LISTA CELOR 10 LUCRĂRI REPREZENTATIVE CARE SUSŢIN CONŢINUTUL TEZEI

1. **Ionuţ Ledeţi**, Adriana Fuliaş✉, Gabriela Vlase, Titus Vlase, Vasile Bercean, Nicolae Doca, Thermal behaviour and kinetic study of some triazoles as potential anti-inflammatory agents, Journal of Thermal Analysis and Calorimetry, 2013, 114(3): 1295-1305, DOI 10.1007/s10973-013-3123-2. IF=2,206/2013; https://link.springer.com/article/10.1007/s10973-013-3123-2
2. **Ionuţ Ledeţi,** Vasile Bercean✉, Anda Alexa, Codruta Soica, Lenuta-Maria Suta, Cristina Dehelean, Cristina Trandafirescu, Delia Muntean, Monica Licker, Adriana Fulias, Preparation and Antibacterial Properties of Substituted 1,2,4-Triazoles, Journal of Chemistry, 2015, Article no. 879343, 1-5, DOI: 10.1155/2015/879343. IF=0,996/2015; https://www.hindawi.com/journals/jchem/2015/879343/
3. **Ionuţ Ledeţi**, Anda Alexa, Vasile Bercean, Gabriela Vlase, Titus Vlase, Lenuţa-Maria Şuta, Adriana Fuliaş✉, Synthesis and Degradation of Schiff Bases Containing Heterocyclic Pharmacophore, International Journal of Molecular Sciences, 2015, 16 (1) 1711-1727, DOI: 10.3390/ijms16011711. IF=3,257/2015; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4307329/
4. **Ionuţ Ledeţi**, Gabriela Vlase✉, Titus Vlase, Vasile Bercean, Adriana Fuliaş, Kinetic of solid state degradation of transitional coordinative compounds containing functionalized 1,2,4 -triazolic ligand, Journal of Thermal Analysis and Calorimetry, 2015, 121(3): 1049-1057, DOI: 10.1007/s10973-015-4520-5. IF=1,781/2015; https://link.springer.com/article/10.1007/s10973-015-4520-5
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6. **Ionuţ Ledeţi**, Ştefana Avram✉, Vasile Bercean, Gabriela Vlase, Titus Vlase, Adriana Ledeţi*, Istvan Zupko, Marius Mioc, Lenuţa-Maria Şuta, Codruta Soica, Cristina Dehelean, Solid-State Characterization and Biological Activity of Betulonic Acid Derivatives, Molecules, 2015, 20(12): 22691-22702, DOI: 10.3390/molecules201219876. IF=2,465/2015. http://www.mdpi.com/1420-3049/20/12/19876
7. **Ionuţ Ledeţi**, Adriana Ledeti✉, Gabriela Vlase, Titus Vlase, Petru Matusz, Vasile Bercean, Lenuta Maria Suta, Doina Piciu, Thermal stability of synthetic thyroid hormone L-thyroxine and L-thyroxine sodium salt hydrate both pure and in pharmaceutical formulations, Journal of Pharmaceutical and Biomedical Analysis, 2016; 125: 33–40**.** IF=3,169/2015; http://www.sciencedirect.com/science/article/pii/S0731708516301443
8. **Ionuţ Ledeţi**, Gabriela Vlase, Titus Vlase, Adriana Fulias✉, Kinetic analysis of solid-state degradation of pure pravastatin versus pharmaceutical formulation, Journal of Thermal Analysis and Calorimetry 06/2015; 121(3):1103-1110, DOI:10.1007/s10973-015-4842-3. IF=1,781/2015; https://link.springer.com/article/10.1007/s10973-015-4842-3
9. **Ionuţ Ledeţi**, Gabriela Vlase, Titus Vlase, Adriana Fulias✉, Lenuta-Maria Suta, Comparative thermal stability of two similar-structure hypolipidemic agents – Simvastatin and Lovastatin. Kinetic Study, Journal of Thermal Analysis and Calorimetry 2016; 125(2): 769-775, DOI:10.1007/s10973-015-5071-5. IF=1,781/2015; https://link.springer.com/article/10.1007/s10973-015-5071-5
10. **Ionuţ Ledeţi**, Gabriela Vlase, Titus Vlase, Lenuta-Maria Suta, Anamaria Todea, Adriana Fulias✉, Selection of solid-state excipients for simvastatin dosage forms through thermal and nonthermal techniques, Journal of Thermal Analysis and Calorimetry 06/2015; 121(3):1093-1102, DOI:10.1007/s10973-015-4832-5. IF=1,781/2015; https://link.springer.com/article/10.1007/s10973-015-4832-5

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Thermal behaviour and kinetic study of some triazoles as potential anti-inflammatory agents

Ionuţ Ledeţi · Adriana Fuliaş · Gabriela Vlase · Titus Vlase · Vasile Bercean · Nicolae Doca

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Abstract Thermogravimetric (TG), differential thermogravimetric analysis and differential scanning calorimetry had been used to characterize the thermal stability of four new heterocyclic compounds with triazolic structure. The four analysed compounds have similar thermal behaviours, namely the thermal mal curves of these new compounds show three thermal events. These compounds were thermally stable up to 110 °C. Above this temperature, the evolution of hydrochloric acid took place as observed by EGA. Identification and the monitoring of gaseous species released during thermal decomposition of pure triazoles in air atmosphere have been carried out by coupled TG–FTIR. Between 110 and 220 °C the main gaseous product is HCl which was identified on the basis of these FTIR spectra. Arguments for a rapid thermooxidation of the four molecules were brought by EGA by identifying the substances which arise from both the destruction of side chains and of triazolic ring. The kinetic analysis of the destruction process of triazolic structure was investigated using the TG data in air for the substance's decomposition in non-isothermal conditions. The isoconversional methods, Kissinger–Akahira–Sunose, Flynn–Wall–Ozawa and Friedman, were applied to determine the activation energy from the analysis of four curves measured at different heating rates. In order to obtain realistic kinetic parameters, even if the decomposition process is a complex one, the non-parametric kinetics method was also used. A good agreement between the data obtained from the four applied methods was found.

Keywords Triazole · Acetic acid derivative · Thermal analysis · Kinetic study · NPK

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Introduction

The chemistry of triazoles has been widely developed because these compounds are versatile ligands in the metal complexes' synthesis and some of them display anti-inflammatory, CNS stimulants or sedatives, antianxiety, antimycotic and antimicrobial properties [1, 2]. Based on these observations, four new compounds from the class of triazoles were synthesized and characterized. The structures of these compounds are presented in Scheme 1.

Moreover, sulphur-containing heterocycles represent an important class of sulphur compounds that are promising for use in practical applications. Among these heterocycles, the mercapto-1,2,4-triazole ring has been studied and so far a variety of biological activities have been reported, such as antibacterial, antifungal, anti-tubercular, anti-mycobacterial, anticancer, diuretic and hypoglycaemic properties [3–6].

The study of thermal behaviour of newly synthesized organic compounds has a great potential and the thermal analysis is used as a quick and reliable technique for studying purity, thermal stability and polymorphism evaluation. Moreover, thermal behaviour is an important tool that should be realised before testing the final formulation, because

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Research Article

Preparation and Antibacterial Properties of Substituted 1,2,4-Triazoles

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Background. Both 1,2,3- and 1,2,4-triazoles are nowadays incorporated in numerous antibacterial pharmaceutical formulations. *Aim*. Our study aimed to prepare three substituted 1,2,4-triazoles and to evaluate their antibacterial properties. *Materials and Methods*. One disubstituted and two trisubstituted 1,2,4-triazoles were prepared and characterised by physical and spectroscopic properties (melting point, FTIR, NMR, and GC-MS). The antibacterial properties were studied against three bacterial strains: *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), and *Pseudomonas aeruginosa* (ATCC 27853), by the agar disk diffusion method and the dilution method with MIC (minimal inhibitory concentration) determination. *Results*. The spectroscopic characterization of compounds and the working protocol for the synthesis of the triazolic derivatives are described. The compounds were obtained with 15–43% yields and with high purities, confirmed by the NMR analysis. The evaluation of biological activities showed that the compounds act as antibacterial agents against *Staphylococcus aureus* (ATCC 25923), while being inactive against *Escherichia coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853). *Conclusions*. Our results indicate that compounds containing 1,2,4-triazolic moiety have great potential in developing a wide variety of new antibacterial formulations.

1. Introduction

Triazolic nucleus is nowadays considered an important moiety in the design and synthesis of bioactive compounds that are associated with numerous biological activities [1] such as antibacterial, antifungal [2], anti-inflammatory [3], anticonvulsant [4], anti-HIV [5], antineoplastic, and antiproliferative [6–13]. Additionally, there are review studies that indicate the fact that 1,2,4-triazoles occupy a distinctive place in the field of medicinal and pharmaceutical chemistry [14, 15], as well as in industry [16]. Also, synthesis and complete characterization by both spectroscopic and thermal techniques were reported in literature for numerous derivatives bearing 1,2,4-triazole moieties [17–20].

According to this, we set our goal in the synthesis, characterization (physical and spectroscopic properties, melting point, FTIR, NMR, and GC-MS), and evaluation of biological activity of three substitutes triazoles (**1**–**3**) against *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), and *Pseudomonas aeruginosa* (ATCC 27853).

2. Materials and Methods

2.1. Chemistry. The reagents were commercial products of analytical purity (Chimopar, Merck, Fluka) and used as received. Melting points were determined on a Böetius PHMK (Veb Analytik, Dresden, Germany) instrument (the values are uncorrected), and thin-layer chromatography

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Article

Synthesis and Degradation of Schiff Bases Containing Heterocyclic Pharmacophore

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Abstract: This paper reports on the synthesis and characterization of two Schiff bases bearing 1,2,4-triazolic moieties, namely 4*H*-4-(2-hydroxy-benzylidene-amino)-5-benzyl-3-mercapto-1,2,4-triazole and 4*H*-4-(4-nitro-benzylidene-amino)-5-benzyl-3-mercapto-1,2,4-triazole using thin layer chromatography, melting interval, elemental analysis, spectroscopy and thermal stability studies.

Keywords: Schiff base; synthesis; triazole; thermal behavior; kinetic study

1. Introduction

Various derivatives of 1,2,4-triazolic nucleus, such as Schiff bases were investigated in the last decades, for the great variety of medical applications such as antimicrobial [1], hypoglycemic [2],

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Kinetic of solid-state degradation of transitional coordinative compounds containing functionalized 1,2,4-triazolic ligand

Ionuţ Ledeţi · Gabriela Vlase · Titus Vlase · Vasile Bercean · Adriana Fuliaş

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Abstract Three coordinative compounds containing Ni(II), Cd(II) and Zn(II) and functionalized 1,2,4-triazolic ligand were prepared and characterized by both thermal and non-thermal methods. The applied instrumental techniques consisted in TG/DTG/HF analysis, FTIR spectroscopy, elemental analysis and complexometric titration, while the decomposition mechanism was evaluated by evolved gas analysis. The kinetic analysis of the thermolysis of the metal complexes was achieved using the thermogravimetric data in air for the main step of decomposition under thermal treatment in non-isothermal conditions. The kinetic parameters were estimated by using three isoconversional methods (Kissinger–Akahira–Sunose, Flynn–Wall–Ozawa and Friedman) and data collected at five different heating rates, $\beta = 5, 7, 10, 12$ and 15 °C min^{-1}. The obtained results were corroborated with the ones obtained by using a different approach of kinetic study, namely the nonparametric kinetics method, which allows a separation of the temperature, respective conversion dependence of the reaction rate. The obtained values for the kinetic parameters are in a good agreement for all the applied protocols.

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Keywords Metal complexes · Functionalized 1,2,4-triazole · Kinetic · NPK method · EGA study

Introduction

Metal complexes gained much attention in various scientific researches, due to their numerous biomedical, technical and agrochemical appliances [1, 2]. The importance of heterocyclic derivatives as pharmacophores, as well as bioactive compounds, is nowadays well known and intensely investigated [3–6]. Among nitrogen-containing heterocycles, 1,2,4-triazoles are studied as pharmacophores in numerous functionalized organic compounds for several well-known biological activities [7–11]. Recent studies indicate that triazoles can be associated with anti-trypanosomal activity [12], nucleotide inhibitors [13] and COX-2 inhibitors [14]. Numerous scientific papers are also reported in the field of metal complexes containing functionalized triazoles as ligands, with and/or without describing their biological activities [15–19]. Supramolecular chemistry of coordinative compounds is a rapidly developing domain in the field of complex combinations aiming towards the design of bioactive and diagnostic agents. Biological activities of coordination compounds created a new class of chemotherapeutic agents for aiming specific physiological and/or pathological targets [20].

The formation of coordinative entities containing as ligand the 1,2,4-triazolic nucleus is in agreement with the structure, existing different binding modes. It is well known that the presence of three endocyclic nitrogens and the possibility of tautomerism [21] may lead to different supramolecular structures. By functionalization of the nucleus by linking to its functional groups that possess complexing capacities, new ligands are obtained. In previous studies

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Betulonic acid

Study of thermal degradation by kinetic approach

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Abstract Even if up to date, betulonic acid (BA) was not investigated for biological activities as much as other triterpenic derivatives like betulinic acid, and there are several papers describing the synthesis, isolation and investigations—both instrumental and biological—of this compound. In this paper, the kinetic behavior associated with thermal decomposition of BA in oxidative conditions is presented. The kinetic study was realized on the main decomposition process which occurs in the 200–300 °C temperature range, according to the ICTAC 2000 protocol, namely employing three isoconversional methods, one differential (Friedman) and two integral (Kissinger–Akahira–Sunose and Flynn–Wall–Ozawa). In order to separate the multistep contributions to the degradation process of BA, the NPK method was employed. This method suggested that the degradation occurs by two parallel processes, with different energetic contributions, with a mean value of 162.1 ± 5.5 kJ mol^{-1}.

Keywords Betulonic acid · Kinetic study · Birch bark · Betulin functionalization · Thermal behavior · NPK method

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Abbreviations

α	Conversion degree
T	Temperature
$f(\alpha)$	Differential conversion function
$g(\alpha)$	Integral conversion function
R	Universal gas constant
β	Heating rate and $\beta = dT/dt$ (where t—time)
$k(T)$	Temperature dependence
A	Pre-exponential factor
E_a	Activation energy given by the Arrhenius equation

Introduction

It is well known that plants are a good source of numerous bioactive molecules, which can be separated, purified, functionalized or included in supramolecular structures [1] in order to modify their biodisponibility. The main advantages of naturally occurring compounds consist in their complex structures which are difficult to be obtained by a total chemical synthesis, starting from simple reagents. Betulin and its derivatives were greatly investigated in the last 10 years, with more than 1500 indexations on Web of Knowledge up to date [2].

Betulonic acid (BA) [3-oxolup-20(29)-en-28-oic acid] (Fig. 1) is a pentacyclic triterpene derivative belonging to the lupane family, which is currently studied for several biological and pharmacological activities. Even if up to date, BA and derivatives were not investigated as much as other compounds from the triterpenoid class (betulin and betulinic acid), and around 150 scientific articles published data regarding antiviral [3], antimalarial [4], antibacterial [5, 6], anti-inflammatory, genotoxic and mutagenic

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Solid-State Characterization and Biological Activity of Betulonic Acid Derivatives

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Abstract: Betulonic acid belongs to the pentacyclic triterpenic derivative class and can be obtained through the selective oxidation of betulin. In this study we set obtaining several functionalized derivatives of this compound by its condensation with several amino compounds such as aminoguanidine, hydroxylamine, *n*-butylamine and thiosemicarbazide as our goal. The functionalization of the parent compound led to several molecules with antiproliferative potential, the most promising being 3–2-carbamothioylhydrazonolup-20(29)-en-28-oic acid.

Keywords: betulonic acid derivatives; triterpene; thermal analysis; synthesis; biological activity; MTT assay

1. Introduction

Naturally occurring compounds have always been an important source of pharmacologically-active molecules, associated with numerous biological targets and receptors. The importance of studying naturally occurring compounds is also sustained by the fact that most plants are accessible resources, the main problems consisting only in separation and purification of the bioactive derivatives contained therein, which can be realized by employing numerous different instrumental and experimental techniques [1–3]. Among all naturally occurring compounds, triterpenoids have been intensely studied in the last decades, since these compounds are widely distributed in numerous plants and possess important biological activities [4–9].

Betulin-skeleton compounds (including acids, aldehydes and their functionalized derivatives) are well studied and recent references for numerous biological activities are reported [10,11], such as treatment of liver fibrosis [12], proapoptotic and inhibition of cell migration in cancer [13,14], antitumour [15,16], anti-mycobacterial [17], hypoglycemic [18], effective adjuvant treatment option in pruritic dry skin [19], antiviral effect [20] and also immunomodulatory [21] and anti-inflammatory activities [22].

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Thermal stability of synthetic thyroid hormone L-thyroxine and L-thyroxine sodium salt hydrate both pure and in pharmaceutical formulations

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ABSTRACT

In this paper, the thermal stability of pure L-thyroxine (THY) and L-thyroxine sodium salt hydrate (THYSS) *vs.* two pharmaceutical solid formulations commercialized on both Romanian and European market (with a content of 100 μg, respectively 200 μg THYSS per tablet) were investigated. In order to determine whether the presence of excipients affects the thermal stability of the active pharmaceutical ingredient (API), the preliminary study of thermal stability in air atmosphere was completed with an *in-depth* solid-state kinetic study. By kinetic analysis, the non-isothermal degradation of the selected active pharmaceutical ingredients *vs.* the solid formulation with strength of 200 μg THYSS per tablet was investigated.

Isoconversional methods (Kissinger–Akahira–Sunose, Flynn-Wall-Ozawa and Friedman) were employed for the estimation of activation energies values, at five different heating rates, β = 5, 7, 10, 12 and 15 °C min^{-1}. Also, a fourth method was applied in the processing of data, namely NPK, allowing an objective separation in the physical and chemical processes that contribute to the thermal degradation of the selected compounds. A discussion of thermal stability from the kinetic point of view is also presented.

1. Introduction

Levo-isomer of thyroxine ((*S*)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]propanoic acid, usually abbreviated as T_4) (Fig. 1) is the primary hormone secreted by the thyroid gland and plays a key-role in regulating metabolic processes and physical development [1]. Thyroxine (THY) is also formulated as pentahydrate sodium salt (THYSS) (Fig. 1), which is the most common active pharmaceutical ingredient (API) used as a substitutive therapy for the inadequate secretion of T_4 in the body. These compounds are mainly used in the treatment of several deficitary-hormone diseases, such as chronic lymphocytic thyroiditis, hypothyroidism, or simple non-endemic goiters [2].

l-Thyroxine (T_4) and triiodo-*l*-thyronine (T_3) are iodine-containing hormones produced in the follicular cells of the thyroid gland from thyroglobulin. THY is a synthetic form of the thyroid hormone thyroxine which is currently used to treat thyroid hormone deficiency, and as a preventer for the recurrence of thyroid cancer. Today, most patients are treated with levothyroxine (THY), or *l*-thyroxine sodium salt hydrate (THYSS), which are currently formulated as numerous brand names, as well as generic versions [3].

According to Drugbank, the marketing of pharmaceutical formulation containing THY started in 1951 with tablets, and up to the date, more than 400 formulations are distributed worldwide.

Abbreviations: α, conversion degree; T, temperature; $f(\alpha)$, the differential conversion function; $g(\alpha)$, the integral conversion function; R, the universal gas constant; β, the heating rate and $\beta = dT/dt$ (where t—time); $k(T)$, a temperature dependence; A, the pre-exponential factor and E_a—the activation energy given by the Arrhenius equation.

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Kinetic analysis of solid-state degradation of pure pravastatin versus pharmaceutical formulation

Ionuţ Ledeţi[1,2] · Gabriela Vlase[1] · Titus Vlase[1] · Adriana Fuliaş[2]

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Abstract In this paper, the kinetic behavior of decomposition of a well-known bioactive substance used for treating dyslipidemia and the prevention of cardiovascular disease drug from statin class, namely pravastatin, was described. The kinetic study was performed on the main decomposition process which occurs at nearly 200 °C, for both pure active substance and a generic commercial formulation that contain 40 mg pravastatin per tablet, using Kissinger, Friedman, Kissinger–Akahira–Sunose, Flynn–Wall–Ozawa and NPK methods. The stability of pravastatin as pure active substance and as tablet was compared by means of kinetic data, and the results suggested that in the solid pharmaceutical formulation, PRV has an increased stability compared to pure active substance.

Keywords Statin · Kinetic study · Pravastatin · Tablet · Thermal behavior · NPK method

Introduction

Pravastatin (PRV) is an active pharmaceutical ingredient mainly used for the treatment of dyslipidemia and the prevention of cardiovascular disease [1], conditioned in solid dosage forms as sodium salt. PRV is mainly prescribed for treating patients who have or are at risk of arteriosclerotic vascular disease and its consequences and strokes [2]. The literature indicates that PRV provides several health benefits such as decreasing the level of total cholesterol, LDL cholesterol and triglycerides [3], while increasing the level HDL cholesterol [4]. Regarding its activity over cardiovascular system, PRV was reported to reduce the risk of death by decreasing the possibility of heart attacks [5]. Other studies revealed that PRV decreases the risk of acute ischemic strokes and transient ischemic attacks (TIAs or mini-strokes) [6].

Nowadays, PRV is administered to patients on dose range from 10 up to 80 mg day^{-1}. The usual starting dose in adults is 40 mg once daily. The starting dose for patients with major liver or kidney dysfunction is 10 mg daily. PRV is commercialized generically following the Bristol–Myers Squibb's patent expiration in April 2006 [7] under several brands in solid formulations containing 10, 20, 40 and 80 mg of active pharmaceutical ingredient. Other studies reveals that PRV stimulates angiogenesis in murine models [8] and improves acetylsalicylic acid-mediated blood platelet inhibition, in vitro [9], while it has been suggested that statins appear to have therapeutic benefits in diseases that are unrelated to elevated serum cholesterol levels, such as pain and inflammation [10]. The importance of PRV active substance and statins is also revealed by review studies that indicate new therapeutic perspectives of statins in autoimmune diseases and cancer, antiatherosclerotic, anti-inflammatory, antioxidant, immunomodulatory and antithrombotic effects [11].

The chemical structure of PRV [(3*R*,5*R*)-3,5-dihydroxy-7-((1*S*,2*S*,6*S*,8*S*,8a*R*)-6-hydroxy-2-methyl-8-(((*S*)-2-methylbutanoyl)oxy)-1,2,6,7,8,8a-hexahydronaphthalen-1-yl)heptanoic acid] consists in a hexahydronaphtalene ring functionalized as a methylbutyrate ester [12] (Fig. 1).

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Comparative thermal stability of two similar-structure hypolipidemic agents

Simvastatin and Lovastatin—kinetic study

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Abstract Simvastatin (SIM) and lovastatin (LOV) are two important active pharmaceutical ingredients from statin class, prescribed in the treatment of hypercholesterolemia. Our study presents the results obtained by our research group regarding the decomposition of SIM and LOV in oxidative atmosphere, by employing three isoconversional methods, namely Friedman, Kissinger–Akahira–Sunose and Flynn–Wall–Ozawa. The results obtained by Friedman method suggested a multistep degradation, while the ones obtained by Kissinger–Akahira–Sunose and Flynn–Wall–Ozawa suggested a single-step degradation. In order to validate the results, we used the NPK method, which allowed a concrete separation and nature of processes that contributed to the degradation of both statins. NPK method showed that both SIM and LOV are degraded by contribution of two distinctive chemical processes, and the mean values of activation energies are also reported.

Keywords Statin · Simvastatin · Lovastatin · Kinetic study · Thermal behavior · NPK method

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Introduction

Statin medication is currently used as most common treating scheme for dyslipidemia [1]. Below their main use as antihypercholesterolemic drugs, statins also prevent cardiovascular disease and are studied for the anticancer, antithrombotic, antiatherosclerotic, anti-inflammatory and antioxidant effects [2].

Lovastatin (LOV) is a naturally occurring active substance found in *Monascus purpureus* [3] and *Pleurotus ostreatus* [4]. The structural formula of LOV ((1*S*,3*R*,7*S*,8*S*,8a*R*)-8-{2-[(2*R*,4*R*)-4-hydroxy-6-oxooxan-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2*S*)-2-methylbutanoate) is presented in Fig. 1.

Simvastatin (SIM) is a statin with a similar structure to LOV, used for hypolipidemic effect, obtained by biochemical functionalization of lovastatin (LOV), by fermentation under *Aspergillus terreus*. The structural formula of SIM ((1S,3R,7S,8aR)-8-(2-((2R,4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl)ethyl)-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate)) is also presented in Fig. 1. As can be seen, SIM and LOV have similar chemical structures, the only difference is in the lateral ester moiety, SIM having two methyl groups attached to butanoate chain in 2,2 position, while LOV having only one in the same position (Fig. 1).

Lovastatin and simvastatin are effective in reducing total and LDL cholesterol, as well as plasma triglycerides and apolipoprotein *B*, by a mechanism previously described in literature [5].

Even if LOV and SIM are biologically inactive in the lactone-form, the in vivo hydrolysis to the open form of β-hydroxyacid determines the apparition of biological activity. Drugbank indicates that both statins are incorporated in solid formulations, as follows: SIM is formulated as tablets or film-coated tablets with a content between 5

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Selection of solid-state excipients for simvastatin dosage forms through thermal and nonthermal techniques

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Abstract The importance of developing new pharmaceutical final formulations is nowadays well known. In this paper, we present the study of compatibility between bioactive antihyperlipidemic agent simvastatin and eight currently used pharmaceutical excipients for developing solid dosage forms, namely starch, microcrystalline cellulose, lactose monohydrate, polyvinylpyrrolidone, colloidal silica, talc, magnesium citrate and sorbitol. The compatibility investigations were carried out under ambient temperature by FTIR spectroscopy studies and PXRD patterns and then completed by the use of thermal analysis (TG/DTG/HF) data to study the influence of temperature over stability of binary mixtures.

Keywords Statin · Compatibility study · Simvastatin · Thermal behavior · Excipient · FTIR · PXRD

Introduction

Statins are nowadays considered the most effective and best-tolerated compounds for treating dyslipidemia [1]. The mechanism of action consists in competitive inhibition of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A), which catalyzes the rate-limiting step in the biosynthesis of cholesterol [1, 2]. Simvastatin (SMV) is a member of the statin class of pharmaceuticals and is nowadays a currently used drug for hypolipidemic effect, generally combined with mass loss diet and physical exercise, in order to decrease elevated levels of cholesterol (or to reduce hypercholesterolemia) [1]. Simvastatin is a synthetic derivative of lovastatin, which is a fermentation product of *Aspergillus terreus*. SMV is commercialized generically following the patent expiration under numerous brands, as a singular active substance (like Zocor®) or in combination with another active substance like sitagliptin (Juvisync®), niacin (Simcor®) or ezetimibe (Vytorin®). Along with the primary use of SMV, studies reported potential cardioprotective effect [2], attenuation of the cerebral vascular endothelial inflammatory response in a rat traumatic brain injury [3] or pleiotropic properties which include anti-inflammatory and immunomodulatory effects [4]. Other recent studies revealed that SMV attenuates the loss of body mass, as well as muscle mass, and improves cardiac function [5], and as well revealed an antihypertensive activity and can modulate the antihypertensive effect of losartan in hypertensive hypercholesterolemic animals and patients [6]. However, several side effects were observed, including muscular or liver problems [7] and increased blood sugar levels [8].

The structural formula of SMV ((1*S*,3*R*,7*S*,8a*R*)-8-(2-((2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl)ethyl)-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate)) contains a hexahydronaphtalene ring functionalized as a dimethylbutyrate ester (Fig. 1). SMV is a lactone-type prodrug that is modified in the liver to active hydroxy acid form. Due to the presence of the lactone moiety, SMV is less soluble in water than other statins, but

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