Compatibility study of Candesartan cilexetil with β-cyclodextrin

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Summary

This article deals with compatibility tests of pharmaceutical mixtures. Methodology for such measurement of compatibility studies using Micro-DSC III is discussed. In comparison with other methods, which are used for this determination, it is a rapid and sensitive screening of active ingredient behavior and excipients in pharmaceutical formulations. So we can obtain beneficial information for drug product formulation.

The aim of this project was to study thermal stability of candesartan cilexetil with cyclodextrin and examine their tendencies to form complex.

Key words: candesartan, isothermal microcalorimetry, Micro-DSC

1. INTRODUCTION

When in the pharmaceutical industry new drug (API) is developed, the formulation of drug product follows. The drug product is composed of API and pharmaceutical carriers. The information of components stability is necessary for the formulation of the new drug product.

Compatibility means mutual tolerance of compounds of drug product. Compatibility studies are carried out by using different analytical methods. The most common is the use of high performance liquid chromatography (HPLC) in combination with mass spectrometry (MS). Another option is isothermal microcalorimetry. When HPLC is used, the mixture of active ingredients and excipients had to be stored under defined condition before measuring. It is made in oven with controlled constant temperature and for different time period – from days to months. Than are these samples dissolved and analysed. An alternative is the isothermal microcalorimetry - method TAM (the Thermal Activity Monitor). It detects the physico-chemical changes of mixtures that occur due to the constant temperature and humidity in the order of days/1/.

The bioavailability of a pharmaceutical active ingredient depends on several factors/2/, a major factor being the solubility in water. Current research provides, that candesartan respectively candesartan cilexetil is relatively biologically available./3/

1.1. MEASURING COMPATIBILITY STUDIES BY Micro-DSC III

It is possible to measure the compatibility of binary or ternary mixtures by using Micro-DSC III (Setaram). There are analysed mixtures of two/three active pharmaceutical substances or combination of one API with one or two excipients. The advantage of measuring the compatibility studies on the Micro-DSC is less time-intensive than the above mentioned techniques. The analysis is carried out only in the order of hours according to chosen parameters.

Device Micro-DSC offers possibility to measure in continuous and isothermal mode in the temperature range -20-120°C. For the compatibility studies are the parameters of measurement set according to the properties of the ingredients in measured mixture. For the selection of appropriate measuring parameters, the mixture is at first analysed on the classic DSC. Some compatibility studies were carried out using only the classic DSC/4/. For the isothermal phase are chosen the temperatures in the range of 35-80°C, spaced at intervals 2-10 °C. One isothermal phase usually takes 2-5 hours. Micro-DSC allows the heating rate from 0.001 °C/min to 1 ° C/min between two isothermal phases. For measuring of compatibilities study shall elect heating rate around 1 °C/min. Measuring of one sample takes 10 - 20 hours./5/

For measuring is used batch cell, which allows to analyse liquid or solid samples (Figure 1). The cells have a volume 1 cm^3, in compatibility studies are used backfills of samples around the 500 mg.

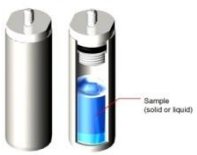

Fig. 1: Batch cell /5/

For comprehensive analysis it is necessary to get behavior of individual components of the mixture in the chosen mode, where the isothermal phase and the phase of continuous heating are diversifying. Evaluation is made by comparing the sum of the thermal flows of the individual ingredients and heat flow of mixture. If heat flows are evaluated as different, components are incompatible./5/

2. EXPERIMENTAL

2.1. Materials

2.1.1.Candesartan cilexetil

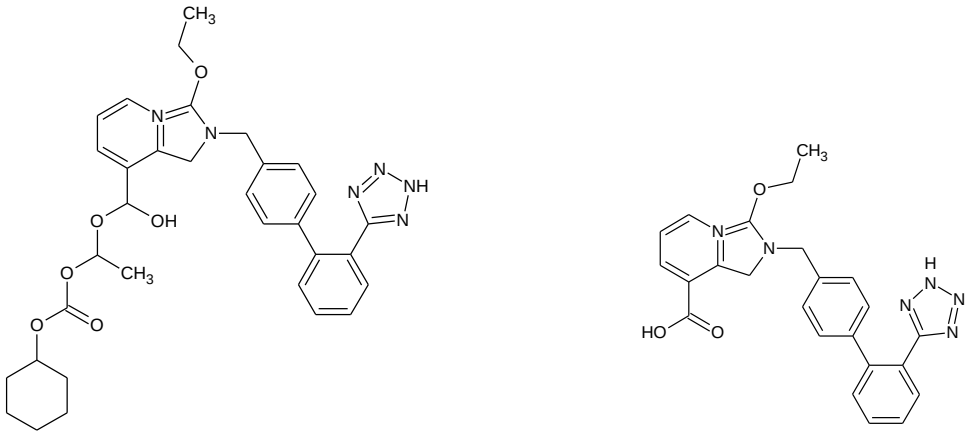

Fig. 2: Molecular structures of candesartan cilexetil and candesartan

Candesartan cilexetil is is found in many polymorphic forms I-XXIII and in amorphous form too/3/. Candesartan falls into therapeutic group of antihypertensive. It selective affects secreting of angiotensin II. In addition to the main use for the treatment of hypertension, it is also used in cases of heart-attack, which damaged the left chamber, or her systolic function. It is often used in combination with ACE inhibitors. It is served like prodrug (candesartan cilexetil), which is converted to the active metabolite (candesartan) in GIT. The original medicine is available on the market like BLOPRESS or ATACAND./3/

2.1.2.Cyclodextrin

β-cyclodextrin (Mw=1135 g/mol) is a circular oligosaccharide, consisting of seven glucose units that create cavity for building the inclusion complex. Cyclodextrins and their derivatives are used in the pharmaceutical industry to the complex formulation of active substances, to increase the solubility of the active substance in the water and thereby improve its bioavailability. /7//8/

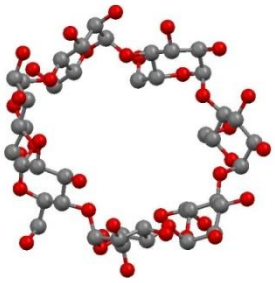

Fig. 3: Molecular structure of β-cyclodextrin/7/

2.2. Thermal stability

2.2.1 .Differential scanning calorimeters (DSC)

The thermal behavior of pure API, pharmaceutical carrier respective their combination produced by different methods was compared by using DSC Pyris 1 (Fig. 4).

There is difference in thermal behavior between some mixtures. The biggest difference could be seen between mixtures and physical mixtures. Mixtures were prepared by kneading (with/without addition of methanol) and co-evaporation method. Physical mixture contains 50% w/w candesartan cilexetil and 50% w/w cyclodextrin. Difference in thermograms indicates physical changes causing by formation of complex of candesartan cilexetil and cyclodextrin (Fig. 4 KN-M). The peak intensity of CAND near 169°C decreases in the case of formation of the complex. There are new endothermic changes near 220°C too. Aplication of FT-IR and Raman spectroscopy confirmed that there was prepared inclusion complex in the case of mixture made by kneading with addition of methanol. In this case the DSC affirmed the complex formation as well.

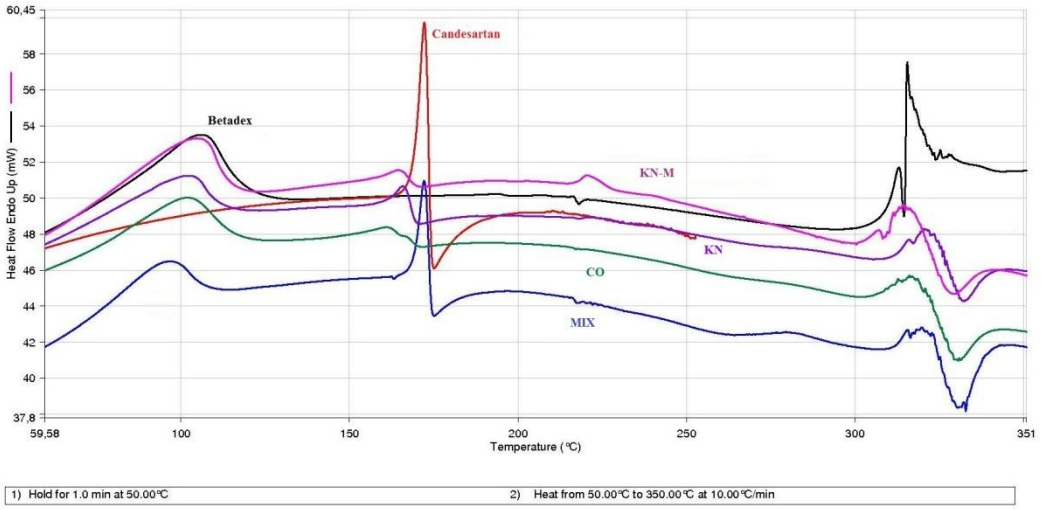

Fig. 4: DSC thermograms of Candesartan, β-cyclodextrin (Betadex), physical mixture (MIX), inclusion komplex of candesartan cilexetil and β-cyclodextrin made by kneading with addition of metanol (KN-M), mixture of candesartan

cilexetil and β-cyclodextrin made by kneading (KN), mixture of candesartan cilexetil and β-cyclodextrin made by co-evaporation method (CO)

2.2.2 .Microcalorimetry (Micro-DSC)

There were compared thermograms of mixtures with the sum of heat flows of pure compounds and with 50% w/w mixture. The measurement combined isothermal mode (4 h) and continual mode (25°C → 35°C → 45°C→ 55°C → 70°C). This method confirmed the thermal stability of candesartan cilexetil with cyclodextrin to 45°C (Fig. 5). It means that over the temperature 45°C are candesartan cilexetil and cyclodextrin incompatible, include complex of this substances.

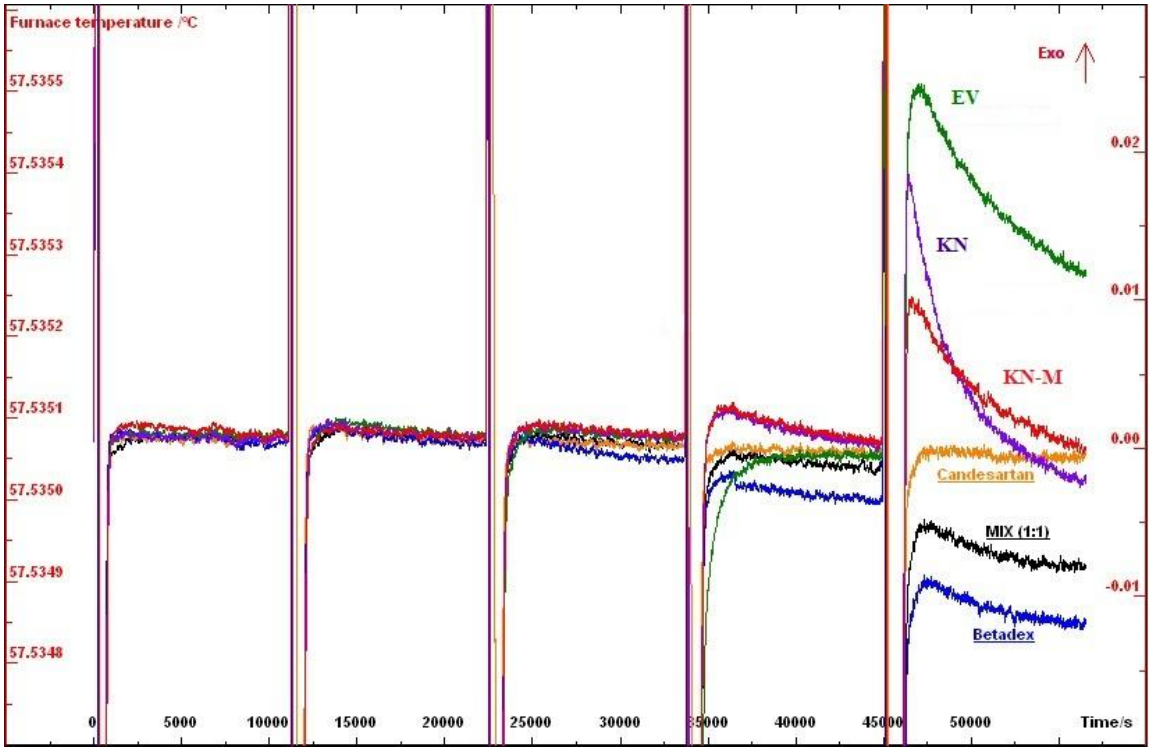

Fig. 5: Micro- DSC thermogram of Candesartan, β-cyclodextrin (Betadex), physical mixture (MIX 1:1), inclusion komplex of candesartan cilexetil and β-cyclodextrin made by kneading with addition of metanol (KN-M), mixture of candesartan cilexetil and β-cyclodextrin made by kneading (KN), mixture of candesartan cilexetil and β-cyclodextrin made by co-evaporation method (CO)

3 . CONCLUSION

The compability of mixtures was examined by Micro-DSC. The thermal study of candesartan cilexetil and cyclodextrin mixtures approved the interaction between those substances caused by increasing temperature and formation of complex. Micro-DSC determined, that candesartan cilexetil and cyclodextrin are incompatible in all mixtures above temperature 45°C.

ACKNOWLEDGEMENT

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