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International Journal of Pharmaceutics 328 (2007) 119–129

INTERNATIONAL JOURNAL OF PHARMACEUTICS

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Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: Selection of polymer–surfactant combinations using solubility parameters and testing the processability

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Received 12 March 2006; received in revised form 6 July 2006; accepted 4 August 2006

Abstract

Formation of solid dispersions as a means to enhance the dissolution rate of poorly soluble Active pharmaceutical ingredients (APIs) typically employs hydrophilic polymer systems and surfactants. While the utility of the surfactant systems in solubilization is well known, the secondary effects of the same on processing and subsequent physical stability of the solid dispersions needs to be studied further.

Physical blends of the poorly soluble API and hydrophilic polymers such as PVP-K30, Plasdone-S630, HPMC-E5, HPMCAS, and Eudragit L100 with mass ratio 1:1 were prepared. The surfactants tested in this study included Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and SLS. Thermal analysis of the API–polymer–surfactant blends suggested that the surfactants caused solvation/plasticization, manifesting in reduction of (i) the melting (T_m) of API (ii) T_g of the polymers and (iii) the combined T_g of the solid dispersion formed from quench cooling. Explanation of these effects of surfactants is attempted based on their physical state (at the temperature of interest), HLB values and similarity of their solubility parameter values with respect to drug–polymer systems.

Furthermore, extruded matrices containing different API–polymer (PVP-K30, Plasdone-S630, and HPMC-E5) mixtures prepared with and without surfactants, were produced by feeding the powder blend through a hot-melt extruder. The melt viscosity of the polymer blends was assessed by torque rheometry using a Haake Rheomix. The physicochemical properties of the extruded API–polymer–surfactant were characterized by differential scanning calorimetry, X-ray diffraction, Raman spectroscopy, and polarized microscopy. The results demonstrated that the glass transition temperature of the carrier polymers decreased as direct result of the surfactants in the extrudate, due to an increase in the chain mobility of polymers. A decrease in the melt viscosity was seen due to a plasticization of the polymer. The drug release profiles of the extruded solid dispersions containing intra granular surfactants were found to fit the dispersions with extra granularly added surfactants.

Keywords: Hot-melt extrusion; Plasticizer; Surfactant; Solid dispersion

1. Introduction

Hot-melt extrusion (HME) technique represents a novel application of polymer processing technology to prepare pharmaceutical dosage forms (Follonier et al., 1994; Zhang and McGinity, 1999, 2000; Ghebre-Sellassie and Martin, 2003). The process involves embedding a drug in a polymer while shaping the composite material to form a pharmaceutical product. Hot-melt extrusion offers several advantages in the preparation of modified release tablets. It is a fast, simple, continuous, solvent free process requiring fewer processing steps than traditional tableting techniques. When used as a molding technique, there are no requirements for compressibility of the materials used in the formulation (Wu and McGinity, 2003). Alternatively, the extrudate from HME can also be milled and mixed with other extragranular excipients, for subsequent incorporation into a capsule or for tabletting purposes. Milled extrudates typically are dense free flowing granulations, a critical attribute in the post-processing of this intermediate to prepare dosage forms. In view of these attributes, an ever-increasing application of HME is evident in the formulation of enhanced release dosage forms (Hülsmann et al., 2000; Nakamichi et al., 2002, Breitenbach, 2002), as well as the sustained release forms (Prapaitrakul et al., 1991; McGinity and Zhang, 2003).

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doi:10.1016/j.ijpharm.2006.08.010

Plasticizers are incorporated into pharmaceutical polymers to facilitate thermal processing, to modify drug release from polymeric systems and to enhance the mechanical properties and surface appearance of the dosage form (Repka and McGinity, 2000; Flosser et al., 2000). When incorporated into a polymeric material, a plasticizer improves the workability and flexibility of the polymer by increasing the intermolecular separation of the polymer molecules (Wang et al., 1997). These result in a reduction in elastic modulus, tensile strength, polymer melt viscosity, and glass transition temperature (T_g). The polymer toughness and flexibility is improved and lower thermal processing temperatures can be employed (Zhu et al., 2003).

The initial challenge to overcome processing an API using a hot-melt extrusion method is to effectively plasticize the polymeric carrier. For instance, Eudragit L100 is a brittle material having a high glass transition temperature of −160 °C. Processing temperatures above the T_g or melting temperature of the polymeric carrier are typically required to soften and lower the polymer melt viscosity to allow adequate flow through the extruder. The addition of a plasticizer will decrease the polymer T_g due to intermolecular interaction with the polymeric chains allowing for lower processing temperatures. Lowering the polymer T_g with plasticizers, therefore, facilitates thermal stability of the composite materials.

Traditional plasticizers used in HME such as TEC, PEG, triacetin, glycerin, diethyl phthalate, propylene glycol are associated with such limitations as toxicity, moderate water solubility, low boiling points, etc. Alternatively, surfactant based plasticization serves the dual purpose of aiding polymer processing, as well as subsequent API solubilization/bioavailability enhancement. This body of work evaluates the role of commonly used surfactant systems in HME processing.

The specific objectives of this research are therefore to investigate the properties of various surfactants as plasticizers for API–polymer systems during hot-melt extrusion process and to characterize the performance of the extruded API–polymer–surfactant matrices. This study examines the effect of surfactants on the processability of the blends, the solubilization of API–polymer solid dispersions, the micro-environmental effects of surfactants (intra-granular versus extra-granular) on the dissolution enhancement from an amorphous matrix, and the combination effects of polymer–surfactants on the drug release properties.

2. Materials and methods

2.1. Materials

Hydroxypropyl methylcellulose (HPMC-E5); polyvinylpyrrolidone K30 (PVP-K30, average MW 44–54 kDa); polyoxyethylene 40 stearate (Myrj-52, HLB = 16.9); polysorbate-80 (Tween-80, HLB = 15.0); Sodium lauryl sulfate (SLS, HLB = 40.0) and sulfobutanedioic acid bis[2-ethylhexyl ester] dioctyl sulfosuccinate (Docusate sodium, HLB = 10) were supplied by Sigma Chemicals (St. Louis, MO). Poloxamer 188 NF (Pluronic F68, HLB = 29.0) was obtained from BASF Corporation (Mount Olive, NJ). Plasdone-S630 was from ISP Technologies Inc., (Wayne, NJ). methacrylic acid–methyl methacrylate copolymer (1:1) (Eudragit L100) was from Rohm America Inc., (Somerset, NJ). Hydroxypropyl methylcellulose acetate succinate (HPMCAS) was supplied by Shin-Etsu (Japan). All chemicals were of laboratory reagent grades.

2.2. Sample preparation

A series of binary physical mixtures of mass ratios 1:1 of API and hydrophilic polymers such as PVP-K30, Plasdone-S630, HPMC-E5, HPMCAS, and Eudragit L100 were prepared by gently mixing accurately weighed quantities using a spatula and pestle for 2 min followed by 15 min of mixing in a turbula mixer. Then, three different amounts of surfactants were added to the API–polymer blends. The solid surfactants (SLS, Pluronic F68, and Myrj-52) were added by simply mixing them with API–polymer blends in a turbula mixer for 15 min. The liquid and semisolid surfactants (Tween-80 and Docusate) were first mixed using spatula in a weigh boat for 5 min followed by mixing in mortar and pestle for additional 10 min. All the samples were stored in a controlled temperature cabinet at 25 °C (25% RH). Blends were considered uniform when three separate DSC thermograms were similar when superimposed.

2.3. Hot-melt extrusion (HME)

The extrusion process was performed using the Haake Rheomix co-rotating intermeshing twin-screw extruder with a L/D of 50 and screw diameter of 16 mm. The screw speed was adjusted to 100 rpm, resulting in a residence time in the extruder, of approximately 2–3 min. Powder blends of various formulations were manually fed into the melt extruder at a rate of −10 g/min. Extrudate collection began 3 min after the run was initiated to allow any material from the previous runs to be extruded prior to sample collection. The melt extrudate was air cooled on a conveyor belt. The extrudate was milled using the Model L1A Fitzmill (Fitzpatrick Co., Elmhurst, IL) in three stages. In the first step, coarse milling was done using knives forward at high speed with screen #1721-0109. This was followed by two steps of fine milling using screen #1722-0033 and screen #1722-0020 with hammers forward at high speed. The resulting milled solid dispersion (particle size range of 25–200 μm) was then used for analysis.

2.4. Solubility parameter calculations

Solubility parameter calculations were performed using Molecular Modeling Pro software (Chem SW Inc., Fairfield, CA) utilizing group contribution approaches (Molecular Modelling Pro., 1991). For polymeric excipients, Hansen's partial solubility parameters were calculated based on the single repeating monomer unit. The solubility parameters of various polymers were matched to those of API and surfactants by observing the relative difference in the total, $\Delta\delta$, as well as partial Hansen solubility parameter values, R (the square root of the sum of squares of differences in dispersion, polarity and hydrogen bonding values).

2.5. Modulated differential scanning calorimetry (mDSC)

DSC measurements were carried out using a TA Instruments Q1000 modulated differential scanning calorimetry (TA Instruments Inc., New Castel, DE). About 5–7 mg sample was accurately weighed and placed in a hermetic aluminum pan with lid and crimp sealed. The measurement was made in two cycles. In first cycle, the samples were heated from 20 to 190 °C at rate of 5 °C/min with a modulation amplitude and period of ±0.796 °C every 60 s, respectively. The sample was quench cooled to 20 °C and then reheated (second cycle) at 5 °C/min to 200 °C at the same ramp rate, modulation amplitude, and period.

2.6. Thermogravimetric analysis (TGA)

In order to determine the evaporative loss in surfactants in the solid dispersion, thermogravimetric analyses were performed using a TA Instruments Hi-res TGA (TA Instruments Inc., New Castel, DE). Samples of approximately 5–10 mg in aluminum pans were heated at a rate of 10 °C/min to 300 °C with nitrogen purge of 60 ml/min, and the loss of weight was recorded.

2.7. Dissolution test

Dissolution testing of hard gelatin capsules containing various solid dispersions was performed using apparatus II on a Van Kel VK7010 Dissolution Tester (VanKel Industries, Edison, NJ) equipped with fiber optic probes (C-Technologies Inc.). The capsules were placed into the dissolution medium (50 mM Phosphate buffer), which was maintained at 37 °C by a circulating bath and agitated at 100 rpm. The amount of drug released into the 900 ml dissolution medium, was determined spectrophotometrically at 263 nm, at specific time intervals. All dissolution tests were performed in triplicates. The percent dissolved API was plotted as a function of time. The dissolution profile of API–polymer systems with intra and extra granular addition of surfactants were compared.

2.8. Powder X-ray diffraction studies (pXRD)

All samples were characterized for X-ray pattern using a KD-2660-N X-ray diffractometer controlled by the D-Max B controller and Datascan MDI software (Rigaku Ultima-plus, Tokyo, Japan) with Cu Kα radiation ($\lambda = 1.54$ Å) generated from a copper source operating at a power level of 40 KV and 40 mA. The test samples were packed into 0.5 mm deep graphite sample holders. The samples were scanned over the range of 3–50° 2-θ at a scan rate of 1 °/min with slit configuration 0.5°, 0.5°, 0.3 and 0.6 mm for divergence, scatter, receiving and monochromator slit, respectively.

2.9. Raman spectroscopy

A HoloLab Series 500 Raman microscope (Kaiser Optical System, Inc., Ann Arbor, MI) was used to obtain Raman spectra of milled extrudates. The laser power was 400 mW. The exposure time was 20 s with a 50× lens. All solid dispersions were analyzed in triplicates.

2.10. Polarized optical microscopy

Sample morphology and crystalline birefringence behavior of the samples were investigated using a polarizing optical microscope (Leitz Lab 12 Pol S, Wild Leitz, Heerbrugg, Switzerland) with a tungsten lamp as the light source. The objects were viewed in the magnification range 200×.

3. Results and discussion

3.1. Choice of carrier polymers for API using solubility parameter as an indicator for miscibility

Similarity in the partial solubility parameters (δ) of the API with the polymers was used initially to screen the polymers to be used as carriers in the solid dispersion. Solubility parameters of the compounds were evaluated from the chemical structures using the Hansen 3-D solubility parameters. This measure of solubility is in the units of (δ/MPa$^{1/2}$). It is calculated by taking the square root of the sum of squares of dispersion, polarity and hydrogen bonding. For polymeric excipients, solubility parameters were calculated based on the average molecular weight. The physical properties of the polymers and surfactants are provided in Table 1.

Compounds with similar values for solubility parameters are likely to be miscible. This is because the energy of mixing within the components is balanced by the energy released by interaction between the components (Greenhalgh et al., 1999). Excipients are classified based on the difference between the solubility parameters of polymer and API ($\Delta\delta$). Greenhalgh et al. (1999) demonstrated that compounds with a $\Delta\delta < 7.0$ MPa$^{1/2}$ are likely to be miscible while compounds with a $\Delta\delta > 10$ MPa$^{1/2}$ are likely to be immiscible (16). Following these guidelines, since the values for δ of the API is calculated to be 33.81 MPa$^{1/2}$, it can be predicted that polymer with a δ of 26–41 MPa$^{1/2}$ should show some miscibility with the drug, whereas an excipient with a δ less than 23 or greater than 41 MPa$^{1/2}$ is likely to be immiscible.

Therefore, from the results summarized in Fig. 1, the polymers in this study can be grouped into three categories based on the $\Delta\delta$. HPMC-E5 and PVP-K30 with a $\Delta\delta < 7.0$ MPa$^{1/2}$

Table 1
Physical properties of polymers and surfactants tested

Compounds	Molecular weight	T_g/T_m (°C)
Plasdone-S630	58000	112
HPMC-E5	30000–50000	146
PVP-K30	45000	172
HPMCAS	18000	122
Eudragit L100	250,000	160
SLS	288.38	204–207
Docusate sodium	444.55	173–179
Tween-80	428.61	−15
Pluronic-F68	236.31	52–6
Myrj-52	328.54	37.8

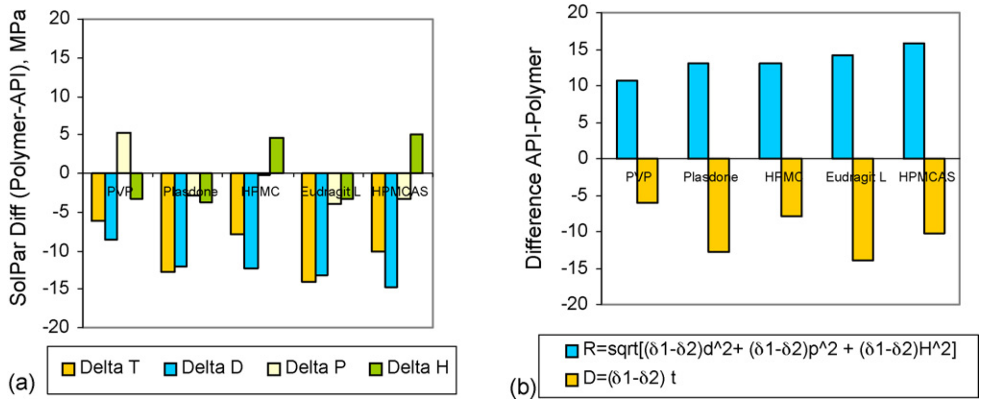

Fig. 1. (a) Solubility parameter difference ($\Delta\delta$) of API-selected polymers and (b) matching solubility parameters of API to various polymers.

are likely to be miscible and form glass solutions when melt extruded with the drug. HPMCAS and Plasdone-S630 (with a $\Delta\delta$ of 7.0–10.0 MPa$^{1/2}$) are likely to be moderately miscible. Whereas Eudragit L100 with $\Delta\delta > 10.0$ MPa$^{1/2}$ is likely to be immiscible and is not expected to form a glass solution.

3.2. *Plasticization of polymers by surfactants: Experimental data*

The glass transition temperature values of API–polymer mixtures and surfactants at different amounts were determined experimentally. The T_g was measured in the second cycle from the reversible heat flow versus temperature plot of the mDSC runs (quench cooled melts). As shown in Table 2, the T_g of the API–polymer decreased with increasing levels of surfactant in the blends, and with 10% Tween-80 in API–Plasdone-S630 mixture, the T_g was reduced from 97 to 67 °C. This was due to an increase in chain mobility of the polymer molecules when the surfactant was incorporated in the polymer matrices. These results demonstrated that Tween-80 was an effective plasticizer for Plasdone. Since the molecular weight of Tween-80 (429 MW) is significantly lower than that of Plasdone (58,000 MW), the presence of the smaller molecules of Tween-80 within the polymer were thought to dilute and weaken the cohesive interactions between the Plasdone chains. This reduced the friction and entanglement by increasing the free volume in the polymer matrix. Likewise, this phenomenon also applies to API–HPMC–E5 and API–PVP-K30 mixtures as shown in Table 2.

In a similar mode, the semi-solid surfactant, Docusate sodium (444 MW) plasticized both HPMC-E5 (30,000–50,000 MW) and PVP-K30 (45,000 MW). In both cases it was observed that the T_g was reduced by as much as 10 °C when 10% Docusate sodium was introduced into the system (Table 3). The extent of T_g reduction of these polymers was lower when Docusate sodium was used as a plasticizer, when compared to Tween-80. This can manifest from a multitude of factors such as the viscosity of plasticizer at the temperature of interest (T_m as indirect measure), miscibility of plasticizer with polymer ($\Delta\delta$, HLB as measures), size of the plasticizer (MW as measure), in addition to the specific chemical interactions with the polymer. The role of each of these factors in the plasticization of polymers will be further discussed in later sections. This of course reduces the friction and entanglement by increasing the free volume in the polymer matrix and reduction in transition and melt temperatures.

Three different amounts of powder surfactants (SLS, Pluronic-F68 and Myrj-52) were tested with all five polymers (PVP-K30, Plasdone-S630, HPMC-E5, HPMCAS, and Eudragit L100). While the presence of Pluronic-F68 and Myrj-52 did not result in any T_g reduction among the various polymers tested, on the other hand, SLS was an instrumental plasticizer

Table 2
Summary of selected mDSC results of API–excipient–Tween-80 blends

Formulations	Surfactant (%)	T_m (°C) (cycle #1)	T_g (°C) (cycle #2)	ΔT_g
API–Plasdone-S630	0	149.31	97.15	–
API–Plasdone-S630–Tween-80	2	148.53	94.31	2.84
API–Plasdone-S630–Tween-80	5	141.36	85.34	11.81
API–Plasdone-S630–Tween-80	10	131.27	67.29	29.86
API–HPMC-E5	0	157.25	82.46	–
API–HPMC-E5–Tween-80	2	160.01	81.45	1.01
API–HPMC-E5–Tween-80	5	154.86	68.22	14.24
API–HPMC-E5–Tween-80	10	148.07	54.9	27.56
API–PVP-K30	0	157.99	111.98	–
API–PVP-K30–Tween-80	2	157.69	112.54	–
API–PVP-K30–Tween-80	5	154.62	106.23	5.75
API–PVP-K30–Tween-80	10	150.23	101.47	10.51

Table 3
Summary of selected mDSC results of API–excipient–Docusate blends

Formulations	Surfactant (%)	T_m (°C) (cycle #1)	T_g (°C) (cycle #2)	ΔT_g
API–HPMC-E5	0	157.25	82.46	–
API–HPMC-E5–Docusate	2	158.04	84.91	–
API–HPMC-E5–Docusate	5	156.06	78.69	3.55
API–HPMC-E5–Docusate	10	153.05	75.85	6.61
API–PVP-K30	0	157.99	111.98	–
API–PVP-K30–Docusate	2	155.78	113.22	–
API–PVP-K30–Docusate	5	153.28	106.54	5.44
API–PVP-K30–Docusate	10	152.04	101.52	10.46

of Eudragit L100, a brittle material having a high glass transition temperature of −160 °C. The T_g or melting temperature of Eudragit L100 is typically required in softening and lowering of the melt viscosity during processing. Therefore, T_g reduction by as much as 15 °C when 10% of SLS was mixed with the API–polymer matrix lends to substantial ease of processing (Table 4). As with both Tween-80 and Docusate sodium, the T_g of HPMC-E5 was reduced by addition of SLS.

In general, a single T_g at an intermediate temperature between the API and the polymer T_g values was found. This supports the prediction from solubility parameter calculation that these polymers are miscible with both API and surfactant, therefore, are likely to form an amorphous solid solution when melt extruded.

3.3. Plasticization of polymers by surfactants: Empirical relations

3.3.1. Effect of partial solubility parameter

The partial Hansen solubility parameter values, R, were determined from the square root of the sum of squares of dispersion, polarity and hydrogen bonding contributions for the polymers and surfactants. Depression in T_g of the polymer by the surfactant is experimentally evaluated. Fig. 2 shows that effect of partial solubility parameters of polymer–surfactant on the depression of the glass transition temperature of the polymer. As expected, the depression in T_g of Plasdone and HPMC-E5 decreased with partial solubility parameter values, δ, of the polymer–surfactants. On the other hand, HPMCAS and PVP-K30 have hardly shown correlation. The applicability of group contribution methods in estimating the partial solubility parameter values of polymers will therefore needed to be tested in greater detail. This probably warrants experimental determination of the partial solubility parameters of commonly used polymers and surfactants, which forms the subject of a future study.

3.3.2. Effect of surfactant melting point and HLB values

Thermal analysis of polymer–surfactant blends suggested that the surfactants caused plasticization, manifesting in reduction of T_g of the polymers and the combined T_g of the solid dispersion formed from quench cooling. Attempts were made to correlate these effects of surfactants based on their diffusional properties, or indirectly their physical state at the temperature of interest. To this end, surfactants with melting points in a wide range, from as low as −15 °C for Tween-80 to as high as 204 °C for SLS were selected. As shown in Fig. 3a, the melting points of surfactants have no correlation with the depression of the glass transition temperature the polymers. Similarly an attempt was made to correlate the above-mentioned effect to HLB values of the surfactants (Fig. 3b). The surfactants tested in this study included Tween-80 (HLB = 15.0), Docusate sodium (>10), Myrj-52 (16.9), Pluronic-F68 (29.0) and SLS (40.0). While it was theoretically expected that a higher HLB value of the surfactant would result in a greater depression in T_g of a given hydrophilic polymer, the experimental results neither proved nor disprove this hypothesis.

3.4. Estimation of evaporative loss of surfactants by thermo gravimetric analysis

The thermal stability of API–polymer–surfactant (50:40:10) mixture was determined using thermo gravimetric analysis (TGA). As shown in Fig. 4, the results from the TGA study for all tested API–polymer and API–polymer–surfactant mixtures did not begin to show signs of thermal decomposition until reaching approximately 200 °C. Thereafter, the blends began

Table 4
Summary of selected mDSC results of API–excipient–SLS blends

Formulations	Surfactant (%)	T_m (°C) (cycle #1)	T_g (°C) (cycle #2)	ΔT_g
API–HPMC-E5	0	157.25	82.46	–
API–HPMC-E5–SLS	2	158.42	82.11	0.35
API–HPMC-E5–SLS	5	159.03	78.71	3.75
API–HPMC-E5–SLS	10	158.74	74.43	8.03
API–Eudragit L100	0	163.33	104.02	–
API–Eudragit L100–SLS	2	165.11	106.22	–
API–Eudragit L100–SLS	5	165.79	95.14	8.88
API–Eudragit L100–SLS	10	165.33	92.77	11.25

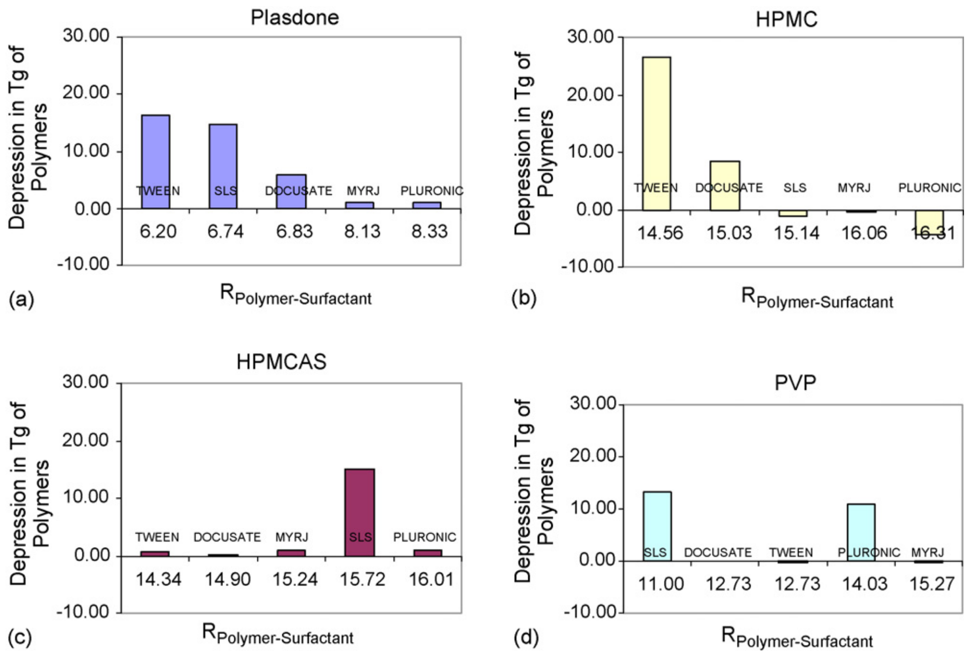

Fig. 2. Effect of partial solubility parameters of polymer–surfactants on depression of T_g of polymers.

to demonstrate a loss in weight possibly due to volatilization and decomposition of the surfactants and the API. Weight loss up to 70 °C (conservatively) was taken as dehydration and the weight change equivalent to moisture content. As demonstrated in the figure below, all surfactants (Tween-80, Docusate, and SLS) were thermally stable at temperatures used for processing as shown in Fig. 4.

3.5. HME processability aided by surfactants

Processing temperatures above the T_g or melting temperature of the polymeric carriers are typically required to soften and lower the polymer melt viscosity to allow adequate flow through the extruder. The addition of a plasticizer will decrease the polymer T_g due to intermolecular interaction with the polymeric chains allowing for lower processing temperatures. Lowering the polymer T_g with plasticizers, therefore, facilitates thermal stability of the composite materials. For comparison, extrudates were prepared with and without the surfactants. Both blends contained the same API to polymer ratio and were processed at two different temperatures, namely 10 °C above and below the glass transition temperature of the pure carrier polymers.

The API–polymer mixtures without the plasticizing surfactant became more flexible, more transparent and changed from a light green to a darker yellow as the temperature increased above T_g of the carrier polymer. In addition, the load and torque decreased as the extrusion temperature was increased (Table 5). For example, for API–Plasdone mixture, the torque was reduced from 55–65 to 25–30 N m when the process temperature increased from 100 to 120 °C. Accordingly, the API–polymer mixtures containing the plasticizing surfactant were much more flexible and transparent as well as changed from a light yellow to translucent when compared with API–polymer mixture when processed at same temperature. For the API–Plasdone mixtures containing Tween-80 extruded at 100 °C, the torque reduced to 28–30 N m (from 55 to 65 N m) and the die pressure decreased from 6–10 to 3–5 bar.

In the same way, Tween-80 efficiently plasticized the API–HPMC-E5 and API–PVP-K30 systems. The torque for

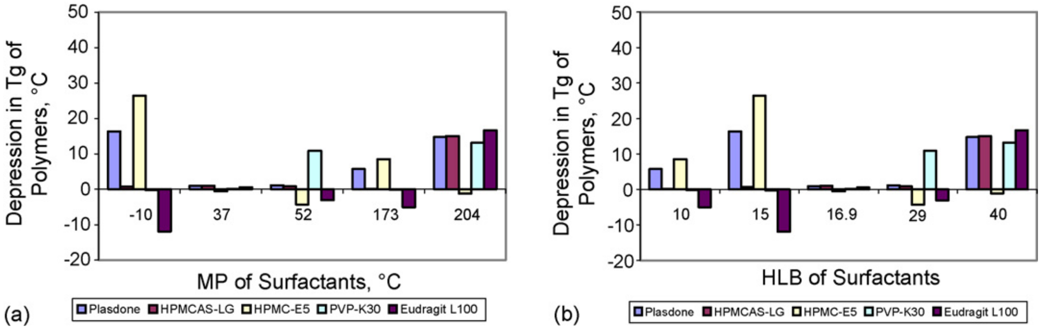

Fig. 3. (a) Effect of melting point of surfactants on depression of T_g of polymers and (b) effect of HLB of surfactants on depression of T_g of polymers.

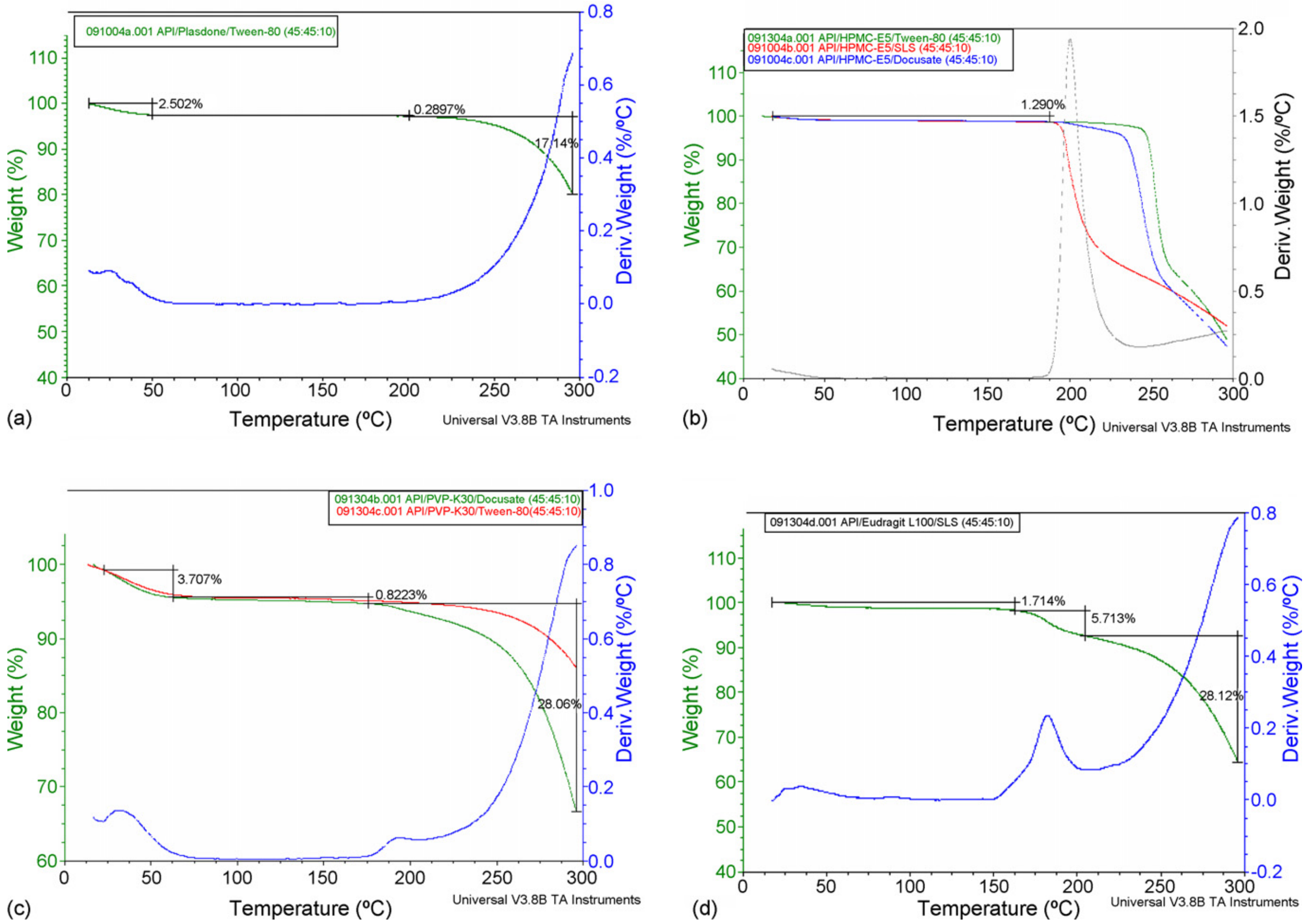

Fig. 4. Thermo gravimetric analysis of (a) API–Plasdone–Tween-80, (b) API–HPMC-E5-(Tween-80–Docusate–SLS), (c) API–PVP–(Tween-80–Docusate), and (d)API–Eudragit L100–SLS mixtures.

API–HPMC-E5 extrudate processed at 135 °C (10 °C below T_g) was reduced from 20–22 to 10–15 N m when Tween-80 was used as plasticizer. For the API–PVP-K30 extrudate processed at 158 °C (10 °C below T_g), torque was decreased from 35–48 to 15–17 N m (with Tween-80 as plasticizer) and to 25–30 N m (with Docusate sodium as plasticizer). Similar reductions were observed at process temperatures 10 °C above the T_g of the carrier polymers.

Table 5
Extrudate torque, die pressure measurements, mDSC results of initial extrudate (5 °C/min) at 10 °C above and below carrier polymer T_g

Materials	Process temperature (°C)	Extrudate T_g (°C)	Torque (N m)	Die pressure (bar)
API–Plasdone-S630	100	77.21	55–65	6–10
	120	79.95	25–30	2–4
API–Plasdone-S630–Tween-80	100	55.89	28–30	3–5
	120	55.74	10–12	1–2
API–HPMC-E5	135	67.09	20–22	2–5
	155	66.20	15–18	1–2
API–HPMC-E5–Tween-80	135	50.87	10–15	2–4
	155	51.04	8–9	0.6–1.8
API–PVP-K30	158	96.73	35–48	1.8–3.0
	178	99.47	15–30	0.1–0.3
API–PVP-K30–Tween-80	158	83.72	15–17	0.3–0.5
	178	81.32	8–10	–
API–PVP-K30–Docusate sodium	158	83.19	25–30	0.4–1.5
	178	83.86	12–15	–

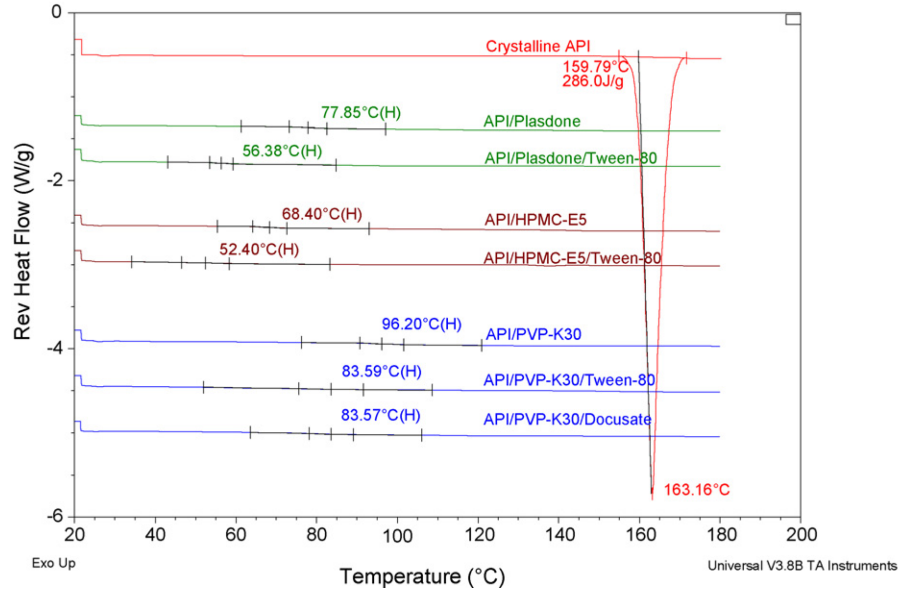

Fig. 5. mDSC results of initial extrudate (5 °C/min) produced at 10 °C below the T_g of the carrier polymer.

The above findings unequivocally support the conclusion that surfactants could be used as plasticizers to soften and lower the polymer melt viscosity, allowing adequate flow and mixing in the extruder during HME process.

3.6. Characteristics of Solid Dispersions: Thermal Analysis

The glass transition temperature values of API–polymer extrudates and API–polymer with intra-granular addition of surfactants (10%, w/w) were determined experimentally. The T_g was measured in the first cycle from the reversible heat flow versus temperature plot of the mDSC runs (ramped at 5 °C/min). Upon extrusion with the carrier polymers, the API-melting peak had essentially completely disappeared, indicating loss of crystallinity in the molten polymer (Fig. 5). The T_g of the API–polymer decreased with the addition of the surfactants, and with Tween-80 in API–Plasdone-S630 mixture, the T_g was reduced from 78 to 56 °C. These results demonstrated that Tween-80 was an effective plasticizer for Plasdone. As with the physical mixtures, Tween-80 was found to dilute and weaken the cohesive interactions between the Plasdone chains. Intense mixing of the softened polymer with the API during HME facilitates molecular interactions between these components, in turn dissolving the API into the carrier matrix. Such interactions resulted in a lower energy needed for phase transition in the extrudates compared to that of the

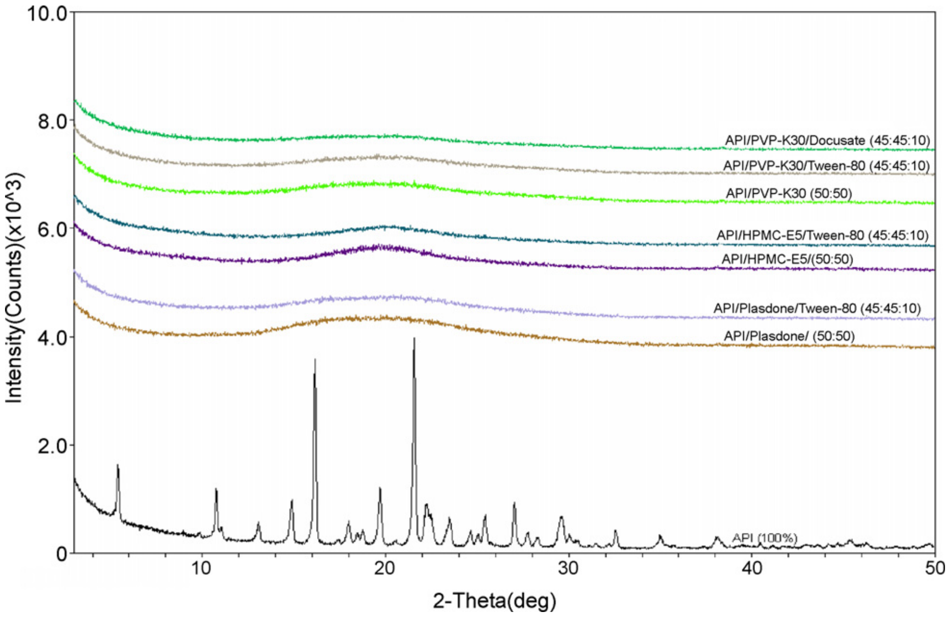

Fig. 6. pXRD patterns of initial extrudates produced at 10 °C below the T_g of the carrier polymer.

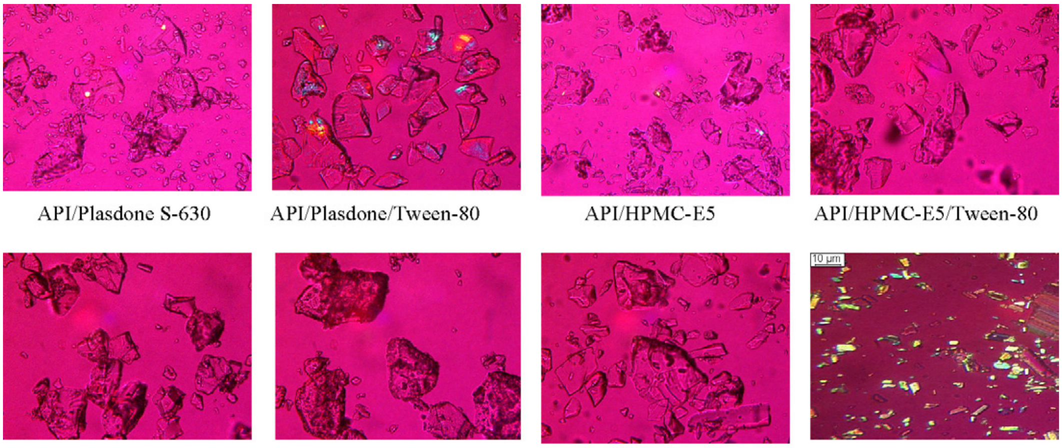
API/Plasdone S-630
API/Plasdone/Tween-80
API/HPMC-E5
API/HPMC-E5/Tween-80
API/PVP-K30
API/PVP-K30/Tween-80
API/PVP-K30/Docusate
Crystalline API

Fig. 7. Photomicrographs of solid dispersions produced by hot-melt extrusion.

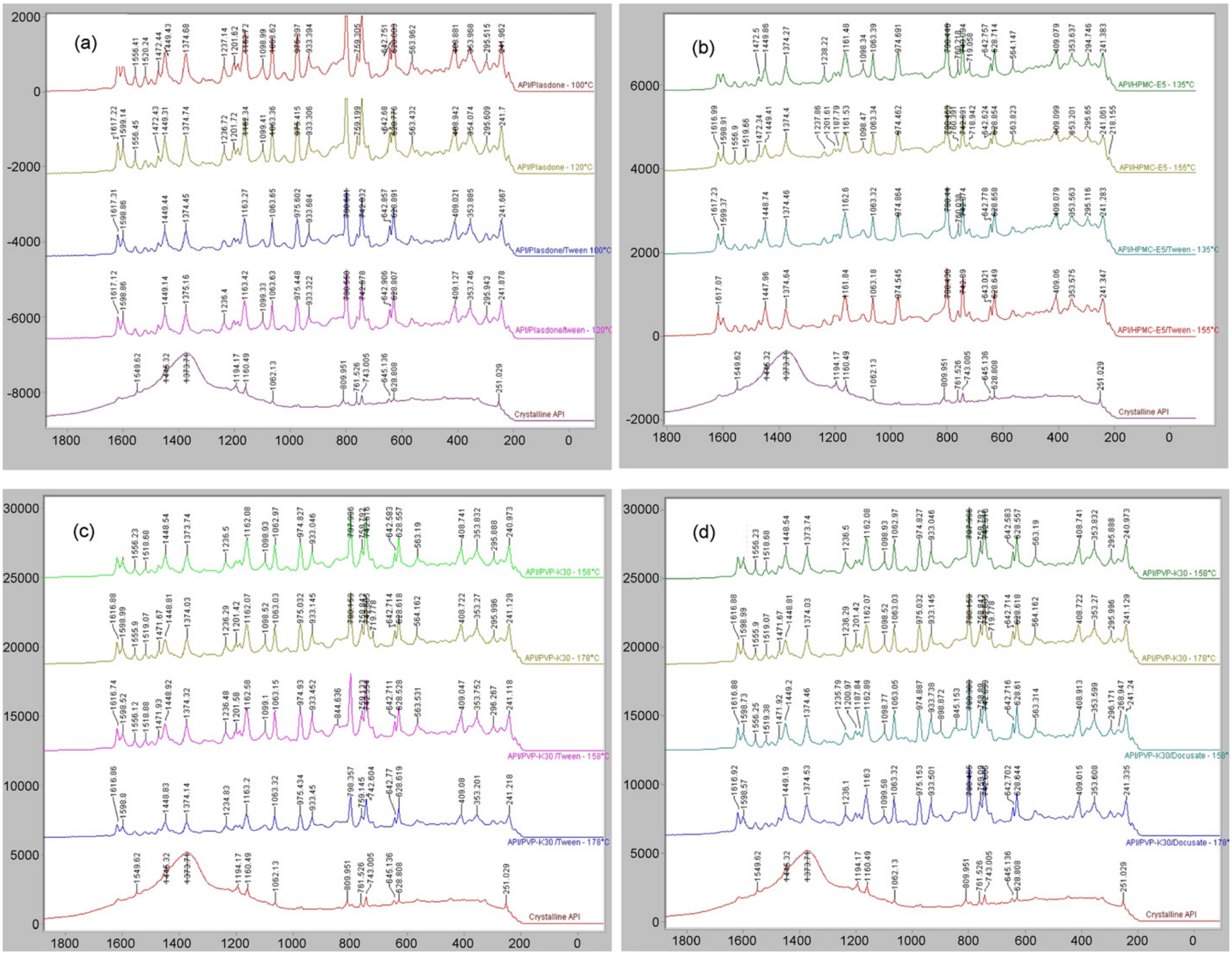

Fig. 8. Raman images of initial extrudates produced at 10 °C below the T_g of the carrier polymer.

API–polymer blend. Likewise, this phenomenon was true by addition of Tween-80 to API–HPMC-E5 and API–PVP-K30 mixtures, in which case the T_g was reduced respectively from 67 to 51 °C and from 99 to 81 °C as summarized in Table 5. These values are similar to the values calculated from the second cycle of measurement of the physical mixtures, indicating phase homogeneity in the HME produced solid dispersions.

3.7. Characteristics of Solid Dispersions: Powder X-ray diffraction

Absence of constructive reflections (peaks at specific 2-θ) in the powder X-ray diffraction patterns indicates the conversion of the API from crystalline to amorphous state. The extrudates prepared by HME at temperatures 10 °C above and below the T_g of the carrier polymer (shown in Table 1) for both the API–polymer mixture with and without surfactant were examined by pXRD to confirm loss of the API crystallinity and the results are shown in Fig. 6. The pure API has clearly multiple peaks notably at 2-θ angles of 10.4°, 14.8°, 16.1°, 19.7° and 21.5°. At 10 °C above the T_g, the API crystallinity appeared to have been completely lost following extrusion for both the API–polymers and API–polymer–surfactant systems. With addition of the surfactants, similar patters are obtained even at the lower extrusion temperature (10 °C below), reflecting the plasticization by surfactant. The X-ray data supported the conclusion that the API formed a solid solution within the carrier matrix. The lack of crystallinity in the extrudates was understood to be as a result of the complete solubilization of the API in the amorphous polymer. This is also promoted by the addition of the surfactants. In contrast, characteristic peaks were observed in the physical mixtures, demonstrating that the API crystal structure remained unchanged. These results are in good agreement with the polarized optical micrographs shown in Fig. 7 and mDSC data in Fig. 5.

3.8. Characteristics of solid dispersions: Raman spectroscopy

Raman spectra of solid dispersions in the 1800–200 cm^{-1} range are given in Fig. 8. The spectrum showed similar homogenous bands, representative of the amorphous form in all the extrudate systems. Several bands present in the amorphous extrudates vanished in the crystalline API: 1617, 1598, 1236, 975, 933, 409 and 353 cm^{-1}. It appears that the vanishing bands are quite strong also regardless of the extrusion temperature (above and below T_g). Raman results support those obtained in the pXRD patterns and mDSC scans and are undoubtedly a result of bands disappearing in the crystalline API. The number of vanishing bands is quite large, revealing that most of

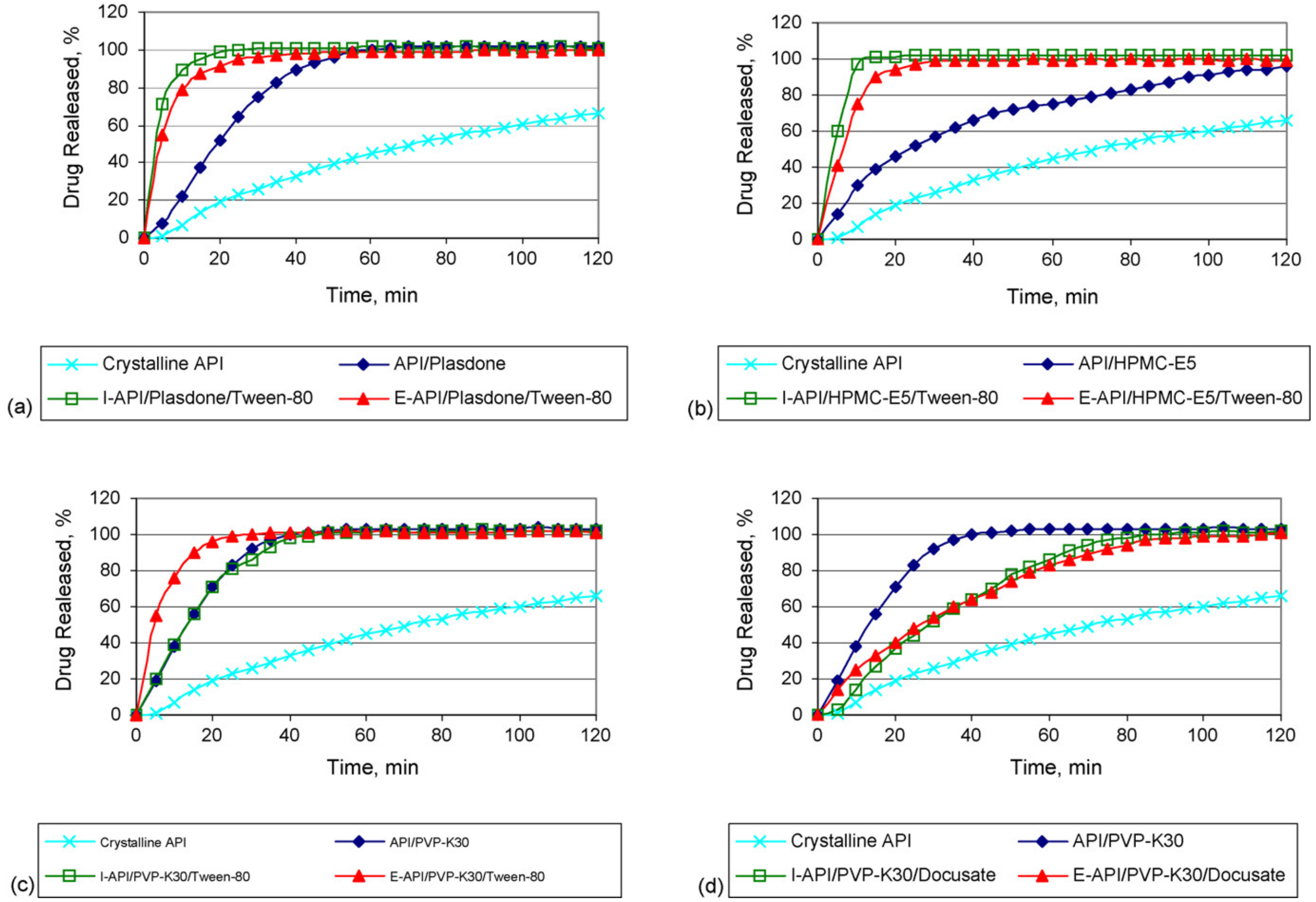

Fig. 9. Dissolution test of (a) API–Plasdone-S630 and API–Plasdone-S630–Tween-80, (b) API–HPMC-E5 and API–HPMC-E5–Tween-80, (c) API–PVP-K30 and API–PVP-K30–Tween-80, and (d) API–PVP-K30 and API–PVP-K30–Docusate sodium.

the fundamentals of one conformer overlap with those of the other.

3.9. Characteristics of solid dispersions: Dissolution testing

Fig. 9 shows the dissolution profiles of the extrudate systems prepared with different carrier polymers and surfactants. While pure API dissolved slowly to the maximum of 65%, all extrudates dissolved completely to 100% over the 120 min timeframe. The release profiles of the API showed that both intra-granular and extra-granular addition of Tween-80 (HLB = 15.7) resulted in similar increase in the release rate of the API in all the systems.

While complete drug dissolution from API–Plasdone system took 60 min in the absence of any surfactant, the same was reduced to 10 min from matrices containing 10% (w/w) Tween-80 (for both intra and extra granular addition). This indicates the remarkable effect of Tween-80 on the enhancement of release rate of the API from Plasdone matrices (Fig. 9a). Likewise, drug release rate enhancement was observed for API–HPMC-E5 system from 100 min without surfactant to less than 15 min for both intra and extra-granular addition of Tween-80 (Fig. 9a). This phenomenon is a combined effect of the micellar solubilization by Tween-80, as well as the reduction in the interfacial tension between the samples and the dissolution media, thus improving dispersibility of solid dispersion. These findings appear to be true for all extrudates formed at either 10 °C above or below the glass transition temperature of the carrier polymers.

However, for the PVP-K30 system shown in Fig. 9c, while extra-granular addition has similar effects as for the Plasdone and HPMC-E5 systems, the intra-granular addition has practically no effect. The reason for this could be due to the higher extrusion temperature (158–178 °C) used to produce the solid dispersions, resulting in thermal denaturation of the surfactant. On the other hand, drug dissolution appeared to be retarded in the case of PVP-K30 + Docusate sodium system. These results are consistent with Chambliss et al. (1981) study, where micellar entrapment of the API by surfactant (at concentrations >CMC, 0.02%, w/v) was reported to be the cause for apparent delay in the drug release. Additionally, the delayed release could not be attributed to (a) pH solubility of Docusate sodium ($pK_a = 2.84$) or (b) complexation with PVP-K30, hard gelatin shells (not reported to date) or with the API (internal findings). The level of Docusate in the dissolution medium therefore should be kept under its critical micellar concentration in order to elicit the in vitro dissolution enhancement by this surfactant.

4. Conclusions

The objective of this work was to investigate the utility of various surfactants as plasticizers for hot-melt extrusion (HME) of binary mixtures of a poorly soluble API and various hydrophilic polymers. The thermal analysis of the solid dispersions suggested that the surfactants caused plasticization, manifesting in reduction of (a) T_m of API, (b) T_g of the polymers, and (c) the combined T_g of the solid dispersion formed from quench cooling. Furthermore, the level of plasticization observed, seems to be correlated to the solubility parameter differences between the various components. No relevant relation was observed with regard to the melting points of surfactants and HLB values of the surfactants. The crystallinity of API was absent following hot-melt processing. The results of the study demonstrated that surfactants such as Tween-80 and Docusate sodium could be used as plasticizers for the various carrier polymers when hot-melt extrusion technique is employed.

Acknowledgements

The authors are grateful to Dr. Zeri Teweldemedhin and Mr. William Polak for their assistance and valuable discussions.

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