ISSN 2304-2354
Number 2, Volume 44, 2013

COMPATIBILITY STUDIES BETWEEN IBUPROFEN AND PHARMACEUTICAL EXCIPIENTS

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Abstract

An important issue during preformulation studies is the identification of possible incompatibilities between the active pharmaceutical ingredient (API) and various excipients. This study aims to investigate the interactions and compatibilities between ibuprofen and some commonly used excipients by two different experimental techniques Differential Scanning Calorimetry (DSC) and High Performance Liquid Chromatography (HPLC). The techniques employed were able to provide different but complementary information, enabling a complete understanding of the possible interactions that occurred in the binary mixtures drug-excipient.

Introduction

Formulation of a drug substance often requires blending of the active pharmaceutical ingredient (API) with different excipients, to improve manufacturability and to boost product's capacity of administering the dose effectively. Excipients are commonly used to facilitate administration, modulate drug release and also stabilize the product against degradation from the environment [1]. However, potential physico-chemical interactions between drugs and excipients can affect the chemical nature, the stability and bioavailability of the products, and consequently, their therapeutic efficacy and safety [2].

Several methods have been used for drug-excipient compatibility screening. Most of them consist in evaluating physical mixtures of the drug and excipients by Differential Scanning Calorimetry (DSC) or accelerated stability tests followed by analytical determination of the drug with High Performance Liquid Chromatography (HPLC) [3,4]. DSC has been proposed as a valuable method of assessing possible incompatibilities between the formulation compounds derived from appearance, shift or disappearance of peaks and/or variations in the corresponding ΔH [5-9]. Although DSC is a valuable technique, conclusions based on DSC results alone can be misleading and inconclusive. Therefore, results obtained with DSC should always be confirmed with other techniques [10]. This study examined the compatibility of ibuprofen, a non steroidal anti-inflammatory drug (NSAID), which exhibits good anti-inflammatory, analgesic and antipyretic properties, with various excipients like magnesium stearate, *lactose monohydrate and* polyvinylpyrrolidone (PVP). Binary mixtures of ibuprofen in a 1:1 ratio with each different excipient were analyzed by DSC and HPLC. The influence of manufacturing processes like simple blending, co-grinding, kneading or tabletting on drug stability was also evaluated.

Materials and methods

Materials

The following materials were used: ibuprofene (Angelini A.C.R.A.F. Ancona, Italy), Magnesium stearate (A.C.E.F., Piacenza, Italy), Lactose monohydrate (Eigenmann & Veronelli; Rho (Milan), Italy), Polyvinylpirrolidone K30 (BASF Aktiengesellschaft, Germany), Ethanol (96% v/v pure Panreach Quimica, Barcelona, Spain), Ethanol HPLC grade (Lichrosolv®, Merck KgaA, Darmstadt, Germany), Water for HPLC (Lichrosolv®, Merck KgaA, Darmstadt, Germany), Acetic acid 99 – 100% (Baker Analyzed® Reagent, J.T. Baker B.V. Netherland), Acetonitrile HPLC grade (Lichrosolv®, Merck KgaA, Darmstadt, Germany).

Methods

Mixture preparation (1:1 w/w)

a) Physical mixtures: 2 g of ibuprofen were gently mixed with 2 g of each excipient in separate mortars.

b) Co-grinded mixtures: The same amounts of ibuprofen and excipients were transferred in a mortar and grinded vigorously with a pestle for five minutes.

c) Kneaded mixtures: The mixed powders were kneaded with ethanol 96% in a mortar until a uniform mass was obtained. Then, the mass was dried in a crystallizer

using a purge of nitrogen gas.

d) Tabletted mixtures: The binary mixtures were compressed by a rotatory tabletting machine Minitech (Ronchi, Milano, Italy) using the following parameters: die diameter 11.28 mm, die depth 16.2 mm, punch penetration 4-5 mm. Two tablets were prepared for each mixture, varying the mass of the mixture in order to maintain a tabletting force of 2 ± 0.20 KN.

The pure drug was subject to the co-grinding, kneading and tabletting technological processes as described for the mixtures. All the samples prepared were analyzed with both DSC and HPLC at time = 0, stored in plastic epprouvets at room temperature, and re-analyzed to evaluate their stability after 6 months (t_1).

Differential Scanning Calorimetry Analysis

Thermal analysis were carried out a DSC apparatus (Pyris 1, Perkin Elmer, Norwalk, USA) equipped with a cooling device (Intracooler 2P, Cooling Accessory, Perkin Elmer). A purge of dry nitrogen gas (20 ml/min) was used for all runs. The DSC apparatus was daily calibrated for temperature and heat flow using a pure sample of indium and zinc as standards.

The parameters used are listed below:

- ***Temperature range:*** 20–150°C for pure ibuprofen and for the mixtures ibuprofen - magnesium stearate at time t_0 and t_1. 2 –300°C for all the other samples at time t_0 and t_1.
- ***Heating rate:*** 10°C/ min
- ***Nitrogen atmosphere***
- ***Sample mass:*** about 2-3 mg
- ***Small and closed aluminum oxide pans*** for ibuprofen and its mixtures at time t_0 and t_1.

High performance Liquid Chromatography

Liquid Chromatography was performed using a Hewlett Packard 1090 Liquid Chromatograph equipped with a diode array detector. The analytical parameters were optimized and then used for the analysis of pure ibuprofen, single excipients and mixtures, before and after storage.

Results and Discussion

Thermal analysis of pure ibuprofen and ibuprofen-excipient mixtures

Pure Ibuprofene

The DSC thermograms of pure, co-grinded, kneaded and tabletted ibuprofen at time t_0 revealed no significant differences between them. The thermal analysis of pure ibuprofen after storage produced a thermogram with no differences with respect to t_0. Whereas, the thermograms of kneaded and tabletted mixtures displayed a narrow peak below the melting point of the pure drug. The obtained data are given in table nr.2.

Table nr.1 HPLC conditions for the analysis of ibuprofen and all the different mixtures

Analytic Conditions	Pure Ibuprofen or Mixtures
Sample	2 mg (ibu) in 1 ml ethanol; 4 mg (mix) in 1ml ethanol
Volume of Injection	5 µl
Column	LiChrocart® (Merck) 125 x 4 mm, LiChrospher® 100 RP-18 (5 µm)
Guard-column	LiChrocart® (Merck) 4 x 4 mm, LiChrospher® 100 RP-18 (5 µm)
Mobile Phase	50:50 H_2O 2% CH_3COOH: Ethanol pH = 3.20
Flow	0.7 ml/min
Elution	Isocratic
Temperature	Ambient

Table nr.2 T onset and ΔH values obtained for the pure, co-grinded and tabletted ibuprofen at time t_0 and t_1

SAMPLE	THERMOGRAM		t_0		t_1	
			ONSET (°C)	H (J/g)	ONSET (°C)	ΔH (J/g)
Pure	a	Peak 1	77.82	91.54	75.85	125.54
Co-grinded	b	Peak1	76.21	91.35	54.54	9.67
		Peak 2	-	-	75.06	123.93
Kneaded	c	Peak 1	75.96	91.51	52.88	28.21
		Peak 2	-	-	73.63	119.83
Tabletted	d	Peak 1	76.39	91.51	74.72	122.55

Ibuprofen – magnesium stearate binary mixtures

ISSN 2304-2354
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A single peak at 58.52 °C with ΔH 79.46 J/g is observed in the DSC thermogram of the physical mixture at time t_0. The co-grinded, kneaded and tabletted mixtures exhibit the same thermal behavior as observed for the physical mixture with an endothermic peak of fusion with T onset respectively to 79.89°C, 55.74°C, 55.39°C. The data are presented in table nr.3. The melting peak of magnesium stearate disappears, while the peak observed is located in temperatures very close to the temperature of the desolvation of magnesium stearate and the melting point of the pure ibuprofen.

Table nr.3 T onset and ΔH values for ibuprofen – magnesium stearate mixtures (physical, co-grinded, kneaded and tabletted) at time t_0 and t_1

MIXTURE	t_0		t_1	
	ONSET (°C)	ΔH (J/g)	ONSET (°C)	ΔH (J/g)
Physical	58.52	79.46	56.62	101.78
Co-grinded	48.17	92.23	55.70	104.83
Kneaded	55.74	68.18	54.55	92.62
Tabletted	55.39	83.39	54.79	118.34

Presumably, the interaction which affects the mixture under examination is due to the formation of a eutectic. Mixtures containing different weight ratios of the two substances were prepared and examined to better understand the phenomenon (Table nr.4). The DSC analysis of the mixtures enabled the construction of a state diagram (Figure nr.1). The thermograms of ibuprofen - magnesium stearate binary mixtures at t_1, show that the interaction observed at time t_0 persists even after 6 months.

The DSC analysis of different mixtures of ibuprofen with lactose showed similar thermograms characterized by: an endothermic peak due to the melting of the drug with T onset between 75 and 76°C; an enlarged endotherm, at temperatures above 120°C, resulting from the overlaying of two peaks, corresponding to the dehydration of the excipient (trend deeply modified with respect to the dehydration of the pure excipient); a peak at about 211°C due to the melting of lactose. The same thermal behavior is observed for the mixtures after the storage period (Table nr.5).

Table nr.4. T onset and ΔH values of ibuprofen – magnesium stearate in different weight ratios

THERMOGRAM		Ibu – Mgst RATIO	ONSET (°C)	ΔH (J/g)
a	Peak 1	90-10	66.08	72.26
	Peak 2		-	-
b	Peak 1	80-20	55.09	121.43
	Peak 2		-	-
c	Peak 1	70-30	55.08	123.08
	Peak 2		-	-
d	Peak 1	60-40	56.92	138.62
	Peak 2		-	-
e	Peak 1	50-50	58.52	79.46
	Peak 2		-	-
f	Peak 1	40-60	57.96	74.38
	Peak 2		68.00	7.79
g	Peak 1	30-70	55.98	58.49
	Peak 2		69.29	30.41
h	Peak 1	20-80	58.24	33.45
	Peak 2		74.00	34.70
i	Peak 1	10-90	57.73	11.66
	Peak 2		84.20	32.40

Ibuprofen – lactose monohydrate binary mixtures

ISSN 2304-2354
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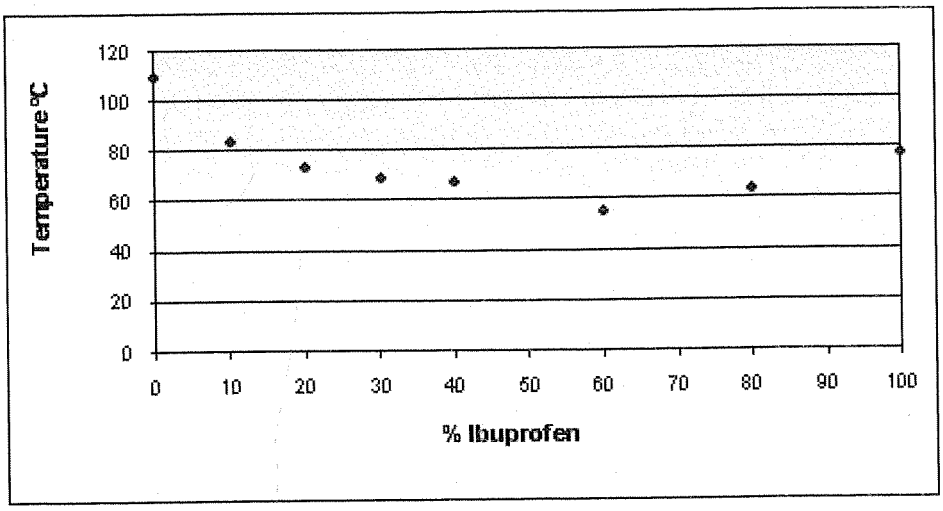


Figure nr.1. State diagram for the system ibuprofen - excipient

Table nr.5. T onset and ΔH values for ibuprofen – lactose monohydrate mixtures (physical, co-grinded, kneaded and tabletted) at time t_0 and t_1

SAMPLE	THERMOGRAM		t_0		t_1	
			ONSET (°C)	ΔH (J/g)	ONSET (°C)	ΔH (J/g)
Physical	a	Peak 1	76.42	47.15	75.18	65.07
		Peak 2	129.54	30.10	127.61	23.73
		Peak 3	211.93	49.02	210.90	63.04
Co-grinded	b	Peak 1	76.02	45.13	75.07	61.77
		Peak 2	127.69	35.04	127.46	37.69
		Peak 3	211.86	50.54	210.35	67.70
Kneaded	c	Peak 1	75.83	45.68	74.70	60.46
		Peak 2	129.12	32.71	128.25	28.70
		Peak 3	206.25	42.30	204.82	58.04
Tabletted	d	Peak 1	75.50	40.84	74.34	56.38
		Peak 2	128.60	31.08	126.75	33.97
		Peak 3	211.65	48.30	209.44	65.16

Ibuprofene – PVP binary mixtures

The thermogram (Table nr.6) revealed a rather wide peak above 50°C, particularly in the DSC curves corresponding to the physical, co-grinded and tabletted mixtures, not related to the melting of ibuprofen, but probably due to an interaction between the two components of the mixture [11].

As already shown in previous studies [12], scanning in high temperature promotes the interaction between the two components of the mixture. Chemical instability of a mixture ketoprofen - PVP K30 stored at 40, 50 and 60°C have also been previously reported [13]. Given the structural analogy of ketoprofen and ibuprofen, it is likely that even the ibuprofen – PVP mixture might be instable.

The mixtures of ibuprofen – PVP at t_1 transformed into a viscous physical form. The DSC curves demonstrated the disappearance of the characteristic ibuprofen fusion peak, indicating a probable interaction between the compounds.

Table nr.6. T onset and ΔH values for ibuprofen – PVP (physical, co-grinded, kneaded and tabletted) at time t_0 and t_1

CURVE	ONSET (°C)	ΔH (J/g)
a	62.66	50.48
b	50.21	40.52
c	-	-
d	53.91	29.86

Summarizing, the outcome of the DSC analysis for all ibuprofen-magnesium stearate and ibuprofen-PVP mixtures revealed incompatibilities between the drug and the excipients. The results were confirmed even in the stored samples analyzed after 6 months (Figure nr.2).

ISSN 2304-2354
Number 2, Volume 44, 2013

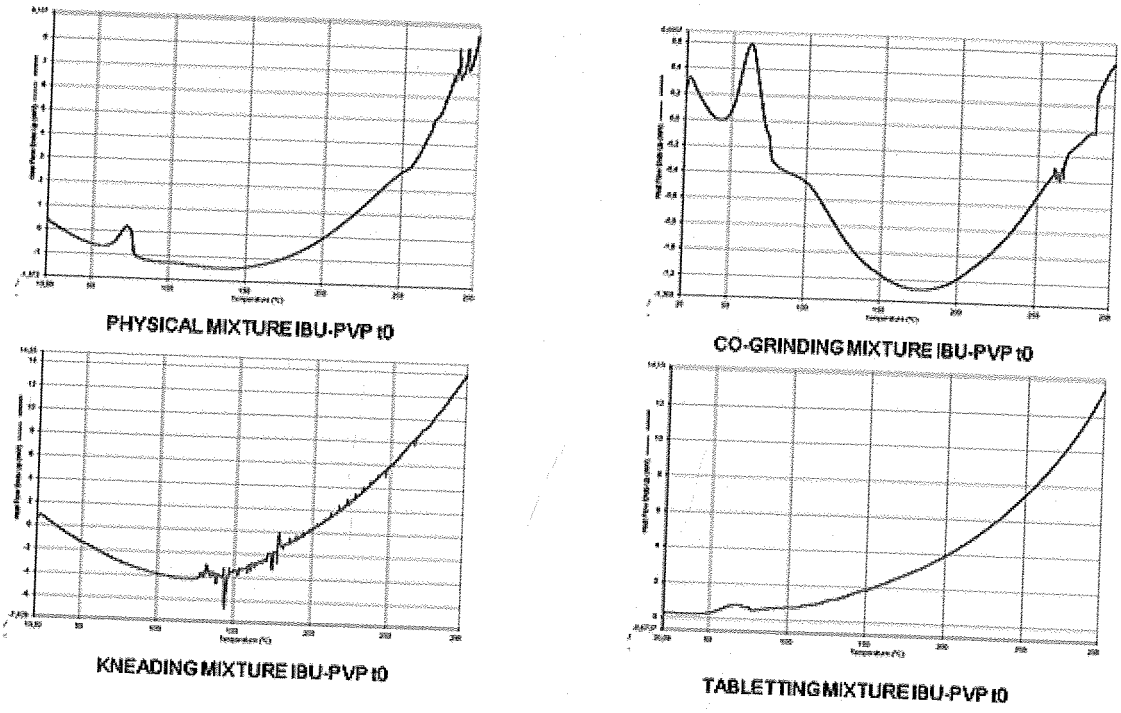
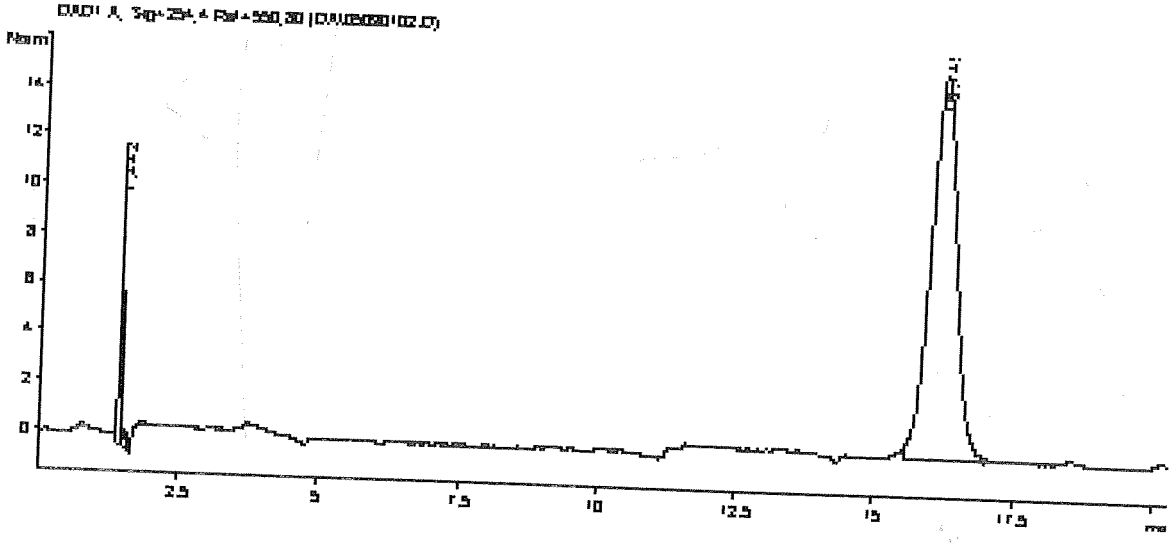


Figure nr.2 DSC curves of ibuprofen – PVP physical, co-grinded, kneaded and tabletted mixtures at t_0

HPLC of pure ibuprofen and its mixtures

Method suitability was tested by injecting each excipient separately, ensuring that there is no co-elution or other interference between the drug and the excipients [14]. All the chromatograms obtained from injection of sample mixtures, immediately after preparation (t0), revealed only one peak corresponding to the retention time of pure ibuprofen.

The chromatograms of the physical, co-grinded, kneaded and tabletted ibuprofen-excipient mixtures, analysed after the storage period, did not reveal any secondary peaks indicating the chemical stability of all mixtures (Figure nr.3).



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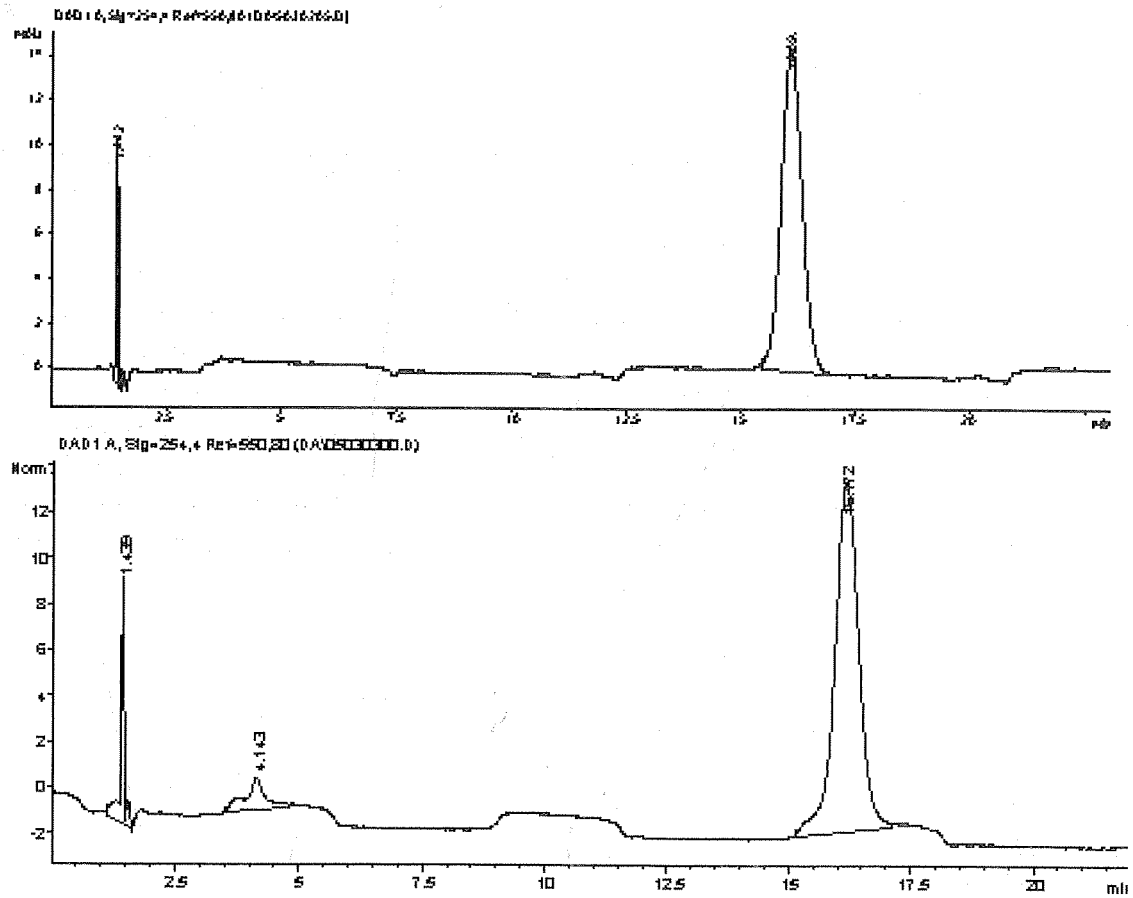

Figure nr.3 HPLC analysis of physical mixtures of ibuprofene + excipients. Chromatograms:
a) Ibuprofen – Magnesium stearate, b) Ibuprofen – Lactose monohydrate, c) Ibuprofen – Polivynilpyrrolidone

Differences were observed only in the mixtures containing ibuprofen-PVP. The small peak at the retention time of 4.14 minutes was present in all the chromatograms of the mixture before and after the storage at room temperature. The peak was more evident in the mixture prepared by co-grinding (Figure nr.4).

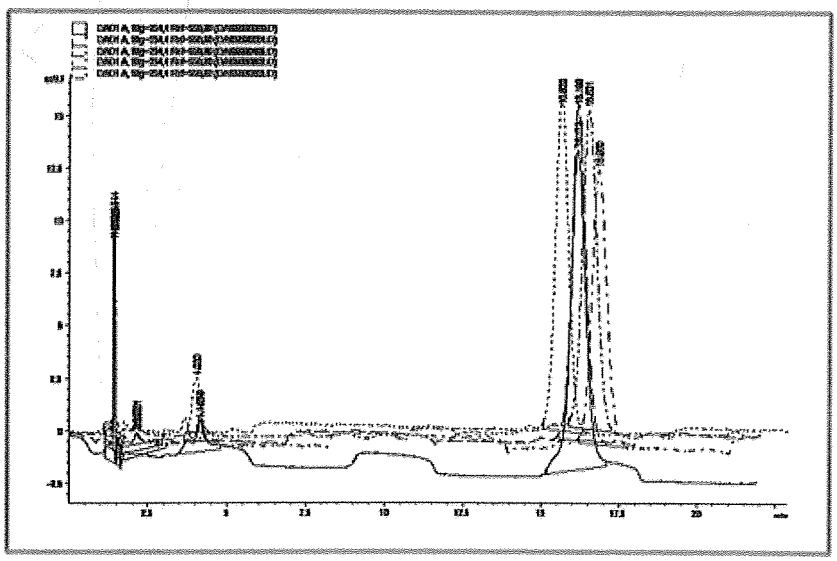

Figure nr.4. A small peak at 4.14 minutes is present in all the chromatograms of the mixture before and after the storage, being more evident in the mixture processed with co-grinding

Conclusions

Selection of the proper excipient during preformulation studies is of major importance. The results obtained in this study were attentively evaluated considering the specifics of each technique. The outcome of the DSC analysis for all ibuprofen-magnesium stearate and ibuprofen-PVP mixtures revealed drug-excipient incompatibilities. The results were confirmed even in the stored samples analyzed after 6 months. On the other hand, the HPLC analysis, revealed differences only in the ibuprofen-PVP mixtures and in the co-grinded ones in particular. However, DSC has some limitation related to the difficulties encountered in the interpretation of the thermograms and pointing out mainly qualitative rather than quantitative effects. In many of the examples discussed above regarding these analysis, the incompatibility is evident at elevated temperatures, and thus they may not be seen at room (real) temperatures for the duration of the product shelf-life. Nevertheless, such information is very helpful for analyzing any instability issues with commercial formulations or during the development of new formulations.

Finally, the techniques employed were able to provide different but complementary information, enabling a complete understanding of the possible interactions that occurred in the binary mixtures drug-excipient.

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