INDAPAMIDE SLOW RELEASE TABLET PREFORMULATION: INTERACTIONS WITH EXCIPIENTS ANALYSIS

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Abstract

Indapamide (IDP) is a medical substance from the category of diuretics related with tiazides, currently used for the treatment of essential hypertension.

A pharmaceutical formulation is considered appropriate when no interactions medicament-excipient or excipient-excipient appears.

The aim of this work was to investigate the compatibility of IDP with the pharmaceutical excipients used in slow release tablets preformulations (1.5 mg/cp), by using thermoanalytical techniques (differential scanning calorimetry (DSC) and thermogravimetry (TG)), X-ray powder diffraction (XRPD) method and Fourier transform infrared spectroscopy (FTIR).

Thermal (DSC, TG), XRPD and FTIR methods were employed to evaluate the behaviour of IDP and excipients used in preformulation (lactose monohydrate, hydroxipropylmethylcellulose (HPMC, hypromellose), colloidal silicon dioxide (aerosil), magnesium stearate), and also of the corresponding indapamide - each excipient alone physical binary mixtures.

Thermoanalytical results (DSC and TG) supported as absence of incompatibility between indapamide and excipients in the physical mixtures. XRPD patterns and FTIR spectra sustained these results, because they did not show evidence on interaction in the solid state.

Based on the results supplied by DSC/TG, XRPD and FTIR, all the excipients were found to be compatible with IDP, so they can be used in formulation of the slow release tablets.

Keywords: Indapamide, slow release tablets, compatibility, DSC, TG, XRPD, FTIR.

PREFORMULAREA COMPRIMATELOR DE INDAPAMID CU CEDARE ÎNTÂRZIATĂ: ANALIZA INTERACȚIUNII CU EXCIPIENȚII

Rezumat

Indapamidul (IDP) este o substanţă medicamentoasă din categoria diureticelor înrudite cu tiazidele, utilizată în tratamentul hipertensiunii arteriale esenţiale.

O formulare este considerată a fi corespunzătoare în lipsa interacţiunilor de tipul medicament/excipient sau excipient/excipient.

Scopul acestui studiu a fost analiza compatibilităţii dintre IDP şi excipienţii utilizaţi în etapa de preformulare a comprimatelor cu cedare întârziată (1,5 mg/cp), folosind tehnicile de analiză termică (analiza calorimetrică diferenţială (DSC), analiza termogravimetrică (TG)), precum şi tehnica difracţiei de raze X (XRPD) şi spectroscopia în infraroşu cu transformantă Fourier (FTIR).

Evaluarea comportamentului IDP, al excipienţilor folosiţi în preformulare

(lactoză monohidrat, hidroxipropilmetilceluloză (HPMC, hipromeloză), dioxid de siliciu coloidal (aerosil), stearat de magneziu), precum şi al amestecurilor binare indapamid-excipienţi, s-a realizat folosind metodele termice (DSC, TG), metodele XRPD şi FTIR.

Rezultatele termoanalitice (DSC şi TG) înregistrate demonstrează absenţa incompatibilităţilor dintre IDP şi excipienţi în cazul amestecării fizice a acestora. Difractogramele XRPD, precum şi spectrele FTIR înregistrate, susţin aceste rezultate, pentru că nici în acest caz nu se înregistrează interacţiuni IDP/excipienţi.

Pe baza rezultatelor DSC/TG, XRPD şi FTIR înregistrate se poate concluziona că toţi excipienţii folosiţi în etapa de preformulare sunt compatibili cu IDP, astfel încât ei pot fi utilizaţi în continuare pentru obţinerea comprimatelor cu cedare întârziată.

Cuvinte cheie: Indapamida, comprimate cu cedare întârziată, compatibilitate, DSC, TG, XRPD, FTIR.

Introduction

Indapamide (Fig. 1), 4-chloro-N-(2-methyl-2,3-dihydroindol-1-yl)-3-sulfamoyl-benzamide, is a thiazide-type diuretic drug used in the treatment of essential hypertension, as well as edema caused by congestive heart failure. IDP has a dual mechanism of action: diuretic effect at the level of the distal tubule in the kidney and a direct vascular effect, both of which contribute to the antihypertensive efficacy of the drug [1,2].

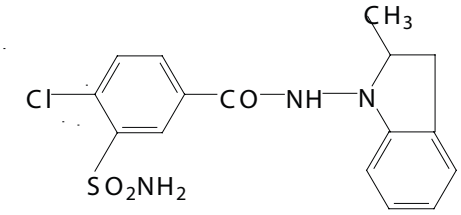

Fig. 1. Chemical structure of indapamide.

Information on the physical and/or chemical interaction drug/excipient is very important in the development of a new drug formulation. Careful selection of the excipients, integral components of all pharmaceutical products, is essential for the development of stable and effective dosage forms. Excipients are often regarded as "inert", although it is known that they can interact with drugs, giving rise to changes in their stability, solubility, dissolution rate and bioavailability. Therefore, in order to accelerate drug development, it would be very useful to obtain knowledge rapidly about potential physical and chemical interactions between drugs and excipients [3,4].

A formulation is considered appropriate when no interactions medicament-excipient or excipient-excipient appears. Preformulation studies, aimed at the assessment of drug-excipient compatibility and identification of suitable dosage form composition, are recognized as an essential phase of the development process [4,5].

Thermal analysis is one of the most frequently used instrumental techniques in the pharmaceutical researches to solve technological problems in the pre-formulation stages of solid dosage forms. Differential scanning calorimetry (DSC) [6] has shown to be an important tool at the outset of any solid dosage form preformulation study, to quickly obtain information about possible interactions among the formulation components, according to appearance, shift or disappearance of endothermic or exothermic peaks and/or variations in the corresponding enthalpy values in thermal curves of drug-excipient mixtures [3,4].

The aim of this work was to evaluate the compatibility between IDP and some pharmaceutical excipients, using thermoanalytical techniques (TG/DSC) with the support of X-ray powder diffraction (XRPD) [6] and Fourier transform infrared spectroscopy (FTIR) [6].

Materials and Method

Materials

IDP was purchased from Pharmazell, Germany (lot number V003). The excipients examined were: lactose monohydrate (Meggle, Germany), hydroxipropylmethylcellulose (HPMC, hypromellose) (JRS Pharma, Germany), colloidal silicon dioxide (aerosil) (Degusa, Germany), magnesium stearate (Union Derivan, Spain).

Physical binary mixture IDP: each excipient alone = 1:1 (w/w) ratio obtained by grinding in the agat mortar were also studied.

Equipments and methods

All analyses were performed using a sample of IDP, single excipients and binary mixtures prepared as described above.

The excipients were selected on the characteristic of the drug and its compatibility with other components. Lactose monohydrate is used in pharmaceutical formulations (tablets and capsules) as diluent for direct compression. In oral products hypromellose is primarily used as a tablet binder, in film coating, and as a matrix for use in slow release tablet formulations. Magnesium stearate is used as lubricant in the tablet making since it decreases friction between the tablet surfaces and dies wall during the ejection process. The colloidal silicon dioxide, because of its small particle

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size and large specific surface area provides a desirable flow characteristic which is exploited to improve the flow properties of dry powders in several processes, like tablet making [7].

Differential scanning calorimetry (DSC)

DSC curves were obtained using a Mettler Toledo DSC 822 apparatus. Samples of individual substances as well as binary mixtures were weighed (Mettler Toledo balance) directly in pierced aluminum pan (2-4 mg), and scanned between 25 and 400°C with a heating rate of 10°C/min under dynamic N_2 atmosphere (flow rate: 50 ml/min).

Thermogravimetric analysis (TG)

TG curves were obtained with a TGA/SDTA 851e thermobalance. The samples were weighed (Mettler Toledo balance) directly in alumina pans (approximately 5 mg), and scanned between 25 and 800°C with a heating rate of 10°C/min under dynamic N_2 atmosphere (50 ml/min).

X-ray powder diffraction (XRPD)

X-ray diffraction patterns were obtained on Bruker D8 Advance equipment, with tube of CuKα1, voltage of 40 kV and current of 40 mA, in the range of 3–65 (2θ), using the powder XRD method.

Fourier transform infrared spectroscopy (FTIR)

Fourier transform infrared (FTIR) spectra were recorded on a Jasco FT IR-6100 spectrometer using KBr discs with a 2cm^{-1} resolution in the range of 4000–400 cm^{-1}.

Results and discussions

The thermoanalytical curves (DSC and TG) of IDP are illustrated in Fig. 2. The DSC diagram of IDP showed a very broad endothermic effect between 74 and 102°C corresponding to the dehydration process followed by its melting endothermic event between 161 and 174°C with a maximum at 168°C (ΔH_{fusion} = –159.35mJ), and finally by a degradation process, which took place at around 240°C. The TG curve exhibited 94.245% of mass loss between 211 and 700°C due to the decomposition of IDP.

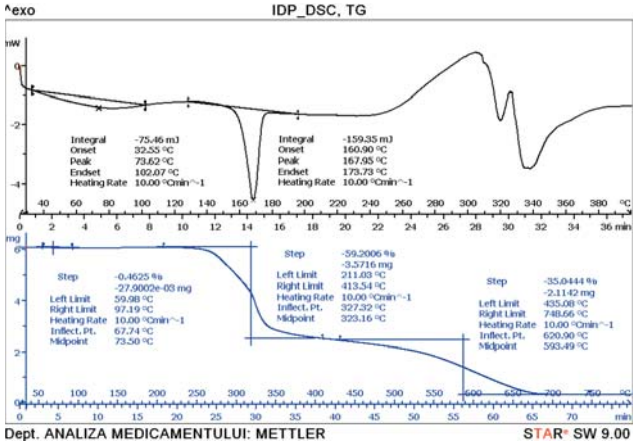

Fig. 2. DSC and TG curves of IDP.

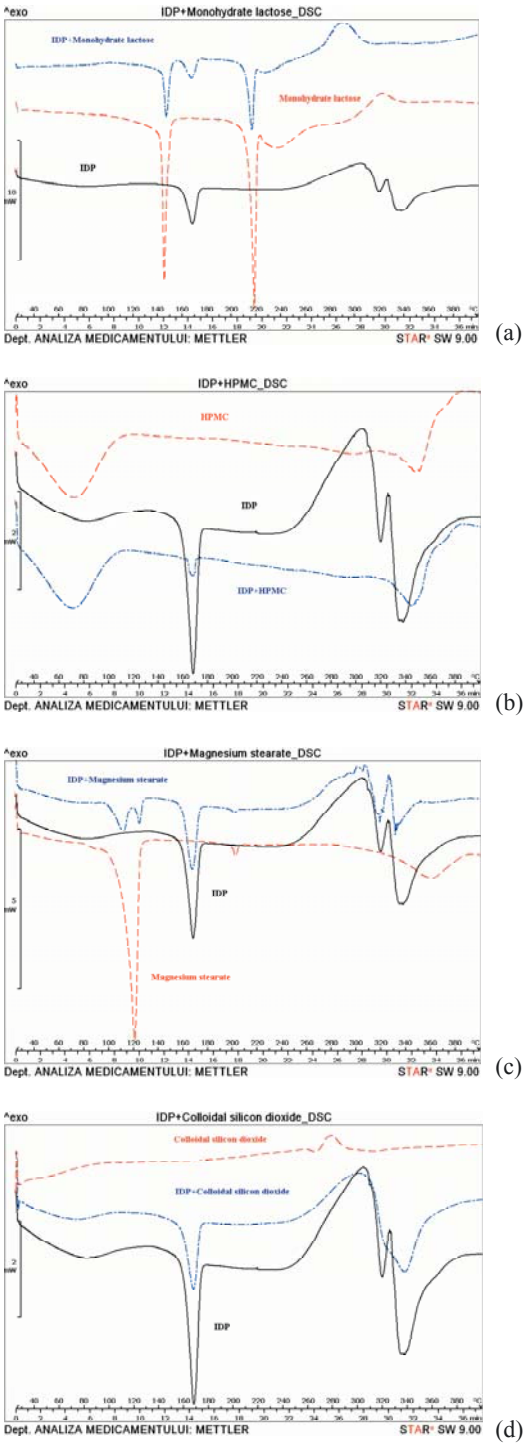

Fig. 3. DSC and TG curves of IDP and 1:1 physical mixtures of IDP with: lactose monohydrate (a), HPMC (b), magnesium stearate (c), colloidal silicon dioxide (d).

Thermal behavior of physical mixtures of IDP/lactose monohydrate is illustrated in Fig. 3a. The DSC curve presents an endothermic peak corresponding to the dehydration process of lactose in a temperature around 144°C, followed by the endothermic melting of IDP which was observed at the same value of the temperature

(approximately 168°C) as it can be seen in his own DSC diagram. After these events, an endothermic peak at 217°C represents the fusion followed by immediate thermal decomposition of lactose and of IDP. In the TG curves a Δm = 61.67% mass loss was observed between 196 and 502°C. The DSC and TG curves of the physical mixtures demonstrated that they represent only the sum of the individual components thermograms, so it can be concluded that there are no alterations in the thermoanalytical profile of the drug in case of mixing with lactose monohydrate.

DSC curve of IDP and HPMC (Fig. 3b) presents an endothermic peak between 45 and 100°C due to the dehydration, followed by the endothermic peak corresponding to the fusion of IDP at 167°C, and the decomposition up to 250°C. In the TG diagram the dehydration is represented by a mass loss of 3.21% and the decomposition by a mass loss of 81%.

DSC curve of IDP and magnesium stearate (Fig. 3c) presented two endothermic events in the 100–127°C temperature range which is characteristic for the dehydration process of magnesium stearate, followed by the endothermic peak of IDP melting at 167°C. The DSC thermogram contains also the melting endotherm of magnesium palmitate (impurity in magnesium stearate), which appears at 203°C as in the DSC single excipient diagram. The decomposition of the two substances begins at 220°C and it is represented in the TG curve as a mass loss of 71%.

The thermal behavior of IDP and colloidal silicon dioxide can be observed in Fig. 3d. The melting peak of IDP appears at the same value of temperature (167°C). The binary mixture did not show incompatibility between these substances.

The TG curves of IDP and of IDP/excipient binary mixtures are presented in Fig. 4. The thermoanalytical data of IDP and IDP in drug/excipient physical mixtures are summarized in Table I.

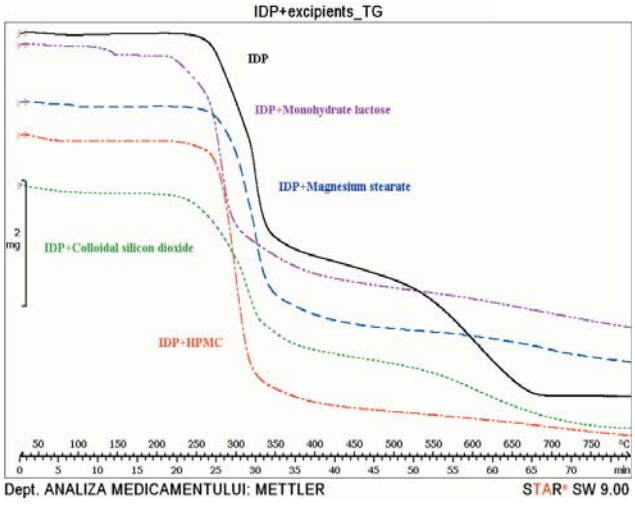

Fig. 4. TG curves of IDP and IDP 1:1 physical mixtures with: monohydrate lactose, HPMC, magnesium stearate, colloidal silicon dioxide.

Table I. Thermoanalytical data of IDP and IDP in drug/excipient physical mixtures.

Samples	DSC		Enthalpy (fusion)/ mJ/g
	T_{onset} (fusion)/ mJ/g	T_{peak} (fusion)/ mJ/g	
Indapamide (IDP)	160.90	167.95	159.35
Lactose monohydrate	160.30	167.45	66.87
Hypromellose (HPMC)	156.80	167.10	59.26
Magnesium stearate	159.53	167.34	107.06
Colloidal silicon dioxide	158.78	167.72	77.98

The thermal profiles of the 1:1 (w/w) physical mixtures of IDP with each of excipients chosen in the preformulation stage substantially reflected the thermal features of the respective individual components. The slight lowering and/or broadening of drug melting endotherm, or the changes that appear in the drug melting enthalpies may be attributed to the mixing process, which lowers the purity of each component in the mixture. No problem of compatibility could therefore be detected using DSC and TG methods.

In order to obtain more information and to support DSC and TG results X-ray diffraction studies were also performed.

IDP has a crystalline structure. The 2θ angle values of the more intense peaks for IDP are 2θ=7.40, 10.74, 13.97, 14.77 and 21.82. In Fig. 5, the X-ray patterns of IDP and of the IDP/excipients binaries are shown. The diffraction peaks of IDP remained unaltered in the physical mixtures. The IDP/excipients mixtures diffraction patterns represents only a sum of the individual components X-ray patterns. It could be concluded that XRPD methods sustains the thermal results, showing compatibility between IDP and the used excipients.

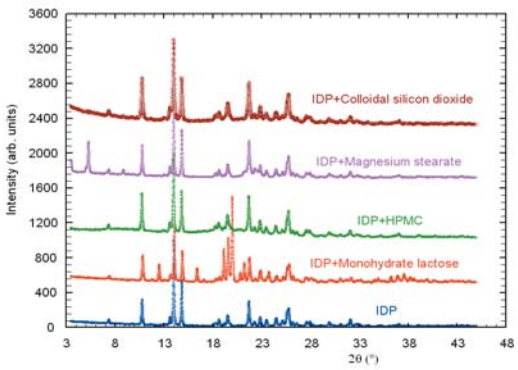

Fig. 5. X–ray diffraction patterns of IDP and 1:1 physical mixtures of IDP with: monohydrate lactose, HPMC, magnesium stearate and colloidal silicon dioxide.

The next step of the present study was represented by the analyze of the FTIR spectra of IDP, of the used pharmaceutical excipients and of their binary mixtures in order to identify a possible chemical interaction between them.

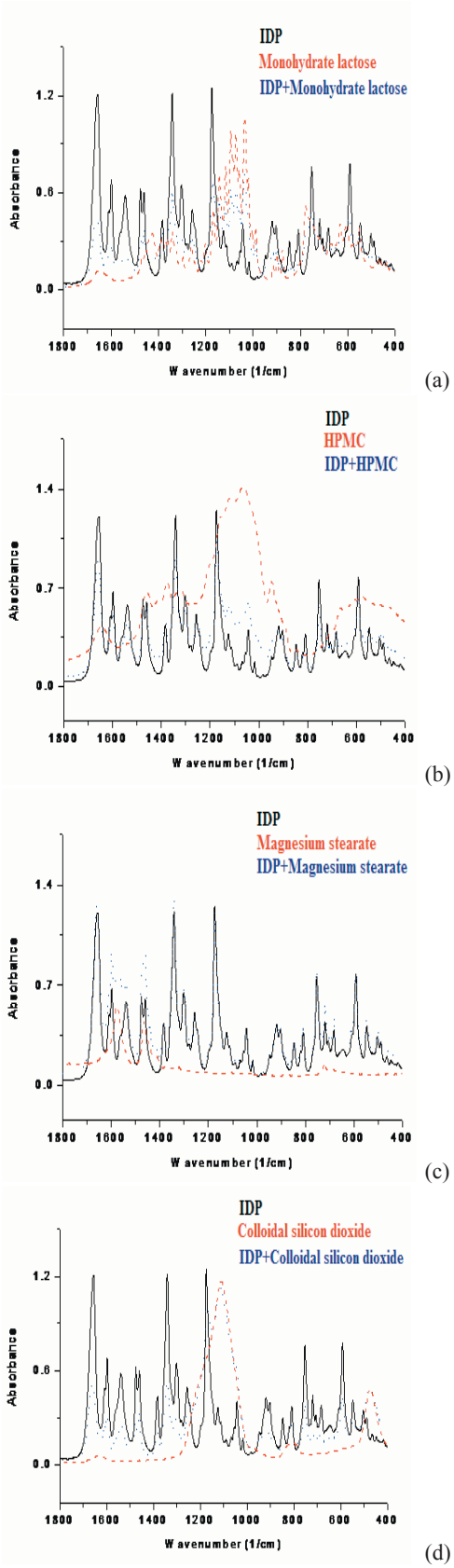

Fig. 6. FTIR spectra of IDP and 1:1 physical mixtures of IDP with: monohydrate lactose (a), HPMC (b), magnesium stearate (c) and colloidal silicon dioxide (d).

FTIR spectrum of IDP is presented in each figure together with single excipient FTIR spectrum and the binary mixtures of IDP and each excipient. The FTIR spectra are showed in Fig. 6.

Two sharp absorption bands at 3654 and 3507 cm^{-1} for hydroxyl functional group of water (located in FTIR spectrum of IDP) are observed in IDP commercial form spectrum [1]. These frequencies are not shifted in binary IDP-lactose monohydrate mixtures (Fig. 6a) [8].

Hypromellose (HPMC) exhibit characteristic bands at ~3400 cm^{-1} (-OH stretching vibration), 2939 cm^{-1} (C-H stretching vibration) and 1114 cm^{-1} (-C-O-C- stretching vibration (Fig. 6b) [9].

Magnesium stearate presents specific absorptions in the 2920-2851 cm^{-1} spectral range, due to the CH_2-CH_3 part of the molecule [10,11]. The other bands located at 1575 and 1461 cm^{-1} are due to the COO- group (Fig. 6c).

In the colloidal silicon dioxide FTIR spectrum (Fig. 6d) the shoulder of about 3468 and 3156 cm^{-1} can be attributed to O-H stretching vibration modes of hydrogen bonded to OH of polymeric association and hydrogen bonded to OH intermolecular or chelate compounds. At medium frequencies the band at around 1640 cm^{-1} corresponds to H-O-H bend of crystallization water. The symmetric stretching Si-O vibration of silica can be ob-served at around 1100 cm^{-1}. At lower frequencies the bands at around 820 and 470 cm^{-1} corresponds to asymmetric Si-O stretching and Si-O bending modes of silica in that order.

FTIR spectra showed that the characteristics bands of indapamide or each excipient alone were not altered in binary mixtures indicating no interactions between IDP and selected excipients as shown in Fig. 6.

Conclusions

The obtained results underline the utility of thermal analysis (DSC, TG), XRDP and FTIR methods as fast screening tools in the final stage of a preformulation compatibility study. Based on our results, obtained using these methods, all mentioned excipients were found to be fully compatible with IDP. We can conclude that the selected excipients can be used for the indapamide slow release tablets (1.5 mg/cp) industrial formulation.

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