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Compatibility of ticagrelor with pharmaceutical excipients studied with thermal and spectroscopic techniques

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Received April 18, 2019, accepted July 1, 2019

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Pharmazie 74: 583-589 (2019) *doi: 10.1691/ph.2019.9070*

The compatibility between ticagrelor and selected excipients (mannitol, calcium phosphate tribasic, sodium carboxymethyl starch, hydroxypropyl cellulose and magnesium stearate) was investigated by differential scanning calorimetry. The compatibility was further corroborated by Raman spectroscopy and isothermal stress testing experiments. These results revealed that ticagrelor has high compatibility with mannitol, calcium phosphate tribasic, sodium carboxymethyl starch, hydroxypropyl cellulose and magnesium stearate.

1. Introduction

Ticagrelor is a nucleoside analogue with a cyclopentane ring and a nitrogen rich aromatic ring, giving the molecule an overall similarity to adenosine (Fig. 1). As a platelet aggregation inhibitor and an antagonist of the P_2Y_{12} receptor, ticagrelor reduces the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) such as unstable angina, non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI) (Jacobson and Boeynaems 2010). It is quickly absorbed from the gut with a peak plasma concentration after about 1.5 h and 36 of bioavailability (Teng et al. 2010). Ticagrelor blocks adenosine diphosphate (ADP) receptors of subtype P_2Y_{12}, however, this blockage is reversible in contrast to the other antiplatelet drugs such as prasugrel, clopidogrel and ticlopidine (Birkeland et al. 2010). Furthermore, ticagrelor does not need hepatic activation, which might work better for patients with genetic variants regarding the enzyme CYP2C19 (Owen et al. 2007; Tantry et al. 2010).

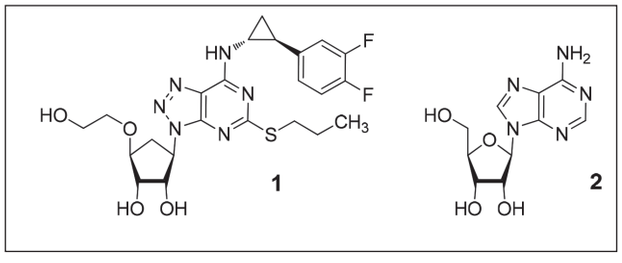


Fig. 1: Structures of ticagrelor **1** and the nucleoside adenosine **2**

For the treatment of patients who have acute coronary syndromes with or without ST-segment elevation, dual antiplatelet therapy with aspirin and clopidogrel is required by current clinical practice guidelines to prevent thrombotic complications (Anderson et al. 2007; Antman 2004; Mauri et al. 2010). However, treatment with clopidogrel would be influenced by the slow and variable transformation of prodrug to the active metabolite, modest and variable platelet inhibition, an increased risk of bleeding and stent thrombosis and myocardial infarction (Jernberg et al. 2006; Kuliczkowski et al. 2009; Mahaffey et al. 2011; Wallentin et al. 2008, 2009; Yusuf et al. 2001). Previous studies have shown that the treatment with ticagrelor instead of clopidogrel would significantly reduce the rate of death from vascular causes, myocardial infarction or stroke, without an increase in the rate of overall major bleeding (Wallentin et al. 2009). Therefore, the development of ticagrelor tablets is of great significance.

Studies of active drug-excipient compatibility plays a key role in the preformulation stage of the development of dosage forms. The potential physical and chemical interactions and incompatibilities between active ingredients and pharmaceutical excipients in solid dosage forms would affect the stability, bioavailability, efficacy and safety of drugs (Clas et al. 1999; Gao et al. 2014; Giron 1998; Mura et al. 1998; Vueba et al. 2005). Thus, the selection of excipient, which can endow the drugs with good bioavailability and productivity, while not affecting the stability of drugs, would significantly alter the efficacy of the drug (Van Tonder et al. 1990; Wang et al. 2014).

Thermal analytical techniques, especially differential scanning calorimetry (DSC), are widely applied in the preformulation stage of development of solid dosage forms for testing the compatibility of excipients with drugs (Ganesh et al. 2013; Gao et al. 2014; Mura et al. 1995, 1998; Pani et al. 2012; Singh 2013; Venkataram et al. 1995). DSC analysis can measure the difference in heat flow between sample and reference under programmed temperature control, indicating physical or chemical discrepancies between sample and reference. During the melting process, even when a small amount of drug's crystalline phase transition occurs, a new endothermic peak will emerge in DSC analysis spectrum. It has been reported that ticagrelor has four crystalline forms with different melting points, the melting ranges of the crystal forms I, II, III of ticagrelor are 146-152 °C, 136-139 °C, 127-132 °C, respectively, and the crystal form IV of ticagrelor melts from 139 °C (Bohlin et al. 2001). The melting of ticagrelor in different crystalline form will show different endothermic peaks in DSC analysis. Generally, the endothermic peak of an excipient with different melting point would not overlap with that of drugs. Therefore, DSC analysis is more accurate and effective than traditional X-ray powder diffraction (XRD) analysis method for the evaluation of drug-excipient compatibility. However, DSC experiments are usually conducted at high temperature and under dry condition, DSC results alone may cause false and questionable conclusions (Clas et al. 1999; Giron 1998; Gingh 2013).

Similar to infrared (IR) spectroscopy, Raman spectroscopy is an effective tool for the evaluation of drug-excipient compatibility. The sample preparation in Raman spectroscopy is simpler than in IR spectroscopy. In addition, moisture has negligible effect on

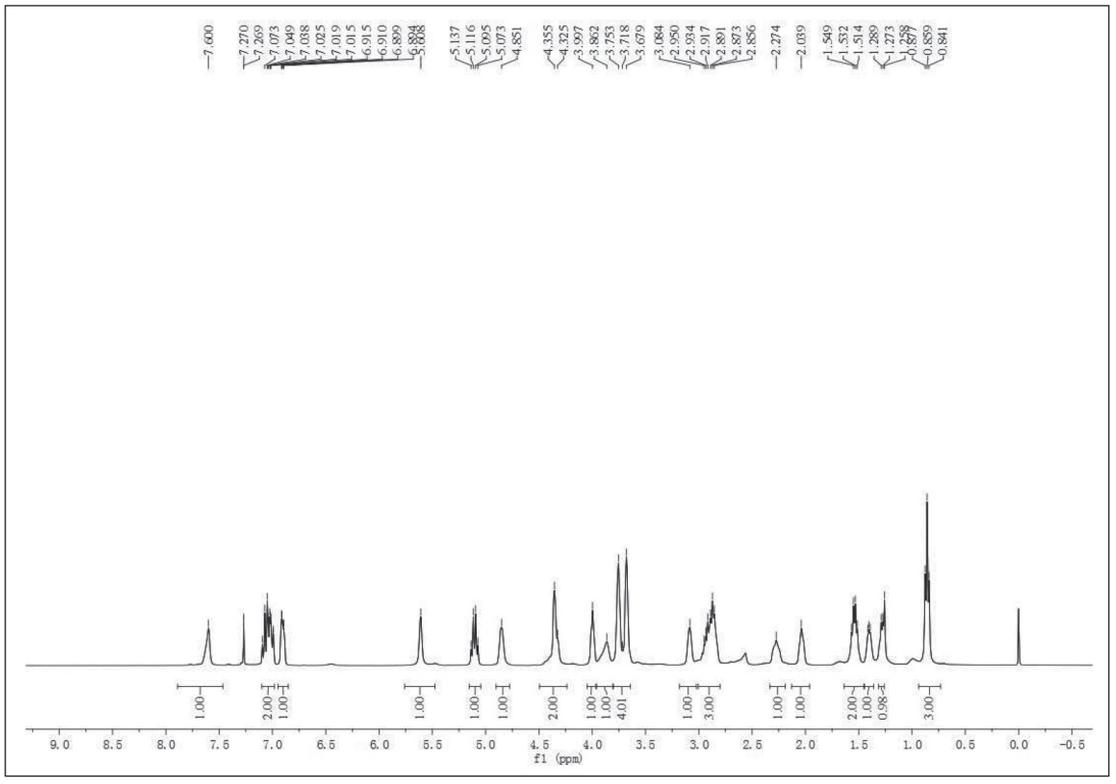


Fig. 2: [1]H NMR spectrum of the synthesized ticagrelor.

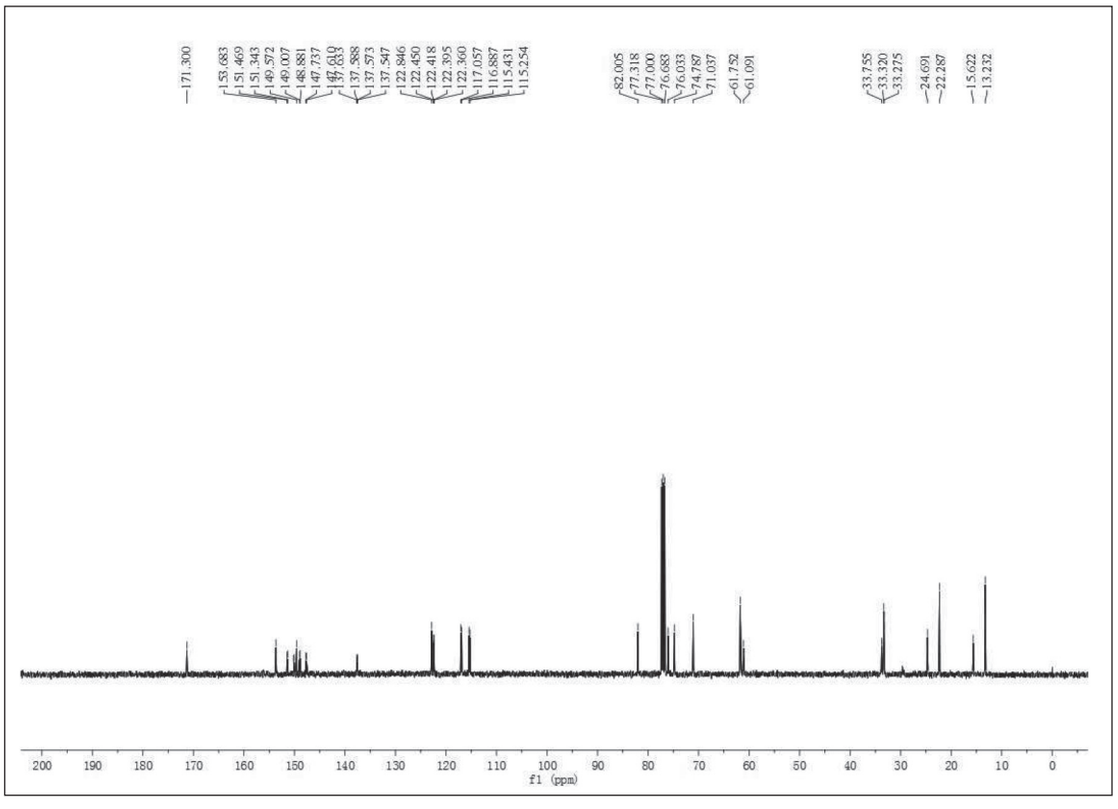
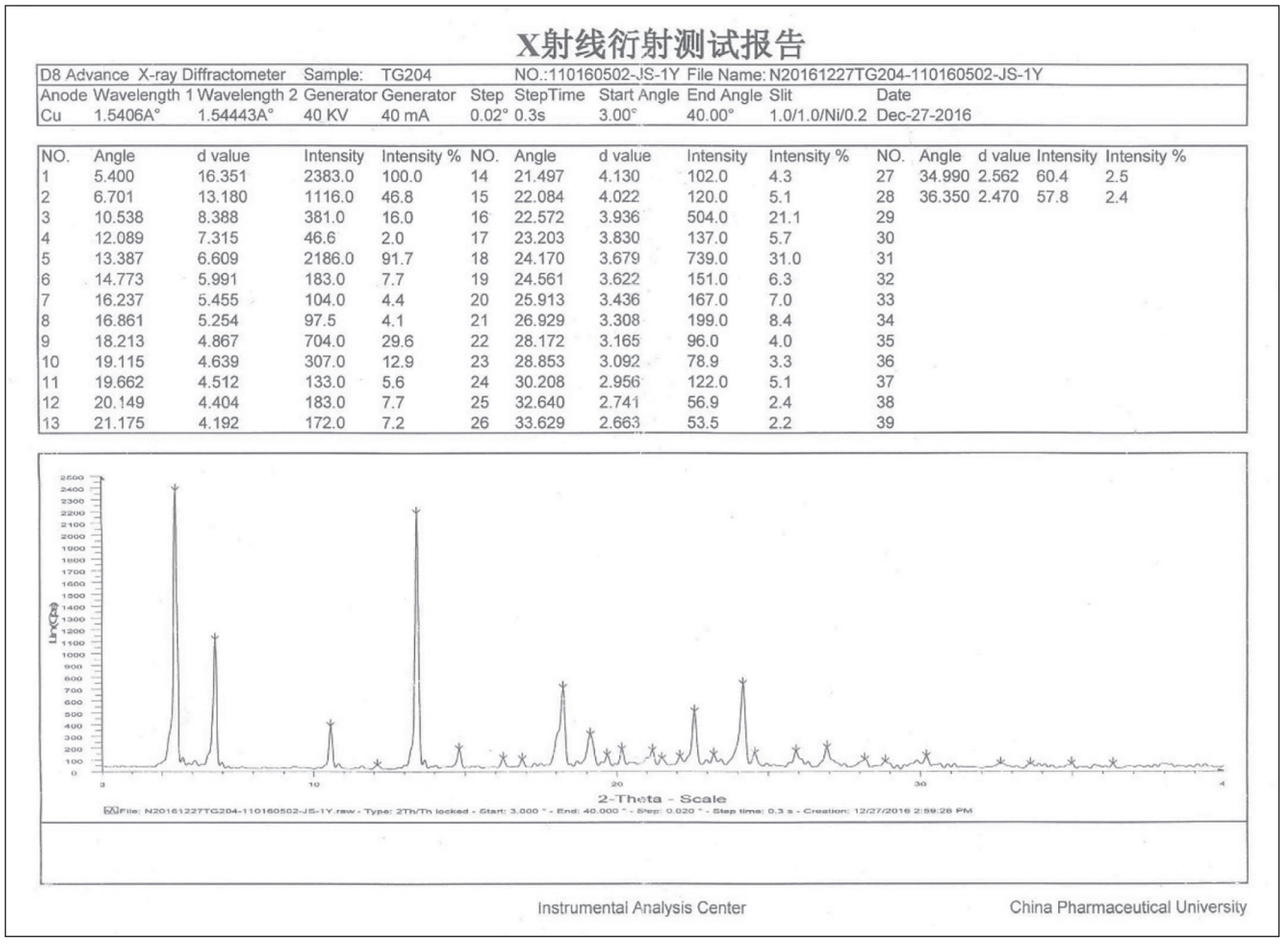


Fig. 3: [13]C NMR spectrum of the synthesized ticagrelor.

Raman spectroscopy compared to IR spectroscopy. The comparison of Raman spectrum of pure drug and drug-excipient complex could further verify the drug-excipient compatibility (Quittmann et al. 2007).

Isothermal stress testing (IST) analysis is now widely used to evaluate the compatibility between drug and excipients. In this method, the drug-excipient complex is stored at a temperature > 50 °C with or without moisture for ~3 weeks, thus, the degra-



X射线衍射测试报告

D8 Advance X-ray Diffractometer		Sample:	TG204		NO.:110160502-JS-1Y		File Name: N20161227TG204-110160502-JS-1Y			
Anode	Wavelength 1	Wavelength 2	Generator	Generator	Step	StepTime	Start Angle	End Angle	Slit	Date
Cu	1.5406A°	1.54443A°	40 KV	40 mA	0.02°	0.3s	3.00°	40.00°	1.0/1.0/Ni/0.2	Dec-27-2016

NO.	Angle	d value	Intensity	Intensity %	NO.	Angle	d value	Intensity	Intensity %	NO.	Angle	d value	Intensity	Intensity %
1	5.400	16.351	2383.0	100.0	14	21.497	4.130	102.0	4.3	27	34.990	2.562	60.4	2.5
2	6.701	13.180	1116.0	46.8	15	22.084	4.022	120.0	5.1	28	36.350	2.470	57.8	2.4
3	10.538	8.388	381.0	16.0	16	22.572	3.936	504.0	21.1	29				
4	12.089	7.315	46.6	2.0	17	23.203	3.830	137.0	5.7	30				
5	13.387	6.609	2186.0	91.7	18	24.170	3.679	739.0	31.0	31				
6	14.773	5.991	183.0	7.7	19	24.561	3.622	151.0	6.3	32				
7	16.237	5.455	104.0	4.4	20	25.913	3.436	167.0	7.0	33				
8	16.861	5.254	97.5	4.1	21	26.929	3.308	199.0	8.4	34				
9	18.213	4.867	704.0	29.6	22	28.172	3.165	96.0	4.0	35				
10	19.115	4.639	307.0	12.9	23	28.853	3.092	78.9	3.3	36				
11	19.662	4.512	133.0	5.6	24	30.208	2.956	122.0	5.1	37				
12	20.149	4.404	183.0	7.7	25	32.640	2.741	56.9	2.4	38				
13	21.175	4.192	172.0	7.2	26	33.629	2.663	53.5	2.2	39				

Fig. 4: XRD spectrum of ticagrelor.

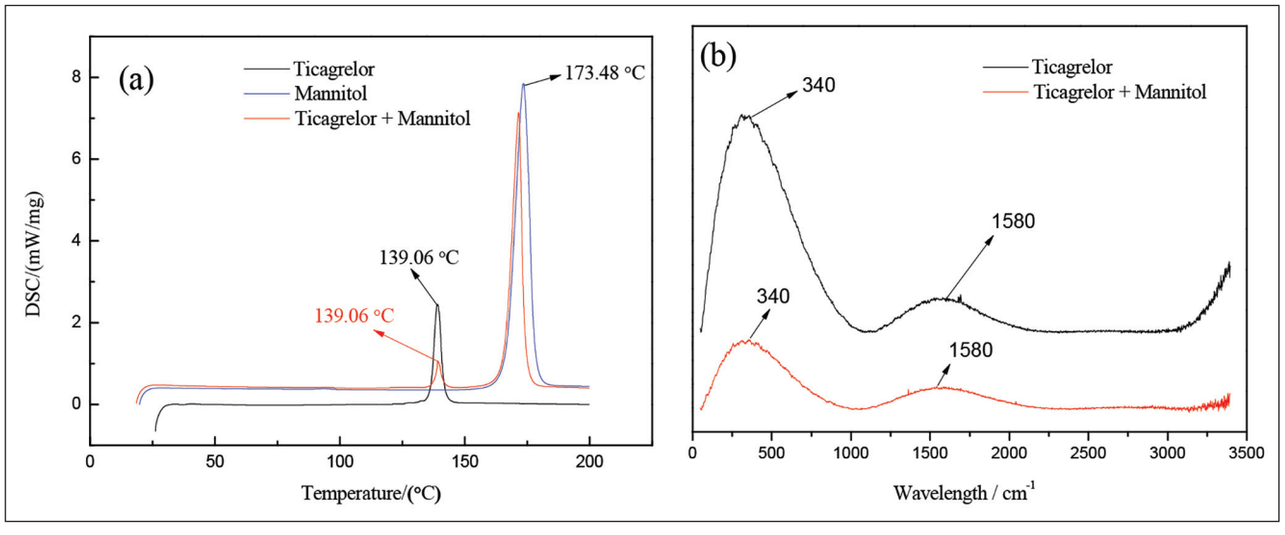


Fig. 5: (a) DSC curve of ticagrelor with mannitol; (b) Raman spectrum of ticagrelor with mannitol.

dation of drug and interaction between drug and excipient is accelerated. Then the drug-excipient complex is analyzed by the change of physical appearance and quantitative determination of drug content using UV-Vis spectroscopy. Therefore, IST analysis is a complementary tool for DSC and Raman spectroscopy to evaluate the compatibility of a drug with selected excipients.

Herein, a combination of DSC, Raman spectroscopy and IST analysis was developed and successfully applied to evaluate the compatibility and stability of ticagrelor in the presence of five pharmaceutical excipients (mannitol and calcium phosphate tribasic as filling agents, sodium carboxymethyl starch as disintegrating agent, hydroxypropyl cellulose as adhesive and magnesium stearate as lubricant). The results demonstrated that ticagrelor

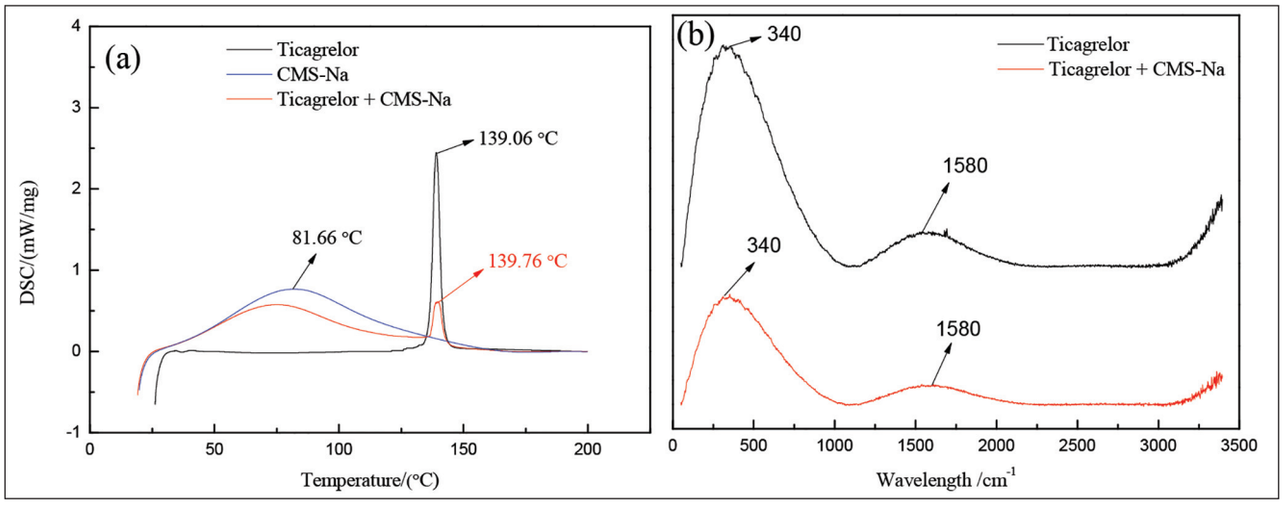


Fig. 6: (a) DSC curve of ticagrelor with sodium carboxymethyl starch (CMS-Na); (b) Raman spectrum of ticagrelor with CMS-Na.

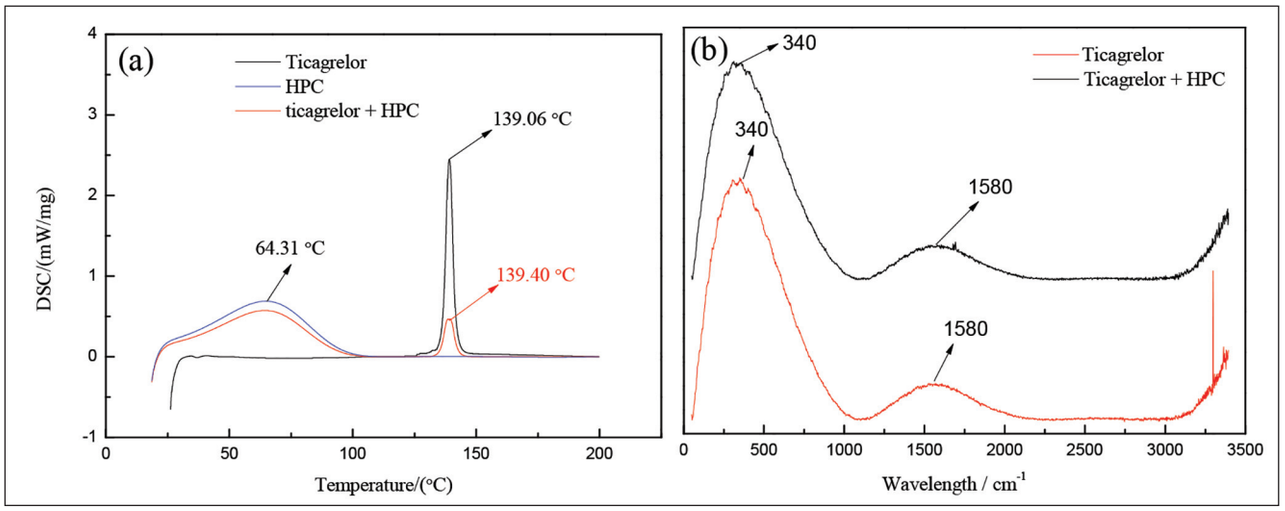


Fig. 7: (a) DSC curve of ticagrelor with hydroxypropyl cellulose (HPC); (b) Raman spectrum of ticagrelor with HPC.

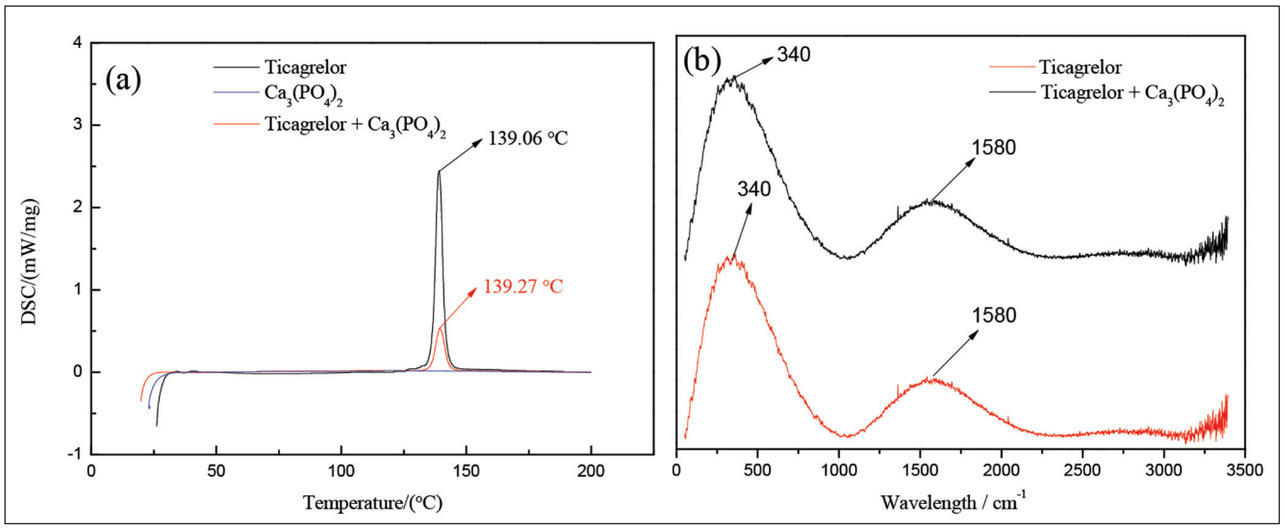


Fig. 8: (a) DSC curve of ticagrelor with $Ca_3(PO_4)_2$; (b) Raman spectrum of ticagrelor with $Ca_3(PO_4)_2$.

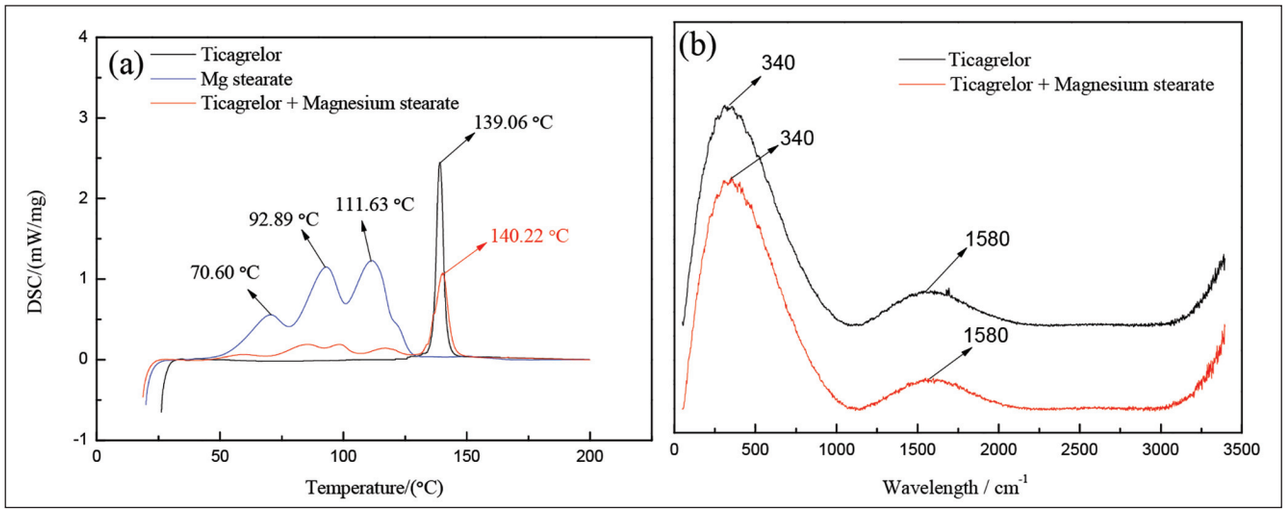


Fig. 9: (a) DSC curve of ticagrelor with magnesium stearate; (b) Raman spectrum of ticagrelor with magnesium stearate.

has a very good compatibility and high stability in the absence and presence of selected excipients.

2. Investigations and results

Ticagrelor was synthesized according to the literature with minor modification (Aufdenblatten et al. 2010; Barrett and Lebold 1990; Dejonghe et al. 2008; Quittmann et al. 2007; Rao and Zhang 2011; Zhang et al. 2012). The product was fully characterized by ^{1}H NMR and ^{13}C NMR (Fig. 2, Fig. 3). According to Bohlin et al. (2001), polymorph form II of ticagrelor has an X-ray powder diffraction (XRD) pattern with 2θ specific peaks at 5.5° (± 0.1°), 6.8° (± 0.1°), 10.6° (± 0.1°), 13.5° (± 0.1°), 14.9° (± 0.1°), 18.3° (± 0.1°), 19.2° (±0.1°), 22.7° (± 0.1°), 24.3° (± 0.1°) and 27.1° (± 0.1°). XRD analysis of the synthesized ticagrelor displays 2θ specific peaks at 5.4°, 6.7°, 10.5°, 13.4°, 14.8°, 18.2°, 19.1°, 22.6°, 24.2°and 27.0° (Fig. 4), which highly matched with the data of referenced drug. These data strongly suggest that the synthesized ticagrelor is in a pure and substantially anhydrous polymorph form II.

Table 1: Onset transition temperature T_{onset}, peak temperature T_{peak} and enthalpy values $\Delta H_{f\,corr}$ of ticagrelor in various drug–excipient mixtures

Sample	Ratio (drug-excipient)	T_{onset} °C	T_{peak} °C	$\Delta H_{f\,corr}$ J g^{-1}
Ticagrelor	-	130.04	139.06	58.08
Ticagrelor + mannitol	1:3	130.28	139.06	56.88
Ticagrelor + CMS-Na	1:3	131.29	139.76	48.00
Ticagrelor + HPC	1:3	131.22	139.40	61.68
Ticagrelor + $Ca_3(PO_4)_2$	1:3	131.95	139.27	55.20
Ticagrelor + magnesium stearate	9:1	130.10	140.22	52.65

$\Delta H_{f\,corr} = \Delta H_{f\,obs}$ /%drug in sample × 100

2.1. Ticagrelor-excipient compatibility testing

DSC curves of ticagrelor, excipients (mannitol, CMS-Na, HPC, $Ca_3(PO_4)_2$ and magnesium stearate) as well as ticagrelor-excipient mixtures are shown in Figs. 5a, 6a, 7a, 8a and 9a. The thermal behavior of ticagrelor, excipients, and the combination of ticagrelor and excipient is compared in the DSC spectra. The corresponding onset transition temperature (T_{onset}), peak temperature (T_{peak}) and enthalpy values (ΔH_f) of ticagrelor and ticagrelor-excipient mixtures are summarized in Table 1.

The Raman spectra of ticagrelor and ticagrelor-excipient mixtures are shown in Figs. 5b, 6b, 7b, 8b and 9b. The compatibility of ticagrelor with excipient can be determined in accordance with the changes of main bands in Raman spectra.

The DSC results show that the melting point of ticagrelor is 139.06 ºC. The data further confirmed that the ticagrelor used in these experiments is exists in crystal form II. Caused by the melting of ticagrelor, the heat of fusion or enthalpy (ΔH_f) was calculated to be 58.08 J g^{-1}. After the melting, no chemical decomposition was detected from DSC results. Therefore, it can be concluded that ticagrelor has good thermal stability and does not contain crystal water. It has been reported that the endothermic peak of drug remains unchanged during the melting process in the majority of cases. However, peak temperature and peak shape would shift or broaden within a small range in different analysis environment or in different mixture of drug and excipient (Mura et al. 1995). Therefore, minor changes of peak temperature and peak shape are allowable.

The DSC curve of mannitol showed an endothermic peak at 173.48 ºC (melting point of mannitol) (Fig. 5a), while the DSC curve of ticagrelor-mannitol mixture showed an endothermic peak at 139.06 ºC with an enthalpy value ΔH_f = 56.88 J g^{-1}. Compared to ticagrelor's melting point (139.06 ºC) and ΔH_f value (58.08 J g^{-1}), minor changes in the DSC curve of the ticagrelor-mannitol mixture indicated a high compatibility of ticagrelor with mannitol. The Raman spectrum of ticagrelor showed two broad absorption bands at 1580 cm^{-1} and 340 cm^{-1} (Fig. 5b). Raman spectrum of ticagrelor-mannitol mixture showed the presence of characteristic absorption bands of ticagrelor (1580 cm^{-1}, 340 cm^{-1}), indicated that there was no change

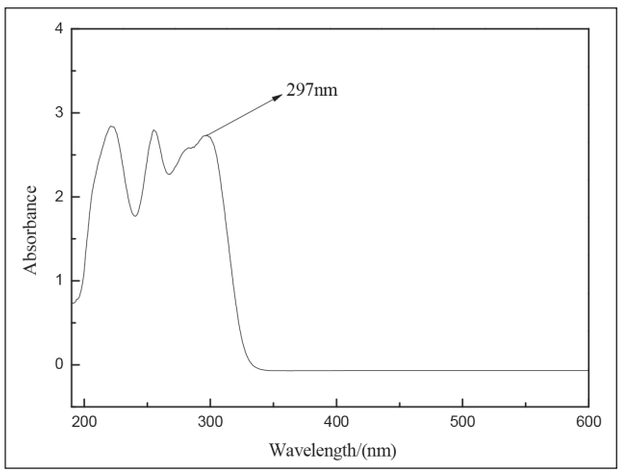


Fig. 10: Absorption spectrum of ticagrelor.

in the structure of ticagrelor. Based on the above results, it could be concluded that ticagrelor is compatible with mannitol.

The DSC trace of CMS-Na showed a broad endothermic peak at 81.66 ºC, probably because of evaporation of adsorbed moisture (Fig. 6a). The melting endotherm of ticagrelor was well retained in the DSC trace of ticagrelor-CMS-Na mixture (139.76 ºC with accompanying ΔH_f value of 48.00 J g^{-1}). In Raman spectrum of ticagrelor-CMS-Na mixture, characteristic bands corresponding to ticagrelor (1580 cm^{-1}, 340 cm^{-1}) were also observed without any new bands in Fig. 6b. Thus, it could be concluded that ticagrelor is compatible with CMS-Na.

Similar to CMS-Na, HPC belongs to the class of cellulose. In the DSC curve of HPC, a broad endothermic peak at 64.31 ºC was observed, due to the evaporation of adsorbed moisture (Fig. 7a). The melting endotherm of ticagrelor was well retained in the DSC trace of ticagrelor-HPC mixture (139.40 ºC with accompanying ΔH_f value of 61.68 J g^{-1}). In Raman spectrum of ticagrelor-HPC mixture, characteristic bands corresponding to ticagrelor (1580 cm^{-1}, 340 cm^{-1}) were observed without any new bands in Fig. 7b. Thus, it can be concluded that ticagrelor is compatible with HPC.

In the DSC scan of $Ca_3(PO_4)_2$, no peak was observed in the range of 40-200 ºC (Fig. 8a). The melting endotherm of ticagrelor was well retained in the DSC trace of ticagrelor-$Ca_3(PO_4)_2$ mixture (139.27 ºC with accompanying ΔH_f value of 55.20 J g^{-1}). In Raman spectrum of ticagrelor-$Ca_3(PO_4)_2$ mixture, characteristic bands corresponding to ticagrelor (1580 cm^{-1} and 340 cm^{-1}) were observed without any new bands (Fig. 8b). Therefore, it was concluded that ticagrelor is compatible with $Ca_3(PO_4)_2$.

The DSC scan of magnesium stearate showed three endothermic peaks at 70.60 ºC, 92.89 ºC and 111.63 ºC (Fig. 9a). The DSC scan of ticagrelor-magnesium stearate mixture showed the melting endotherm of ticagrelor (140.22 ºC with accompanying ΔH_f value of 52.65 J g^{-1}). These results suggests that there is no interaction between magnesium stearate and ticagrelor. In addition, the Raman spectrum of ticagrelor-magnesium stearate mixture only showed the characteristic bands corresponding to ticagrelor (1580 cm^{-1} and 340 cm^{-1}) without any new band (Fig. 9b). Thus, it was concluded that ticagrelor is compatible with magnesium stearate.

Table 2: Results of analysis of IST samples after 3 weeks of storage at stressed conditions

Sample	Ratio (drug-excipient)	% Remaining
Ticagrelor	-	100%
Ticagrelor + mannitol	1:3	99.1%
Ticagrelor + CMS-Na	1:3	98.9%
Ticagrelor + HPC	1:3	101.3%
Ticagrelor + $Ca_3(PO_4)_2$	1:3	98.7%
Ticagrelor + magnesium stearate	9:1	99.4%

2.2. Isothermal stressed testing

Before the analysis of IST samples, UV absorption spectrum of ticagrelor was conducted within the range of 190-800 nm. The maximum absorbance was found at 297 nm (Fig. 10). Therefore, the determination of remaining drug content of IST samples was conducted based on UV absorption at 297 nm.

Results of analysis of IST samples are listed in Table 2, the changes of drug content could manifest the compatibility of drug and excipient. According to the results, there is very small change in the drug content of the samples after 3 weeks of storage of drug-excipient mixtures under stressed conditions of IST studies. This demonstrates that ticagrelor has high stability in drug-excipients mixture of IST sample. Therefore, the IST results further corroborate that all the selected excipients are compatible with ticagrelor.

3. Discussion

In summary, the compatibility between ticagrelor and excipients (mannitol, CMS-Na, HPC, $Ca_3(PO_4)_2$ and magnesium stearate) was evaluated by DSC, Raman spectroscopy and IST techniques. The results confirmed that compatibility of ticagrelor and the related excipients can be rapidly assessed according to DSC exothermic peak position and the unit mass of heat release. Furthermore, the IST analysis after storage of a mixture of ticagrelor and individual excipient under stressed condition can be chosen as a method to consolidate the compatibility results. In this study, DSC analysis and IST method were successfully employed to assess the compatibility of ticagrelor with the excipients. The results indicated that ticagrelor has high stability and compatibility with the selected excipients even after 3 weeks of storage of drug-excipient mixtures under stressed conditions. Therefore, the results corroborated the selected excipients can be used in the further development of immediate release tablet formulations.

4. Experimental

4.1. Materials and instrumentation

Mannitol, calcium phosphate tribasic and magnesium stearate were purchased from Titan Scientific Co. Ltd. (Shanghai, China). Sodium carboxymethyl starch (CMS-Na) was purchased from Zhanwang Pharmaceutical Co. Ltd. (Huzhou, China). Hydroxypropyl cellulose (HPC) was purchased from Chineway Pharmaceutical Tech. Co. Ltd. (Shanghai, China). All chemical compounds were analytical grade and used without further purification.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance-III 400 MHz Spectrometer (at 400 and 100 MHz, respectively) using tetramethylsilane (TMS) as an internal standard. Splitting patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m).

^{1}H NMR and ^{13}C NMR data of the synthesized ticagrelor are listed as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.10 – 6.98 (m, 2H), 6.90 (dd, *J* = 6.4, *J* = 1.9 Hz, 1H), 5.61 (s, 1H), 5.11 (q, *J* = 8.6 Hz, *J* = 1H), 4.85 (s, 1H), 4.34 (d, *J* = 11.8 Hz, 2H), 4.00 (s, 1H), 3.86 (s, 1H), 3.80 – 3.64 (m, 4H), 3.08 (s, 1H), 3.01 – 2.80 (m, 3H), 2.27 (s, 1H), 2.04 (s, 1H), 1.54 (dd, *J* = 14.1, *J* = 7.0 Hz, 2H), 1.45 – 1.36 (m, 1H), 1.28 (d, *J* = 6.7 Hz, 1H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.3, 153.7, 150.8 (dd, *J* = 129.0, *J* = 12.7 Hz), 149.6, 148.3 (dd, *J* = 127.9, *J* = 12.7 Hz), 137.6 (dd, *J* = 5.1, *J* = 3.5 Hz), 122.9, 122.4 (dd, *J* = 5.7, *J* = 3.4 Hz), 117.0 (d, *J* = 17.1 Hz), 115.3 (d, *J* = 17.8 Hz), 82.0, 76.0, 74.8, 71.0, 61.8, 61.1, 33.8, 33.3, 33.3, 24.7, 22.3, 15.6, 13.2.

4.2. Differential scanning calorimetry

DSC analysis was conducted at DSC 200 F3 Maia® thermal analyzer (Netzsch, Germany). Individual samples (ticagrelor and excipients) as well as mixtures of ticagrelor and selected excipients were weighed directly in the pierced DSC aluminum pan and then were scanned in the temperature range of 20 – 200 °C with a heating rate of 10 °C min^{-1} under an atmosphere of dry nitrogen.

4.3. Raman spectroscopy

Raman spectra were recorded in the range of 40-3500 cm^{-1} on a DXR Raman Spectrometer (Thermo Scientific, USA) equipped with a 532 nm laser.

4.4. IR spectroscopy

Absorption spectra of ticagrelor, and ticagrelor-excipient mixtures were recorded on a UV-2450 spectrophotometer (Shimadzu Corp., Kyoto, Japan) in the range of 190 – 600 nm using potassium bromide disks.

4.5. Isothermal stress testing

For IST studies (Pani et al. 2012), drug and five excipients (mannitol, calcium phosphate tribasic, sodium carboxymethyl starch, hydroxypropyl cellulose and magnesium stearate) were weighed in 4 mL glass vials and mixed on a vortex mixer for 2 min, respectively. And then 10 % (w/w) water was added to the vial and the mixture was further mixed with a glass capillary (both ends of which were heat sealed). All of the vials were sealed with teflon-lined screw caps and stored at 40 ºC in a hot air oven (RXH-7-12/c, Changhong Pharmaceutical Machinery and Equipment Factory, Changsha, China) for 3 weeks. These samples were periodically analyzed with UV spectrophotometer in case of any change. Drug-excipient blend without addition of water was used as control compound and stored in refrigerator.

Acknowledgements: This work was supported by the Fujian Education and Scientific Research Project for Young and Middle-aged Teachers (JAT170827 and JAT170819), and the Research Program for Xiamen Overseas Students 2016 funded by Xiamen Municipal Human Resources and Social Security Bureau.

Conflicts of interest: None declared.

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