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THERMAL ANALYSIS APPLIED IN THE OSMOTIC TABLETS PRE-FORMULATION STUDIES

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Osmotically controlled and oral drug delivery systems utilize osmotic pressure for controlled delivery of active agent(s). Drug delivery from these systems, to a large extent, is independent of the physiological factors of the gastrointestinal tract and these systems can be utilized for systemic as well as targeted delivery of drugs. We apply the thermal methods and IR spectroscopy to study compatibility between atenolol and several excipients usually found in the osmotic systems formulations (Polyethylene oxide, *MW* 3350, 100000, 200000 and 5000000; HPMC K4000, magnesium stearate and cellulose acetate.

Cellulose acetate, HPMC K4000 and magnesium stearate have essentially no interaction with atenolol otherwise all Polyethylene oxide excipients modifies significantly the drug melting point indicating some extend of interaction.

Keywords: *atenolol, compatibility, DSC, osmotic system, TG*

Introduction

In recent years, considerable attention has been focused to the development of novel drug delivery systems (NDDS). The reason for this paradigm shift is relatively low cost of development and required time for introducing a NDDS ($20–50 million and 3–4 years, respectively) as compared to a new chemical entity (approximately $500 million and 10–12 years, respectively). In the form of NDDS, an existing drug molecule can get a 'new life' thereby, increasing its market value, competitiveness, and patent life [1]. Among the various NDDS available in the market, oral controlled release (CR) systems hold the major market share because of their obvious advantages of ease of administration and better patient compliance [2]. CR delivery systems provide desired concentration of drug at the absorption site allowing maintenance of plasma concentrations within the therapeutic range and reducing the dosing frequency.

Osmotic systems utilize the principles of osmotic pressure for the delivery of drugs. Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the properties of drug and system [3]. Alza Corporation of the USA (now merged with Johnson and Johnson, USA) was first to develop an oral osmotic pump and today also, they are the leaders in this field with a technology named OROS. The oral osmotic pumps have certainly come a long way and the available products based on this technology [4] and number of patents granted in the last few years makes its presence felt in the market. Finally osmotic pumps can be used as experimental tool to determine important pharmacokinetic parameters of new or existing drugs and at the same time, they can also be utilized to deliver drug at a controlled and predetermined rate.

In preformulation studies many in vitro and in vivo tests are conducted to evaluate the optimal dosage form. However even it reaches the desired dissolution and absorption profile the dosage form chemical stability must be investigate to prove the formulation resistance during the shelf life (normally two years).

To avoid wasting time with inappropriate drugs and dosage forms, it is very important to begin the clinical phases with formulations fully characterized from the physicochemical point of view [5–9]. While most excipients have no direct pharmacological action, they do perform either useful tasks or damaging actions (such as speeding up degradation of the drug) [6]. In this sense devising a quick and accurate method to test and select the best candidates for stable dosage forms would constitute a real breakthrough in the preformulation pharmacy.

The procedure employed so far is mostly based on the annealing of binary mixtures under stress conditions following by chromatographic analysis (HPLC). Some disadvantages of chromatographic analysis as large amounts of drug required, large time consume to prepare test solutions and high investment (all compared with thermal analysis) suggests that could be interesting use other techniques in this project phase. Thus thermal analysis offers significant

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advantages in saving time, substance and money to detect compatibility/incompatibility in binary mixtures [10], furthermore, this methods coupled with other techniques (infrared spectroscopy (FTIR), X-rays scattering, microscopies) may be much better exploited though their systematic and concurrent use along with the standard methods [11].

Interactions in the solid state between the active ingredient(s) and excipients in pharmaceutical dosage forms can give rise to changes in the stability, solubility, dissolution rate and bioavailability of drugs [11]. So when an excipient affect negatively some of the factors above we can assume it is incompatible with that drug.

Differential scanning calorimetry (DSC) and thermogravimetric analysis (TG) have shown to be a powerful tool for investigating and predicting physicochemical incompatibility between an active ingredient and pharmaceutical excipients. DSC allows rapid evaluation of possible interactions between the formulation components according to appearance, shift, or disappearance of endothermic or exothermic peaks and/or variations in the relevant enthalpy values in thermal curves of drug–excipients mixtures [12]. Because DSC curves bring valuable information, it is very important to observing them and not only looks to numeric values.

By consulting the literature we were not able to find a standard procedure to treat and storage the drug and excipients mixtures before submit them to thermal analysis. Some authors prepared 1:1 physical mixtures and submitted direct to analysis [13]; or prepared 1:1 physical mixtures blending for 5 min in a mortar submitting to 40±1°C and 75% relative humidity for 4 weeks before analysis [14]; or prepared physical mixtures with pharmaceutical active and excipient in different proportions following by compression at 3 t for 2 min, breaking and sieving (75–150 μm) before analysis [12]; or prepared 1:1 and different proportions of physical mixtures with and without add an amount of water submitting to 50°C for 1 h before analysis [15]; or prepared 1:1 physical mixtures blending, triturating and kneading with ethanol, separately in a mortar, drying in desiccators and submitting to 60°C for 3 weeks before analysis [16] and etc. Keeping in mind that we do not intend to use thermal analysis coupled with FTIR to replace the complete stability protocol for pharmaceutical products suggested by authorities but only have physicochemical information about the formulation proposed avoiding future problems, furthermore as there is no standard procedures for compatibility studies we have established the conditions according to climatic zone we are located. Thus the conditions were established based on Brazilian official stability guide for solid pharmaceutical products (RE no. 1, date: 29, month: July, year: 2005) excepted about the time extension that was reduced to 15 days.

It is known that in case of products stored or administered in the solid form is essential to understand the role of water/moisture [7]. Thus reaction with water may modify the properties of the active ingredient, and such a reaction may be facilitated by the excipient which is often the vehicle of ambient moisture into the formulation. The temperature can affect the formulation too because it usually leads to faster degradation (oxidation, phase changes) and this is why we believe that factors like these should have been included in the investigation.

The active ingredient studied is atenolol which have been incorporated in the push pull osmotic pump [17, 18]. Atenolol is a β-adrenolytic, cardioselectivee drug, having no intrinsic sympathomimetic activity. It comes as a white powder, nearly insoluble in water or organic solvents (acetone and chloroform) with melting point of 150°C. β receptor blocking drugs were introduced in 1966, to treat cardiovascular disorders. These drugs are especially efficient in cases of coronary failure (angina pectoris), arterial hypertension and cardiac arrhythmia. The synthesis of atenolol was first reported in 1970 [19] and the first pharmacological and clinical studies were made in 1973 and 1974 [20–22].

Compatibility studies with atenolol and different excipients used in osmotic and hydrophilic extended release matrix systems were not found in our previous literature review. Thus, here we will present such a systematic compatibility study for atenolol with polyethylene oxide derivatives (poliox NF10, NF80, coagulant with high molecular masses (PEO)), polyethylene glycols (PEG), hydroxypropylmethylcellulose (HPMC), magnesium stearate (MGST) and cellulose acetate (CA). With their very high molecular mass, poliox resins are viscoelastic, so their aqueous solutions can reduce spattering and misting potential. Poliox resins can form association compounds with many other substances to achieve a wide variety of additional, useful formulation properties.

DSC/TG curves of the drug and individual excipients were compared with those of each drug–excipient blend in the 1:1 (by mass) ratio, because it is normally used in many articles and because it has the advantage of maximize the likelihood of an interaction.

Accepting incompatibility as a consequence of the existence of negative selective interactions between substances, FTIR technique can be applied in the determination of the nature and strength of these interactions. This technique has been widely used in similar cases due to its sensibility to detect system spectral changes provoked by interactions such as hydrogen bonding and because it has been demonstrated to be a rapid, versatile, and reproducible technique.

As possible interactions between pharmaceutical active and excipients can affect the vibration of groups on molecules segments, we coupled this technique with thermal analysis and compared the infrared spectra of pure substances and their binary blends [23]. Thus we supposed if some interaction exists between the molecules, a shift in a functional group band in binary blend spectra would be observed.

Support of this approach comes from general belief that the thermal properties and FTIR spectra superposition of pure excipients and active ingredient must be obtained in the binary blends to certify that any negative impact will be observed in the aspect of formulation of osmotic dosage forms.

Experimental

Materials

The polyethylene oxide derivatives as poliox NF10, molecular mass (*MW*) 100.000, batch RB24555SfH5; poliox NF80, *MW* 200.000, batch RI1555S5II; Poliox Coagulant *MW* 5.000.000, batch 0355S5C3, were all purchased by Dow Chemical Company (USA); PEG 3350 batch DG133997, by Clariant Brasil (Brazil); cellulose acetate 398 N10, batch CA 01279NF, by Eastman Chemical Company (USA); HPMC K 4000, batch WP127306, by M.P.I. Pharmaceutica GMBH (Brazil); MGST, batch MGSV50020, by Forlab Chitec S/A Comercio INT (Brazil); atenolol racemic mixture, batch 4528A2R11, by Galena Química e Farmacêutica LTDA, (Brazil).

Each 1:1 binary drug excipient mixtures were prepared by weighing the appropriate amount of the components (total 1 g) in order to produce a physical mixture by grinding them for 2 min.

The mixture samples were stored in containers after being prepared and the treatment below was applied up to 15 days.

- Closed container in ambient temperature, 30°C (I)
- Open container in ambient temperature and controlled humidity, 30°C and 75% relative humidity (*RH*) (II)
- Closed container in controlled temperature, 40°C (III)

Methods

Thermal analyses by Shimadzu DSC-50 in dry nitrogen atmosphere (flow rate 100 mL min^{-1}) temperature scanning rate was 5°C min^{-1} up to 200°C. About 2 mg of each sample were weighed using closed aluminium pans. Thermogravimetric Analyses by Shimadzu TGA-50 were also made in dry nitrogen atmosphere (flow rate 50 mL min^{-1}) and temperature scanning rate was 5°C min^{-1} up to 500°C. About 5 mg of each sample were weighed using open aluminum pans.

FTIR by Perkin Elmer Spectrum One. The interval of sample analyses was 650–4000 cm^{-1} with 2 cm^{-1} resolution. The spectra shown result from subtraction of the background contribution.

Results and discussion

The mixtures of atenolol and excipients were analyzed and the compatibility results will be present in this work. Furthermore the sensitivity of different techniques as thermal analysis and FTIR was compared and the concomitant use of them was explored. All the qualitative data are presented in the figures and the quantitative ones are presented in the Tables 1–3. Table 1 show the characteristic temperature and enthalpy values for Atenolol alone and in the presence of excipients in different conditions. The other two Tables 2 and 3 show the TG data for the blends that presented changes in endothermic peak shape or decrease in the enthalpy values for DSC curves.

Pure atenolol was submitted to the same conditions of mixtures to be sure that no alteration in the melting point DSC curve would be observed. According to the Fig. 1 and Table 1, pure atenolol presented the same melting point even after exposed to high temperature and humidity.

Atenolol and CA (1:1) mixture

DSC scans and FTIR for CA and atenolol mixtures were made. DSC curves (Fig. 2) showed no change in endothermic peak shape and the enthalpy value was

Table 1 Peak temperature and enthalpy values for melting of atenolol with and without excipients after exposure to three different storage conditions

Storage conditions	Atenolol	+ CA	+ HPMC	+ MGST	+ PEG	+ PEO NF10	+PEO NF80	+PEO coagulant
				T_{peak}/°C				
I	154.72	154.40	154.52	154.26	146.37	147.80	148.42	154.22
II	153.99	154.39	154.61	154.18	143.84	147.45	148.94	154.22
III	154.13	154.37	154.60	154.32	146.53	147.30	146.51	154.23
				enthalpy/J g^{-1}				
I	172.45	65.62	54.76	66.76	35.49	29.34	34.28	32.59
II	124.89	76.25	55.06	65.96	24.57	23.88	32.96	35.46
III	154.92	68.37	59.09	69.79	37.26	27.53	26.70	33.97

Table 2 Onset and mass loss data from TG of pure atenolol and blends with PEG and PEO derivatives

Storage condition	Atenolol	+ PEG	+ PEO NF10	+PEO NF80	+PEO coagulant
			onset		
I	278.08	289.05	304.23	300.08	308.41
			mass loss/%		
I	68.97	81.069	83.03	64.367	84.152

Table 3 Onset and mass loss data from TG of pure excipients

Storage condition	PEG	PEO NF10	PEO NF80	PEO coagulant
		onset		
I	358.98	363.25	357.81	389.70
		mass loss/%		
I	96.07	95.18	95.27	94.00

near to expected. FTIR (not inserted) showed no changes in spectra, thus no interaction occurred between the substances.

Atenolol and HPMC (1:1) mixture

According to Fig. 3, HPMC showed some amount of water in the polymer as we could see in the low temperatures of DSC curve, furthermore the melting point and endothermic peak shape of the blending were not affected by the different conditions of storage. Despite the difference between the enthalpy value obtained and the expected we assumed that it was not relevant, thus no interaction was observed between atenolol and HPMC. No changes in FTIR spectra were observed (figure not inserted).

Atenolol and MGST (1:1) mixture

Atenolol and MGST blend in Fig. 4 showed a short slope in the based line at the beginning of the MGST DSC scans. Probably it represented the water loss before 100°C according to literature that describes two molecules of water per unit formula of MGST [24–26]). Another value described in the literature was the MGST melting point as 120°C and it is possible to see in Fig. 4 a small peak decrease around this temperature. Probably it represents the MGST melting point that was attenuated by the great atenolol melting point extension.

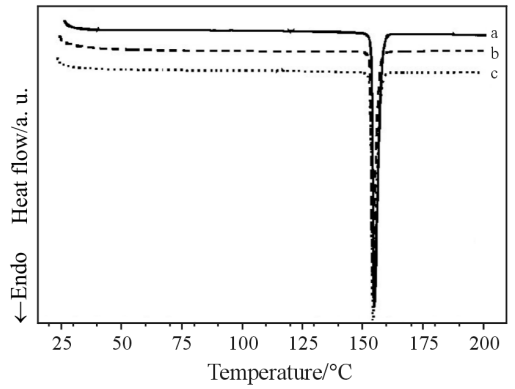

Fig. 1 DSC curves of a – atenolol, condition (I), b – atenolol condition (II) and c – atenolol condition (III)

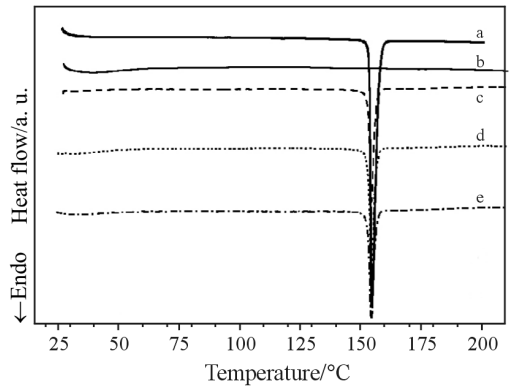

Fig. 2 DSC curves of a – atenolol; b – CA; c – atenolol:CA mixture, condition (I); d – atenolol:CA condition (II) and e – atenolol:CA condition (III)

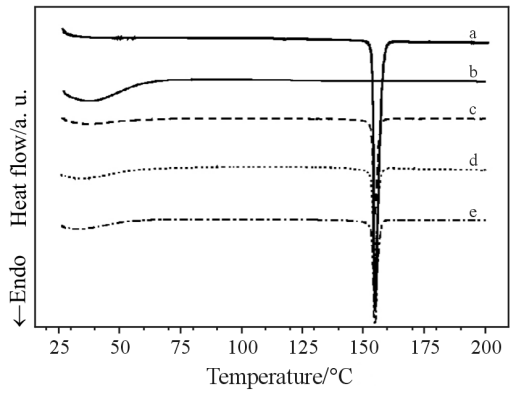

Fig. 3 DSC curves of a – atenolol; b – HPMC; c – atenolol:HPMC mixture, condition (I); d – atenolol:HPMC, condition (II) and e – atenolol:HPMC condition (III)

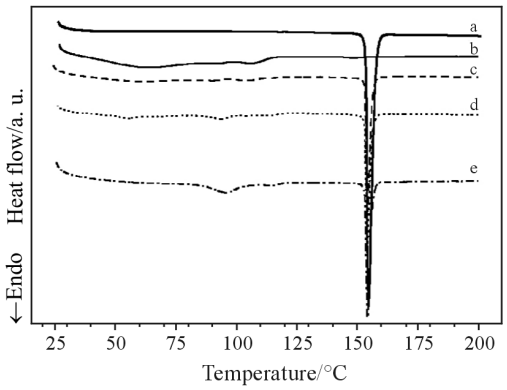

Fig. 4 DSC curves of a – atenolol; b – MGST;
c – atenolol:MGST mixture, condition (I);
d – atenolol:MGST, condition (II) and
e – atenolol:MGST condition (III)

No interaction was found between MGST and atenolol as described by other authors. DSC curves (Fig. 4) showed no modifications in the atenolol melting point and enthalpy of atenolol. Again, no changes in blend FTIR spectra were observed (figure not inserted), thus no interaction occurred between the substances.

Atenolol and PEG 3350 (1:1) mixture

Atenolol and PEG blend DSC scans were presented in Fig. 5. FTIR showed no interaction occurred between atenolol and PEG even exposed to temperature and humidity. The spectra of the blends were similar to superposition of the pure substances spectra. DSC scans showed a first endothermic event attributed to PEG melting near at 60°C and a second endothermic event attributed to atenolol melting. The shift of atenolol melting point to a low temperature (–8°C) and the enthalpy decrease indicated interaction between the substances. In this case TG was applied to verify if thermal degradation of atenolol was accelerated by the presence of PEG.

TG data showed in Tables 2 and 3 revealed that atenolol thermal degradation (onset) was not accelerated (decrease) by PEG presence and blend behavior was intermediated to pure substances.

Atenolol and PEO (1:1) mixture

The FTIR and DSC scans (Figs 7–9) of atenolol blends with three PEO derivatives were investigated. FTIR spectra showed no interaction between atenolol and PEO (1:1) mixtures even exposed to temperature and humidity and were similar to the superposition of the pure substances, as we can see in Fig. 6. DSC curves showed a first endothermic event attributed to PEO melting point (65 to 70°C) and a second endothermic event attributed to atenolol melting point. The shift of atenolol melting point to a low temperature (154 to 147°C) and the enthalpy value decrease observed in blends with poliox NF 10 and NF 80 (Table 1) was remarkable indicating interaction between the substances. DSC curve of atenolol and poliox coagulant

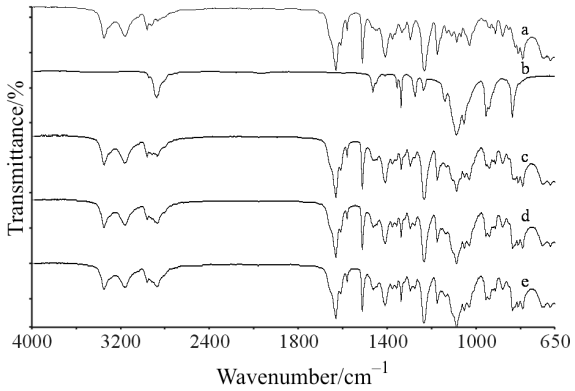

Fig. 6 FTIR spectra of a – atenolol; b – poliox NF 10;
c – atenolol:poliox NF 10, condition (I);
d – atenolol:poliox NF 10, condition (II) and
e – atenolol:poliox NF 10 condition (III)

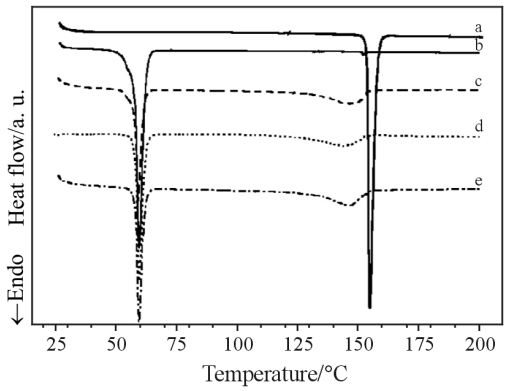

Fig. 5 DSC curves of a – atenolol; b – PEG 3350;
c – atenolol:PEG mixture, condition (I);
d – atenolol:PEG, condition (II) and
e – atenolol:PEG condition (III)

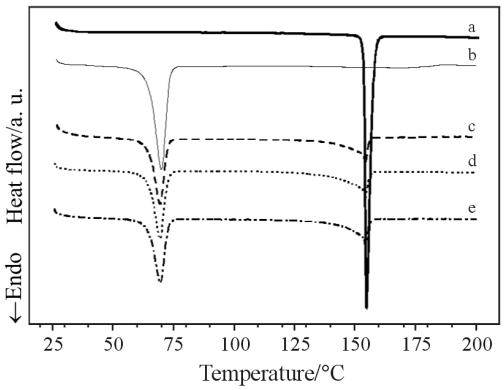

Fig. 7 DSC curves of a – atenolol; b – poliox coagulant;
c – atenolol:poliox mixture, condition (I);
d – atenolol:poliox, condition (II) and
e – atenolol:poliox condition (III)

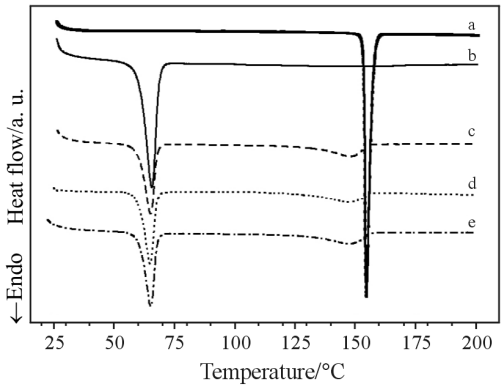

Fig. 8 DSC curves of a – atenolol; b – poliox NF10; c – atenolol:poliox mixture, condition (I); d – atenolol:poliox, condition (II) and e – atenolol:poliox condition (III)

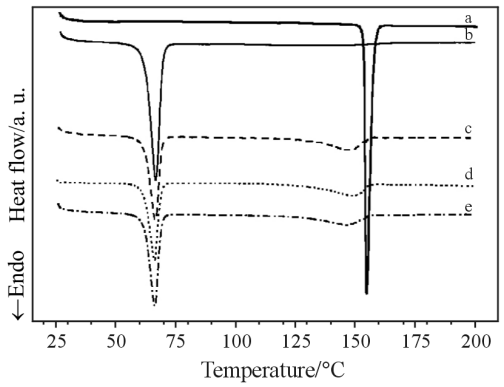

Fig. 9 DSC curves of a – atenolol; b – poliox NF80; c – atenolol:poliox mixture, condition (I); d – atenolol:poliox, condition (II) and e – atenolol:poliox condition (III)

blend (Fig. 7) showed despite of atenolol melting point keep constant about 154°C both the enthalpy decrease and the change in endothermic peak shape were remarkable. As atenolol and PEG blend, TG data presented in Tables 2 and 3 revealed that atenolol thermal degradation (onset) was not accelerated (decrease) by PEO presence and for all blends the behavior was intermediated to pure substances.

Conclusions

In this work, as many drug–excipient compatibility studies, we have searched for differences between data of pure compounds and those of their mixtures.

If no interaction is expected, the same behavior for pure compounds and their mixtures will be observed. For this principle we called 'no interaction hypothesis'. Thus the interactions indicators were explored as a function of moisture and temperature treatment. These interactions indicators are mostly qualitative in nature, for example, peak modified intensities, new peak positions, modified peak shape but enthalpies of melting are quantitative data since they may be expressed as a fractional change. This work not attempted in depth interpretation of our quantitative results since the aim was simply that of finds interactions of a drug with different excipients.

According with our results no interactions were observed using FTIR for all blends. However when DSC curves were obtained we were able to observe interactions occurring between atenolol with PEG and PEO. MGST and CA showed no interactions with atenolol. Furthermore conditions storage did not influence in the results but maybe more time would be necessary to trigger the chemical reactions.

With TG results coupled to DSC we were able to conclude that atenolol interaction with PEG and PEO (observed in DSC curves) did not decrease the atenolol onset (278.08°C) and the mass loss was not maximized. In the Tables 2 and 3 we can see the intermediated onsets for blends compared to pure atenolol and pure excipients as expected for compatible substances (for mass loss the same was observed). The endothermic peak change and the enthalpy value decrease observed in DSC curves could be explained, based on some observations in the literature [27–29], with the amorphizing effect of the polymers on the crystalline active ingredient. This kind of interactions can produce solid dispersions that usually increases solubility of drugs and as consequence increases their bioavailability. A careful analysis must be done because despite presenting interactions with PEG and PEO we can't conclude atenolol presents incompatibility with them because factors like solubility and bioavailability can be affected positively in this case.

This study demonstrated that DSC technique was more sensitive technique in revealing effects of interaction than FTIR. Furthermore was very important to associate DSC with TG results to get the right conclusions. Only after TG analyses curves we were able to conclude that all osmotic tablet excipients verified in this work were compatible with atenolol.

References

1 R. K. Verma, D. M. Krishna and S. Garg, J. Control. Release, 79 (2002) 7.
2 R. K. Verma and S. Garg, Pharm. Technol., OnLine (http://www.pharmaportal.com), 25 (2001) 1.
3 F. Theeuwes, D. R. Swanson, G. Guittard, A. Ayer and S. Khanna, Br. J. Clin. Pharmacol., 19 (1985) 69S.
4 G. Santus and R. W. Baker, J. Control. Release, 35 (1995) 1.
5 C. Ahlneck and P. Lundgren, Acta Pharm. Suec., 22 (1985) 305.

6 Crowley and L. Martini, Pharm. Techn. Europe, 13 (2001) 26.
7 C. Ahlneck and G. Zografi, Int. J. Pharm., 62 (1990) 87.
8 D. C Monkhouse, Drug Dev. Ind. Pharm., 10 (1984) 1373.
9 J. T. Carstensen, Drug Dev. Ind. Pharm., 14 (1988) 1927.
10 G. Bruni, L. Amici, V. Berbenni, A. Marini and A. Orlandi, J. Therm. Anal. Cal., 68 (2002) 561.
11 A. Marini, V. Berbenni, M. Pegoretti, G. Bruni, P. Cofrancesco, C. Sinistri and M. Villa, J. Therm. Anal. Cal., 73 (2003) 547.
12 P. Mura, P. Gratteri and M. T Faucci, J. Therm. Anal. Cal., 68 (2002) 541.
13 S. R. Desai, M. M. Shaikh and S. R. Dharwadkar, J. Therm. Anal. Cal., 71 (2003) 651.
14 D. Kiss, R. Zelko, Cs. Novák and Zs Éhen, J. Therm. Anal. Cal., 84 (2006) 447.
15 C. E. P. Malan, M. M. de Villiers and A. P. Lötter, J. Pharm. Biomed. Anal., 15 (1997) 549.
16 P. Mura, G. P. Bettinetti, M. T. Faucci, A. Manderioli and P. L. Parrini, Thermochim. Acta, 321 (1998) 59.
17 P. S. L. Wong, B. Barclay, J. C. Deters and F. Theeuwes, US Patent 4,612,008, Sept. 16, 1986.
18 R. Cortese and F. Theeuwes, US Patent 4,327,725, May 4, 1982.
19 A. M. Barrett, D. J. Hull, Lecount, C. J. Squire and J. Carter (ICI Ltd.), Ger. Offen., 73 (1970) 120.
20 J. F. Giudicelli. J. R. Boissier, Y. Dumas and C. Advenier, Compt. Rend. Soc. Biol., 167 (1973) 232.
21 L. Hansson, H. Aberg, S. Jameson, B. Karlberg and R. Malmcrona, Acta Med. Scand., 194 (1973) 549.
22 A. Amery, L. Billiet and R. Fagard, N. Engl. J. Med., 290 (1974) 284.
23 Chamekh Ould M´Bareck, Q. T. Nguyen, M. Metayer, J. M. Saiter and M. R. Garda, Polymer, 45 (2004) 4181.
24 A. Marini, V. Berbenni, S. M. Moioli, G. Bruni, P. Cofrancesco, C. Margheritis and M. Villa, J. Therm. Anal. Cal., 73 (2003) 529.
25 T. A. Miller and P. York, Int. J. Pharm., 23 (1985) 55.
26 S. A. Sharp, M. Celik, A. W. Newman and H. G. Brittain, Struct. Chem., 8 (1997) 2.
27 K. Matsumoto, Y. Nakai, E. Yonemochi, T. Ogucgi and K. Yamamoto, Int. J. Pharm., 108 (1994) 167.
28 M. Moneghini, A. Carcno, G. Zingone and B. Perissutti, Int. J. Pharm., 175 (1998) 177.
29 K. Daniel-Mwambete, S. Torrado, C. Cuesta-Bandera, F. Ponce-Gordo and J. J. Torrado, Int. J. Pharm., 272 (2004) 29.

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