

THERMOANALYTICAL STUDY OF ACECLOFENAC FORMULATIONS WITH REGULAR MAIZE STARCH AND WAXY MAIZE STARCH

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ABSTRACT

Production of tablets in pharmaceutical industry often is required to mixture the active ingredient (drug) with an inert material. Starch is shown as a good alternative material to be used as excipient. Thus, in this investigation the techniques: thermogravimetry and derivative thermogravimetry (TG/DTG), differential scanning calorimetry (DSC as well as thermomicroscopy were performed with aim to verify existence of interactions between aceclofenac (2-[2-[2-(2,6-dichlorophenyl)amino]phenyl]acetyl]oxalacetic) with regular maize starch and waxy maize starch. Binary and physical mixtures of aceclofenac and starch in ratios 2:1, 1:1 and 1:2 (drug:starch) studied by the instrumental techniques showed that no interactions occurs between the drug and starches in any ratio, being maintained the properties of aceclofenac.

Keywords: Thermal analysis, aceclofenac, excipient, regular maize starch, waxy maize starch; interaction drug:excipient

INTRODUCTION

The excipients are inactive ingredients, these are substances they have no therapeutic activity and be used for bring stability in physicochemical properties as well as organoleptic characteristics of pharmaceutical products (Oliveira & Storpirtis, 1999). Excipients are so important that Robertson (1999) conducted a study which found 3816 of these substances in a sample of 12132 drugs.

Starch is a widely used and studied excipients, because in most cases the starch does not interact with active principle formulation (Souza & Ferrão, 2006; Parisotto *et al.*, 2005). However each botanical source of starch can give different characteristics as example higher amylose or amylopectin levels depending on the case (Liu, Ramsden & Corke, 1997).

The 2-[2-[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxalacetic, is a white crystalline solid, insoluble in water, commonly known as aceclofenac. It belongs to the class of nonsteroidal anti-inflammatory drugs (NSAIDs); chemically being a derivative of aryl acetic acid. This is a non-selective cyclooxygenase (COX) reducing metabolites and providing anti-inflammatory, analgesic and antipyretic effects. It has been prescribed mainly in diseases such as rheumatoid arthritis, ankylosing spondylitis and osteoarthritis (Yamazaki *et al.*, 1997; Shakeel *et al.*, 2007; Colman *et al.*, 2015).

The objective of this study was to investigate the possible interactions occurring between aceclofenac drug and regular maize starch and waxy maize starch. The used techniques were: thermogravimetry/derivative thermogravimetry (TG/DTG), differential scanning calorimetry (DSC) and thermomicroscopy.

MATERIAL AND METHODS

Materials and methods

The sample used in this study was aceclofenac pharmaceutical grade (b), lot: 11020326A acquired in the city of Ponta Grossa -Paraná, Brazil. The regular maize starch (a) and waxy maize starch (f) were extracted using the methodology described in the literature (Whistler, 1964; Colman *et al.*, 2012).

Mixtures Aceclofenac : starch

The mixtures were made by dispersing the proportions of drug:starch in water to give a mixture with final mass of 1 g, the following proportions were used in ratios drug:starch (2:1 (c), 1:1 (d) and 1:2 (e)) for regular maize starch and (2:1 (g), 1:1 (h) and 1:2 (i)) for waxy maize starch. After agitation and homogenization of the dispersion was performed for 10 min, followed by filtration and evaporation of water in oven with air circulation at 45 °C for 24 h (Colman *et al.*, 2015).

Instrumental analysis

Thermogravimetry and derivative thermogravimetry (TG/DTG)

The thermogravimetric curves (TG) were obtained using the thermal analysis system TGA-50 (Shimadzu, Japan), where the samples were heated from 35 °C to 650 °C using open alumina crucibles with approximately 5.0 mg of the sample under a synthetic air flow of 150 mL min⁻¹ at a heating rate of 10 °C min⁻¹. The instrument was preliminarily calibrated according to the recommendations of the manufacturer. All mass loss percentages were determined using TA-60WS data analysis software, as well as first derivative (DTG) was calculated. This mathematic resource is useful in determining the main steps and temperatures of mass loss (Cordoba *et al.*, 2013; Alberton *et al.*, 2014; Leone *et al.*, 2014; Ribeiro *et al.*, 2014; Colman *et al.*, 2015).

Differential Scanning Calorimetry (DSC)

The DSC curves were obtained using the thermal analysis system model DSC-Q200 (TA-Instruments, USA). The curves were recorded under an N₂ flow of 50 mL min⁻¹, heating rate of 10 °C min⁻¹ and samples weighing about 5 mg in aluminium crucibles with perforated lid. The instrument was previously calibrated according to the recommendations of the manufacturer (standard Indium 99.99% purity, *m.p.* = 156.6°C, Δ*H* = 28.56 J g⁻¹). The results were calculated using Universal Analysis 2000 software (Cordoba *et al.*, 2013; Colman *et al.*, 2015; Malucelli *et al.*, 2015).

Thermomicroscopy

The images were obtained by coupling a digital microscope upon DSC cell. The microscope is equipped with color CMOS sensor and lens glass 2M pixel resolution with magnification 800x. The software AMCAP V9.016 was used for capturing images.

RESULTS AND DISCUSSION

Mixtures Aceclofenac : regular maize starch

The TG/DTG curves are show in Fig. 1 and results for regular maize starch (a), aceclofenac (b), mixtures (c-e) are shown in Table 1. The thermal decomposition of regular maize starch (a) occurs in three stages of mass loss. The first step according to the literature (Liu et al., 2009), is associated with dehydration, followed by stability. Once anhydrous the sample is stable up to 223 °C, after this temperature the decomposition and oxidation of organic material takes place in two consecutive stages of mass loss, with final residue corresponding to 0.18% of initial mass.

The aceclofenac (b) is anhydrous and thermally stable up to 161 °C, after that temperature its thermal decomposition occurs in two consecutive stages of mass loss, with final residue corresponding to 0.74% of its initial mass.

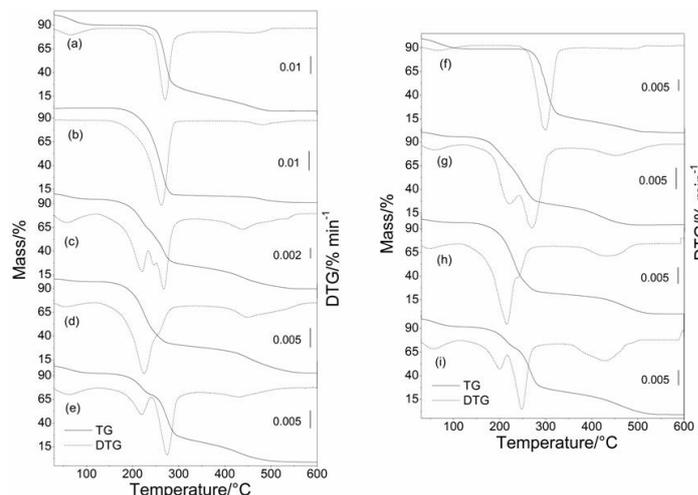


Figure 1 TG/DTG curves of: regular maize starch (a), aceclofenac (b), (c) mixture aceclofenac:regular maize starch (2:1), (d) mixture aceclofenac:regular maize starch (1:1) and (e) mixture aceclofenac:regular maize starch (1:2), waxy maize starch (f), aceclofenac (b), (g) mixture aceclofenac:waxy maize starch (2:1), (h) mixture aceclofenac:waxy maize starch (1:1) and (i) mixture aceclofenac:waxy maize starch (1:2).

The TG/DTG curves of mixtures aceclofenac: regular maize starch show thermal decomposition in three (d) and four (c, e) steps. Due to the sum of steps of thermal decomposition of the starch and aceclofenac, the first step is attributed to dehydration of the starch present in the sample portion. The final residue corresponds to 0.56% (c) 0.95% (d) and 0.58% (e) of the initial mass sample, respectively.

Table 1 Results TG and DTG of: regular maize starch (a), aceclofenac (b), (c) mixture aceclofenac:regular maize starch (2:1), (d) mixture aceclofenac:regular maize starch (1:1) and (e) mixture aceclofenac:regular maize starch (1:2)

Sample	TG and DTG Steps					
	1 st	Stability	2 nd	3 rd	4 th	
(a)	ΔT/°C	30-107	107-223	223-366	366-523	-
	Tp/°C	66.72	-	269.83	442.43	-
	Δm/%	10.01	-	73.98	15.83	-
(b)	ΔT/°C	161-371	-	371-545	-	-
	Tp/°C	262.49	-	480.2	-	-
	Δm/%	92.38	-	6.88	-	-
(c)	ΔT/°C	30-100	100-134	134-234	234-335	335-561
	Tp/°C	57.64	-	220.35	246.54 (shoulder)	437.91
	Δm/%	5.36	-	31.07	267.80	536.21
(d)	ΔT/°C	30-99	99-142	142-350	350-570	-
	Tp/°C	96.90	-	225.11	449.38	-
	Δm/%	2.73	-	255.58 (shoulder)	70.06	-
(e)	ΔT/°C	30-110	110-154	154-241	241-348	348-539
	Tp/°C	61.55	-	219.40	274.58	431.20
	Δm/%	7.37	-	22.21	4+8.85	20.99

(*) Δm mass loss/%, ΔT temperature range, Tp peak temperature

DSC curves are shown in Fig. 2 and the obtained results in Table 2. The sample (a) does not present any thermal event at the temperature range. The profile of DSC curve show endothermic peak due to melting of aceclofenac (b), for

mixtures there were no major changes in temperature related to the portion of aceclofenac melting. The values of melting enthalpy decreased proportionally with the increase in regular maize starch samples.

Table 2 DSC results of: regular maize starch (a), aceclofenac (b), (c) mixture aceclofenac:regular maize starch (2:1), (d) mixture aceclofenac:regular maize starch (1:1) and (e) mixture aceclofenac:regular maize starch (1:2), waxy maize starch (f), aceclofenac (b), (g) mixture aceclofenac:waxy maize starch (2:1), (h) mixture aceclofenac:waxy maize starch (1:1) and (i) mixture aceclofenac:waxy maize starch (1:2)

DSC regular maize starch					DSC waxy maize starch				
Samples	T _{on} /°C	T _p /°C	T _{end} /°C	ΔH/J g ⁻¹	Samples	T _{on} /°C	T _p /°C	T _{end} /°C	ΔH/J g ⁻¹
(a)	-	-	-	-	(f)	-	-	-	-
(b)	152.68	156.12	159.99	158.6	(b)	152.68	156.12	159.99	158.6
(c)	153.28	154.79	157.31	79.04	(g)	150.36	155.88	161.45	78.85
(d)	151.62	154.46	158.12	49.40	(h)	151.35	154.50	158.65	53.59
(e)	150.94	153.49	156.17	24.55	(i)	150.79	153.24	156.42	28.71

(*) “T_{on}” Onset temperature, “T_p” Peak temperature, “T_{end}” Endset temperature, “ΔH” Melting enthalpy

The thermomicroscopy show in Fig. 2 that the melting occurs in aceclofenac fraction of the mixtures. The greater amount of aceclofenac and the greater reflection of light at temperatures above 165 °C were observed. This occurs because the fused fraction of aceclofenac sample (b) has a greater capacity to reflect light from the microscope. It can be observed that the fraction of the sample corresponding to the starch which no visible change in the temperature

range studied, suggesting the formation of a physical mixture, without chemical interaction between the regular maize starch and aceclofenac.

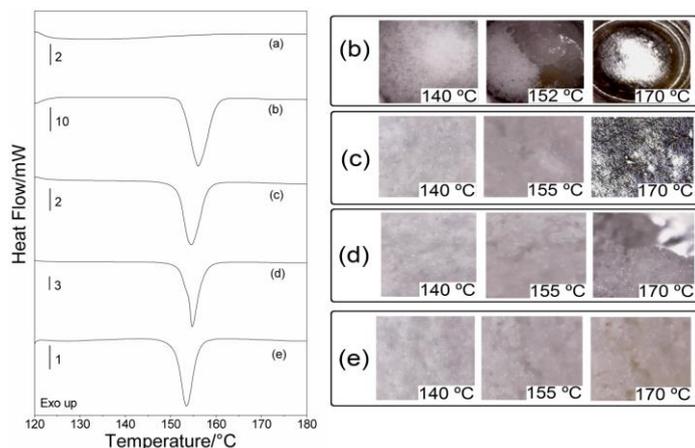


Figure 2 DSC curves (left) and Thermomicroscopy (right): regular maize starch (a), aceclofenac (b), (c) mixture aceclofenac:regular maize starch (2:1), (d) mixture aceclofenac:regular maize starch (1:1) and (e) mixture aceclofenac:regular maize starch (1:2).

Mixtures Aceclofenac:waxy maize starch

The TG/DTG curves are shown in Fig. 1 and TG/DTG results for waxy maize starch (f), aceclofenac (b), mixtures (g-i) are show in Table 3. The thermal decomposition of waxy maize starch (a) occurs in three stages of mass loss. The first step according to the literature (Malucelli et al., 2015; Oliveira et al., 2013; Liu et al., 2009), is associated with dehydration, the anhydrous sample is stable up to 232 °C, after this temperature the decomposition and oxidation of organic material takes place in two consecutive stages of mass loss, with final residue corresponding to 0.62% of the initial mass.

Table 3 Results TG and DTG of: waxy maize starch (f), aceclofenac (b), (g) mixture aceclofenac:waxy maize starch (2:1), (h) mixture aceclofenac:waxy maize starch (1:1) and (i) mixture aceclofenac:waxy maize starch (1:2)

Sample	TG and DTG Steps					
	1 st	Stability	2 nd	3 rd	4 th	
(f)	ΔT/°C	30-122	122-232	232-351	351-521	-
	Tp/°C	68.18	-	298.3	481.11	-
	Δm/%	11.31	-	72.83	15.24	-
(b)	ΔT/°C	161-371	-	371-545	-	-
	Tp/°C	262.49	-	480.2	-	-
	Δm/%	92.38	-	6.88	-	-
(g)	ΔT/°C	30-95	95-142	142-356	356-543	-
	Tp/°C	59	-	219.61	451.05	-
	Δm/%	4.41	-	74.21	20.54	-
(h)	ΔT/°C	30-86	86-141	141-351	351-536	-
	Tp/°C	50.12	-	231.07	468.51	-
	Δm/%	5.28	-	73.95	19.98	-
(i)	ΔT/°C	30-101	101-146	146-233	233-353	353-534
	Tp/°C	58.32	-	215.28	266.36	400.86
	Δm/%	7.73	-	22.61	47.08	22.17

(*) Δm mass loss/%, ΔT temperature range, Tp peak temperature

The TG/DTG curves of mixtures aceclofenac: waxy maize starch (g-i) profile show thermal decomposition that occurs in three (g-h) and four (i) steps. The DTG curves shows the existence of two consecutive and overlapping steps, associated with the second mass loss observed in the TG curve, this is not observed for waxy maize starch (f), so the thermal decomposition mixtures (g-i) presents a step more than the starch (f).

The first step is attributed to dehydration of the starch present in the sample portion. The anhydrous samples show some behaviour in thermal stability. The decomposition and oxidation of organic matter takes place in three consecutive steps of mass loss, with formation of final residue corresponds to 0.84% (g) 0.79% (h) and 0.41% (i), respectively, of the initial mass sample.

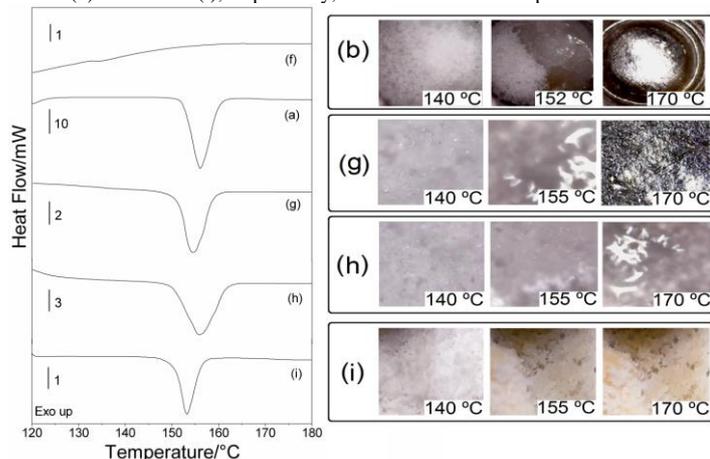


Figure 3 DSC curves (left) and Thermomicroscopy (right): waxy maize starch (f), aceclofenac (b), (g) mixture aceclofenac:waxy maize starch (2:1), (h) mixture aceclofenac:waxy maize starch (1:1) and (i) mixture aceclofenac:waxy maize starch (1:2)

DSC curves show in Fig. 3 and results of DSC are show in Table 2. The waxy maize starch (f) does not present any thermal event at the temperature range of studied, the profile of curves show melting pick of aceclofenac (b), as well as, for mixtures aceclofenac:regular maize starch, for the DSC study of mixtures aceclofenac:waxy maize starch (g-i) there were no major changes in temperature related to the portion of the aceclofenac melting, the melting enthalpy decreased proportionally the increase in regular waxy starch samples. The thermomicroscopy shows Fig. 3 that the melting occurs in aceclofenac fraction of the mixtures, suggesting the formation of a physical mixture, without chemical interaction between the waxy maize starch and the aceclofenac.

CONCLUSION

Thermoanalytical techniques were important analytical tools for evaluating possible interactions between drugs and excipients. The profile of the TG and DTG curves suggests that the decomposition occurs as physical mixtures of two substances. The found results of DSC and thermomicroscopy suggesting the formation of a physical mixture, without chemical interaction between the regular and waxy maize starch and aceclofenac. This fact confirm that these two starchs can be used as excipient in formulations containing aceclofenac.

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