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Selection of solid-state excipients for simvastatin dosage forms through thermal and nonthermal techniques

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Abstract The importance of developing new pharmaceutical final formulations is nowadays well known. In this paper, we present the study of compatibility between bioactive antihyperlipidemic agent simvastatin and eight currently used pharmaceutical excipients for developing solid dosage forms, namely starch, microcrystalline cellulose, lactose monohydrate, polyvinylpyrrolidone, colloidal silica, talc, magnesium citrate and sorbitol. The compatibility investigations were carried out under ambient temperature by FTIR spectroscopy studies and PXRD patterns and then completed by the use of thermal analysis (TG/DTG/HF) data to study the influence of temperature over stability of binary mixtures.

Keywords Statin · Compatibility study · Simvastatin · Thermal behavior · Excipient · FTIR · PXRD

Introduction

Statins are nowadays considered the most effective and best-tolerated compounds for treating dyslipidemia [1]. The mechanism of action consists in competitive inhibition of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A), which catalyzes the rate-limiting step in the biosynthesis of cholesterol [1, 2]. Simvastatin (SMV) is a member of the statin class of pharmaceuticals and is nowadays a currently used drug for hypolipidemic effect, generally combined with mass loss diet and physical exercise, in order to decrease elevated levels of cholesterol (or to reduce hypercholesterolemia) [1]. Simvastatin is a synthetic derivative of lovastatin, which is a fermentation product of *Aspergillus terreus*. SMV is commercialized generically following the patent expiration under numerous brands, as a singular active substance (like Zocor®) or in combination with another active substance like sitagliptin (Juvisync®), niacin (Simcor®) or ezetimibe (Vytorin®). Along with the primary use of SMV, studies reported potential cardioprotective effect [2], attenuation of the cerebral vascular endothelial inflammatory response in a rat traumatic brain injury [3] or pleiotropic properties which include anti-inflammatory and immunomodulatory effects [4]. Other recent studies revealed that SMV attenuates the loss of body mass, as well as muscle mass, and improves cardiac function [5], and as well revealed an antihypertensive activity and can modulate the antihypertensive effect of losartan in hypertensive hypercholesterolemic animals and patients [6]. However, several side effects were observed, including muscular or liver problems [7] and increased blood sugar levels [8].

The structural formula of SMV ((1*S*,3*R*,7*S*,8a*R*)-8-(2-((2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl)ethyl)-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate)) contains a hexahydronaphtalene ring functionalized as a dimethylbutyrate ester (Fig. 1). SMV is a lactone-type prodrug that is modified in the liver to active hydroxy acid form. Due to the presence of the lactone moiety, SMV is less soluble in water than other statins, but

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this seems to have insignificant effects over clinical biodisponibility [1].

Excipients are nowadays considered "key compounds" in the field of pharmaceutical technology, due to the fact that can influence the lifetime of a formulation and as well can modulate the biodisponibility. The presence of excipients can induce in solid formulation, mainly physical and chemical interactions, while in vivo can lead to physiological ones [9]. Several instrumental techniques were employed in the analysis of newly obtained derivatives [10], but as well in evaluation of compatibility/incompatibility of active pharmaceutical ingredients (API) with excipients, namely thermoanalytical ones [11–13], FTIR spectroscopy [14], DSC [15] and XRD [16]. For a complete understanding of solid-state stability and decomposition, kinetic analysis can be performed on both bioactive/potentially bioactive molecules [17–20].

In this study, we set our goal in the evaluation of compatibility/incompatibility study of binary systems containing SMV and eight different pharmaceutical excipients currently used in solid formulations, namely starch (St), microcrystalline cellulose (MC), lactose monohydrate (LM), polyvinylpyrrolidone (PVP), colloidal silica ($SiO_{2\_}$), talc (T), magnesium citrate (MgC) and sorbitol (Sb). The importance of the study is also sustained by the fact that design of new solid dosage forms is mainly based after a careful selection of excipients, leading to the development of new generic formulations. All the mixtures were analyzed comparatively to SMV and pure excipients by FTIR spectroscopy, PXRD patterns and thermal analysis (TG/DTG/HF). According to our knowledge, the thermal behavior of simvastatin was evaluated only in inert nitrogen atmosphere [21], while the analysis of compatibility study by employing three instrumental techniques and with the use of selected excipients was not previously reported.

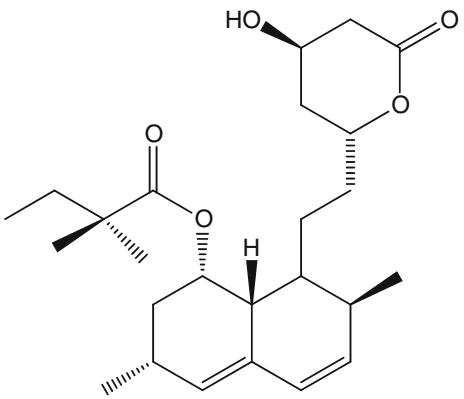


Fig. 1 Chemical structure of simvastatin (SMV)

Materials and methods

Simvastatin (SMV) was obtained from Fluka (pharmaceutical grade) used as received, without further purification. The used excipients (pharmaceutical grade) were used as received, as follows: starch (Grain Processing Corporation, USA), microcrystalline cellulose (ParChem Trading Ltd., USA), lactose monohydrate (Tablettose 80, Meggle, Germany), polyvinylpyrrolidone (BASF, Germany), colloidal silica (Aerosil 200 Evonik Degussa, Germany), talc (Luzenac Pharma, Italy), magnesium citrate (Fluka, Germany) and sorbitol (Sigma, Germany).

The SMV + excipient samples consisted of equal masses of SMV and each excipient. Physical mixtures were prepared by simple mixing of the two substances in an agate mortar with pestle for approximately 5 min. The 1:1 mass ratio was chosen in order to maximize the probability of observing any interaction.

Attenuated total reflection Fourier transform infrared spectroscopy (ATR-FTIR) spectra of the samples were obtained in attenuated total reflectance (ATR) mode on a Bruker Vertex 70 (Bruker Daltonik GmbH, Germany) spectrometer equipped with a Platinium ATR, Bruker Diamond Type A225/Q. Spectra were collected in the 4000–400 cm^{-1} spectral range, with a resolution of 1 cm^{-1} and with 64 co-added scans.

The phase composition of the powders was established by X-ray diffraction, using a Rigaku Ultima IV instrument operating at 40 kV and 40 mA. The X-ray diffraction patterns were recorded using the monochromated CuK_{α} radiation.

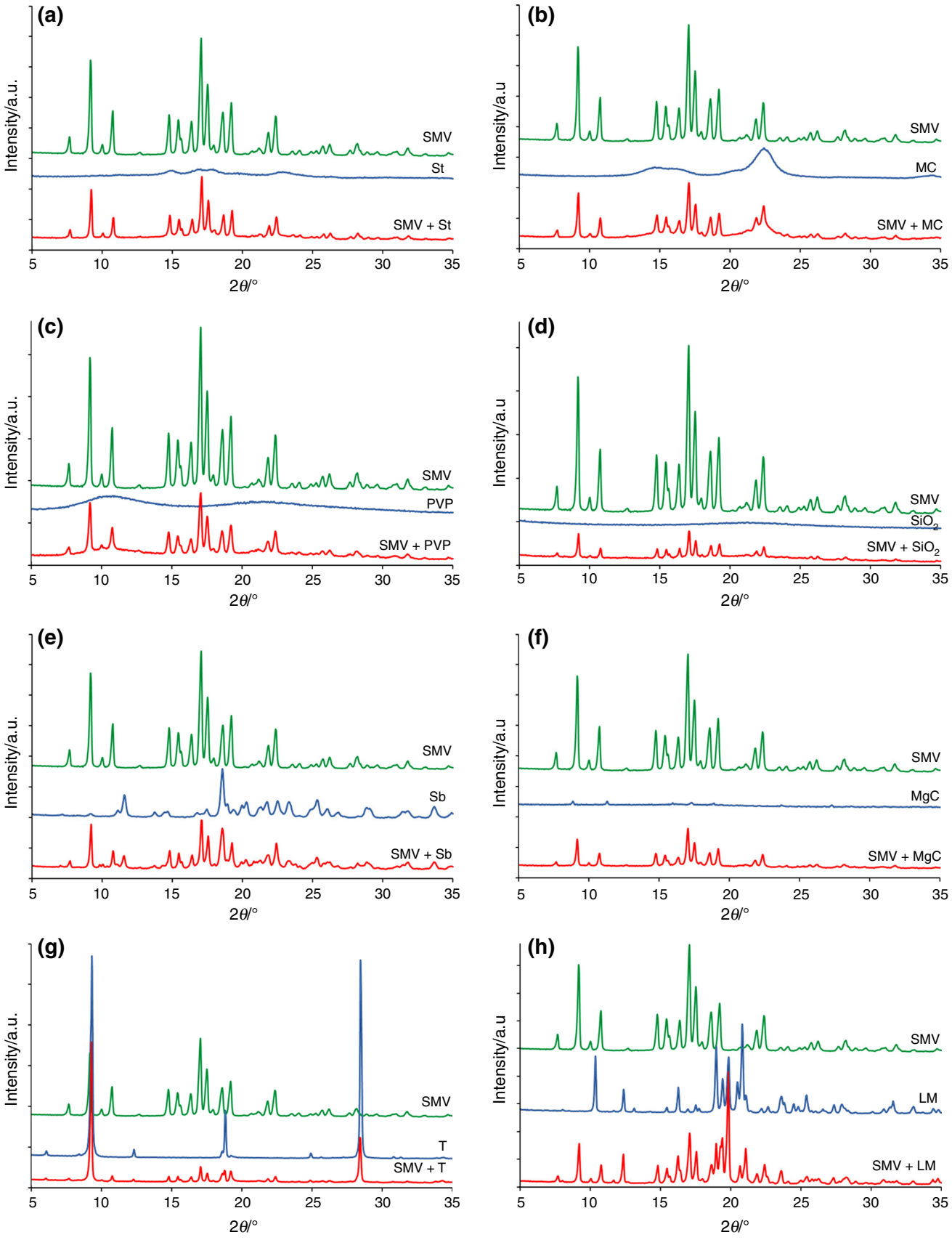
The thermoanalytical TG/DTG/HF curves were drawn up in an air atmosphere and under non-isothermal conditions at a heating rate $\beta = 10$ °C min^{-1} using a Perkin-Elmer DIAMOND equipment. Samples of masses of approximately 5 mg were put into aluminum crucibles and heated by increasing temperature from ambient up to 500 °C. For determining the thermal effects, the DTA data (μV) were converted into HF (heat flow) data (mW).

In order to evaluate the accuracy of the measurements, three repetitions have been performed with this experimental protocol for the samples and the obtained results were practically identical.

Results and discussion

PXRD study

The first instrumental technique used in the evaluation of interactions between SMV and excipients was the drawing up of the PXRD patterns of SMV, pure excipients and


(a)
Intensity/a.u.
SMV
St
SMV + St
5 10 15 20 25 30 35
2θ/°
(b)
Intensity/a.u
SMV
MC
SMV + MC
5 10 15 20 25 30 35
2θ/°
(c)
Intensity/a.u.
SMV
PVP
SMV + PVP
5 10 15 20 25 30 35
2θ/°
(d)
Intensity/a.u
SMV
SiO2
SMV + SiO2
5 10 15 20 25 30 35
2θ/°
(e)
Intensity/a.u.
SMV
Sb
SMV + Sb
5 10 15 20 25 30 35
2θ/°
(f)
Intensity/a.u
SMV
MgC
SMV + MgC
5 10 15 20 25 30 35
2θ/°
(g)
Intensity/a.u.
SMV
T
SMV + T
5 10 15 20 25 30 35
2θ/°
(h)
Intensity/a.u
SMV
LM
SMV + LM
5 10 15 20 25 30 35
2θ/°

◀**Fig. 2** X-ray diffractogram patterns for SMV, excipient and 1:1 (m/m) mixture at room temperature, for: **a** starch, **b** microcrystalline cellulose, **c** polyvinylpyrrolidone, **d** colloidal silica, **e** sorbitol, **f** magnesium citrate, **g** talc and **h** lactose monohydrate

physical mixtures, the three of them being plotted as intensity (arbitrary units) versus diffraction angle (2θ). The use of this technique is sustained by the fact that a crystalline compound displays a unique set of diffraction peaks, and the interaction between two crystalline compounds or between a crystalline compound and an amorphous one modifies the aspect of the PXRD pattern. The use of XRD analysis in the evaluation of interactions between active substances and excipients was previously reported in the literature and is an important tool for the selection of suitable excipients in new solid dosage forms, along other instrumental techniques [9, 22–26].

The PXRD patterns of SMV, excipients and their 1:1 (m/m) physical mixtures with excipients maintained at 25 °C are presented in Fig. 2. The analysis of the PXRD of SMV reveals the main diffraction peaks at (as 2θ values): 7.6; 9.25; 9.95; 10.7; 14.75; 15.4; 16.35; 17.05; 17.5; 18.55; 19.2; 21.80; 22.30; 25.65; 26.15; 27.6; 28.05 and 31.65, revealing the characteristic crystallinity of SMV. The PXRD pattern for mixtures did not reveal any additional lines related to those present in the patterns of the individual components. In seven analyzed cases, the pattern of mixture consists of the superimposition of the patterns observed for pure compounds. According to this, the analysis of (a)–(i) samples in Fig. 8 reveals that the presence of excipients under ambient condition does not influence the crystallinity and nature of the active substance.

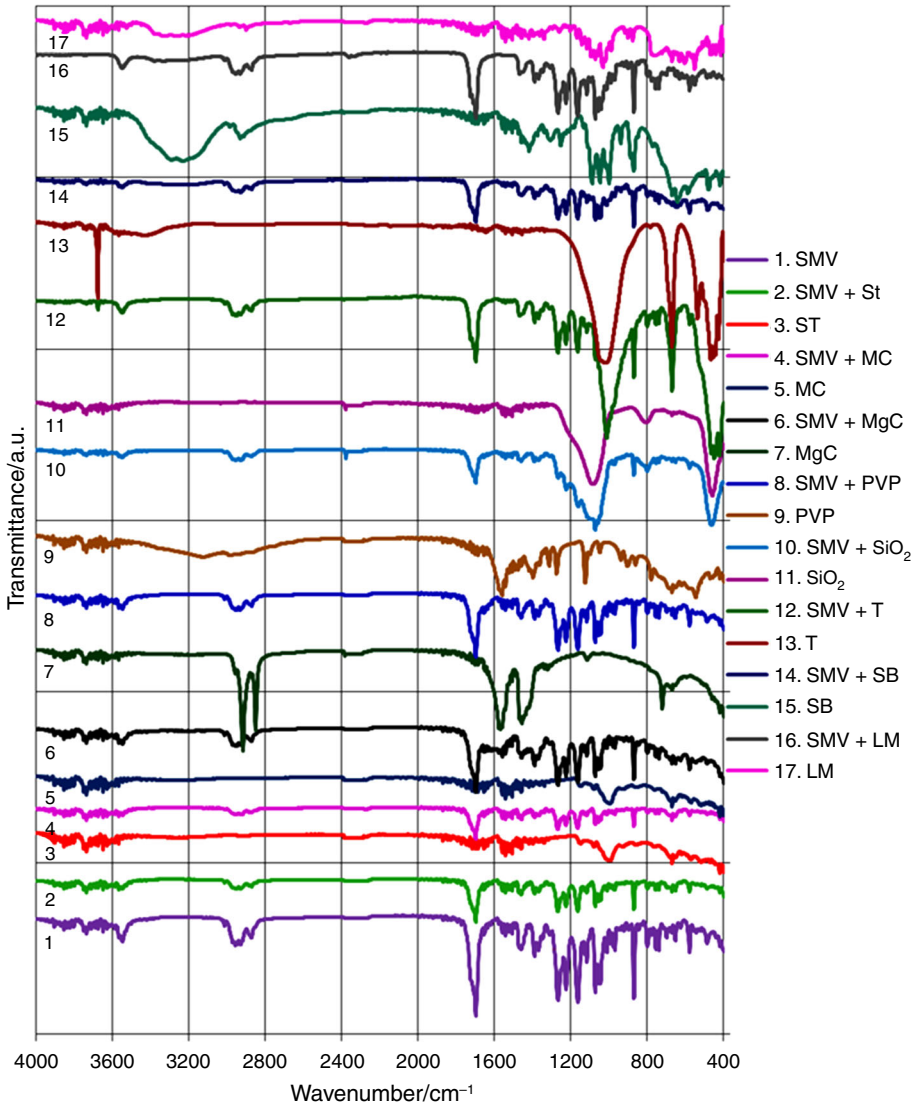


Fig. 3 ATR-FTIR spectra for SMV, excipients and binary mixtures

Table 1 Comparative ATR-FTIR data for characteristic bands of SMV as pure drug and in binary mixtures

Sample	Characteristic ATR-FTIR bands/cm^{-1}				
	ν_{O-H}	ν_{C-H}	$\nu_{C=O}$	$\delta_{C-O-C\ lactone}$	$\delta_{C-O-C\ ester}$
SMV	3545	2947; 2923; 2868; 1456	1695	1265	1161
SMV + St	3544	2949; 2922; 2866;1456	1697	1263	1159
SMV + MC	3545	2949; 2918; 2866; 1456	1697	1263	1161
SMV + MgC	3545	2949; 2918; 2866; 1457	1696	1261	1161
SMV + PVP	3543	2945; 2920; 2868; 1457	1697	1265	1161
SMV + SiO_2	3543	2945; 2918; 2866; 1456	1704	–	–
SMV + T	3541	2944; 2920; 2866; 1448	1690	1260	1161
SMV + SB	3543	2945; 2925; 2868; 1456	1695	1263	1161
SMV + LM	3537	2948; 2920; 2869; 1450	1691;1720	1260	1161

Differences in the X-ray pattern of the drug–excipient mixtures compared to those of individual drugs and excipient indicate possible incompatibility of the drugs with the excipient and were observed solely, in the case of SMV + LM mixture (Fig. 2h). One can notice the disappearance of the characteristic peak at 10.30° from lactose in the binary system, suggesting a possible interaction. In order to achieve a deeper evaluation of the compatibility/incompatibility study of SMV with selected excipients, a spectroscopic technique (FTIR) and a thermoanalytical one were used.

ATR-FTIR study

In order to evaluate the results obtained by PXRD patterns regarding the compatibility of SMV with excipients, a fast, reproducible and accurate spectroscopic technique was used, namely ATR-FTIR. The comparatively obtained FTIR spectra are presented in Fig. 3.

By the analysis of ATR-FTIR spectrum of pure SMV, the presence of several characteristic bands is observed. According to the structural skeleton of SMV, the characteristic bands are associated with stretching of free O–H group, symmetric and asymmetric stretching of C–H, esteric carbonyl C=O stretch and bending of both C–O–C lactone and ester moiety. Due to the fact that interactions are expected to occur by modification of SMV structure, mainly on reactive functional group and not to the hydrocarbonated chain, the disappearance, shifting and/or alliteration of characteristic bands of SMV in binary mixtures was analyzed. The comparative results are given in Table 1.

The analysis of the FTIR spectra drawn up for the binary mixtures is in good agreement with the results obtained by PXRD patterns for the five analyzed excipients, namely St, MC, MgC, PVP and SB. This technique indicates that under ambient condition, the structure of SMV is unaltered by the presence of these compounds in the physical

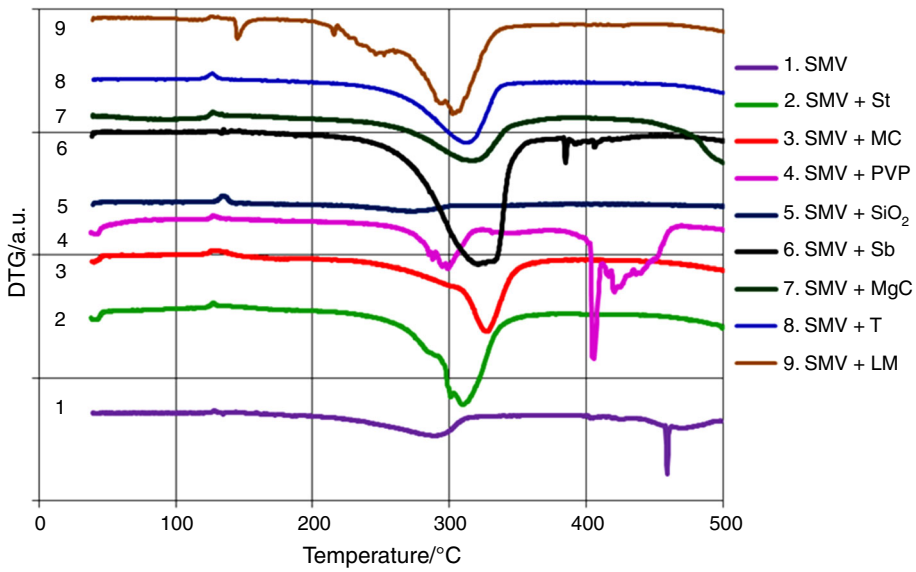


Fig. 4 Superimposed DTG curves for active substance (SMV) and analyzed binary mixtures

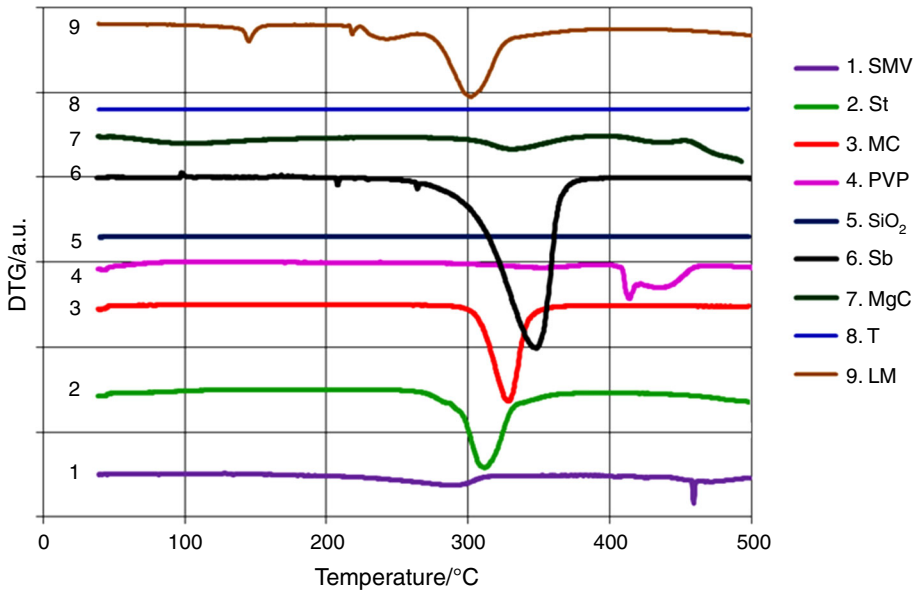


Fig. 5 Superimposed DTG curves for active substance (SMV) and analyzed excipients

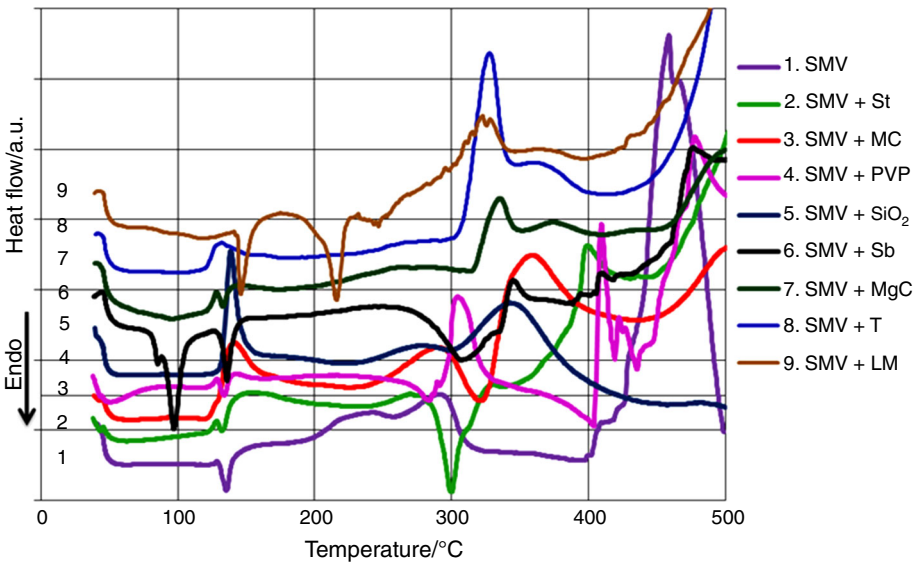


Fig. 6 Superimposed HF curves for active substance (SMV) and analyzed binary mixtures

mixture. All the characteristic FTIR bands of SMV are shifted in mixtures to different wavenumbers (within a range of ± 5 cm^{-1}), suggesting that no interactions occur. The results are different at the analysis of SMV + SiO_2 mixture: A considerable shifting of carbonyl stretch is observed, accompanied by the disappearance of bending for both lactonic and esteric C–O–C groups. This fact suggests that due to the presence of colloidal silicon dioxide, an alliteration of lactonic moiety is induced. The fact that no modifications are observed for O–H and C–H stretching indicate that these groups are unaltered by the presence of excipient. The analysis of FTIR spectra of SMV + T could suggest an interaction by the involving of C=O functional group, but the interaction can be confirmed only by thermal study. The last-prepared mixture, SMV + LM, indicates the alliteration of both O–H group and C=O group. The first is downshifted by 8 cm^{-1}, while the last is split as a doublet that is upshifted by 29 cm^{-1}. This result is in a good agreement with the one suggested by the PXRD pattern of the SMV + LM mixture. According to the ATR-FTIR study, we can tentatively suppose that under ambient conditions, SMV is incompatible with three of the analyzed excipients, namely SiO_2, T and LM. For a better understanding of these interactions, a third instrumental technique was used, namely thermal analysis.

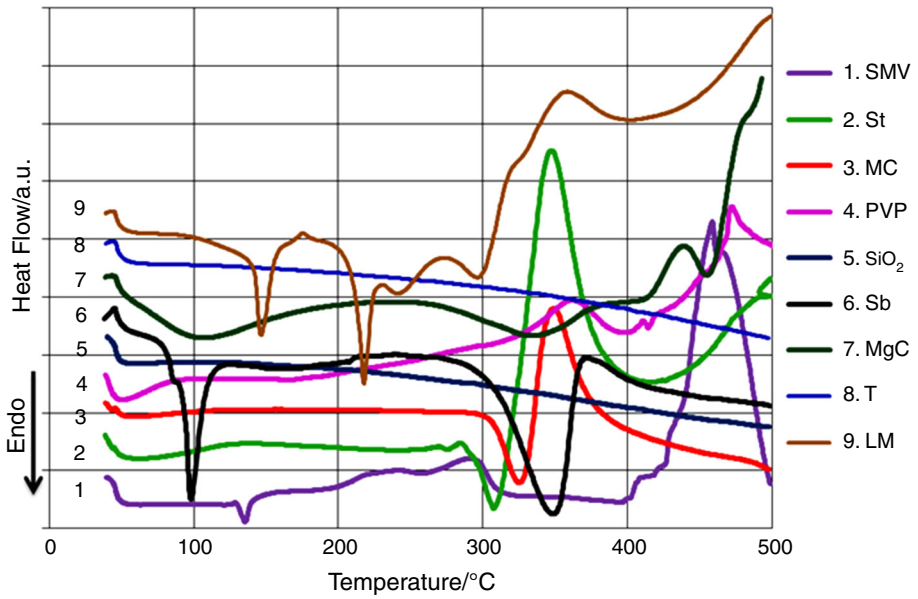


Fig. 7 Superimposed HF curves for active substance (SMV) and analyzed excipients

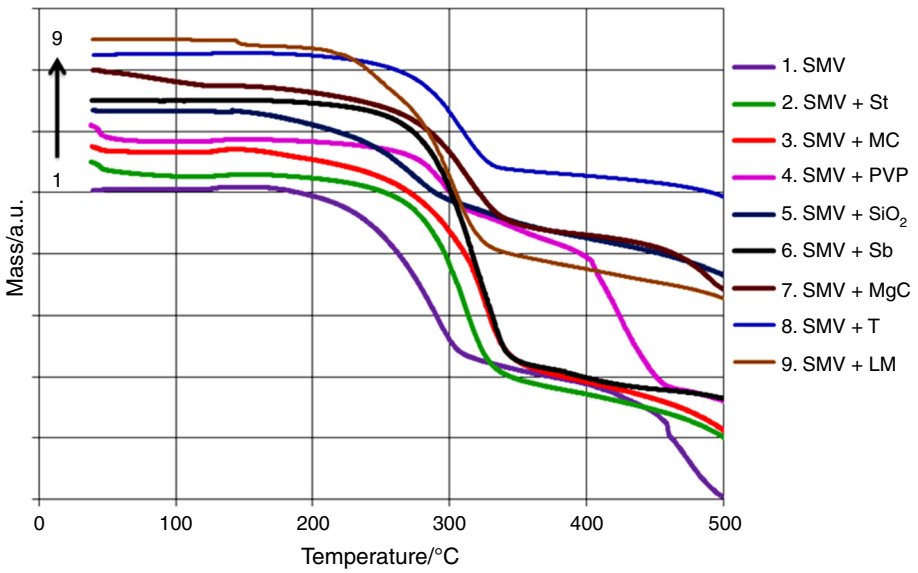


Fig. 8 Superimposed TG curves for active substance (SMV) and analyzed binary mixtures

TG/DTG/HF analysis

Thermal analysis is reported as one of the most sensitive techniques for evaluation of compatibility between a bioactive compound and excipients [22] in solid-state. According to this, thermal analysis was employed for describing the comparative behavior under heating for SMV versus binary mixtures.

The thermoanalytical curves of SMV obtained during heating at $\beta = 10$ °C min^{-1} in air atmosphere exhibit a multistadial decomposition route. SMV is thermally stable up to 160 °C, when a process with a mass gain occurs. The process of mass gain is in good agreement with the chemical structure of the SMV, which contains a six-membered lactone ring, which is thermally stable in inert and anhydrous atmosphere and under heating. The lactone moiety is, however, susceptible to degradation in the presence of water vapors, including a study regarding the effects of humidity on the hydrolysis of simvastatin in tablet [27]. The lactone ring opening is confirmed by the observed mass gain of 3.85 %, suggesting an increase in molar mass of SMV of 16.11 g mol^{-1} (theoretical mass gain 4.30 %) which corresponds to one mol of water per mol of SMV.

This process is followed by other processes in 360–500 °C temperature range, the last one occurring with a rapid mass loss in the 450–500 °C temperature range. These processes are accompanied by maximums on the DTG curve: The mass gain is revealed by the peak at

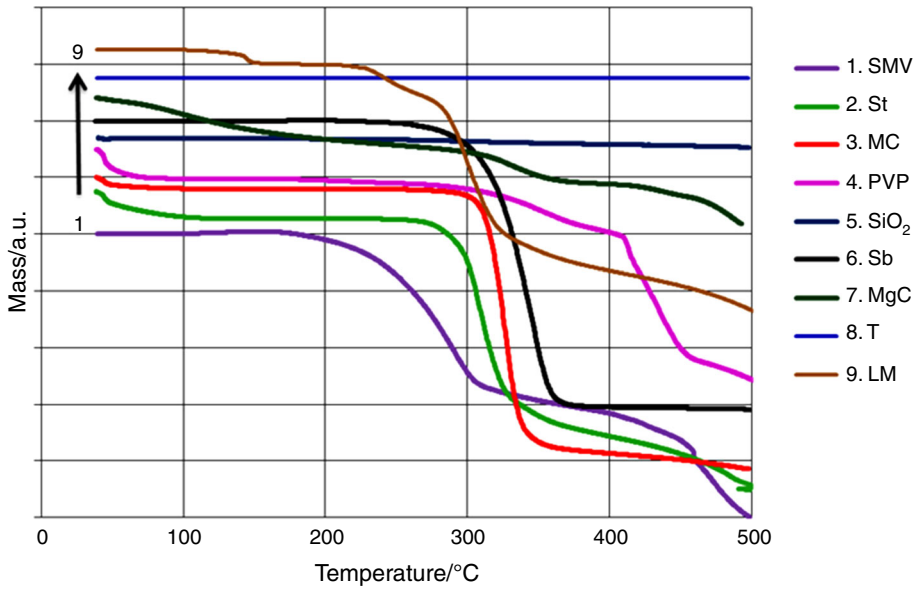


Fig. 9 Superimposed TG curves for active substance (SMV) and analyzed excipients

Table 2 Thermoanalytical data of the drug/excipient physical mixtures

Samples	Process	TG		DTG_{max}/°C	HF		Δm/%
		T_{onset}/°C	T_{final}/°C		T_{onset}/°C	T_{peak}/°C	
SMV	I	160	360	282	123	134	56
	II	360	500	459	186	285	43
SMV + ST	I	177	349	307	127	130	66
	II	349	500	–	272	298	16
SMV + MC	I	157	368	323	113	139	72
	II	368	500	–	280	316; 353	18
SMV + PVP	I	192	320	294	124	132	23
	II	321	410	405	254	280; 302	14
	III	410	500	419	366	401; 409	47
SMV + SiO_2	I	140	288	267	120	134	29
	II	288	500	–	293	337	26
SMV + Sb	I	171	344	316	70	84; 96; 135	83
	II	344	500	384	260	304; 342	13
SMV + MgC	I	43	115	–	47	90	5
	II	115	367	308	127	132	47
	III	367	500	–	252	309; 332	17
SMV + T	I	169	331	305	112	127	34
	II	331	500	–	296	325; 357	9
SMV + LM	I	89	189	144	137	145	3
	II	189	353	244; 301	176	215; 241	68
	III	353	500	–	287	320	12

159–163 °C and then by two processes of mass loss, at 282 °C (first process) and 459 °C (second process). The associated heat effects with these processes are revealed by the analysis of HF curve. The endothermic effect at 134 °C is due to melting of SMV, followed by two exothermic effects, with peaks at 285 and 459 °C (intense) which can be associated with the processes of oxidative degradation of molecular edifice of SMV.

The thermoanalytical curves for the active substance SMV, excipients and physical mixtures, respectively, are

presented in Figs. 4–9. In the case of SMV, the thermoanalytical curves obtained in air atmosphere present a thermal decomposition in two steps which are different in nature: The first process represents the melting and has an endothermic effect, and the second one is the degradation which is accompanied by a mass loss and an exothermic peak on the HF curve. The mass loss of the entire decomposition is an important one, the residual mass being ≈ 1 %.

For the thermal compatibility studies with excipients, the heat flow curve of active substance has been compared with the mixture curve in order to observe some difference of the processes which were attributed to the pure substances (SMV and/or excipient). Some of the excipients used in this study are part of commercial pharmaceutical formulation of SMV having different roles: lubricants (SiO_2) or diluents (MC and St). In addition, the compatibility of SMV with another type of excipients was performed. Excipients with different roles and belonging to different classes were chosen.

The thermoanalytical data of the SMV binary mixtures are given in Table 2. For identifying relevant changes in the thermal profile of active substance, the curves of the individual constituents and the SMV–excipient mixtures were presented, respectively.

According to the data given in Table 2, in some cases, the binary mixtures presented modification of the pure SMV thermal profile. The physical mixture with St, MC, PVP, SB and MgC showed shifts in the melting peak value to lower or higher temperatures, but in all five cases, the shifts are <5 °C. For these five mixtures, it can be observed that the differences are small and the thermal interactions are not proved.

For the mixtures with T and SiO_2, the total absence of the melting process of active substance was observed, and in the respective temperature range, an exothermal-nature process occurs, by an accentuated peak with maximum at 134 and 127 °C, respectively. Another argument for possible physicochemical interactions is the total mass loss corresponding to mixtures with T and SiO_2. Considering the thermal inertia of both excipient, T and SiO_2, the total mass loss would be equal to 50 %. This fact is due to the blending mass ratio of mixture (SMV/excipient (w/w) = 1:1). In the case of SMV + LM mixture, the melting peak of SMV is not appearing. The first process identified on the HF curve is the one with $T_{peak} = 145$ °C and corresponds to the excipient HF profile having an endothermal effect also (see Fig. 6).

These interactions determined by thermal analysis and found for the mixtures with LM, T and SiO_2 are superior and conclusive comparing with the results obtained using two other analysis techniques: X-ray powder diffraction and UATR-FTIR, especially which revealed some changes in the spectra of binary mixtures. The superiority of thermoanalytical technique resides from the fact that the interactions can be screened versus temperature, offering valuable information about interactions that took place not only at ambient conditions, but also at high temperatures that can be achieved even in pharmaceutical industry during development of a final formulation.

Conclusions

The obtained results from this study confirmed the utility and reliability of using thermoanalytical study as a preliminary tool in developing new solid pharmaceutical formulations. Along with other instrumental techniques, thermoanalysis is considered a valuable, sensitive and convenient tool for a rapid screening of a wide range of selected excipients, suggesting the occurrence of drug–excipient interactions.

These results are considered as useful tools in the pharmaceutical research of new formulations with SMV, because all the compounds that are used in those dosage forms should be thermally stable and inert comparative to other components of the dosage form.

Based on the thermoanalytical results and confirmed by PXRD and ATR-FTIR, no evidence of interaction was observed between SMV and St, MC, PVP, SB and MgC. Interactions were suspected between SMV and T, and SiO_2 and LM, from both FTIR and thermal analysis.

Therefore, before preparing a new generic pharmaceutical formulation of SMV, it is recommended to evaluate the excipient effect for talc, colloidal silicon dioxide and lactose, as they can modify the content and behavior of active substance and following this the biodisponibility.

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