



Short communication

Water-soluble loratadine inclusion complex: Analytical control of the preparation by microwave irradiation

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ABSTRACT

The majority of active pharmaceutical ingredients are poorly soluble in water. The rate-determining step of absorption is the dissolution of these drugs. Inclusion complexation with cyclodextrin derivatives can lead to improved aqueous solubility and bioavailability of pharmaceuticals due to the formation of co-crystals through hydrogen-bonding between the components. Inclusion complexes of loratadine were prepared by a convenient new method involving microwave irradiation and the products were compared with those of a conventional preparation method. Dissolution studies demonstrated that the solubility and rate of dissolution of loratadine increased in both of the methods used. The interactions between the components were investigated by thermal analysis and Fourier Transform Infrared studies. The microwave treatment did not cause any chemical changes in the loratadine molecule.

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1. Introduction

It is estimated that 40% or more of active pharmaceutical ingredients identified through combinatorial screening programs are poorly soluble in water [1]. The bioavailability of drugs depends on their solubility and permeability. The drugs belonging in class II of the Biopharmaceutical Classification System have high membrane permeability, and the limiting factor of their absorption is therefore their solubility [2].

One of the methods applied to increase solubility is to prepare inclusion complexes with cyclodextrins (CDs) [3–5]. Such complexes have found extensive application in many fields, including pharmaceutical technology (to increase the aqueous solubility, dissolution rate, bioavailability and stability of drugs, to reduce bitterness and to decrease tissue irritation upon dosing) [6]. CDs are usually used for solubility enhancement from the preclinical stage during drug development. The methods widely utilized to prepare inclusion complexes are coprecipitation, kneading, freeze-drying and co-grinding [7]. They often involve time-consuming manufacturing processes and generally require large amounts of solvents. There is therefore a need for faster and more convenient processes for the preparation. Microwave (MW) irradiation,

a method recently used to prepare CD inclusion complexes, has the major advantages of shorter reaction times and higher yields of products [8]. In pharmaceutical technology, MW has been used because of its thermal effect in drying processes (granules or crystals), and for the sterilization of injections and infusions [9–11].

Loratadine (LOR) (Fig. 1) is a second-generation tricyclic H₁ antihistamine, marketed for its non-sedating properties. H₁ antihistamines prevent and suppress the responses to histamine or allergen in the nose and conjunctivae, thereby eliminating such symptoms as itching, congestion, rhinorrhoea, tearing and sneezing [12]. The solubility of LOR depends on the pH: on increase of the pH, the solubility decreases exponentially. Because of this, its bioavailability exhibits high variability, which is a disadvantage for its oral administration [13] because the drug may suffer a reduced therapeutic efficacy.

In general kneading, which is a simple and scaleable preparation method, gives the best results [14], but in this case the removal of the solvent could be a critical parameter in the preparation. In the present work the applicability of MW irradiation to prepare inclusion complexes without chemical change was studied. The conventional (kneaded product; KP) and a convenient preparation technique using MW irradiation treatment were compared in the case of LOR + dimethyl-β-CD (DIMEB) inclusion complexes. Dissolution studies were performed with the paddle method, and the interactions of the components were investigated by

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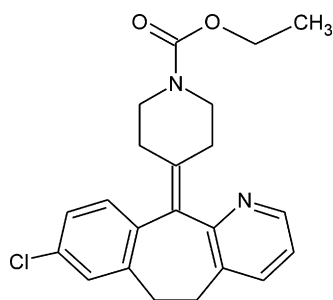


Fig. 1. Chemical structure of loratadine.

thermoanalytical methods [15] and Fourier Transform Infrared (FT-IR) spectrometry.

2. Materials and methods

2.1. Materials

Heptakis-2,6-di-*O*-methyl- β -cyclodextrin (DIMEB) was purchased from Cyclolab (Fig. 2); LOR (ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate) was kindly provided by TEVA Pharmaceutical Industries Ltd. (Hungary); other chemicals were of analytical reagent grade purity.

2.2. Preparation of products

Homogeneous powder mixtures of LOR and the appropriate amount of DIMEB were prepared in three molar ratios (LOR:DIMEB=1:1, 1:2 and 1:3), the same mass of 50% alcohol was then added to the mixtures, and they were next homogenized, and treated in a MW oven (Milestone Ethos TC MW apparatus, Advanced Microwave Labstation, Italy). The method of MW treatment was as follows: 150 W, 90 s, 60 °C, and the samples were then dried under vacuum [7]. As a control KPs were made: the physical mixtures were suspended in the same mass of 50% ethanol, and the solvent was evaporated at room temperature. The products were ground and sieved (100 μ m), and stored at room temperature under normal conditions. The

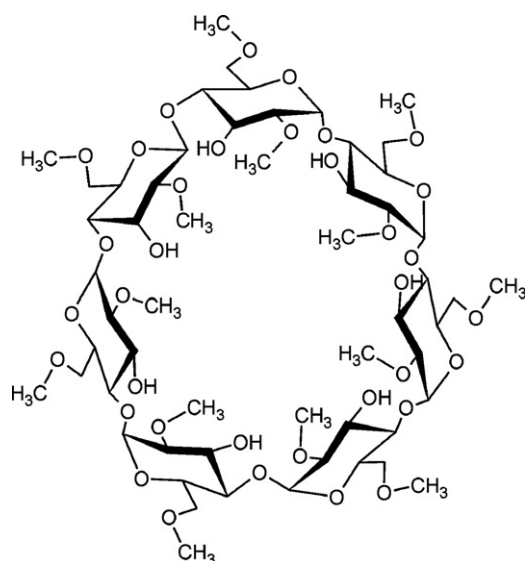


Fig. 2. Chemical structure of DIMEB.

actual LOR load of products was determined spectrophotometrically.

2.3. Dissolution study

In vitro dissolution studies (min. three parallel measurements) were performed in simulated intestinal medium (SIM) (phosphate buffer; pH 7.0 ± 0.1 ; 0.1 M) using the modified rotating paddle method. 50 mg of LOR, or product containing 50 mg of LOR (considering the LOR load of products and water content) was measured and added to 100 ml of SIM (100 rpm at 37 ± 0.1 °C). Aliquots were withdrawn at 5, 10, 15, 30, 60, 90 and 120 min and immediately filtered. At each sampling time, an equal volume of fresh SIM was added, and the correction for the cumulative dilution was calculated. The concentration of LOR was measured spectrophotometrically at 248 nm after the suitable dilution (Unicam UV/VIS spectrometer, Unicam, UK). The calibration curve was determined between 0 and 28 μ g/ml, the slope was 0.0366, the linearity (r^2) was 0.9997. There was no absorption of DIMEB at the absorption maximum of the LOR. The limit of quantification (LOQ) value was 500 μ g/l.

2.4. Thermoanalytical studies

2.4.1. Differential scanning calorimetry (DSC)

The DSC records were obtained with a Mettler Toledo DSC 821^e apparatus. Between 2 and 5 mg of sample was crimped in a standard aluminum pan (40 μ l) and heated from 25 to 300 °C at a heating rate of 5 °C/min under a constant purge of argon at 10 l/h.

2.4.2. Thermogravimetric measurements

The TG, DTG and DTA curves were recorded in parallel in platinum crucibles with the same thermal program (heating range 25–300 °C, heating rate 5 °C/min), using a MOM Derivatograph-C (MOM Co., Hungary). The reference was a crucible containing aluminum oxide.

2.5. FT-IR analysis

The sample with a LOR content of 0.5 mg was ground and mixed with 150 mg of dry KBr in an agate mortar, and the mixture was then compressed into a disc at 10 t. Each disc was scanned 64 times at a resolution of 4 cm^{-1} over the wavenumber region 4000–400 cm^{-1} with an FT-IR spectrometer (Thermo Nicolet AVATAR 330, USA). The evaluation was carried out with the GRAMS/AI Ver. 7 program.

3. Results and discussion

3.1. Dissolution study

The investigated active pharmaceutical ingredient LOR has different solubility properties at the various pH levels in the gastrointestinal tract. LOR can undergo protonation on the N of the pyridine ring in acidic media, forming salts with good solubility; in contrast, in SIM it is practically insoluble (0.38 mg/100 ml). Since LOR is a weak base, it is absorbed from the intestine. Accordingly, the dissolution properties were studied in SIM. The dissolution curves are demonstrated in Fig. 3. For both the KP and MW products, the dissolution rate and the solubility of LOR depended on the molar ratio. At 1:1, the quantity dissolved was about 60%, whereas for the 1:2 and 1:3 products close to 100% release was observed. These investigations revealed that the KP and MW products yield similar dissolution results.

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