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Comparison of HPMC based polymers performance as carriers for manufacture of solid dispersions using the melt extruder

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ABSTRACT

Preparation of amorphous solid dispersions using hot-melt extrusion process for poorly water soluble compounds which degrade on melting remains a challenge due to exposure to high temperatures. The aim of this study was to develop a physically and chemically stable amorphous solid dispersion of a poorly water-soluble compound, NVS981, which is highly thermal sensitive and degrades upon melting at 165 °C. Hydroxypropyl Methyl Cellulose (HPMC) based polymers; HPMC 3cps, HPMC phthalate (HPMCP) and HPMC acetyl succinate (HPMCAS) were selected as carriers to prepare solid dispersions using hot melt extrusion because of their relatively low glass transition temperatures. The solid dispersions were compared for their ease of manufacturing, physical stability such as recrystallization potential, phase separation, molecular mobility and enhancement of drug dissolution. Two different drug loads of 20 and 50% (w/w) were studied in each polymer system. It was interesting to note that solid dispersions with 50% (w/w) drug load were easier to process in the melt extruder compared to 20% (w/w) drug load in all three carriers, which was attributed to the plasticizing behavior of the drug substance. Upon storage at accelerated stability conditions, no phase separation was observed in HPMC 3cps and HPMCAS solid dispersions at the lower and higher drug load, whereas for HPMCP, phase separation was observed at higher drug load after 3 months. The pharmaceutical performance of these solid dispersions was evaluated by studying drug dissolution in pH 6.8 phosphate buffer. Drug release from solid dispersion prepared from polymers used for enteric coating, i.e. HPMCP and HPMCAS was faster compared with the water soluble polymer HPMC 3cps. In conclusion, of the 3 polymers studied for preparing solid dispersions of thermally sensitive compound using hot melt extrusion, HPMCAS was found to be the most promising as it was easily processible and provided stable solid dispersions with enhanced dissolution.

1. Introduction

Solid dispersions have been extensively studied to improve oral bioavailability of compounds which in general show poor dissolution characteristics, including those with low aqueous solubility (Serajuddin, 1999; Leuner and Dressman, 2000). Among the various techniques to manufacture solid dispersions, hot melt extrusion has gained popularity relative to traditional techniques such as solvent evaporation, since the hot melt extrusion process can be performed continuously at commercially meaningful scale with minimal dust formation (Crowley et al., 2007; Repka et al., 2007, 2008; Breitenbach, 2002). The shear force imparted by the extruder can effectively deaggregate and disperse drug in polymer matrix. Crystalline drugs may be converted to their amorphous forms depending on processing conditions such as temperature settings and screw configuration and speed. However, the biggest challenge related to the use of melt extruder is the high temperatures that the drug is exposed to during the extrusion process, which may lead to substantial degradation for thermally sensitive compounds (Sheng et al., 2008).

In the recent past there are numerous publications discussing the manufacture of amorphous solid dispersions starting with crystalline compounds using melt extruder (Follonier et al., 1994; Breitenbach, 2002; Ghebre-Sellassie and Martin, 2003; Repka et al., 2002). Most of the compounds used were either of low melting point or were thermally stable, which exhibit few challenges during the melt extrusion processing. Preparation of amorphous solid dispersions of compounds with high melting points (>200 °C) or those which degrade upon melting using melt extrusion remains a challenge. In such cases, one alternative is to first convert the crystalline form of the drug substance to amorphous form possibly by solvent evaporation method, and then subjected to melt extrusion

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Table 1
NVS 981 physico-chemical properties.

Properties	NVS 981
MW	810.47
Solubility in water (mg/ml)	<0.1
Melting point	165 °C
T_g	75 °C
T_k (Kauzmann temp)	−54 °C (T_m/2 in K) 25 °C (T_g − 50 in K)
Degradation temperature	Degrades upon melting
Strong or Fragile glass former	Fragile (T_m/T_g (in K) = 1.25); D (VTF eq) = 6.18 (fragile)

process in the presence of suitable polymers. The other possible way of converting the high melting compounds to amorphous form would be to introduce suitable solubilizing agent/carriers in the formulation which could solubilize the compound under the selected melt extrusion conditions.

In case of thermally sensitive compounds, the choice of the suitable carrier polymers and equipment settings (which include screw speed and barrel temperature) greatly influence the extent of drug crystallinity and the degradation profile of the solid dispersions. Numerous water-soluble carriers, surfactants and plasticizers have been investigated to prepare solid dispersions. These materials include polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), Tween 80 and sugars (Serajuddin, 1999; Repka and McGinity, 2000; Ghebremeskel et al., 2007). However, in the past several years this research has been broadened to include water insoluble polymers such as Eudragit® and enteric coating polymers such as Hydroxypropyl Methyl Cellulose Phthalate (HPMCP) (Goracinova et al., 1995) and Hydroxypropyl Methyl Cellulose Acetyl Succinate (HPMCAS) (Al-Obaidi and Buckton, 2009; Curatolo et al., 2009; Konno and Taylor, 2008; Ghebremeskel et al., 2007). The improvement in drug dissolution from such matrices has been attributed to increased surface area due to a reduction in agglomeration and particle size and improved wetting properties of select polymers. HPMCP and HPMCAS have found extensive use in enteric coatings as these polymers are insoluble in gastric fluid but will swell and dissolve rapidly in the mildly alkaline pH of the upper intestine (Nakamichi et al., 2002; Henrist and Remon, 1999). There are not many publications in the literature comparing the melt extrusion processing parameters with changes in polymers used for making solid dispersions.

The objective of this study was to develop a suitable amorphous solid dispersion formulation for a poorly water soluble compound, NVS981, using melt extrusion. In addition, this study also aimed to compare the ease of processibility, physical stability and dissolution behavior of NVS981 solid dispersions prepared using enteric-coating polymers, HPMCP and HPMCAS and non-enteric coating polymer HPMC 3cps.

The challenge with NVS981 was that it is a high melting compound, degrades on melting and is very thermally sensitive to chemical degradation (Table 1). Solvent evaporation method to manufacture solid dispersions was not possible in this case due to the low solubility of the polymers in the organic solvents, which were found suitable for dissolving crystalline form of NVS981. The only alternative was to use melt extrusion process as an alternative to solvent evaporation method for manufacture of solid dispersions. Due to the need for high drug loading and poor solubility of NVS981 in various polymers and solubilizers, it was not possible to convert the drug substance into amorphous form directly in the melt extruder at temperatures below its melting point. Therefore NVS981 was first converted to amorphous form using solvent evaporation and then melt extruded with either non-enteric coating polymer HPMC 3cps or enteric coating polymers HPMCP or HPMCAS. As the formation of solid dispersions is often accompanied by partial loss of drug crystallinity, amorphous NVS981 was used as a starting material for a meaningful comparison between the polymers.

It has been well noted in literature that there exists a gap in the predictability of the solid dispersions with respect to physical stability (phase separation and recrystallization) and dissolution behavior (Craig, 2002). Changes in drug dissolution on account of drug recrystallization and appearance of newer polymorphs represent a challenge. The phenomenon of drug recrystallization is attributed to residual molecular mobility, which has been measured using thermally stimulating depolarization current at glass transition temperatures with some success (Shmeis et al., 2004; Bhugra et al., 2008; Boutonnet-Fagegaltier et al., 2002). Recently, the Flory–Huggins theory, originally used to predict miscibility of polymer blends has been invoked to explain the relative differences in the dissolution behavior of drug from polymer matrices. The computed χ-parameter (interaction parameter) may be useful in rank ordering various polymers for altering the dissolution characteristics of the drug (Greenhalgh et al., 1999; Ghebremeskel et al., 2007).

In this study, the interaction parameter, the χ-value for each polymer–drug combination, and drug substance molecular mobility in the three solid dispersions, were calculated in an attempt to understand the correlation between the interaction value and molecular mobility to physical stability and enhancement of the dissolution of the model hydrophobic drug.

2. Materials and methods

2.1. Materials

The drug substance used in this study is a Novartis compound, NVS981 (Table 1). HPMC 3cps was obtained from Dow Chemicals, USA, HPMC phthalate (HPMCP, HP50) and HPMC acetyl succinate (HPMCAS) were obtained from Shin Etsu, USA. All other materials used were of reagent grade.

2.2. Preparation of solid dispersions

For these studies, crystalline NVS981 was first converted to amorphous form by using a solvent evaporation procedure. NVS981 was first dissolved in methylene chloride by sonication. The solvent was then removed by Rotovap method and the amorphous nature of the NVS981 was confirmed by powder X-ray diffraction (XRPD) and modulated differential scanning calorimetry (MDSC).

Propylene glycol was used as a plasticizer for manufacture of solid dispersions of NVS981 with polymers in the hot melt extruder. Propylene glycol was first mixed with the polymer at a level described in Table 2, followed by addition of amorphous NVS981 at a 20% or 50% (w/w) level. Hot melt extrusion of drug–polymer blends was performed on a Haake Minilab extruder (Minilab 557-2200, Thermoelectron) consisting of a twin co-rotating screws, which are used for mixing as well as transporting the material along. The screw rate of the twin co-rotating screws was kept at 100–200 rpm. The temperature settings for extrusion of the samples and the amount of plasticizer used depended on the polymer and are described in Table 2. The extruded material was collected after quench cooling to room temperature, then milled using a Fitz mill and screened using a 0.8 mm mesh. The milled material (granules) was stored at room temperature in amber colored glass bottles because NVS981 is light sensitive.

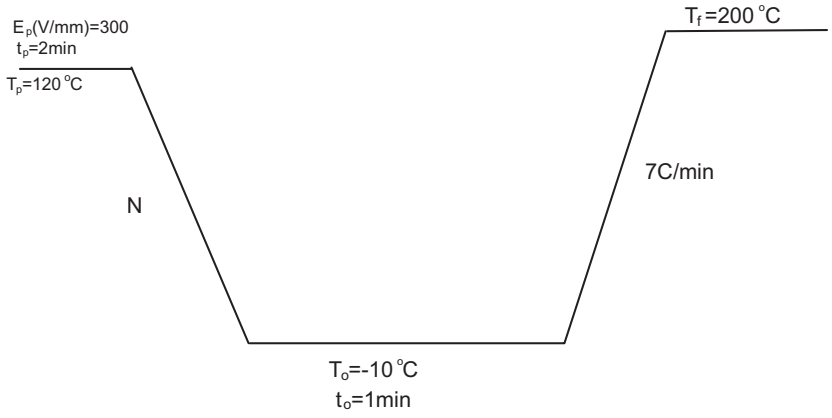
2.3. Characterization of solid dispersions

2.3.1. Modulated differential scanning calorimetry (MDSC)

MDSC was performed using a differential scanning calorimeter Q1000DSC (TA instruments, New Castle, Delaware, USA).

Table 2
Composition and process parameters used for solid dispersion preparation using melt extruder.

Polymer	Drug load (%w/w)	Propylene glycol (%)	Process temp. (°C)	Extruder screw RPM
HPMC 3 cps	20	3.75	130	150
	50	0	130	150
HPMCAS	20	3.75	120	150
	50	2	130	150
HPMCP	20	4.5	130	150
	50	2.5	130	150



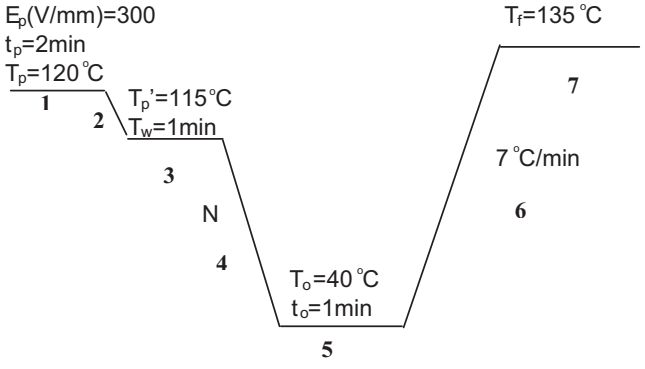
Scheme 1. Representation of TSDC experiment procedure where T_p is polarization temperature, t_p is polarization time, T_o is freezing temperature, t_o is the holding time at freezing temperature and T_f is final temperature to which a sample is heated.

Instrument calibration was run using Indium supplied by TA Instruments. The sample was placed in an aluminum DSC pan, and its weight accurately recorded. The pan was covered with a lid with pinholes. The sample cell was equilibrated at 0 °C for 8 min, then heated to 200 °C in a nitrogen atmosphere under modulation conditions of ±1.0 °C for every 60 s with an underlying heating rate of 2 °C/min.

2.3.2. Determination of molecular mobility using thermally stimulated current (TSC)

2.3.2.1. Thermally stimulated depolarization current (TSDC). The TSDC experiment was used to detect and localize the different relaxations occurring at the glass transition temperature (T_g). Depolarization current measurements were performed on a TSC II instrument (Setaram instrument, Caluire, France). The instrument was calibrated for temperature using NIST (National Institute of Standards and Technology) indium. Samples (~2–3 mg) were weighed into aluminum DSC pans, covered with a small piece of Teflon, and placed between the electrodes of a parallel plane capacitor that was then shielded by a Faraday cage, evacuated to 10^{-4} mbar, and flushed several times with 1.1 bar of high purity helium prior to experiments. TSDC experiments were conducted according to the procedure shown in Scheme 1. In all experiments, the following parameters were used: polarization time (t_p) = 2 min, polarizing field intensity (E_p) = 300 V mm^{-1}, freezing temperature (T_o) = −10 °C, holding time at the freezing temperature (t_o) = 1 min., heating rate (r) = 7 °C/min, and the final temperature to which a sample was heated (T_f) = 200 °C. Cooling was conducted using liquid nitrogen connected to the Faraday cage according to the Newtonian cooling mode (N), which allows the sample to reach the freezing temperature T_o, as fast as possible ($N \geq 20$ °C/min). T_p, the polarization temperature, was varied between experiments as presented in Table 5. The polarization temperature for each material was set 15–30 °C higher than the glass transition temperature obtained by DSC to ensure that all molecular dipolar motions below, at or above the glass transition as detected by DSC were activated.

2.3.2.2. Thermal windowing. Apart from TSDC experiments, further thermal windowing experiments were used to study the details of each complex relaxation as shown in Scheme 2. In all experiments, the following parameters were used: the polarization time (t_p) = 2 min, polarizing field intensity (E_p) = 300 V mm^{-1}, isothermal holding time after turning the field off (t_w) in step 3 = 1 min, isothermal holding time at the freezing temperature (t_o) in step 5 = 1 min, heating rate (r) = 7 °C/min, and width of the polarizing window in the thermal windowing experiment, $\Delta T = T_p - T_p' = 5$ °C. By decreasing the polarization temperature systematically, while keeping T constant, different single modes or narrowly distributed relaxations will be selectively activated and will show as peaks with a maximum temperature T_m (note that the temperature of peak maximum T_m decreases as T_p decreases). As discussed above, cooling was conducted using liquid nitrogen connected to the Faraday cage according to the Newtonian cooling mode ($N \geq 20$ °C/min). The experimental parameters that varied between experiments were T_p, the polarization temperature,



Scheme 2. Representation of TSDC thermal windowing procedure where T_p is polarization temperature, t_p is polarization time, T_p' is temperature to which the sample is cooled, T_w is the holding time at T_p', T_o is freezing temperature, t_o is the holding time at freezing temperature and T_f is final temperature to which a sample is heated.

T_o, the freezing temperature, and T_f, the final temperature to which a sample was heated. The experimental conditions used are presented in the results section under their respective figures.

2.4. In vitro dissolution testing

Solid dispersion granules of NVS981 with different HPMC based polymers was mixed with extragranular excipients such as Lactose, Crospovidone and Magnesium stearate and compressed into 9 mm round tablets for 50% drug load solid dispersions and 6-mm round tablets for 20% drug load solid dispersions using a compression force of 1500–2500 lb. In vitro dissolution at 37 °C was performed using a USP 24 method 2 (paddle method) dissolution apparatus. Dissolution of samples was studied in 1000 ml, pH 6.8 phosphate buffer (0.05 M) using paddle method at paddle speed of 50 rpm. The medium chosen was non-sink condition but based on in vivo data was predictive for NVS981. Samples were taken at 5, 10, 15 and 30 min and filtered using a 0.45-μm filter and analyzed for NVS981 content using a reversed-phase HPLC method.

2.5. Physical stability

Physical stability, such as recrystallization and phase separation was studied for the different solid dispersions stored under accelerated stability conditions of 40 °C/75% RH for 3 months. Samples were characterized using MDSC and Powder X-ray diffraction and the results were compared with the stability predicted by TSC.

3. Results and discussion

3.1. Ease of manufacturing

Various parameters such as polymer glass transition temperature, processing temperature, drug substance and polymer degradation temperature and amount of plasticizer required, dictate the ease of manufacturing of solid dispersions using melt extruder. Trials evaluating the ease of processing and the effect of temperature on the preparation and chemical stability of solid dispersions at a 20% and 50% (w/w) level of the NVS981 were conducted on the melt extruder. The two challenges encountered while preparing solid dispersions of NVS981 were firstly that the drug substance degrades on melting and secondly the drug substance is very susceptible to chemical degradation at high temperatures (Table 1). Since NVS981 could not be converted to amorphous form by melting, the drug substance needed to be converted to amorphous form via solvent evaporation method. Although the T_g of NVS981 was low (75 °C), in order to form a single phase miscible system by melt extrusion with polymer, processing temperatures above the T_g of NVS981 were needed. Preliminary MDSC studies indicated that propylene glycol was the most suitable plasticizer to provide single phase solid dispersion of NVS981 with various water-soluble and enteric polymers and also facilitated using low processing temperatures on the melt extruder.

Table 3
Assay of NVS981 amorphous drug substance prepared by solvent evaporation method and different solid dispersions prepared by melt extrusion.

Solid dispersions	% Assay of NVS981
NVS981 amorphous drug substance	97.0
20%w/w NVS981 in HPMCAS	95.0
50%w/w NVS981 in HPMCAS	97.6
20%w/w NVS981 in HPMC 3cps	95.5
50%w/w NVS981 in HPMC 3cps	96.1
20%w/w NVS981 in HPMCP	80.7
50%w/w NVS981 in HPMCP	98.0

As shown in Table 2, the quantity of plasticizer needed varied depending upon the polymer as well as the drug load. It was noted that the amount of plasticizer needed for processing high drug loading of 50% (w/w) in combination with each of the polymer was lower compared to the 20% drug loading and in fact no plasticizer was needed for 50% NVS981 solid dispersions with HPMC 3cps during melt extrusion. This can be attributed to the drug substance itself having a plasticizer effect on the polymer due to its low T_g. Therefore, it is important to note that during melt extrusion process, the use of drug substance (with low melting point or T_g) as a plasticizer should not be ruled out. Further, it was noted that HPMCP polymer required higher concentrations of plasticizer compared to HPMC 3cps or HPMCAS which possibly could be attributed to the higher T_g (142–150 °C) of HPMCP compared to HPMC 3cps or HPMCAS. A high resistance (high torque values) to forming a molecular miscible system was observed with HPMCP compared to the other two polymer systems. It is possible that the amount of plasticizer needed to reduce the elastic modulus, tensile strength, polymer melt viscosity and glass transition temperature of HPMCP may be higher compared to the other two grade HPMC polymers. But for all the polymers studied, the variations in processing temperatures and plasticizer levels as shown in Table 2 were able to provide a single phase miscible system initially as observed by MDSC. Comparing the processability by melt extrusion of the 3 polymers, HPMC 3cps was more easily processible compared to HPMCAS, which in turn was easier to process compared to HPMCP.

Since NVS981 is very sensitive to high temperature and pressure, the chemical stability of the solid dispersions was studied by determining the assay and the degradation profile of the drug substance after melt extrusion. As shown in Table 3, no significant degradation of the drug substance was observed for all solid dispersions studied except 20% NVS981 in HPMCP polymer, in which higher degradation was observed. This could be the result of high torque observed during the processing of 20% (w/w) NVS981 HPMCP solid dispersion resulting in higher internal temperature or the degradation could be coming from propylene glycol which was present at higher concentrations in 20% (w/w) NVS981 HPMCP

Table 4
Physical stability of solid dispersions upon storage at accelerated conditions of 40 °C/75% RH.

Solid dispersion	Condition	MDSC T_g (°C)	Comment
20% NVS981–HPMC 3cps solid dispersion	Initial	T_g = 74.8	No phase separation on stability
	40 °/75%RH/3M closed	T_g = 75.0	
50% NVS981–HPMC 3cps solid dispersion	Initial	T_g = 77	No phase separation on stability
	40 °C/75%RH/3M closed	T_g = 74.7	
20% NVS981–HPMCP solid dispersion	Initial	T_g = 52.4	Phase separation observed at 3 M stored at 40 °C/75% RH
	40 °C/75%RH/3M closed	T_g = 79.0 and 150.0	
50% NVS981–HPMCP solid dispersion	Initial	T_g = 78.24	Phase separation observed at 3 M stored at 40 °C/75% RH
	40 °C/75%RH/3M closed	T_g = 70.83 and 113.78	
20% NVS981–HPMCAS solid dispersion	Initial	T_g = 78.3	No phase separation on stability
	40 °C/75%RH/3M closed	T_g = 89.0	
50% NVS981–HPMCAS solid dispersion	Initial	T_g = 71.9	No phase separation on stability
	40 °C/75%RH/3M closed	T_g = 80.42	

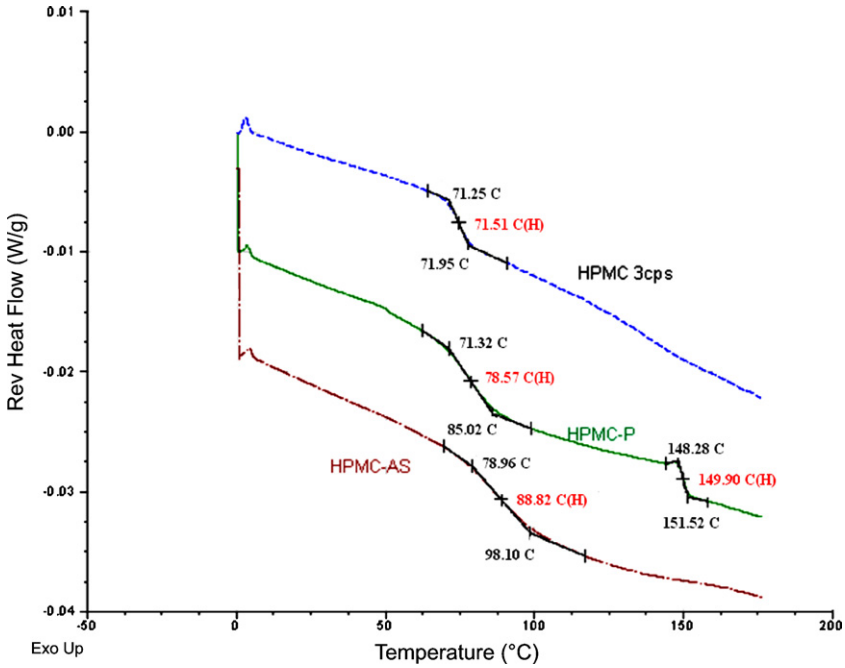


Fig. 1. MDSC for 20% NVS981 solid dispersion with HPMCAS, HPMC 3cps and HPMCP stored under accelerated stability conditions of 40 °C/75%RH for 3 months.

solid dispersion. Overall, processing with suitable concentrations of plasticizer and low temperatures resulted in acceptable solid dispersions using melt extruder.

3.2. Physical stability

The physical stability of NVS981 solid dispersions with the three polymers HPMC 3cps, HPMCP and HPMCAS at 20% and 50% drug loading was studied under accelerated stability conditions and the results are shown in Table 4. A single T_g (indicating molecular miscibility) was observed for all the 3 polymers with T_g ranging from 70 to 85 °C, as measured by MDSC, immediately after the manufacture at the 2 drug loads of 20 and 50%. Upon storage under accelerated stability conditions for 3 months, no phase separation was observed for solid dispersions made with HPMC 3cps and HPMCAS as studied by MDSC and no re-crystallization

Table 5a
Extent of substitution of HPM based polymers.

Polymer	Extent of substitution (wt%)				
	Methoxyl	Hydroxypropyl	Acetyl	Succinoyl	Pthalyl
HPMC 3 cps	*22.3*	*7.1*	–	–	–
HPMC phthalate[a]	22.3	7.1	–	–	22.5
HPMC acetate succinate (HF)[b]	23.6	7.3	11.3	7.3	–

[a] Extent of substitution obtained from Fukasawa and Obara (2003).
[b] Extent of substitution obtained from Fukasawa and Obara (2004).

Table 5b
Solubility parameter calculation for the drug NVS981.

Group	Number of groups	V (cm^3/mol)	$\sum V$	F_d (J$^{1/2}$ cm$^{2/3}$ mol^{-1})	F_p (J$^{1/2}$ cm$^{2/3}$ mol^{-1})	E_h (J/mol)	$\sum F_d$	$\sum F_p^2$	$\sum E_h$
–CH_2–	12	16.1	193.2	270	0	0	3240	0	0
>CH–	12	–1	–12	80	0	0	960	0	0
Cl–	1	24	24	450	550	400	450	302,500	400
–CO–	5	10.8	54	290	770	2000	1450	2,964,500	10,000
–CH_3	8	33.5	268	420	0	0	3360	0	0
–CH=	2	13.5	27	200	0	0	400	0	0
>C=	2	–5.5	–11	70	0	0	140	0	0
–OH	2	10	20	210	500	20,000	420	500,000	40,000
Ring closure (5+atoms)	4	16	64	190	0	0	760	0	0
–O–	3	3.8	11.4	100	400	3000	300	480,000	9000
>C<	1	–19.2	–19.2	–70	0	0	–70	0	0
–N<	1	–9	–9	20	800	5000	20	640,000	5000
–CO–O–	1	18	18	390	490	7000	390	240,100	7000
			628.4				11,820	5,127,100	71,400

$\delta_d = \sum F_d/V = 18.81\,\mathrm{J}^{1/2}/\mathrm{cm}^{3/2}$; $\delta_p = \sqrt{\sum F_p^2}/V = 3.60\,\mathrm{J}^{1/2}/\mathrm{cm}^{3/2}$; $\delta_h = \sqrt{\sum E_h/V} = 10.65\,\mathrm{J}^{1/2}/\mathrm{cm}^{3/2}$; $\delta = \sqrt{\delta_d^2 + \delta_p^2 + \delta_h^2} = 21.92\ \mathrm{J}^{1/2}/\mathrm{cm}^{3/2}$.

Table 5c
Drug–polymer interactions based on solubility parameters.

Polymer	δ_d	δ_p	δ_h	δ	$\Delta\delta$
HPMC 3cps	24.31	13.75	28.65	40.01	18.09
HPMC phthalate	23.77	12.38	26.49	37.69	15.77
HPMC acetate succinate	23.29	12.57	26.19	37.23	15.31

peaks were observed suggesting the system was physically stable. For solid dispersions prepared using HPMCP, phase separation of the T_g's was observed for 50% drug loading as shown in Table 4 and Fig. 1. These results clearly suggest that the NVS981–HPMCP solid dispersion system is saturated and that the additional polymer separates out.

3.3. Solubility parameters

The solubility parameter represents the relative enthalpy of interaction between two substances and predicts that two substances with equal solubility parameters should be mutually soluble. This is in accordance with the general observation that chemical and structural similarity favors solubility. Despite its limitations, the difference between the solubility parameters ($\Delta\delta$) may point to the extent of interaction between the polymer excipient and API (Greenhalgh et al., 1999) and has use for the rational selection of carriers.

The molar volume for the drug and polymers was determined by the group contribution method using the method of Fedors. Solubility parameters of the compounds were evaluated using the group contribution method using the method of Van Krevelen and Hoftyzer (1976), as shown in Table 5b. The average molar composition for the polymeric excipients used for the calculation is shown in Table 5a. The solubility parameter for the polymers was calculated using the group contribution method considering the average molar composition, as shown in Table 5c. The differences in the solubility parameters suggest greater interaction between NVS981 and HPMCAS and HPMCP compared to HPMC 3cps.

3.4. Comparison of molecular mobility

As TSDC is highly sensitive in detecting any underlying small transitions, studies were carried out to confirm the absence or presence of phase separation in HPMC 3cps, HPMCAS and HPMCP solid dispersions, respectively, as shown in Figs. 2a, 3a and 4a. The TSDC spectra also showed a similar trend as MDSC, with a single T_g in case of HPMCAS and HPMC 3cps solid dispersion, and two overlapping relaxations at 79 °C and 138 °C (7 °C/min heating rate) in case of HPMCP. The first peak corresponds to a α-relaxation that is associated with the glass transition event and is in agreement to what was obtained by MDSC.

Further, to understand the data obtained by the experiments with TSDC, thermal windowing was applied to the solid dispersions, as shown in Figs 2b, 3b and 4b. The peak represents the resolution of the TSDC spectrum into their individual relaxations, where each relaxation is characterized by a temperature dependent relaxation time $\tau(T)$. These peaks are obtained by varying the polarization temperature, T_p from 120 °C to 50 °C in intervals (width of the polarization window) $\Delta T = T_p - T_p{}' = 5$ °C. By decreasing the polarization temperature systematically, while keeping ΔT constant, different single modes or narrowly distributed relaxations will be selectively activated and will show as peaks with a maximum temperature, T_m. Thus, it was possible to experimentally resolve heterogeneous and broadly distributed relaxations encountered in real systems into narrowly distributed components, fractions, or segments. From a single thermal windowing experiment, the temperature dependent relaxation time

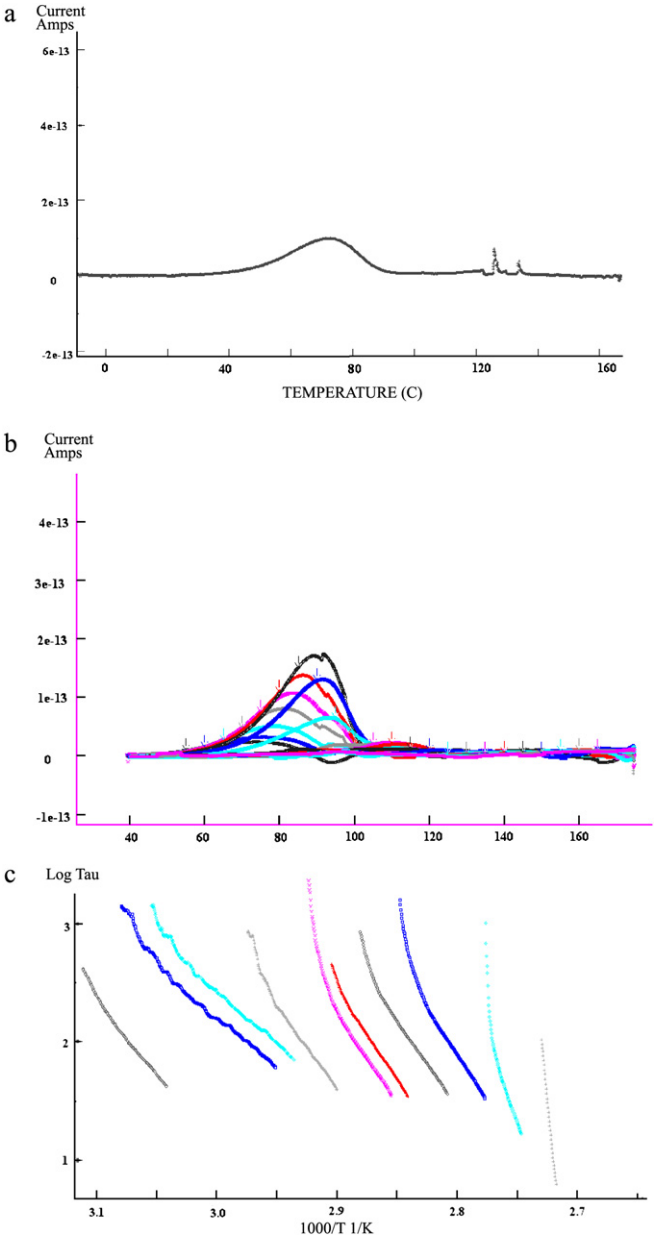


Fig. 2. (a) TSDC for 20% NSV981 solid dispersion with HPMCAS; (b) Thermal windowing (TW) components of the relaxations observed for 20% NSV981 solid dispersion with HPMC AS. Polarization temperature T_p varied from 50 °C to 120 °C with the intervals $\Delta T = T_p - T_p{}' = 5$ °C. (c) Relaxation map of 20% NSV981 solid dispersion with HPMCAS [$\log_{10}\tau(T)$ vs.$1/T$ plots for TW peaks in (b)].

$\tau(T)$, which is indicative of molecular mobility, of a single relaxation mode(s) was directly calculated. As can be seen from Table 6, the activation enthalpy is around 3.20 kcal/mol for HPMCAS solid dispersion as compared to ~9.0 kcal/mol for HPMCP. The activation enthalpy is the least for HPMC-3cps, ~1.4 kcal/mol. The curvature in the relaxation curve as in the lines of $\log_{10}\tau(T)$ vs. $1/T$, seen in Figs. 2c, 3c and 4c clearly shows that all the mobility in case of HPMC 3cps are converging towards one direction thus making it

Table 6
Parameters obtained for 20% ASM solid dispersion with HPMCAS, HPMCP, HPMC 3cps using thermally stimulated current (TSC).

Polymer	T_p (°C) range	T_m (°C) range	Average $\log_{10}\tau(T)$	Average ΔH (kcal/mol)	r^2
HPMCAS	50–100	57–106.3	−46.2	3.20	0.99
HPMCP	55–120	67–114	−139.2	9.0	0.99
HPMC 3cps	55–105	61–108	−19.6	1.49	0.99

a more stable solid dispersion in comparison to HPMCAS and to the least stable HPMCP solid dispersion. The thermal windowing experiments suggests that the molecular relaxation in HPMC 3cps and to a certain extent HPMCAS solid dispersions were more homogenous compared to relaxation pattern observed in HPMCP solid dispersion which could be called more heterogeneous. This observation may also explain the phase separation observed in the NVS981–HPMCP solid dispersions with time.

3.5. Dissolution results

Based on the dissolution results, it was noted that the NVS981 solid dispersions with HPMCP (enteric coated polymer) significantly improved the dissolution of NVS981 compared to either HPMCAS or HPMC 3cps (Fig. 5). The 2 possible explanations for

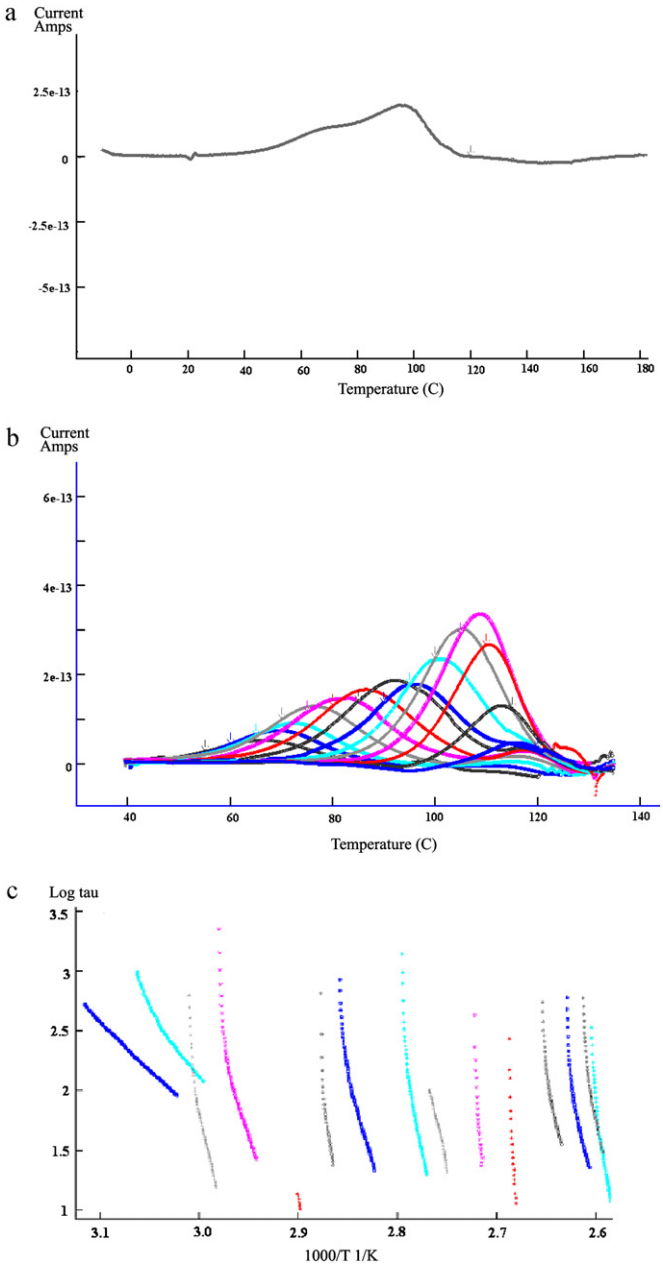


Fig. 3. (a) TSDC for 20% NSV981 solid dispersion with HPMCP; (b) Thermal windowing (TW) components of the relaxations observed for 20% NSV981 solid dispersion with HPMCP. Polarization temperature T_p varied from 50 °C to 120 °C with the intervals $\Delta T = T_p - T_p{}' = 5$ °C. (c) Relaxation map of 20% NVS981 solid dispersion with HPMC-P [$\log_{10}\tau(T)$ vs.$1/T$ plots for TW peaks in (b)].

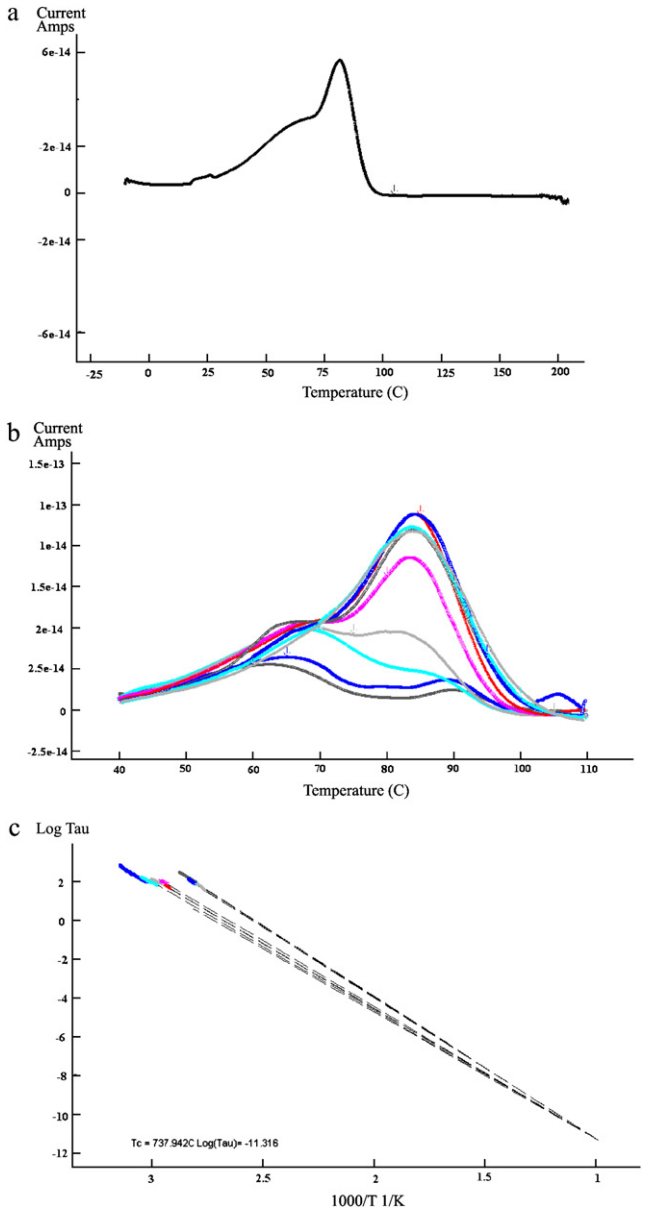


Fig. 4. (a) TSDC for 20% NSV981 solid dispersion with HPMC 3cps; (b) Thermal windowing (TW) components of the relaxations observed for 20% NSV981 solid dispersion with HPMC 3cps. Polarization temperature T_p varied from 50 °C to 120 °C with the intervals $\Delta T = T_p - T_p{}' = 5$ °C. (c) Relaxation map of 20% NVS981 solid dispersion with HPMC 3cps [$\log_{10}\tau(T)$ vs.$1/T$ plots for TW peaks in (b)].

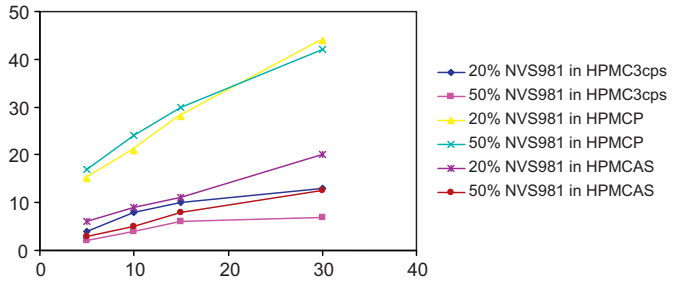


Fig. 5. Dissolution studies of NVS981 solid dispersions with HPMC 3cps, HPMCP and HPMCAS in pH 6.8 media.

the improvement in dissolution observed with HPMCP could be that firstly HPMCP being an enteric coating polymer helps in the dissolution at higher pH and secondly it could be related to the high interaction observed between drug substance and HPMCP as measured by the interaction parameter. The in vivo results in dog for all the 3 solid dispersions (data not shown) indicated a similar trend, with HPMCP solid dispersion improving the bioavailability considerably compared to HPMCAS or HPMC 3cps.

4. Conclusions

Compounds with low T_g and high chemical sensitivity to temperatures, could be successfully processed as solid dispersions using melt extrusion by first converting to amorphous form and then melt extruding in the presence of polymers. Comparing the melt extrusion processing suitability of the 3 polymers, HPMC 3cps, HPMCAS and HPMCP used to prepare solid dispersions of NVS981, HPMC 3cps and HPMCAS polymers were found to be easier to process compared to HPMCP. HPMC 3cps and HPMCAS needed less amount of plasticizer and lower temperatures compared to HPMCP. This observation could be partly attributed to the high T_g of HPMCP and its viscosity. Knowing that the phase separation is the first step before recrystallization and physical instability, HPMCP indicated phase separation compared to the other polymers even at 20% drug load, which is attributed to the super saturation of the polymer matrix with the amorphous drug substance and heterogeneous distribution of molecular mobility in the solid dispersion matrix. Despite the processing challenges and physical instability observed with HPMCP, the dissolution was considerably higher for NVS981–HPMCP solid dispersion even under non-sink conditions compared to the other polymers, suggesting the polymer could be maintaining supersaturation conditions for a longer time due to the strong interaction calculated between the drug substance and HPMCP. In conclusion, of the 3 polymers studied for preparing solid dispersions of a thermally sensitive compound using hot melt extrusion, HPMC acetyl succinate was found to be the most promising as it was easy to process and provided stable solid dispersions with enhanced dissolution.

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