Thermal analysis studies on the compatibility of furosemide with solid state and liquid crystalline excipients

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Abstract

In the context of the present study, the thermal behavior of furosemide and the solid state excipients, sodium alginate, poly(ethylene oxide), poly(vinylpyrrolidone), lactose monohydrate and magnesium stearate, using Differential Scanning Calorimetry (DSC), was probed. It was found that the thermal behavior of these solid-state pharmaceutical excipients and furosemide correlates nicely with the literature relevant data. Regarding the furosemide-excipients mixtures, the DSC scans appear as a compilation of the thermal curves of each excipient. This suggests that the formulations containing these mixtures, may retain their stability over time. This information, which arises from the cooperativity of materials, their thermal stability and behavioris very helpful for the research and development of safe and effective pharmaceutical formulations. DSC experiments were also carried out with chimeric bilayers (called "liposomes"), composed of hydrogenated soy phosphatidylcholine (HSPC) and poly(*n*-butylacrylate)-*b*-poly(acrylic acid) block copolymer with 70 % content of poly(acrylic acid (PnBA-*b*-PAA 30/70) with the addition of furosemide at the molar ratio of 9:0.1:1.0 in the system HSPC:PnBA-*b*-PAA 30/70:furosemide. Chimeric liposomal systems were characterized as "fluid-like" by their DSC curves, which may be potentially translated as an easy way for release of furosemide from the advanced delivery system.

Keywords:: differential scanning calorimetry; cooperativity; stability; chimeric liposomal systems; magnesium stearate; lactose

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1. INTRODUCTION

Furosemide is used as a loop diuretic for the treatment of fluid retention (edema) from various origins, such as heart failure or kidney disease and high blood pressure. It is a week acid (p*K*a= 3.9), poorly soluble in the upper gastrointestinal tract, but it has high permeability through the stomach, and it is thus categorized as Class IV in the biopharmaceutical classification system [1]. Upon its entrance in intestinal fluids, the drug is rapidly released from the currently used formulations, with a high peak of natriuretic and diuretic effect that causes displeasure to patients. As a result, slower and more controllable intestinal release formulations are preferred because of a lower initial diuretic effect and a more extended duration of action.

Aiming towards the optimum delivery of furosemide, in order to provide a more effective therapy, devoid of high peak natriuretic and diuretic adverse effects, we have previously reported on its modified release profile from matrix and compression coated tablets [2-4].

Estimation of drug-excipient interactions is a crucial step in pre-formulation studies on drug development aiding to establishing the ideal ratios between excipients/drug(s), stability, absorption, bioavailability of dosage forms, and

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manufacturability. Differential scanning calorimetry (DSC) has a principal role in the pre-formulation studies [5-7]. According to Bruylants *et al.* [5], DSC is widely used for studies of stability and folding of biomolecules, but it can be also applied in order to understand biomolecular interactions, thus being an interesting technique in the process of drug design and development of final formulations.

In the context of the present study, we have probed the thermal behavior of furosemide and the solid state excipients, sodium alginate, poly(ethylene oxide) (PEO MW: $4x10^6$, PEO MW: 7×10^6), poly(vinylpyrrolidone) (PVP MW: 10,000, MW: 29,000 and MW: 55,000), lactose monohydrate and magnesium stearate. Moreover, thermal analysis studies on the mixtures of these materials and DSC experiments on chimeric bilayers (called "liposomes") were also conducted.

To the best of our knowledge, this is the first report in the literature on pre-formulation studies using solid and liquid crystalline state excipients, for comparison purposes, with and without furosemide. The aim of this investigation was to study the co-operability of these materials and their suitability for preparing solid and colloidal pharmaceutical formulations of furosemide. These pre-formulation studies could serve as the first step to develop diverse formulation of furosemide, i.e. tablets and liquid liposomal suspensions.

2. MATERIALS AND METHODS

2. 1. Materials

Sodium alginate 2 wt% solution viscosity (viscosity in the range 4-12cP, of 1 wt% solution in water 25 °C, product No: 90005-38-3), poly(ethylene oxide) (PEO MW: 4×10^6, PEO MW: 7×10^6, product No: 25322-68-3), poly(vinylpyrrolidone) (PVP MW: 10,000, MW: 29,000, and MW: 55,000, product No: 9003-39-8) and furosemide (product No: 54-31-9) were purchased from Sigma-Aldrich (Darmstadt, Germany). α-Lactose monohydrate (product No: 10039-26-6) was purchased from Merck (Athens, Greece), and magnesium stearate was obtained from Riedel-De Haen (Bucharest, Romania). The phospholipid, which was used for producing bilayer and liposomal formulations, was the hydrogenated soy phosphatidylcholine (HSPC). It was of analytical grade and purchased from Avanti Polar Lipids Inc., (Albaster, AL, USA) and used without any further purification. Chloroform and all other reagents were of analytical grade and purchased from Sigma–Aldrich Chemical Co (Darmstadt, Germany). Poly(*n*-butylacrylate)-*b*-poly(acrylic acid) (PnBA-*b*-PAA) block copolymers with 70 % content of PAA were also used. The synthesis is briefly described in [26].

2. 2. Methods

2. 2. 1. Preparation of mixtures of furosemide:PEO MW :4×10^6 (1.0 : 1.0) and furosemide:PEO MW: 7×10^6 (1.0 : 1.0)

Furosemide and poly(ethylene oxide) were weighed in the molar ratio 1.0 : 1.0 and inserted in two clean vials. The vials were tightly closed and placed in a Turbula T2F (Switzerland) mixing apparatus for 10 min at 32 rpm.

2. 2. 2. Preparation of the mixture of furosemide : poly(vinylpyrrolidone) : sodium alginate : magnesium stearate (1.0 : 0.5 : 1.0 : 0.01)

Furosemide, poly(vinylpyrrolidone) (MW: 55,000) and sodium alginate, in the molar ratio 1.0 : 0.5 : 1.0, were placed in a vial and weighed. The vial was tightly closed and placed in the Turbula T2F mixing apparatus (Switzerland) for 10 min at 32 rpm. The mixture was then removed from the mixing apparatus and the already weighed micronized magnesium stearate was added to the vial and mixed for another 3 min at 32 rpm.

2. 2. 3. Preparation of the system HSPC : PnBA-*b*-PAA 30/70 : furosemide

Preparation of the liposomes used in the present study, is described in our previous publication [26]. Pure lipid and mixed/chimeric bilayers were prepared by mixing the appropriate amounts of HSPC, PnBA-b-PAA 30/70 and furosemide [9 : 0.0 : 0.0 (pure HSPC liposomes); 9 : 0.1 : 0.0 and 9 : 0.1 : 0.1 molar ratio] in chloroform/methanol (1:1 v/v) solutions and the subsequent evaporation of the solvents under vacuum and heat. Vacuum was applied, and the mixed phospholipids/copolymer/furosemide thin film was formed by slow removal of the solvent at 50 °C. The mixed film was maintained under vacuum for at least 24 h in a desiccator to remove traces of solvent and subsequently it was hydrated

in HPLC-grade water. The HSPC : PnBA-b-PAA 30/70 mixed/chimeric lipid films were hydrated in HPLC-grade water by slowly stirring for 1 h, in a water bath above the phase transition of lipids (41 °C). The resultant multilamellar vesicles (MLVs) were subjected to two, 5-min sonication cycles (amplitude 70, cycle 0,7) interrupted by a 5-min resting period, in water bath, using a probe sonicator (UP 200S, dr. hielsher GmbH, Berlin, Germany). The resultant small unilamellar vesicles (SUVs) were allowed to anneal for 30 min.

2. 3. Differential scanning calorimetry

DSC experiments were performed on an 822e Mettler-Toledo (Schwerzenbach, Switzerland) calorimeter calibrated with pure indium (T_m = 156.6 °C) and water. Sealed aluminum 40 µl crucibles were used as sample holders. The dried material was weighed into the aluminum crucibles. An empty aluminum crucible was used as a reference. The heating cycle was performed from 25 to 270 °C, at 5 °C min^{-1}. All samples were scanned until identical curves were obtained. Errors were evaluated on the basis of at least three replicas. Enthalpy changes and characteristic transition temperature were calculated using the Mettler-Toledo STARe software. The measurements took place under a N_2 atmosphere.

3. RESULTS AND DISCUSSION

3. 1. DSC curves of pure excipients

As shown in Figure 1a, sodium alginate shows an endotherm in the temperature range of ~120 - 190 °C, with a center at 166.3 °C. This broad peak is characteristic for dehydration, occurring during the heating of sodium alginate under a N_2 atmosphere, and is attributed to the many hydrophilic groups present in the molecule of this biopolymer. Despite the fact that this substance was placed in dry form, it still had some moisture content. At the increase in the temperature, arterial exothermic peaks (starting at about 200 °C) are observed, indicating the gradual decomposition of the molecule. The first degradation occurs in the temperature range of 30 – 100 °C, possibly due to the initial dehydration process. The loss of physically bounded water took place in this temperature range. Two more degradation processes occur in the regions of 100 - 130 °C and 130 – 180 °C, probably due to alginate backbone destruction and hydroxyl groups loss (chemical degradation process). These thermotropic parameters are consistent with those recorded in the literature, according to which, upon heating of sodium alginate under a N_2 atmosphere, an endothermic peak (dehydration) appears at about 100 °C, followed by an exothermic peak (decay) which, depending on the heating rate, appears between 240 - 260 °C [10-14]. In the present study, the enthalpy, Δ*H*, of the dehydration was found to be equal to -383.6 J mol^{-1}. Additionally, due to the temperature range limitations of the DSC instrument used, decomposition of the carbon chain that starts beyond 300 °C according to the literature [8], could not be seen.

Magnesium stearate exhibited two endothermic peaks in the temperature range of ~90 – 120 °C, with centers at 88.4 and 111.8 °C (Fig. 1b). According to the literature, the DSC curve of magnesium stearate shows endothermic events: the first at 84.3 - 97.4 °C corresponding to dehydration; second at 112.6 - 121.9 °C and a third at 150.6 - 158.7 °C, indicating melting of palmitic and stearic acid compounds [9]. The obtained peaks are attributed to successive loss events of adsorbed structural water molecules (the yellow peak probably refers to the melting of magnesium stearate), and are in line with the literature findings [10-14]. With the increase in the temperature, an endothermic peak is observed, probably due to the low amount of magnesium palmitate that may coexist [15]. Decomposition of the molecule, based on literature, begins at temperatures higher than 200 °C, but due to the instrument limitations mentioned above, these peaks could not be observed.

Regarding lactose monohydrate, two characteristic endotherms are observed, when the temperature gradually increases (Fig. 1c). The DSC diagram shows an endothermic peak at 147 °C, which represents the loss of crystalline water [16,17]. At 209.8 °C an acute endothermic peak appears, which is consistent with literature data [10,11,13,15,18-20] suggesting that at approximately 200-225 °C, the *β*-lactose portion in the molecule melts. After this endothermic phenomenon, thermal decomposition of *β*-lactose follows, which is characterized as caramelization.

Figure 2 shows DSC curves of PVP of different molecular weights, MW: 10,000 (Fig. 2a), MW: 29,000 (Fig. 2b) and MW: 55,000 (Fig. 2c).

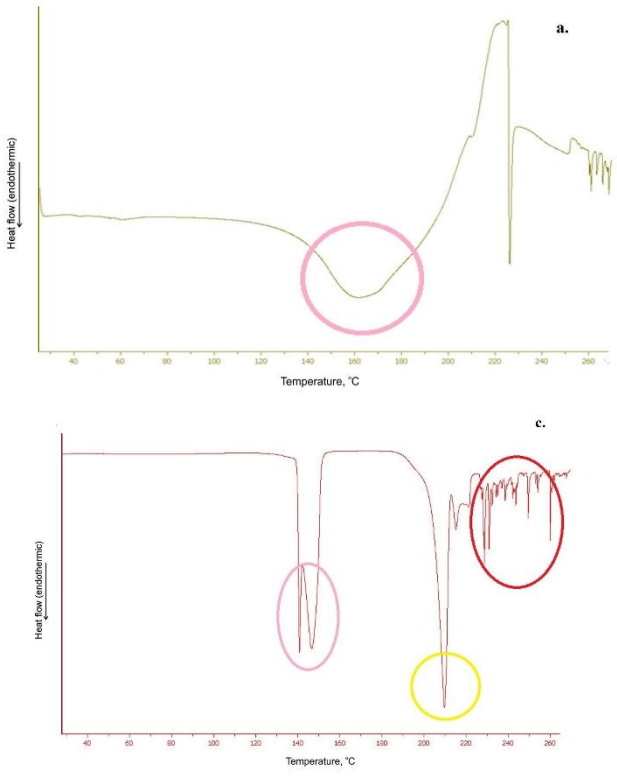

Figure 1. DSC curves of a. sodium alginate, b. magnesium stearate and c. lactose monohydrate (circles indicate characteristic peaks)

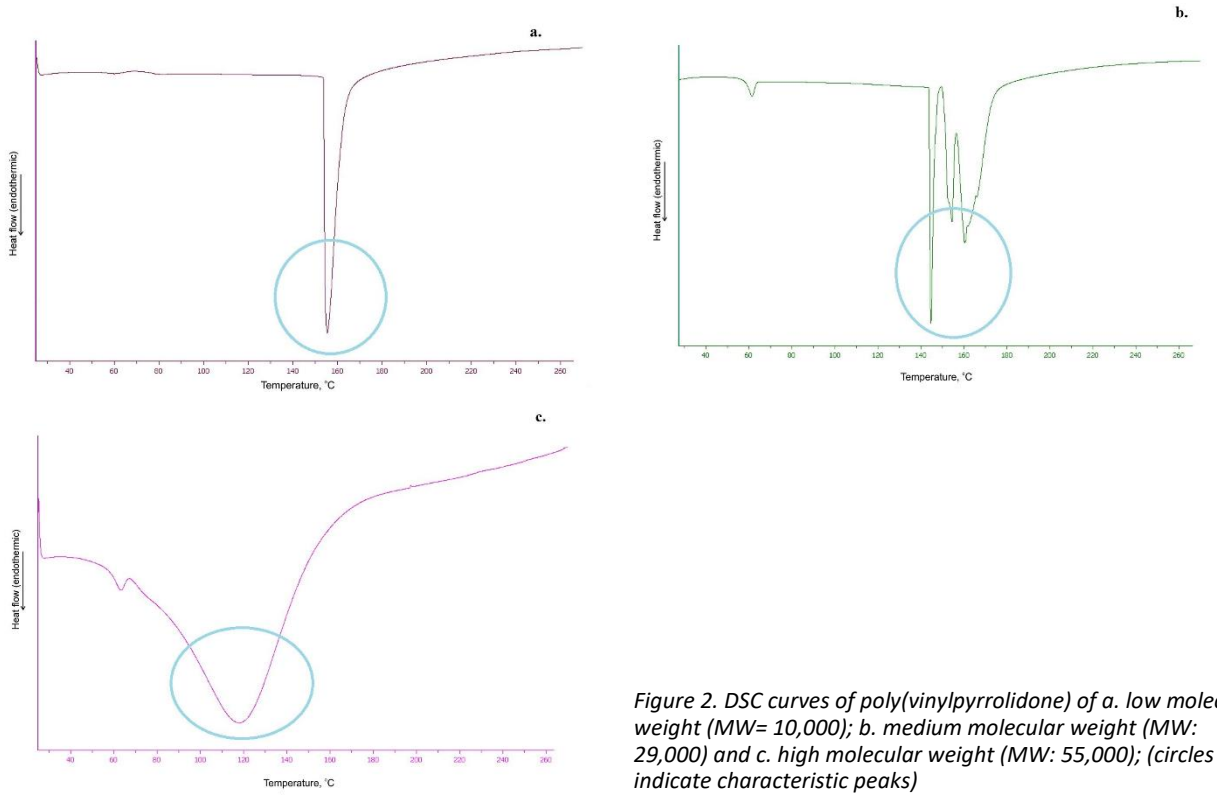

Figure 2. DSC curves of poly(vinylpyrrolidone) of a. low molecular weight (MW= 10,000); b. medium molecular weight (MW: 29,000) and c. high molecular weight (MW: 55,000); (circles indicate characteristic peaks)

The Δ*H* values of glass transition increase as the molecular weight of PVP increases [10,13,15,21]. Namely, Δ*H*= -141.5 J mol^{-1} for MW: 10,000, -171.7 J mol^{-1} for MW:29,000 and -237.0 J mol^{-1} for MW:55,000. The melting events of PVP are located in the temperature range of 150-180 °C, depending on the molecular weight (Fig. 2). Thus, PVP

MW: 10,000 exhibits a melting event at 155.5 °C (Fig. 2a), PVP MW: 29.000 at 144.8 °C while it is possible that the peaks, appearing in the range 145-160 °C, are due to the presence of PVP molecules of various molecular weights that coexist (Fig. 2b). PVP MW: 55,000 shows an expanded peak at about 120 °C (Fig. 2c).

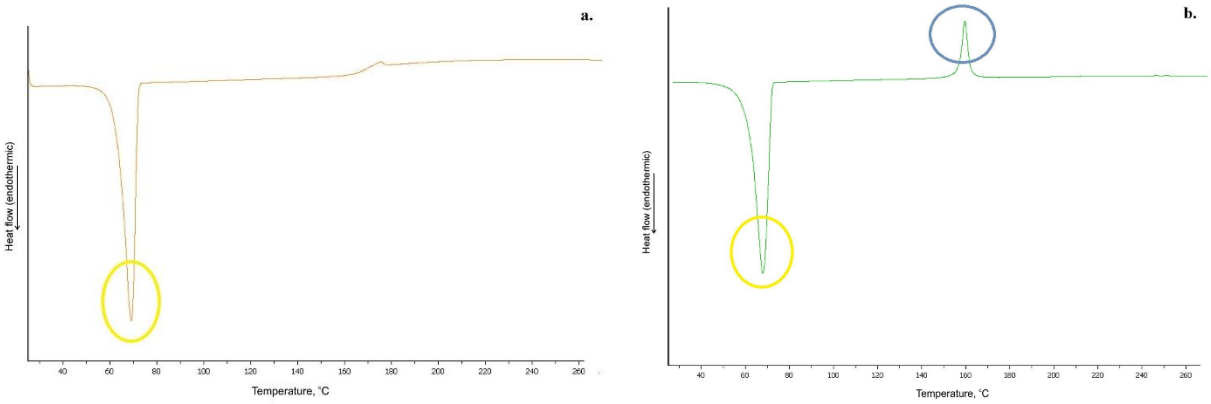

Figure 3. DSC curves of poly(ethylene)oxide of a. MW=4,000,000 and b. MW=7,000,000 (circles indicate characteristic peaks)

Poly(ethylene oxide) (PEO) of MW: 4,000,000 and MW: 7,000,000, when heated, show an endothermic effect, centered at 69.1 and 68.0 °C, respectively (Fig. 3). This is the acid peak, describing melting of these polymers. It is well documented, that, in the case of poly(ethylene oxide), heating rate selected by DSC determines the melting point; if the heating rate increases, the melting temperature of this polymer increases [22,23]. Probably, if a heating rate of more than 5 °C min^{-1}, was used, the peaks would be translocated to higher temperatures. It has been reported that as the PEO molecular weight increases, the amount of heat required to melt (*i.e*. enthalpy) increases, because these polymers exhibit a higher tendency for crystallization and a higher degree of crystallization [23]. This rule is valid from the molecular weights of 20,000 and above. That is why the tested solid PEO of MW: 4×10^6 and MW: 7×10^6 melted at similar temperatures, while exothermic events appeared at 180 and 160 °C, respectively. Probably, at these temperatures decomposition is taking place [24].

Thermotropic parameters of the active substance, furosemide, were examined showing that it melts near 219 °C (Fig. 4), but this endothermic phenomenon is not so obvious, since an immediate acute exothermic process takes place (Fig. 4). This exothermic process is due to decomposition of furosemide and the subsequent formation of either the anhydride by dimerization ($\Delta H_{dimerization}$ = 98.8 J mol^{-1}) or the amide, by evaporation ($\Delta H_{evaporation}$ = 98.8 J mol^{-1}) [25]. In Figure 4, where the fragment of these two phenomena is magnified, the peak representing the furosemide melt, is easily decipherable.

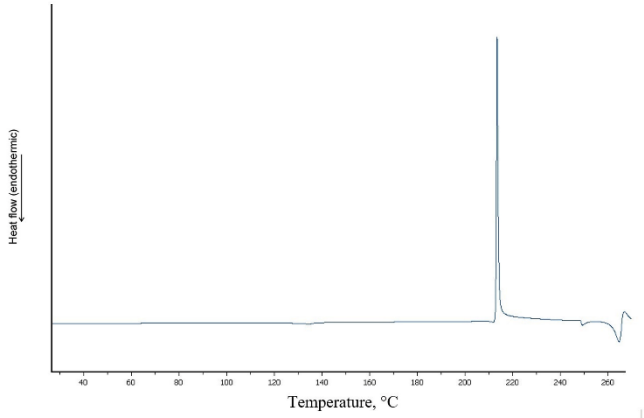

Figure 4. DSC curve of furosemide

3. 2. DSC curves of mixtures of solid state excipients

Thermotropic properties of mixtures are the "sum" of those of their individual components, only if the components are compatible with each other. Taking this into account, if there is a missing or disappearing peak (present though in the DSC curve of the "pure" component) or the peak size changes significantly or when a new endotherm or exotherm (new peak) appears, it could be deduced that there is incompatibility between the components in the mixture. However, even in the case of compatibility of the components, slight changes in the shape, height and range of the peaks are likely to be expected, due to possible changes in the 3D structure of the components within the mixture. When DSC findings show evidence of possible incompatibility, it is advisable to apply other methods in conjunction in order to reach a definite conclusion about compatibility of components [16].

The DSC curve of the mixture furosemide: PEO MW: 4,000,000, in 1:1 mass ratio (Fig. 5a), shows that these two materials (active substance and the excipient) show compatibility without heat-induced interactions between them. The thermotropic parameters of this mixture are identical to those of the individual components, when separately analyzed; subtle differences noted, are due to the new three-dimensional structure characteristics of the mixture (Fig. 5a). The same phenomena were observed in the case of the mixture furosemide: PEO MW: 7,000,000, 1:1 mass ratio (Fig. 5b).

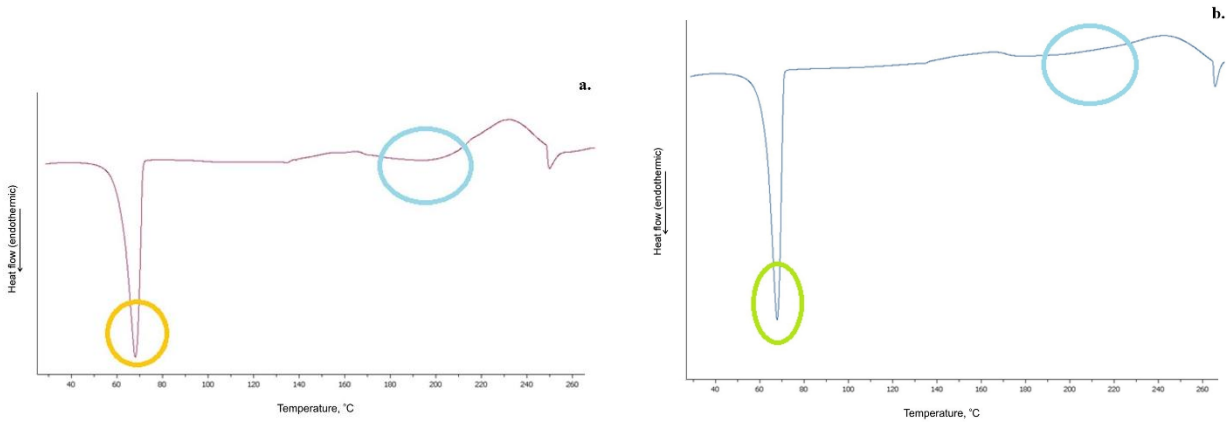

Figure 5. DSC curves of furosemide: PEO mixtures at 1:1 mass ratio: a. PEO MW=4,000,000; b. PEO MW=7,000,000; circles designate characteristic peaks

The DSC curve of the 4-component mixture: furosemide: PVP (MW=55000) : sodium alginate : magnesium stearate in the mass ratio 1.0 : 0.5 : 1.0 : 0.01, respectively, is shown in Figure 6. The results suggest that these four components (the active substance and the three excipients) are compatible without heat-induced interactions between them. The thermotropic parameters of the mixture are identical to those shown by the individual components, when separately analyzed, with some slight differences, attributable to different structural characteristics arising in the mixture.

3. 3. DSC curves of mixtures of liquid crystalline excipients

Liposomes belong to the liquid crystalline phase. Chimeric or polymer-grafted liposomes are used in order to overcome stability limitations of liposomes. In parallel, liposomes are attractive drug delivery carriers for numerous biomedical applications. The lipid bilayers are part of the liposome structure, so the investigation of their thermotropic characteristics is very important. In our ongoing research on thermotropic properties of the bilayers, we have investigated the chimeric liposomal system HSPC: PnBA-*b*-PAA 30/70, in a molar ratio of 9: 0.1, since in the case of bilayers a more distinct transition heating around 54 °C was observed compared to this liposomal system at other molar ratios used in our previous published data [26]. In the present work, we have used the same DSC protocol as described in our previous publication [26]. The active substance furosemide was also incorporated in this system in order to investigate whether the system is negatively or positively affected by the cooperativity of the excipient and the active substance (HSPC : PnBA-*b*-PAA 30/70 : furosemide in the molar ratio of 9 : 0.1 : 1.0, respectively). The obtained DSC curves are presented in Figure 7.

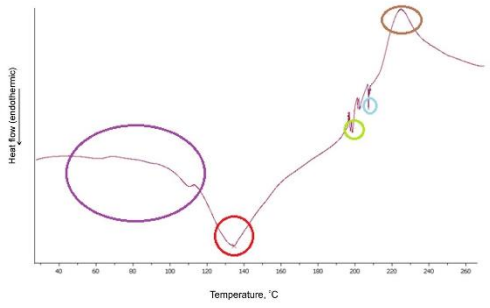

Figure 6. DSC curve of the mixture furosemide : PVP (MW=55000) : : sodium alginate : magnesium stearate at the mass ratio 1.0 : 0.5 : 1.0 : 0.01, respectively (circles designate characteristic peaks)

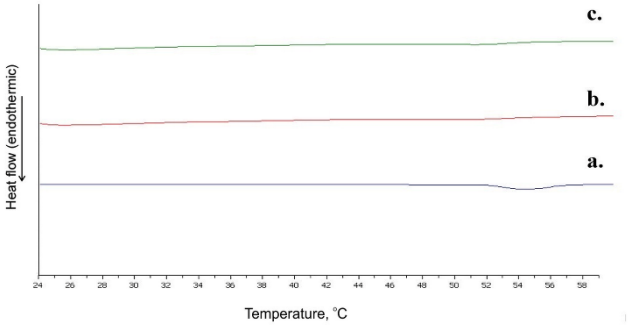

Figure 7. DSC curves during heating of a. HSPC liposomes; b. the chimeric liposomal system HSPC : PnBA-b-PAA 30/70 in the molar ratio of 9 : 0.1, respectively; c. the chimeric colloidal dispersion of HSPC : PnBA-b-PAA 30/70 : furosemide at the molar ratio of 9 : 0.1 : 1.0, respectively

The medium used to hydrate the thin lipid films and make colloidal dispersions was PBS, since its osmolality and concentration of ions resemble those in the human body (isotonic solutions). Furthermore, the citrate buffer was used to fully hydrate the bilayers (over PBS), in order to examine the potential modification in configuration of the liposome part and predict the system change, when potentially approaching the acidic micro-environment of a tumor, inflammation site, etc. With regard to the DSC curves of DSC heating phenomena of the investigated systems, it is obvious that the incorporation of PnBA-*b*-PAA (30/70) causes a significant change in the thermotropic behavior of HSPC liposomes. As shown in Figure 7, T_{onset} (temperature at which the thermal event starts) and $T_{m.}$ (temperature at which heat capacity (ΔC_p) at constant pressure. is maximum) $T_{onset,m}$ and T_m temperatures are slightly reduced in the systems HSPC : PnBA-b-PAA 30/70 : furosemide 9 : 0.1 : 0.0 and 9 : 0.1 : 1.0, as compared to HSPC liposomes. A possible explanation for this small decrease could be the interference of the PnBA block between the lipid chains, which subsequently increases chain distances and leads to melting at lower temperatures (Table 1). The $\Delta T_{1/2}$ values remain almost identical, indicating cooperativity of the materials in all systems [27]. Conversely, the ΔH_m values are significantly reduced. This finding translates as a much smaller prerequisite amount of energy to overcome van der Waals forces between the HSPC molecules. Liquefaction of the bilayer of the liposomes is evident, since the peak of the main transition is so enlarged that it is no longer visible at 54 °C (Figure. 7). This is probably related to a solution-like model, as the presence of the copolymer rather plays a role of doping [27-29]. The copolymer modifies the shape and size distribution of nanoclusters-nanodomains, since it probably penetrates the interior of the bilayer, making it more fluidic [19]. To the best of our knowledge this is the first report in literature, where DSC is used for quantification of interactions of furosemide with chimeric liposomes. The obtained results could serve as a roadmap for design and development of liposomal formulations of furosemide.

Table 1. Calorimetric values of liquid -crystalline excipients without and with furosemide.

	$T_{onset,1}$[a] / °C	T_1[b] / °C	$\Delta T_{1/2,1}$[c] / °C	ΔH_1[d] / J mol^{-1}
HSPC pure liposomes	52.1	54.3	3.09	42.7
HSPC : PnBA-b-PAA 30/70 : Furosemide (9 : 0.1 : 0.0 molar ratio)	49.0	51.9	3.15	9.0
HSPC : PnBA-b-PAA 30/70 : Furosemide (9 : 0.1 : 1.0 molar ratio)	49.0	51.8	3.15	14.5

[a]T_{onset}: temperature at which the thermal event starts; [b]T: temperature at which heat capacity (ΔC_p) at constant pressure. is maximum; [c]$\Delta T_{1/2}$: half width at half peak height of the transition; [d]ΔH: transition enthalpy normalized per mol of ingredient.

4. CONCLUSION

The results produced by these investigations demonstrated the co-operability of the studied materials and their suitability for preparing solid and colloidal pharmaceutical formulations with furosemide. Concerning the solid-state pharmaceutical excipients and furosemide, their separate DSC curves matched those reported in the literature. Regarding the excipients-furosemide mixtures, DSC scans appeared as compilations of thermal curves of each excipient (the total scan looks as if the individual scans are overlapped over each other). This finding suggests that the

formulations containing these components, may retain their stability over time. Moreover, the chimeric liposomal systems, characterized as "fluid-like" by their DSC curves, could offer facile release of furosemide due to limited interactions of the drug with the polymer grafted lipid bilayers in future release studies. This information, which arises from the cooperativity of materials, their thermal stability and behavior, is very helpful for the research and development of novel, safe and effective pharmaceutical formulations with furosemide.

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REFERENCES

[1] Strauch S, Jantratid E, Dressman JB, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Barends DM. Biowaiver monographs for immediate release solid oral dosage forms: mefloquine hydrochloride. *J Pharm Sci.* 2011; 100: 11-21.

[2] Vlachou M and Papaïoannou G. Preparation and characterization of the inclusion complex of furosemide with hydroxypropyl-β-cyclodextrin. *J Biomater Appl.* 2003; 17: 197–206.

[3] Efentakis M and Vlachou M. Evaluation of high molecular weight poly(oxyethyle) (polyox) polymer: studies of flow properties and release rates of furosemide and captopril from controlled-release hard gelatin capsules. *Pharm Dev Technol.* 2000; 5: 339-346.

[4] Vlachou M, Geraniou E., Siamidi A, Modified release of furosemide from Eudragits® and poly(ethylene oxide)-based matrices and dry-coated tablets *Acta Pharm.* 2020; 10: 49-61 https://doi.org/10.2478/acph-2019-0043

[5] Bruylants G, Woutres J, Michaux C. Differential scanning calorimetry in life science: thermodynamics, stability, molecular recognition and application in drug design. *Curr Med Chem.* 2005; 12: 2011-2020.

[6] Narang AS, Desai D, Badawy S. Impact of excipient interactions on solid dosage form stability. *Pharm Res.* 2012; 29: 2660-2683.

[7] Chadha R, Bhandari S. Drug-excipient compatibility screening-Role of thermoanalytical and spectroscopic techniques. *J Pharm Biom Anal.* 2014; 87: 82-97.

[8] Soares JP, Santos JE, Chierice GO, Cavalheiro ETG. Thermal behavior of alginic acid and its sodium salt. *Eclética Quimica.* 2004; 29: 57-63.

[9] Freire F.D., Aragão, C.F.S., de Lima e Moura, T.F.A. *et al.* Compatibility study between chlorpropamide and excipients in their physical mixtures. *J Therm Anal Calorim.* 2009; 97: 355. https://doi.org/10.1007/s10973-009-0258-2

[10] Rus LM, Tomuta I, Iuga C, Maier C, Kacso I, Borodi G, Bratu I, Bojita M. Compatibility studies of indapamide/pharmaceutical excipients used in tablet reformulation. *Farmacia.* 2002; 60: 92-101.

[11] Lima NGPB, Lima IPB, Barros DMC, Oliveira TS, Raffin FN, Moura TFA, Medeiros ACD, Gomes APB, Aragão CSF. Compatibility studies of trioxsalen with excipients by DSC, DTA, and FTIR. *J Therm Anal Calorim* 2014; 115: 2311-2318.

[12] Wang Y, Luo YH, Zhao J, Sun BW. Selection of excipients for dispersible tablets of itraconazole through the application of thermal techniques and Raman spectroscopy. *J Therm Anal Calorim.* 2014; 115: 2391-2400.

[13] Teleginski LK, Maciel AB, Mendes C, Segatto Silva MA, Bernardi LS, Oliveira PR. Fluconazole – excipient compatibility studies as the first step in the development of formulation candidate for biowaiver. *J Therm Anal Calorim*. 2015; 120: 771-781.

[14] Marian E, Jurca T, Kacso I, Borodi J, Rus LM, Bratu I. Compatibility study between simvastatin and excipients in their physical mixtures. *Revistance de Chimie* (Bucharest), 2015; 66: 803-807.

[15] Chaves LL, Rolim LA, Gonçalves MLCM, Vieira ACC, Alves LDS, Soares MFR, Soares-Sobrinho JL, Lima MCA, Rolim-Neto PJ. Study of stability and drug-excipient compatibility of diethylcarbamazine citrate. *J Therm Anal Calorim.* 2013; 111: 2179-2186.

[16] Lavor EP, Navarro MVM, Freire FD, Aragão CFS, RaffinFN, Barbosa EG, Moura TFA, Application of thermal analysis to the study of antituberculosis drugs-excipient compatibility. *J Therm Anal Calorim.* 2014; 115: 2303-2309.

[17] GombÁs, Á., Szabó-Révész, P., Kata, M. et al. Quantitative Determination of Crystallinity of α-lactose monohydrate by DSC . *J Therm Anal Calorim.* 2002; 68: 503. https://doi.org/10.1023/A:1016039819247

[18] Júlio TA, Zâmara IF, Garcia JS, Trevisan MG. Compatibility of sildenafil citrate and pharmaceutical excipients by thermal analysis and LC-UV. *J Therm Anal Calorim.* 2013; 111: 2037-2044.

[19] Munavirov BV, Filippov AV, Rudakova MA, Antzutkin ON. Polyacrylic acid modifies local and lateral mobilities in lipid. membranes. *J Dispers Sci technol*..2014; 35:6, 848-858. doi:10.1080/01932691.2013.823096

[20] Pires, S.A., Mussel, W.N., Oliveira, M.A. and Yoshida, M.I. Compatibility studies of ciprofibrate with excipients by DSC, XRPD, and FTIR. In: IX Congresso Brasileiro de AnáliseTérmica e Calorimetria. Serra Negra. 2014; 1 doi:***10.13140/2.1.3578.4640*** *Conference: IX Brazilian Congress in Thermal Analysis and Calorimetry, At Serra Negra - São Paulo.*

[21] Li J, Zhao J, Tao L, Wang J, Waknis V, Pan D, Hubert M, Raghavan K. Patel J. the effect of polymeric excipients on the physical properties and performance of amorphous dispersions: Part I, Free volume and glass transition. *Pharm Res.* 2015; 32: 500-515.

[22] Craig DQM. A review of thermal methods used for the analysis of the crystal form, solution thermodynamics and glass transition behaviour of polyethylene glycols. *Thermochimica Acta.* 1995; 248: 189-203.

[23] Pielichowski K, Flejtuch K. Differential scanning calorimetry studies on poly(ethylene glycol) with different molecular weights for thermal energy storage materials. *Polym Adv Technol.* 2002 ;13: 690-696.
[24] Seongok H, Chongyoup K, Dongsook K. Thermal degradation of poly(ethylene Glycol). *Polym Degrad Stab.* 1995; 47: 203-208.
[25] Cássia R, Semaan FS. Thermal behavior of furosemide. *J Therm Anal Calorim.* 2013; 111: 1933-1937.
[26] Kyrili A, Choutoulesi M, Pippa N, Meristoudi A, Pispas S, Demetzos C. Design and development of pH-sensitive liposomes by evaluating the thermotropic behavior of their chimeric bilayers. *J Therm Anal Calorim.* 2017; 127: 1381-1392.
[27] Chen J, He C, Lin A, Xu F, Wang F, Zhao B, Liu X, Chen Z, Cai B. Brucine-loaded liposomes composed of HSPC and DPPC at different ratios: in vitro and in vivo evaluation. *Drug Dev Ind Pharm.* 2014; 40(2): 244-251.
[28] Di Foggia M, Bonora S, Tinti A, Tugnoli V. DSC and Raman study of DMPC liposomes in presence of Ibuprofen at different pH. *J Therm Anal Calorim.* 2016; 127(2): 1407-1417. doi:10.1007/s10973-016-5408-8.
[29] Pippa N, Gardikis K, Pispas S. Demetzos C. The physicochemical/thermodynamic balance of advanced drug liposomal delivery systems. *J Therm Anal Calorim.* 2014; 116: 99–105.

SAŽETAK

Termička analiza kompatibilnosti furosemida sa ekscipijensima u čvrstim stanju i stanju tečnih kristala

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(Naučni rad)

U ovoj studiji, ispitino je termičko ponašanje furosemida i čvrstih pomoćnih supstanci, natrijum-alginata, poli (etilen oksida), poli (vinilpirolidona), laktoze-monohidrata i magnezijum-stearata, korisćenjem diferencijalne skenirajuće kalorimetrije (DSC). Utvrđeno je da termičko ponašanje čistih čvrstih farmaceutskih pomoćnih sastojaka i furosemida korelira sa relevantnim podacima iz literature. Što se tiče smeša furosemida sa pomenutim ekscipijensima, DSC analiza ukazuje na kompilaciju termograma svakog ekscipijensa. Ovaj rezultat sugeriše da formulacije koje sadrže pomenute smeše mogu zadržati svoju stabilnost tokom vremena. Informacije koje proizilaze iz kooperativnosti materijala, njihove termičke stabilnosti i ponašanja veoma su korisne za istraživanje i razvoj sigurnih i efikasnih farmaceutskih formulacija. DSC eksperimenti su takođe izvedeni sa himernim lipidnim dvoslojevima (zvanim „liposomi“), sastavljenim od hidrogenizovanog fosfatidilholina iz soje (HSPC) i poli (n-butilakrilat) -b-poli (akrilne kiseline) blok-kopolimera sa 70% sadržaja poli (akrilne kiseline) (PnBA-b-PAA 30/70) sa dodatkom furosemida u molarnom odnosu 9: 0,1: 1,0 u sistemu HSPC: PnBA-b-PAA 30/70: furosemid. Himerni liposomalni sistemi su okarakterisani kao „tečni" na osnovu dobijenih DSC kriva, što se potencijalno može iskoristiti kao lak način za formulaciju naprednih sistema za isporuku furosemida.

Ključne reči: diferencijalna skenirajuća kalorimetrija; kooperativnost; stabilnost; himerni liposomalni sistemi; magnezijum-stearat; laktoza