

COMPATIBILITY STUDIES OF INDAPAMIDE/PHARMACEUTICAL EXCIPIENTS USED IN TABLET PREFORMULATION

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Abstract

Indapamide (IDP) is a non-thiazide sulphonamide diuretic drug, currently used for the treatment of essential hypertension.

A pharmaceutical formulation is considered appropriate when no interactions drug-excipient or excipient-excipient occur.

The purpose of the present work was to study the compatibility of IDP with the pharmaceutical excipients employed in immediate release tablets preformulations (2.5 mg/cp), by using thermoanalytical techniques (differential scanning calorimetry (DSC) and thermogravimetry (TG)) with the support of X-ray powder diffraction (XRPD) and Fourier transform infrared spectroscopy (FTIR).

In this respect, thermal analysis (DSC, TG), XRPD and FTIR methods were employed to evaluate the behaviour of IDP and excipients used in formulation (lactose monohydrate, microcrystalline cellulose, sodium amidoglycolate, polyvinylpyrrolidone, colloidal silicon dioxide (aerosil), magnesium stearate), but also its corresponding physical binary mixtures.

FTIR, thermal analysis (DSC, TG) and XRPD methods applied to the mentioned physical mixtures did not show evidence of interactions in the solid state.

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

Rezumat

Indapamidul (IDP) este o substanță medicamentoasă, utilizată în tratamentul hipertensiunii arteriale esențiale.

Una din condițiile unei formulări corespunzătoare este absența interacțiunilor de tipul medicament/excipient sau excipient/excipient.

Scopul acestui studiu a fost analiza compatibilității dintre IDP și excipienții utilizați în etapa de preformulare a comprimatelor cu cedare imediată (2,5mg/cp), folosind tehnicile de analiză termică (analiza calorimetrică diferențială (DSC), analiza termogravimetrică (TG)) precum și tehnica difracției de raze X (XRPD) și spectroscopia în infraroșu cu transformantă Fourier (FTIR).

În acest sens a fost studiat comportamentul termic (DSC și TG) și spectral (XRPD și FTIR) al IDP, al excipienților utilizați în formularea comprimatelor (lactoza monohidrat, celuloza microcristalină, amidonglicolat de sodiu, polivinilpirolidona, dioxid de siliciu coloidal (aerosil), stearat de magneziu), precum și al amestecurilor binare indapamid/excipienți.

Rezultatele termoanalitice (DSC și TG) înregistrate demonstrează absența incompatibilităților dintre IDP și excipienți în cazul amestecării fizice a acestora. Spectrele FTIR precum și difractogramele XRPD înregistrate susțin aceste rezultate, pentru că nici în acest caz nu se înregistrează interacțiuni IDP/excipienți.

Pe baza rezultatelor DSC/TG, XRPD și FTIR înregistrate se poate concluziona că toți excipienții folosiți în etapa de preformulare sunt compatibili cu IDP, astfel încât ei pot fi utilizați pentru obținerea comprimatelor cu cedare imediată.

Keywords: indapamide, compatibility, differential scanning calorimetry (DSC), thermogravimetry (TG), X-ray powder diffraction (XRPD), Fourier transform infrared spectroscopy (FTIR)

Introduction

Indapamide (Figure 1), 4-chloro-N-(2-methyl-2,3-dihydroindol-1-yl)- 3-sulfamoyl-benzamide, is a non-thiazide sulfonamide diuretic drug, primarily used in the treatment of hypertension as well as oedema caused by congestive heart failure. It acts by preventing the kidney from reabsorbing salt and water that are intended for being eliminated in the urine. The loss of salt from the muscle causes miorelaxation and resulting in lowering blood pressure [1].

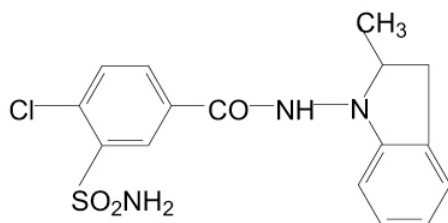


Figure 1

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. The successful formulation of a stable and effective solid dosage form depends on a careful selection of the excipients. Although

excipients traditionally have been thought of as being inert, they have shown possible interactions with the drug, preventing its absorption and bioavailability [2].

A formulation is considered appropriate when no interactions drug-excipient or excipient-excipient occur. In this sense, devising a quick and accurate method to test and select the best excipients for stable dosage forms constitute, a real achievement in the pre-formulation stage [3].

Thermal analysis is one of the most frequently used instrumental techniques on pharmaceutical researches to solve technological problems in the pre-formulation stages of solid dosage forms. In particular, differential scanning calorimetry (DSC) [4] has been proposed as a rapid method for evaluating physico-chemical interactions between the formulation components and therefore selecting excipients with suitable compatibility [2].

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) [4] and Fourier transform infrared spectroscopy (FTIR) [4].

Materials and Methods

Materials

IDP was purchased from Pharmazell, Germany (lot number V003). The excipients examined were: lactose monohydrate (Meggle, Germany), microcrystalline cellulose and sodium starch glycolate (JRS Pharma, Germany), polyvinylpyrrolidone (BASF, Germany), colloidal silicon dioxide (aerosil) (Degusa, Germany), magnesium stearate (Union Derivan, Spain).

Physical binary mixture IDP: each excipient alone = 1:1 mass/mass ratio obtained by grinding in the agate mortar were also studied.

Equipments and methods

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

The selection of adequate excipients for the formulation was based on the characteristics of the drug and its compatibility with other components. Lactose monohydrate and microcrystalline cellulose are widely used in pharmaceutical formulations (tablets and capsules) as diluents. The first one can be used for direct compression. Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. Polyvinyl pyrrolidone (PVP) is a synthetic colloid, water

soluble and diverse organic solvent, having a high viscosity and the capacity to form complexes. Magnesium stearate is used as lubricant in the tablet formulation since it decreases friction between the tablet surface and die-wall during the ejection process. The colloidal silicon dioxide, because of its small particle 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 manufacturing [5].

Differential scanning calorimetry (DSC)

DSC curves were obtained in a Mettler Toledo DSC 822 cell using aluminum crucibles with about 2mg of samples, under dynamic N₂ atmosphere (flow rate: 50 mL/min) and at a heating rate of 10°C/min in the temperature range 25 - 400°C.

Thermogravimetric analysis (TG)

TG curves were obtained with a TGA/SDTA 851e thermobalance in the temperature range of 25–800°C, using platinum crucibles with approximately 5mg of sample, under dynamic N₂ atmosphere (50mL/min) and at a heating rate of 10°C/min.

X-ray powder diffraction (XRPD)

For characterization of crystallinity, X-ray diffraction patterns were obtained on Bruker D8 Advance equipment, with tube of CuK α 1, voltage of 40kV and current of 40mA, in the range 3-65 (2 θ), 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 4000–400cm⁻¹.

Results and Discussion

The thermoanalytical curves (DSC and TG) of IDP are illustrated in Fig. 2. The DSC curve of IDP showed a first endothermic event between 161 and 174°C ($\Delta H_{\text{fusion}} = -159.35\text{mJ}$), with a melting temperature of $T_{\text{onset}} = 161^\circ\text{C}$. The TG curve exhibited 94.245% of mass loss between 211 and 700°C due to the decomposition of IDP.

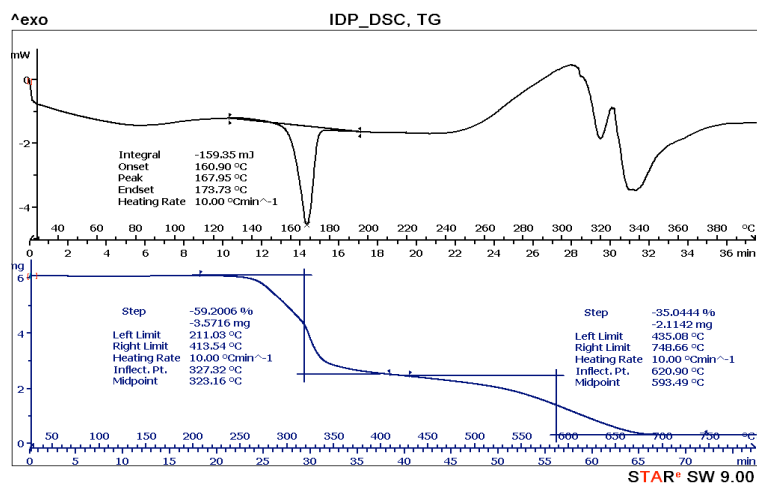


Figure 2

Differential scanning calorimetry (DSC), thermogravimetry (TG) curves of IDP

Thermal behaviour of physical mixtures of IDP and lactose monohydrate is illustrated in Fig. 3. The DSC curve presents an endothermic peak corresponding to the dehydration process of lactose at a temperature around 144°C. In the 161°C range it was observed the endothermic peak due to the melting of IDP. After this, an endothermic peak at 217°C represents the fusion followed by immediate thermal decomposition of lactose. In the TG curves a $\Delta m = 61.67\%$ mass loss was observed between 196 and 502°C. The DSC and TG curves of the physical mixtures demonstrated that there are no alterations in the thermoanalytical profiles of the drug.

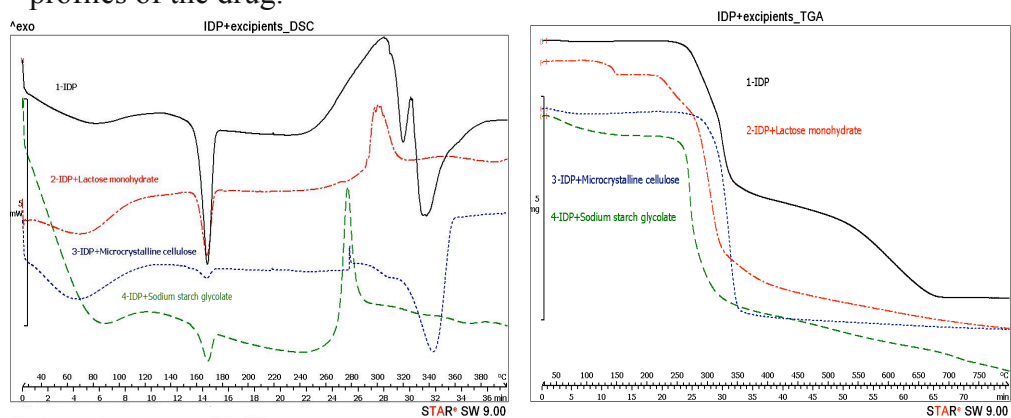


Figure 3

DSC and TG curves of IDP and 1:1 physical mixtures (IDP, lactose monohydrate, microcrystalline cellulose, sodium starch glycolate)

DSC curve of IDP and microcrystalline cellulose present an endothermic peak due to the dehydration of the two substances followed by the endothermic peak corresponding to the fusion of IDP at 160°C (Fig. 3). The TG of the 1:1 mixture exhibited 86.3171% of mass loss between 222 and 505°C due to the decomposition of IDP and microcrystalline cellulose (Fig. 3).

DSC curve of IDP and sodium starch glycolate presented the melting peak of IDP at approximately the same value of temperature (160°C), and the TG curve showed a $\Delta m=58\%$ mass loss observed between 215 and 433°C (Fig. 3).

The DSC curve of the physical mixture IDP with PVP (Fig. 4) exhibited the characteristic IDP fusion peak. The TG curve (Fig. 4) showed that the sample was stable up to 300°C, followed by thermal decomposition, with a corresponding mass loss of 82.2496%.

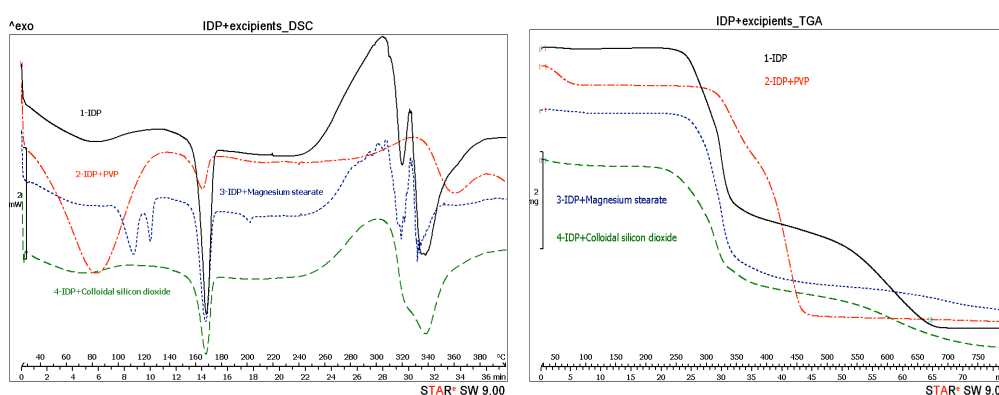


Figure 4

DSC and TG curves of IDP and 1:1 physical mixtures (IDP, PVP, magnesium stearate, colloidal silicon dioxide)

DSC curve of IDP and magnesium stearate (Fig. 4) 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 (160°C).

The thermal behaviour can be observed in Fig. 4, the binary mixture of IDP and colloidal silicon dioxide showing no incompatibility between these substances.

All the thermic profiles of mixtures can be considered as a superposition of DSC and TG curves of pure IDP and excipients, as a proof of compatibility between IDP with the used excipients.

The results obtained from the DSC curves of binary mixtures are summarized in Table I.

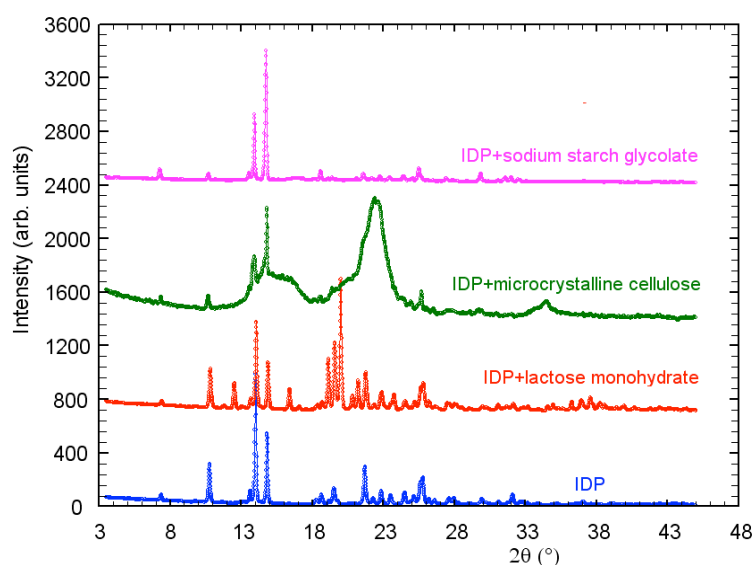
Table I

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
Microcrystalline cellulose	158.47	167.27	15.47
Sodium starch glycolate	159.75	168.15	38.54
Polyvinylpyrrolidone (PVP)	154.81	164.76	39.29
Magnesium stearate	159.53	167.34	107.06
Colloidal silicon dioxide	158.78	167.82	77.98

X-ray diffraction studies were then performed, in order to obtain more information to support DSC and TG results.

The studied drug has a crystalline structure. The 2θ angle values of the more intense peaks for IDP are $2\theta=10.74$, 13.97 and 14.77 . In figures 5 and 6, the X-ray diffractograms of IDP and of the binary mixtures are shown. According to our experience, XRPD methods showed compatibility between IDP and the used excipients since the diffraction peaks of IDP remained unaltered within the physical mixtures.

**Figure 5**

X-ray diffraction spectra of IDP and 1:1 binary mixtures of IDP: lactose monohydrate, microcrystalline cellulose and sodium starch glycolate

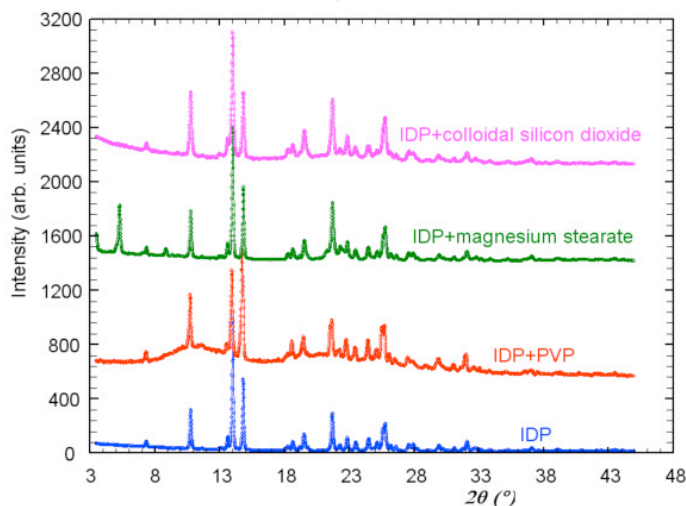


Figure 6

X-ray diffraction spectra of IDP and 1:1 binary mixtures of IDP: PVP, magnesium stearate and colloidal silicon dioxide

The subsequent step of the present study was to analyze 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.

FTIR spectrum of IDP is presented in each figure together with the binary mixtures of IDP and each excipient. The FTIR spectra are showed in figures 7 and 8.

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

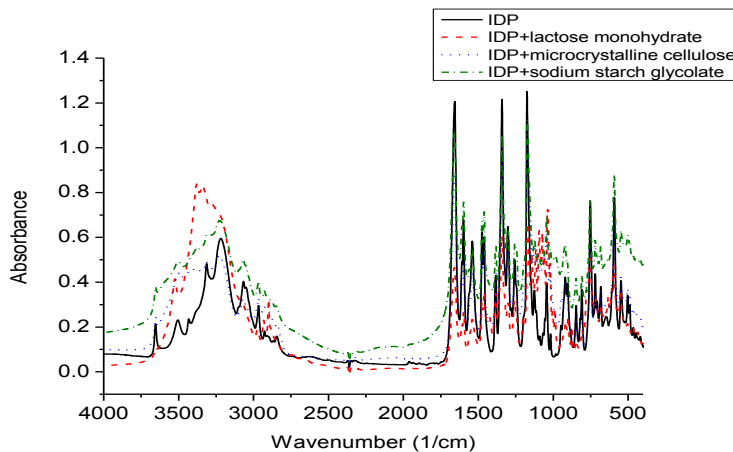


Figure 7

FTIR spectra of IDP and 1:1 physical mixtures (IDP, lactose monohydrate, microcrystalline cellulose, sodium starch glycolate)

Microcrystalline cellulose exhibited characteristic bands at $\sim 3400\text{cm}^{-1}$ (-OH stretching vibration), 2939cm^{-1} (C-H stretching vibration) and 1114cm^{-1} (-C-O-C- stretching vibration).

FTIR spectrum of PVP displayed a broad peak at about $3000\text{--}3700\text{cm}^{-1}$ due to O-H stretching vibrations of absorbed water. In PVP's FTIR spectrum there is also a strong band for C=O at 1660cm^{-1} , a wide strong band due to -OH bending vibration and the bands in the $670\text{--}730\text{cm}^{-1}$ spectral domain.

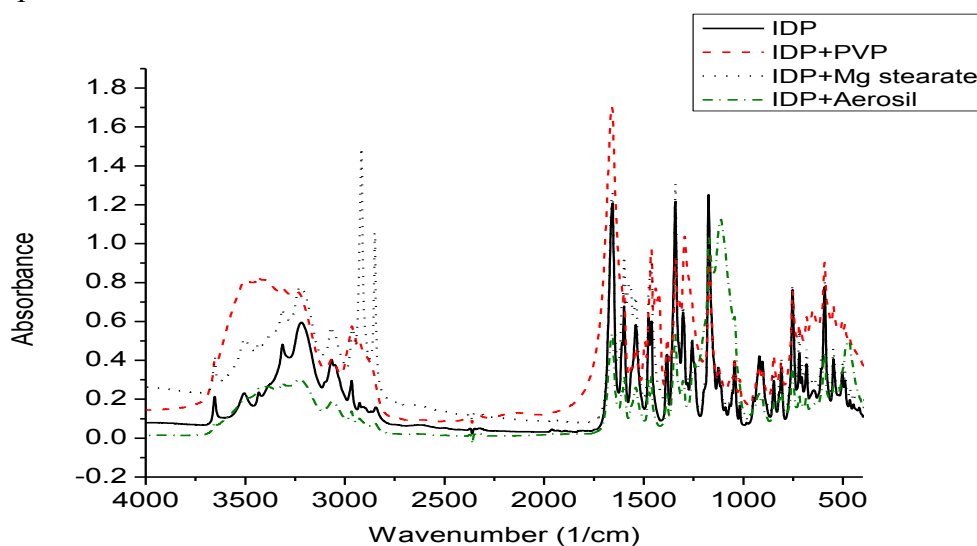


Figure 8

FTIR spectra of IDP and 1:1 physical mixtures (IDP, PVP, magnesium stearate, colloidal silicon dioxide)

Magnesium stearate presents specific absorptions in the $2920\text{--}2851\text{cm}^{-1}$ spectral range, due to the $\text{CH}_2\text{--CH}_3$ part of the molecule. The other bands located at 1575 and 1461cm^{-1} are due to the COO^- group.

In the colloidal silicon dioxide FTIR spectrum the shoulder of about 3468 and 3156cm^{-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 1640cm^{-1} corresponds to H-O-H bend of crystallization water. The symmetric stretching Si-O vibration of silica can be observed at around 1100cm^{-1} . At lower frequencies the bands at around 820 and 470cm^{-1} correspond to asymmetric Si-O stretching and Si-O bending modes of silica in that order.

FTIR spectra showed that the characteristic bands of indapamide or each excipient alone were not altered in binary mixtures indicating no interactions between IDP and the selected excipients as shown in Figures 7 and 8.

Conclusions

The results demonstrated the applicability of FTIR, thermal analysis (DSC, TG) and XRPD methods as fast screening tools to check compatibility in early stages of a preformulation process. Based on our results, all mentioned excipients were found to be fully compatible with IDP. We can conclude that the selected excipients can be further used for formulating indapamide immediate release tablets (2.5mg/cp).

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Manuscript received: April 10th 2011