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Research Article

COMPATIBILITY OF ITOPRIDE HCL WITH CERTAIN FORMULATION EXCIPIENTS

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ABSTRACT

Itopride HCl (ITO) is a novel prokinetic agent, currently used for the treatment of various gastrointestinal motility disorders. As a step forward towards the formulation of that drug, the purpose of the present article was to study the compatibility of ITO with some pharmaceutical excipients that might be utilized during its formulation in specific dosage form. Keeping in mind that a pharmaceutical formulation is considered appropriate when no interactions, drug-excipient or excipient-excipient, occur. Compatibility screening of drugs with excipients is recognized as one of the mandatory factors and is at the forefront of drug product science and technology research. For that purpose thermoanalytical technique (differential scanning calorimetry, DSC) and Fourier transform infrared spectroscopy (FTIR) were used. The results obtained upon utilizing both techniques, thermal analysis (DSC), and FTIR were found to be very useful in making decision about selecting the best excipient that is expected not to cause any problem when formulated with the candidate drug, ITO. Of the excipients tested: hydroxypropyl methylcellulose, ethylcellulose, Eudragit RSpm, Carbopol 934p, microcrystalline cellulose, citric acid, sodium bicarbonate, magnesium stearate, sodium carboxy methylcellulose and their corresponding physical mixtures with the drug (1:1 w/w). The drug was found compatible with all excipients investigated.

Keywords: Itopride HCl, Differential Scanning Calorimetry, Fourier Transform Infrared Spectroscopy, Compatibility Studies.

INTRODUCTION

ITO HCl is a novel prokinetic agent. This drug was first developed and marketed in Japan 1995[1]. ITO has anticholinesterase activity as well as dopamine D2- receptor antagonistic activity and is being used for the symptomatic treatment of various gastrointestinal motility disorders. Itopride activates the gastrointestinal motility through synergism of its dopamine D2-receptor antagonistic action and its acetylcholinesterase-inhibitory action. In addition to these actions, ITO HCl has an antiemetic action, which is based on its dopamine D2-receptor antagonistic action. This mode of action of ITO, which involves both the anti-acetylcholinesterase activity and dopamine D2 antagonism is unique for that drug and is essentially different from the mechanism of action of other prokinetic drugs[2].

It is well known that a quick and accurate method to test and select the best excipients for ideal dosage forms constitutes a real achievement in the pre-formulation stage[3]. The successful formulation of a stable and effective dosage forms depends on the careful selection of the excipients that are added to facilitate administration, promote formulation, achieve consistent release, improve bioavailability and/or therapeutic activity of the drug and protect it from degradation. A formulation is considered appropriate when no interactions drug-excipient or excipient-excipient occur. Although excipients traditionally have been thought of as being inert chemically and pharmacologically, they have shown possible interactions with drugs, preventing their absorption and bioavailability. Yusuke et al [4] studied the effect of excipients on the absorption of water soluble drugs. They found that excipients can affect the membrane functions and lead to increase or decrease in membrane permeability. Accordingly, they reached to the same fact that a more effective formulation is based on selection of the suitable excipient. Drug product stability in physical aspects such as organoleptic properties, dissolution slowdown or chemical aspect as drug or excipient degradation reslted from the interaction of excipients with drugs in the dosage form[5]. Physiological factors or processes such as the pH of the microenvironment, the stability of a drug substance in the GI tract and the permeability of GI membranes to the drug can also be altered significantly if the excipient selected is not compatible with the drug[6-9].

Thermoanalytical technique (differential scanning calorimetry, DSC) and Fourier transform infrared spectroscopy (FTIR) were the most frequently used instrumental techniques in

pharmaceutical research to solve technological problems in the pre-formulation stages. Both techniques have been proposed as the most rapid methods for evaluating physico-chemical interactions between the formulation components and therefore help selecting suitable excipients[10-11].

The aim of the present article was to evaluate the compatibility between ITO and some pharmaceutical excipients, using thermoanalytical technique (DSC) with the support of Fourier transform infrared spectroscopy (FTIR).

MATERIALS AND METHODS

ITO HCl was purchased from Hangzhou Uniwise International Co, China (lot number WIN 130208). The excipients examined were: hydroxypropyl methylcellulose (Aldrich Chemical Company, USA), ethylcellulose (Merck, Germany), microcrystalline cellulose (FMC international Co., Belfast, Ireland), sodiumcarboxy methylcellulose (Pharmazell, Germany), Eudragit RSpm (Rhom pharma, GMBH, Darmstadt, Germany), Carbopol 934p (Merck, Germany), sodium bicarbonate and citric acid (Al Gomhoria Co, Egypt), magnesium stearate (Alba Chemical Company, USA).

1-Differential scanning calorimetry (DSC):

DSC thermograms for ITO HCl alone, suggested excipients viz: hydroxypropyl methylcellulose, ethylcellulose, Eudragit RSpm, Carbopol 934p, microcrystalline cellulose, citric acid, sodium bicarbonate, magnesium stearate and Sodium carboxy methylcellulose as well as physical mixtures of the drug and each excipient in a ratio of 1:1 (w/w) were obtained using Shimadzu DSC-50 equipment. During this investigation 3 mg of the samples were crimped in a closed aluminium pans and then scanned under dynamic N_2 atmosphere (flow rate: 25 mL/min) and at a heating rate of 10°C/min. at a temperature range of 25 - 400°C. The equipment was calibrated under the same conditions.

2-Fourier transform infrared spectroscopy (FTIR):

FTIR spectra were recorded for the drug, excipients eg. hydroxypropyl methylcellulose, ethylcellulose, Eudragit RSpm, Carbopol 934p, microcrystalline cellulose, citric acid, sodium bicarbonate, magnesium stearate and Sodium carboxy methylcellulose as well as their physical mixtures in ratios of 1:1 (w/w). Samples were mixed with KBr and made into discs with a 2 cm^{-1} resolution in the range of 4000–500cm^{-1} using Shimadzu 470, (schimadzu, Japan) FTIR spectrometer.

RESULTS AND DISCUSSION

The DSC thermogram of ITO HCl is illustrated in Fig. 1. The DSC curve of ITO showed an endothermic peak at 195°C with a melting temperature of 195°C as a result of melting of the drug. The results obtained are in agreement with Yong et al [1].

Thermal behavior of physical mixtures of ITO and hydroxypropyl methylcellulose (HPMC) is illustrated in Fig. 2. The DSC thermogram exhibited a broad endothermic peak which may be attributed to vaporization of adsorbed moisture of HPMC, at a temperature around 60°C. In the same time the endothermic peak characteristic of melting of ITO was observed at 195°C. The DSC curve of the physical mixtures demonstrated that there is no change in the thermoanalytical profiles of the drug and the excipient and the DSC curve of the physical mixture was superposition of the drug and the excipient under investigation.

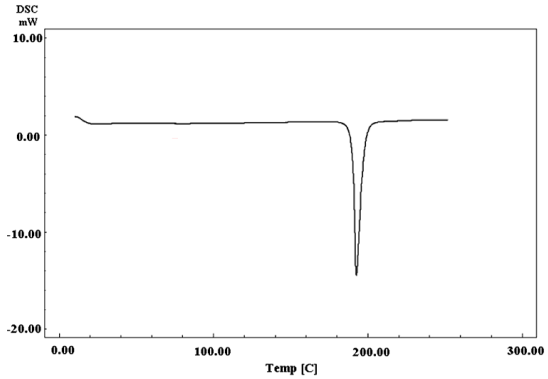

Figure 1: Differential scanning calorimetry (DSC) curve of ITO HCL

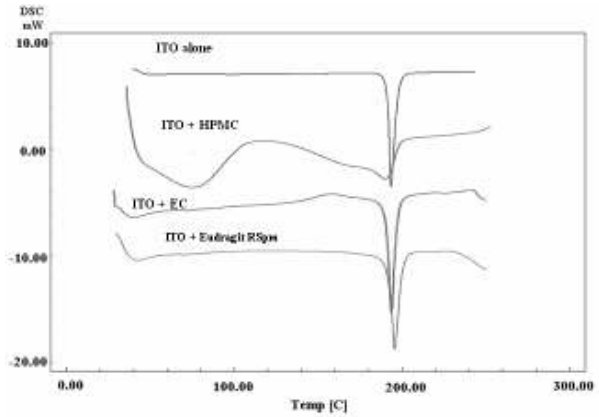

Figure 2: DSC curve of ITO and its 1:1w/w physical mixtures with, HPMC, ethylcellulose EC, Eudragit RSpm

DSC curve of ITO HCl and ethylcellulose physical mixture exhibited an endothermic peak due to the dehydration of the excipient followed by the endothermic peak corresponding to the fusion of the drug at 195°C (Fig. 2).

DSC curve of ITO and Eudragit RSpm showed an endothermic peak of ITO at approximately the same temperature (195°C) (Fig. 2).

The DSC curve of the physical mixture ITO with Carbopol 934p (Fig. 3) exhibited the characteristic ITO fusion peak without any change. the thermal properties of a physical mixture are the sum of the individual components, and this thermogram can be compared with those of the drug and the excipient alone.

DSC curve of ITO HCl and microcrystalline cellulose (Fig. 3) presented two endothermic events at 40–80°C temperature range which is characteristic for the dehydration process of microcrystalline cellulose, followed by the endothermic peak of ITO HCl melting at 195°C. Hauter.K.G et al: Pharm Dev & Technology (2000) 5 (3) 303-310

Microcrystalline Cellulose as a Source of Moisture

The thermal behavior of the binary mixture of ITO and citric acid showed no incompatibility between these substances.

The combination of ITO with sodium bicarbonate (Figure 4) reflected the characteristic features of the drug and the carrier which indicates the compatibility between the drug and sodium bicarbonate.

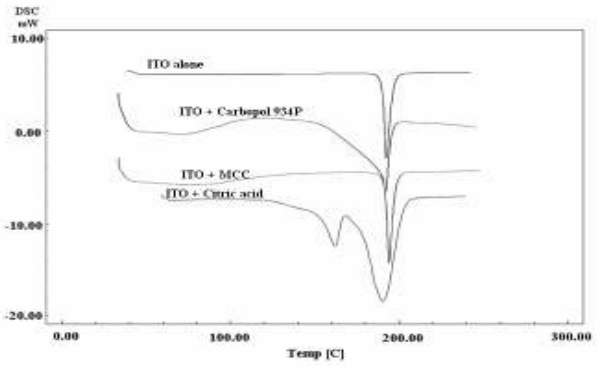

Figure 3: DSC curve of ITO and 1:1 w/w physical mixtures of it with Carbopol 934p, microcrystalline cellulose MCC, and citric acid

DSC curve of ITO and magnesium stearate (Fig. 4) presented two endothermic events at 70–110°C temperature range which is characteristic for the dehydration process of magnesium stearate, followed by the endothermic peak of ITO melting (195°C).

The DSC thermograms in Figure 4 show that the physical mixture of the drug with sodium carboxymethylcellulose exhibits the characteristic features of the drug and the polymer used, indicating the compatibility between the drug and polymer.

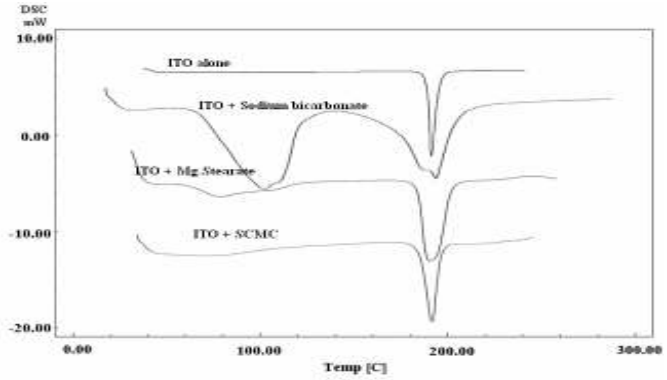

Figure 4: DSC curve of ITO and 1:1 physical mixtures of it with sodium bicarbonate, magnesium stearate, sodiumcarpoxy methylcellulose SCMC

All the thermal profiles of ITO-excipient mixtures obtained were superposition of the curves of pure ITO and the respective excipient, an observation that proves the compatibility between ITO with the excipients investigated.

The subsequent step of the present study was to analyze the FTIR spectra of ITO, of the suggested pharmaceutical excipients and of their binary mixtures in order to detect the presence of possible chemical interaction between them.

FTIR spectrum of ITO is presented at the top of each figure together with the binary mixtures of ITO and each excipient. These spectra are shown in Figures 5-7.

The characteristic peaks of the pure ITO at 3280.70 cm^{-1}, 3226.85 cm^{-1} (NH asymmetric and symmetric str.), 2944.32 cm^{-1}(C – H str. of aromatic nucleus), 2623.67 cm^{-1} (C – H str. of methyl group), 1652.07 cm^{-1} (C = O bending), 1580.94, 1546.48, 1511.82 cm^{-1} (C = C aromatic str.),1229.83 cm^{-1} (C – N aromatic str.) 1015.11 cm^{-1} (C – O aromatic str.), respectively are shown in figures 5-7.

FTIR spectrum of HPMC with ITO is shown in Figure 5.The peak at 3283.26 to 3227.76 cm^{-1} is due to OH vibrational stretching [7]. The symmetric stretching mode for methyl and hydroxypropyl group is found at 2943.61 cm^{-1}.

The maximum of the absorption band due to hydroxyl group of EC, (3281.24 cm^{-1}) was detected. The results (Fig. 5) show a similar behaviour for the EC/ITO mixture.

The IR spectra of the mixture of ITO and Eudragit RSpm are shown in Figure 5. The spectral observations indicated that the principal IR absorption peaks observed in the spectra of ITO alone were superposition to those of the spectra of the mixture. These results indicated that there is no interaction between the drug and the polymer.

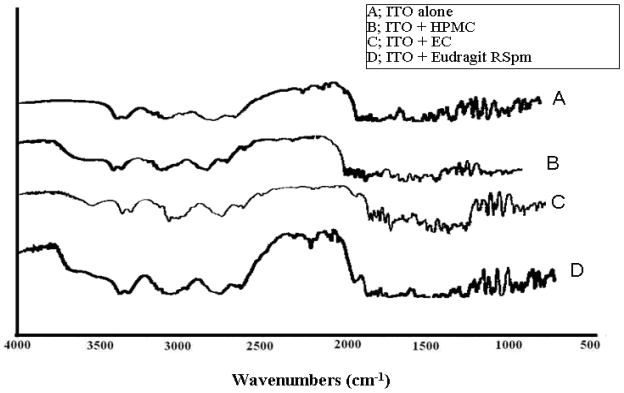

Figure 5: FTIR spectra of ITO and 1:1 physical mixtures of the drug with HPMC, ethylcellulose EC, Eudragit RSpm

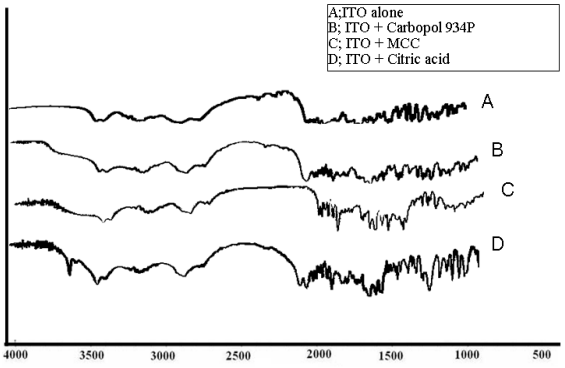

Figure 6: FTIR spectra of ITO and 1:1 physical mixtures of the drug with Carbopol 934p, microcrystalline cellulose MCC, and citric acid

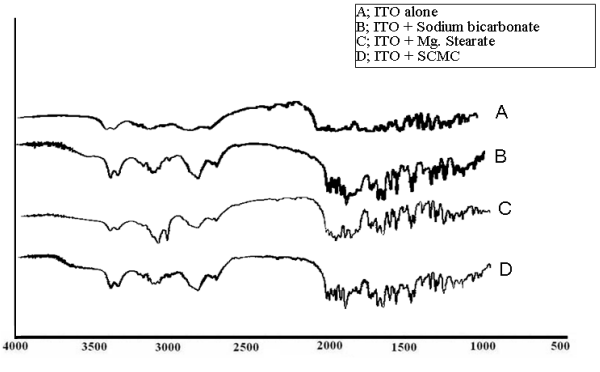

Figure 7: FTIR spectra of ITO and 1:1 physical mixtures (ITO, sodium bicarbonate, magnesium stearate, sodiumcarpoxy methylcellulose SCMC)

The FTIR spectra of ITO alone and ITO /Carbopol 934p mixture are shown in Fig 6 . For both C934p, their FTIR spectra showed a peak at 2945.12 cm^{-1}, representing OH stretching vibration, O-H and intramolecular hydrogen bonding. The prominent peak 1708.76 cm^{-1} was assigned to carbonyl C=O stretching band, while the peak at 1403.51 $cm^{-1}$was assigned to C-O / O-H The band at 1268.73 cm^{-1} was assigned to C-O-C of acrylates.

Microcrystalline cellulose exhibited characteristic bands at ~ 3283.45cm^{-1} (-OH stretching vibration), 2943.42cm^{-1} (C-H stretching vibration) and 1129.04cm^{-1} (-C-O-C- stretching vibration).

Magnesium stearate presents specific absorption peak at 2918.24-2849.86cm^{-1} spectral range, due to the CH_2-CH_3 part of the molecule. The other bands located at 1580.86 and 1468.65cm^{-1} are due to the COO- group.

All the characteristic peaks of the pure ITO HCl appeared in the same positions in the physical mixture with citric acid, sodium bicarbonate, sodiumcarboxy methylcellulose also are similar as there are no extra peaks or significant shift indicating no chemical interaction between ITO and excipients.

CONCLUSION

The results obtained demonstrated the applicability of FTIR and thermal analysis (DSC) methods as fast screening tools to check compatibility of drugs with excipients in early stages of preformulation process. Based on these results, all mentioned excipients were found to be fully compatible with ITO. It can be conclude that the selected excipients can be used for formulating Itopride HCl sustained release tablets.

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