Interactions Analysis between Furazolidone and Excipients used in Pharmaceutical Forms

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Furazolidone, 3-(5-Nitrofurfurylidineamino)-2-oxazolidinone, is a synthetic nitrofuran derivative, therapeutically effective as a bactericidal agent. Excipients are important components of pharmaceutical formulations and they can take an active part in the improvement of the characteristics of the pharmaceutical formulations. In order to investigate the possible interactions between furazolidone and excipients used in tablets formulations, for the studies of compatibility the differential scanning calorimetry (DSC) were used, completed by X-ray powder diffraction (XRPD) and Fourier transform infrared spectroscopy (FTIR). Based on their frequent use in preformulations, the four different excipients: lactose (anhydre), magnesium stearate, talc and starch were blended with furazolidone. The samples were prepared by physical mixing of the furazolidone and excipients in a proportion of 1:1 and 1:0.25 (w:w). The presence of the melting and of the decomposition signals of the pure furazolidon and of the corresponding excipients in the DSC traces supported the absence of incompatibility between furazolidone and these excipients use in the physical mixtures. XRPD patterns and FTIR spectra sustained these results, they did not show evidence in interactions in the solid state between bioactive substance and excipients. Based on the results supplied by DSC, XRPD and FTIR, all excipients were found to be compatible with furazolidone so they can be used in formulation of the slow release tablets.

Keywords: furazolidone, compatibility, DSC, XRPD, FTIR

Furazolidone (FUR) is a synthetic nitrofuran derivative, therapeutically effective as a bactericidal agent. Furazolidone and other nitrofuran derivatives have been used for more than 30 years in medicine for the treatment of gastrointestinal infections in animals and humans. Furazolidone is used to treat infectious diseases caused by susceptible microorganisms: dysentery, paratyphoid fever, giardiasis, food intoxications, trichomoniasis, infectious wounds and burns and chronic alcoholism. The main pharmaceutical uses of nitro aromatic compounds (RNO_2) are as antibacterial and anticancer agents [1].

The chemical structure of furazolidone is presented in figure 1.
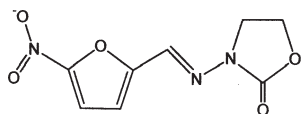

Fig. 1. Structure of furazolidone

IR-spectroscopy and X-ray diffraction are well known methods of drug analysis and have an exclusively great significance in investigations of interactions between drugs and excipients in pharmaceutical formulations [2]. Many authors successfully use the combination of these two methods. Usually, IR spectroscopy precedes X-ray diffraction studies [3, 4].

Differential scanning calorimetry (DSC) is a rapid analytical technique commonly used for evaluating drug–excipient interactions through the appearance, shift or disappearance of endo- or exothermal effects and/or variations in the relevant enthalpy values [5].

The purpose of this article is to evaluate the compatibility of FUR with common pharmaceutical excipients, used in the solid dosage form by DSC, Fourier transformed infrared (FT-IR) and X-ray powder diffraction patterns (XRPD).

Experimental part
Material and methods

The furazolidone FUR active substance and the excipients: starch, lactose monohydrate (lactose), magnesium stearate and talc were obtained from Terapia S.A./Ranbaxy, Cluj-Napoca, Romania as pure compounds, in order to be used for medical purpose.

Binary physical mixtures FUR: each excipient was prepared in different ratios: FUR:lactose monohydrate 1:1, FUR:magnesium stearate 1:0.25, FUR : starch 1:1 and FUR: talcum powder 1:0.25, obtained by grinding in the agate mortar with pestle for approximately 15 min.

FTIR spectra were obtained with JASCO 6100 FTIR spectrometer in the 4000-400 cm^{-1} spectral domain with a resolution of 4 cm^{-1} using the well known KBr pellet technique.

X-ray powder diffraction pattern was obtained using Bruker D8 Advance diffractometer, sealed Cu tube λ = 1.5406 A°, equipped with an incident beam Ge 111 monochromator.

DSC curves were obtained in a DSC-60 Shimadzu calorimeter cell using aluminum crucibles with about ~2mg of samples, under dynamic N_2 atmosphere (flow rate: 50 mL/min) and at a heating rate of 10°C/min in the temperature range 25 - 400°C.

Results and discussions

The subsequent step of the present study was to analyze the FTIR spectra of FUR, of the used pharmaceutical excipients and of their binary mixtures in order to identify a possible chemical interaction between them [6,7].

FTIR spectrum of FUR is presented in each figure together with the binary mixtures of FUR and each excipient. The FTIR spectra are showed in figures 2 - 5.

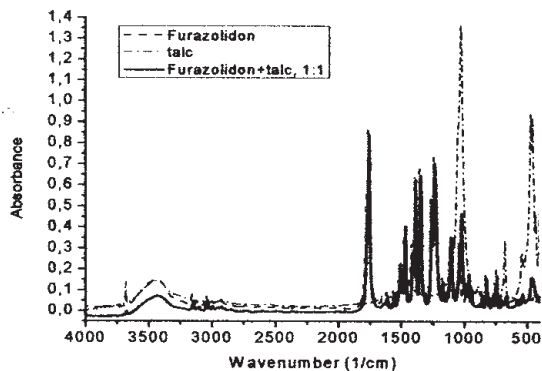* email: marian_eleonora@yahoo.com; Tel.: 0729159838

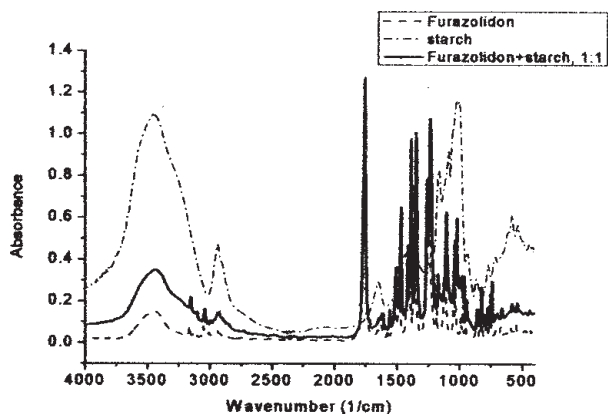Fig. 2. FT-IR spectra of FUR and binary mixture with talc

Fig. 4. FT-IR spectra of FUR and binary mixture with lactose

Fig. 3. FT-IR spectra of FUR and binary mixture with starch

Fig. 5. FT-IR spectra of FUR and binary mixture with magnesium stearate

Furazolidone shows infrared absorption peak for C-NO$_2$ nitro compounds at 1546 cm^{-1}, C-N at 841cm^{-1}, C=O(stretch) at 1759 cm^{-1}, C-O (stretch) at 1252 cm^{-1} and C=N stretching ranged between 1689-1471cm^{-1}.

The infrared spectra of the initial compounds clearly exhibits the presence of talc by the very sharp O-H stretching at 3674 cm^{-1} (which is badly overlapped by vibration of talc-like hydroxyl group stretching at 3670 cm^{-1}) and the sharp symmetric Si-O-Si stretching at 667 cm^{-1}.

Magnesium stearate presents specific absorptions in the 2920-2851cm^{-1} spectral range, due to the CH$_2$-CH$_3$ part of the molecule [8]. The other bands located at 1575 and 1461cm^{-1} are due to the stretching vibration of - COO- group. Figure 4 shows that all spectra of the crystalline lactose contained the bands at 3600–3200 cm^{-1} (stretching vibration of the hydroxyl group), the weak band at 1650 cm^{-1} (bending vibration of the hydroxyl groups of crystal water) and the band at 1200–1070 cm^{-1} (asymmetric stretching vibration of C-O-C in the glucose and galactose) [9].

Starch present specific absorbtion at the 3445 cm^{-1} (O-H hydrogen bonding stretching vibration), 2931 cm^{-1}, 1010 cm^{-1} (specific to the crystalline starch) and at 996 cm^{-1} (-OH group at C-6, water sensitive). In the binary mixture the peak from 1010 cm^{-1} decreased in frequency, and the peak at 996 cm^{-1} disappeared (corresponding to intramolecular hydrogen bonding) [10,11]. Also the intensity peak from 3445 cm^{-1} is significantly decreased.

In the FTIR spectra of physical mixtures the characteristic absorption bands of furazolidone and of each excipient were identified; these bands are not affected by interactions between drug and excipient [12]. As a consequence, a real physical mixture of these two components was obtained [13].
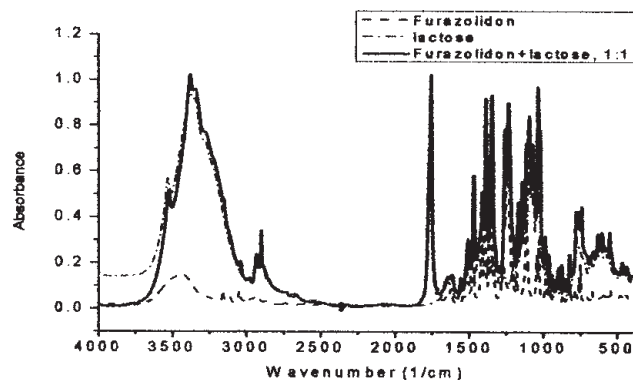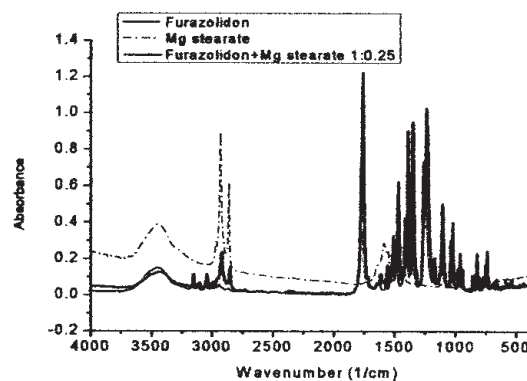
In figures 6 - 9 are shown X-Ray powder diffraction patterns for starting compounds and for compound obtained by mechanical mixture. One can see that the X-Ray powder diffraction patterns for samples obtained by mechanical mixture of actives compounds with different ingredient are sum of patterns corresponding to each component, i.e. no new compound is formed; there are no interactions (physical or chemical between drug and excipients) [14].

According to our experiment, XRPD methods showed compatibility between FUR and the used excipients since the diffraction peaks of FUR remained unaltered within the physical mixtures.

The results obtained from the DSC curves of binary mixtures are summarized in table 1and shown in figure 10.

The DSC curve of FUR showed a first endothermic event between 255 and 260°C, with a melting temperature of Tonset=257.84°C.
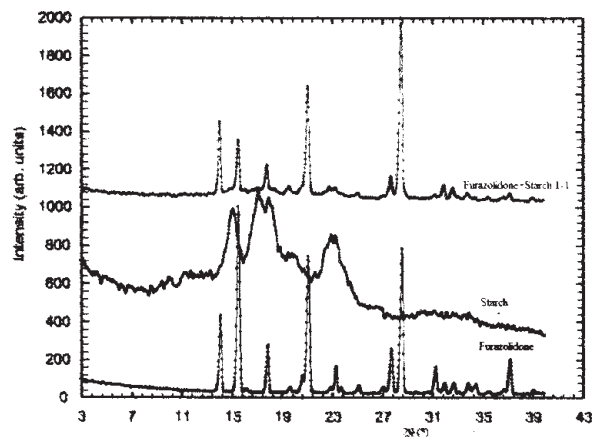
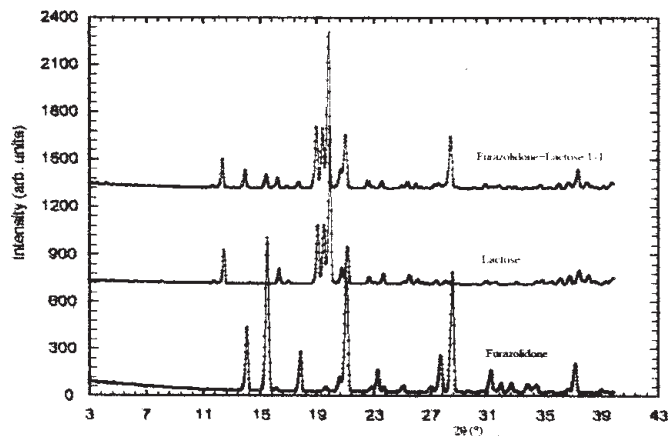

Fig. 6. XRPD patterns for FUR, Starch and binary mixtures
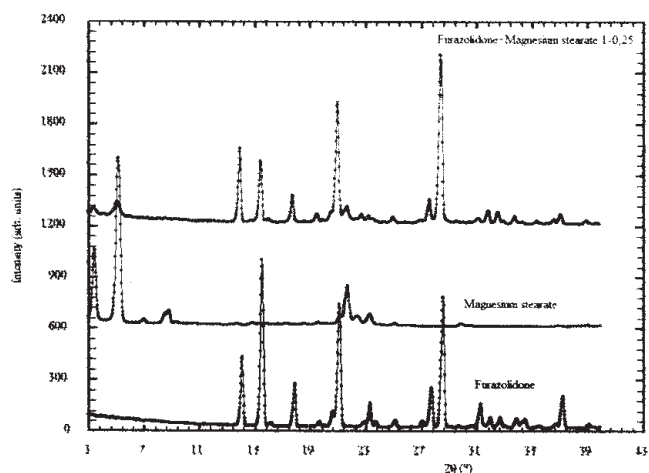
Fig 7. XRPD patterns for FUR, Lactose and binary mixtures

Fig 9. XRPD patterns for FUR, Talc and binary mixtures

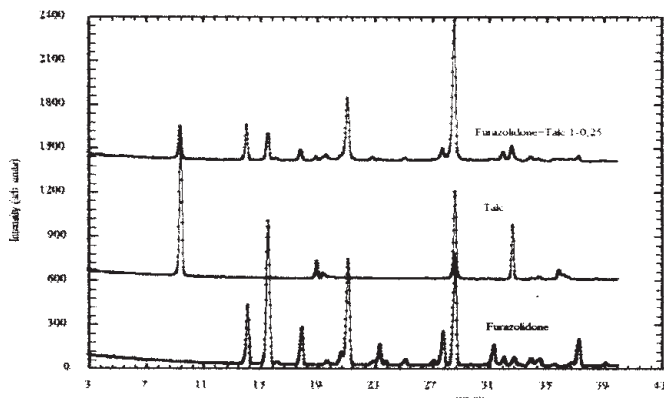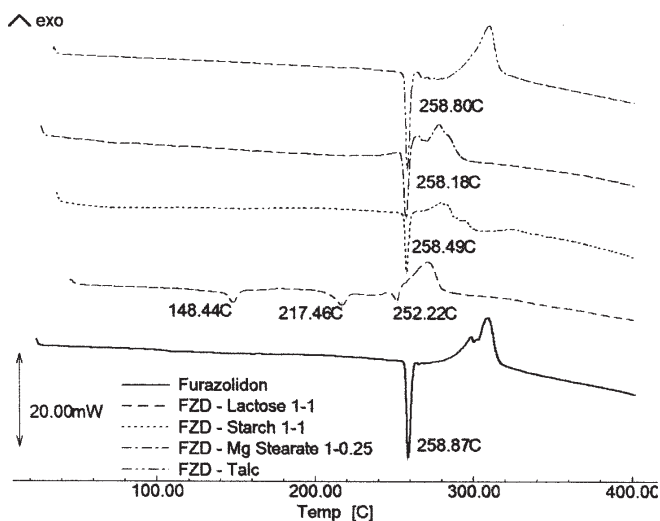Fig 8. XRPD patterns for FUR, Magnesium stearate and binary mixtures

Fig. 10. Differential scanning calorimetry (DSC) of furazolidone and physical mixtures

Samples	Tonset (fusion)/ mJ/g	Tpeak (fusion)/ mJ/g	Enthalpy (fusion)/ mJ/g	Thermal event	Start decomposition (°C)
FUR	257.84	258.87	-218.05	Melting FUR	~275
FUR-Starch	255.10	258.49	-113.12	Melting FUR	~270
FUR-Lactose	145.84 210.92 249.56	148.44 217.46 252.22	-46.74 -72.93 -41.53	Dehydration lactose Decomposition lactose Melting FUR	~260
FUR- Mg stearate	67.67 256.04	79.34 258.18	-8.91 -182.43	Dehydration Mg stearate Melting FUR	~265
FUR-Talc	257.64	258.80	-200.81	Melting FUR	~260

DSC curve of FUR and starch presented the melting peak of FUR at approximately the same value of temperature (259°C). DSC curve of FUR and lactose presented three endothermic events in the 145–253°C temperature range which is characteristic for the dehydration and decompostion process of lactose, followed by the endothermic peak of FUR melting 258.87°C) [15]. DSC curve of FUR and magnesium stearate presented two endothermic events in the 100–259°C temperature range which is characteristic for the dehydration process of magnesium stearate, followed by the endothermic peak of FUR melting 258.87°C) [16,17]. All the thermic profiles of mixtures can be considered as a superposition of DSC curves of pure FUR and excipients, as a proof of compatibility between FUR with the used excipients. The similar thermal behaviour, with a like characteristic temperatures of pure compounds and drug-excipient mixtures suggest the existence of drug-excipient physical mixtures, with the lack of chemical transformations which could affect the structure of each component [18-20].

Conclusions
The results demonstrated the applicability of FTIR, XRDP and differential scanning calorimetry (DSC) 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 FUR.

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