https://doi.org/10.31925/farmacia.2022.3.6 **ORIGINAL ARTICLE**

THERMAL COMPATIBILITY ASSESSMENT OF SELECTED EXCIPIENTS USED IN THE ORAL ANTI-CANCER FORMULATION CONTAINING BUSULFAN

PAWEŁ RAMOS *

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

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

Manuscript received: January 2022

Abstract

Oral anti-cancer drugs such as busulfan served in tablet forms except active pharmaceutical ingredient contain excipients in the formulation. Excipients must be selected so as not to cause an interaction with the API. This is especially important in the design of anti-cancer drugs. Each interaction between the excipient and the API may be translated into the deterioration of the therapeutic effects by changing the properties of the API in the final formulation. The thermogravimetry analysis can be used as a quick and cheap method of testing the compatibility of API with an excipient in preformulation studies. In this assessed examination, the compatibility of busulfan with selected excipients used in the manufacturing of tablet form was studied. TG/DTG/D2TG analysis was done for busulfan, tested excipients, and binary mixture API with an excipient. The study has shown that busulfan is incompatible with anhydrous glucose, sucrose, lactose monohydrate, microcrystalline cellulose, and starch, but the tested API is compatible with chitosan and stearate magnesium. Additionally, thermogravimetry analysis has shown that stearate magnesium causes increased thermal stability of the busulfan.

Rezumat

Medicamentele orale anticanceroase, care conțin busulfan sub formă de comprimate, conțin excipienți selectați astfel încât aceștia să nu provoace o interacțiune cu substanța activă (API). Fiecare interacțiune dintre excipient și API poate fi tradusă în diminuarea efectelor terapeutice prin modificarea proprietăților API în formularea finală. Analiza termogravimetrică poate fi utilizată ca metodă rapidă și ieftină de testare a compatibilității API cu un excipient în cadrul studiilor de preformulare. În acest studiu s-a evaluat compatibilitatea busulfanului cu diferiți excipienți utilizați la fabricarea comprimatelor. Analiza TG/DTG/D2TG a fost efectuată pentru busulfan, excipienții testați și amestecul binar API cu un excipient. Studiul a arătat că busulfanul este incompatibil cu glucoza anhidră, zaharoza, lactoza monohidrat, celuloza microcristalină și amidonul, dar este compatibil cu chitosanul și stearatul de magneziu. În plus, analiza termogravimetrică a arătat că stearatul de magneziu crește stabilitatea termică crescută a busulfanului.

Keywords: busulfan, excipients, compatibility studies, oral chemotherapy, TG, DTG, D2TG

Introduction

The finished drugs, in addition to the API (active pharmaceutical substance), contain excipients [1, 2]. Excipients perform many important functions in drug formulations. Excipients in the formulation of solid drug forms are used to: fill the mass of the tablet, improve the appearance and taste of the drug, stabilization of the API in the drug formulation [1-4]. The excipients are also used to affect the kinetics and the place of release of the API in the body [1, 4]. Excipients should be selected in the final formulation of drugs so that they do not cause any interaction with the active pharmaceutical substance (API) [1, 3]. Excipients also cannot exert a therapeutic effect on the body [1, 2]. Each interaction between the excipient and the active pharmaceutical ingredient may be translated into the deterioration of the therapeutic effects by changing the properties of the API in the final formulation [1-3]. This is of particular importance in the oral therapy of cancer. Due to a number of side effects, cytostatic drugs must be precisely dispensed and the therapeutic effects of their use must be predictable [5].

Busulfan is a chemotherapy drug that belongs to an alkylating agent. The mechanism of action of busulfan relies on by sticking to one of the DNA strands of the cancer cell [6-8]. It is caused that the cancer cell cannot divide into two new cells. Busulfan is used in chronic myeloid leukaemia (CML), myelodysplastic syndromes (MDS), and other types of cancer that need treatment with a stem cell or bone marrow transplant [6-8]. Side effects of busulfan include: bone marrow myelosuppression with pancytopenia, pulmonary fibrosis, damage to the central nervous system, hepatic vein occlusion syndrome and damage to the gastrointestinal mucosa [6-8].

In addition to non-thermal methods such as high-performance liquid chromatography (HPLC), Fourier transform infrared spectroscopy (FTIR), X-Ray spectroscopy, thermal methods such as differential scanning calorimetric (DSC), thermogravimetry (TG) are also used to assess API interactions with excipients in preformulation studies [9-12]. The thermogravimetric analysis (TGA) is often used in preformulation studies [12-14]. The advantages of this method include the use of a small sample volume, speed of execution, and repeatability of results [12]. The TG analysis consists of measuring the mass loss of the studied sample as the heating temperature increases. The obtained results are saved in the form of thermograms [12-14]. To increase the reading efficiency of TGA curves, a simultaneous differential thermogravimetric analysis (DTG) is performed. DTG is the first derivative of the thermogravimetry curve relative to temperature [12-14]. The obtained differences in the thermograms and analysed parameters of the decomposition of the tested API and the mixture of the API with the tested excipient may be due to the existing interaction between them [12, 14].

The aim of this work was to assess the interaction between busulfan and excipients used in the production of the tablets. The studies used analysis of the obtained thermograms (TGA and DTG) of busulfan, excipients and mixtures of busulfan-excipient in weight ratio 1:1.

Materials and Methods

Tested samples

In this study, busulfan was used. Busulfan is an anti-cancer drug that belongs to the group of sulfonic acid esters [6-8]. Due to the good absorption profile from the gastrointestinal tract, it can be administered orally in the form of tablets [6-8]. In this study, selected excipients applied in the technology of solid dosage forms were used. From the excipients of the experiment, anhydrous glucose, sucrose, lactose monohydrate, micro-crystalline cellulose, chitosan, starch and magnesium stearate were selected.

Anhydrous glucose is a monosaccharide that occurs as colourless crystals or a sweet-tasting white powder [1, 15, 16]. Glucose is obtained by the hydrolysis of potato starch. In pharmacy, glucose may be used as a diluent for tablets and capsules, a therapeutic agent, tonic agent [15].

Sucrose is a disaccharide that contains one molecule of glucose and one molecule of fructose [1, 15]. Sucrose occurs in the form of colourless crystals or a sweet-tasting white powder [15, 16]. In pharmacy, sucrose may be used as a coating agent, auxiliary for granulation, suspending the agent, a sweetener, tablet binders; diluent for tablets and capsules, tablet filler, therapeutic agent, viscosity enhancing agent [15].

Lactose monohydrate is a disaccharide that contains one molecule of D-glucose and one molecule of β-D-galactose [1, 15, 16]. Lactose is a white crystalline powder with a slightly sweet taste [16]. In pharmacy, lactose may be used as tablet binder, tablet and capsule diluent, tablet and capsule filler, dry powder inhaler carrier, lyophilisation aid [15].

Microcrystalline cellulose is obtained from α-cellulose by a chemical and mechanical process of grinding aggregates [1, 15, 16]. Microcrystalline cellulose is a fine, snow-white powder with a high level of purity [16]. In pharmacy, microcrystalline cellulose may be used as tablet and capsule diluent, tablet disintegrant, adsorbent, suspending agent [15].

Chitosan is an organic polysaccharide obtained by deacetylating chitin [15, 17]. It is commonly found in the shells of insects, marine crustaceans and the cell walls of some species of fungi [17]. In pharmacy, chitosan may be used, such as coating agent, tablet disintegrant, tablet binder, viscosity increasing agent, film-forming agent, mucoadhesive [15].

Starch is a polysaccharide which, on hydrolysis, breaks down into dextrins, then maltose (disaccharide) and finally D-glucose [1, 15, 16]. Starch is a reserve material of plants [16]. In pharmacy, starch may be used, such as tablet and capsule filler, binding agent, compression aid, disintegrant, tablet and capsule diluent [15].

Magnesium stearate is the magnesium salt of stearic acid [1, 15, 16]. It is a white powder insoluble in water, alcohol and ether, but dissolving in benzene [16]. In pharmacy, it is used as a tablet and capsule lubricant [15].

Busulfan and all excipients were purchased from Sigma-Aldrich Company, USA.

Preparation of samples to measurements

All analyses were performed using the samples of single drug, single excipients (glucose anhydrous, sucrose, lactose monohydrate, microcrystalline cellulose, chitosan, starch, magnesium stearate) and binary mixture of busulfan with each excipient separately. In experiment, weight ratio 1:1 of busulfan-excipient was used. Ratio API-excipient was obtained by grinding in the porcelain mortar. The mass of examined samples was determined using the CPA weight Sartorius (Germany).

Thermogravimetric measurements

The thermal decomposition of busulfan, excipients and the mixture of the both was determined by thermo-gravimetric analysis (TGA). Thermogravimeter TG 209 F3 Tarsus produced by Netzsch (Germany) was used. In the research the dynamic test, running under conditions linear growth temperature was used. Changes in mass (Δm) were recorded as a result of heating the sample under the conditions of a linear temperature increase. These changes were plotted as a function of temperature (T), obtaining the TG curve [18, 19]:

$$\Delta m = \int (T).$$

At the same time, the measurement of the mass change rate (dm/dt) was recorded. It allowed to obtain a differential thermogravimetric curve (DTG) [18, 19]:

$$dm/dt = \int (T).$$

Additionally, all peaks of maximum mass loss recorded on the first derivative (DTG) curves were presented by the second derivative (D2TG). The TG, DTG and D2TG curves were recorded for 10 mg of tested samples at a heating rate of 30 °K *per* minute, in the temperature range of 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 (Germany).

Results and Discussion

The examinations of API-excipients compatibility represents an important phase in the preformulation stage for the development of solid dosage forms. The selection of the proper excipient during preformulation examinations is of prime importance. Thermal techniques such as thermogravimetry (TG) can be used in the initial stage of preformulation studies [20, 21]. The TG, DTG and D2TG curves of busulfan, selected excipients, and binary mixtures of both ingredients at 1:1 mass ratio are presented in Figures 1 and 2. All analysed decomposition parameters of TG and DTG curves tested samples are presented in Table I and Table II.

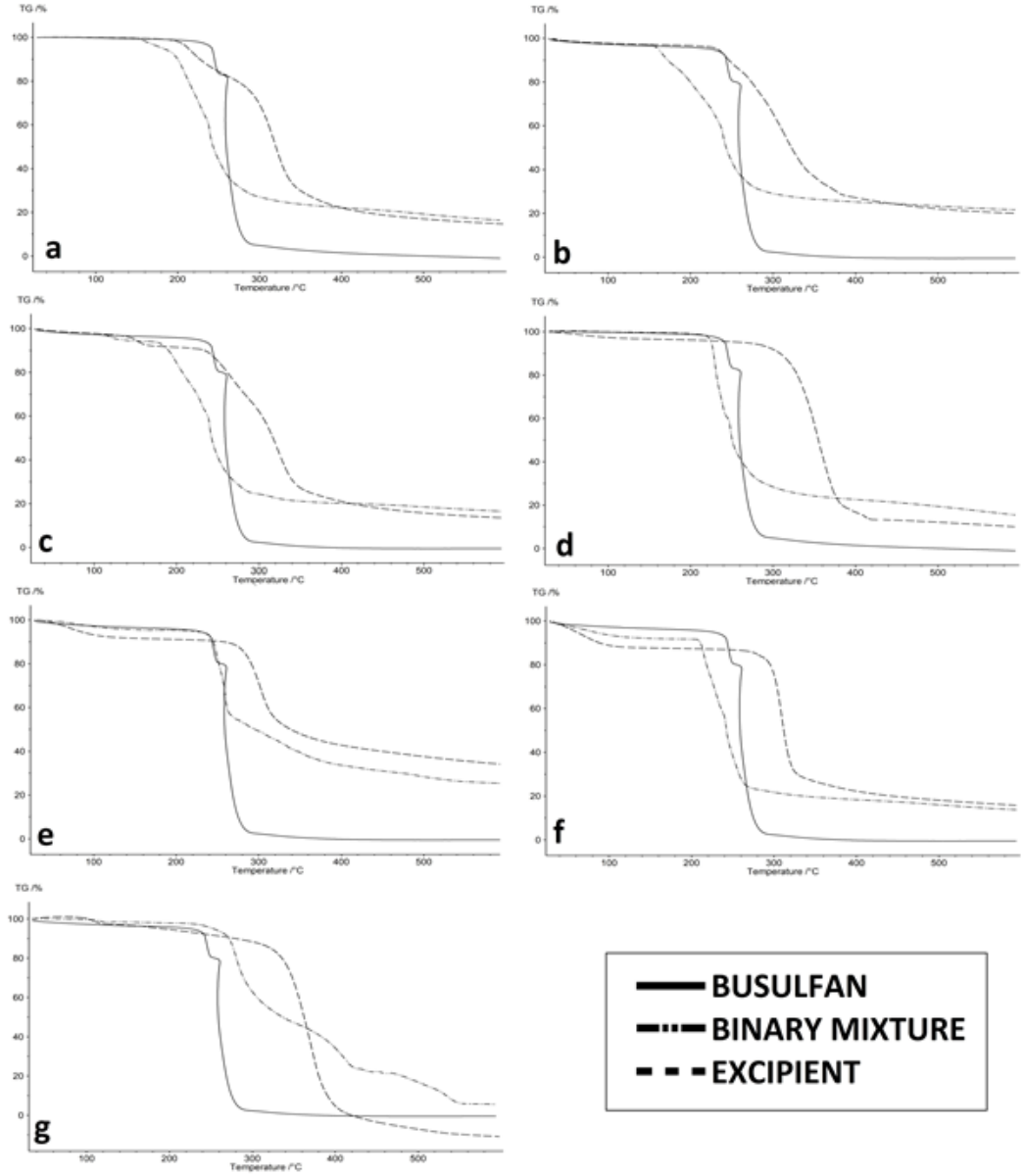

Figure 1.

TG curves of busulfan, tested excipients, and binary mixture busulfan with (a) glucose anhydrous, (b) sucrose, (c) lactose monohydrate, (d) microcrystalline cellulose, (e) chitosan, (f) starch, (g) magnesium stearate. All binary mixtures of API and excipients were prepared in weight ratio 1:1.

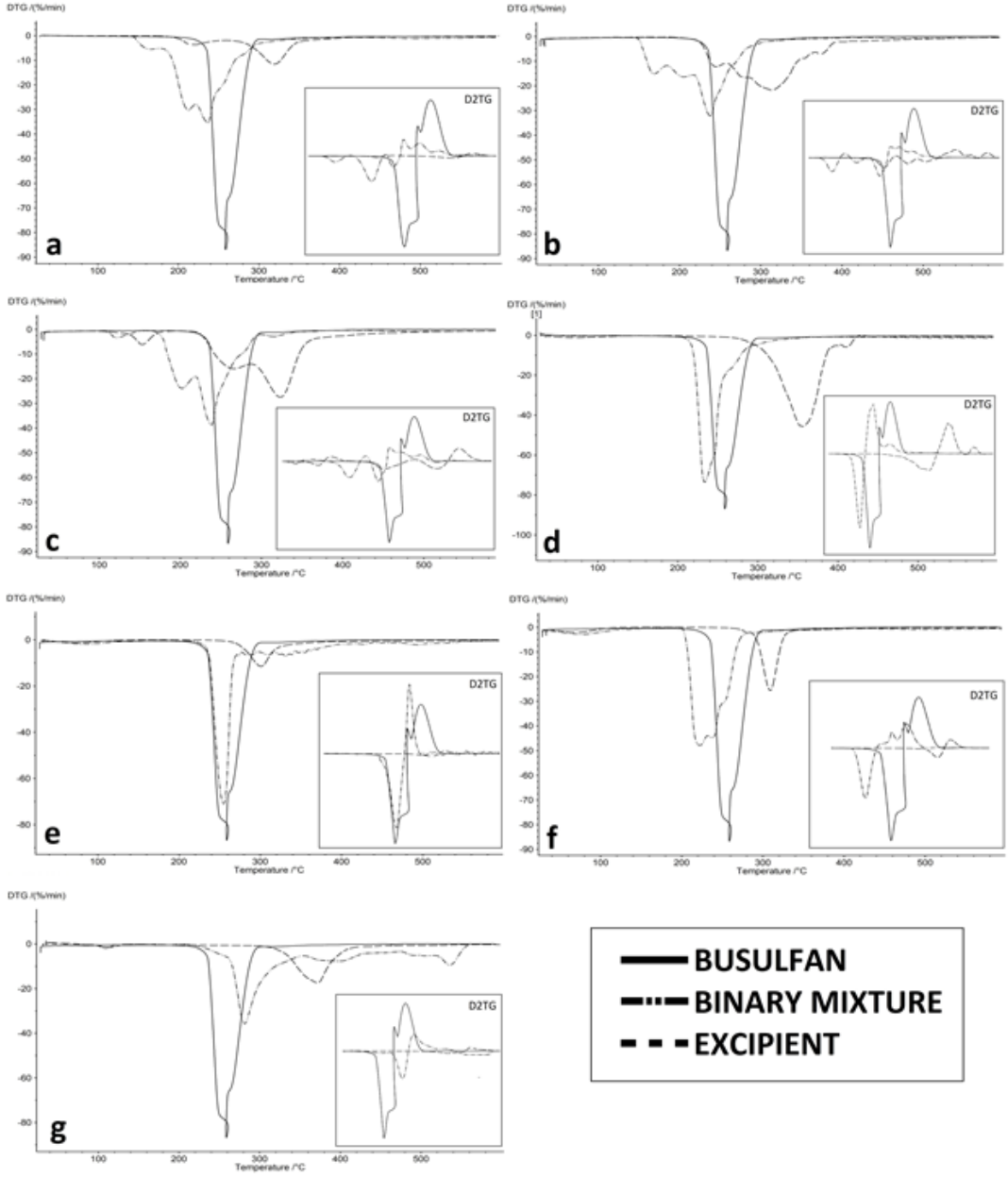

Figure 2.

DTG and D2TG curves of busulfan, tested excipients, and binary mixture busulfan with (a) glucose anhydrous, (b) sucrose, (c) lactose monohydrate, (d) microcrystalline cellulose, (e) chitosan, (f) starch, (g) magnesium stearate. All binary mixtures of API and excipients were prepared in weight ratio 1:1.

Table I

Characteristic parameters of TGA curves of the busulfan, tested excipiens, and binary mixture of busulfan with excipient (weight ratio 1:1)

Tested samples		TG parameters				
		Onset [°C]	Mid [°C]	Infelction [°C]	End [°C]	Mass change [%]
API	Busulfan	249.8	259.2	258.2	272.7	96.01
EXCIPIENTS	Glucose anhydrous	201.3	310.5	319.7	345.4	-76.49
	Sucrose	247.5	307.4	317.1	360.1	-66.75
	Lactose monohydrate	239.9	309.1	323.8	353.1	-70.86
	Microcrystalline cellulose	322.9	352.6	361.2	380	-76.67
	Chitosan	282.9	307.9	301	323.6	-33.75
	Starch	297.9	312.6	309.1	322.3	-49.53
	Magnesium stearate	341.4	366.8	372.1	393.2	-88.24

Tested samples		TG parameters				
		Onset [°C]	Mid [°C]	Infelction [°C]	End [°C]	Mass change [%]
BINARY MIXTURES	Busulfan/Glucose anhydrous	200	233.8	237.4	266.9	-71.73
	Busulfan/Sucrose	166.2	234	239	261.2	-66.52
	Busulfan/Lactose monohydrate	208.2	237.4	239.6	266.5	-71.39
	Busulfan/Microcrystalline cellulose	221	240.3	234.2	258.5	-69.46
	Busulfan/Chitosan	245.9	258.9	254.7	271.7	-49.89
	Busulfan/Starch	209	241.5	218.5	269.9	-60.06
	Busulfan/Magnesium stearate	268.2	284.5	378.5	378.5	-39.91

Table II

Characteristic parameters of DTG curves of the busulfan, tested excipients, and binary mixture of busulfan with excipient (weight ratio 1:1)

Tested samples		DTG parameters					
		Stage I		Stage II		Stage III	
		Peak [°C]	Mass change [%/min.]	Peak [°C]	Mass change [%/min.]	Peak [°C]	Mass change [%/min.]
API	Busulfan	258.6	-86.88	-	-	-	-
EXCIPIENTS	Glucose anhydrous	217	-3.61	320	-11.5	-	-
	Sucrose	245	-12.28	314	-21.78	-	-
	Lactose monohydrate	154	-6.14	265	-15.95	324	-27.42
	Microcrystalline cellulose	71	-1.2	357	-45.62	-	-
	Chitosan	72	-1.39	302	-11.62	-	-
	Starch	73	-2.04	308	-25.51	-	-
	Magnesium stearate	109	-1.84	372	-17.49	-	-
BINARY MIXTURES	Busulfan/Glucose anhydrous	164	-5.53	237	-35.33	-	-
	Busulfan/Sucrose	169	-15.1	238	-32.28	-	-
	Busulfan/Lactose monohydrate	123	-3.09	203	-23.88	219	-34.8
	Busulfan/Microcrystalline cellulose	233.3	-73.5	-	-	-	-
	Busulfan/Chitosan	87	-1.79	254	-74.8	-	-
	Busulfan/Starch	78	-2.32	222	-47.88	-	-
	Busulfan/Magnesium stearate	114	-1.9	282	-35.36	-	-

In Figures 1 and 2, TG, DTG and D2TG curves of busulfan, excipients and binary mixtures both ingredients are marked as solid, dashed, and dot/dashed lines respectively.

TG curve showed that the temperature onset of the decomposition of busulfan was 249.8°C and one mass loss stage could be observed (-96.01%) (Table I). The DTG curve of busulfan presented one peak corresponding with TG curve. The DTG stage of mass loss occurred in the temperature range 205°C to 304°C with a maximum peak in 258.6°C and mass change -86.88%/min (Table II).

The thermogravimetric curves for all tested excipients have typical mileages corresponding with literature [22-36]. The DTG curve for glucose anhydrous has two stages [22]. The first stage of mass loss occurred in the temperature range 171°C to 258°C with a maximum peak in 217°C. The second stage of mass loss occurred in temperature range 258°C to 392°C with a maximum peak in 320°C (Figures 1a and 2a, Table I and Table II) [22, 23].

The DTG curve for sucrose has two stages [24, 25]. The first stage mass loss occurred in the temperature range 186°C to 258°C with a maximum peak in 245°C. This stage is related to the caramelization of sucrose and it is in good agreement with the literature [24]. The last stage of mass loss begins in 258°C with a maximum peak in 314.1°C and corresponded with the creation of black, charred solid substance (Figures 1b and 2b, Table I and Table II) [24].

The DTG curve of lactose monohydrate presented three peaks corresponding with the thermogravimetric curve. The first stage mass loss occurred in the temperature range 92°C to 188°C with maximum peak in 154°C. This stage is related with water release [26, 27]. The second stage occurred in temperature range 206°C to 288°C with maximum peak in 265°C and is associated with a new water release [28]. The last stage begins in temperature 288°C with maximum peak in 324°C and is associated with a continue degradation of lactose (Figures 1c and 2c, Table I and Table II) [28].

The DTG curve for microcrystalline cellulose has two stages [29, 30]. The first stage mass loss occurred in the temperature range 41°C to 134°C with a maximum peak in 71°C. This stage was due to the evaporation of

absorbed water [29]. The last stage mass loss occurred in the temperature rang 254°C to 434°C. Second stage has a maximum mass loss peak in 357°C. This stage is related to proper thermal degradation of cellulose with formation of a charred residue (Figures 1d and 2d, Table I and Table II) [29].

The DTG curve for chitosan has two stages [31]. The first stage mass loss occurred in the temperature range 34°C to 144°C with a maximum peak in 72°C. Stage one is related to water release [31]. The second stage of mass loss occurred in temperature range 229°C to 424°C with a maximum peak in 357°C. Second stage is related to the complete decomposition of chitosan (Figures 1e and 2e, Table I and Table II) [32].

The DTG curve for starch has two stages of mass loss. The first stage occurred in the temperature range 38°C to 120°C with a maximum peak in 73°C. First stage is related to moisture evaporation [33]. The last stage occurred in temperature range 262°C to 354°C with a maximum peak in 308°C and it associated with a thermal degradation of starch (Figures 1f and 2f, Table I and Table II) [34].

The DTG curve for magnesium stearate has two peaks of mass loss corresponding with TG curve. The first stage occurred in the temperature range 87°C to 129°C with a maximum peak in 109°C and is related to water release [26]. The second stage occurred in temperature range 280°C to 455°C. The last stage has a maximum mass loss peak in 372°C and is related to the decomposition of magnesium stearate (Figures 1g and 2g, Table I and Table II) [26, 35].

TG curves (Figures 1a - 1d, 1f) showed that the thermal decomposition begins at lower temperature for busulfan in binary mixture with glucose anhydrous, sucrose, lactose monohydrate, microcrystalline cellulose and starch compared to pure drug. The binary mixture of busulfan with glucose anhydrous, sucrose, lactose monohydrate, microcrystalline cellulose, and starch decomposition starts earlier by 49.8°C, 83.6°C, 41.6°C, 28.8°C and 40.8°C respectively (Table. I). On the DTG curves (Figures 2a - 2d, 2f) for binary mixtures API-excipients we can observe a shift in the peak of maximum weight loss towards a lower temperature. For busulfan with glucose anhydrous, sucrose, lactose monohydrate, microcrystalline cellulose and starch the peak of maximum weight loss are shifted to a lower value by 21.6°C, 20.6°C, 39.6°C, 25.3°C and 36.6°C respectively (Table. II). DTG curves for binary mixture look more like an excipient than an API. Especially for the binary mixture busulfan with glucose anhydrous, sucrose and lactose monohydrate (Figures 2a - 2c). This may indicate the incompatibility of busulfan with these excipients. Other authors also indicated interactions between active pharmaceutical ingredients and excipients by thermal analysis [27, 36-39]. Interactions were recorded for isoniazid-lactose [27], diclofenac-lactose [35], procaine-lactose [36], enalapril-microcrystalline cellulose [37], metformin-starch [38].

Figures 1e and 2e presented TG and DTG curves for binary mixture busulfan with chitosan in ratio 1:1. The recorded termogravimetric curves show that the studied API is compatible with the chitosan. The onset temperature of decomposition for tested busulfan and binary mixture busulfan with tested excipient is not change (Table I). On the DTG curve (Figure 2e) we can observe that the maximum loss mass peak for API has coincided with the peak for binary mixture API-excipient (Table II). This fact indicated that there was no interaction between busulfan and chitosan. It has been proven that the chitosan is compatible with atenolol [39], hydrocortisone [40].

An interesting result was recorded for the binary mixture busulfan with magnesium stearate. TG curve (Figure 1g) for binary mixture showed that the decomposition started later by 23.4°C compared to pure busulfan (Table I). DTG curve (Figure 2g) for busulfan-magnesium stearate was shown to shift the maximum loss mass peak from 258.6°C to 282°C. These results confirmed that the magnesium stearate is compatible with busulfan and causes increased thermal stability of this API. A similar beneficial effect of the excipient on the API was recorded for amitriptyline hydrochloride [41]. Compatibility with magnesium stearate was confirmed thermally method for atenolol [39], ceftriaxone [42].

Conclusions

The compatibility study of busulfan with selected excipients used in solid dosage forms using TG analysis pointed out that: Busulfan is incompatible with tested mono-, di- and polysaccharides. TG/DTG/D2TG curves for binary mixtures API with glucose anhydrous, sucrose, lactose monohydrate, microcrystalline cellulose and starch indicate a lower onset temperature of the decomposition process compared to pure busulfan. Tested API is compatible with chitosan and magnesium stearate. This is indicated by the recorded TG/DTG/D2TG curves. Additionally, magnesium stearate has got an influence on the increased thermal stability of the busulfan. The use of this excipient in formulation caused an onset decomposition delay of 23.4°C.

The thermogravimetric analysis may be used for the preliminary examination of compatibility busulfan with excipients in pre-formulation studies.

Acknowledgement

This work was financially supported by Medical University of Silesia in Katowice, grant number: PCN-1-033/N/1/F.

Conflict of interest

The authors declare no conflict of interest.

References

1. Allen LV, Ansel HC, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. 10th edition. Philadelphia, Baltimore, New York, London, Buenos Aires, Hong Kong, Sydney, Tokyo: Lippincott Williams and Wilkins; 2014.
2. Bharate SS, Bharate SB, Bajaj AN, Interactions and incompatibilities of pharmaceutical excipients with active pharmaceutical ingredients: a comprehensive review. *J Excip Food Chem.*, 2010; 1(3): 3-26.
3. Elder DP, Kuentz M, Holm R, Pharmaceutical excipients – quality, regulatory and biopharmaceutical considerations. *Eur J Pharm Scien*., 2016; 87: 88-99.
4. Polski A, Iwaniak K, Naleśniak M, Poleszak E, The excipients used in the non-coated tablests – a review. *Medicina Internacia Revuo*, 2014; 26(102): 10-18.
5. Aslam MS, Naveed S, Ahmed A, Abbas Z, Gull I, Side Effects of Chemotherapy in Cancer Patients and Evaluation of Patients Opinion about Starvation Based Differential Chemotherapy. *J Cancer Therapy*, 2014; 5(8): 817-822.
6. Hassan M, The role of busulfan in bone marrow transplantation. *Med Oncol.*, 1999; 16(3): 166-176.
7. Swiss Pharmaceutical Society, Index Nominum: International Drug Directory 20th edition. Germany: MedPharm; 2011.
8. Myers AL, Kawedia JD, Champlin RE, Kramer MA, Nieto Y, Ghose R, Andersson BS, Clarifying Busulfan Metabolism and Drug Interactions to Support New Therapeutic Drug Monitoring Strategies: A Comprehensive Review. *Expert Opin Drug Metab Toxicol.*, 2017; 13(9): 901-923.
9. Prado de Barros Lima I, Naiana Gondim PB, Lima Denise MC, Barros Thays S, Oliveira Cândida MS, Mendonça Euzébio G, Barbosa Fernanda N, Raffin Túlio FA, de Lima e Moura Ana Paula B, Márcio Ferrari G, Compatibility study between hydroquinone and the excipients used in semi-solid pharmaceutical forms by thermal and non-thermal techniques. *J Therm Anal Calorim.*, 2015; 120: 719-732
10. Rusu A, Ciurba A, Birsan M, Antonoaea P, Szekely-Szentmiklosi B, Fulop I, Pascu GA, Todoran N, Compatibility study of four binary combinations of active ingredients for dermal film forming systems. *Farmacia*, 2020; 68(5): 800-811.
11. Rezende RLO, Santoro MIRM, Matos JR, Stability and compatibility study on enalapril maleate using thermoanalytical techniques. *J Therm Anal Calorim.*, 2008, 93(3): 881-886.
12. Soares de Mendonça CM, Prado de Barros Lima I, Flávio Soares Aragão C, Barreto Gomes AP, Thermal compatibility between hydroquinone and retinoic acid in pharmaceutical formulations. *J Therm Anal Calorim.*, 2014; 115: 2277-2285.
13. Koga N, Ozawa's kinetic method for analyzing thermo-analytical curves. History and theoretical fundaments. *J Therm Anal Calorim.*, 2013; 113: 1527-1541.
14. Monajjemzadeh F, Ghaderi F, Thermal Analysis Methods in Pharmaceutical Quality Control. *J Mol Pharm Org Process Res.*, 2015; 3: 1-2.
15. Rowe RC, Sheskey PJ, Quinn ME, Habdbook of Pharmaceutical Excipients. 6th edition. London, Chicago: Pharmaceutical Press; 2009.
16. Janicki S, Fiebig A, Applied pharmacy. Poland: PZWL publishing house; 1999, (available in Polish).
17. Kumar S, Koh J, Physiochemical, optical and biological activity of chitosan-chromone derivative for biomedical applications. *Int J Mol Sci.*, 2012; 13(5): 6102-6116.
18. Gabbott P, (Ed.), Principles and applications of thermal analysis, Blackwell Publishing, Oxford 2008.
19. Haines PJ, (Ed.), Principles of thermal analysis and calorimetry, Royal Society of Chemistry, Cambridge, 2002.
20. Gupta KR, Pounikar AR, Umekar MJ, Drug excipient compatibility testing protocols and characterization: A review. *Asian J Chem Sci.*, 2019; 6(3): 1-22.
21. Oliveira GGG, Feitosa A, Loureiro K, Fernandes AR, Souto EB, Severino P, Compatibility study of paracetamol, chlorpheniramine maleate and phenylephrine hydrochloride in physical mixtures. *Saudi Pharm J.*, 2017; 25(1): 99-103.
22. Saavedra-Leosa MZ, Alvarez-Salasb C, Esneider-Alcala MA, Toxqui-Terán A, Pérez-García SA, Ruiz-Cabrera MA, Towards an improved calorimetric methodology for glass transition temperature determination in amorphous sugars. *CyTA - Journal of Food*, 2012; 10(4): 258-267.
23. Wei-Hsien H, Wen-Ting C, Ling-Chun C, Hong-Liang L, Shan-Yang L, Non-isothermal Dehydration Kinetics of Glucose Monohydrate, Maltose Monohydrate and Trehalose Dihydrate by Thermal Analysis and DSC-FTIR Study. *J Biomed Pharm Sci.*, 2018; 1(1): 1-6.
24. Zhao Z, Hayashi S, Xu W, Wu Z, Tanaka S, Sun S, Zhang M, Kanayama K, Umemura K, A Novel Eco-Friendly Wood Adhesive Composed by Sucrose and Ammonium Dihydrogen Phosphate. *Polymers (Basel)*, 2018; 10 (1251): 1-14.
25. Wang C, Dou B, Song Y, Chen H, Yang M, Xu Y, Kinetic Study on Non-isothermal Pyrolysis of Sucrose Biomass. *Energy Fuels*, 2014; 28(6): 3793-3801.
26. Ilyes K, Casian T, Hales D, Borodi G, Rus L, Stiufius R, Tomuta I. Applying the principles of quality by design (QbD) coupled with multivariate data analysis (MVDA) in establishing the impact of raw material variability for extended release tablets. *Farmacia*, 2021; 69(3): 481-497.
27. Lavor EP, Navarro MVM, Freire FD, Aragão CFS, Raffin FN, Barbosa EG, de Lima e Moura TFA, Application of thermal analysis to the study of antituberculosis drugs–excipient compatibility. *J Therm Anal Calorim.*, 2014; 115: 2303-2309.
28. Listiohadi Y, Hourigan JA, Sleigh RW, Steele RJ, Thermal analysis of amorphous lactose and α-lactose monohydrate. *Dairy Sci Technol.*, 2009; 89: 43-67.
29. Suxia R, Xiuxuan S, Tingzhou L, Qinglin W, The Effect of Chemical and High-Pressure Homogenization Treatment Conditions on the Morphology of Cellulose Nanoparticles. *J Nanomat.*, 2014; 2014: Art. ID 582913: 1-11.
30. Kuthi FAA, Norzali NRA, Badri KH, Thermal characteristics of microcrystalline cellulose from oil palm biomass. *Malaysian J Analyt Sci.*, 2016; 20(5): 1112-1122.
31. Katugampola P, Winstead C, Adeleke A, Thermal stability of carboxymethyl chitosan varying the degree

of substitution. *Int J Pharm Sci Invent.*, 2014; 3(5): 42-48.
32. Liao SK, Hung CC, Lin MF, A Kinetic Study of Thermal Degradations of Chitosan/Polycaprolactam Blends. *Macromolec Res.*, 2004; 12: 466-473.
33. Zhu J, Zhang S, Zhang B, Qiao D, Structural features and thermal property of propionylated starches with different amylose/amylopectin ratio. *Int J Biol Macromol.*, 2017; 97: 123-130.
34. Kaczmarska K, Żymankowska-Kumon S, Grabowska B, Bobrowski A, Cukrowicz S, Study of thermal degradation of starch-based binder by TG-DTG-DSC Py-GC/MS and DRIFTS. *Arch Found Engine.*, 2019; 19(4): 21-26.
35. Tița B, Fuliaș A, Bandur G, Tiț a D, Babe V, Application of Thermal Analysis to Study the Compatibility of Sodium Diclofenac with Different Pharmaceutical Excipients. *Rev Chim (Bucharest)*, 2011; 62(4): 443-454.
36. Fuliaş A, Ledeţi I, Vlase G, Popoiu C, Hegheş A, Bilanin M, Vlase T, Gheorgheosu D, Craina M, Ardelean S, Ferechide D, Mărginean O, Moş L, Thermal behaviour of procaine and benzocaine Part II: compatibility study with some pharmaceutical excipients used in solid dosage forms. *Chem Cent J.*, 2013; 7(1): 140: 1-10.
37. Cotton ML, Wu DW, Vadas EB, Drug-excipient interaction study of enalapril maleate using thermal analysis and scanning electron microscopy. *Int J Pharm.*, 1987; 40(1-2): 129-142.
38. Santos AFO, Basílio IDJr, de Souza FS, Medeiros AFD, Pinto MF, de Santana DP, Macdo RO, Application of thermal analysis in study of binary mixtures with metformin. *J Therm Anal Calorim.*, 2008; 93: 361-364.
39. Wesołowski M, Rojek B, Thermogravimetric detection of incompatibilities between atenolol and excipients using multivariate techniques. *J Therm Anal Calorim.*, 2013; 113: 169-177.
40. Rojek B, Wesołowski M, Compatibility studies of hydrocortisone with excipients using thermogravimetric analysis supported by multivariate statistical analysis. *J Therm Anal Calorim.*, 2017; 127: 543-553.
41. Sena K, Manchandaa A, Mehtaa T, Mab AWK, Chaudhuri B, Formulation design for inkjet-based 3D printed tablets. *Int J Pharm.*, 2020; 584: 119430: 1-11.
42. Manimekalai P, Manavalan R, Selection of excipients for the formulation of Ceftriaxone sodium loaded chitosan Nanoparticle through drug - Excipient compatibility testing. *Int J PharmTech Res.*, 2015; 8(1): 5-10.