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STABILITY STUDIES ON NIFEDIPINE TABLETS USING THERMOGRAVIMETRY AND DIFFERENTIAL SCANNING CALORIMETRY

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A formulation of nifedipine tablets was prepared in the present research. The tablets were conditioned in amber-colored glass containers and placed in a climatized room at 40°C and relative humidity of 75% for 180 days. Differential scanning calorimetry (DSC) and thermogravimetry (TG) were used in order to evaluate the thermal properties of nifedipine, the excipients and two well-known nifedipine degradation products. The results demonstrated that there is no evidence on the interaction between nifedipine and excipients, or degradation products.

Keywords: *differential scanning calorimetry (DSC), nifedipine, stability studies, thermogravimetry (TG)*

Introduction

Currently, arterial hypertension constitutes one of the most prevalent health problems [1]. Hypertension treatment may be carried out with or without the use of medication and a pharmacological treatment, including several groups of pharmaceutical compounds, e.g. diuretics, adrenergic inhibitors, direct vasodilatory agents, calcium channel blockers, angiotensin conversion enzyme inhibitors, and angiotensin II receptor antagonists [2].

Nifedipine is a pharmaceutical blocking agent of calcium channels used in the treatment of systemic arterial hypertension [3]. It reveals an effective antihypertensive efficacy which is similar to that of diuretics, beta-adrenergic blockers and angiotensin conversion enzyme inhibitors [4, 5]. Nifedipine, (1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3-5-pyridine dicarboxylic acid dimethyl ester) [6] may suffer alterations due to light exposure [7, 8]. According to Merck Index its melting point varies between 172 and 174°C [9].

The stability of a formulation can be defined with the time in which it keeps its stability and biological activity [10] which is different of the chemical stability of the active compound when it is alone [11].

When a drug is altered by interacting with excipients or by changes in stock conditions its stability may be affected [12]. In case of a pharmaceutical formulation an acceptable storage period is when the amount of the active compound does not decrease more than 10% after formulation as long as eventual degradation products are identified [13].

Temperature may accelerate the majority of processes which result degradation of pharmaceutical compounds and formulations which is the starting point of a considerable number of artificial ageing simulation methods [14, 10].

DSC and TG provide important data on the evaluation of stability of a pharmaceutical formulation [15]. The obtained information can be completed with the results of spectroscopic and chromatographic methods which became essential in modern methodologies of formulation development [16, 17]. Interactions between pharmaceutical drugs and excipients may generate several compatibility problems which affect the stability of the formulation [18]. DSC is systematically employed for the compatibility studies between pharmaceutical drugs and excipients with success as it can be concluded from the large number of published papers in this field. Kiss *et al.* [19] studied the compatibility between metronidazol and different excipients and detecting interaction between metronidazol and calcium diphosphate dehydrate.

Silva *et al.* [20] investigated the thermal behavior of fluoxetine hydrochloride and capsules containing the mixture of the drug with excipients. The obtained DSC curves revealed compatibility between the active drug and excipients. Hekmatara *et al.* [21] prepared microspheres of diltiazem hydrochloride and examined the thermal analytical behavior of the formulation of components and of the microspheres. It was stated that preparation conditions influenced the morphology and size of particles.

Fujisawa and Kimura [22] used a thermal analysis in order to verify molecular interactions

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between antiulcer pharmaceutical drugs and β-cyclodextrine. In a related research Aki *et al.* [23] assessed the antimicrobial activity of amoxicillin when complexed with different types of cyclodextrins and observed differences in the activity caused by the inclusion complex formation. Cides *et al.* [24] studied the thermal behavior of glymepirid and made compatibility studies between the drug and pharmaceutical excipients of daily use, such as sodium amidoglycolate, microcrystalline cellulose, magnesium stearate, lactose and plasdone. Some sort of interaction was observed between glymepirid and magnesium stearate and plasdone.

Experimental

The novelty of the present study is to evaluate the compatibility between nifedipine and modern pharmaceutical excipients, particularly hydroxiypropylmethylcellulose (hpmc), as well as the evaluation of the thermal properties of two decomposition products of nifedipine.

The objective of the present work is to examine the thermal behavior of the single constituents (pharmaceutical drug and excipients) as well as the tablets of nifedipine by means of TG and DSC and, besides to determine the stability of the formulation via high performance liquid chromatography.

Materials

- nifedipine (batch 406059, Zambon), nifedipine USP reference standard (batch KOD401), nifedipine nitrophenylpyridine USP standard (batch K46360), and nifedipine nitrosophenylpyridine USP standard (batch K46370) as drug and
- microcrystalline cellulose (batch 103, Reliance), magnesium stearate (batch MGSV 40372, Faci), silicon dioxide (batch 20704/2, Cabot), hydroxypropylmethylcellulose 100 – hpmc 100 (batch SI22012N21, Colorcon), hydroxypropylmethylcellulose 50 – hpmc 50 (batch PJ 09012406, Colorcon) as excipients have been investigated.

Methods

Preparation of formulation

Tablets containing 20 mg of nifedipine were prepared in a light-protected environment by direct compression in a Lawes compressor (model 10) and a group of matrices and biconcave punctures with 6 mm in diameter were used. The constituents in the formulation were: nifedipine, microcrystalline cellulose, hpmc 100, hpmc 50, magnesium stearate, silicon dioxide.

Storage experiments

Tablets were put into an amber-colored glass and placed for 180 days in a special acclimatized room which was equipped with a Mecalor air conditioner operating at 40 (±2°C) and the relative humidity was kept at 75 (±5%) [25].

Dosage

The amount of nifedipine in the tablets was determined via high performance liquid chromatography (HPLC) according to [7] using PerkinElmer equipment which possessed a UV/VIS detector.

Thermal analytical tests

Nifedipine, USP standards, excipients and tablets before and after storage were measured using DSC, Mettler Toledo 822^e at atmosphere of synthetic air, with a flow rate of 50.0 mL min^{-1}, and at a heating rate of 10°C min^{-1}, between 25–350°C using aluminium crucible with a perforated lid cover. The initial mass of nifedipine and excipients was around 5 mg. The initial mass of reference standards – nifedipine nitrophenylpyridine USP, nifedipine nitrosophenylpyridine USP and nifedipine USP – was around 1 mg. For the tablet analysis ten pieces were used with an initial mass of about 50000 mg.

TG curves were obtained by the aid of Mettler Toledo TG/SDTA 851^e equipment at synthetic air atmosphere (flow rate: 50.0 mL min^{-1}, heating rate of 10°C min^{-1}) using alumina crucible in the 25–800°C temperature range. The initial sample masses were around 6 mg.

Results and discussion

Figure 1 shows the DSC curves of the nifedipine standard (Fig. 1a) and the one was used for formulation (Fig. 1b).

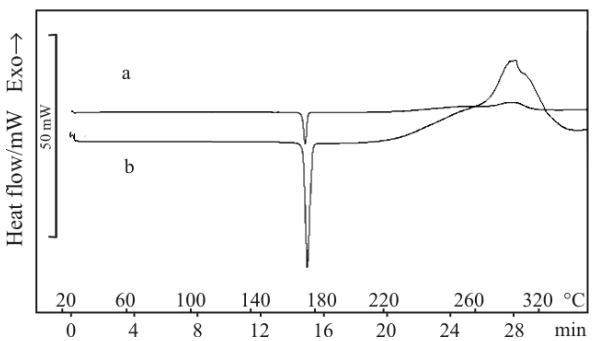

Fig. 1 DSC curves of a – nifedipine standard and b – nifedipine used for tablet making

The first endotherm effect (peak temperature is 173°C) is due to the fusion while the second, which is an exotherm one between 220–340°C is – according to the TG experiments (Fig. 2) – is representative to the thermal decomposition of nifedipine.

According to their DSC curves the thermal behavior of the two nifedipines was practically the same. Riga *et al.* reported that nifedipine has three polymorphic forms: polymorph I (melting range: 169–173°C), polymorph II (melting range: 161–163°C), and polymorph III (melting point: 150°C) [26]. Polymorph I is known as pure nifedipine and it is commercially available. Consequently, with regard to its melting point, the presently investigated nifedipine sample (Fig. 1 curve b) behaves as polymorph I.

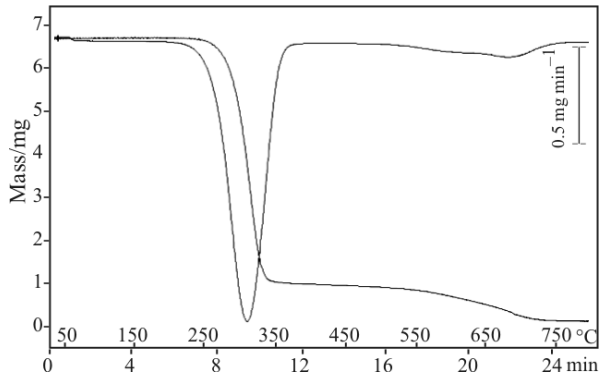

Fig. 2 TG/DTG curves of nifedipine sample

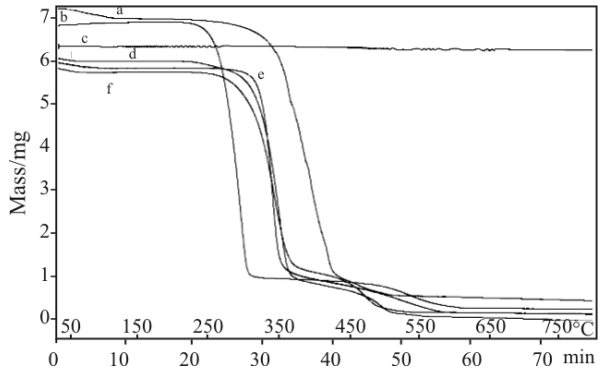

Fig. 3 TG curves of a – magnesium stearate, b – nifedipine, c – silicon dioxide, d – HPMC 50, e – microcrystalline cellulose, f – HPMC 100

In Fig. 3 the TG curves of nifedipine and the pure excipients are collected while Fig. 4 shows the TG curves of the tablets before and after storage. Their thermal decomposition ranges are summarized in Table 1.

It was found that magnesium stearate is thermally stable up to 290°C. Microcrystalline cellulose is thermally stable up to 285°C, and hpmc 50 and hpmc 100 are thermally stable up to 240°C. Silicon dioxide does not decompose in the temperature range under analysis. Nifedipine is thermally stable up to 210°C. The TG curves of the tablets before and after storage show that the formulation is thermally stable up to 210°C which corresponds well to the initial decomposition temperature of pure nifedipine.

Figure 5 shows the DSC curves of nifedipine and excipients compared to the DSC curves of the tablets before and after 180 days of storage.

DSC curves of cellulose, HPMC 100 and HPMC 50 are initially exhibited wide endotherm peaks representing dehydration starting around 40–50°C. The DSC curves of the tables show also wide endotherm peaks around 45°C probably due to dehydration of these three excipients. Magnesium stearate reveals a wide endotherm peak between

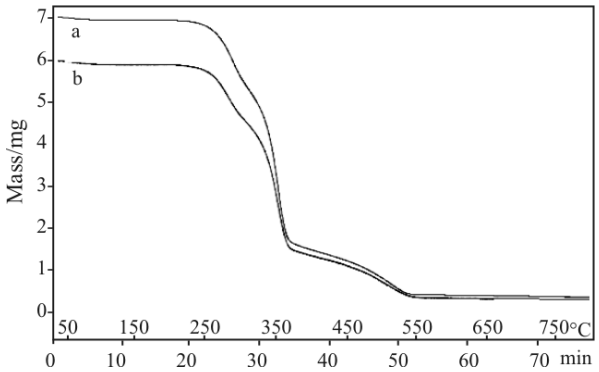

Fig. 4 TG curves of tablets a – before storage and b – after 180 days of storage

Table 1 Thermal decomposition of nifedipine and excipients

Component	Decomposition range/°C	Mass loss/%
Nifedipine	210–390	85.2
Microcrystallnie cellulose	285–350	76.3
HPMC 100	240–390	81.5
HPMC 50	240–380	86.2
Magnesium stearate	290–401	63.2
Silicon dioxide	–	0.00
Tablets (before acclimatized exposure)	215–360	77.0
Tablets (180 days after acclimatized exposure)	220–360	77.0

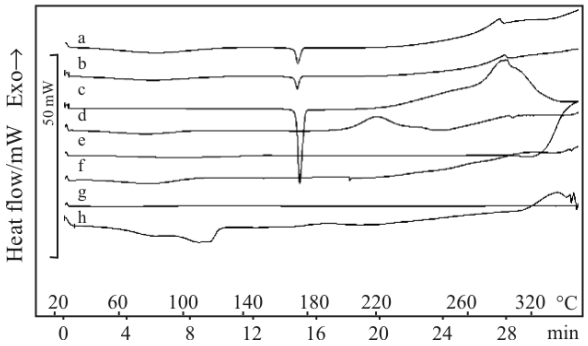

Fig. 5 DSC curves of tablet a – before storage, b – after storage, c – nifedipine, d – HPMC 50, e – microcrystalline cellulose, f – HPMC 100, g – silicon dioxide, h – magnesium stearate

45–90°C followed by another endotherm one up to 109°C. This second peak is not present in the DSC curves of the tablets probably due to the low amount of this excipient in the formulation. Silicon dioxide does not present any thermal event in the investigated temperature range.

The DSC curve of tablet before storage (Fig. 5, curve a) shows the fusion of nifedipine takes place between 170–176°C showing no alteration compared to the melting range when nifedipine is alone. Similarly to the previous statement, the thermal decomposition of nifedipine (around 309°C, Fig. 2) is not influenced by the storage. The similar thermal behavior of nifedipine alone and in its tablet denies the occurrence of any chemical interaction between nifedipine and the excipients upon tablet making as well as during its storage which is supported by the results of the HPLC analysis of tablets (Fig. 6) as well.

Besides the observed retention time (around 15 min) the result of the nifedipine content determination in the tablet after storage was 98.8 m/m%.

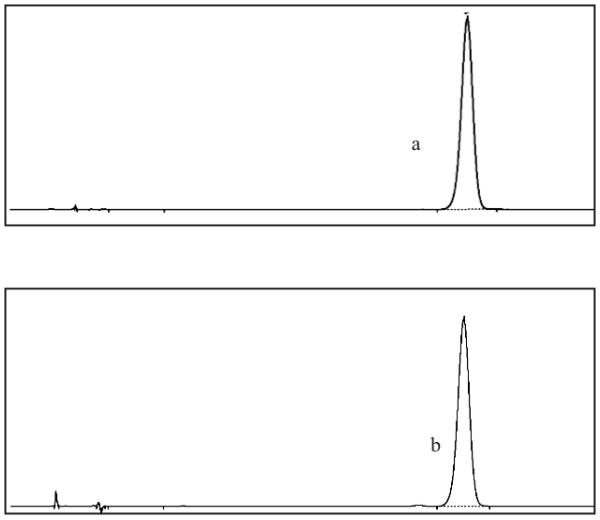

Fig. 6 HPLC chromatograms for a – tablet and b – for the standard solution

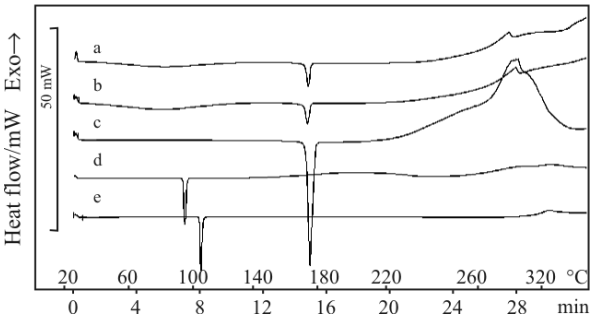

Fig. 7 DSC curves of tablets a – before and b – after storage, c – nifedipine, d – nifedipine nitrophenylpyridine, e – nifedipine nitrosophenylpyridine

Figure 7 summarizes the DSC curves of nifedipine and its degradation products, nifedipine nitrophenylpyridine, nifedipine nitrosophenylpyridine and the DSC curves of the tablets both before and after storage.

In the DSC curves endotherm peaks are visible between 103–108°C for nifedipine nitrophenylpyridine and nifedipine nitrosophenylpyridine and between 93–98°C for nitrosophenyl. Since these peaks are not present in the DSC curves of the tables, it can be concluded that no visible amount of degradation product can be present in these formulates.

Conclusions

In order to qualify a pharmaceutical formulation some parameters must be analyzed, e.g. the degree of purity of the active compound used in its production, the interaction between the drug and the excipients used for the formulation.

The investigated formulations were considered as stable ones. There were no signs of interaction between nifedipine and excipients, which supports the stability of the pharmaceutical drug in its formulation and after storage the tablets. Finally, presence of the representative degradation products of nifedipine was not detected by DSC methods.

References

1 L. S. Pescatello, B. A. Franklin, R. Fagard, W. B. Farquhar, G. A. Kelley and C. A. Ray, Med. Sci. Sports Exerc., 36 (2004) 533.
2 Sociedade Brasileira de Hipertensão, V Diretrizes Brasileiras de Hipertensão. URL: http://www.sbh.org.br/documentos/index.asp.
3 H. P. Rang, M. M. Dale and J. M. Ritter, Farmacologia, Guanabara Koogan 1997, p. 234.
4 J. L. Reid, Am. J. Med., 86 (1989) 2.
5 A. J. Man in't Veld, Calcium antagonists in hypertension. Am. J. Med., 86 (1989) 6.

6 Martindale, The Extra Pharmacopoeia, 30th Ed. London, The Pharmaceutical Press 1993, p. 374.
7 United States Pharmacopoeia and National Formulary, 2005, pp. 1377–1379.
8 L. A. Trissel, Stability of Compounded Formulations, Washington, Amer. Pharm. Assoc., 2000, pp. 440–450.
9 The Merck Index, 20th Ed. 1996, p. 6620.
10 E. B. Vadas, Stability of pharmaceutical products, A. R. Genaro, Ed., Remington's: The science and practice of pharmacy, 20th Ed., Easton Pennsylvania, Mack Publishing Company 2000, pp. 986–994.
11 H. C. Ansel, N. G. Popovich and L. V. Allen, Pharmaceutical Dosage Forms and Drug Delivery Systems, Williams & Wilkins 1995, p. 182.
12 K. A. Connors, G. L. Amidon and V. L. Stella, Chemical stability of pharmaceuticals, A handbook for pharmacists, New York, John Wiley 1986, p. 847.
13 S. Casadio, Tecnologia Farmacêutica, 2ª Ed., Milano, Cisalpino – Goliardica 1972, pp. 1668–1702.
14 D. B. Wiest, S. S. Garner, L. R. Pagacz and V. Ziegler, Am. J. Hosp. Pharm., 49 (1992) 1467.
15 D. Giron, J. Therm. Anal. Cal., 68 (2002) 335.
16 B. D. Glass, Cs. Novák and M. E. Brown, J. Therm. Anal. Cal., 77 (2004) 1013.
17 S. D. Clas, C. R. Dalton and B. C. Hancock, Pharm. Sci. Technol., 2 (1999) 311.
18 V. A. Drebushchak, T. P. Shakhtshneider, S. A. Apenina, A. S. Medvedeva, L. P. Safronova and V. V. Boldyrev, J. Therm. Anal. Cal., 86 (2006) 303.
19 D. Kiss, R. Zelkó, Cs. Novák and Zs. Éhen, J. Therm. Anal. Cal., 84 (2006) 447.
20 M. A. S. Silva, R. G. Kelmann, T. Foppa, A. P. Cruz, C. D. Bertol, T. Sartoril, A. Granada, F. Carmignan and S. Murakami, J. Therm. Anal. Cal., 87 (2006) 463.
21 T. Hekmara, G. Regdon, P. Sipos, I. Erõs and H. Pintye-Hódi, J. Therm. Anal. Cal., 86 (2006) 287.
22 M. Fujisawa, T. Kimura, J. Therm. Anal. Cal., 85 (2006) 589.
23 H. Aki, Y. Nakashima, Y. Kawasaki and T. Niiya, J. Therm. Anal. Cal., 85 (2006) 685.
24 L. C. S. Cides, A. A. S. Araújo, M. Santos-Filho and J. R. Matos, J. Therm. Anal. Cal., 84 (2006) 441.
25 Resolução RE no. 1, de 29 de julho de 2005 da ANVISA, Publicado no D.O.U. – Diário Oficial da União; Poder Executivo, de 01 de agosto de 2005.
26 A. Riga, C. D. S. Kellen, M. L. A. Gonçalves and S. A. Kenneth, Thermal-Analytical Characterization of a Polymorphic Drug Nifedipine, Workbook of V CBRATEC 2006, p. 405.

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