Journal of Molecular Structure 1062 (2014) 1–12

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

Orlistat interaction with sibutramine and carnitine. A physicochemical and theoretical study

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HIGHLIGHTS

- Chemical reactions are detected between orlistat and sibutramine at low temperatures.
- Reaction between orlistat and carnitine is not carried out due to the lack of chlorine atoms.
- Experimental reactions and stabilities are explained by theoretical calculations.
- Good agreement between theoretical and experimental results is obtained.
- Its IR spectra are predicted using DFT calculation.

ARTICLE INFO

Article history:
Received 11 October 2013
Received in revised form 27 December 2013
Accepted 28 December 2013
Available online 17 January 2014

Keywords:
Orlistat–sibutramine–carnitine polypills
Thermal characterization
Cyclic DSC
Theoretical chemistry
Orlistat degradation by-products

ABSTRACT

Chemical degradation of orlistat, (ORT) after melting and reaction of decomposition byproducts with sibutramine, SIB was studied. Interactions between the active pharmaceutical ingredients by using thermal analysis, TA, methods and other experimental techniques such as PXRD, IR and UV–vis spectroscopies were carried out to investigate chemical reactions between components. It was found that orlistat melts with decomposition and byproducts quickly affect sibutramine molecule and then reacting also with carnitine, CRN when the three active pharmaceutical ingredients (API's) are mixed. However ORT byproducts do not react when ORT is mixed only with carnitine. It was found that compounds containing chlorine atoms react easily with orlistat when the temperature increases up to its melting point. Some reaction mechanisms of orlistat decomposition are proposed, the fragments in the mechanisms were found in the corresponding mass spectra. Results obtained indicate that special studies should be carried out in the formulation stage before the final composition of a poly-pill could be established. Similar results are commonly found for compounds very prone to react in presence of water, light and/or temperature. In order to explain the reactivity of orlistat with sibutramine and carnitine, theoretical calculations were carried out and the results are in agreement with the experimental results.

1. Introduction

Fixed dose combinations (FDC) or polypills for metabolic syndrome in the early stage of formulation were studied in order to determine the possible interactions among active pharmaceutical ingredients, API's. Study of possible chemical interactions and incompatibilities among drugs are considered critical requirements in the development of fixed-dose combination pharmaceuticals [1,3]. In the last years, great effort and investment have been made in order to develop a FDC for the control and treatment of metabolic syndrome diseases (MSD) such as diabetes, obesity, high arterial pressure, hypoglycemia and cholesterolemia.

Initially, a polypill for metabolic syndrome is proposed to contain three active pharmaceutical ingredients: orlistat, ORT; sibutramine, SIB, and carnitine, CRN. There are few reports in the literature concerning the solid and semiliquid state interaction amongst the API's been considered for these formulations. Thus, studies on the interactions between these API's and its possible synergic effects, were carried out in our laboratory, by using different techniques such as Thermal Analyses, X-ray diffraction, IR, and UV–Vis spectroscopy. Also, theoretical study was carried out to

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http://dx.doi.org/10.1016/j.molstruc.2013.12.072

explain the experimental results. It is known that the clinical studies are very expensive and time consuming, therefore it is highly desirable to study the physical and chemical interactions among the API's within the polypill before the formulation is given. A quick and easy method to determine these interactions and the possible reaction products would be very convenient to avoid the loss of time and money in the development and formulation of polypills.

Thus, in the present work thermal analysis and other techniques studies were carried out to determine chemical interactions of the three API's used in the proposed polypill, before expensive clinical and further studies were carried out. ORT in a formulation with SIB is not reported in any pharmacopoeia. Several analytical methods such as high-performance liquid chromatography, HPLC, high performance thin layer chromatography, HPTLC and spectrophotometry are reported for the study of SIB and ORT. There are reports in the literature of several analytical methods for ORT determination in pharmaceutical formulations and biological matrices.

Orlistat, also called Tetrahydrolipstatin, (N-formil-L-leucine(S)-1-[(2*S*,3*S*)-3-hexyl-4-oxo-2-oxetanyl]methyl dodecyl ester) depicted in Fig. 1, with a molecular weight of 496.23 g/mol, is a modified derivative (hydrogenated) of a lipostatin obtained from soil bacteria (Streptomyces toxytincini). Orlistat commercially named Xenical™ blocks the digestion of fat in the gut and the availability of fat soluble vitamins (A, D, E and K). Side effects of orlistat, are flatus and discharge, oily spotting and oily stool, also diarrhea, incontinence and abdominal pain can occur. ORT inhibits the breakdown of dietary fat irreversibly blocking the active site of gastrointestinal enzyme lipase, preventing the hydrolysis of triglycerides into absorbable fatty acid and glycerides [1,2], so the unabsorbed fat is consequently excreted. People participating in studies to determine the ORT mechanism for weight reduction show a decrease in lipids and cholesterol in blood, [3,4]. ORT may promote hyperphagia through the suppression of endogenous saciety peptide cholecytokinin (CEK). There are no reported studies of chemical reactions of orlistat with other API's, although this compound is very sensitive and prone to hydrolysis and thermolysis when stored at temperatures near to its melting temperature (44.71 °C). Orlistat chemical structure is presented in Fig. 1. Simple and accurate analytical method to determine the interactions with other API's (sibutramine, carnitine), is reported herein, when a polypill is in early development and pre-formulated stage, prior to be used in clinical studies.

Sibutramine hydrochloride monohydrate was used for the treatment of obesity in more than 40 countries around the world. Sibutramine (Meridia™, Reductil™), has a well-proven efficacy, since one and two-year clinical studies demonstrated that SIB together with a low caloric diet produced a sustained weight-loss effect.

SIB currently is a racemic mixture of the (+) and (−) enantiomers of cyclobutanemethanamine, 1-(4-chlorophenyl)-N,N-dimethyl-A-(2-methylpropyl), it is depicted in Fig. 2. It is a reuptake inhibitor of activity for norefedrine, serotonin and possibly for dopamine as well, [5–9].

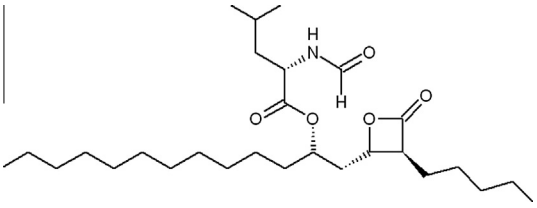

Fig. 1. Orlistat chemical structure.

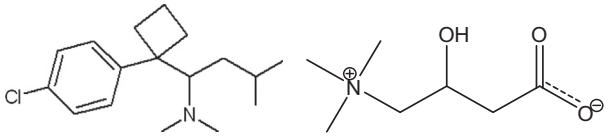

Fig. 2. Chemical structure of sibutramine and carnitine.

2. Experimental

2.1. Materials

Pure drug samples were kindly given by More Pharma Corporation SRL de C.V. (México), methanol was purchased from Aldrich, ultra pure water was obtained from a water purification system (Methrom, Ltd.). Other chemicals were analytical-reagent grade from Aldrich. Purified grade water was obtained by reverse osmosis and filtration using a Milli-Q system (Millipore, Milford MA, USA) for preparing all solutions.

2.2. Equipment

Thermal analysis system consisted of a model 2050 Differential Scanning Calorimetric module, DSC, for normal or/and cyclic thermal analysis, and a model 2010 Thermal-Gravimetric Analysis, TGA module, both of them made by T.A. Instruments, Ltd. Heating rate was in most studies of 10 °C/min.

UV–Vis spectrometer, model Genesis 10uv made by Thermo Scientific Ltd., was used for spectroscopic analyses of pure API's and their mixtures at different temperatures.

A SRI Model 8610C Chromatograph was used to identify pure compounds and different byproducts by chemical interactions among the API's.

X-ray diffraction powder method patterns were obtained when Siemens model Kristalloflex 5000 diffractometer, with Cu used as target and 1.504 Å kα radiation was applied. X-ray diffraction patterns of crystalline pure compounds and by-products of chemical interactions between the API's at temperatures above 45 °C were determined by this method.

Supercomputer Kam-Balam UNAM was used for obtaining the more reactive molecular structures of the API's by theoretical calculations. These conformational analyses allowed us to found the more stable and reactive functional groups for each molecule. Besides, some molecular reactions were proposed, only to explain the chemical degradation process between ORT, SIB and CRN.

2.3. Stability of orlistat

Orlistat is characterized by having an aliphatic hydrocarbon backbone bearing a β-lactone moiety and an *N*-formyl-L-leucyl side chain in δ-position to the lactone C=O C-atom and was suspected to be unstable at high temperature and prone to hydrolysis. Thermal and hydrolytic degradation processes of ORT have been reported in literature, and all main degradation products isolated, characterized and synthesized. Orlistat was reported to be stable under dry condition when heated up to melting point and no decomposition was seen on exposure of solid drug powder to light in a photostability chamber [10]. Orlistat degradation products produced by human carboxyl ester lipase have also been described [11]. All studied samples in both solid and solution state remained colorless. However in our study chemical interactions with sibutramine were detected at temperatures above 45 °C.

ORT has been reported to be thermally unstable and the main products characterized and synthesized [12]. In order to determine that similar degradation processes were carried in both the API's