https://doi.org/10.31925/farmacia.2021.3.22 **ORIGINAL ARTICLE**

COMPATIBILITY STUDIES OF SELECTED MUCOLYTIC DRUGS WITH EXCIPIENTS USED IN SOLID DOSAGE FORMS: THERMOGRAVIMETRY ANALYSIS

PAWEŁ RAMOS *

Department of Biophysics, Faculty of Pharmaceutical Sciences in Sosnowiec, Medical University of Silesia, Katowice, Jedności 8, 41-200 Sosnowiec, Poland

**corresponding author: pawelramos@sum.edu.pl*

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Abstract

The drugs except active pharmaceutical ingredient (API) contain excipients in formulations. In drugs formulations, it is important that API and excipient are compatible. As a quick and cheap method of testing the compatibility of API with an excipient, thermal methods can be used, including thermogravimetry analysis. In this study, the assessed compatibility of selected mucolytic drugs (ambroxol, bromhexine, acetylcysteine) with excipients (magnesium stearate, lactose monohydrate, starch) is used in solid dosage form. TG and DTG analysis were done for pure API, excipients, and binary mixture API/excipient with different ratio. The study has shown that the tested mucolytic drugs are compatible with magnesium stearate, but are incompatible with lactose monohydrate. The Maillard reaction is responsible for this incompatibility, which was additionally confirmed by a colorimetric method. The starch and acetylcysteine are compatible, but starch and ambroxol are incompatible. The measurements for compatibility bromhexine witch starch are ambiguous. The obtained results proved the usefulness of TG and DTG measurements for initial examination of compatibility API/excipient in preformulation studies.

Rezumat

Medicamentele, cu excepția principiului activ (API), conțin în formulări excipienți, iar aceștia trebuie să fie compatibili. Pentru testarea compatibilității API cu un excipient, pot fi utilizate metode termice, inclusiv analize termogravimetrice. În acest studiu, evaluarea compatibilității medicamentelor mucolitice selectate (ambroxol, bromhexină și acetilcisteină) cu excipienții stearat de magneziu, lactoză monohidrat și amidon, s-a realizat pentru forme farmaceutice solide. Analiza TG și DTG s-a efectuat pentru API pur, excipienți și amestec binar API/excipient, în raport diferit. Studiul a demonstrat că substanțele mucolitice testate sunt compatibile cu stearatul de magneziu, dar sunt incompatibile cu lactoza monohidrat. Amidonul și acetilcisteina pot fi formulate împreună, în timp ce amidonul și ambroxolul s-au dovedit incompatibile. Determinările pentru stabilirea asocierii amidonului cu bromhexinul sunt neconcludente. Rezultatele obținute au dovedit utilitatea măsurătorilor TG și DTG pentru testarea inițială a compatibilității API/excipient în studiile de preformulare.

Keywords: mucolytic drugs, excipients, TG, DTG, compatibility studies, colour measurement

Introduction

The drugs except active pharmaceutical ingredient (API) additionally contain excipients in formulations [1]. Excipients used in drugs have very important functions, among others: they increase the stability of the active substance in drug, affect the kinetics and the place of release of the active substance, give the appropriate pharmaceutical form of the drug or improve the appearance and taste of the drug [1-3]. Excipients, unlike the API, cannot have a therapeutic effect on the body [1]. In the formulation of the drug form, it is very important to select excipients properly. They should not interact with the active pharmaceutical ingredient contained in the drug [2]. Excipients should not change the physico-chemical properties of the active pharmaceutical ingredient in the formulation. Interactions between the excipient and the API in the drug may reduce the stability of the drug formulation or weaken the drug's effect during pharmacotherapy [1, 2].

In the pharmaceutical industry, many methods such as Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetric (DSC), high-performance liquid chromatography (HPLC), X-Ray spectroscopy are used to study the interaction between the active pharmaceutical ingredient (API) and the excipient in formulating the drug form [4-6].

The thermogravimetric analysis (TGA) can also be used as a quick and cheap method for determining the interaction between an active pharmaceutical ingredient and an excipient in a drug [6-8]. The thermogravimetric analysis (TGA) consists in measuring the mass loss of the analysed substance as the heating temperature increases. During the measurement, the decomposition of the tested sample is recorded, which is saved in the

form of thermograms. To increase reading efficiency of TGA curves, a simultaneous differential thermogravimetric analysis (DTG) is performed. DTG is the first derivative of the TG curve relative to temperature [6-8]. The differences in the analysed parameters of the decomposition of the tested active drug substance (API) and the mixture of the active substance with the excipient may be due to the existing interaction between them [6-8].

The aim of this study was to assess the interaction of selected mucolytic drugs with excipients used in the production of solid drug forms. The study used analysis of the obtained thermograms (TGA and DTG) of active pharmaceutical ingredient (API), excipients and mixtures of both substances in different ratio.

Ambroxol, bromhexine and acetylcysteine from mucolytic drugs were tested. They are one of the most commonly used mucolytic drugs in upper respiratory tract infection with thick secretions [9-13]. The general mechanism of action of the studied drugs is to dilute secretions in the bronchial tree by stimulating the secretion of surfactant in the lungs, breaking down mucus glycoproteins into smaller particles and stimulating ciliary movement in the bronchi [9-13]. In addition, acetylcysteine has antioxidant activity, thanks to which it neutralizes free radicals formed in respiratory cells during the inflammatory process [14].

Among the excipients, magnesium stearate, lactose and starch were used for the study. They are one of the most commonly used excipients in the preparation of solid forms of the drugs [1-3]. Magnesium stearate is a glidant used to reduce friction between the powder particles used to make the tablet mass [3, 15]. The addition of magnesium stearate facilitates compression on the matrix of tablets because it prevents the tablet from sticking to it [15]. Lactose and starch are used as substances that fill the tablet mass when the weight of the drug substance used to make the tablet is too small [3, 15].

Materials and Methods

Samples and binary mixtures

The samples used in this study were selected mucolytic drugs (ambroxole hydrochloride, bromhexine hydrochloride, acetylcysteine) and excipients (magnesium stearate, lactose monohydrate, starch from corn). All API and excipients were purchased from Sigma-Aldrich company.

All analyses were performed using the samples of single mucolytic drugs (ambroxole, bromhexine, acetycysteine), single excipients (magnesium stearate, lactose monohydrate, starch), and binary mixture of API with each excipients separately. In experiment, different weight ratio of API/excipient: 2:1, 1:1, and 1:2 was used. Ratio API/excipient was obtained by grinding in the porcelain mortar. The mass of the tested samples was determined using the CPA weight Sartorius company (Germany).

Thermogravimetric analysis (TGA)

The thermal stability of mucolytic drugs, excipients and the mixture of the both were determined by thermogravimetric analysis.

Thermogravimeter TG 209 F3 Tarsus produced by Netzsch (Germany) was used. The TG and DTG curves were recorded for 10 mg of the tested samples at a heating rate of 10 K/min, in the temperature range 35 - 600°C under N_2 atmosphere. The total flow nitrogen rate was 50 mL/min. Al_2O_3 crucible type use for measured. The samples curves were analysed using Proteus 6.1 software produced by Netzsch company (Germany).

Colour measurement

Colorimetric examination in the CIE L*a*b* colour system was performed. NH 310 colorimeter produced by 3nh (China) was used. Analyses of colour parameters were done for binary mixtures ambroxol, bromhexine and acetylcysteine with lactose monohydrate. The tested samples were measured in the first day and 1 month after storage in the dark at temperature 25°C and 50°C. In this test, an Universal Oven U with circulation of air, Memmert GmbH+ Co. KG, Germany, was used. Measurements were done three times for each sample. The received values were averaged.

The parameters L* (lightness), a* (redness), and b* (yellowness), were used to study changes in the colour of the samples. L* refers to the lightness of the samples and it ranges from black (0) to white (100). A negative value of a* indicates green, while a* positive one indicates red colour. Positive and negative b* indicates yellow and blue colour respectively [17, 18].

Results and Discussion

The TG and DTG curves recorded for the ambroxole, bromhexine, acetylcysteine, magnesium stearate and physical binary mixture tested API with magnesium stearate in different weight ratio are presented on Figure 1. The analysed decomposition parameters of TG and DTG curves of the magnesium stearate, tested API, and binary mixture of mucolytic drugs with magnesium stearate are presented in Table I and Table II.

In Figure 1 TG and DTG curves of ambroxol (Figures 1a and 1b), bromhexine (Figures 1c and 1d) and acetylcysteine (Figures 1e and 1f) are presented. TG curve showed that ambroxol was thermally stable up to 249.6°C and the two mass losses stage could be observed (Figure 1a). The temperature onset of decomposition of ambroxol is 249.6°C. The first stage of mass loss is -27.4%, and the second stage of mass loss is -33.7%. The DTG curve (Figure 1b, Table II) of ambroxol presented two peaks corresponding with TG curve. The first stage of mass loss occurred in

the temperature range 219°C - 290°C with maximum peak in 254.7°C. The second stage occurred in temperature range 290°C - 402°C with maximum peak in 357.1°C.

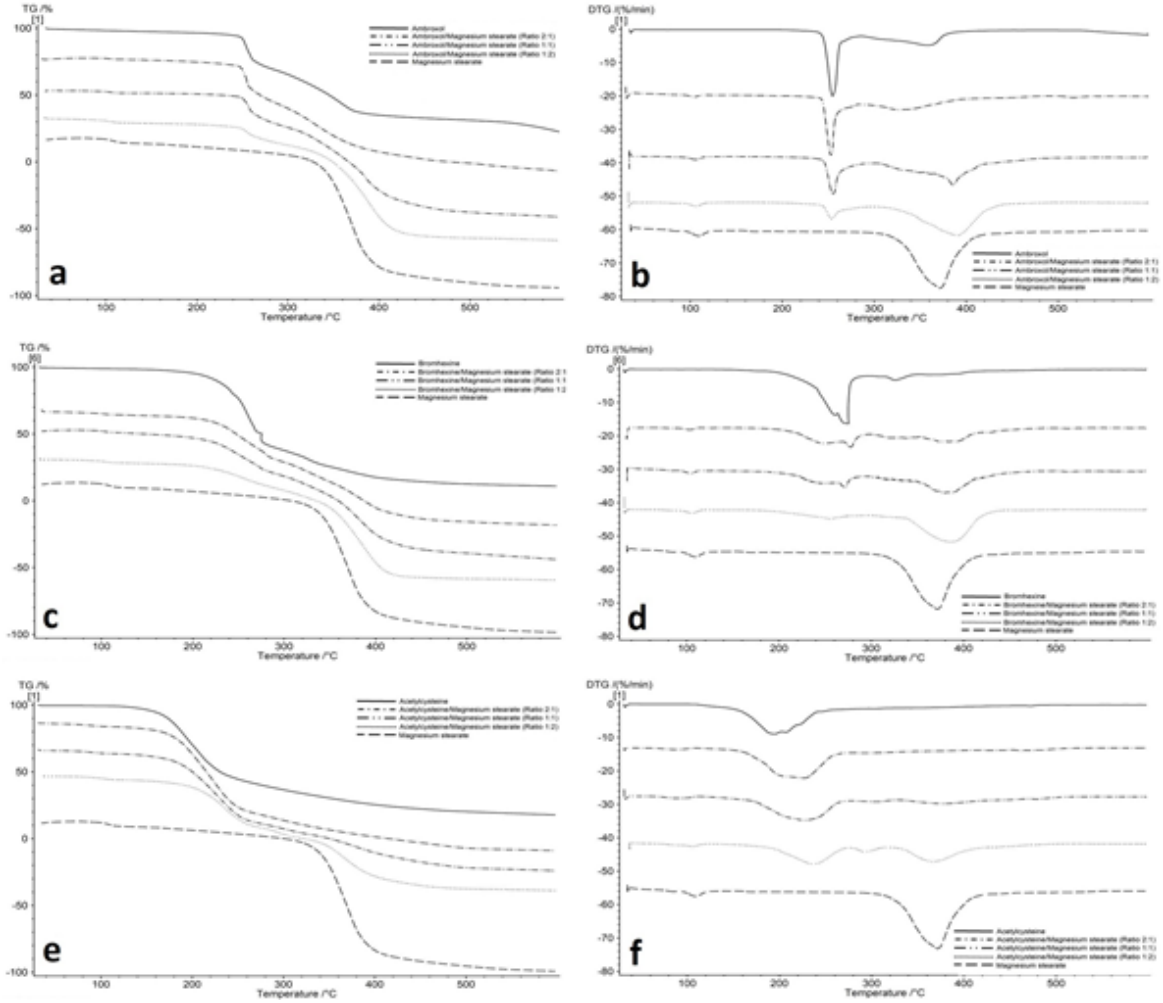

Figure 1.

TG (a, c, e) and DTG (b, d, f) curves of tested API (solid line), magnesium stearate (dash line) and binary mixture of API and magnesium stearate in ratio (w:w) 2:1 (dash/dot/dot line), 1:1 (dash/dot line) and 1:2 (dot line)

Table I

Characteristic parameters of TGA curves of the magnesium stearate, tested mucolytic drugs, and binary mixture of API with excipient in different ratio

Tested samples		TG parameters				
		Onset (°C)	Mid (°C)	Infelction (°C)	End (°C)	Mass change (%)
Magnesium stearate		341.5	366.8	372.1	393.5	-89.33
Ambroxol		249.6	287.3	254.4	280.8	-52.32
Ambroxol/Magnesium stearate (Ratio w:w)	2:1	249.4	287.6	253.3	280.2	-63.53
	1:1	250.3	348.4	255.2	316.3	-74.31
	1:2	248.5	375.0	389.5	416.8	-74.65
Bromhexine		228.7	264.8	268.3	304.6	-78.50
Bromhexine/Magnesium stearate (Ratio w:w)	2:1	224.7	316.9	278.5	377.3	-67.97
	1:1	223.0	338.5	379.6	419.1	-78.39
	1:2	325.0	368.9	385.7	411.0	-78.60
Acetylcysteine		170.0	207.0	193.8	249.8	-68.23
Acetylcysteine/Magnesium stearate (Ratio w:w)	2:1	179.5	223.0	267.1	-73.23	-73.23
	1:1	187.0	235.5	225.7	285.7	-66.30
	1:2	205.0	298.6	237.0	327.6	-69.15

Table II

Characteristic parameters of DTG curves of the magnesium stearate, tested mucolytic drugs, and binary mixture of API with excipient in different ratio

Tested samples		DTG weight loss rate							
		Stage I		Stage II		Stage III		Stage IV	
		Peak (°C)	Mass change (%/min)	Peak (°C)	Mass change (%/min)	Peak (°C)	Mass change (%/min)	Peak (°C)	Mass change (%/min)
Magnesium stearate		109.1	-1.84	371.5	-17.49	-	-	-	-
Ambroxol		254.7	-19.98	357.1	-4.81	-	-	-	-
Ambroxol/Magnesium stearate (Ratio w:w)	2:1	104.1	-0.69	252.9	-18.08	326.9	-4.58	-	-
	1:1	105.9	-0.95	255.3	-11.26	385.4	-8.61	-	-
	1:2	106.4	-1.23	254.0	-4.95	389.8	-9.99	-	-
Bromhexine		274.9	-16.36	326.1	-3.34	375.0	-1.70	-	-
Bromhexine/Magnesium stearate (Ratio w:w)	2:1	103.1	-0.78	277.6	-5.86	375.3	-4.34	-	-
	1:1	104.0	-1.03	271.2	-4.98	379.2	-6.84	-	-
	1:2	106.0	-1.12	254.5	-2.80	386.8	-9.70	-	-
Acetylcysteine		195.3	-8.97	345.0	-1.71	-	-	-	-
Acetylcysteine/Magnesium stearate (Ratio w:w)	2:1	88.5	-0.65	226.7	-9.20	298.0	-1.68	461.6	-0.97
	1:1	90.5	-0.67	227.6	-7.25	305.0	-1.73	378.8	-2.32
	1:2	105.7	-0.92	236.4	-6.21	293.5	-2.51	367.0	-5.48

Thermogravimetry curve of bromhexine showed that the onset of thermally decomposition is 228.7°C. In Figure 1c we can observed III stages of mass loss. The first stage of mass loss is -55.98%, the second stage of mass loss is -12.9%, and the third stage of mass loss is -9.3%. The DTG curve showed (Figure 1d) three peaks corresponding with TG curve. The first stage of mass loss occurred in the temperature range 168°C - 294°C, with the maximum peak in 274.9°C. The second stage of mass loss occurred in the temperature range 294°C - 348°C with maximum peak in 326.1°C. The third stage of mass loss occurred in the temperature range 348°C - 422°C with maximum peak in 380°C.

Figures 1e and 1f present the TG and DTG curves of acetylcysteine. TG curve showed that the decomposition of acetylcysteine begins in 170°C and the one mass loss stage could be observed with mass loss -61.73%. The DTG curve (Figure 1f, Table II) of acetylcysteine presented one peak corresponding with TG curve. The single mass loss occurred in the temperature range 109°C - 293°C with maximum peak in 195.3°C.

The TG curves of magnesium stearate (dashed line) presented in Figures 1a, 1c and 1e showed that the thermally decomposition begins at 341.5°C and contain two stages. The mass loss in the first stage is -3.7% and the second stage is -92.6%. The DTG curves of magnesium stearate presented two peaks corresponding with TG curves (Figures 1b, 1d and 1f, Table II). DTG I stage of mass loss occurred in temperature range 84.5°C - 130°C with maximum peak in 109.1°C. This stage is related with water release and it is in good agreement with the literature [19-21]. The second stage occurred in the temperature range 289.7°C - 449.5°C, with maximum peak in 371.5°C and mass change -19.49 (%/min.). The second stage is related with the decomposition of magnesium stearate. Magnesium stearate used in pharmaceutical formulation can exist in different polymorphic forms [22, 23]. This fact can impact on information recorded on TG/DTG curves. Therefore, it is important to perform TGA measurements for each new series of excipient.

Figure 1 presents TG/DTG curves for the binary mixtures of magnesium stearate with ambroxol, bromhexine, and acetylcysteine in different ratio (w:w). The recorded thermogravimetric curves show that the studied mucolytic drugs are compatible with the tested excipient. The onset temperature of decomposition for tested API and mixtures API with magnesium stearate are no change (Figure 1, Table I).

In all recorded DTG curves, we can observe the overlap of the recorded temperature peaks for pure API and a binary mixture of API with magnesium stearate. In addition, we can observe a gradual disappearance of the maximum weight loss peak of the ambroxol (254.7°C), bromhexine (274.9°C), acetylcysteine (195.3°C) and an increase of the maximum weight loss peak of the magnesium stearate (371.5°C) as the content of excipient increases. This indicates that there is no interaction between the tested API and the excipient. Other authors recorded a similar relationship for diclofenac sodium [20], indapamide [21], enalapril [24], hydrocortisone [25] confirmed by the other analytical methods like DSC, XRDP, FTIR.

The TG/DTG curves recorded for the tested mucolytic drugs, lactose monohydrate and physical binary mixture API with lactose monohydrate in different weight ratio are presented in Figure 2. The analysed decomposition parameters of TG and DTG curves of the lactose monohydrate, tested API, and binary mixture of API with tested excipient were presented in Table III and Table IV.

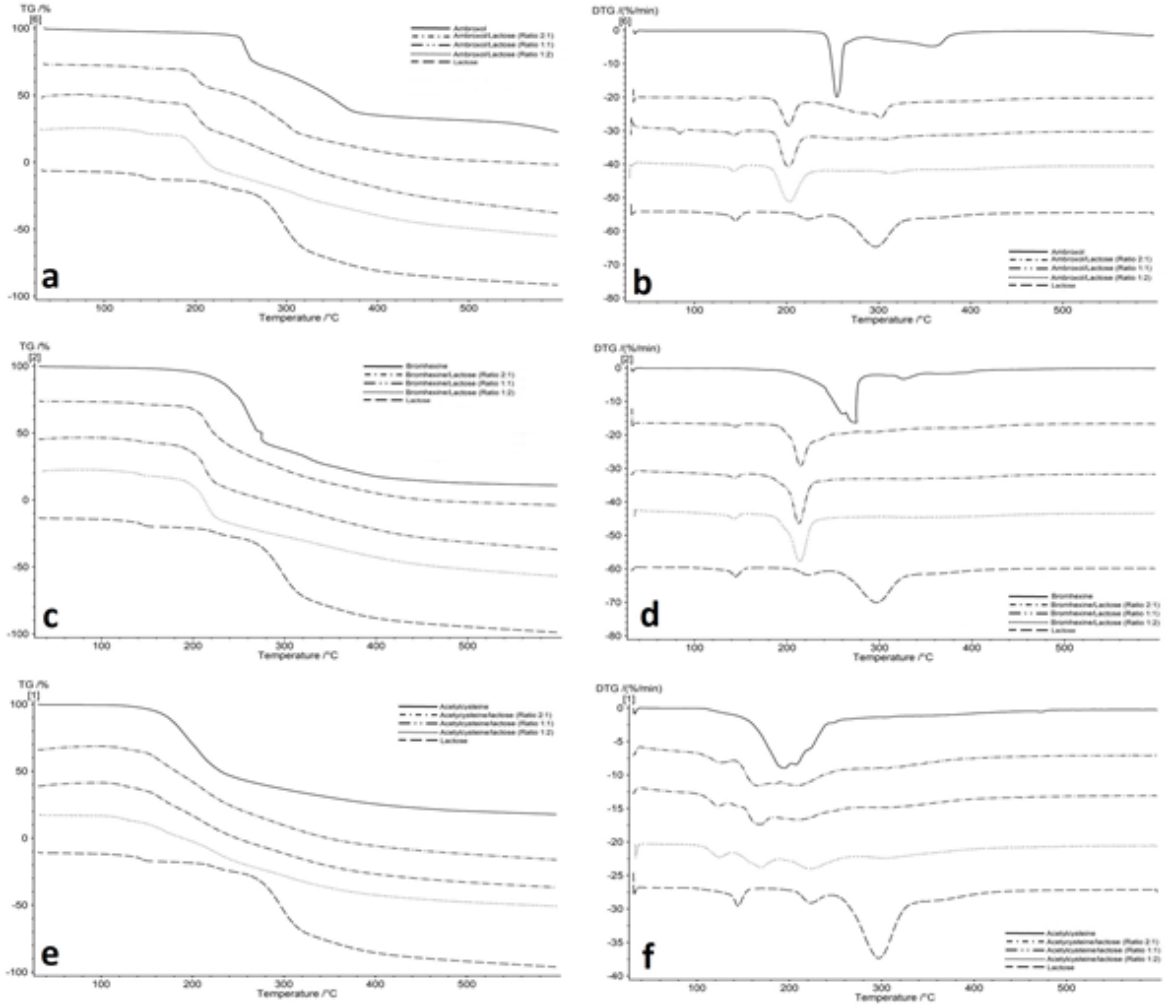

Figure 2.

TG (a, c, e) and DTG (b, d, f) curves of tested API (solid line), lactose monohydrate (dash line) and binary mixture of API and lasctose monohydrate in ratio (w:w) 2:1 (dash/dot/dot line), 1:1 (dash/dot line) and 1:2 (dot line)

Table III

Characteristic parameters of TGA curves of the lactose monohydrate, tested mucolytic drugs, and binary mixture of API with excipient in different ratio

Tested samples		TG parameters				
		Onset (°C)	Mid (°C)	Infelction (°C)	End (°C)	Mass change (%)
Lactose monohydrate		277.5	297.7	296.2	328.4	-61.95
Ambroxol		249.6	287.3	254.4	280.8	-52.32
Ambroxol/Lactose monohydrate (Ratio w:w)	2:1	192.9	273.7	202.1	265.8	-58.13
	1:1	191.3	228.6	202.1	248.1	-54.05
	1:2	189.5	214.3	202.6	246.8	-54.98
Bromhexine		228.7	264.8	268.3	304.6	-78.50
Bromhexine/Lactose monohydrate (Ratio w:w)	2:1	204.9	241.0	214.4	258.6	-63.92
	1:1	201.5	218.4	212.7	240.7	-58.76
	1:2	201.4	216.8	214.1	239.0	-54.63
Acetylcysteine		170.0	207.0	193.8	249.8	-68.23
Acetylcysteine/Lactose monohydrate (Ratio w:w)	2:1	151.3	214.2	165.5	303.4	-66.73
	1:1	152.2	219.9	169.8	301.9	-57.29
	1:2	154.6	224.5	220.7	322.8	-53.63

Table IV

Characteristic parameters of DTG curves of the lactose monohydrate, tested mucolytic drugs, and binary mixture of API with excipient in different ratio

Tested samples		DTG weight loss rate							
		Stage I		Stage II		Stage III		Stage IV	
		Peak (°C)	Mass change (%/min)	Peak (°C)	Mass change (%/min)	Peak (°C)	Mass change (%/min)	Peak (°C)	Mass change (%/min)
Lactose monohydrate		144.4	-2.86	223.6	-2.41	296.7	-10.64	-	-
Ambroxol		254.7	-19.98	357.1	-4.81	-	-	-	-
Ambroxol/Lactose monohydrate (Ratio w:w)	2:1	144.4	-0.92	202.1	-8.55	302.1	-6.26	-	-
	1:1	83.6	-1.29	142.9	-1.80	202.2	-11.29	305.6	-3.05
	1:2	142.8	-2.14	203.0	-11.23	313.2	-2.69	-	-
Bromhexine		274.9	-16.36	326.1	-3.34	375.0	-1.70	-	-
Bromhexine/Lactose monohydrate (Ratio w:w)	2:1	144.3	-1.05	214.5	-12.82	378.5	-1.52	-	-
	1:1	142.8	-1.63	212.7	-15.20	371.2	-1.72	-	-
	1:2	142.5	-2.09	213.7	-14.82	335.8	-1.69		
Acetylcysteine		195.3	-8.97	345.0	-1.71	-	-	-	-
Acetylcysteine / Lactose monohydrate (Ratio w:w)	2:1	125.3	-1.47	165.4	-4.95	288.1	-2.39	345.4	-1.63
	1:1	122.9	-1.91	168.5	-4.64	209.8	-3.96	295.0	-2.13
	1:2	124.3	-2.01	169.3	-3.53	222.1	-3.71	303.0	-2.15

Thermogravimetric curves of lactose monohydrate (dashed line) presented in Figures 2a, 2c and 2e showed that the thermally decomposition is stated at 277.5°C and contain three stages. The mass loss in I, II and III stages are -6.21%, -7.45% and -62.52% respectively. The DTG curve of lactose monohydrate presented three peaks corresponding with TG curve (Figures 2b, 2d and 2f, Table IV). DTG first stage of mass loss occurred in the temperature range 89.9°C - 169°C with maximum peak in 144.4°C. This stage is related with water release and it is in good agreement with the literature [20, 21, 27]. The second stage occurred in the temperature range 187°C - 246°C with maximum peak in 223.6°C and it is associated with a new water release [26]. The third stage begins at temperature 223.6°C and mass change -10.64 (%/min.) and it is associated with a continue degradation of lactose [26]. The maximum peak for the last stage is at 296.7°C.

Due to the comparison of the TG and DTG curves of the tested API, lactose monohydrate and their binary mixtures, it can be concluded that the stability of the analysed API in these mixtures has changed. Tested excipient increased the thermal degradation of all tested mucolytic drugs. The TG curve of the binary mixtures, regardless of the used ratio API and lactose, confirm the reaction between lactose monohydrate and ambroxol (Figure 2a), bromhexine (Figure 2c), acetylcysteine (Figure 2e), evidenced by the premature mass loss. The thermal decomposition begins at lower temperature for all tested mucolytic drugs. Compared to the pure tested API binary mixture of ambroxol and lactose monohydrate in ratio 2:1, 1:1 and 1:2 decomposition starts earlier 56.7°C, 58.3°C and 60.1°C respectively (Table III). The binary mixture of bromhexine and lactose monohydrate in ratio 2:1, 1:1 and 1:2 decomposition starts earlier 23.8°C, 27.2°C and 27.3°C respectively (Table III). The binary mixture of acetylcysteine and lactose monohydrate in ratio 2:1, 1:1 and 1:2 decomposition starts earlier 18.7°C, 17.8°C and 15.4°C respectively (Table III). The Maillard reaction can by responsible for these interactions [1]. Millard reaction occurs between lactose (reducing sugar) and the primary or secondary amino group in the drug [1, 27]. All tested mucolytic drugs present the amino group in their structure. The primary amino group has got ambroxol and bromhexine. The secondary amino group has got ambroxol and acetylcysteine [16]. The colorimetric method was used to confirm the Maillard reaction. The Maillard reaction is accompanied by yellowing or browning of the sample [1, 17, 18]. The intensity of the colour increases with the increasing temperature and storage time of the mixture API/ excipient [1, 18]. Location of colours in CIE L*a*b* space for the tested samples is illustrated in Figure 3. Axes L*, a* and b* define the 3D colour space CIE.

Measurement in the CIE L*a*b* colour system has shown that the used stored conditions caused colour changes of binary mixture of mucolytic drugs with lactose monohydrate. This is more evident in samples stored at 50°C. Binary mixture ambroxol with lactose shows the largest colour change towards yellow (b* parameter). Ambroxol has got two amino groups in the structure so that the Mallard reaction can occur in the most intensive way. This indicates a large incompatibility of ambroxol with lactose monohydrate among the studied mucolytic drugs. It is confirmed by TG/DTG analysis in this work.

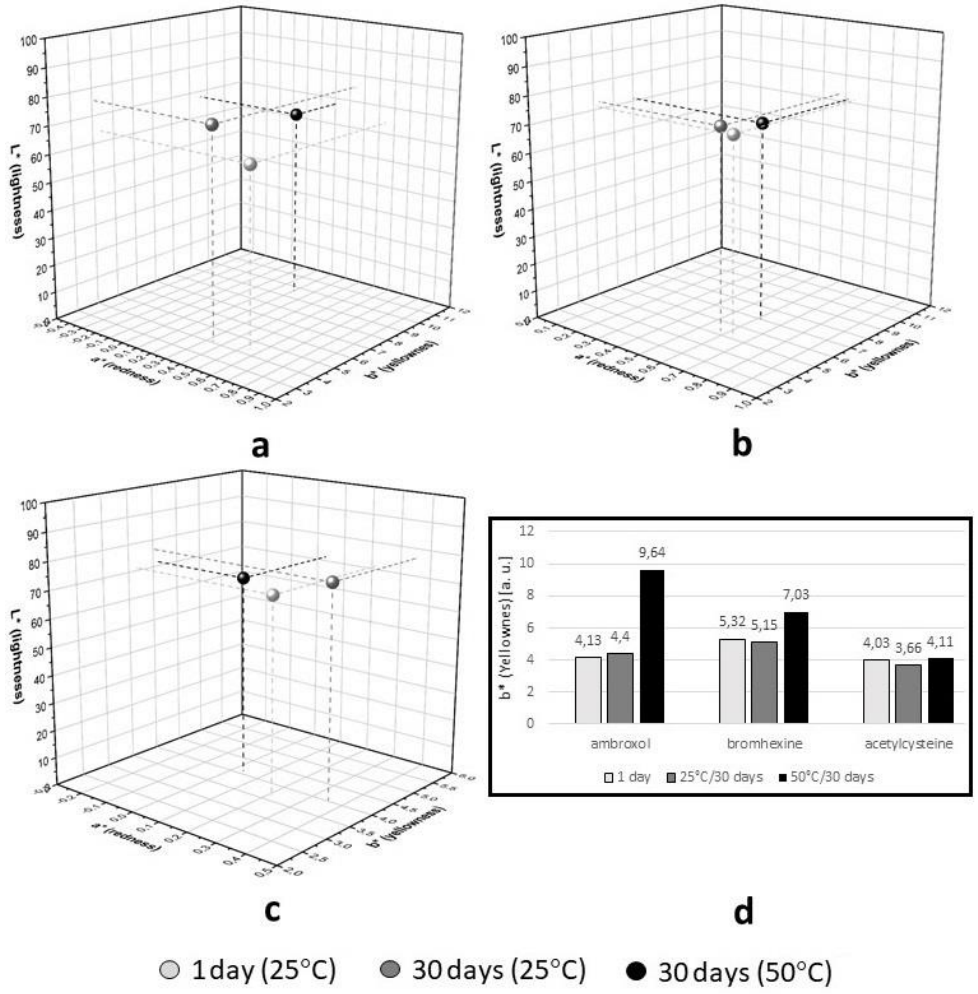

Figure 3.

Analysis of colour in the 3D (CIE L*a*b*) space for binary mixtures of (a) ambroxol, (b) bromhexine, (c) acetylcysteine with lactose monohydrate. (d) Analysis of yellowness (b*) of binary mixtures. Standard deviation (SD) for L*, a*, b* is ±0.05, ±0.03 and ±0.04 respectively

TG and DTG curves of tested mucolytic drugs, starch, and binary physical mixtures of both ingredients at different weight ratios are presented in Figure 4. Decomposition parameters of the tested samples are presented in Table V and VI.

Figures 4a, 4c and 4e presents the TG curve of starch (dash line). TG analysis indicated that the decomposition of starch is started in 298.5°C and presents two stages of mass loss. The first and the second stage of mass loss is -10.8% and -73.5% respectively. The DTG curve of starch presented two peaks corresponding with the TG curve (Figures 4b, 4d and 4f, Table VI). The first stage of mass loss occurred in the temperature range 37°C - 117°C with the maximum peak at 71.7°C and it is related to the moisture evaporation [28, 29]. The second stage is occurred in the temperature range 255°C - 349°C, with the maximum peak at 309°C and it is associated with a thermal degradation of starch [28, 30].

The TG curve (Figure 3a) showed that the thermal decomposition begun at lower temperature for ambroxol in binary mixture with starch compared to pure drug. The binary mixture of ambroxol with starch in ratio 2:1, 1:1 and 1:2 decomposition starts earlier 19.3°C, 19.4°C and 18.6°C respectively (Table V). On the DTG curve, (Figure 4b) we can observe a shift in the peak of maximum weight loss towards a lower temperature. On the DTG curve, we cannot observe a gradual disappearance of the maximum weigh loss peak for drug and an increase the peak for excipient with an increase in the proportion of excipient. This may indicate the incompatibility of ambroxol with starch. Other author indicated interactions between the starch and metformin (antidiabetic drug) by thermal analysis [31].

Thermal decomposition of acetylcysteine in binary mixture with starch begins at slightly lower temperature. The onset temperature of decomposition for acetyl-cysteine/starch in ratio 2:1, 1:1 and 1:2 starts earlier at 4.9°C, 5.6°C and 6.2°C respectively (Figure 4e, Table V). However, by analysing the DTG curve (Figure 4f) we can observe the overlap of the thermal peak

coming from drug and excipient in the binary mixture. DTG curve shows disappearance of the maximum weigh loss peak for acetylcysteine and an increase the peak for starch with an increase in the proportion of excipient. These facts may indicate the lack of interaction between the two tested substances.

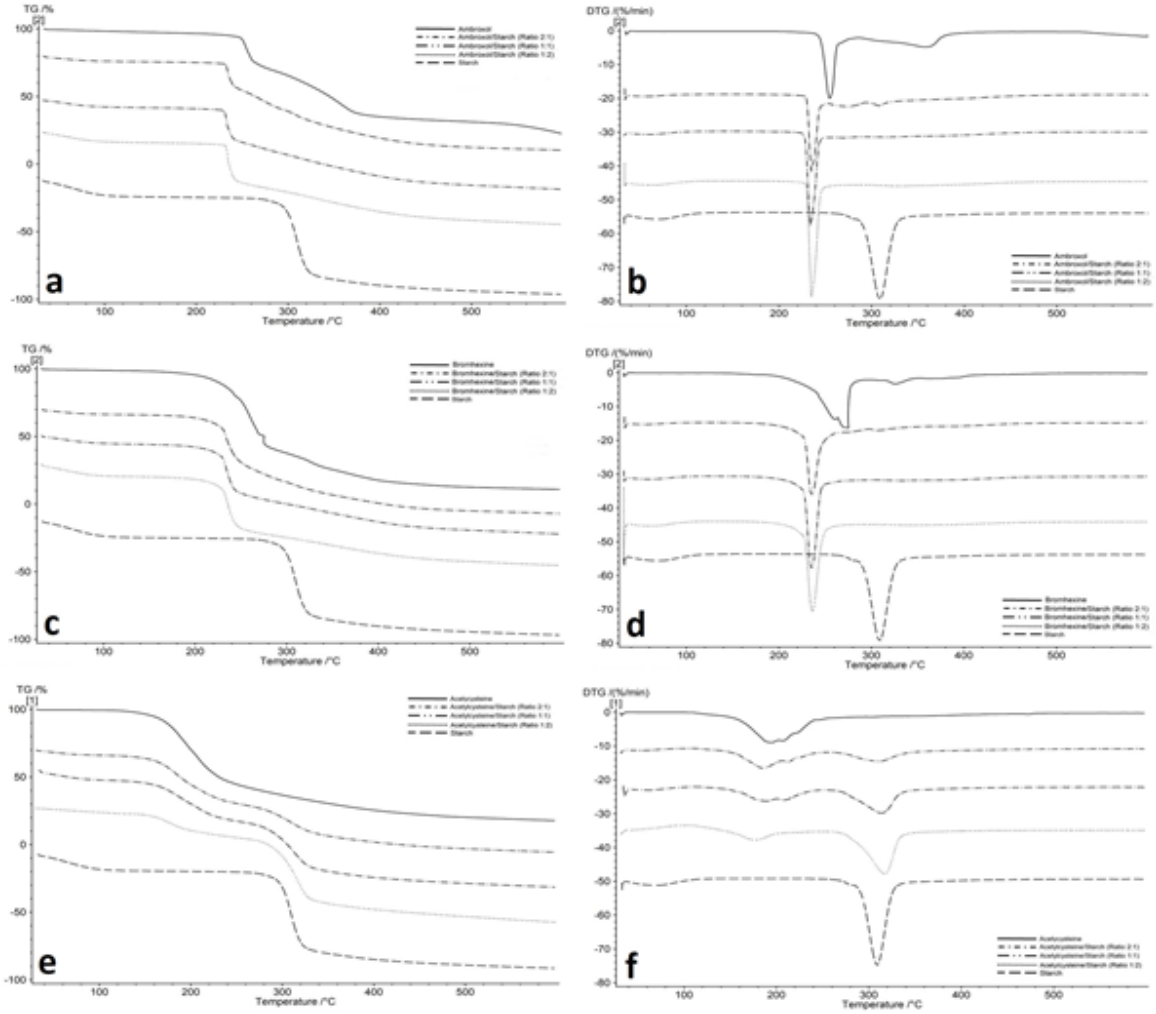

Figure 4.

TG (a, c, e) and DTG (b, d, f) curves of tested API (solid line), starch (dash line) and binary mixture of API and starch in ratio (w:w) 2:1 (dash/dot/dot line), 1:1 (dash/dot line) and 1:2 (dot line)

Table V

Characteristic parameters of TGA curves of the starch, tested mucolytic drugs and binary mixture of API with excipient in different ratio

Tested samples		TG parameters				
		Onset (°C)	Mid (°C)	Infelction (°C)	End (°C)	Mass change (%)
Starch		298.5	313.0	309.1	322.3	-47.94
Ambroxol		249.6	287.3	254.4	280.8	-52.32
Ambroxol/Starch (Ratio w:w)	2:1	230.3	277.5	236.4	260.6	-50.33
	1:1	230.2	261.8	233.5	245.4	-39.90
	1:2	231.0	244.7	236.1	246.2	-38.18
Bromhexine		228.7	264.8	268.3	304.6	-78.50
Bromhexine/Starch (Ratio w:w)	2:1	227.0	248.3	235.5	260.7	-59.27
	1:1	227.8	240.3	235.5	250.4	-47.50
	1:2	228.8	241.2	236.5	249.3	-42.36
Acetylcysteine		168.2	207.0	193.8	249.8	-68.23
Acetylcysteine/Starch (Ratio w:w)	2:1	163.3	238.5	185.7	276.9	-52.05
	1:1	162.6	298.2	314.3	336.5	-54.38
	1:2	162.0	301.5	317.3	331.8	-69.36

Table VI

Characteristic parameters of DTG curves of the starch, tested mucolytic drugs and binary mixture of API with excipient in different ratio

Tested samples		DTG weight loss rate							
		Stage I		Stage II		Stage III		Stage IV	
		Peak (°C)	Mass change (%/min)	Peak (°C)	Mass change (%/min)	Peak (°C)	Mass change (%/min)	Peak (°C)	Mass change (%/min)
Starch		71.7	-2.05	309.0	-25.60	-	-	-	-
Ambroxol		254.7	-19.98	357.1	-4.81	-	-	-	-
Ambroxol/Starch (Ratio w:w)	2:1	57.5	-0.69	234.9	-22.76	274.0	-3.67	308.2	-3.41
	1:1	61.1	-1.02	233.7	-27.92	-	-	-	-
	1:2	64.9	-1.33	234.8	-34.13	-	-	-	-
Bromhexine		274.9	-16.36	326.1	-3.34	375.0	-1.70	-	-
Bromhexine/Starch (Ratio w:w)	2:1	55.2	-0.66	235.5	-21.31	306.2	-2.45	376.9	-1.23
	1:1	58.8	-1.02	235.4	-27.25	337.3	-1.42	-	-
	1:2	61.2	-1.48	236.2	-26.00	341.1	-1.26	-	-
Acetylcysteine		195.3	-8.97	345.0	-1.71	-	-	-	-
Acetylcysteine/Starch (Ratio w:w)	2:1	54.2	-0.73	185.5	-5.95	311.6	-3.93	-	-
	1:1	62.2	-1.10	188.8	-4.42	313.5	-7.95	-	-
	1:2	48.8	-0.26	176.1	-3.42	317.3	-13.45	-	-

Figure 4c presents the TG curves of bromhexine in binary mixture with starch in different ratio. The TG curves indicated that the onset temperature of decomposition for the binary mixture API and excipient has not changed comparing to initial temperature of decomposition for the pure bromhexine (Table V). This fact may indicate that the drug is compatible with the excipient. However, on the DTG curve (Figure 4d) we cannot distinguish the gradual disappearance of the drug thermal peak, and the increase excipient thermal peak with the increase in its amount. This makes it difficult to interpret the result unambiguously. For the bromhexine and starch, additional analyses should be performed by another analytical method.

Conclusions

The thermogravimetric examination of ambroxol, bromhexine, acetylcysteine with selected excipients used in the solid dosage forms pointed out that all tested mucolytic drugs are compatible with magnesium stearate. This is indicated by the recorded TG/DTG curves. The tested mucolytic drugs are incompatible with lactose monohydrate. Millards reaction is responsible for this interactions. This was additionally confirmed by a colourimetric method using the CIE Lab analysis system. The binary mixture of starch and acetyl-cysteine are compatible. However, a mixture of starch and ambroxol shows interactions. The obtained results for the binary mixture bromhexine/starch, regardless of the ratio used, are inconclusive and should be done by different confirmatory analytical method. The TG and DTG measurements may be used together to the initial study of drugs compatibility with excipients in preformulation examinations.

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Conflict of interest

The authors declare no conflict of interest.

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