Discovering New Crystalline Forms of Atorvastatin Calcium

- New Strategies for Screening -

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von

Herr M. Sc. Yong Suk Jin

geb. am: 12.03.1974 in Jeju, Südkorea

Gutachter:

1. Prof. Dr.-Ing. habil. Dr. h.c. Joachim Ulrich

2. Prof. Dr.-Ing. Kwang-Joo Kim

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Table of contents

1. Introduction

The majority of drug substances are formulated as solid forms due to their patient convenience and compliance, with most marketed drug products containing crystalline drug substance and/ or excipients [BYR99]. In addition, drug substances have been becoming more structurally complex, with a variety of functional groups, which may form a number of intra- and intermolecular interactions and which may tend to be crystallized in different arrangements and/ or conformations of the molecules, i.e., different solid-state forms like polymorphs, solvates and amorphous state. These solid forms can differ widely in their physicochemical, mechanical and biopharmaceutical properties, and thus can influence the quality, safety and efficacy of the drug products [BRI99], [USD07].

The big pharmaceutical companies which have blockbuster drugs are often using patents on different solid forms to extend the exclusive usage of their drugs, whereas the generic competitors are interested in new polymorphs, solvates and salts to bypass existing patents and to enable earlier marketing of a generic version. Also, new solid forms can offer enhanced possibilities to modulate and design drug products with improved or desired properties.

Atorvastatin used as a cholesterol-lowering agent for the treatment of hypercholesterolemia is a synthetic statin, 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor, which catalyzes the rate-limiting step in cholesterol biosynthesis [LEA97]. Atorvastatin was marketed as its calcium salt (2:1) in crystalline trihydrate designated Form I under the brand name LIPITOR® [BRI97]. It has become the world's best-selling drug in the history of pharmaceuticals with sales of more than US$ 10 billion/year [ASS11]. Due to its huge market it has prompted the competition between the innovator and generic challengers to grow more and more. A large number of patents concerning different crystalline forms as well as processes for amorphous forms have been published.

The primary objective of this work is to discover new strategies to disclose polymorphs and solvates and to find new crystalline forms of atorvastatin calcium (ATC) [CHO10], [LEE08], [LIM09], [JIN11a]. In order to achieve this goal, this work is divided into 2 parts. The first part is taking a close look at the previously reported solid forms of ATC to derive a proper polymorph screening strategy. The second part deals with the generation and characterization of the newly discovered crystalline forms.

2. Background

2.1 Solid forms of drug substance

Most of drug substances, active pharmaceutical ingredients (APIs), exist in different solid forms [CHA03], [HE00], [HIL06], [STE01]. The various solid forms of an API may have different properties such as solubility, stability, hygroscopicity and density [BYR95], [BYR99], [BYR02], [GRA99]. Solid forms can be subdivided two main classes: amorphous form and crystalline form.

2.1.1 Amorphous form

Molecules tend to arrange themselves into regular repeating units in the solid state creating a three dimensional array which is defined as a crystal. If there is no regular repeating unit, i.e., lack a long-range order of molecule, the solid form is termed amorphous form, also named glass [YU01]. However, it may have local or short-range molecular order [SHA06]. The amorphous form is generally known to be thermodynamically unstable and a reactive compared to the crystal form which has a lower energy [PET06].

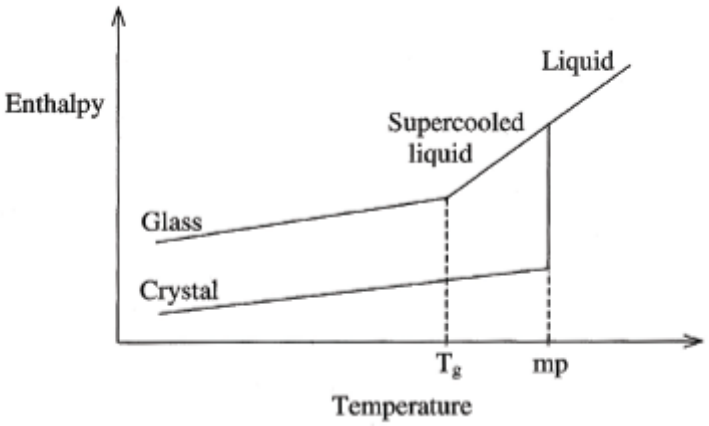


Figure 2.1 Schematic plot of enthalpy as a function of temperature for condensed materials [PET06]

In some pharmaceutical applications, the amorphous materials can be advantageous concerning an improved bioavailability because their high energy state lead to a higher solubility and dissolution rate. On the properties of pharmaceutical amorphous solids, a number of good reviews have been published [HAN97], [HIL04], [YU01].

On the other hand, due to the higher energy the amorphous form is more physically unstable than the crystalline form and it tends to crystallize to a more stable crystalline form [CRA99], [CUI07], [YU01]. It has also been shown that the increase in molecular mobility decreases chemical stability [GUO00]. Since this can create a problem during manufacturing and storage, therefore, the conditions of processing and storage have to be carefully controlled [ZHA04].

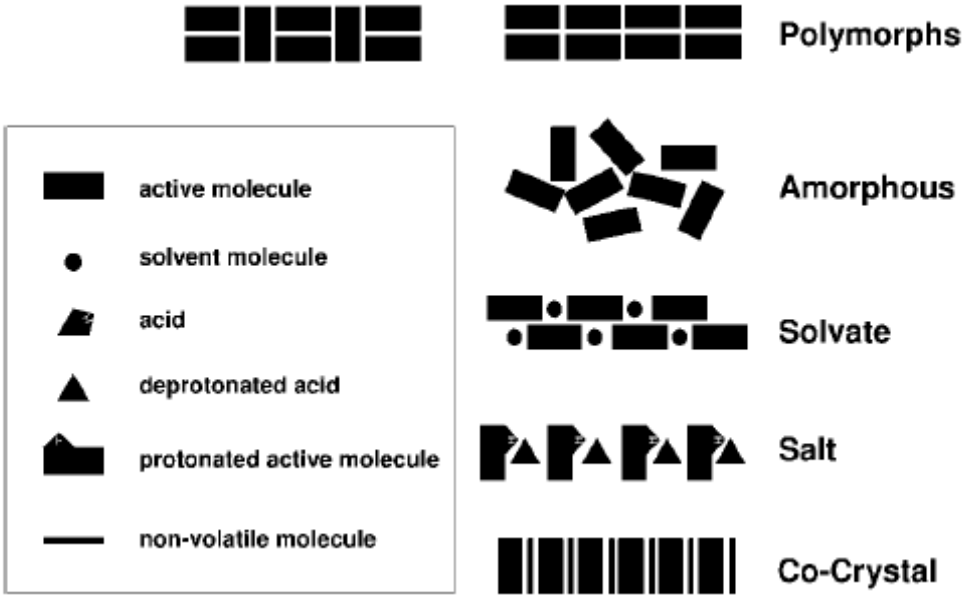


Figure 2.2 Schematic depiction of various types of solid forms [HIL06]

2.1.2 Crystalline form

The crystalline form is characterized by the regular arrangement of building blocks which may be molecules and group of molecules [ATK06], [BYR99]. The regular repeating unit of a crystalline form is termed the unit cell and the way building blocks arrange themselves in the unit cell is referred to as crystal packing [MAS02]. Depending on whether the crystal packing is composed of one component, API molecule, or multi-components, API and one or more

other components, crystalline forms can be classified into one- and multi-component systems [ROD04].

In 1965, McCrone defined a polymorph as “a solid crystalline phase of a given compound resulting from the possibility of at least two crystalline arrangements of the molecules of that compound in the solid state” [McC65]. According to this definition, polymorphs of an API are one-component systems being composed of only API molecules. In recent publications, a broader definition for polymorphs has been used: polymorphs are crystalline solids of the same chemical composition which differ in their unit cells [BRI07], [HIL06]. The later definition implies that polymorphs may also represent multi-component systems.

The incorporation of solvent molecules into the crystal lattice of an API results in a crystalline multi-component system containing at least the API, as neutral molecule or as ion plus counterion, and the solvent(s). A solvate is defined as a crystalline multi-component system in which a solvent(s) “is coordinated in or accommodated by the crystal structure” [GRI06]. In case the solvent is water, the solid form is named hydrate. Various types of multi-component systems have been described such as solvates, salts and co-crystals [KHA95], [SHA08], [STA06]. Co-crystals consist of two or more components that are solid at ambient conditions [VIS06].

Different crystalline forms, polymorphs, can have either monotropic or enantiotropic relationships [BUR79], [GRU96], [LOH06] which may be illustrated using energy-temperature diagrams as Figure 2.3. The Gibbs free energy of a polymorph, G, is expressed as:

$$G = H - TS \tag{2-1}$$

where H is the enthalpy, T is the absolute temperature and S is the entropy [BER99]. At a given temperature and a constant pressure, only one polymorph is thermodynamically stable. The stable form is that with the lowest Gibbs free energy in the given conditions and is the least soluble form. The order of polymorph stability is defined by the difference in Gibbs free energies. In an enantiotropic system the stable polymorph having the lower Gibbs energy is different above and below a transition temperature. At the transition temperature, the difference in Gibbs free energies is zero. In a monotropic system one polymorph is always stable than the other below the melting point of either form. In addition to thermodynamics the existence of different polymorphs is controlled by kinetics. Therefore, other thermodynamically unstable forms with a higher Gibbs free energy can exist in the given conditions, and are termed metastable forms.

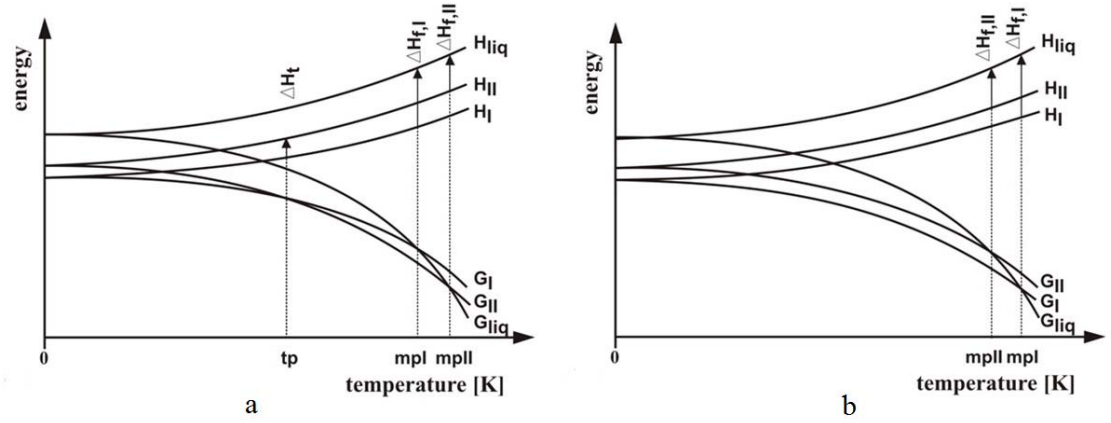


Figure 2.3 Energy-temperature diagrams for an enantiotropic (a) and a monotropic (b) system; *G* is the Gibbs energy, *H* is the enthalpy, *ΔH* is the change in enthalpy, mp is the melting point, tp is the transition point and the subscripts I, II and liq refer to polymorph I, polymorph II and to the liquid phase [GRU96]

Further information on polymorphism and its applications in the pharmaceutical industry is given in a number of publications (e.g., [BRI99], [HAL69], [HAL75], [HIL06], [KHA95], [McC65], [THR95], [THR00]).

2.1.3 Solid state properties

The solid state properties of an API can affect all stages involved in the development of pharmaceutical solid dosage forms including processing, quality control and regulatory affairs [BYR99]. Hence, the fact that different solid forms of an API exhibit different properties makes the study and control of the solid form an issue of utmost importance for pharmaceutical industry. The relevance of the topic becomes evident in the ICH Q6A Guidance on specifications [INT99]. The guidance describes the possible existence of different solid forms and the necessity to set an acceptance criterion for the solid form content present in the drug substance in case the drug product safety, performance or efficacy is affected by the solid form. The various solid forms of an API may have differences in properties such as solubility, chemical stability, hygroscopicity, compression behaviour, flow properties, melting points and density [BYR95], [BYR02]. The physical properties that vary between different solid forms are listed in Table 2.1 [GRA99]. Thus, there is the chance to choose or even to design the solid form with the properties best suited for the product [BLA07], [ULR07].

Table 2.1 List of physical properties that differ among various solid forms [GRA99]

Type of properties	Physical properties
Packing properties	Molar volume and density
	Refractive index
	Conductivity, electrical and thermal
	Hygroscopicity
Thermodynamic properties	Melting and sublimation temperatures
	Internal energy (i.e., Structural energy)
	Enthalpy (i.e., Heat content)
	Heat capacity
	Entropy
	Free energy and chemical potential
	Thermodynamic activity
	Vapor pressure
	Solubility
Spectroscopic properties	Electronic transitions (i.e., UV-Vis spectra)
	Vibrational transitions (i.e., MIR, NIR and Raman spectra)
	Rotational transitions (i.e., Far-IR or microwave spectra)
	Nuclear spin transitions (i.e., NMR spectra)
Kinetic properties	Dissolution rate
	Rates of solid state reactions
	Stability
Surface properties	Surface free energy
	Interfacial tensions
	Habit (i.e., shape)
Mechanical properties	Hardness
	Tensile strength
	Compactibility, tableting
	Handling, flow, and blending

In the development of a new drug product, developers want to identify and characterize as many solid forms of their compound as possible. They usually file patents on all the different solid forms during development. Thus, when initial patents on the compound itself expire, they try to extend a product's life by moving to another patent of solid forms. On the other hand, generic challengers will target unprotected solid forms to avoid patent infringement.

2.1.4 Analytical techniques

A variety of different analytical techniques can be used to identify and characterize the solid forms of an API. In this work, the following techniques were applied: X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermal gravimetry (TG), optical microscopy and Raman spectroscopy.

XRPD is quite important and effective method for distinguishing crystal structures of drug substance powders. This technique is based on Bragg's law ($n\lambda = 2d\ sin\theta$), where n is the order of the diffraction pattern, λ is the wavelength of the radiation, d is the distance between the planes in the crystal and θ is the angle of beam diffraction. More detailed fundamentals and applications of XRPD can be found in a number of publications [AZA58], [BER02], [BRI95], [JEN96].

The thermal analysis techniques, DSC and TG, are widely used for the characterization of purity, polymorphism, solvation and degradation of drug substances [CRA06]. [GIR86]. DSC determines change of enthalpy by measuring the difference in heat flow between the sample and an inert reference. Thermal changes can be endothermic (melting, sublimation, desolvation, etc.) or exothermic (crystallization, decomposition, etc.). TG method is a useful for the quantitative determination of the solvent content of a solid. A combination of DSC with TG can be a powerful technique for understanding thermal events at a certain range of temperature applied externally.

Optical microscopy allows the visual observation of crystals such as crystal size, shape and colour. Applications of optical microscopy in the identification of polymorphic compounds are discussed by many authors [HAR60], [HAR64], [McC78], [POR51].

Raman spectroscopy is a kind of vibrational spectroscopy. The Raman spectrum obtained for a compound is characteristic of that compound, since its vibrational frequencies depend on molecular parameters such as bond strength and the masses of the two atoms [SCH95]. The strengths of intramolecular bonds are affected by intermolecular interactions. Thus,

vibrational spectroscopy is sensitive to the local environment of a molecule which is different in different solid forms. Major applications include the identification, characterization and quantification of solid forms [AAL07], [BEE04]. Furthermore, vibrational spectroscopy is a valuable tool in the study of solid form transformations [AMA07], [HAU05], [SHA06].

2.2 Atorvastatin calcium (ATC)

Statins are a class of drug substances used to lower cholesterol levels and to prevent cardiovascular disease by inhibiting the 3-hydroxy-3methyl-glutaryl-coenzyme A reductase enzyme (HMG-CoA reductase) which plays a central role in the biosynthesis of cholesterol in the liver [SCA94], [SAC96].

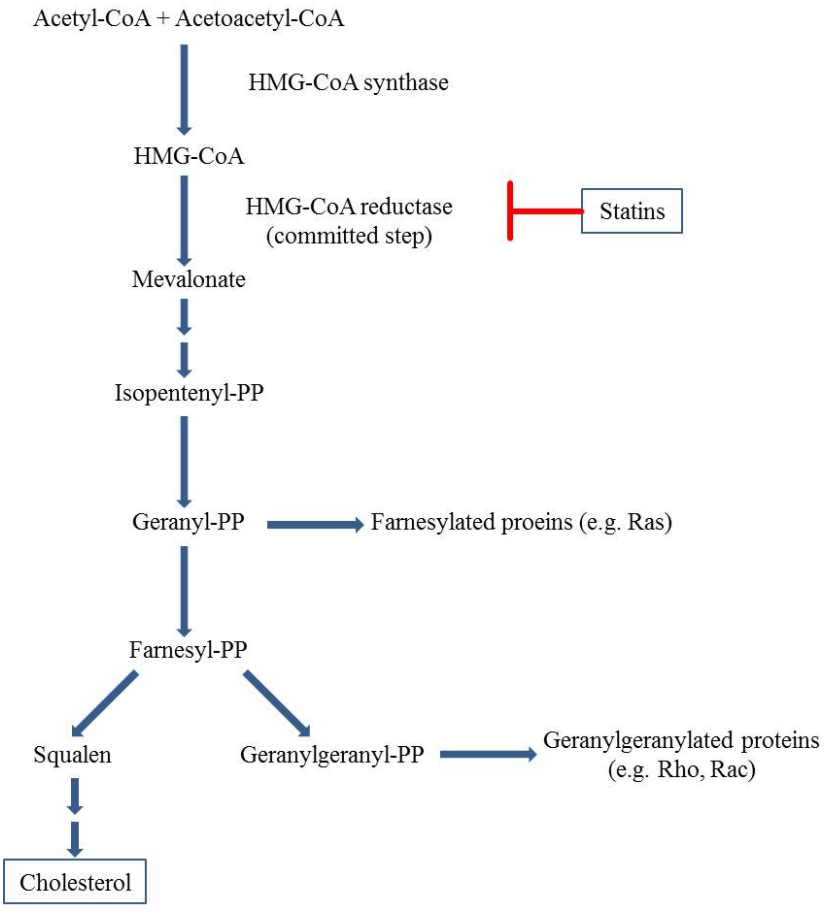
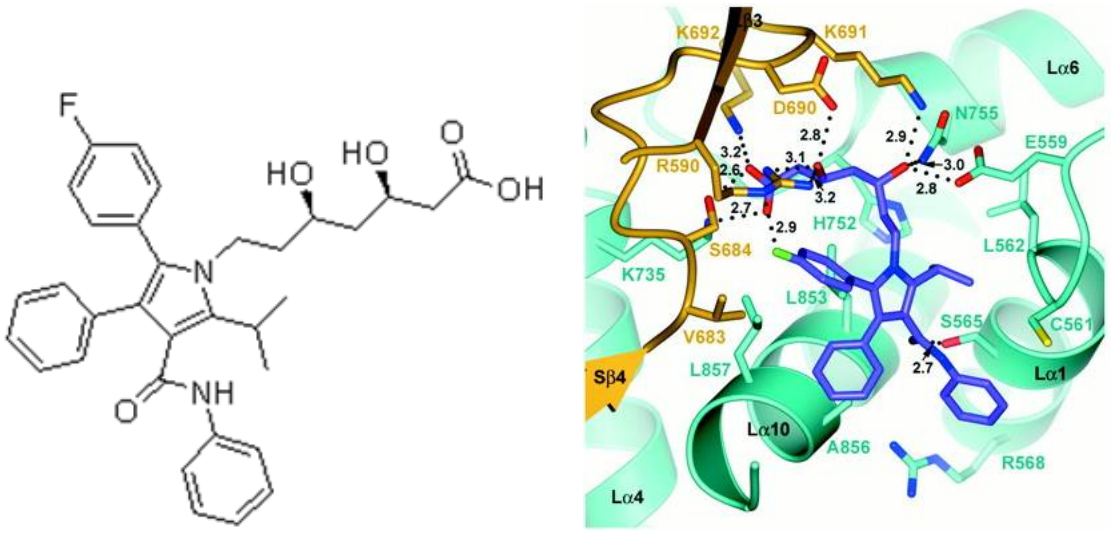


Figure 2.4 Statins inhibit HMG-CoA reductase in cholesterol biosynthesis pathway [LIE06]

A number of statins are on the market: lovastatin, pravastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, rosuvastatin, pitavastatin and are also found in some drug combinations such as CADUET® (atorvastatin and amlodipine). Atorvastatin, chemically known as (3*R*,5*R*)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid, is a member of the statins developed by the Warner-Lambert Company.



(a) (b)

Figure 2.5 The chemical structure of atorvastatin (a) and the mode of binding of atorvastatin to human HMG-CoA reductase (b) [IST01]

The United States patent No. 5,273,995 [ROT93] discloses atorvastatin and its pharmaceutically acceptable salts. Atorvastatin was formulated as its calcium salt (2:1) in an amorphous form in its early development phase I and II [BAU92], [BRO92]. However, it was found that this amorphous salt could exist in a crystal form during phase III clinical studies and then finally ATC was marketed as crystalline trihydrate, designated Form I [BRI97], by Warner-Lambert Company in early 1997 under the name LIPITOR® (Pfizer merged with Warner-Lambert in 2000, hereinafter collectively referred as "Pfizer").

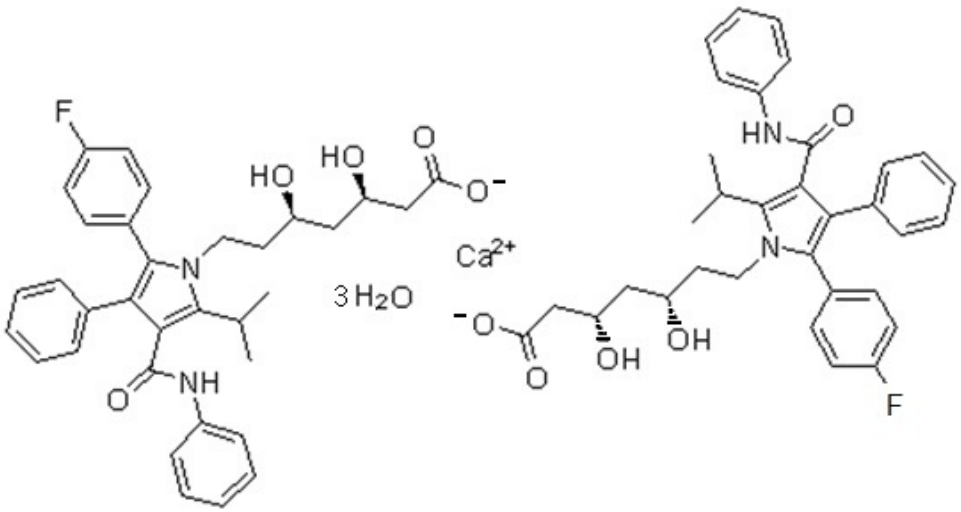


Figure 2.6 The chemical structure of atorvastatin calcium (ATC) trihydrate

Surprisingly, LIPITOR® has become the world's best-selling drug in the history of pharmaceuticals with more than US$125 billion in sales over 14.5 years [ASS11]. For that reason the intense competitions between the innovator and generic drug manufacturers prompted by the huge market has led to a countless number of patent applications claiming different crystal forms as well as processes for generating amorphous ATC.

2.3 Objectives of the study

The main objective of this work is to discover new strategies to disclose polymorphs and solvates and to find new crystalline forms of atorvastatin calcium (ATC). The specific aims of the study were:

- To survey on solid forms of ATC in the literature upto date in order to gain a preliminary insight into their crystallization characteristics. Database searching, analyzing documents, mining data and condensation to a matrix of crystallization should be performed.
- To design a proper screening method in order to enhance the probability and efficiency. Minimizing bottleneck steps, coverage of crystallization variables and maximizing speed of screening should be considered.

- To perform a crystal form screening on ATC. The priority of target combinations in the matrix should be employed.
- To characterize the new crystal forms obtained. Optical microscopy, XRPD, DSC, TG and Raman spectroscopy should be applied.
- To investigate influence of the solvent molecules incorporated in the new crystal forms on their crystal structures.
- To test an applicability of the screening method designed for ATC to another drug substance, i.e., rosuvastatin calcium (RTC).

3. Study on solid forms of ATC

After the commercial launching of ATC in early 1997, a large number of solid forms of ATC have been disclosed in the literature. Jin and Ulrich [JIN09b] reported a study of crystal forms of ATC which is the base of this chapter.

In this work, the literature survey on solid forms of ATC was performed as follows:

Database searching

2 databases were chosen for searching work. *SciFinder® 2007* and *Espacenet patent search (http://worldwide.espacenet.com/)* were used with a search term of "atorvastatin".

Processing data

Collecting and comparing the results returned from 2 databases. Duplicates or family patents were excluded in the list.

Analysing documents

Identifying bibliographic information, kind of solid forms, manufacturing processes, physicochemical properties and claims.

Mining data

Picking and classifying useful patterns and relationships.

3.1 Crystal forms of ATC

According to the above literature survey, 67 crystal forms of ATC were found in 21 published patents or patent applications, no journal paper could be found, and reported [JIN09b]. Since then, additional crystal forms have been disclosed in patents as well as journal papers up to date as 78 crystal forms cumulatively shown in Table 3.1. Representative patent documents, as international patent applications as possible, among their family patents were selected from the search returns (The legal status of patent, for example, applied, granted, re-examined, abandoned, invalid and so on, is not considered in this thesis. Any type of patent or patent application published is hereinafter collectively referred as "patent").

The Roman numerals and characteristic letters of forms were designated by applicants of their patents, respectively. For this reason the labels of forms can be overlapping in some patents

such as the Forms V ~ XIX, by Pfizer and Teva, even though their XRPD patterns are different of each other. In order to avoid confusing, these forms having same numeral or letter are relabelled for distinction in this thesis as listed in Table 3.1.

Table 3.1 Crystal forms of ATC in the literature

Applicants or authors	Forms	Relabelled forms	References
Pfizer	I, II, IV		[BRI97]
	III		[McK97]
	V ~ XIX		[BYR03]
	XX ~ XXX		[KRZ06]
Teva	V	V(T)	[AYA01]
	VI ~ XII	VI(T) ~ XII(T)	[ARO02]
	IXa, XIV,	IXa(T), XIV(T),	[TES03]
	XVI, XVII	XVI(T), XVII(T)	
	XVIII, XIX	XVIII(T), XIX(T)	[LIF06]
	F		[BLA04]
	T1		[PIN07]
	Unlabelled	T2, T3	[LEV08]
Morepen	VI	M-1	[SUR04]
	M-2, M-3, M-4		[SUR06]
Ciba	X,	X(C),	[SCH02]

Applicants or authors	Forms	Relabelled forms	References
	A, B1, B2, C, D, E		
Biocon	V	V(B)	[MAT02]
Dr. Reddy's	VI, VII	VI(R), VII(R)	[RED03]
Ivax	Fa, Je		[FAU03]
Ranbaxy	R		[KUM05]
Egis	B-52		[BAR06]
Matrix	M		[GOG07]
Apotex	*Unlabelled*	P	[MUR08]
Actavis	A1		[DIX09]
Chongkundang	Ga		[AHN09]
An *et al.*	3		[AN09]
Jin *et al.*	MD-1*, MD-2*		[JIN09c]
Rao V *et al.*	Unlabelled	R2	[RAO11]
Medichem	MCK-I, MCK-II, MCK-III		[CHO11]
Kyungbo	α		[LEE12]

* Forms MD-1 and MD-2 were discovered in this work. Chapter 4 describes these new crystal forms in detail

It is noteworthy with applicant of patents that 30 crystal forms, 39% in total 78 forms, were discovered by the innovator Pfizer. Drug developers usually screen and file patents on all the different solid forms during their development stage and they can extend the life of the

product through another patent of solid forms or small modifications, so-called “evergreen patent strategy” [THO09]. On the other hand, generic manufacturers will target on new solid forms which are unprotected to avoid patent infringement.

3.2 Amorphous form of ATC

Not only crystal forms but also processes for producing the amorphous form can be targeted by generic challengers because the prior art processes for the amorphous form are not suitable for a large scale production with problems in filtration and drying as described in Pfizer’s early patent, WO 9703959 [BRI97].

The amorphous ATC is known as an unstable substance which picks up moisture easily and is reactive with atmospheric oxygen causing the formation of the epoxide impurity. Thus there still exists a need to develop processes providing consistent purity and stability.

Table 3.2 Processes for the preparation of amorphous ATC

Applicants or authors	References
Pfizer	[DEB06], [LIN97], [LOR04], [ROS05]
Ranbaxy	[KUM00], [KUM05]
LEK	[ANT04], [PFL01], [SOR02]
Egis	[GRE01]
Teva	[ARO02], [PIN06] [TES04]
Cadila	[AGA02], [AGA03], [DWI10], [KHA11], [MOD08]
Biocon	[JOY02], [POO03], [SRI06]
Zentiva	[MIR07], [RAD03], [STA11]
Chemi SpA	[TUR03]

Applicants or authors	References
Sebastian *et al.*	[SEB04]
Richter Gedeon	[CZI04]
Ercros	[FAJ06], [FAJ07]
Jubilant	[BHA06], [GUP07]
Apotex	[CHE05]
EOS	[DAB05]
Dr. Reddy's	[GUD06]
Apollo	[VEN06]
Zejiang Xindonggang	[CHE06], [CHE07]
Korpran Res Lab	[VIT07]
Morepen	[SUR08]
Beijing Wanquan Sunshine Med.	[WAN09]
Zhejiang Jingxin Pharm	[JIN09a]
Matrix	[RAO09]
Zhongqi Pharm. Tech.	[ZHE09]
M J Inst. of Res	[VAS09]
IAC in Chungnam Univ.	[HWA09]
Actavis	[DIX09]
Daewoong	[CHO10]
Guangdong HEC	[LIN10], [LIU10]

3.3 Crystallization methods and solvents

Classification of crystallization methods and solvents used in the literature were carried out and analysed their frequencies in total cases of preparing the crystal forms and the amorphous form of ATC. As expected, the solvent mediated slurry conversion method was used most frequently for generating new crystal forms whereas the precipitation method was disclosed often for the amorphous form. But it should be noted that the process for the amorphous forms would not be repeated in terms of method and solvent used in patent applications required “new” or “improved” processes to avoid infringement prior arts. In practice, spray drying or freeze drying methods are more popular and easily adoptable for industrial production of amorphous substances.

Table 3.3 Crystallization methods used for crystalline and amorphous forms of ATC in the literature

Type of methods	For crystal forms, [% in total cases]	For amorphous forms, [% in total cases]
Slurry conversion	50	0
Cooling	18	11
Precipitation (anti solvent)	10	52
Evaporation	10	11
Spray drying	0	15
The others	12	11

The solvent is also a crucial parameter for the outcome of crystallization as discussed in the background. Table 3.4 shows the types of solvents used and their frequencies in processes disclosed in the literature.

Binary aqueous solvent mixtures, such as methanol/water mixture and acetonitrile/water mixture, were used frequently for crystal forms. This can be explained by the solubility of

ATC related to its chemical structure having various functional groups such as hydrophobic benzene rings, hydrocarbon chains as well as hydrophilic amides, amines, alcohols, carboxylates and a calcium ion. Reportedly, ATC is very slightly soluble in distilled water, pH 7.4 phosphate buffer and slightly soluble in water, ethanol, acetonitrile but freely soluble in methanol and dimethylsulfoxide.

Table 3.4 Solvents used for crystalline and amorphous forms of ATC in the literature

Types of solvents					For crystal forms, [% in total cases]	For amorphous forms, [% in total cases]
Mixing	Single				28	41
	Binary				69	39
	Ternary or more				3	17
Polarity	Polar	Protic	Aqueous	Alcoholic	32	12
				Nonalcoholic	31	4
			Nonaqueous		28	8
		Aprotic			1	16
	Nonpolar or mix				7	53

Solvents were also classified using a cluster analysis reported by Gu *et al.* [GU04]. In cases of solvent mixtures, the first used or major solvent seemed to be dominantly affecting the property of solvent mixtures was chosen for a group. This grouping is plausible with the explanation of structural similarities in some solvent groups as discussed in chapter 5.

Consequently, a matrix of crystallization of ATC is derived from mining data described in the literature as shown in Figure 3.1. Which combination of method and solvent is used and how many crystal forms are generated by a certain combination can be seen at a single glance on this matrix. Furthermore, the more important point of this survey and study provides a route

for efficient and minimized screening to find new crystal forms as the primary objective of this work.

Basic utilization of this matrix in crystallization experiments may be summarized as follows:

Preferential target combinations

Blanks and blocks less-filled with crystal forms although neighbouring blocks filled with crystal forms

Blanks added around blocks filled with crystal forms along a column of same solvent group

Pushed back on the priority list of experiments

Blocks filled already with over 3 crystal forms

Columns or lines filled with amorphous predominantly over crystal forms

Group	1st or major solvent	2nd or anti solvent	Slurry conversion	Precipitation	Cooling	Evaporation	Spray drying	the others
15	Water		I, XIV(T), A1					III, XVI(T) Amorphous
		MeOH	I, XXVI, α					
		EtOH	V(B)	R2				
		IPA	A		Amorphous			
		1-BuOH			VIII(T), Amorphous			
		THF	XII, XXIX					
11	MeOH		IV, XXII, M		IV	Amorphous	Amorphous	Amorphous
		Water	II, III, XIII, XXVI	V(T), Amorphous	V(T), B-52	XX	Amorphous	
		Hexane		Amorphous	B-52			
		DPE		Amorphous				
		Diethyl ether		Amorphous				
		t-BuOH		Amorphous				
		TBME	X(C)	Amorphous				
		DCM/Water		3				
		THF/Water		R, MCK-I, MCK-III				
10	Ethylene glycol		XXVIII, XXX			Amorphous		
		Water	MD-2	Amorphous		Amorphous	Amorphous	
	Propylene glycol		P			Amorphous		
7	Acetonitrile (AN)		B2					Amorphous
		Water	V, XV, XVI, VI(R), VII(R), XXI, XXIII, XXIX, XXV			V, XI		XVIII
		THF				B1		
		Toluene/TBME						
		DMF/Water	XVII					
6	DMF	Water		MD-1		VI, VIII		
	DMSO	Water		Amorphous				Amorphous
5	MEK		XIX, XI(T)				Amorphous	
		heptane			E			
	Acetone		XVIII(T), XIX(T)	Amorphous		Amorphous	Amorphous	Amorphous
		Water	VII	VI(T), M-1, Amorphous	M-2, F	VII, IX, M-3, Amorphous		
		EtOH/Water			T3			
		Diethyl ether		Amorphous				
4	EtOH		VII(T)		VIII(T)	Amorphous		VII(T) Amorphous
		Water	D, T1	V(T), XII(T), Amorphous	X(T), IV, XVII(T), Amorphous	XX, Amorphous	Amorphous	
		THF/Water			MCK-II			
	IPA		XI(T)	Amorphous	Amorphous	Amorphous		
		Water	X, XIV, XXI, C		X		Amorphous	
	1-BuOH		IV, IX(T)		IX(T)	Amorphous		
		Hexane		IX(T)				
		IPA						
		TBME	IX(T)	Amorphous				
		Water		Amorphous	IXa(T)	Amorphous	Amorphous	
3	IPAc	Water	Ga					
	EA					Amorphous	Amorphous	
		nonpolar hydrocarbon		Amorphous	Amorphous			
	THF							Amorphous
		Toluene		Amorphous		Amorphous		
		Heptane/IPA		Amorphous				
		Cyclohexane		Amorphous				
		Water/AN		XXI				
		Water		V(T), Amorphous				
	DCM				M-4	Amorphous	Amorphous	
		IPE		Amorphous				
	2-Methyl THF							Amorphous
		Hexane/TBME		Amorphous				
2	TBME		T2	Amorphous				
	1,4-Dioxane	TBME		Amorphous				
1	n-Octane		Je					
	Toluene	Heptane		Amorphous				
	Cyclohexane			Amorphous				
	Iso-Octane	Water	Fa					

Figure 3.1 Matrix of crystallization methods and solvents with the corresponding crystal and amorphous forms of ATC

3.4 Hydrates and solvates

To identify a new crystal form, characterizing solid properties and comparing them with data of the previously reported crystal forms are essential steps. Before doing that, the information related to hydration/solvation states of them in the literature were investigated and listed in Table 3.5. A high solvent-incorporating propensity of ATC can be seen that exist in a various states of hydrates, solvates as well as mixed solvates in which different solvent molecules are incorporated.

Table 3.5 Hydration/solvation states of crystal forms of ATC in the literature

Forms	Hydration/solvation states	Forms	Hydration/solvation states
I	Trihydrate	XIV(T)	N/A
II	?hyrate	XVI(T)	N/A
III	?hyrate	XVII(T)	N/A
IV	?hyrate	XVIII(T)	Acetone solvate
V	Trihydrate	XIX(T)	Acetone solvate
VI	?hyrate	V(B)	?hydrate
VII	Sesquihydrate	VI(R)	Trihydrate
VIII	Dihydrate	VII(R)	Trihydrate
IX	N/A	X(C)	N/A
X	Trihydrate	α	Dihydrate or trihydrate
XI	?hyrate	A	N/A
XII	?hyrate	A1	N/A
XIII	?hyrate	B1	N/A

Forms	Hydration/solvation states	Forms	Hydration/solvation states
XIV	Hexahydrate	B2	N/A
XV	Trihydrate	B-52	N/A
XVI	Tetrahydrate acetonitrile solvate	C	N/A
XVII	solvate	D	N/A
XVIII	?hydrate acetonitrile solvate	E	N/A
XIX	Methylethylketone solvate	F	N/A
XX	N/A	Fa	Organic solvent free
XXI	N/A	Ga	Anhydrate
XXII	N/A	Je	Organic solvent free
XXIII	N/A	M	?hydrate
XXIV	N/A	M-1	Trihydrate
XXV	N/A	M-2	Trihydrate
XXVI	N/A	M-3	Trihydrate
XXVII	N/A	M-4	Trihydrate
XXVIII	N/A	MCK-I	Trihydrate
XXIX	N/A	MCK-II	Trihydrate
XXX	N/A	MCK-III	Trihydrate
V(T)	Anhydrate ~ nonahydrate	MD-1	Dihydrate
VI(T)	N/A	MD-2	Dihydrate
VII(T)	?hydrate	P	Propylene glycol solvate

Forms	Hydration/solvation states	Forms	Hydration/solvation states
VIII(T)	?hydrate ethanol solvate	R	N/A
IX(T)	Butanol solvate	R2	N/A
IXa(T)	N/A	T1	N/A
X(T)	?hydrate ethanol solvate	T2	N/A
XI(T)	N/A	T3	N/A
XII(T)	N/A	3	Trihydrate

?) A certain range of hydration/solvation in which can exist

N/A) Information is not available in the literature

4. Finding new crystal forms of ATC

4.1 Screening design

Normally, polymorph screening is one of the most time and cost consuming steps during the pre-formulation stage of a new drug development by an innovator. However, here are different needs and purposes from the point of view of the challenge to manufacture a generic version of a polymorphic or solvate form of the drug substance. In this work, therefore, an alternative approach to polymorph screening is suggested and attempted.

To avoid all the previously reported large numbers of crystal forms described in the patents and literature, and requiring at the same time, to consider an easily adoptable crystallization process, and ultimately to enhance the probability of discovering new crystal forms, an efficient and minimized screening strategy was derived by using the result of a matrix study on the solid forms of ATC in chapter 3.

Table 4.1 Selection guide to screening experiments in this work

Terms	Limitations	Preferred
Solvents	Toxic (Class 1)*	Less toxic (Class 2 or 3)*
	High frequently used in matrix**	Low frequently used in matrix**
	High frequently used for amorphous forms in matrix**	High frequently used for crystal forms in matrix**
	Viscos	Easily removable
	High or low boiling	Cheap
Crystallization methods	Non-conventional	Conventional
	Required specific equipment	Adoptable in normal crystallizer
	High frequently attempted in a particular solvent in matrix**	Low frequently attempted in a particular solvent in matrix**
Conditions	Harsh	Mild
	High or low temperature	Ambient temperature

* Three classes of organic solvents in ICH guideline Q3C (R3) [INT99]

** See Figure 3.1

Based on the above selection guide and the matrix in Figure 3.1, the following sequence of an experimental screening is suggested (see Figure 4.1):

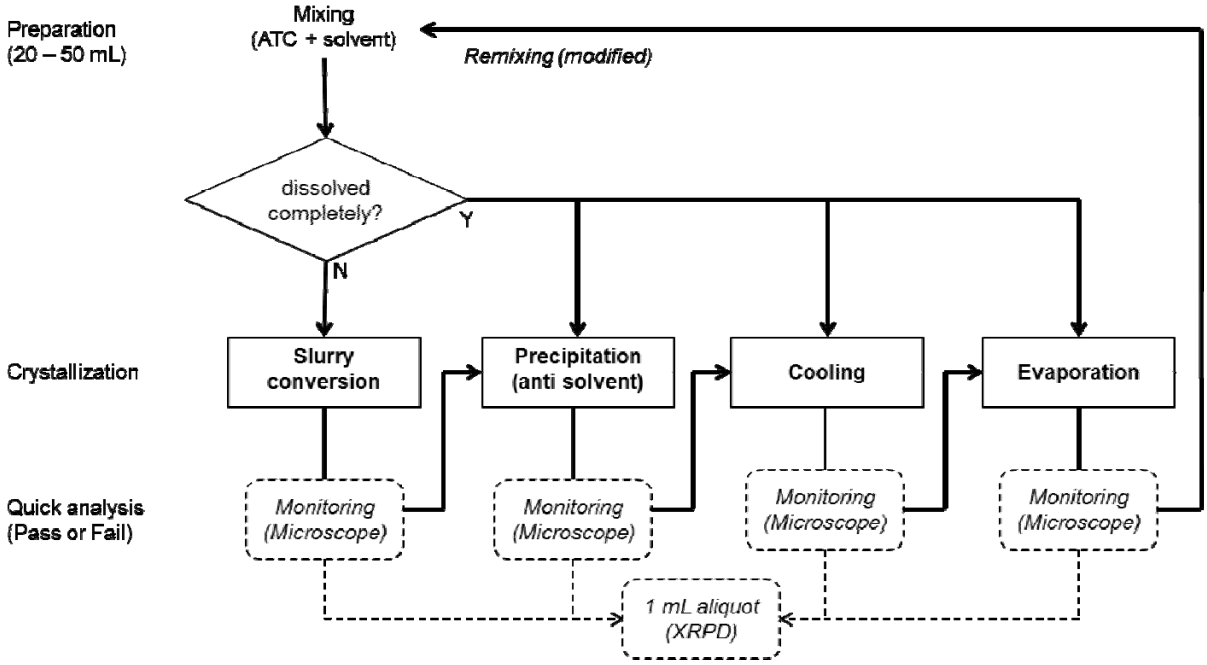


Figure 4.1 Designed flow diagram for screening experiments

Figure 4.1 shows a flow diagram for the screening experiments of this work. To avoid an "endless loop" of a certain condition with the same crystallization method(s), a parameter of a condition should be modified when a batch arrives at a repeated cycle of same method(s). Process parameters can be varied as follows [HIL06]:

Slurry conversion

Solvent or solvent mixture type, temperature, ratio of solvent to solid, solubility, temperature programs, stirring/shaking rate and incubation time.

Precipitation

Solvent, anti-solvent, rate of addition, order of mixing and temperature.

Cooling

Solvent or solvent mixture type, cooling profile, temperature at start/end and concentration.

Evaporation

Solvent or solvent mixture type, initial concentration, evaporation rate, temperature, pressure, ambient relative humidity and surface area of evaporation vessel.

4.2 Materials

The amorphous atorvastatin calcium (ATC) was provided by Daewoong Pharmaceutical Co., Ltd., South Korea with a Certificate of Analysis shown in Table 4.2 and was used as starting material.

All the organic solvents were purchased (HPLC or reagent grade) from commercial suppliers and used as obtained without further purification. Distilled water was used for the crystallization experiments.

Table 4.2 Analytical result of ATC (Batch No. ATV-S1-08061301) in a Certificate of Analysis provided by the supplier

Items	Test methods	Results
Description	Visual inspection	White powder
Assay	High Performance Liquid Chromatography (HPLC)	98.4%
Water content	Karl Fisher Titration (KF)	2.8%
Residual solvents	Gas Chromatography (GC)	Methanol 20 ppm Acetone 21 ppm Isopropylether 121 ppm

4.3 Characterization methods

X-ray powder diffraction (XRPD)

The XRPD patterns of samples were obtained by a Bruker D4 diffractometer with CuK_α radiation with a wavelength of λ = 1.5405 Å. Samples were scanned over a 2-theta (2θ) range of 3 - 40 °, with a step size of 0.005 ° and an acquisition time of 3 s/step.

Raman spectroscopy

Raman spectra of samples were recorded by a Bruker RFS 100/S spectrometer with a Nd:YAG laser power (λ = 1064 nm). Samples were scanned over a wavenumber range of 10 - 3500 cm^{-1}.

Thermal analysis

DSC and TG were conducted simultaneously using a Netzsch STA-409 system. The experiments were performed with a heating rate of 5 °C/min from 30 °C to 250 °C under helium flow.

Optical microscopy

The microscopic images of samples in solutions were monitored and recorded by a Keyence VHX-500F and an Olympus BH2 microscope.

^{1}H-NMR

^{1}H-NMR analysis was used for the confirmation of the identical chemical structure or chemical degradation by a Varian Gemini 2000 at the frequency of 400 MHz at 27 °C in deuterium substituted solvent of dimethylsulfoxide (DMSO-d_6, 0.03% v/v TMS).

4.3.1 Preliminary analysis

The preliminary analysis required of the amorphous form of ATC as starting material of screening experiments is described below as XRPD pattern and ^{1}H-NMR chart in Figures 4.2 and 4.3.

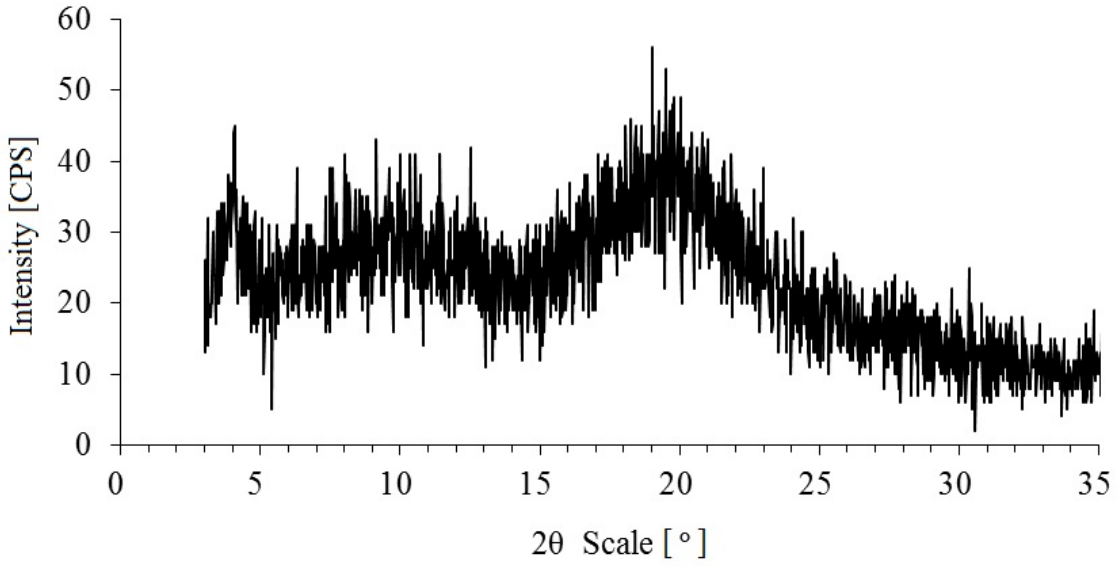


Figure 4.2 XRPD pattern of ATC **(**Batch No. ATV-S1-08061301)

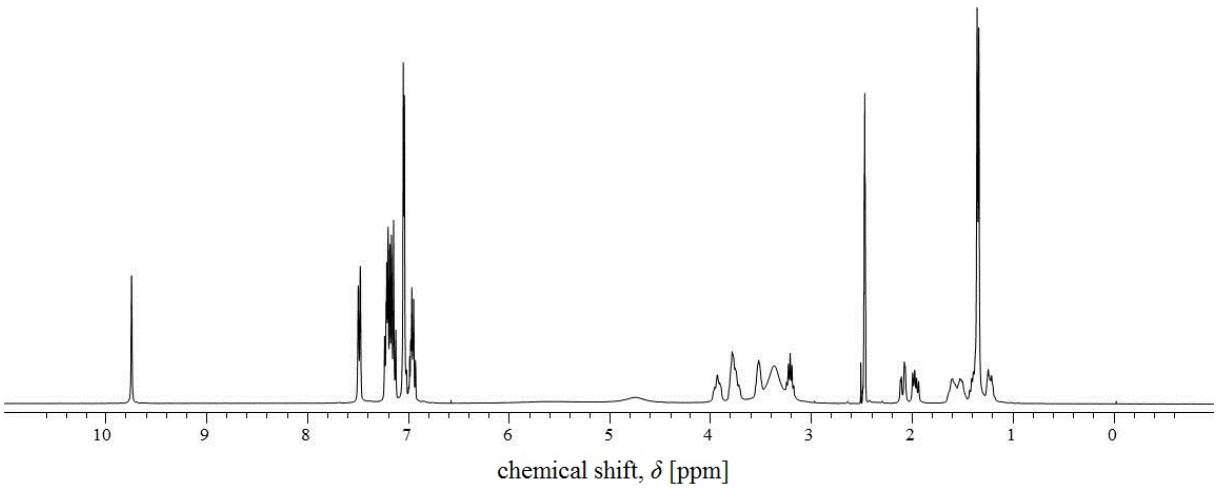


Figure 4.3 ^{1}H NMR chart of ATC **(**Batch No. ATV-S1-08061301), 400 MHz, DMSO-d_6

4.4 New crystal Form MD-1

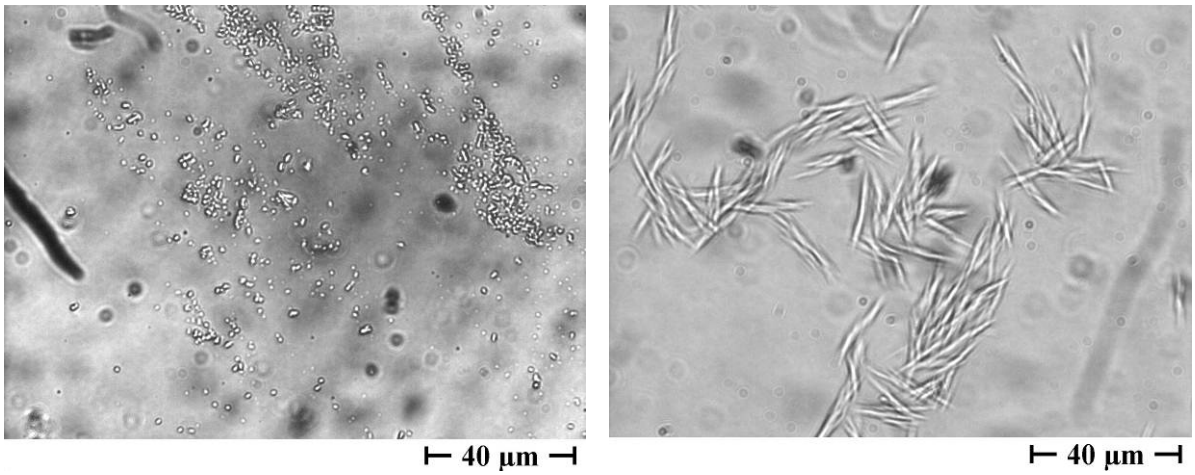
4.4.1 Preparation

1.0 g of amorphous ATC was dissolved completely in 20 mL of DMF/Water (9:1) at 20 °C. 20 mL of water was added dropwise for 5-6 minutes to the solution to precipitate. After stirring at the same temperature for 4 hours, the resulting mixture was filtered under reduced pressure and the obtained solids were air-dried at ambient temperature (20 -25 °C) for 2 days to receive Form MD-1 of ATC.

4.4.2 Analytical data

All the following analytical data were compared to those of previously reported forms. Consequently, it is apparent that Form MD-1 is a new crystal form of ATC.

Microscopic images



a b

Figure 4.4 Microscopic images of the initial (amorphous form, a) and the final suspension (Form MD-1, b [JIN09c], [JIN10]) during the slurry conversion

The XRPD pattern, the Raman spectrum and the DSC/TG profile are given in Figures 4.5, 4.6 and 4.7.

XRPD pattern

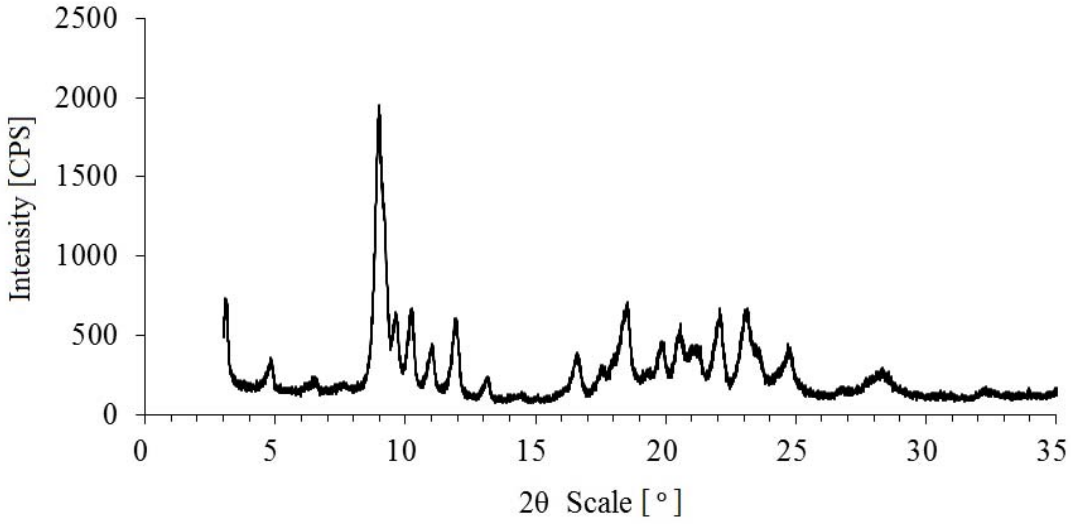


Figure 4.5 XRPD pattern of Form MD-1 [JIN09c], [JIN10], [JIN11a]

Table 4.3 Characteristic peaks of Form MD-1 [JIN11a]

2θ [°]	Relative intensity [%]	2θ [°]	Relative intensity [%]
3.1	36.4	18.0	18.4
4.8	17.3	18.5	35.9
9.0	100.0	19.9	23.3
9.2	69.3	20.5	26.9
9.6	32.2	21.2	21.6
10.2	34.4	22.1	32.7
11.0	22.3	23.1	33.5
12.0	30.8	23.6	20.1
16.6	19.3	24.7	21.6
17.6	15.7	28.3	15.0

Raman spectrum

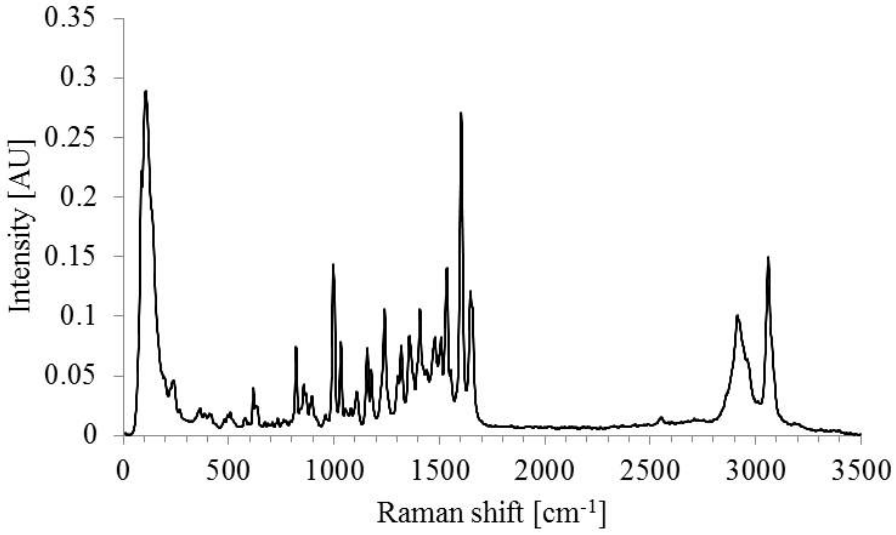


Figure 4.6 Raman spectrum of Form MD-1 characterized by the following 20 most intense peaks expressed in cm^{-1}: 3061, 2914, 1647, 1603, 1554, 1537, 1509, 1480, 1442, 1409, 1358, 1319, 1304, 1240, 1177, 1158, 1034, 997, 821, 106 [JIN09c], [JIN10], [JIN11a]

DSC/TG profile

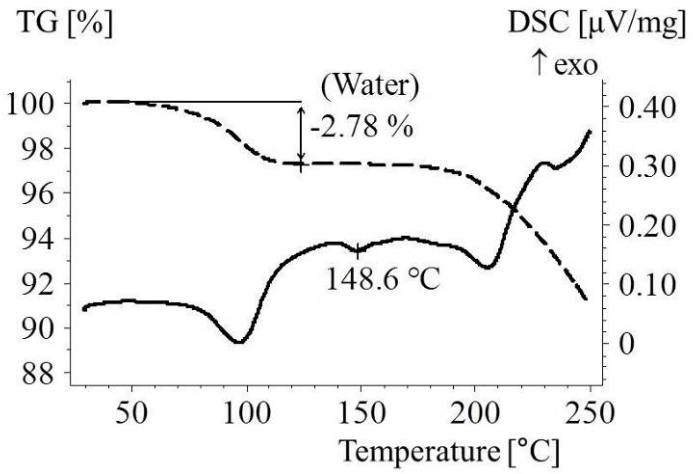


Figure 4.7 DSC/TG profile of Form MD-1 [JIN09c], [JIN10], [JIN11a]; the water content of Form MD-1 was also determined by Karl-Fisher titration. The resulting range of 2.69 – 3.10 % of the water content is corresponding to a dihydrate which contains theoretically 3.02 % of water

4.5 New crystal form MD-2

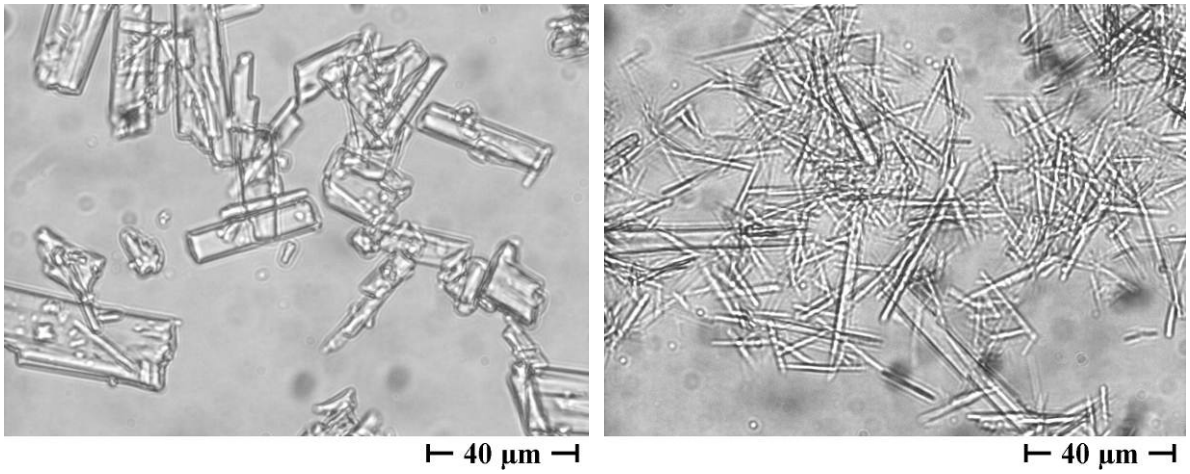
4.5.1 Preparation

1.0 g of amorphous ATC was slurried in 10 mL of ethylene glycol at room temperature for about 1 day for an *in situ* generation of Form XXX [KRZ06]. 10 mL of water was added dropwise for 10 minutes to the solution. The suspension was then slurried for about 1 day. 100 mL of water was added at once and then the resulting suspension was stirred for about 1 day. The solids were recovered with vacuum filtration and were air dried at ambient temperature (20 -25 °C) to receive the Form MD-2 of ATC.

4.5.2 Analytical data

All the following analytical data were compared to those of previously reported forms. Consequently, it is apparent that Form MD-2 is also a new crystal form of ATC. The microscopic images, the XRPD pattern, the Raman spectrum and the DSC/TG profile for the new form are shown in the Figures 4.8, 4.9, 4.10 and 4.11, respectively.

Microscopic images



a b

Figure 4.8 Microscopic images of the initially generated Form XXX (a) and the final suspension (Form MD-2, b [JIN09c], [JIN10]) during the slurry conversion

XRPD pattern

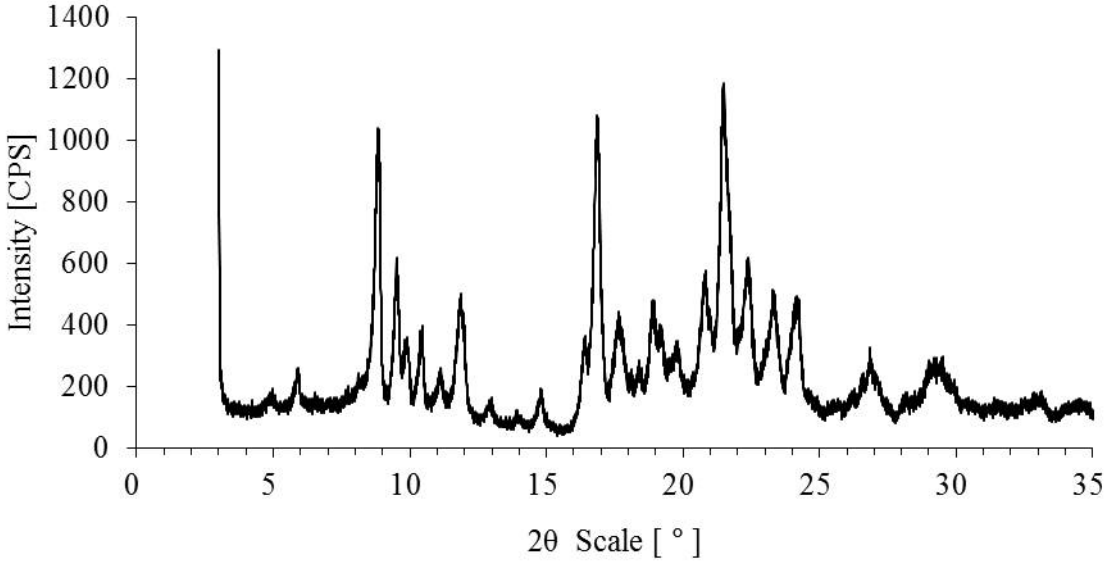


Figure 4.9 XRPD pattern of Form MD-2 [JIN09c], [JIN10]

Table 4.4 Characteristic peaks of Form MD-2

2θ [°]	Relative intensity [%]	2θ [°]	Relative intensity [%]
3.0	90.6	17.6	49.3
5.9	24.2	18.9	21.3
8.9	100.0	20.2	18.1
9.4	20.1	20.8	32.8
9.5	19.8	21.6	55.3
11.1	18.0	22.4	20.7
11.9	42.8	23.3	34.8
13.0	17.5	24.3	26.8
14.8	22.7	25.7	16.5
16.9	32.1	26.9	23.1

Raman spectrum

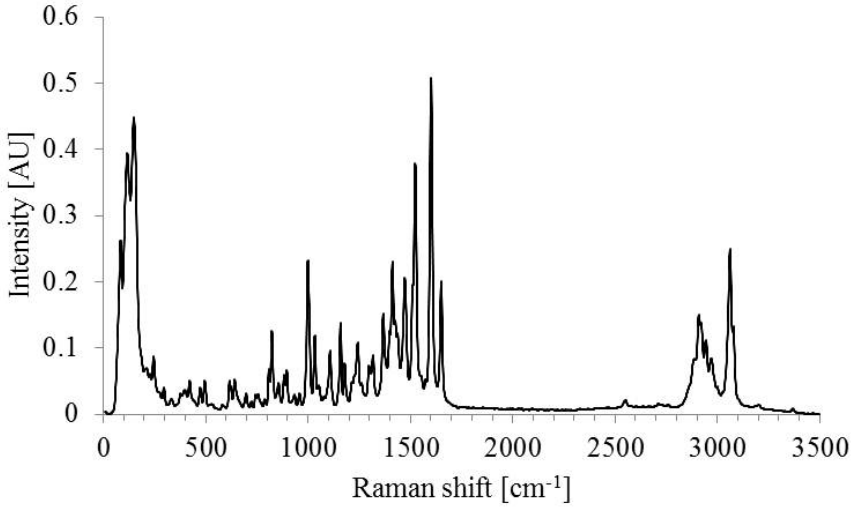


Figure 4.10 Raman spectrum of Form MD-2 characterized by the following 20 most intense peaks expressed in cm^{-1}: 3059, 2907, 1649, 1603, 1524, 1470, 1410, 1366, 1314, 1238, 1157, 1105, 1032, 997, 884, 824, 243, 147, 116, 83 [JIN09c], [JIN10]

DSC/TG profile

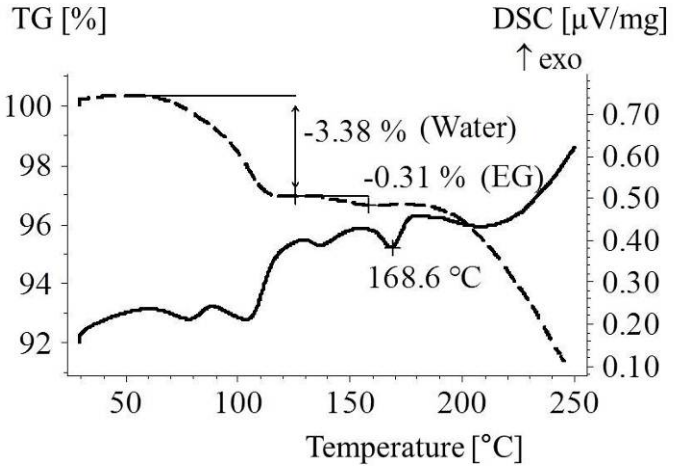


Figure 4.11 DSC/TG profile of Form MD-2 [JIN09c], [JIN10]; the water content of Form MD-2 was also determined by Karl-Fisher titration. The resulting range of 3.12 – 3.41 % of water content is corresponding to a dihydrate which contains theoretically 3.02 % of water. Small amount of ethylene glycol was also detected and these results suggest that Form MD-2 may exist in a mixed solvate form

4.6 Acceptability of new crystal forms

In this chapter, the possibility and acceptability of the above two new crystal forms are evaluated considering an industrial need for further development.

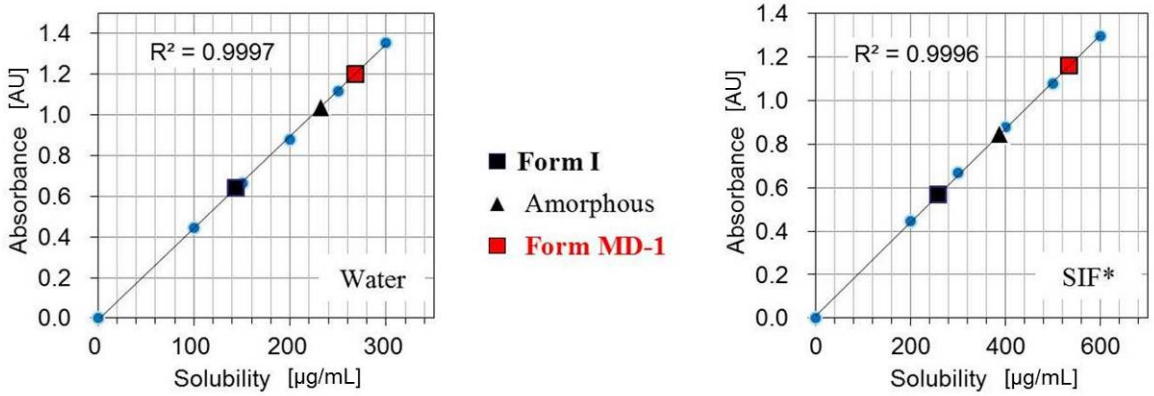
The following points of view are considered:

Is it patentable? – Novelty, utility and so on (patent laws)

Is it suitable for large scale production? – Crystallization method and conditions

Is it suitable for tableting? – Solid properties related to the formulation of drug substance

Not only scientific views but also industrial views are reflected in this evaluation. Reviewing and opinions were supported by the department of attorney, API production and drug formulation research at Daewoong Pharmaceutical Co., Ltd., Korea, which the author of this thesis belongs to.



Solubility ± SD [μg/mL], n=3, at 25 °C, UV 247 nm

Solid form	Hydration	Water	SIF *
Form I **	Trihydrate	143.2±0.2	258.5±0.2
Amorphous **	-	232.0±0.1	388.6±0.1
Form MD-1	Dihydrate	267.9±0.1	533.8±0.4

Figure 4.12 Solubility data of Form I, amorphous form and Form MD-1 in water and SIF (* Simulated Intestinal Fluid, pH 6.8 buffer solution 0.05M) [JIN11a]. ** Form I and the amorphous form were prepared according to the procedures disclosed in patents [BRI97], [LIN97]

Form MD-1 can be crystallized by a simple precipitation method under mild conditions. There were no other problems in a normal tableting process which are not known for the amorphous form and Form I of ATC. After considering the above positive things, it has been decided that Form MD-1 becomes a candidate for the generic drug development and should be claimed by a patent application [JIN11a].

In case of Form MD-2 which was initially prepared from the previous Form XXX, several attempts were made to prepare Form MD-2 directly from the amorphous form met failure in the reproducibility tests. It seemed that Form MD-2 could be generated *via* Form XXX from an amorphous state in an ethylene glycol/water solvent system. For this reason, its novelty is lacking for the patent. An additional disadvantage of Form MD-2 was reported in the tableting process mentioned above with a trouble caused by its sticky property.

However, an interesting transformation behavior related to Form MD-2 and solvent molecules was found and described in chapter 5 in detail.

5. Discussion

5.1 Crystallization of ATC

The literature survey on solid forms of ATC has shown that 78 crystal forms and the amorphous form including the new Forms MD-1 and MD-2 are discovered in this work. The question arises whether these 78 crystal forms can be categorized in different types of individual polymorphs or solvates.

Based on their similarities in XRPD pattern and with respect to the result on the study on the solvents and methods used in the crystallization processes described in chapter 3, these forms are found to be dividable into 23 structure groups reflecting their relationships of spectral characteristics and crystallization methods. So, the forms occupying each group can be considered very closely related crystal structures. The crystal forms may be categorized into 3 types according to their nature of crystallization. Type A is the polymorph/ solvate crystallized from an amorphous ATC or a completely dissolved ATC in a certain solvent system. Type S is related to a variation of solvation level of other types. Forms belonging to type T are derived by certain phase transformations among types A and S.

Table 5.1 Crystal structure groups of ATC

Groups	Forms	Types
1	I, IX, MCK-III, V(B), α	A, S, T
2	II, III, XIII, XXVI	A, S, T
3	IV, X, XVIII, VII(T), VIII(T), IX(T), X(T), XVII(T), MCK-II, A	A, S, T
4	V(T), XII(T), XX, 3, D, MCK-I, M-3, M-4	A, S
5	R2, XI(T), C, A1, X(C), T-2	A, T
6	XXVIII	A
7	XXX	A, T

Groups	Forms	Types
8	VII, XII, VI(T), XVIII(T), XIX(T), R, M-1, M-2, T-3, F, M,	A, T
9	V, B1, B2, XXV, XIX, XXI, XXIII	A, S, T
10	XIV, XVI, XVII	A, S
11	XV	A
12	XI	A
13	VI	A
14	VIII, VI(R), VII(R), XXVII	A, S
15	MD-1	A
16	Ga	A
17	Fa	A, T
18	Je	T
19	XIV(T), XVI(T)	S, T
20	XXII	T
21	MD-2	T
22	XXIV	T
23	XXIX	T

The amorphous or completely dissolved ATC was found to be crystallized in at least 17 different crystal structure groups. The most distinguished aspect of the structure group 1 is the use of water or water-abundant solvent mixtures in crystallization. Forms I, MCK-III, V(B) and α are reported to be crystallized in water with a small portion of alcohol. In the case of Form IX, although having a very similar XRPD pattern, prepared by evaporating a solution of

amorphous ATC in acetone/water (6:4, v/v), several experimental trials have led always to Form I which was probably caused by increasing water portions of the solution during evaporation.

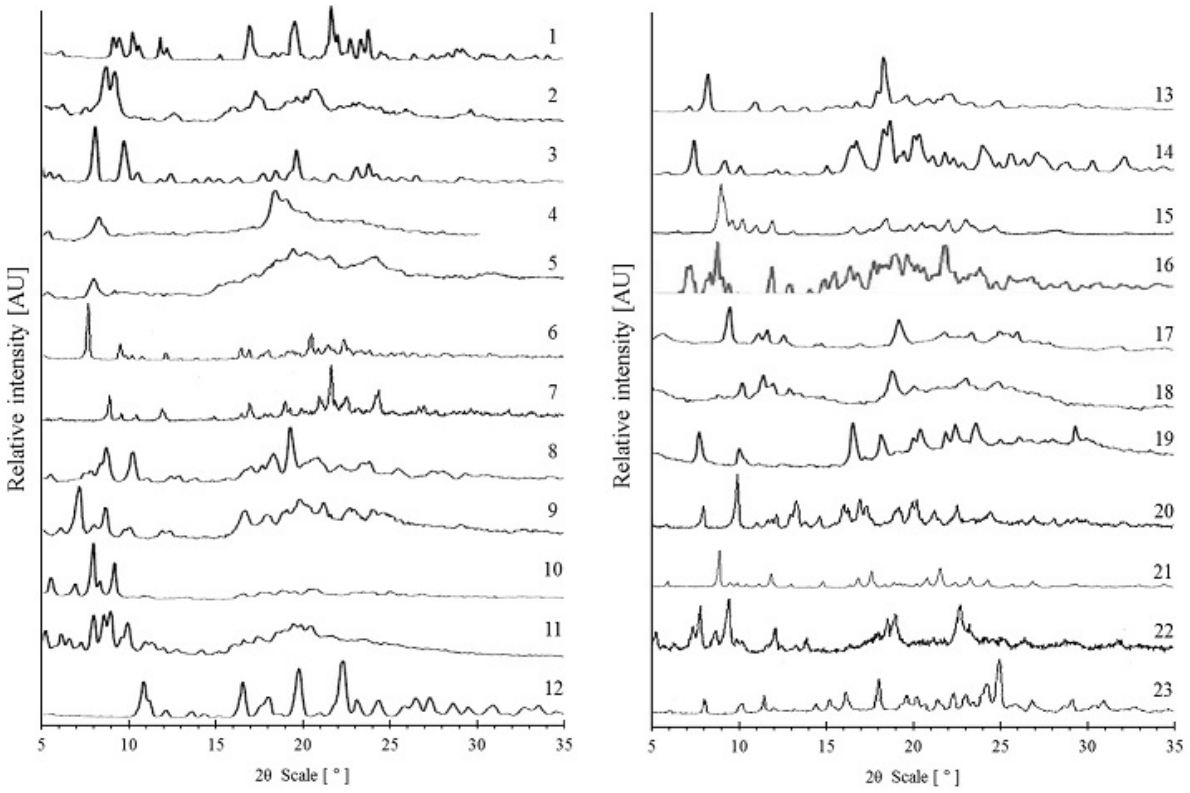


Figure 5.1 XRPD patterns of the representative crystal forms which correspond to each crystal structure group 1 to 23

The structure groups 2 to 7 can be prepared by an alcohol or alcohol/water solvent system. In group 2, Forms II, XIII and XXVI are crystallized by slurring in methanol/water (3:2 - 8/2, v/v). Forms IV, X, VIII(T), X(T) and A of group 3 are precipitated by cooling an alcohol/water mixture. The Forms of group 4 and 5 are noteworthy that their low XRPD intensities close to disordered or amorphous although they are showing apparent microscopic shapes before filtration (see Fig. 5.2). This behavior can be explained as a typical example of a so-called “transient solvate” as an unstable solvate which is immediately desolvated during the isolation process [GRI06].

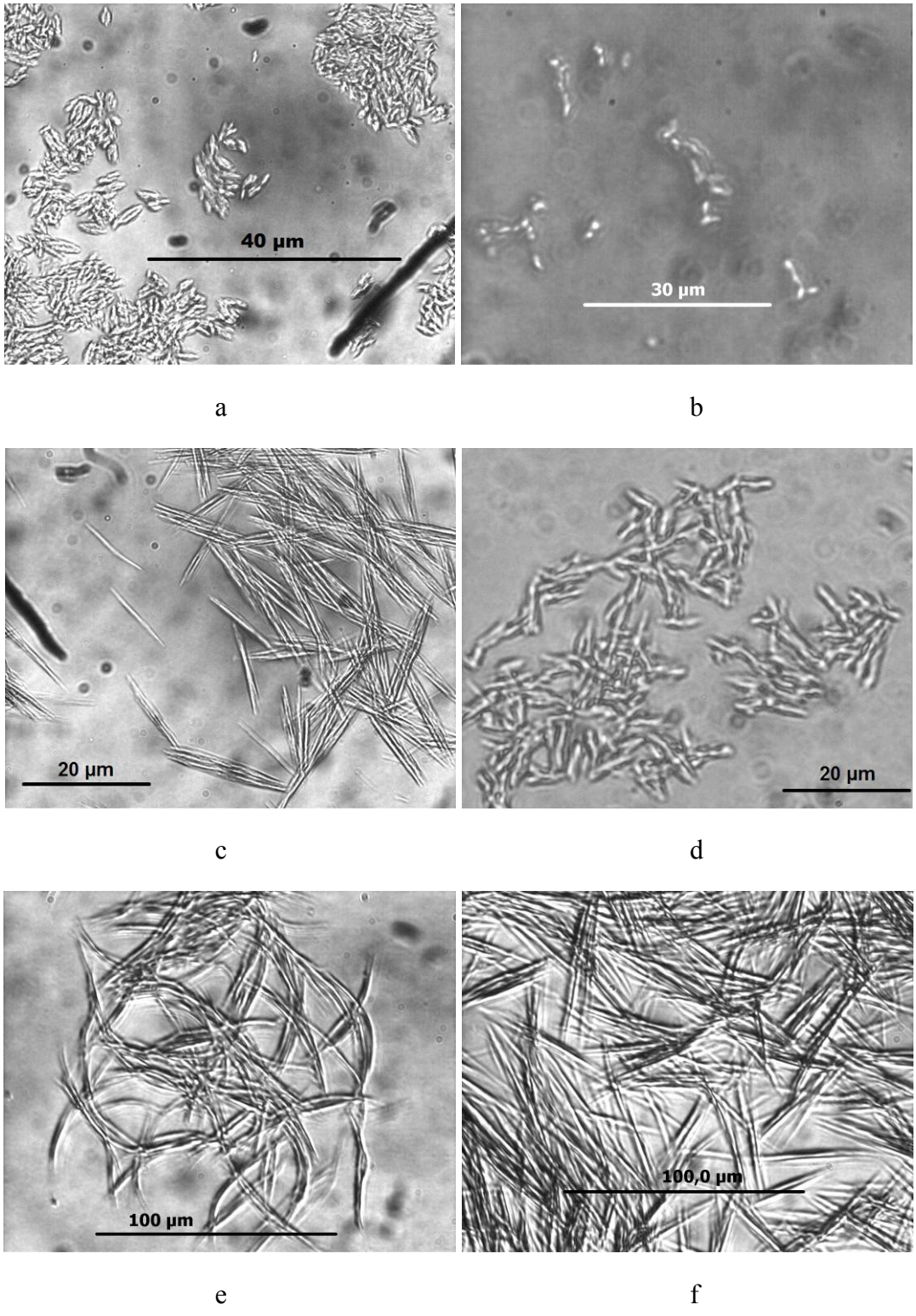


Figure 5.2 Microscopic images of various crystal forms of ATC: Forms II (group 2, a), X (group 3, b), V(T) (group 4, c), XXVIII (group 6, d), VII (group 8, e) and V (group 9, f)

In a different type of alcohol such as ethylene glycol having two hydroxyl (-OH), Forms XXVIII (group 6) and XXX (group 7) can be crystallized at 50 °C or room temperature, respectively.

Forms of group 8, except Form R, are prepared by slurring in a mixture of acetone/water. A process for preparing Form R is reported that dissolving ATC in a solvent mixture comprising tetrahydrofuran and methanol is heated up to reflux and then precipitated by addition of water as an anti-solvent.

In an acetonitrile/water (9:1, v/v) mixture, the forms of group 9 (Forms V, B1, B2), group 10 (Forms XVI, XVII) and group 11 (Form XV) are prepared by slurring with various periods of mixing. Alternatively, the group 12 (Form XI) can be obtained by a slow evaporation of the same solvent.

Using a dimethyl formamide (DMF) and water mixture, a variation of crystallization methods leads to different crystal structures. Form VI (group 13) is prepared by exposure to a DMF/water (9:1, v/v) vapor for 20 days, Form VIII (group 14) by a fast evaporation of the same solvent and Form MD-1 (group 15) by a precipitation with additional water at 20 °C or below can be obtained.

Water-immiscible or non-polar solvents such as isopropyl acetate and isooctane are used to prepare Forms Ga (group 16) and Fa (group 17), respectively.

Forms belonging to the type S can be regarded as modifications of solvation levels. A solvation level is often caused by an incorporation of solvent molecule(s) into the crystal lattice, i.e. solvation, or a removing of solvent molecule(s) from the crystal lattice, i.e. desolvation, during crystallization.

The additional structure groups 18 to 23 can be prepared by phase transformations from the previous structure groups.

5.2 Approach to an efficient polymorph screening

Since more than 70 crystal forms of ATC are already disclosed and blocked by the previously published patents, an alternative screening strategy approach is required for this work which is related to an industrial purpose to develop a generic version based on a different polymorph or solvate of ATC. Therefore, it is not necessary to apply a high-throughput screening (HTS) which can be operated in wide range of conditions and can make thousands of trial

automatically, moreover, numerous experimental trials by HTS which is often outsourced but not helpful this case.

Firstly, a matrix of crystallization (see Figure 3.1) was prepared from the study on solid forms of ATC described in chapter 3. The matrix, which gives the combination of crystallization methods and solvents is used previously and shows how many crystal forms are generated by a certain combination at a single glance. Basic utilization of this matrix for screening experiments is also summarized to enhance the possibility of finding new crystal forms by suggesting which blocks in the matrix should be preferentially targeted or pushed back on the priority list of experiments, where should be concentrated with careful modified condition factors when the following screening cycle runs.

Secondly, a minimized screening method was designed as a sequential cycle, which covers four conventional crystallization methods at one cycle of a single sample prepared. The choice of solvent system and crystallization method was preferentially considered by the priority list derived from the matrix. Optical microscopic observation did assist to catch whether crystals/ particles appeared or not in a running cycle of the experiment. Since just one drop, approximately 0.02 mL, of each sample solution was taken for monitoring, the loss of original volume of sample solution, normally 20 -50 mL at start, might be neglected, then further experimental cycles were practically uninfluenced. Furthermore, this microscopic image monitoring has provided a quick *Pass or Fail* decision to enhance speed and efficiency of screening. Only when some conversion or appearance of a new crystal shapes was captured, 0.5 – 1.0 mL aliquot was filtered and dried quickly under vacuum, approximately 5 – 20 mg was obtained, then analyzed by XRPD. The remaining sample solution of still enough volume could be running further cycles, sometimes with condition factors modified.

A small amount of crystals separated for XRPD analysis may be appropriate to scarify for some diffraction quality, e.g. resolution or signal to noise ratio. However, the primary objective is to identify potential new forms and not necessarily to impeccably characterize them with a sufficient amount at this stage. A simple comparison of a long range ordered pattern obtained with the previously reported pattern was acceptable for discrimination. As long as the pattern allows identification of possible new crystal forms, this sample can subsequently be isolated from a scaled up batch and then fully characterized, e.g. XRPD DSC/TG and Raman.

As a result of the above approach, two new crystalline Forms MD-1 and MD-2 of ATC have been discovered and characterized as described in chapter 4, therefore the screening method

designed by this work provides at least one or more of the following advantages:

1. Efficiency of screening can be increased by concentrating to the priority target(s) with high possibility among the blocks of matrix.
2. Bottleneck steps, e.g. filtering, drying and analyzing for individual batches, can be minimized by a combination of microscopic monitoring and aliquot XRPD analysis.
3. Four conventional crystallizations can be performed by sequential cycle(s) of a single sample preparation.
4. Quick *Pass or Fail* decision can accelerate the speed of screening and avoid the separation of unwanted forms.

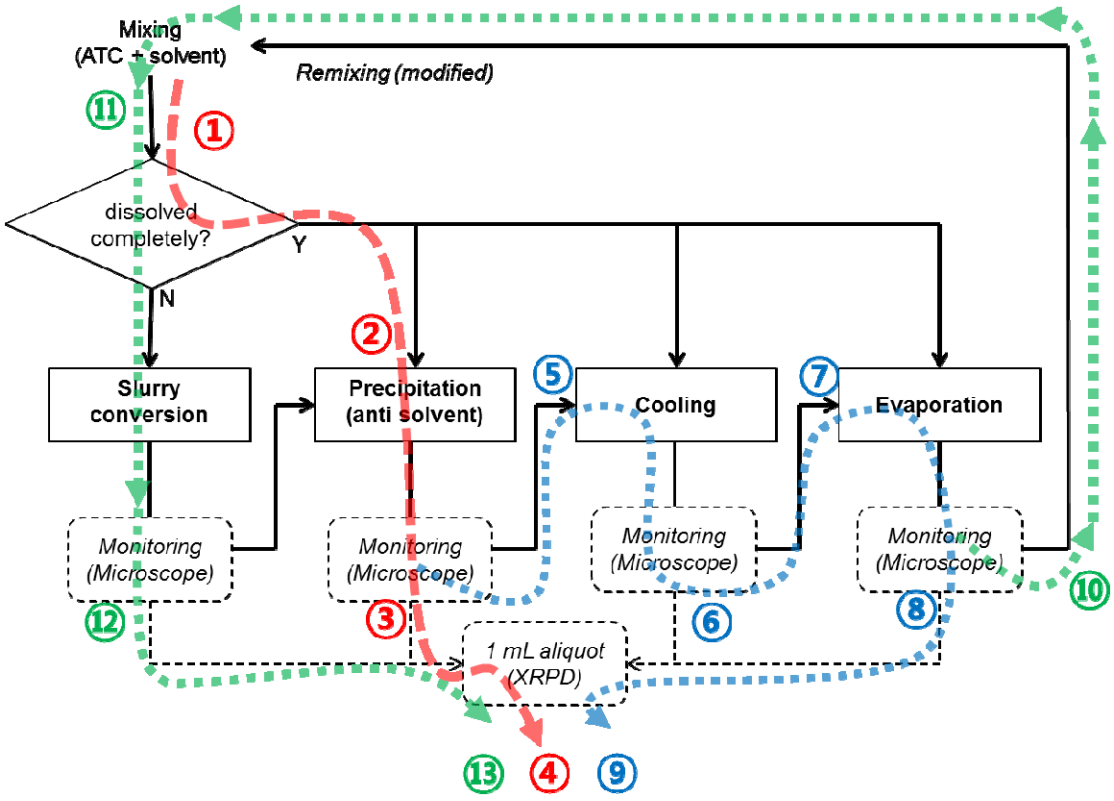


Figure 5.3 An experimental cycle of sequential screening. ① 1.0 g of ATC + 20 mL of DMF/water (9:1, v/v), ② added 20 mL of water, ③ crystals appeared (*Pass*), ④ Form MD-1, ⑤ heated to clear then cooled, ⑥ amorphous aggregates (*Fail*), ⑦ heated and evaporated slowly, ⑧ crystals appeared (*Pass*), ⑨ Form VIII ⑩ oily residue, ⑪ 10 mL of DMF/water (6:4, v/v), ⑫ crystals appeared (*Pass*), ⑬ Form VIII

The practical applicability of this study has been substantiated with an additional achievement of work on another API of statin drug, rosuvastatin calcium.

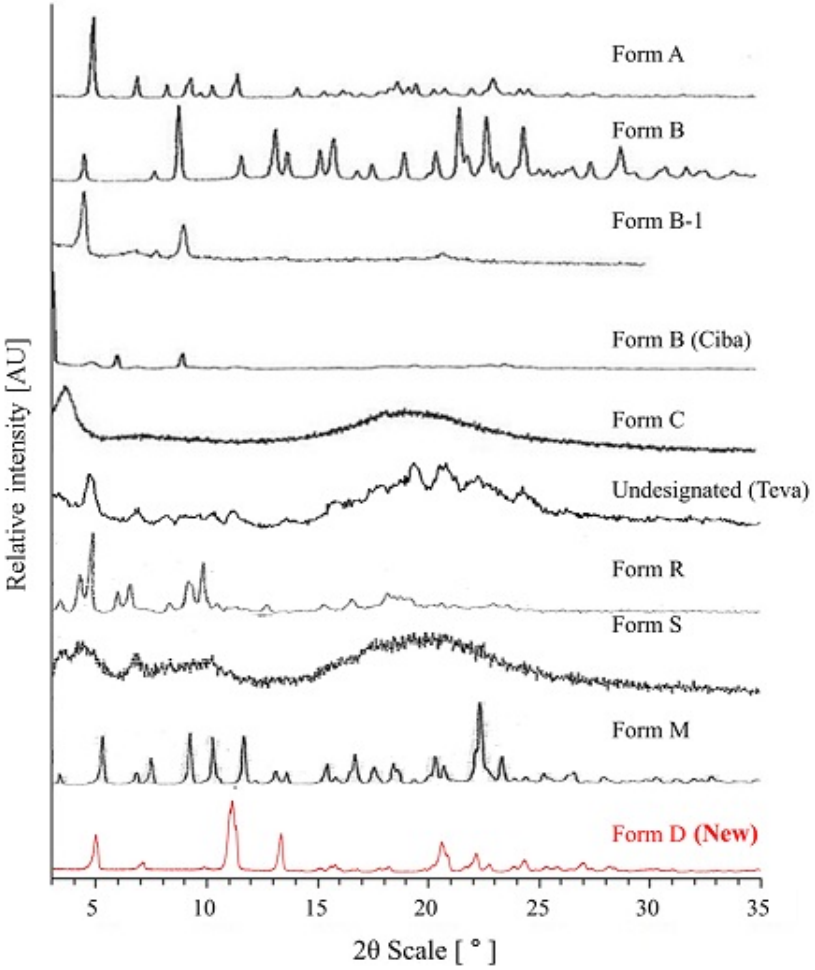


Figure 5.4 XRPD pattern of crystal forms of rosuvastatin calcium (RTC)

Rosuvastatin calcium (RTC), chemically known as bis[(E)-7-[4-(4-fluorophenyl-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxy-hept-6-enoic acid] calcium salt, is marketed as its amorphous form by AstraZeneca as CRESTOR®.

A lower number than the case of ATC, but not a small number of crystal forms of RTC have been found in the literature survey. Although already 9 crystal forms of RTC exist as Form A [TAY00], Forms B, B-1 [BOO05], another Form B, Form C [BLA06], an undesignated form [WIZ08], Form R, S [SET11] and Form M [SAT12], a new crystal form of RTC, designated as Form D, was discovered successfully in a short period of time and claimed by a patent

application [JIN11b] as a candidate for development of a generic API of RTC with an advantageous property of low water content and non-hygroscopicity [JIN12].

5.3 Solvent molecules in a crystal

Solution crystallization is the most common technique used to isolate and purify many drug substances in the pharmaceutical industry. The solvent molecules used in crystallization, which have usually low molecular weight and low volume, sometimes become incorporated into the crystal lattice during crystallization and the amount of solvent incorporated can depend upon the crystallization procedure and condition under which the substance is maintained, such as the temperature, concentration and pressure. In some cases, solvates may contain more than one type of solvent molecule in the crystal lattice. As described in chapter 3, binary aqueous solvent mixtures, such as alcohol/water solvent mixtures, are used extensively in the preparation of ATC (see Table 3.4). As a result of this, a few mixed solvates of ATC were reported (see Table 3.5). It is particularly relevant to a part of this work how different solvent molecules have an impact on the crystal structure of a mixed solvate of water and an organic solvent.

However, the organic solvent molecules in a drug substance are considered, in principle, to be impurities and regulated by authorities such as the ICH guideline Q3C on residual solvents. Therefore a suitable desolvation process for reducing their content as much as possible would be favorable.

Generally, solvation/ desolvation of crystals may lead to a different crystal structure or a disordered state; on the contrary, it may not cause a significant difference in the crystal structure. Both examples are observed and characterized in the discovering new crystalline solvates of ATC, especially when more than one solvent is incorporated in one crystal systems, however, keeping structure and physical properties.

In Figure 5.4, a non-destructive desolvation can be seen between two solvates, one isolated as hemi DMF solvate and another as dihydrate (Form MD-1), that show almost same XRPD pattern, except for small shifts due to the different states of solvation.

A hemi DMF solvate was isolated at the initial gel formation by addition of water to a DMF/water (9:1, v/v) solvent mixture. After 2 hours stirring the mobility of solution was increased sufficiently, then Form MD-1 as dihydrate was isolated with almost retained structure. This result indicates that a solvate formed firstly and it desolvated via displacement

by water molecules without changing the long range ordered structure. Similar examples of non-destructive desolvation were reported in the United State patent application [ARO07] providing processes for removing residual organic solvent from crystals of ATC.

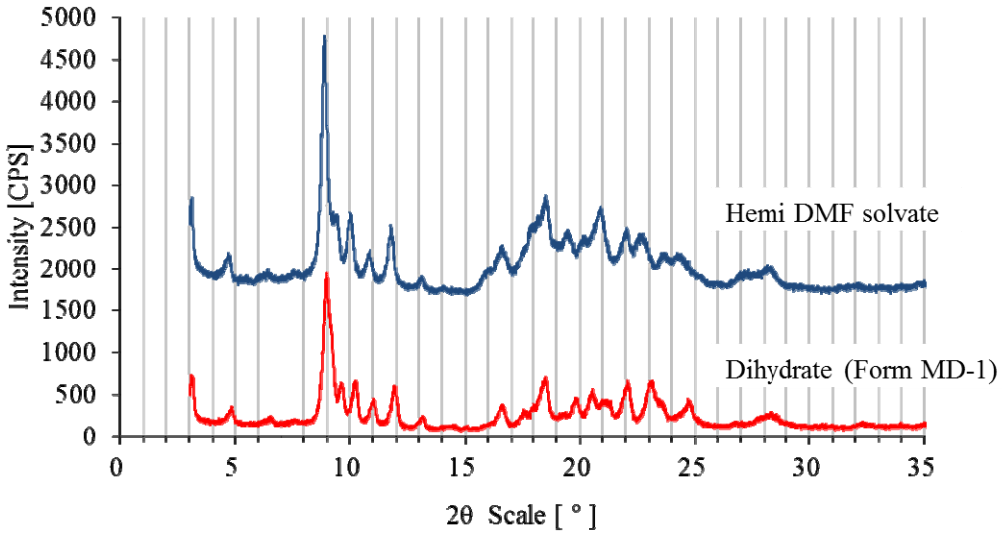


Figure 5.5 XRPD pattern of two solvates with different states of solvation

In contrast, a destructive/ reconstructive desolvation process was also observed. Form XXX as a solvate was prepared in an ethylene glycol solvent [KRZ06] and a desolvation was induced by addition of water. The ethylene glycol molecules incorporated in Form XXX solvate were substituted gradually by water molecules, i.e. hydration occurred simultaneously, causing apparent structural reconstruction. This process of desolvation combined with hydration, shown in Figure 5.6, can be seen more clearly in the changes of microscopic images, thermal analytical data and molar content of solvents as shown in Figures 5.7, 5.8 and 5.9.

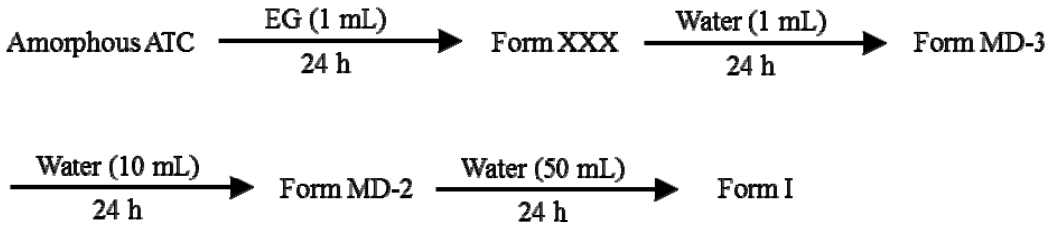


Figure 5.6 Schematic desolvation/ hydration processes from Form XXX to Form I

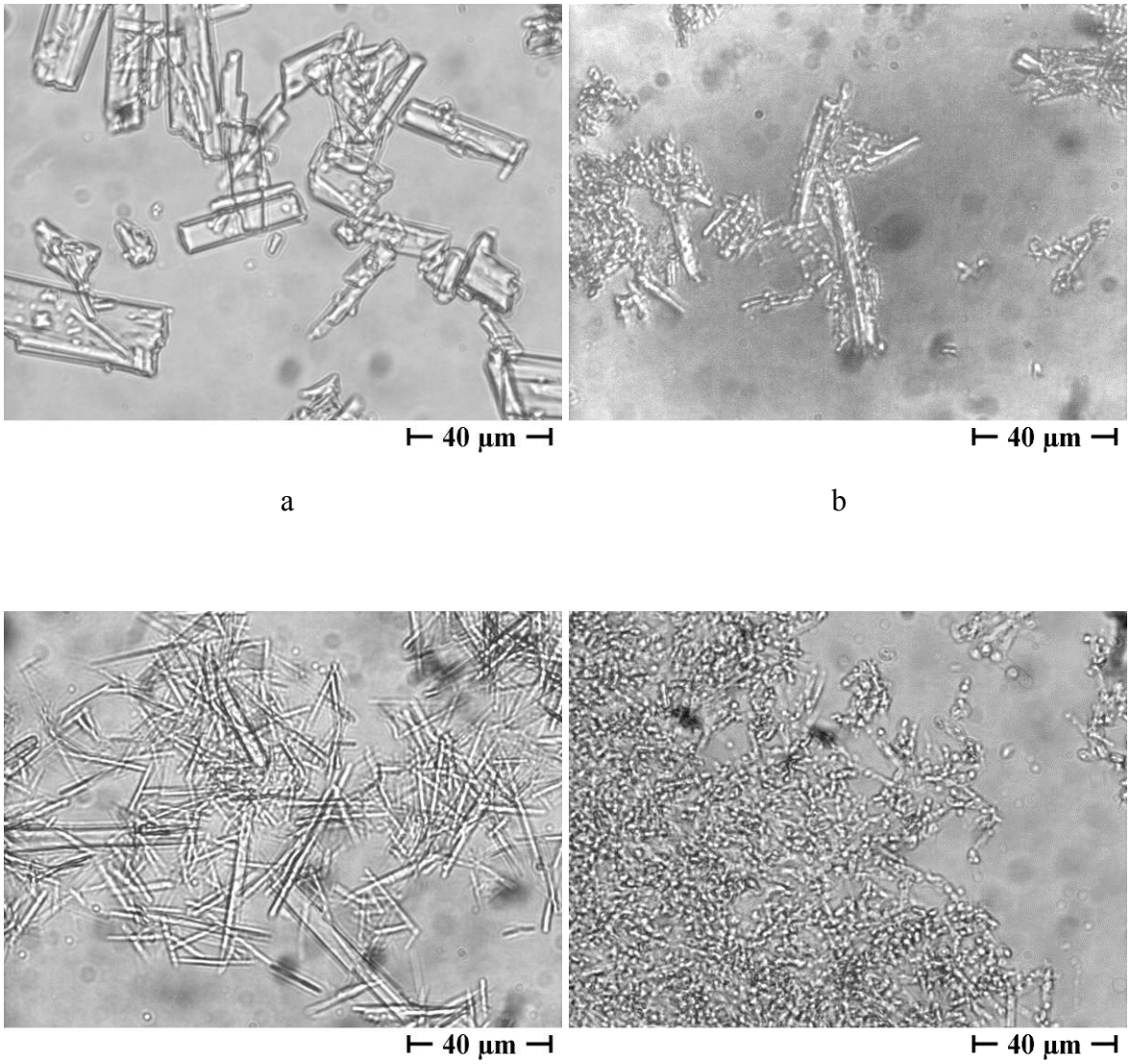


Figure 5.7 Changes of microscopic image during desolvation/ hydration: Forms XXX (a), MD-3 (b), MD-2 (c) and I (d) [JIN09c], [JIN10]

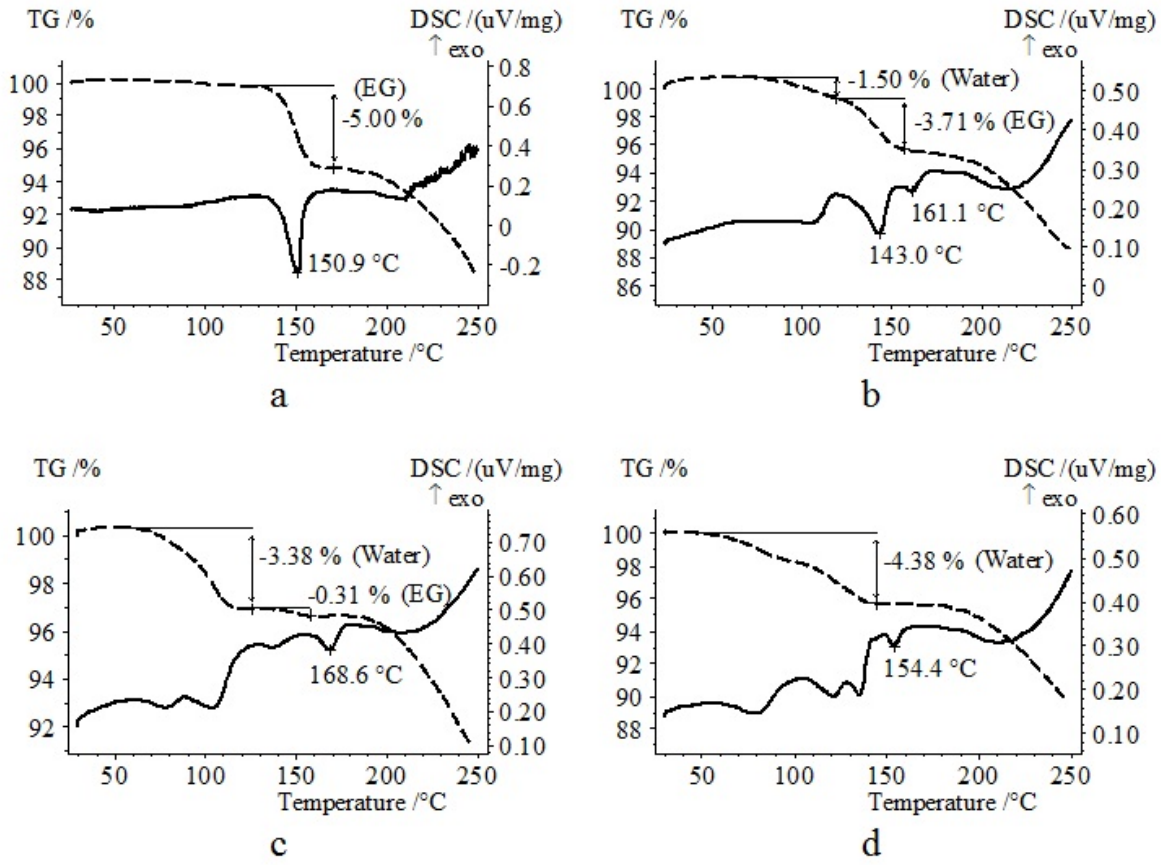


Figure 5.8 Changes of DSC/TG profile during desolvation/ hydration: Forms XXX (a), MD-3 (b), MD-2 (c) and I (d) [JIN09c], [JIN10]

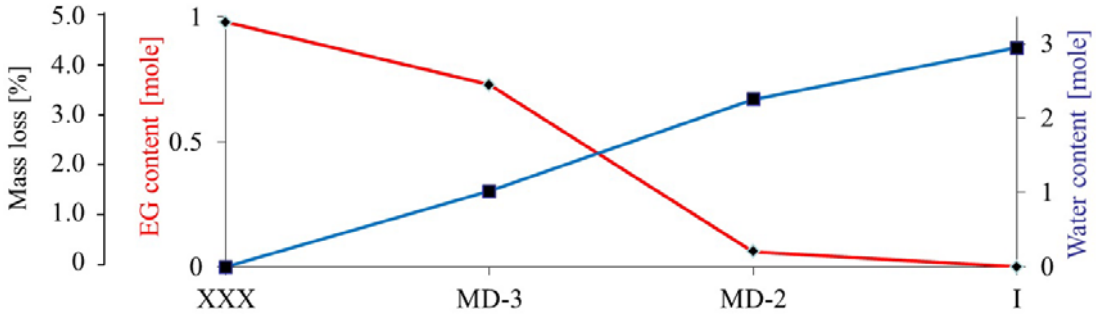


Figure 5.9 Changes of molar content of two solvents during desolvation/ hydration

In Figure 5.8, Form XXX shows one endothermic peak at 150.9 °C due to the release of an organic solvent with a weight loss of 5.00%, corresponded to approximately 1 mole of ethylene glycol. Upon increasing the amounts of water added, the weight loss due to desolvation reduces and the weight loss due to dehydration is increased step by step and finally, the Form I as trihydrate without organic solvent is crystallized. Form MD-2 shows two broad endothermic events due to dehydration with a weight loss of 3.38%, corresponded to approximately 2 mole of water, below 120 °C and a small weight loss due to desolvation were detecteed. The profile of Form MD-2 is clearly different compared to that of the other or previously reported crystals.

In Figure 5.10, the changes of XRPD pattern during this slurry transformation from Form XXX into Form I can be seen. The pattern of Forms XXX and I are exactly matching with the pattern in the references [BRI97], [KRZ06] and Form MD-2 has distinguishable pattern from all the others. In the case of MD-3 it can be assumed to be a mixture of two Forms XXX and MD-2 because it contains the mixed pattern of both.

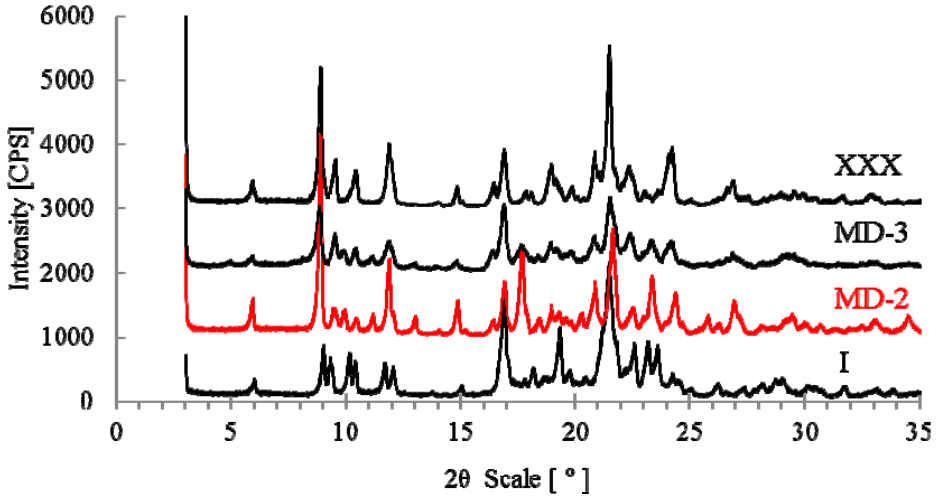


Figure 5.10 XRPD pattern of ATC Forms XXX, MD-3, MD-2 and I [JIN09c], [JIN10]

No significant differences can be seen in their Raman spectra except for a few small changes that could be detected at 2800 – 3000 cm^{-1}. However, the similarity in Raman spectra can provide reasonable evidence that the four solvates may exist in closely related structures, which can be strongly affected by the interplay of two different solvent molecules in one

crystal. Consequently, the above analytical results indicate the desolvation/ hydration process of Form XXX is a reconstructive process forming a new intermediate Form MD-2 with high molecular structural flexibility of ATC.

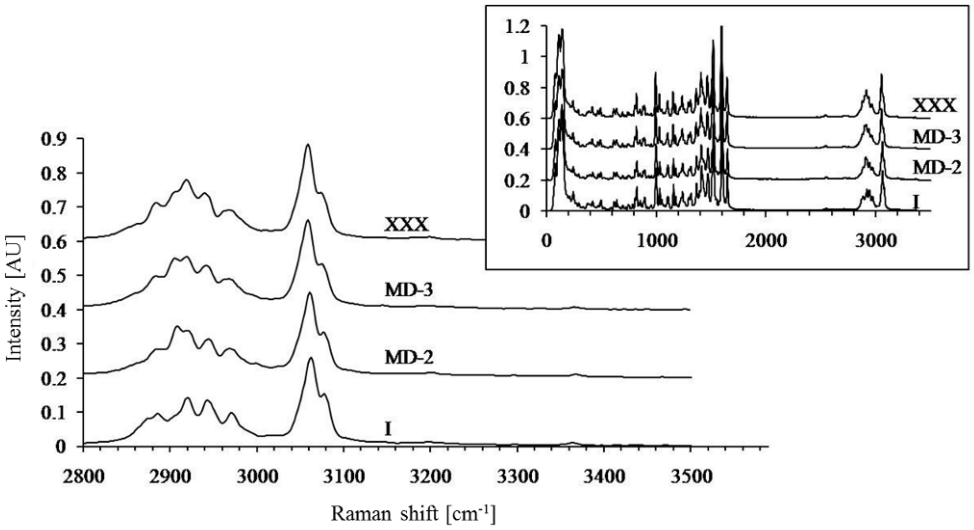


Figure 5.11 Raman spectra of ATC Forms XXX, MD-3, MD-2 and I [JIN09c], [JIN10]

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6. Conclusions

Based on the results of study and experiments, it can be concluded as follows:

1. The literature study has shown that 78 crystalline ATC with a wide variety of hydration/ solvation levels were disclosed in 26 published patents and 2 journal papers. Based on their similarities in XRPD pattern and with respect to the result on the study on the solvents and methods used in the crystallization processes, these forms are found to be dividable into 23 structure groups composed of 17 different groups crystallized from the amorphous or completely dissolved ATC and the additional 6 groups by phase transformations from the previous structure groups. The processes for producing the amorphous ATC were also found in 49 published patents. Classification of crystallization methods and solvents used in the literature were carried out and analyzed their frequencies in total cases.
2. A matrix of crystallization methods and solvents with the corresponding crystalline and amorphous forms of ATC, as shown in Figure 3.1, was derived from the above results. Which combination blocks/ blanks in this matrix should be preferentially targeted or pushed back on the priority list of experimental screening was also suggested by considering the probability of the existence of new crystal forms.
3. In order to enhance the possibility of finding new crystal forms, a minimized and efficient screening method was designed as a sequential cycle (see Figures 4.1 and 5.3), which covers four conventional crystallization methods at one cycle of a single sample preparation. Optical microscopic monitoring has assisted to catch whether crystals/ particles appeared or not in a running cycle of the experiment and it has provided a quick *Pass or Fail* decision which can accelerate the speed of screening and avoid the separation of unwanted forms. A small aliquot analysis by XRPD was acceptable for simple comparison of an obtained pattern with the previously reported pattern and therefore, it enabled the remaining sample solution to be running further cycles with still enough volume.
4. By using this screening method, two new crystalline Forms MD-1 and MD-2 of ATC have been successfully discovered although a large number of crystalline forms were already published. Especially, Form MD-1 has been evaluated to be positive, with its acceptable crystallization conditions and improved solubility, and then become a candidate for development of generic ATC with filing a patent application. In the case

of Form MD-2, it has been dropped for further development because of its indirect preparation method and a trouble caused by its sticky property in a tableting process.

5. A case of more than one solvent molecule incorporated in one crystal system and its phase transition behavior on desolvation process was reported. In a DMF/water solvent mixture, a hemi DMF solvate formed first and it desolvated via displacement by water molecules then Form MD-1 as dihydrate was isolated with almost retained structure, i.e., non-destructive desolvation was observed. Contrastively, a destructive/ reconstructive desolvation process was also investigated in an ethylene glycol/water solvent mixture. The ethylene glycol molecules incorporated in Form XXX were substituted gradually by water molecules, i.e. hydration occurred simultaneously, causing apparent structural reconstruction to Form MD-2 and finally Form I as trihydrate without organic solvent. Upon increasing the amounts of water added, the solvation level reduces and the hydration level is increased step by step. It indicates that these four solvates may exist in closely related structures, which can be strongly affected by the interplay of two different solvent molecules in one crystal. Consequently, the ATC can exist in much more complicated number of cases in different solvation/ hydration levels. Therefore, there is still a need for a systematic study on the phase transition behavior of ATC including, particularly, mixed solvate states thereof.
6. An expanded work on another API of statin drug, rosuvastatin calcium (RTC) has been accomplished by using the screening method suggested in the study on ATC. Despite there are already 9 crystal forms of RTC known, a novel crystal form, designated as Form D, was discovered and a patent was successfully applied for.

7. Summary

Solid APIs (active pharmaceutical ingredients) can exist in different physical structures without a change in chemical composition. This phenomenon, known as polymorphism, has several implications on pharmaceutical development and manufacturing. Various solid forms of an API can possess different physical and chemical properties, which may affect processing characteristics and stability, as well as the performance of a drug product.

Traditionally, polymorph screening is relying on time-consuming experimental efforts. If of an API are already quite a number of polymorphic modifications known, there will be only a low probability that the discovery will succeed. Therefore, alternative designs of screening methods that enable an efficient screening output are greatly needed.

The primary objective of this work was to discover new strategies to disclose polymorphs and solvates and to find new crystalline forms of ATC (atorvastatin calcium). ATC was found to be an excellent polymorphs/ solvates former with molecular flexibility. At least 23 different crystal structure groups of ATC were found among 78 crystalline forms of ATC disclosed in the literature. However, additional two more crystalline solvates were discovered successfully by using a sequential screening cycle method with a quick *Pass or Fail* decidable aliquot monitoring and analysis, which were assisted by optical microscope and XRPD.

Additionally, a case of more than one different solvent molecule incorporated in one crystal system and its phase transition behavior on the desolvation process was investigated. Both examples of non-destructive and destructive desolvation combined with hydration were observed and characterized. The change in crystal structures affected by the movement of two different solvents during the crystallization processes were described, too.

8. Zusammenfassung

Feste APIs (pharmazeutische Wirkstoffen) können in verschiedenen physikalischen Strukturen auftreten ohne Änderung der chemischen Zusammensetzung. Dieses Phänomen, bekannt unter dem Namen Polymorphismus, kann sich vielfach auf die pharmazeutische Entwicklung und Herstellung auswirken. Viele feste Formen von API können verschiedene physikalische und chemische Eigenschaften besitzen, welche wiederrum Verarbeitungs- oder Stabilitätseigenschaften sowie die Wirkung des Arzneimittels beeinflussen bzw. beeinträchtigen können.

Traditionell ist ein Screening nach Polymorphen auf zeitaufwendigen experimentellen Aufwand angewiesen. Falls von einem API bereits eine Vielzahl an polymorphen Modifikationen bekannt sind, so ist die Wahrscheinlichkeit ein neues Polymorph zu entdecken nur sehr gering. Aufgrund dessen werden alternative Arten von Screeningmethoden, welche eine effektive Screeningleistung ermöglicht, dringend benötigt.

Das primäre Ziel dieser Arbeit war es neue Strategien für die Suche nach Polymorphen und Solvaten sowie neue kristalline Formen von ATC (Atorvastatin Calcium) zu finden. Es hat sich herausgestellt, dass ATC ein hervorragender Polymorph-/Solvatbildner mit molekularer Flexibilität ist. Aus der Literatur bekannt sind Entdeckungen von mindestens 23 verschiedenen Kristallstrukturgruppen von ATC innerhalb von 78 kristallinen Modifikationen. Es wurden jedoch durch die erfolgreiche Anwendung der „Sequential Screening Cycle“-Methode zusätzlich zwei neue kristalline Solvate entdeckt und patentiert. Dabei wurde die hier erstellte, schnelle „Pass or Fail“ Teilprobenüberwachung und –analyse, welche durch optische Mikroskopie und XRPD unterstützt wurde, verwendet.

Zusätzlich wurde ein Fall von mehreren Solvatmolekülen eingebaut in ein Kristallsystem und deren Verhalten bei der Phasenumwandlung auf den Desolvatisierungsprozess untersucht. Beide Beispiele, die nicht-destruktive und die destruktive Desolvatisierung, kombiniert mit Hydratation, wurden beobachtet und charakterisiert. Darüber hinaus wurde die Veränderung in der Kristallstruktur, beeinflusst durch die Bewegung von zwei verschiedenen Lösungsmitteln während der Kristallisation, beschrieben.

9. Notation and abbreviations

AN	Acetonitrile
API	Active Pharmaceutical Ingredient
ATC	Atorvastatin calcium (2:1 salt)
AU	Arbitrary Unit
BuOH	Butanol
CPS	Counts per second
DCM	Dichloromethane
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DMSO-d_6	Deuterated dimethyl sulfoxide
DPE	Dipropyl ether
DSC	Differential Scanning Calorimeter / Calorimetry
EA	Ethyl acetate
EG	Ethylene glycol
EtOH	Ethanol
G	Gibb's free energy
H	Enthalpy
HMG-CoA	3-Hydroxy-3-Methyl-Gluraryl-Coenzyme A
^{1}H-NMR	Proton Nuclear Magnetic Resonance
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonization
IPA	Isopropanol
IPAc	Isopropyl acetate
MeOH	Methanol
mp	Melting point
PP	Pyrophosphate
RTC	Rosuvastatin calcium (2:1) salt
S	Entropy
SD	Standard Deviation
T	Temperature
TBME	tert-Butyl methyl ether
TG	Thermogravimetry

Tg	Glass transition temperature
THF	Tetrahydrofuran
TMS	Trimethyl silane
tp	Transition point
XRPD	X-ray powder diffraction
δ	Chemical shift
θ	Angle of beam diffraction
λ	Wavelength of radiation

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11. Appendix

11.1 Data collection - XRPD peak locations

Forms	2θ [°]											
I	9.2	9.5	10.3	10.6	11.9	12.2	17.1	19.5	21.6	22.0	22.7	23.3
	23.7	24.4	28.9	29.2								
II	5.6	7.4	8.5	9.0	12.4*	15.8*	17.1-17.4*		19.5	20.5	22.7-23.2*	
	25.7*	29.5										
III	4.1	5.0	5.8	7.7	8.5	16.0	16.6	17.7	18.3	18.9	19.5	20.0
	20.3	21.1	21.7	23.3	24.4	25.0	25.4					
IV	4.9	5.4	5.9	8.0	9.7	10.4	12.4	17.7	18.4	19.2	19.6	21.7
	23.0	23.7	24.1									
V	4.9*	6.0	7.0	8.0*	8.6	9.9	16.6	19.0	21.1			
VI	7.2	8.3	11.0	12.4	13.8	16.8	18.5	19.7*	20.9	25.0*		
VII	8.6	10.2	12.4*	12.8*	17.6	18.3*	19.3	22.2*	23.4*	23.8*	25.5*	
VIII	7.5	9.2	10.0	12.1	12.8	13.8	15.1	16.7*	18.6*	20.3*	21.2	21.9
	22.4	25.8	26.5	27.4*	30.5							
IX	8.8	9.4*	11.2-11.7*		16.7	17.5*	19.3*	21.4*	22.4*	23.2*	29.0*	
X	4.7	5.2	5.8	6.9	7.9	9.2	9.5	10.3*	11.8	16.1	16.9	19.1
	19.8	21.4	22.3*	23.7*	24.4	28.7						
XI	10.8*	12.0	13.5	16.5	17.6-18.0*		19.7	22.3	23.2	24.4	25.8	26.5
	27.3	28.7	29.5	30.9*	32.8*	33.6*	36.0*	38.5*				
XII	5.4	7.7	8.0	8.6	8.9	9.9	10.4*	12.5	13.9*	16.2	17.8	19.4
	20.8	21.7	22.4-22.6*		24.3	25.5	26.2	27.1				
XIII	8.4	8.9	15.7*	16.4*	17.6*	18.1*	19.7*	20.8*	23.8*			
XIV	5.4	6.7	7.7	8.1	9.0	16.5*	17.6*	18.0-18.7*		19.5*		
XV	5.7	6.1	6.8	7.5	8.1	8.5	9.5	10.5*	19.1-19.6*			
XVI	5.2	6.4	7.5	8.7	10.5*	12.0*	12.7*	16.7	18.3*	19.5	20.1-20.4*	
	21.2-21.9*		22.9-23.3*		24.4-*25.0							
XVII	5.0	6.1	7.3	7.9	8.5	9.1	10.0	12.1*	14.8	16.0-16.5*		17.5*
	19.0*	19.5	20.2*	21.3	21.6	22.0						
XVIII	8.0	9.2*	9.7*	12.1	16.6*	18.5						
XIX	5.2	6.3	7.0	8.6	10.5	11.6*	12.7*	14.0	16.7*	18.9	20.8	23.6*
	25.5*											
XX	7.5-9.0*		17.5-26.0*									
XXI	3.1	4.1	5.0	6.3	7.6	8.6	9.2	10.1	12.2	16.7*	18.2*	19.2*
	20.1*	20.5*	23.2*	29.6*								
XXII	4.0	4.9	8.0	10.0	11.1	11.7	12.2	13.1	13.5	14.0	14.8	16.1
	16.4	17.0	17.4	17.7	19.2	20.0	20.3	21.3	22.6	24.5*	27.0	28.1
	28.9*	29.4*										

Forms	**2θ [°]**											
XXIII	3.2	4.1	5.0	6.3	7.2	7.7	8.1	8.5	9.1	10.1	10.5	12.1
	12.8	13.3	16.7*	18.4*	19.1	20.2*	21.0	21.4	23.2*	24.3	25.2	29.3
XXIV	2.9	4.6	5.2	7.4	7.8	8.7	9.5	10.0	12.2*	12.5	13.4	13.9
	17.3*	18.0	18.6	19.0*	20.6	21.2*	22.3*	22.7	23.2	24.2	24.5*	25.0*
	26.4*	28.8*	31.8									
XXV	3.1	5.2*	6.4	7.4*	7.9*	8.7*	10.4*	12.0*	12.7*	16.6*	18.1*	19.2*
	20.0	20.7	22.8*	23.2*	24.4*	25.6*	26.5*	29.3*				
XXVI	3.7	7.3	8.4	9.0	12.2	16.0*	17.1*	17.7*	18.7	20.1	20.7	22.3*
	23.0*	25.2*	28.7*									
XXVII	3.5	3.9	4.6	7.1*	7.5	7.9*	9.6	9.9	10.6	11.8	13.0*	15.3
	16.6*	17.2	18.7	22.6*	23.8	25.1						
XXVIII	7.6	9.5	12.2	16.5	17.0	18.0	19.2	19.5	20.5	20.9	21.5	21.8
	22.3*	23.3	23.8									
XXIX	8.0	10.2	11.5	14.5	15.3	16.2*	18.0	19.6	20.2	20.6	21.4	22.3
	23.0	23.9	24.2	24.9	25.9*	26.9	28.6	29.1	30.4	30.9		
XXX	3.1	9.0	9.7	10.5	12.0	16.5	17.0	19.0	19.3	19.9	20.9	21.1
	21.6	22.5*	24.3	26.7	27.0	27.6	29.6	31.8				
V(T)	5.3	8.3	18.0-23.0*									
VI(T)	3.5	5.1	7.7	8.2	8.7	10.0	12.5	13.8	16.2	17.2	17.9	18.3
	19.5	20.4	20.9	21.7	22.4	23.2	24.3	25.5				
VII(T)	4.7	7.8	9.3	12.0	17.1	18.2	18.5-21.8*		21.8-25.0*			
VIII(T)	4.8	5.2	5.9	7.0	8.0	9.3	9.6	10.4	11.9	16.3	17.1*	17.9
	18.6	19.2	20.0	20.8	21.2	21.6	22.4	22.8	23.9	24.7	25.6	26.5
	29.0											
IX(T)	4.7	5.2	5.7	7.0	7.9	9.4	10.2	12.0	17.0	17.4	18.2	19.1
	19.9	21.4	22.5	23.5	24.8*	26.1	28.7	30.0				
X(T)	4.8	5.3	5.9	9.6	10.3	11.5	12.0	16.1	16.3	16.9	17.4	18.2
	19.2	19.4	20.0	20.8	21.6	22.0	22.8	23.6	24.6	25.0	25.5	26.2
	26.8	27.4	28.0	30.3								
XI(T)	3.2	3.7	5.1	6.3	7.8	8.6	9.8	11.2	11.8	12.4	15.4	18.7
	19.9	20.5	24.0									
XIa(T)	9.3	9.5	15.7	20.5	21.1	22.8	23.8	24.0	25.3	26.4	26.8	27.2
	29.2	31.6										
XII(T)	2.1	8.0	8.4	11.8	18.2	19.0	19.8	20.7				
XIV(T)	7.6	9.8	16.5	18.1	20.0	20.4	21.9	22.4	23.6	29.4		
XVI(T)	7.7	9.9	16.5	17.7	18.3	20.0*	21.9*	29.5				
XVII(T)	7.8	9.5	10.2	18.2	19.1	20.6	21.4	23.6	25.3	26.2	30.1	
XVIII(T)	3.0	3.8	8.0	8.9	10.4	18.0	18.8	19.6				
XIX(T)	3.3	4.2	5.6	8.2	17.0	19.2	22.0					
V(B)	5.3	8.6	8.7	9.0	9.8	10.1	11.3	16.7	18.0	19.2	21.5	22.6

Forms	**2θ [°]**											
	23.2	23.6	24.3	24.6	26.3	28.2	28.8	29.2	30.4	31.9	37.4	
VI(R)	3.9	4.5	7.5	7.9	9.2	18.9						
VII(R)	4.6	7.5	9.2	18.6	18.9	20.2						
X(C)	3.7	4.1	4.6	4.8	5.1	5.5	9.1	10.5	11.1	16.1	18.9	20.9
	27.9											
α	8.8*	9.6*	11.9	16.9*	19.6	21.7*	23.5*	29.7*				
A	3.1	3.4	3.6	3.7	4.0	4.1	4.5	4.6	5.2	5.5	6.2	6.5
	7.4	8.6	9.3	9.6	11.2	12.8	15.3	17.0	18.6	31.0		
A1	5.3*	8.3*	15.7*									
B1	2.4	3.7	3.9	4.2	4.5	4.7	4.9	5.3	6.1	7.1	8.6	10.1
	12.1	14.2	17.0	27.9								
B2	3.7	3.9	4.3	4.6	4.9	5.3	7.0	7.5	8.6	10.4	12.3	14.0
	17.2	28.1										
B-52	4.5	4.7	5.3	5.8	7.8	9.5	10.2	12.2	16.1	16.5	16.9	17.1
	17.5	17.9	18.2	18.7	19.1	19.4	20.0	20.4	21.6	22.0	22.6	22.9
	23.3	24.1	26.2									
C	3.7	4.2	4.4	4.6	5.2	5.6	6.9	7.7	8.3	9.8	11.3	17.1
	24.0	28.8										
D	4.8	6.4	7.7	10.3	16.9	31.0	33.7					
E	4.6	9.4	26.8									
F	2.7	3.7	5.4	6.8	7.7	8.7	10.2	12.6	13.8	17.2	17.9	19.4
	20.8	22.5	24.2	25.5	27.8							
Fa	10.2	11.3	11.9	13.0	18.9	23.1	25.0					
Ga	3.3	4.5	4.8	7.2	8.3	8.8	9.4	11.9	14.9	15.6	16.4	16.8
	17.8	18.1	19.1	19.7	20.3	20.7	21.9	23.3	24.8	23.9	25.6	26.4
	26.9	28.9	29.8	30.8	32.0	33.4						
Je	5.7	9.5	11.1	11.7	12.7	19.3	22.0	22.7	23.5	25.0	26.1	
M	4.7	5.5	5.9	8.2	9.6	10.4	11.0	16.3*	18.6*	11.0	20.3	21.9
	23.7											
M-1	3.8	7.7	8.7	10.2	12.6	17.9	18.4	19.4	20.3	20.8	22.5	25.6
M-2	7.6	8.2	8.6	10.2	16.9	17.7	18.1	18.4	19.4	20.1	20.4	20.8
	27.1	29.3	32.8									
M-3	8.0	8.3	8.6	18.2	18.8	19.5	20.2	29.3	36.0			
M-4	2.7	5.5	8.2	10.9	18.3	19.0	20.0	31.7				
MCK-I	4.1	5.3	6.4	6.8	7.9	8.7	8.7	9.4	11.0	11.9	18.1	18.2
	18.7	20.4	21.6	22.8	23.2	29.6	32.7	33.5	36.2	37.2		
MCK-II	2.8	4.7	5.3	7.8	9.5	19.3	20.2	21.4	22.8	23.4		
MCK-III	3.0	4.6	6.0	8.9	9.3	10.1	10.4	11.6	16.9	18.2	19.2	21.5
	22.2	22.5	23.2	23.6	24.3	28.9						
MD-1	3.1	4.8	9.0	9.2	9.6	10.2	11.0	12.0	16.6	17.6	18.0	18.5

Forms	**2θ [°]**											
	19.9	20.5	21.2	22.1	23.1	23.6	24.7	28.3*				
MD-2	3.0	5.9	8.9	9.4	9.5	11.1	11.9	13.0	14.8	16.9	17.6	18.9
	20.2	20.8	21.6	22.4	23.3	25.7	26.9					
P	Not available											
R	3.6	8.2	8.6	10.2	18.1	18.4	19.3	20.4	20.8	21.2	23.8	
R2	See reference [RAO11]											
T1	2.9	4.9	5.7	8.3	9.0	18.4	19.9*					
T2	3.2	4.2	7.8	8.6	9.3	10.0	11.3	17.7	18.4-21.2*			
T3	3.7	5.5	6.6	7.8	8.6	8.9	10.3	13.9	17.2	17.9	19.5	20.9
3	See reference [AN09]											

* Broad

11.2 Data collection - Raman peaks

Forms	Raman shift [cm^{-1}]										
I	3071	3061	2951	2941	2918	2883	1649	1601	1524	1468	1414
	1368	1318	1296	1238	1163	1158	1103	1051	1032	997	895
	855	824	810	639	614	494	419	243	139	116	99
I*	3080	1512	1439	142							
II*	1663	359									
III*	2938	1660	1510	1481	1427	1182	859				
IV*	423	215	132								
V	3062	1652	1604	1528	1478	1440	1413	1397	1368	1158	1034
	1001	825	245	224	130						
VI	3058	2935	1651	1603	1556	1525	1478	1412	1157	997	
VII	3060	2927	1649	1603	1524	1476	1412	1397	1368	1159	1034
	998	824	114								
VIII	3065	2923	1658	1603	1531	1510	1481	1413	997	121	
X	3062	2911	1650	1603	1525	1478	1411	1369	1240	1158	1034
	999	824	116								
XII	3064	2973	2926	1652	1603	1527	1470	1410	1367	1240	1159
	1034	1002	823								
XX	3059	1649	1604	1558	1528	1480	1412	1244	1178	1158	1034
	999	892	855	818	618						
XXII	3059	1671	1603	1526	1410	1364	1243	1157	1033	998	855
	820	618									
XXIV	3062	2972	2922	2555	2263	1651	1603	1527	1473	1413	1398
	1370	1301	1240	1179	1160	1112	1056	1034	1000	961	925
	900	857	825	811	789	697	643	617	500	422	298
	247	217	133								
XXV	3063	2933	2257	1654	1605	1528	1477	1412	1397	1368	1320
	1243	1181	1159	1112	1058	1034	1001	901	859	825	726
	697	644	617	495	422	300	245	224	138		
XXVII	3063	2927	1658	1604	1578	1559	1527	1481	1411	1368	1314
	1240	1158	1112	1034	998	898	858	821	736	634	618
	581	512	366	288	130						
XXVIII	3376	3060	2940	2882	1640	1603	1525	1468	1412	1369	1316
	1298	1242	1180	1159	1090	1062	1034	999	863	824	755
	699	642	617	478	422	405	341	296	248	148	
MD-1	3061	2914	1647	1603	1554	1537	1509	1480	1442	1409	1358
	1319	1304	1240	1177	1158	1034	997	821	106		

Forms	**Raman shift [cm^{-1}]**										
MD-2	3059	2907	1649	1603	1524	1470	1410	1366	1314	1238	1157
	1105	1032	997	884	824	243	147	116	83		

* Peaks available in reference [BYR03]

11.3 Data collection – Solid-state ^{13}C NMR peaks

Forms	Chemical shift [ppm]										
I	182.8	178.4	166.7*	159.3	137.0	134.9	131.1	129.5	127.6	123.5	120.9
	118.2	113.8	73.1	70.5	68.1	64.9	47.4	41.9	40.2	26.4	25.2
	21.3										
II	209.1	206.8	181.0*	163.0*	161.0*	140.5	134.8	133.3	129.0	122.9	121.4
	120.3	119.0	117.1	115.7	114.7	70.6	69.0	68.0	67.3	49.4	48.9
	43.4	42.3	41.7	40.2	27.5	22.8*					
III	214.8	209.3	202.3	184.9	166.7	161.0*	140.1	135.2	131.8	128.9	124.3
	122.2	117.2	114.9	69.8	67.3	65.6	44.1	40.4	35.4	27.0	24.1
	22.1	19.9									
IV	186.4	184.9	181.4	179.3	166.1*	159.0*	134.7	129.2	127.1	122.7	119.8
	115.7	71.5	67.9	66.3	63.5	46.1	43.4	42.1	40.0	25.9	20.3
	19.4	17.9									
V	185.7	176.8	166.9	138.7	136.3	133.0	128.4	122.0	117.0	116.3	68.0
	43.1	25.6	19.9								
VI	176.5	168.2	159.8	136.8	127.8	122.3	118.8	113.7	88.2	79.3	70.5
	43.3	36.9	31.9	25.9	22.5						
VII	186.5	183.3	176.8	166.5	163.1	159.2	137.6	128.3	122.3	119.2	74.5
	70.3	68.3	66.2	43.5	40.3	26.3	24.9	20.2			
VIII	186.1	179.5	167.9	139.4	132.9	128.7	124.7	121.8	116.6	67.0	43.3
	26.7	24.7	20.9	20.1							
X	187.0	179.5	165.5	161.0	159.4	137.9	134.8	129.4	127.9	123.2	119.9
	71.1	43.7	40.9	26.4	25.3	20.3	18.3				
XX	180.7	166.8	162.9	161.0	134.7	128.5	122.5	118.6	69.8	41.8	26.1
	21.7										
XXII	182.1	166.6	164.1	161.8	143.7	139.4	136.1	134.2	139.1	123.4	119.7
	115.7	68.7	45.1	43.9	39.1	37.4	26.8	22.7	20.6	18.3	
XXIV	187.5	185.2	184.2	180.5	179.0	178.4	177.4	166.8	162.7	160.9	138.7
	136.2	133.7	128.7	124.4	122.4	121.2	120.5	118.0	115.7	69.8	67.4
	65.7	46.4	44.3	43.5	40.6	26.7	25.5	21.8	19.6		
XXV	186.3	185.0	182.5	177.0	167.0	166.2	162.8	160.9	138.6	136.1	133.4
	129.2	128.5	126.0	124.0	121.5	120.7	118.0	116.8	116.0	69.9	68.0
	46.4	43.3	40.9	25.7	25.2	21.3	20.0	0.6			
XXVII	179.7	166.0	163.6	161.7	140.7	133.8	128.8	122.4	115.3	72.5	70.9
	66.6	41.8	27.3	22.0							

Forms	**Chemical shift [ppm]**										
XXVIII	184.1	183.4	181.2	180.9	166.8	162.5	160.5	138.1	137.5	135.3	134.5
	132.8	131.4	131.1	130.0	129.6	127.7	123.9	123.1	121.4	120.6	118.4
	117.6	113.1	73.7	73.1	71.7	66.8	65.9	63.9	46.7	43.0	26.5
	24.7	23.8	21.4	21.0							
XXX	181.0	177.2	167.2	162.5	160.5	137.8	137.1	135.4	134.4	132.3	131.2
	129.9	128.2	127.4	123.7	123.1	121.8	120.9	118.6	117.8	113.9	67.9
	65.4	63.9	47.5	47.0	46.2	43.3	41.5	40.5	26.2	25.5	24.9
	21.8	21.4									
V(T)	176.0-186.0*		167.1	161.0	135.1	128.7	122.5	118.9	115.6	63.0-73.0*	
	42.3	41.8	40.4	25.9	21.9						
VIII(T)	186.5	178.8	166.4	159.8	139.8	138.3	137.0	135.1	134.2	129.2	128.8
	126.6	122.8	121.8	120.1	119.5	116.0	114.1	73.3	70.8	46.1	44.1
	43.4	41.5	40.8	40.3	26.1	25.2	24.8	20.0	17.8		
IX(T)	186.6	178.4	166.3	159.9	139.4	138.3	136.8	135.1	134.3	129.4	128.6
	126.7	122.8	121.7	120.2	119.5	116.0	114.3	73.4	71.0	46.4	40.4
	26.1	24.9	20.4	18.0							
X(T)	186.1	184.3	181.1	179.3	166.2	159.4	138.0	134.5	128.9	126.7	122.4
	119.5	115.9	71.1	67.5	66.2	63.1	43.4	24.9	20.6	19.6	18.7
	17.7										
XVII(T)	20.6*	19.6	18.8	10.4*	8.9	8.0*	3.8*	3.0			
XIX(T)	22.0*	19.2*	17.0*	8.2	5.6	4.2	3.3				
V(B)	183.4	177.6	166.4	161.6	159.5	157.9	136.4	134.4	130.2	128.8	127.5
	122.7	120.1	117.0	112.9	72.3	69.5	67.3	64.0	59.6	46.5	40.5
	25.5	24.0	20.4								
α	224.4	224.2	221.6	217.8	216.1	214.6	214.4	210.2	181.7	179.3	177.6
	165.9	161.5	159.5	136.8	134.2	130.3	128.7	120.7	120.0	117.3	113.9
	112.9	74.0	72.1	70.8	69.5	68.3	67.1	66.4	64.9	64.1	49.3
	47.7	46.5	45.8	45.3	44.6	42.3	40.7	39.4	36.8	35.2	25.4
	23.9	20.2	18.5								
F	188.2	184.3	177.4	167.5	162.6	161.0	139.8	138.2	135.8	134.1	132.0
	131.2	130.5	129.0	128.0	127.2	125.5	124.0	123.5	122.8	122.1	120.7
	117.6	116.6	115.2	112.8	72.9	71.7	69.4	67.1	63.2	46.3	44.1
	40.6	36.4	32.1	31.1	28.2	27.4	25.8	22.5	20.9	20.0	
Fa	237.9	218.0	214.2	210.2	208.5	202.6	200.8	196.9	195.0	194.2	193.2
	182.3	179.4	178.0	165.9	158.6	143.8	141.2	136.5	134.7	130.7	129.0
	123.0	120.6	117.6	113.8	109.5	106.9	102.7	85.3	84.0	72.6	70.0
	67.6	64.4	56.9	55.2	53.4	51.1	49.4	47.0	46.3	41.5	39.7
	26.1	24.5	23.3	20.7	16.1						

Forms	Chemical shift [ppm]										
Ga	187.5	182.2	179.2	164.6	138.1	127.4	122.3	116.3	69.1	67.3	41.1
	25.1	21.6	19.0								
Je	214.5	212.2	210.8	208.1	205.9	203.1	201.6	201.1	186.2	183.3	182.3
	181.9	179.8	178.8	167.1	166.4	166.3	165.3	158.7	136.6	134.6	130.9
	128.3	123.1	121.1	117.5	115.8	114.6	114.0	113.6	83.6	71.0	65.5
	63.2	62.8	57.0	54.7	52.8	51.0	48.5	43.0	41.0	40.6	35.1
	34.5	33.6	33.2	32.1	26.2	23.4	20.2				
M-1	190.6	186.9	179.5	169.1	162.7	137.5	131.2	123.0	119.4	73.6	72.3
	68.9	46.0	42.8	38.3	33.9	29.4	27.8	24.3	21.9		
MCK-I	186.4	184.5	178.7	166.5	159.7*	138.4	137.2	134.3	129.2	126.8	122.9
	122	119.7	116.1	114.3	73.6	71.3	66.7	65.3	46.3	43.5	40.9
	26.3	25.2	20.2	17.9							
MCK-II	186.1	184.4	178.7	166.6	159.6*	138.3	137.2	134.3	129.2	126.8	122.9
	122	119.7	116	114.1	73.7	66.6	65.3	46.1	43.8	41.5	26.3
	25.5	20.2	17.9								
MCK-III	182.5	178.2	166.6	162.6	159.8*	137	134.8	130.6	129.2	123.2	120.6
	117.8	113.4	72.8	70.2	67.8	64.6	48.3	47.1	46.4	43	41.3
	39.8	26.1	24.8	20.9							

* Broad

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Ich versichere hiermit ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und nur unter Benutzung der angegebenen Literatur und Hilfsmittel angefertigt habe. Die aus fremden Quellen direkt oder indirekt übernommenen Stellen sind als solche kenntlich gemacht und werden in der Arbeit aufgeführt.

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November, 2012 Yong Suk Jin

Curriculum Vitae

1. Personal Information

Family Name:	Jin
Given Name	Yong Suk
Academic Degree	M.Sc.
Date of Birth:	March 12, 1974
Gender	Male
Place of Birth:	Jeju, South Korea
Nationality:	South Korean
Home Address	Wolpi-dong 498-11, Sangrok-gu, Ansan-si, Gyeonggi-do 426-855, South Korea
E-mail:	ys6262@daewoong.co.kr, ys6262@gmail.com

2. Education

09/2006-09/2009	PhD Student (Research Assistant), Thermal Process Technology, Center for Engineering Sciences, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany
03/1997-02/1999	Master of Science in Organic Chemistry, Graduate School of Chung-Ang University, Seoul, South Korea
03/1993-02/1997	Bachelor of Science in Chemistry, Department of Natural Sciences, Chung-Ang University, Seoul, South Korea

3. Professional Experience

10/2009-present	Chief Research Scientist, API Research Center, Life Science Research Institute, Daewoong Pharmaceutical Co., Ltd., South Korea
07/2001-09/2006	Principal Research Scientist, R&D Center, Daewoong Pharmaceutical Co., Ltd., South Korea
03/1999-06/2001	Researcher, Central Research Institute, Hanlim Pharmaceutical Co., Ltd., South Korea

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