Study of the drug release profile of novel polymer-drug matrix formulations prepared by hot melt extrusion

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Abstract

Hot Melt Extrusion (HME) is an emerging technology in the pharmaceutical industry for manufacturing drug delivery devices. In the HME process, the polymer and drug are melted and mixed with the help of heat and mechanical stresses. HME offers various advantages compared to other pharmaceutical processes; it is a solvent-free process, it is possible to manufacture different dosage forms including implants, tablets, granules, pellets, it can enhance the solubility and bioavailability of poorly water-soluble drugs, and it is a continuous process. However, due to the involvement of heat and shear stresses, the processing of heat-sensitive polymers, e.g. PLA, with drugs is challenging. Polylactide (PLA) is a bioresorbable FDA approved biopolymer. In recent years PLA has gained particular interest in the medical industry, and PLA-based drug-eluting implants are used in many different applications, including dental, cardiac, orthopaedic and tissue engineering applications. The benefit of using PLA-based drug-eluting implants is that they slowly release the entrapped drug and degrade naturally into non-toxic by-products over time, excluding the need for any surgical method for their removal. However, despite the advantages of HME processing, achieving consistent quality products can be challenging. One of the challenges faced by the pharmaceutical industry is that large ratios of new drug entities belong to class BCS II, which are poorly water-soluble drugs. Poor solubility of drugs has been a major hindrance to the development of more effective drug delivery methods. Soluplus (polyvinyl-caprolactam polyvinyl-acetate copolymer polyethylene glycol graft) is an amphiphilic polymer and has the ability to solubilise the poorly water-soluble drugs and has been developed to enhance the bioavailability of poorly water-soluble drugs.

In this work, we explore the production of drug-loaded PLA and Soluplus products with a HME process. Two different drugs, including ibuprofen and dexamethasone, are extruded with PLA. Further, ibuprofen which is a poorly water-soluble drug (melting point 77°C) is extruded with Soluplus. The purpose is to investigate the processability as well as the effect of drug loadings and processing conditions, including temperature and screw speed, on the drug release profile. DSC is used to study the miscibility of the polymer-drug matrix, FTIR is used to study the interaction of polymer-drug matrix, and drug-dissolution tester is used to study the percentage drug release.

Key Words: HME, PLA, Soluplus, ibuprofen, drug release profile

1. *INTRODUCTION*

Polylactic Acid (PLA) is a semi-crystalline polymer. PLA has some very useful characteristics, e.g., it has good mechanical properties and has shown better dimensional stability than other commonly used polymers, e.g., Polytertafluoroethylene (PTFE). PLA does not require a high processing temperature as it has a melting point in the range of 150-160°C. Another major benefit of using PLA is that it is biodegradable, which means that over time PLA based drug-eluting implants will naturally degrade into non-toxic by-products and removed from the body without the need of any painful surgical procedure, unlike permanent medical implants. Due to these properties, PLA has gained popularity in the medical industry in the last few decades, and it has been used for making temporary drug-eluting implants for different applications (Abd Alsaheb et al., 2015; Destefano et al., 2020; Pawar et al., 2014). However, the main challenge associated with PLA is it is a heat-sensitive polymer, and it tends to degrade when processed at a high temperature.

One of the main challenges faced by the pharmaceutical industry is that a large amount of newly developed drugs belong to class BCS II; which is poorly water-soluble drugs (Bhowmik et al., 2012; Schittny et al., 2020; Van Den Mooter, 2012). Solubility is an important physicochemical factor affecting the absorption and consequently

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the therapeutic effectiveness of the drug. To enhance the solubility and bioavailability of poorly water-soluble drugs is challenging, and different methods have been developed to tackle this issue. Different methods which have been used to enhance the solubility of poorly water-soluble drugs, include liquisolid, microionization of the drug, addition of surfactants, and solid dispersion. However, presently solid dispersion has proved to be a promising method to enhance the solubility and bioavailability of poorly water-soluble drugs. Solid dispersion is a method in which a drug is dispersed in a polymer carrier matrix (Nikghalb et al., 2012). HME well known method to prepare solid dispersion; HME is a process in which drug is melt and mixed with the polymer with the help of temperature and mechanical stresses (Tiwari et al., 2016). In a HME process drug is dispersed within polymer at molecular level, and this in turn can help to enhance the dissolution and bioavailability of poorly soluble drugs (Saerens et al., 2014). In solid dispersion the drug can either be in crystalline or amorphous form. With the amorphous form of drug enhanced dissolution rates are achieved, but one of the main challenge associated with amorphous solid dispersion (ASD) is that it is a metastable state which means that the drug can return to crystalline form with time (Saerens et al., 2012).

Soluplus is a polyethylene glycol graft polyvinyl caprolactam-polyvinyl acetate copolymer. Soluplus is specially designed polymer to prepare a solid solution. Soluplus can solubilise poorly water-soluble drugs and results in enhancing the bioavailability drugs (BASF, 2019). In the literature, Soluplus has been used with different poorly soluble drugs, and the results have shown increased dissolution rates (Agrawal et al., 2016; Shamma & Basha, 2013). In this study, Soluplus is used with ibuprofen. Ibuprofen is a poorly water-soluble drug, belong to non-steroidal anti-inflammatory drugs (NSAID); it is commonly used for pain relief and fever (Jan et al., 2012).

This work aimed to prepare polymer drug formulations for controlled release using HME. For this purpose, two different polymers including PLA and soluplus were used with ibuprofen and dexamethasone. The effect of different processing conditions on the drug release profile of polymer drug matrix was studied. In this work HME is used to prepare polymer drug formulations to study the drug release profile of polymer drug matrix. aforementioned HME can help to form solid dispersion, so this aspect would be advantageous to process Soluplus with ibuprofen. In the case of PLA with ibuprofen and dexamethasone, processing can be challenging, as PLA is a heat sensitive polymer, and it tends to degrade in the presence of mechanical stresses and high temperature.

2. MATERIALS

PLA ($C_3H_4O_2$) grade Ingeo^{TM} Biopolymer 2003D and was purchased from NatureWorks LLC. Soluplus was purchased from BASF. Ibuprofen and dexamethasone were purchased from Sigma-Aldrich Ltd.

3.EXPERIMENTS

A twin-screw extruder was used to prepare polymer-drug samples. Before processing, polymers were dried in the oven for 4 hours at 65°C. PLA was mixed with ibuprofen and dexamethasone separately, and Soluplus was mixed with ibuprofen and fed to the twin-screw extruder. Table 1 lists the composition and processing conditions for all the samples

Table 1. polymer-drug formulation produced using HME

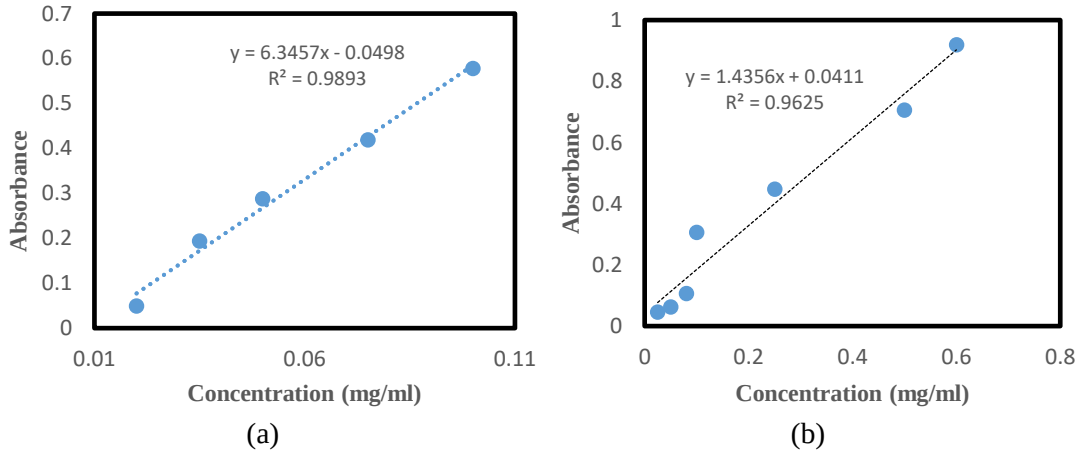
Sample	Polymer	Drug	% Drug	Temperature ('C)	Screw speed (rpm)
1	PLA	Ibuprofen	5%	180	100
2	PLA	Ibuprofen	5%	160	50
3	PLA	Ibuprofen	1%	180	100
4	PLA	Dexamethasone	5%	180	50
5	PLA	Dexamethasone	10%	180	50
6	Soluplus	Ibuprofen	10%	100	50

4. CHARACTERISATION

4.1. DRUG RELEASE STUDY

USP dissolution tester apparatus was used to study the percentage release profile of the polymer drug matrix (see figure 1). After extrusion (24 hours after processing) weighted polymer-drug samples were placed inside the tank filled with 500 ml Phosphate buffer solution (PBS) with pH 7.4. The apparatus was set at 37°C and 50 rpm. In the first hour, a 1 ml sample was taken every 10 mins. After the first hour samples were taken after 2, 3,4,5,6, 22, 24, 28 and 48 hours. After taking the sample, tanks were again filled with same amount of PBS solution to keep the volume of the PBS constant during the process. Samples were analysed using a UV-vis spectrophotometer. To study the dissolution profile of all the samples, a standard calibration curve for ibuprofen and dexamethasone was calculated (see figure 2a &2b). For the ibuprofen standard calibration curve, the stock solution was prepared by taking 1 mg of ibuprofen in 500 µL PBS. Six different dilutions were prepared from the stock solution with following concentrations: 0.025 mg/ml, 0.05 mg/ml, 0.08 mg/ml, 0.1 mg/ml, 0.25 mg/ml, 0.5 mg/ml, and 0.6 mg/ml. The same procedure was repeated for calculating the dexamethasone calibration curve. The percentage release profile of all the samples was calculated using standard procedure (Jan et al., 2012; Shah et al., 1997).

Figure 1. Dissolution tester to study the %drug release



(a) (b)

Figure 2. (a) standard calibration curve for dexamethasone, (b) standard calibration curve for ibuprofen

4.2. FTIR

All extruded samples in the form of films were analysed using FTIR. FTIR was used to study the polymer drug interactions.

4.3. DSC

Differential scanning calorimetry was used to study the solid state of ibuprofen in soluplus. Three cycles were used, first the sample was heated from 30-250°C using 10°C/min heating rate, then in the cooling cycle sample was cooled using a -10°C/min cooling rate, followed by a second heating cycle alike to first heating cycle. Sample measurements were recorded in a nitrogen atmosphere.

3. *RESULT*

Ibuprofen is a poorly soluble drug, while PLA is known as hydrophobic polymer, and for this reason, in literature, PLA has not been extruded with poorly water-soluble drugs. The purpose of processing PLA with the ibuprofen was to investigate the extrudability of PLA with ibuprofen, to study the effect of processing conditions on the drug release profile and to study the miscibility of ibuprofen with the drug at given processing conditions. The glass transition temperature of PLA is around 60-65°C, and the meting point is 150-160°C. As a rule of thumb, the extrusion temperature is usually 40-50°C higher than the melting point of the polymer. However, here to extrude PLA with the ibuprofen, two temperatures, 160°C and 180°C, were selected, and to process PLA with dexamethasone, a 180°C temperature was maintained. The reason for choosing these temperatures is that it was not possible to extrude PLA below 160°C with the drug. At the same time, a temperature higher than 180°C was not selected to avoid the degradation of polymer and drug. In the case of PLA and ibuprofen, to study the effect of processing conditions on the drug release profile, two different temperatures, two screw speeds and two drug loadings, were used. Figure 3 (a) shows the drug release profile of PLA loaded with ibuprofen. Table 2 lists the percentage of drug release after 48 hours. When the concentration of the ibuprofen was kept constant, and temperature and screw speed were varied (sample 1 & 2) not much difference could be observed in the drug release profile studied over the 48 hours, both samples showed an almost similar trend. A very slow-release profile was observed for sample 1 & 2, and only 6.63% and 6.59% drug was released respectively after 48 hours. On the other hand, with lower drug concentration at higher temperature and screw speed (sample 3 compared with sample 2), comparatively faster drug release was observed with 29.43% drug released after 48 hours. However, during the drug release study, the percentage of drug released kept on fluctuating; it kept on increasing and decreasing and a regular trend could not be observed. A similar case was also observed with PLA and dexamethasone. For PLA and dexamethasone again a very slow-release profile was observed, and only 4.96% and 2.79% drug released after 48 hours for sample 4 and sample 5 respectively. For sample 4 and sample 5, when the temperature and screw speed were kept constant and only the drug concentration was varied, a slightly faster drug release was observed with lower drug concentration (see figure 3b).

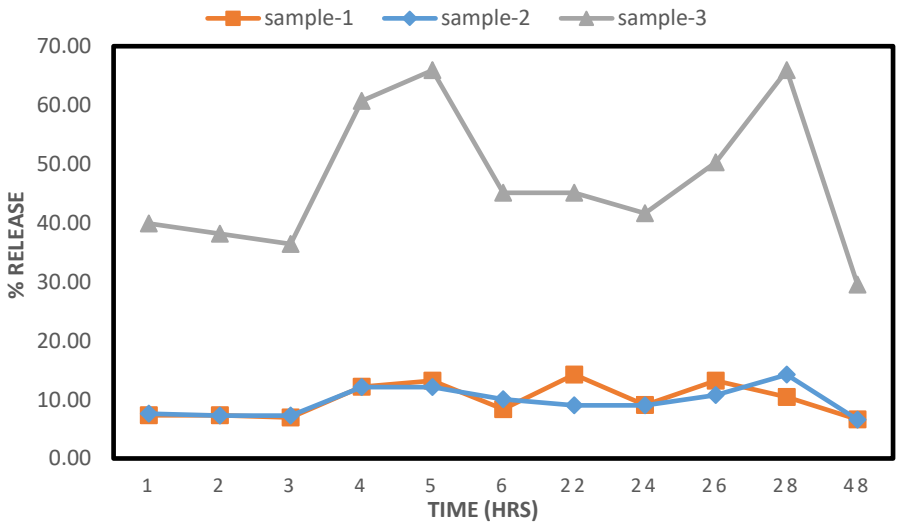
An FTIR study was carried out to study the interactions between the polymer and drug. Figure 5 shows the FTIR analysis of PLA loaded with ibuprofen and dexamethasone. For PLA loaded with ibuprofen, the position of a majority of bands remained unchanged compared to pure PLA spectra, a comparison was made with PLA spectra reported in the literature (Mofokeng et al., 2012). However, a slight change in the peak at wavenumber 1361 cm^{-1} was observed with ibuprofen concentration. While for PLA loaded with dexamethasone drug, a change in peaks at wavenumber 1359 cm^{-1}, and 2947 cm^{-1} was observed. Slight changes in bands at these wavenumbers suggest an association of drug with polymer.

For soluplus and ibuprofen a high drug release rate was observed, and almost 90.11% drug was released after 48 hours. Among all samples, Soluplus with 10% ibuprofen showed a faster release rate (see figure 4). The processing temperature for Soluplus loaded with ibuprofen sample was 100°C, higher than the melting point of

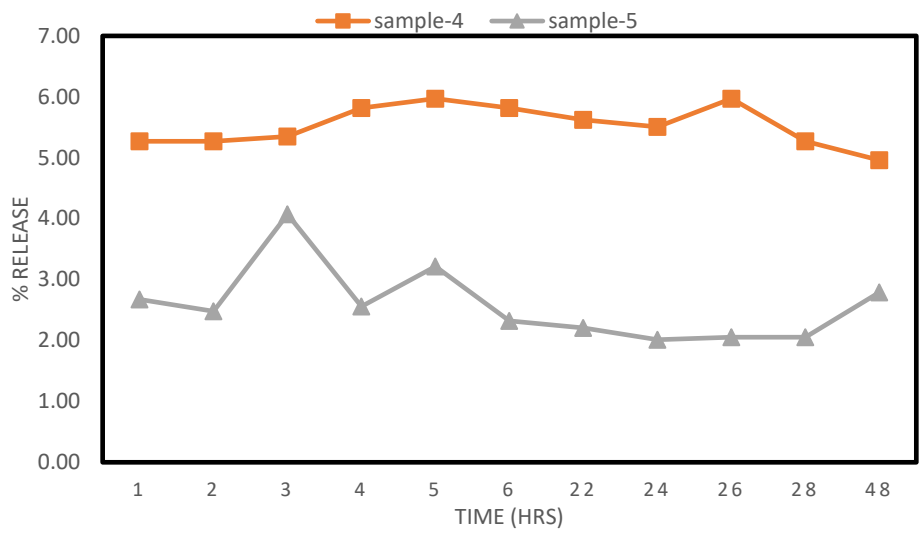
ibuprofen but much lower than the melting temperature of soluplus; still, at these conditions, it was possible to extrude soluplus with ibuprofen. Aforementioned, amorphous solid dispersion is one of the effective methods to enhance the solubility and the bioavailability of the poorly soluble drug. To investigate the formation of ASD at these conditions, DSC analysis was carried out. DSC analysis showed that ibuprofen was still in crystalline form at these processing conditions as an ibuprofen melting peak was still observed during the first heating cycle. Figure 6 shows first heating cycle only, as no peak could be observed for the first cooling and second heating cycle.

Table 2. %drug release profile of all samples

% release after 48 hours	
Sample	**% drug release**
1	6.63
2	6.59
3	29.48
4	4.96
5	2.79
6	90.11



(a)



(b)

Figure 3 (a) % drug release of PLA with ibuprofen, (b) % drug release of PLA with dexamethasone

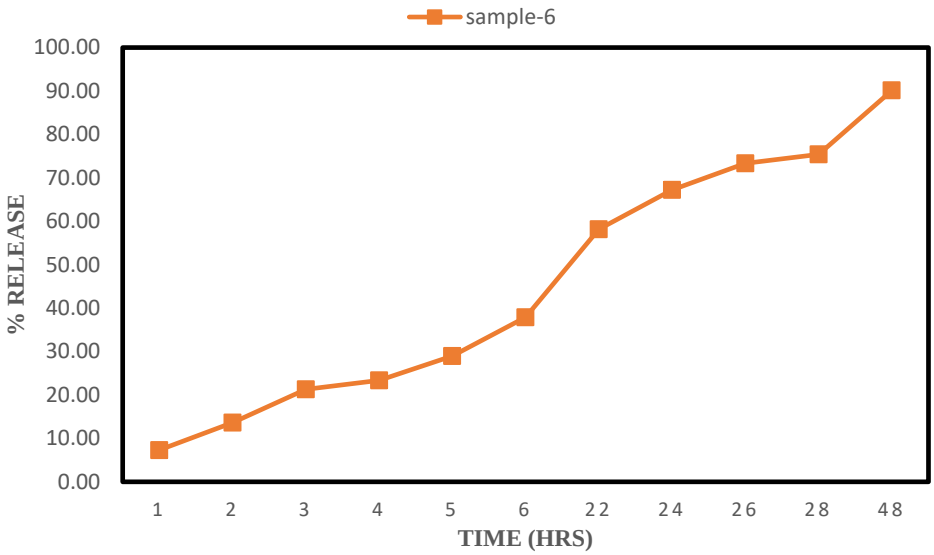


Figure 4 % drug release of soluplus and ibuprofen

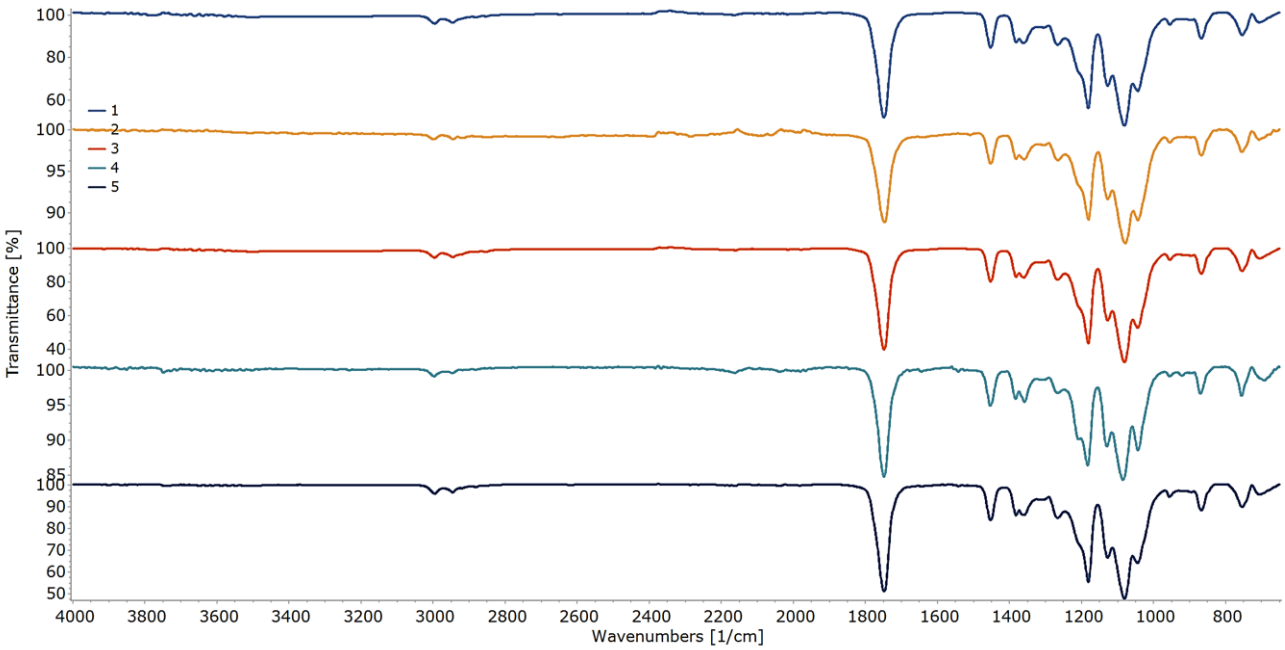


Figure 5 FTIR analysis of PLA loaded with ibuprofen and dexamethasone

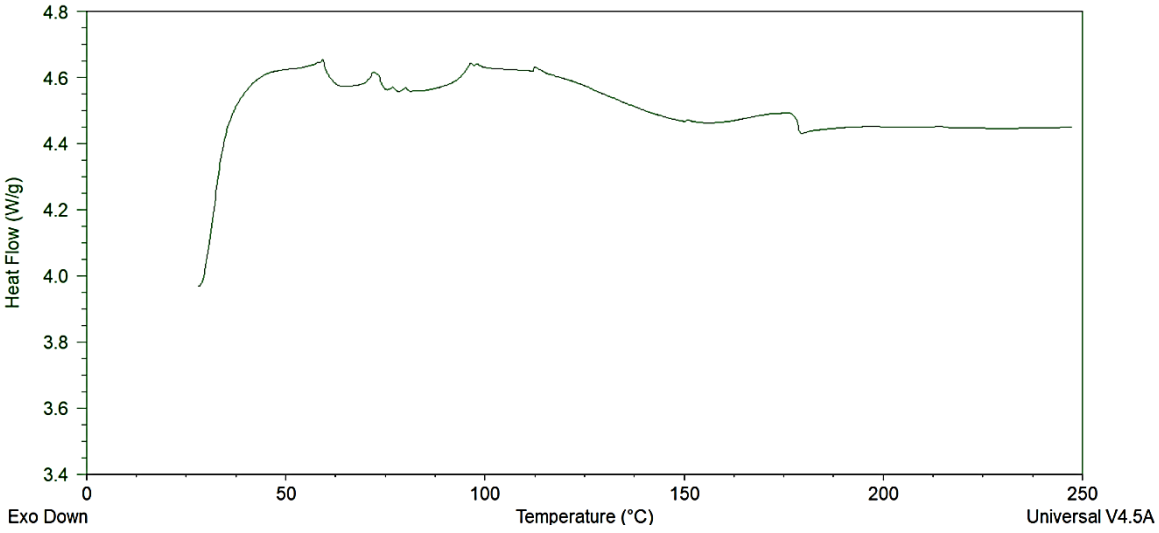


Figure 6 DSC analysis of soluplus loaded with ibuprofen

5. CONCLUSION

In this study effect of processing conditions including screw speed, temperature and drug loading on the dissolution profile of the polymer-drug matrix was studied. It was possible to extrude all the formulations using HME process. In varying processing temperature, screw speed and drug loading; drug loading was found to have the greatest influence on the release profile. In the case of PLA with ibuprofen a very slow drug release profile was observed. This might be due to degradation of ibuprofen during the process as the processing temperature was substantially higher than the melting point of ibuprofen. In the case of soluplus loaded with ibuprofen, improved drug release profile was achieved.

6. FURTHER WORK

Stability analysis of the all the samples will be carried out using HPLC and TGA. Further, Design of Experiment (DoE) approach will be used to examine the effect of processing conditions for soluplus loaded with ibuprofen (currently only one condition was examined). Ibuprofen is known to have plasticisation effect when used in higher quantity usually more than 25-30 wt.%. Higher ibuprofen loadings with PLA to investigate whether it is

possible to lower the processing temperature. In the case of soluplus and PLA, a range of different processing conditions including temperature, screw speed, feed rates and drug loading will be investigated, drug release profile at all conditions will be studied.

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