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Role of thermodynamic, kinetic and structural factors in the recrystallization behavior of amorphous erythromycin salts

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ABSTRACT

Amorphous form has become an important drug delivery strategy for poorly water soluble drugs. However, amorphous form has inherent physical instability due to its tendency to recrystallize to stable crystalline form. In the present study, amorphous forms of erythromycin free base (ED) and its salts namely, stearate (ES), phosphate (EP) and thiocyanate (ET) were generated by *in situ* melt quenching and evaluated for their crystallization tendency. Salts were characterized for kinetic, thermodynamic and structural factors to understand crystallization behavior. Kinetics of crystallization followed the order as ES > EP > ET > ED. Fragility and molecular mobility does not completely explain these findings. However, configurational entropy (S_{conf}), indicative of entropic barrier to crystallization, followed the order as ET > EP > ES > ED. Lower crystallization tendency of ED can be explained by its lower thermodynamic driving force for crystallization (H_{conf}). This correlated well with different structural parameters for the counter ions.

1. Introduction

Current drug discovery approaches, including high throughput screening and combinatorial chemistry, have led to new drug candidates having poor biopharmaceutical performance [1]. Amongst all the strategies, salt formation is one of the prime approach, to optimize the physicochemical properties of ionizable drug candidates [2,3]. Similarly, amorphous form generation is another delivery platform for water insoluble drug candidates [4–6]. Recently, a combined approach of salt formation and amorphous form generation, namely, amorphous salt form, has been utilized to harness the advantages of both the salt form as well as of the amorphous form [7,8]. Atorvastatin calcium, rosuvastatin calcium and quinapril hydrochloride are some examples of commercially available amorphous salt forms.

Physical stability of an amorphous salt form is affected by the nature and type of the counterion. For example, amorphous salts with strongly interacting counterions generally have a higher glass transition temperature (T_g) and improved physical stability, compared to amorphous form of the unionized drug [9–13]. Similarly, the recrystallization behavior from the amorphous form also differs in different salt forms [10–12,14]. Kinetic, thermodynamic and structural factors contribute to the physical stability of amorphous form. Effect of counterions on these factors has been studied, with emphasis on ionic interactions [15], ionic radius [11], pK_a of the counterion [9,12], electrophilicity index [9,12] and hydrogen bonding [14]. Previous work from our lab reported the crystallization behavior of amorphous atorvastatin salts [10] and amorphous prazosin salts [14]. It was observed that the strength of ionic interaction affects the T_g and crystallization behavior of drug salts. However, these studies primarily evaluated the effect of kinetic factors (*i.e.* molecular mobility) on the crystallization behavior of amorphous salts, without assessing the role of thermodynamic factors. This was due to concomitant degradation of drug salts along with melting, thus precluding the determination of thermodynamic parameters.

The present work is aimed at evaluating the role of counterion on both kinetic and thermodynamic factors, and their impact on physical stability of amorphous salts. Erythromycin dihydrate free base (ED) and its salts, namely, erythromycin stearate (ES), erythromycin phosphate (EP) and erythromycin thiocyanate (ET) were selected for this study. Erythromycins (Fig. 1) are macrolide antibiotics, and contains a 14-membered lactone ring with ten asymmetric centers and two sugars (L-cladinose and D-desosamine) [16]. Salt formation in erythromycins involves generation of a positive character on the tertiary amino group, thus rendering a basic character to the desosamine ring of erythromycin (pK_a 8.8). Different erythromycin salts have been reported with counterions such as stearate, phosphate, thiocyanate, gluceptate, sulfamate, lactobionate and ethyl phosphate [16].

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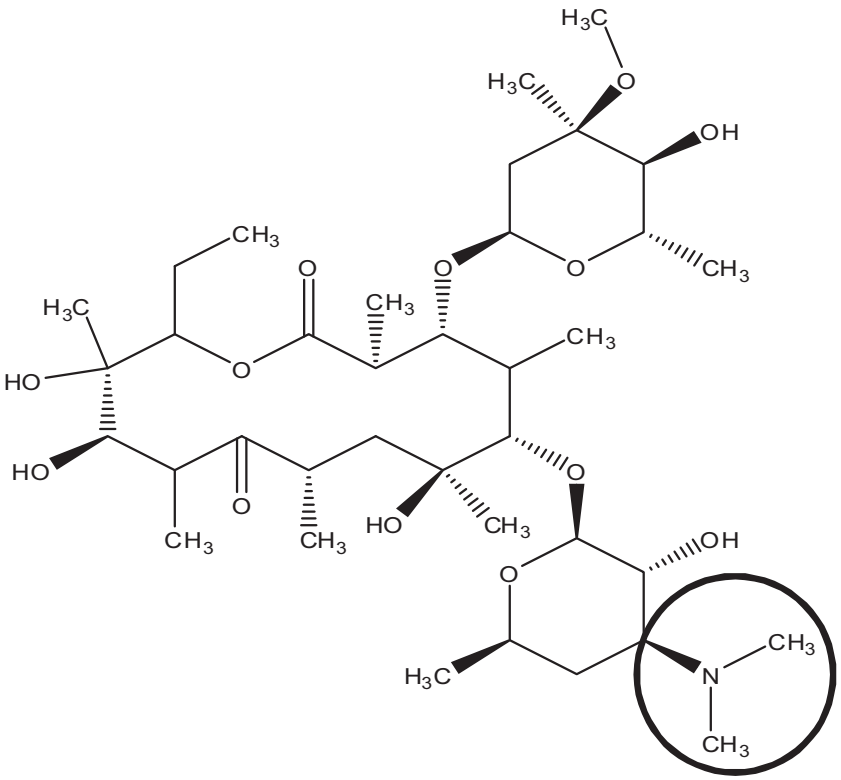

Fig. 1. Structure of erythromycin (encircled portion shows the tertiary amino group that provides a basic character to the desosamine ring of erythromycin).

2. Materials and methods

2.1. Materials

ED and EP were received as gratis samples from Century Pharmaceuticals Limited, India, and ES and ET were received from Mehta Pharmaceutical Industries, India. All samples had purity of >99.5% and were used '*as received*'. All other chemicals were of analytical reagent grade.

2.2. Differential scanning calorimetry (DSC)

DSC heating curves of samples were obtained using DSC Q2000 (TA Instruments, USA). DSC cell was purged with dry nitrogen at 50 ml min^{-1}. Instrument was calibrated prior to analysis, using high purity standard of indium and sapphire (aluminum oxide) for temperature-heat flow and heat capacity (C_p) measurement, respectively. Accurately weighed sample (5–8 mg) were crimped in aluminum pans and run in the temperature range of 298–483 K, at 10 K min^{-1} heating rate. T_g was reported as the onset temperature, while endothermic transitions were reported as the midpoint value.

2.3. Thermogravimetric analysis (TGA)

Weight loss of samples as a function of temperature was determined using Mettler Toledo 851e TGA (Mettler Toledo, Switzerland). Samples were placed in alumina crucibles and heated at 10 K min^{-1}, under nitrogen purge (50 ml min^{-1}), in the range of 298–483 K.

2.4. Hot stage microscopy (HSM)

Thermal behavior of samples was observed using Leica DMLP polarized microscope (Leica Microsystems Wetzlar GmbH, Germany), equipped with Linkam LTS 350 hot stage. Photomicrographs were acquired using JVS color video camera and analyzed using Linksys32 software. Samples were mounted in silicone oil and heated from 298 K to 483 K at 10 K min^{-1}.

2.5. Optical and polarized light microscopy

Particle characteristics were assessed by optical and polarized microscopy using a Leica DMLP polarized light microscope (Leica Microsystems, Germany). Photomicrographs were acquired using JVS color video camera and processed using Linksys® software.

2.6. Karl Fischer (KF) titration

Water content was determined by KF titration, using pyridine-free reagents and the dead stop end point method (Karl Fischer titrator 794 Basic Titrino, automatic burette 794 for presentation of solvent, 703 Ti stand; Metrohm AG, Switzerland). Analytical grade disodium tartrate dihydrate (15.65% water content) was used as the KF standard.

2.7. Powder X-ray diffraction (PXRD)

PXRD pattern of samples was recorded at room temperature on Bruker's D8 advance Diffractometer (Bruker, Germany) with a 2θ compensating slit and CuKα radiation (1.54 Å), at 40 kV, 40 mA passing through nickel filter. Analysis was performed in a continuous mode with a step size of 0.01° and scan rate of 1 s/step over an angular range of 3–40° 2θ. Obtained diffractograms were analyzed with DIFFRACplus EVA® (version 9.0) diffraction software.

2.8. Generation of amorphous forms

Amorphous ED and its salts were freshly prepared using *in situ* melt quenching in DSC. Crystalline samples were heated to 5 K