s), C = concentration of solute dissolved at a particular time ($mol \cdot cm^{-3}$), C_S = equilibrium solubility ($mol \cdot cm^{-3}$), D = diffusivity ($cm^2 \cdot s^{-1}$) , h = apparent thickness (cm) of the aqueous boundary layer (depends on rate of stirring and the temperature), and A = surface area available for dissolution (cm^2).

The equation shows that the drug particle size and size distribution are very important to the dissolution rate, since the total contacting surface area of the drug particles will be changed accordingly. We can expect a higher dissolution rate if the particle size gets smaller. Furthermore, the narrower the drug particle size distribution, the more uniform the total dissolution time distribution needed for complete dissolution of drugs in polymer melt will be (Liu, Gogos, 2012).

In order to raise the dissolution rate, the surface area available have to be consider. All of we know in extrusion process, the dispersive mixing may break up the drug agglomerates or individual particles due to the high shear forces generated by the high shear screw elements such as wide kneading blocks or Maddock elements (Tadmor, Gogos, 2006). Then, the total contacting surface area of the drug particles to the polymeric melt will be increased, thus the dissolution rate will increased. And the distributive mixing can homogenize the drug concentration dissolved in the polymeric melt, and leading more polymer melt into contact with the suspended drug particles. In this way, both effects can raise or maintain the dissolution rate.

If the mixer set temperature increases, on the one hand, the diffusion coefficient will increase due to the increased temperature and resultant decreased matrix viscosity; on the other hand, C_s also will increase. Both of these factors will contribute to an increase of the API dissolution rate in the molten polymer excipient. As the screw speed increases, the distributive mixing is improved within the chamber as well, and thus a higher concentration gradient around the drug particulates is available. Moreover, the thickness of the mass transfer boundary layer decreases as the screw speed increases. Both effects contribute to an increased dissolution rate.

CHAPTER 2

MATERIALS AND METHORDS

2.1 Materials

Acetaminophen (APAP) (Spectrum Chemicals, Gardena, CA) was used as the model crystalline API. APAP is a water-soluble BCS I drug with a T_m of 169–170 ° C. Acetaminophen consists of a benzene ring core, substituted by one hydroxyl group and the nitrogen atom of an amide group in the para (1, 4) pattern. The amide group is acetamide (ethanamide). It is an extensively conjugated system, as the lone pair on the hydroxyl oxygen, the benzene pi cloud, the nitrogen lone pair, the p orbital on the carbonyl carbon, and the lone pair on the carbonyl oxygen are all conjugated. The presence of two activating groups also make the benzene ring highly reactive toward electrophilic aromatic substitution. As the substituents are ortho, para-directing and para with respect to each other, all positions on the ring are more or less equally activated. The conjugation also greatly reduces the basicity of the oxygen and the nitrogen, while making the hydroxyl acidic through delocalization of charge developed on the phenoxide anion.

Eudragit® E is a copolymer composed of neutral methyl and butyl methacrylate, and dimethylaminoethyl methacrylate repeating units. It has a T_g ~45˚C. The molar ratio of three monomers, methyl methacrylate, butyl methacrylate and dimethylaminoethyl methacrylate, is 2:1:1 (Envonik, 2009). Two grades are available which have the same chemical structure and molecular weight: one is Eudragit® E PO (E PO) in powder form; the other is Eudragit® E 100 in granular form. This copolymer is soluble up to pH=5 and

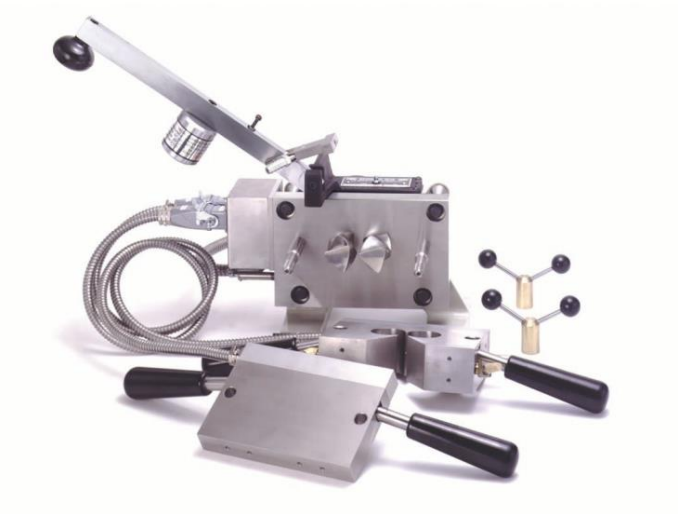
above this pH value is capable of swelling and becoming permeable to water. It is widely used for masking unpleasant tastes and odors of drugs, protecting drugs against moisture, and as a drug excipient for pharmaceutical applications.

2.2 Methods

2.2.1 Batch Mixer

A batch mixer is used to experimentally investigate the effects of extrusion process parameters on the drug-polymer mixing. The batch mixer is a heated high-shear laminar mixer, which has been extensively used in the plastics and rubber industry to simulate the extrusion process or optimize the formulation. The laboratory scale batch mixer used requires only 30-60 g of the material and many experiments can be performed in a short period, thus making it an attractive choice for the HME study (Ghebre-Sellassie and Martin, 2007). Furthermore, the screw speeds can be controlled separately without altering the residence time in a batch mixer, which is difficult to realize if an extruder is used.

All the runs were performed in a Brabender FE-2000 batch intensive mixer utilizing counter-rotating screws, as illustrated in Figure 3.1. The batch mixer barrel is heated electrically and cooled by air. The melt temperature sensor measures the actual processed material temperature during melting and mixing; the torque meter can record the resistance of material to the flow created by the counter-rotation of the screws. Generally, about 70-75 vol. % fill degree of the chamber is recommended for good mixing because the resulting “folding” of the free surfaces is beneficial to distributive mixing. The free volume in the mixing chamber is 60 cc.



(a)

(b)

Figure 2.1 The batch mixer (a) and roller screws (b) (Manufactured by Brabender Corp.)

Source: Liu, H. (May 2010). Hot Melt Mixing/Extrusion and Dissolution of Drug (Indomethacin) in Acrylic Copolymer Matrices. Otto H. York Department of Chemical, Biological and Pharmaceutical Engineering. Newark, New Jersey Institute of Technology. Ph.D Dissertation.

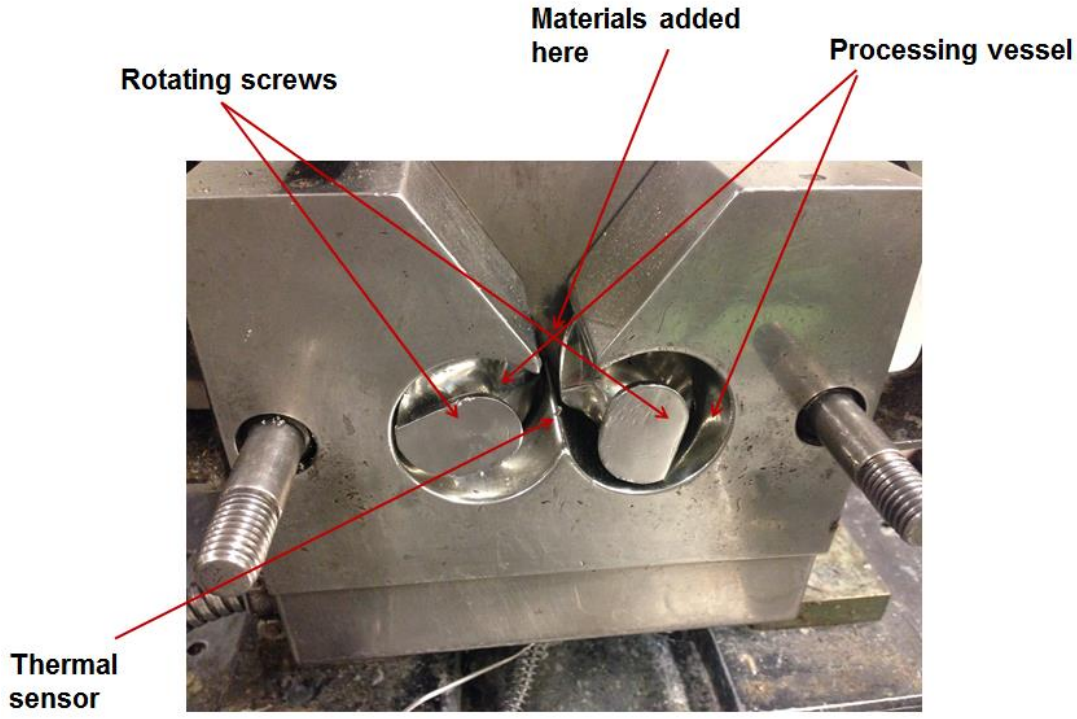


Figure 2.2 The inside of the assembled Brabender batch mixer (without the front plate).

Source: Z. Tadmor, C.G. Gogos, "*Principles of Polymer Processing*," Hoboken, NJ, USA, 2nd edition, 2006.

The Brabender batch mixer (Shown as Figures 2.1 and 2.2) was used for compounding of the materials. All the experiment runs were performed in a Brabender FE-2000 batch intensive mixer utilizing Σ-co-rotating screws, as illustrated in Figure 2.1. During mixing the torque arising from the resistance of material to the flow created by the counter-rotation of the screws, is recorded along with the melt temperature. The batch mixer barrel is heated with electrical power and cooled down by air. All the materials were mixed at 50 rpm for 20 min, while the set temperature of the mixer was 140°C. The polymer will be processed for 10 minutes before we add the additive.

CHAPTER 3

RESULTS AND DISCUSSION

3.1 Dispersion, Distribution, and Dissolution

To determine the characteristic constants that describe the dissolution kinetics of an API in a molten polymeric excipient, we melt-mixed the API in the polymer matrix at different concentrations and temperatures following the addition protocol mentioned in Materials and Methods.

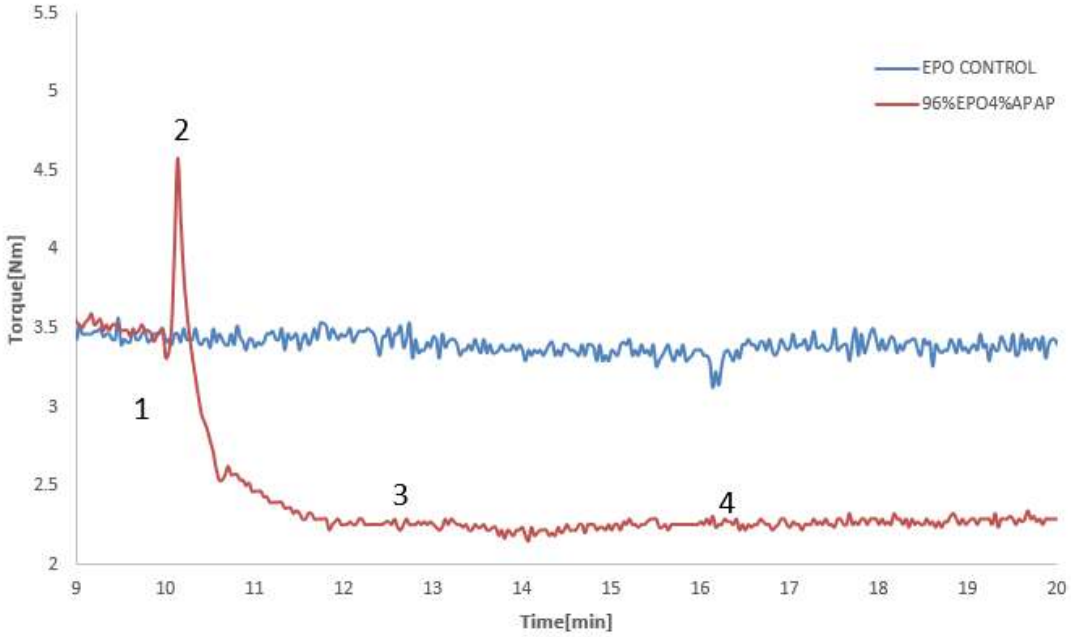


Figure 3.1 96%EPO-4%APAP vs. 100%EPO control**.**

Figure 3.1 compares the torque traces of pure EPO (control) and the sample containing 96%EPO-4%APAP. From the control sample, it can be seen that EPO has reached steady state at ~9 min. We can also see that the polymer remains stable for a another 11 min, giving us a processing window of 20 min, in which we melt the polymer,

allow it to reach steady state, then add the API, dissolve it, and finally allow the binary formulation to reach steady state. From the torque tracer of the sample with the drug, we can see that the formulation also remains stable for 10 min (after the addition of the API). In the sample with 4% API, the torque fluctuation before the point of the maximum torque after the addition of APAP, indicates the feeding surge, the wetting of the API particles surface and their dispersion and distribution in the molten polymer matrix. The final equilibrium torque is associated with the apparent viscosity of the dissolved drug/polymer melt mixture in the mixing chamber.

The dispersion, distribution and dissolution of an API occur at the same time after the addition of the API in the molten polymer. To minimize the effect of dispersion and distribution of the API in the polymer matrix, we have kept the addition time and the amount of API we are adding in the molten polymer to a minimum. The evolution of the torque trace resulting from the addition of the API in the molten polymer can be used to approximate the amount of the API dissolved while it is dispersed and distributed in the molten polymer matrix. To do this we divide the torque trace into the following parts: 1-2 is the part beginning with the addition of the drug and ending at the maximum value of torque recorded during after the drug is added. 2-3 is from the point where torque is maximized until the drug fully dissolves. 3-4 is the steady state torque following the dissolution of the drug (respective points on Figure 3.1). The following "cartoon representation" of the evolving state of dispersive mixing and dissolution (Figure. 3.2) is also used to help depict the phenomena occurring above:

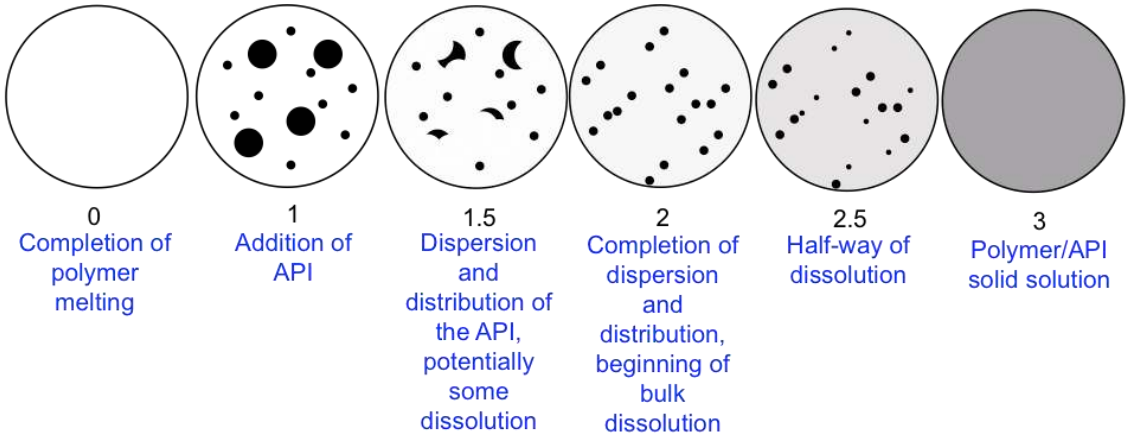


Figure 3.2 Cartoon representation of the dispersion, distribution and dissolution of APAP in molten Soluplus.

For polymer matrices filled with particulate additives of dimensional aspect ratios near unity, that is, nearly spherical, the rheological behavior at low volume fraction concentrations φ_v < 10% resembles the shear thinning nature of the unfilled polymer matrix, except that the viscosity is higher and increases with particulate concentration. In other words, as expected from suspension theory, the suspended particulates do not interact strongly and do not form a particulate network structure. Figure 3.3 plots the steady state ratio of the viscosities of suspensions of spherical particles in Newtonian liquids, μs, to the viscosity of Newtonian fluid, μf (blue data points). It was constructed by Tomas using the data of a number of investigators. A variety of uniform-sized particles having diameters of 1-400 μm were used. They included PS and polymethyl methacrylate (PMMA) beads, rubber latex, and glass spheres. To avoid settling, either the density of the suspending medium was adjusted or a medium of high viscosity was used. The maximum packing density was determined by extrapolating a plot of ***1/[(μs/μf)-1] vs.*** φ to zero, giving φm = 0.625, very close to that of randomly packed spheres of equal size.

Table 3.1 Suspension/fluid and Standard Error (SE)

APAP %	Suspension/fluid	SE
3	1.14	0.028359
4	1.16	0.009616
5	1.20	0.051369
10	1.52	0.048851

In Figure 3.3 we also plot the torque ratio (which is proportional to the viscosity of the molten materials) of point 2 over point 1 (red data points, values in Table 3.1) for different drug concentrations and compare these with the viscosity ratios of suspensions from Tomas. It can be seen that for both data sets, the viscosity ratios for similar volume fractions of added/suspended particles are very close. This is a strong indication that, only a small portion of the added API has dissolved during the dispersion and distribution of the API particles in the molten polymer matrix (between point 1 and 2). If a substantial portion had dissolved, then the viscosity ratios for the API particles would be significantly lower compared to these for non-dissolving particles, due to the plasticization effect of the dissolved API on the polymer. Therefore we can safely assume that the part of the curve corresponding to the dissolution of the API (points 2 to 3) is due to the full amount the drug added in the molten polymer.

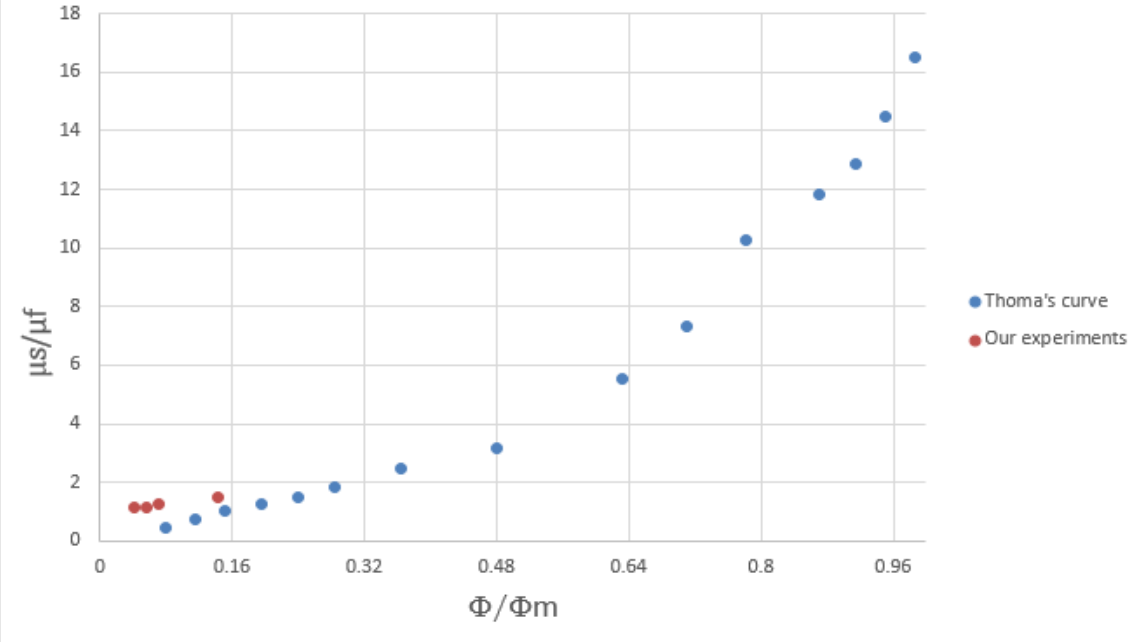


Figure 3.3 Comparison of viscosity ratios of suspensions (Thomas et al) and viscosity ratios of suspended drug particles in molten polymer matrix (this work)**.**

3.2 Dissolution

3.2.1 Drugs Concentration Effect

Figure 3.5 shows the torque traces corresponding to the dissolution process of the API into the molten polymer (points 2-4 in Figure 3.1) of formulations containing different amount of APAP. Since the dissolution of a crystalline API is a physical reaction, it can be described by rate laws governing chemical reactions. The differential rate law describes how the rate of reaction varies with the concentration of various species, drugs in this case, in the system. The rate of drugs dissolved is proportional to the rate of change in concentrations of the drug, meaning, the rate is proportional to a derivative of a concentration. The rate of the change either increases or decreases as time passes. In exponential decay, the rate of change decreases over time - the rate of the decay becomes slower with increasing time. Since the rate of change is not constant across the entire

graph, these functions are not straight lines. Generally, there are three reaction orders, such as zero order, first order, and second order. As Table 3.2 showing below:

Table 3.2 A Characteristic Plot of Rate Law

Reaction Order	Differential Rate Law	Integrated Rate Law	Characteristic Kinetic Plot	Slope of Kinetic Plot
Zero	$-d[A]/dt = k$	$[A]=[A]_0 - kt$	[A] vs. t	- k
First	$-d[A]/dt = k[A]$	$[A]=[A]_0 \exp(-kt)$	ln[A] vs. t	- k
Second	$-d[A]/dt = k[A]^2$	$[A]=[A]_0/(1+kt[A]_0)$	1/[A] vs. t	- k

In this work, we consider the rate in torque drop to be proportional to the rate of dissolution of the API in the molten polymer, by virtue of the plasticization effect of the API. We can, therefore, plot [**A**] vs. t, ln[**A**] vs. t, and 1/[**A**] vs. t to determine the reaction rate order which the dissolution of the API corresponds to.

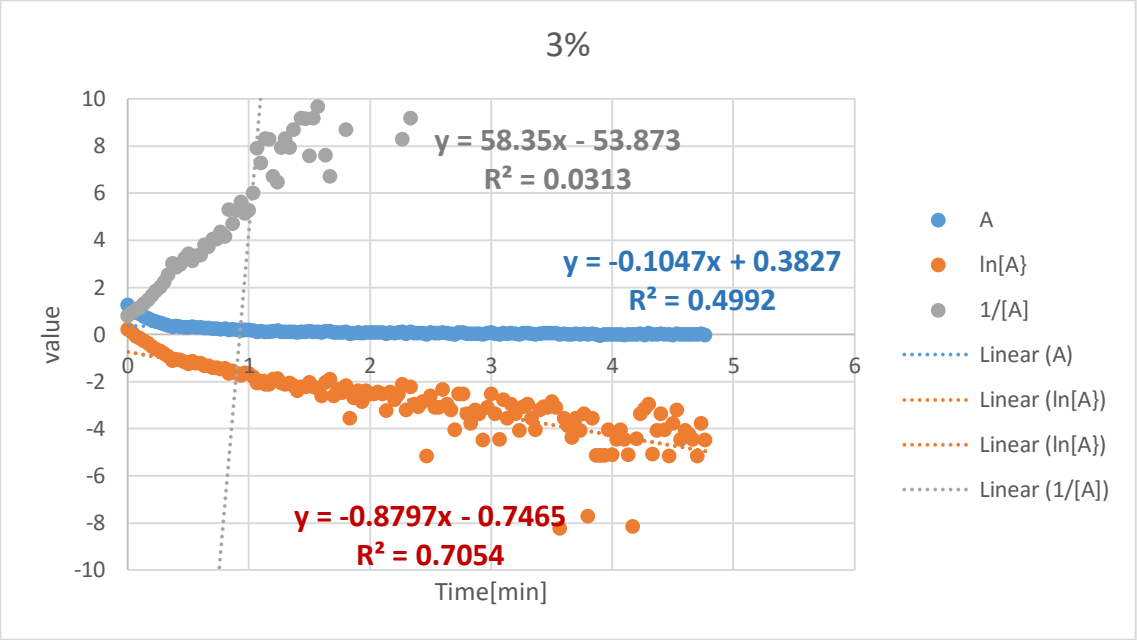


Figure 3.4 The relationship of [A] vs.t, ln[A] vs.t, and 1/[A] vs.t.

Figure 3.4, shows the torque of 4% APAP plotted as [A], ln[A], and 1/[A] with time t. From the trend lines corresponding the above plots, we see that the best approximation to a straight line is obtained from a first order reaction (R^2= 0.7054), where R^2 is "The Plotting Fitted Values": a statistical measure of how close the data are to the fitted regression line.

Table 3.3 The Function of Dissolution Curve in Each Order.

Zero Order	$y = 58.35 \times t - 53.873,\ R^2 = 0.0313$
First Order	$y = -0.8797 \times t - 0.7465,\ R^2 = 0.7054$
Second Order	$y = -0.1047 \times t + 0.3827,\ R^2 = 0.4992$

Because 0.7054 > 0.4992 > 0.0313, we consider the dissolution of APAP to be characterized by *first order reaction kinetics*. That is:

$$\mathbf{y = Ne^{(-kt)}} \tag{3.0}$$

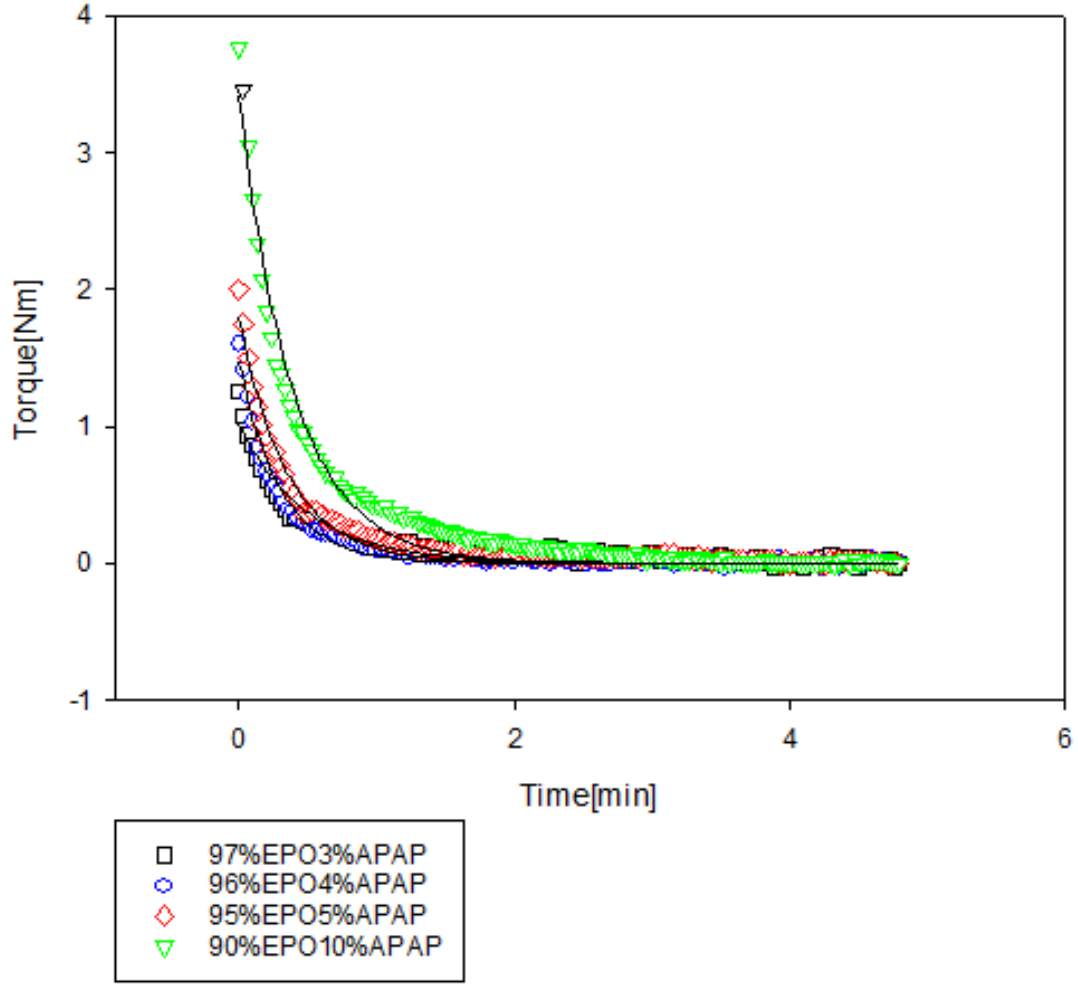


Figure 3.5 Torque decrease of the melt processed formulation during the dissolution of various amount of APAP.

Figure 3.5 shows the torque decrease of the melt-processed formulation due to the dissolution of different concentrations of APAP, curve fitted with the exponential decay model, while Table 3.4 shows the calculated parameters of the exponential decay model for the different concentrations of APAP. The torque drop evolution due to the

dissolution and the resulting *plasticization effect of the dissolved APAP on the melt viscosity of Soluplus* is consistent with the amount of drug added to the molten polymer: For the highest concentration of API added (10%) the initial toque at which the dissolution of the API begins, is highest compared to the lower concentrations due to the higher volume fraction of suspended solid particles in the melt, as discussed above. Additionally, the drop in torque for the highest concentration of drug is also the highest, since it involves the largest fraction of the dissolving drug, which acts as a plasticizer for the polymer melt.

Table 3.4 Exponential Decay Model Parameters

Concentration	3%	4%	5%	10%
N[Pre-exponential Number]	1.01	1.48	1.79	3.41
k	2.01	3.31	2.83	2.53
$\mathbf{R^2}$	0.93	0.98	0.97	0.97

The physical meaning of the parameters of the exponential decay function are as follows: (**N**) is the scaling factor of the decay function and corresponds to the value of the y-axis (torque/viscosity) at t=0 (before any dissolution takes place). In our case (**N**) corresponds to the highest value of torque, which is proportional to the amount of the added API, following the addition, dispersion and distribution of the API in the polymer melt, and the initiation of the API dissolution (point 2 in Figure 3.1). Plotting the value of (**N**) vs. the initial concentration of APAP in the formulation yields a straight line, the slope of which denotes the proportionality between the amounts of API added and the

corresponding increase in the torque of the melt. (**k**) in the exponential decay function indicates the decay rate of the material's torque or viscosity due, in this case, to the dissolution rate of the API. We consider this to be a constant with an average value of 2.46 ± 0.24, the relative standard error being within acceptable range (< 10%).

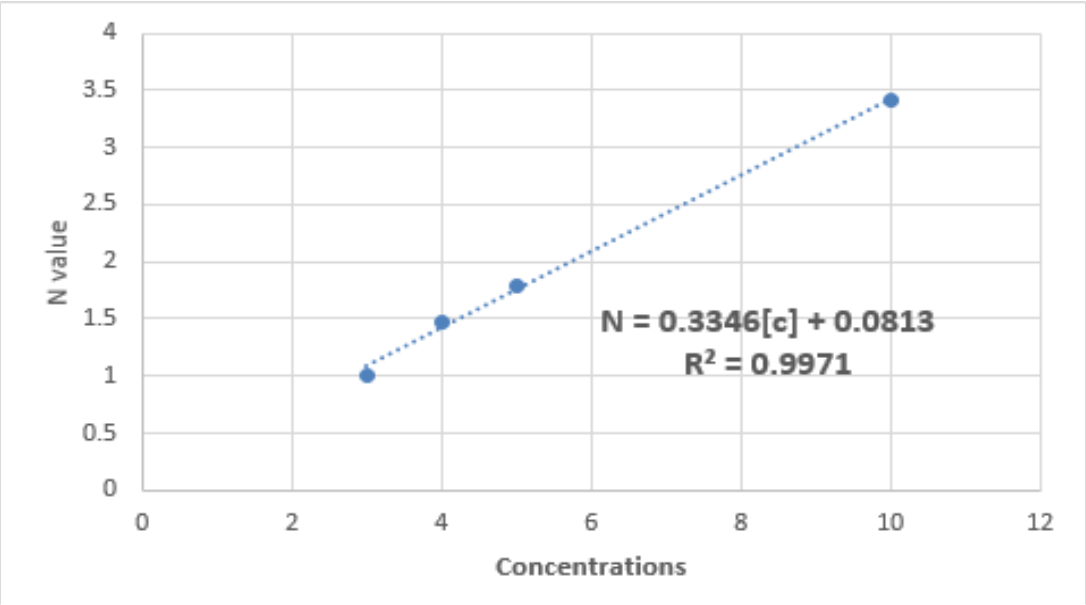


Figure 3.6 The relationship between **N** and Initial APAP Concentration.

Table 3.5 [**k**] Value Results at Different Concentrations of added particulate APAP with Standard Deviation and Standard Error Values

Concentration	3	5	10	AV	SD	SE
k	2.01	2.83	2.53	2.46	0.41	0.24

The result obtained indicate that **k** is not a function of the initial concentration of the added APAP.

3.2.2 Dissolution of the API at Different Processing Temperatures

To determine the relationship between dissolution of the API and processing temperature, as well as the activation energy for dissolution, we carried out experiments *at a fixed API concentration (4%)* at three different temperatures, namely, 130˚, 140˚ and 150˚C. We

chose these three temperatures, because they are within the "HME Processing Window" for the APAP/EPO system. Figure 3.7 shows the torque drop of the molten formulation after the addition of 4% APAP at these three different temperatures.

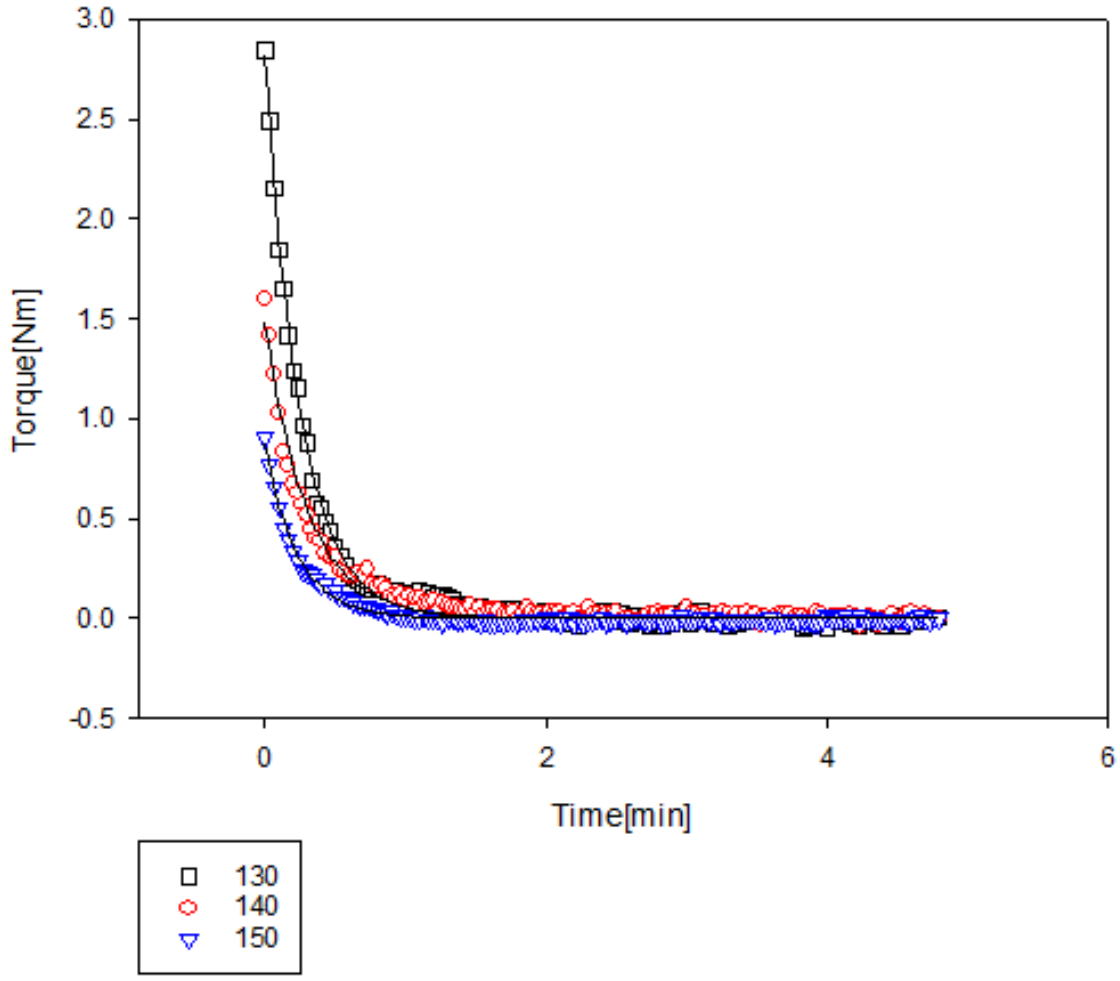


Figure 3.7 Torque Decay Values due to the Dissolution of 4% APAP at 130˚C, 140˚C and 150˚C.

Table 3.6 Model Parameters in Different Temperature

Temperature(°C)	130	140	150
N[Pre-exponential Number]	2.81	1.48	0.87
k	3.99	3.31	4.31
R^2	0.99	0.98	0.99

Table 3.6 lists the parameters determined from curve fitting of the exponential decay model to the experimental data obtained at different temperatures.

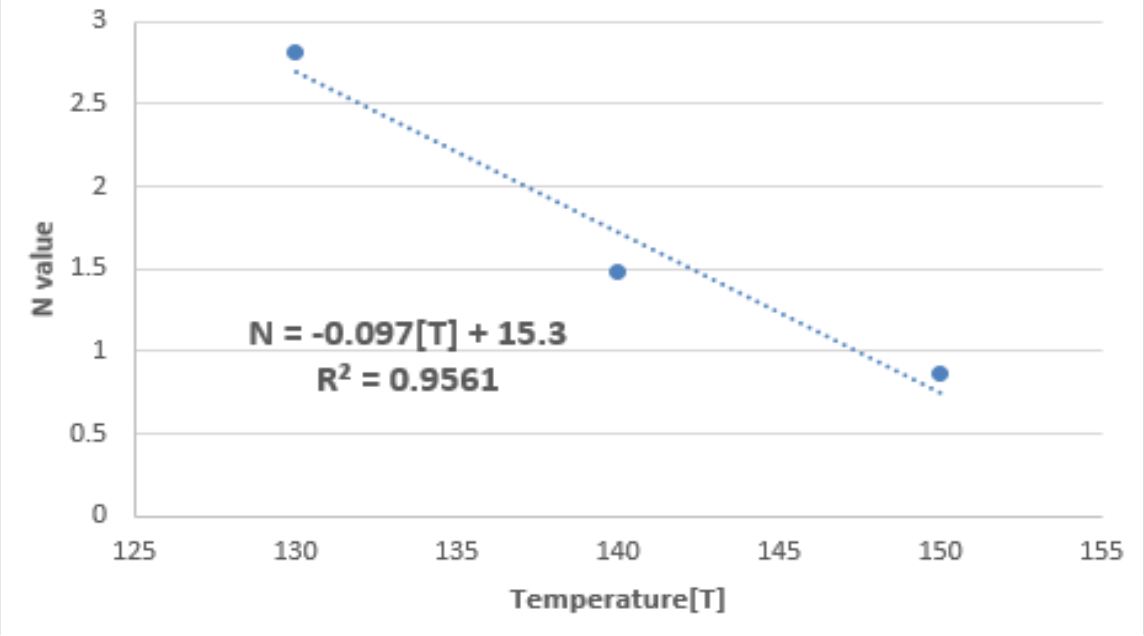


Figure 3.8 The relationship between **N** and Temperature.

According to the Arrhenius Equation, describing an "Arrhenius rate process" the k value can be represented as follows:

$$\ln k = \ln k_0 - \frac{E_a}{RT} \tag{3.1}$$

The ln[k] is a function of $[\frac{1}{T}]$, the slope of Equation 3.1(Slope $= \frac{d_{\ln[k]}}{d_{\frac{1}{T}}}$) equals $\frac{E_a}{R}$ which R refers gas constant and E_a can be defined as the minimum energy required to start a reaction (Generally, $E_a = f(T)$). Table 3.7 lists the each ln[k] values corresponding to different temperatures. The value of slope ($\frac{d_{\ln[k]}}{d_{\frac{1}{T}}} = \frac{E_a}{R}$) can be regard as a constant value cause its Standard Error value is small enough (generally, less than 10% of Average value). So the activation energy for APIs dissolution process in excipients is insensitive for temperature [T] as present in Figure3.9.

Table 3.7 The relationship between ln[k] and $\frac{1}{T}$

T	130	140	150	AV	SD	SE
$\frac{1}{T}$	0.00248	0.00242	0.00236			
ln[k]	1.38459	1.19804	1.46177	1.30	0.13	0.08
$\frac{E_a}{R}$	558.199	494.968	618.549	557.2	61.8	35.7

The value and units of the Gas Constant **R** is: 8.3145[J/mol.ºK]. Therefore, the Activation Energy for Dissolution as measured by the viscosity decrease of the dissolving APAP in EPO system is E_a = (557.2)(8.3145) = 4.6 [kJ/mol] and does not vary with temperature in the range of 130 - 150ºC.

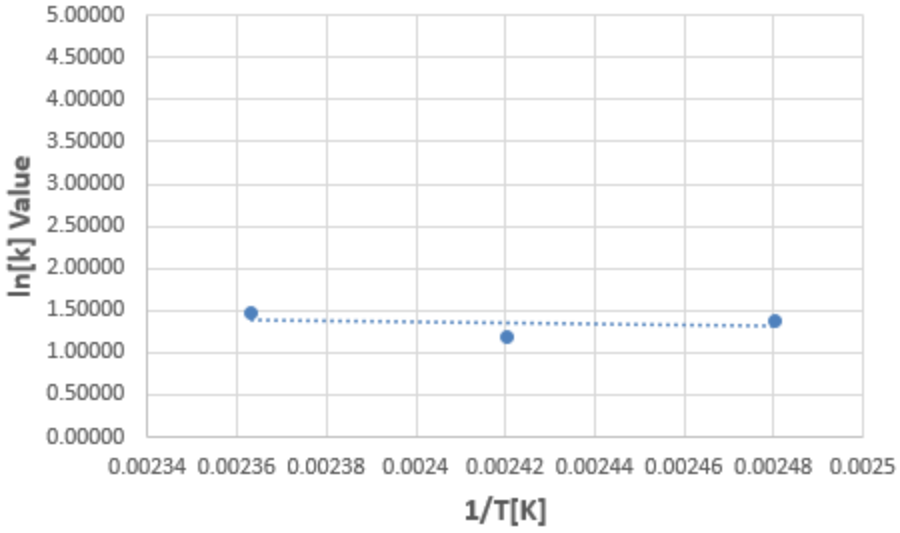


Figure 3.9 The relationship between ln[k] and $\frac{1}{T}$.

Using these two parameters **N** and **k** evaluated through the torque time decay results in the Brabender internal mixer, the exponential decay function can depict the kinetics of drug's dissolution in the APAP/EPO system in the API concentration range of 3 – 10% and in the Processing Temperature range of 130 - 150ºC. It was found that in these ranges, neither the drag concentration, nor the processing temperature affect **k**. On the other hand **N (that is, the torque or system viscosity)** is affected by both processing temperature and added APAP particulates concentration. The first dependence is Arrhenius in nature, and the second obeys the solid suspension viscosity-concentration behavior. Combining Figure 3.6 and Figure 3.8, the **N** behavior can be depicted by the function of concentration and temperature, shown in Equation 3.2 and Equation 3.3 below

$$N = 0.3346 \times [C] + 0.0813, \ R^2 = 0.9971 \quad (3.2)$$

$$N = -0.0972 \times [T] + 15.32, \ R^2 = 0.9561 \quad (3.3)$$

Thus, keeping temperature constant and different concentration of drugs we can use function Equation (3.4) to get its dissolution kinetics; conversely, for the same drug concentration but different process temperature, Equation (3.5) can be used to determine the time dependent dissolution $y = Ne^{(-kt)}$, where the **y** value equals **N** when **t** = 0 and when **t** = ∞ then **N** or **y** = 0.

$$y = N[0.3346 \times C + 0.0813] \times \exp(-k \times t) \quad (3.4)$$

$$y = N[-0.0972 \times T + 15.324] \times \exp(-k \times t) \quad (3.5)$$

The time required for the torque to reach a value equal to ($\mathbf{N/e^5}$) = 0.0067**N** (0.0165**N**) can be considered safely to be the time needed for complete dissolution of the APAP in EPO under given conditions in the experimental ranges used. And this time should be given as a guide to the appropriate average residence time to be used for HME.

CHAPTER 4

SUMMARY AND CONCLUSIONS

4.1 Summary

The NJIT/PPI research group studying pharmaceutical Hot Melt Extrusion, within which the author of this thesis worked, considers this process to be a *special case of reactive polymer compounding,* in which the particulate additive compounded *dissolves* during compounding. In other words, the dissolution process represents the "reaction", not a chemical one but a physical one. In this work, we examined experimentally the process of an API dissolving in polymer excipient with a focus of minimizing the effects of dispersive and distributive mixing after the addition of the API particulates into the molten EPO during batch mixing/processing in a Brabender mixer. In this way we were able to follow the exponential decay in the Brabender torque and determine the dissolution kinetics of the API, since it is the only physical process taking place after the addition of the API. The torque reduction is entirely attributable to the dissolution of the API, which acts as a plasticizer, reducing the polymer excipient viscosity. Acetaminophen (APAP) and Eudragit® E PO (EPO) were chosen as the model API and polymer. The experimental times required for the complete reduction of the torque under different processing conditions are taken as the minimum required residence times during Hot Melt Extrusion.

The analysis of the entirety of the experimental work conducted with APAP dissolving in EPO under different process temperatures and at different APAP concentrations, resulted in the specification of the two dissolution rates expressions,

namely, Equation 3.3. and Equation 3.4. The dissolution of APIs in polymer excipients is an exponential decay and characterized by two different decay function parameters, **N** and **k**.

With the two rate expressions (Equations 3.3. and 3.4) and specific values of the parameters for the APAP/EPO API/polymer excipient pair is possible for oral dosage engineers and scientists to *specify* the Hot Melt Extrusion (HME) *minimum residence times*, which will guarantee the complete dissolution of the API and at the same time *minimize the API degradation* during HME. All this eliminates the need of conducting costly and time-consuming HME experiments. Therefore, the work conducted in this thesis represents a powerful *methodology* of specifying the *HME process "operating window" for any API/Polymer excipient pair.*

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