NOVEL FORMULATIONS OF A POORLY SOLUBLE DRUG USING THE EXTRUSION PROCESS

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Abstract

Novel formulations of a poorly soluble drug using the extrusion process

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Key words: HME, thermolabile drug: artemisinin, Soluplus®, polymorphism, stability.

Hot melt extrusion has attracted recent interest from the pharmaceutical industry and academia as an innovative drug delivery technology. This novel technique has been shown to be a viable and robust method for preparing different drug delivery systems including pellets, implants, tablets, capsules and granules. The aim of this research was to understand hot melt extrusion processing and explore its pharmaceutical applications. Two applications of hot melt extrusion (HME) have been investigated to improve the properties of poorly soluble thermolabile drugs; polymeric solid dispersions and solid state polymorphic transformation.

HME is a solvent free, continuous and readily scalable technique which is increasingly being considered as a viable alternative to conventionally used batch techniques. However, the high temperature and shear forces imparted by the extrusion process can limit its applications with heat sensitive active pharmaceutical ingredients (APIs). Artemisinin was selected as a model drug which being thermolabile in nature and possesses processing challenges to processing HME. A low Tg amphiphillic copolymer, Soluplus® was selected as a matrix material. Drug-polymer compatibility was studied using rotational rheometry and thermal characterisation. The drug was found to be completely dissolved within the polymer, although some discolouration of the mixture was observed, indicating degradation of the API. The addition of a

small percentage of citric acid to the formulation was found to prevent this degradation by increasing the pH. The dissolution profile of the formulation was approximately five times higher compared to that of the pure drug. The pharmacokinetic study was carried out using Albino rats to calculate bioavailability. The area under plasma concentration time curve ($AUC_{0\text{-}24hr}$) and peak plasma concentration (C_{max}) were four times higher for the prepared solid dispersion compared to that of pure artemisinin. Extruded solid dispersions were found to be amorphous in nature and maintained stability for 2 years.

A second route to improving the solubility of poorly soluble APIs was also investigated. It was found that under carefully controlled conditions, high temperature extrusion (HTE) could be used to achieve polymorphic transformation with a number of APIs. This solvent-free continuous process was demonstrated with artemisinin, piracetam, carbamazepine and chlorpropamide. Artemisinin was used as a detailed case study of stability, solvent mediated transformation and mechanism of polymrophic transformation during extrusion, using computational modelling and model shear flows. At high temperature, phase transformation from orthorhombic to triclinic crystals was found to occur via the vapour phase. Under mechanical stress the crystalline structure was disrupted, leading to new surfaces being continuously formed and exposed to high temperatures; thus accelerating the transformation process. Polymorphic transformation during HTE was found to comprise three stages; i) preheating and conveying; ii) vapour phase transformation and size reduction and iii) continuous transformation and agglomeration. The triclinic form showed four times greater dissolution

rate as compared to the orthorhombic form. The triclinic form showed two fold increase in bioavailability in Albino rats.

List of Publications

- Chaitrali Kulkarni, Adrian Kelly, Tim Gough, Anant Paradkar, Technology for obtaining stabilized metastable polymorph, Patent application number: PCT/GB/ 1208489.3
- Chaitrali Kulkarni, John Kendrick, Adrian Kelly, Tim Gough, RC Dash, Anant Paradkar, Solid state polymorphic transformation of artemisinin in high temperature extrusion technique, *CrystEngComm.* **15** (2013) 6297-6300.
- Chaitrali Kulkarni, Adrian Kelly, John Kendrick, Tim Gough, Anant Paradkar, Mechanism of polymorphic transformation of artemisinin during high temperature extrusion process, *Cryst. Growth Des.* **13** (2013) 5157–5161.
- Chaitrali Kulkarni, Adrian Kelly, Tim Gough, Anant Paradkar, Processing of thermolabile drug using hot melt extrusion, *Pharm. Res.* (Under preparation).
- Chaitrali Kulkarni, Adrian Kelly, Tim Gough, Anant Paradkar, An investigation of solvent mediated polymorphic transformation of artemisinin, *Cryst Growth Des.* (Under preperation).

International Conference Contributions

- Chaitrali Kulkarni, Ravindra Dhumal, Kelly, Tim Gough, Anant Paradkar, Solid dispersion of thermolabile drug artemisinin using hot melt extrusion, Indian Pharmaceutical Congress, 2010, Manipal, India.
- Chaitrali Kulkarni, Ravindra Dhumal, Adrian Kelly, Tim Gough, Anant Paradkar, Processing of thermolabile drug using hot melt extrusion, UK-Pharm Sci Conference, 2011, Nottingham, UK.
- Chaitrali Kulkarni, Adrian Kelly, Tim Gough, Anant Paradkar, Stability study of artemisinin-soluplus solid dispersion, Amorphous Conference, 2012, Greenwich, UK.
- Chaitrali Kulkarni, John Kendrick, Adrian Kelly, Tim Gough, Anant Paradkar, Polymorphic transformation of artemisinin by high temperature extrusion, BCCG Conference, 2013, Manchester, UK.

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Abbreviations

1.	ACT	artemisinin combination based therapy
2.	APIs	Active Pharmaceutical Ingredients
3.	art	artemisinin
4.	AUC	Areas Under Curve
5.	BCS	Biopharmaceutical Classification System
6.	BDDH	Bravais - Freidel - Donnay - Harker
7.	CSD	Cambridge Structural Database
8.	CVFF	Consistent Valence Force Field
9.	DMF	dimethylformamide
10.	DSC	Differential Scanning Calorimetry
11.	DTS	deuterated triglycine sulphate
12.	EDTA	edetate disodium
13.	FDA	Food and Drug Administration
14.	FTIR	Fourier Transform Infrared
15.	GC-MS	Gas Chromatography Mass Spectrometry
16.	GMP	Good Manufacturing Practice
17.	HME	Hot Melt Etrusion
18.	HPC	hydroxypropyl cellulose
19.	HPLC	High Performance Liquid Chromatography
20.	HPLC-MS	High Performance Liquid Chromatography-Mass Spectrometry
21.	HPMC	hydroxypropyl methyl cellulose
22.	HTE	High Temperature Extrusion

23.	IP	Intellectual Property
24.	NIR	Near Infra Red
25.	NMR	Nuclear Magnetic Resonance
26.	PADT	PharmaForm Abuse Deterrent Technology
27.	PAT	Process Analytical Technique
28.	PCFF	Polymer Consistent Force Field
29.	PEO	Polyethylene Oxide
30.	PGA	poly (glycolide)
31.	PLA	poly (lactide)
32.	PLGA	poly (lactide-co-glycolide)
33.	PVP	polyvinylpyrrolidone
34.	PVP	polyvinylpyrrolidone
35.	PXRD	Powder X-ray Diffraction
36.	QbD	Quality by Design
37.	QeQ	Equilibrated Charges
38.	RH	Relative Humidity
39.	SCF	Super Critical Fluid
40.	SEM	Scanning Electron Microscopy
41.	SFCC	Solvent Free Continuous Co-crystallisation
42.	SLS	sodium lauryl sulphate
43.	UV	Ultra-Violet
44.	WTO	World Health Organisation

Symbols

1.	r^2	coefficient of determination
2.	Tg	Glass transition temperature
3.	C_{max}	maximum plasma concentration
4.	T_{max}	Time to reach C_{max}
5.	w/w	weight / weight

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1. Introduction

Hot Melt Extrusion (HME) has attracted recent interest from the pharmaceutical industry and academia as a technology which can enable innovative drug delivery routes. The aim of this research was to explore novel applications of HME to achieve stabilised systems of poorly water soluble Active Pharmaceutical Ingredients (APIs) using polymeric solid dispersions and continuous polymorphic transformation. Figure 1.1 shows advantages of HME in the pharmaceutical industry.

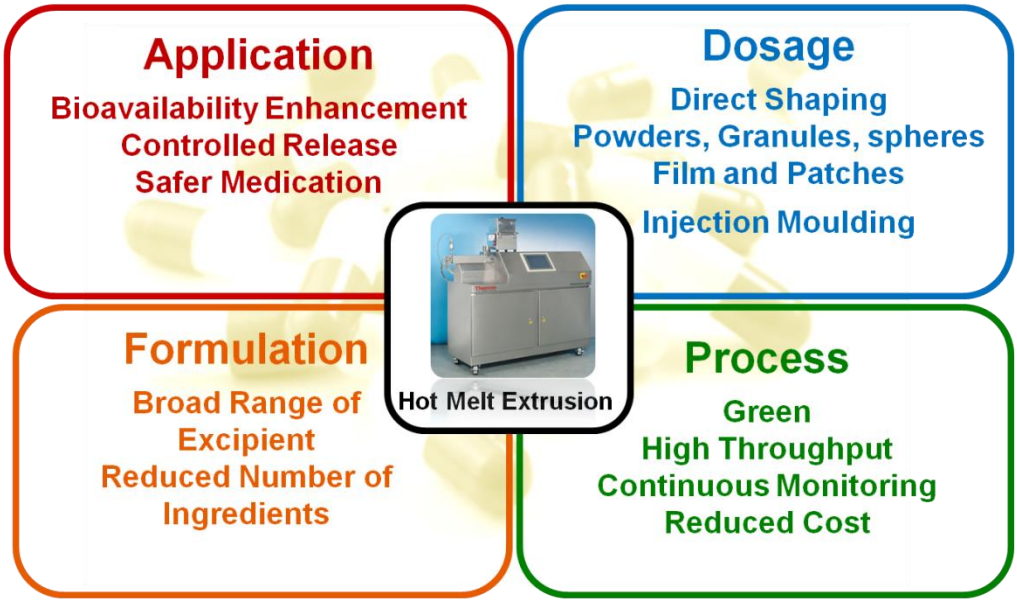


Figure 1.1 Advantages of HME in the Pharmaceutical Industry

The pharmaceutical industry shares a secret that, although it discovers many advanced and innovative drugs, its manufacturing technologies lag behind those of the detergent and potato chip industries. However, there is now a drive to improve and modernise production methodologies. The US Food and Drug Administration (FDA) has actively encouraged the pharmaceutical industry to take up manufacturing innovation in order to improve quality (Leila *et al*., 2003). Many new processing techniques have been introduced to the pharmaceutical industry as a result, to improve the effectiveness and efficiency of all steps of the manufacturing process, including design, control and quality assurance.

Hot Melt Extrusion (HME) is a green manufacturing approach which has recently attracted interest from the pharmaceutical industry and academia as an innovative manufacturing process to produce new drug delivery systems. This novel technique has been shown to be a viable and robust method for preparing different drug delivery systems including pellets, implants, tablets, capsules and granules (Crowley *et al*., 2007). HME offers many advantages over conventional pharmaceutical processing techniques. Typically, in HME, no solvent is used and fewer operation steps are involved. The hazardous nature of most organic solvents and the presence of residual solvents after drying in conventional processes may be problematic and costly. Complicated processing conditions and disposal of the associated waste can create significant environmental concerns regarding these manufacturing techniques. As a result, alternative technologies are sought by the pharmaceutical industry to overcome some of these challenges (Maniruzzaman *et al*., 2012). A key advantage of HME is that it can be

achieved through a single continuous processing step which makes it economical. Continuous manufacturing to produce chemicals, APIs and final dosage forms is gaining widespread attention. Although the potential advantages over traditional batch processes have been widely reported, continuous processes are only slowly being implemented (Poechlauer *et al*., 2012). In addition, the US FDA has emphasised the need for process innovation through better process understanding by adapting Process Analytical Technology (PAT). HME is well suited to meet the proposed FDA guidelines for PAT in the design, analysis and control of the extrusion process by continuous monitoring.

1.1. Research objectives and approach

The main aim of this research was to explore novel pharmaceutical applications of hot melt extrusion technology. The challenges and opportunities stemming from poorly soluble molecules for oral delivery have been explored and considered in the wider context of how the pharmaceutical industry is adopting unconventional technologies to bring new drugs into the market. Figure 1.2 indicates pharmaceutical applications of HME technology.

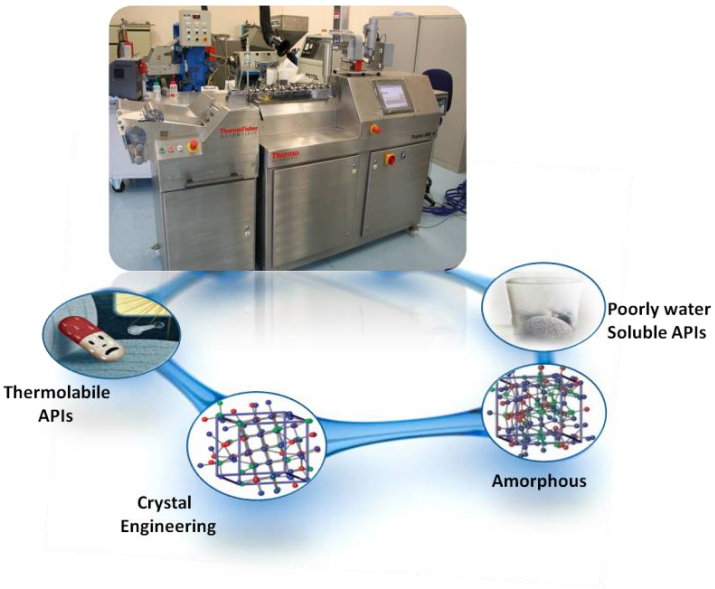


Figure 1.2 Applications of HME technology

Specific objectives of this research were:

- To investigate and address challenges in the application of HME for processing solid dispersions containing thermolabile drugs
- To explore the application of HME to cause polymorphic transformation during processing
- To develop a mechanistic understanding of polymorphic transformation during extrusion
- To investigate solvent mediated polymorphic transformation
- To confirm the biopharmaceutical performance of the amorphous and metastable polymorphic states achieved by extrusion

Schematic presentation of the research work has been shown in figure 1.3.

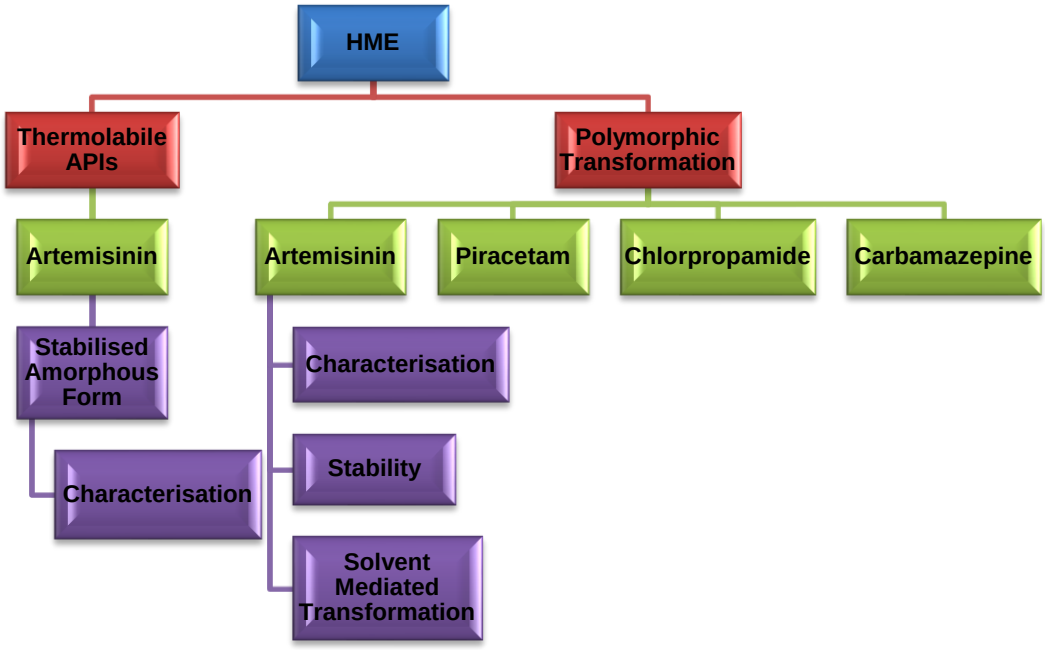


Figure 1.3 A schematic representation of the research structure

1.2. Thesis outline

Chapter 2 provides a background and is divided into three major sections; firstly the concept of a solid dispersion is presented, including a description of its types and different methods of preparation. The second section describes the basics of polymorphs and their significance to the pharmaceutical industry. The final section provides an introduction to the hot melt extrusion technique, its principles, pharmaceutical applications, advantages and limitations.

Chapter 3 describes details of the materials and methods adopted in the present work and has been divided into two major sections; solid dispersions of artemisinin and polymorphic transformation using HME. The solid dispersion section provides details of the HME methodology, composition variables and characterisation including *in-vitro* and *in-vivo* evaluations of the

optimised artemisinin – Soluplus® systems. The section about polymorphic transformation using HME describes the optimisation of process parameters, characterisation procedures, experiments performed to understand the mechanism, stability of the polymorph, computational techniques used and bioavailability studies.

Chapter 4 contains the results and discussion of artemisinin solid dispersion studies. An important outcome of this work related to avoiding artemisinin degradation during extrusion by selecting a stabiliser, thus achieving four times more bioavailability compared to the crystalline drug.

Chapter 5 explains how a stabilised triclinic form of artemisinin was generated and investigates the crystal transformation of other drugs. A major focus of this chapter is to explain the mechanism of polymorphic transformation of artemisinin using results from a shear cell and other techniques. Another important aspect is the mechanistic understanding of stability of the triclinic form and the role of solvents in destabilisation. Chapter 5 also details a bioavailability study and polymorphic transformation studies on other model molecules including chlorpropamide, piracetam and carbamazepine.

Chapter 6 provides an overall summary and conclusions of the work presented in this thesis and the scope for future work.

Chapter 7 contains references to published work cited within the thesis.

2. Background

This chapter includes introduction to solid dispersion, polymorphs and hot melt extrusion technique. A schematic presentation of the chapter is shown in figure 2.1.

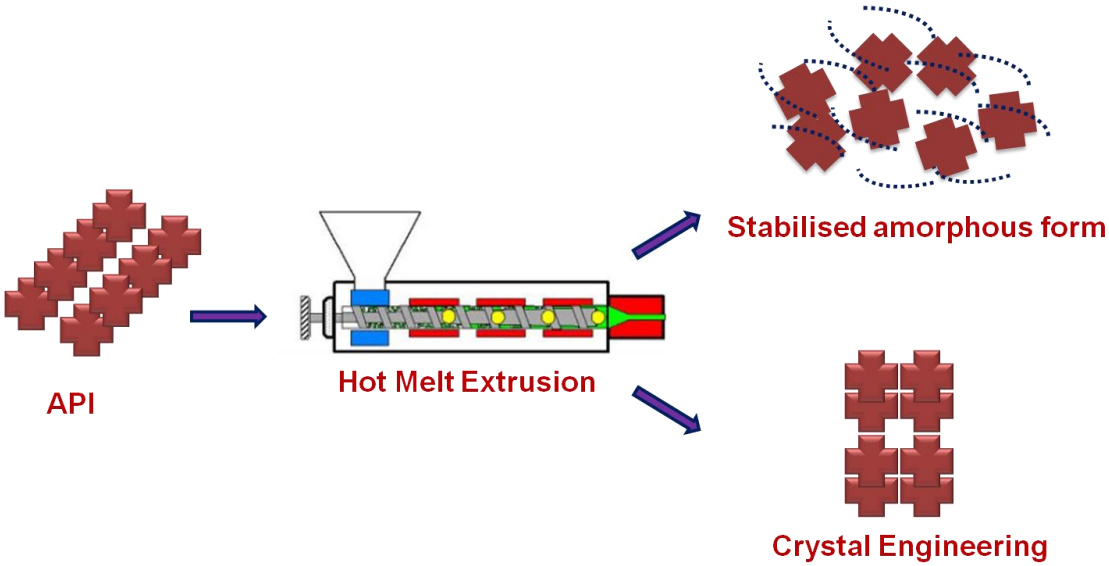


Figure 2.1 A schematic presentation of background

2.1. Introduction

A significant number of APIs in the market have been confirmed to have low solubility and bioavailability. Although different approaches such as solubilisation, size reduction and complexation using cyclodextrin have been proposed to increase solubility and oral absorption of such drugs, these techniques have not solved the problems of many drugs (Sharma *et al*., 2010). Drug solubilisation in either aqueous or organic medium using surfactants or co-solvents gives liquid formulations which are generally objectionable from a commercialisation and patient point of view. Reduced particle size of the drug may be considered commonly to improve dissolution rate. Various techniques are available to obtain fine particles including grinding, controlled precipitation by changing solvent and temperature, ball milling and conventional trituration (Goldberg *et al.*, 1966). A faster dissolution rate may not be achieved in many cases by particle size reduction because of strong van der Waals forces between non polar molecules. The solvent method is a better option to achieve fine particle size but it is not applicable for many drugs due to the use of toxic solvents (Muhammad *et al*., 2001). Also, the application of fine powders in dosage forms may not be feasible due to low wettability and handling difficulties.

In dosage form design, it is important to understand pharmaceutical techniques to achieve enhanced dissolution, absorption and efficacy of APIs. Therefore, the study of method of preparation, selection of suitable carrier, analysis of physical properties will be a vital approach in effective and practical dosage form development.

2.2. Solid state chemistry

Solid state chemistry deals with study of the synthesis, structure and properties of solid state materials. It has a strong connection between solid state physics, mineralogy, crystallography, ceramics, metallurgy, thermodynamics, material science and electronics with an aim of the synthesis of novel materials and their characterisation. There have been major advances in solid state and materials chemistry in the last two decades that are an integral part of life (Janse, 2002; Disalvo, 2000 and Bishop *et al*., 1996). The study of solid-state chemistry of drugs covers many scientific disciplines within the pharmaceutical industry from discovery to successful marketing. It is known that an understanding of the molecular structure of the solid state can lead to better design and control of drug performance. The isolation, identification and characterisation of a new molecule by advanced techniques is one of the most active areas of modern solid state chemistry (Kanatzidis *et al*., 2007; Hilfiker *et al*., 2007; Byrn *et al*., 1999 and Braga *et al*., 2010). The aim of researchers in the field of solid state pharmaceutical chemistry is to provide each drug in a solid state which has optimum properties for any given application (Byrn *et al*., 1994).

2.3. Solid forms

The pharmaceutical industry invests considerable resources in identifying novel APIs with desirable physicochemical properties which could be later formulated into drugs. Nevertheless, to be considered for commercial use, an API's physicochemical properties, which are generally dependent upon dosage form, must be controllable and must adhere to the guidelines set up by the regulatory authorities e.g. US FDA. APIs are commonly formulated in

the solid state such as tablets, capsules, granules, powder etc. because chemical stability is better in this form compared to alternatives (Morissette *et al.,* 2004). Moreover, solid state formulations offer more practical means of processing, handling and packaging the APIs and they are the preferred choice by most patients because of their easy uptake in the body. An API can exist in a number of solid forms such as amorphous, polymorphs, solvates, salts and co-crystals (as shown in figure 2.2). Each form may display its own unique physicochemical properties of pharmaceutical importance including mechanical, surface, physical, thermal and chemical properties, that can profoundly affect bioavailability, solubility, hygroscopicity, stability, processability and other characteristics of the drug (Byrn *et al*., 1995). Such diversity offers the opportunity of tuning key physiochemical properties of the pharmaceutical product without compromising the physiological activity of the API as the molecular structure is preserved.

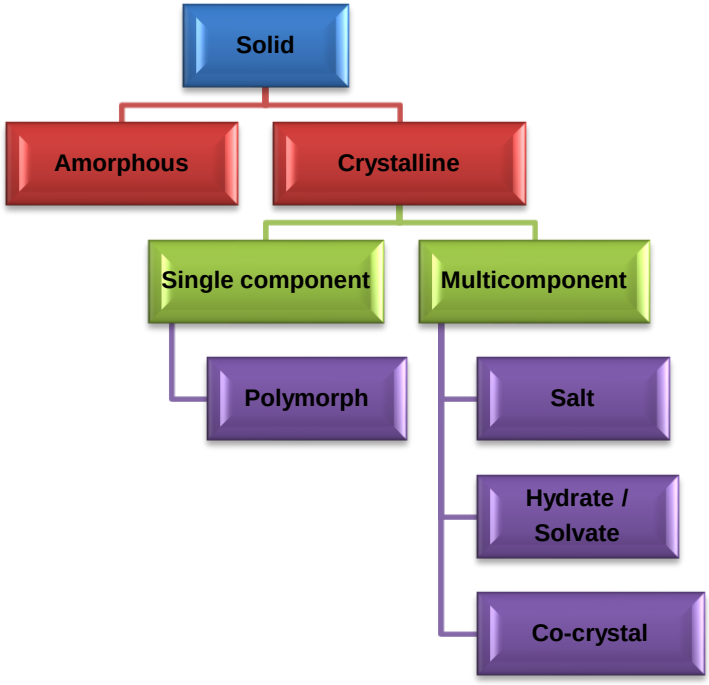


Figure 2.2 Classification of solid forms (Byrn *et al*., 1995)

It has been estimated that more than 40% of APIs suffer from a bioavailability issue because of their low water solubility. Due to the advent of computational chemistry and the importance of lipophilic receptors, this percentage is expected to increase (Kerns *et al*., 2001). This is a major drawback for drug formulations because many new potential drugs fail in the formulation stage. The formulation of such compounds for oral delivery exhibits one of the most common and difficult challenges to formulation scientists. More than 80% of marketed formulations are in the solid form and 90% of these are crystalline in nature. An enhancement of the solubility of a drug may improve its bioavailability. Identifying the optimum form of an API is scientifically and clinically preferable (Byrn *et al*., 1999). Research over the past decade has changed the paradigm of 'one molecule, one crystal' to 'one molecule, many crystals and therefore many properties' (Braga *et al*., 2010). This is shown schematically in figure 2.3.

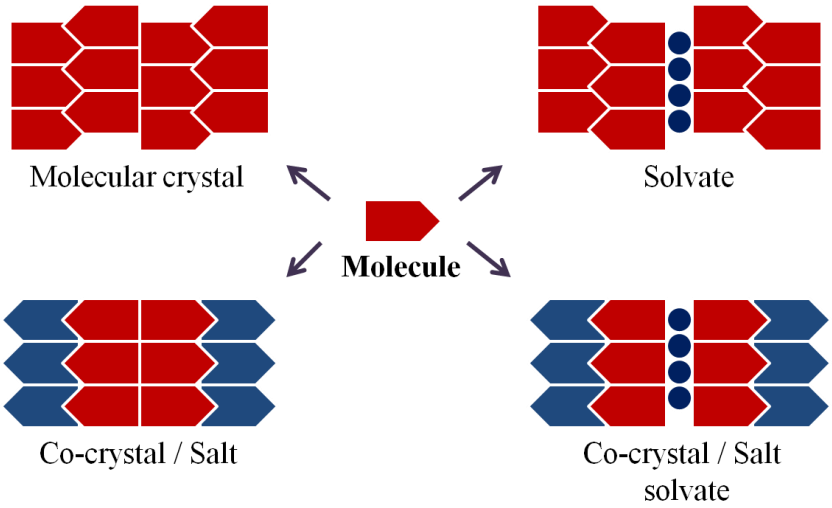


Figure 2.3 Arrangement of molecules in different structures

Experimental efforts and creative approaches can reveal new forms with advantageous properties. The exploration of crystal forms can have a

significant impact on applied and fundamental science because the different crystal forms may show different physicochemical properties. The range of crystalline forms that are possible for an API are shown is figure 2.4.

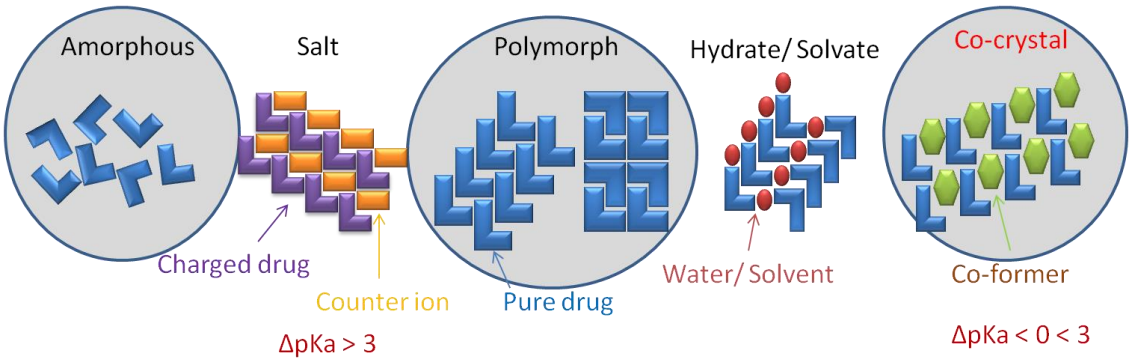


Figure 2.4 Possible solid forms for an API

Generally, for an API which has low water solubility; it may be preferable to use an amorphous or more soluble form. The amorphous form consists of disordered arrangement of molecules which do not form a distinguishable crystal lattice. The amorphous form has a stability issue but this can be stabilised by forming a solid dispersion.

2.4. Solid dispersions

Currently, more than 60% of drug candidates suffer from poor water solubility. This results in potential products not reaching the market. Over the last 20-30 years solid dispersion is a new horizon in drug delivery system to enhance dissolution rate and oral bioavailability (Seckiguchi *et al*., 1964). This section highlights various approaches in solid dispersion technology. A schematic of the section is shown in figure 2.5.

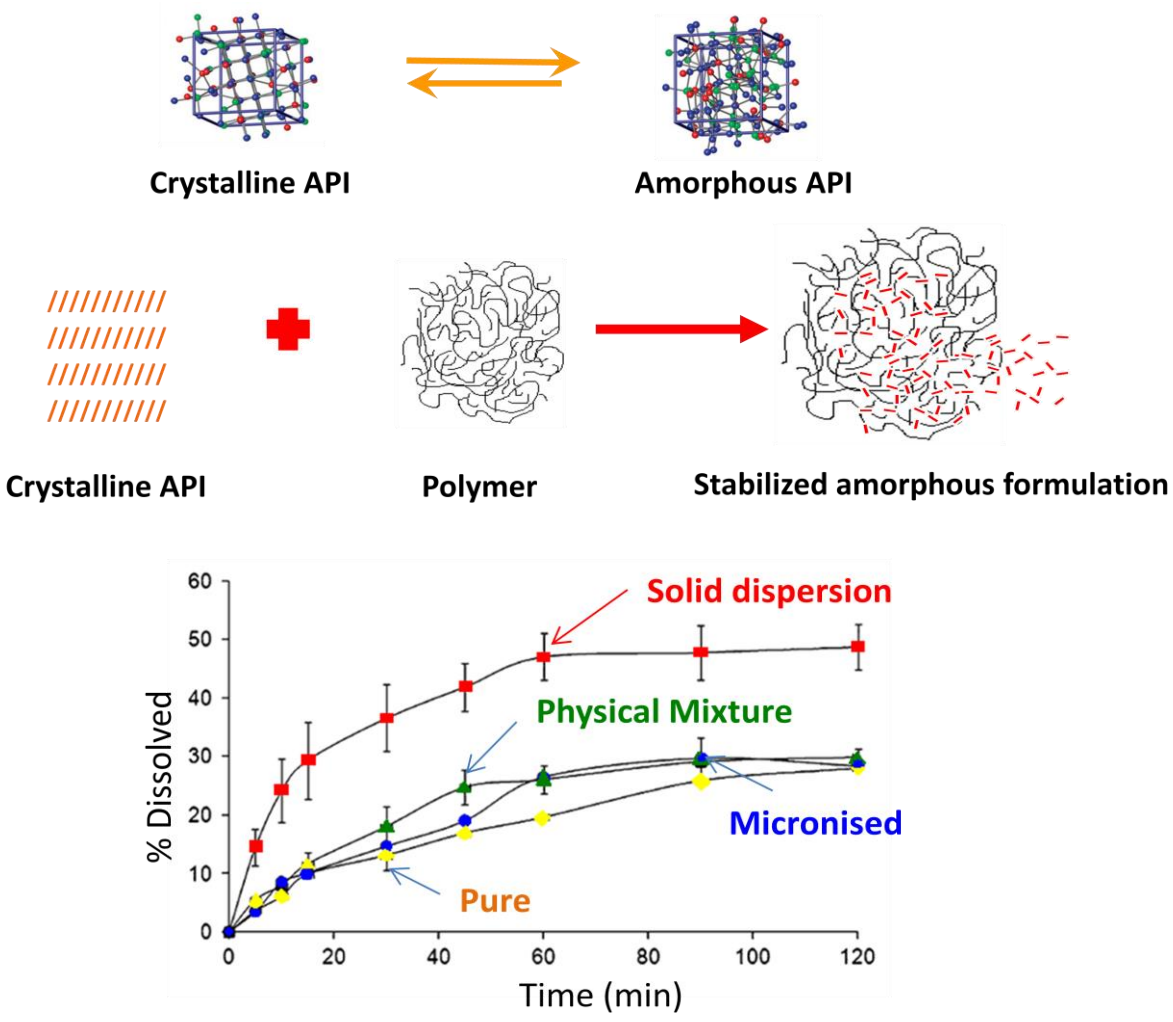


Figure 2.5 A schematic presentation of solid dispersions (Nijlen *et al*., 2007)

In 1961, Seckiguchi and Obi demonstrated a practical technique to overcome the bioavailability issue of a poorly water soluble drug which was termed a 'solid dispersion' (Seckiguchi *et al*., 1964). Solid dispersion technology deals with groups of solids containing at least two components, normally a hydrophobic drug and a hydrophilic matrix. This matrix can be either in a crystalline or an amorphous form. Chiou and Riegelman defined solid dispersion as a “dispersion of one or more active moieties into an inert carrier at solid state prepared by a fusion, solvent or melting-solvent method” (Chiou *et al*., 1969). Traditionally, water soluble or water miscible polymers like polyethylene glycol, polyvinylpyrrolidone or low molecular weight compounds like urea, mannitol or citric acid were used as carriers. Typical polymer matrices are listed in table 2.1.

Table 2.1 Polymers used in solid dispersions

Chemical name	Trade name	Glass transition temperature (°C)	Melting point (°C)
Hydroxypropyl cellulose	Klucel®	130	-
Ethyl cellulose	Ethocel®	133	240
Polyethylene oxide	Polyox®WSR	-50	65-80
Polyethylene glycol	Carbowax®	-20	37-63
PVP	Kollidon®	168	-
Hydroxypropyl methyl cellulose	Methocel®	175	-
Cellulose	-	165	192

acetate phthalate			
Polyethylene	-	-125	140

Compared to conventional dosage forms, the advantages of solid dispersion are schematically presented in figure 2.6.

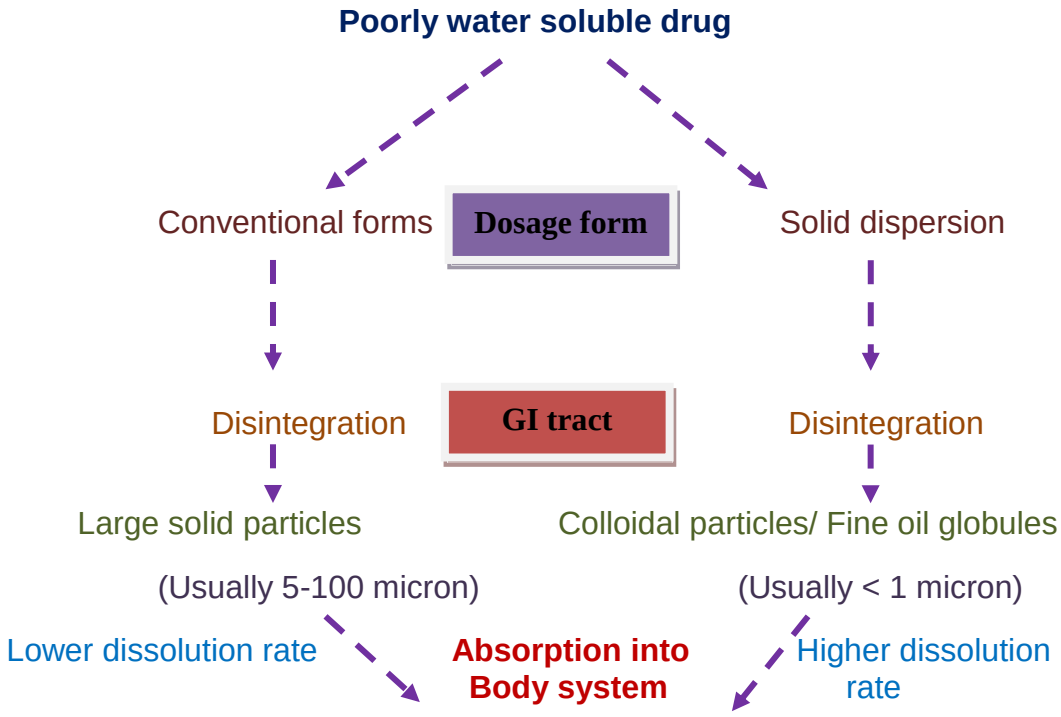


Figure 2.6 A schematic presentation of bioavailability enhancement of a poorly soluble drug (Singh *et al.*, 2011)

For conventional tablets and capsules, the primary particle size formed by disintegration is the rate limiting step for dissolution. In this case the average particle size is 5 µm even though a higher particle size is preferable for handling and manufacturing while solid dispersions dissolve immediately to saturate the GI fluid. Initially the main objective of solid dispersions was purely to increase the solubility of poorly water soluble drugs, but recently

this concept has been applied to the formation of sustained release drugs and to change solid state properties (James *et al.,* 1997).

Due to their potential to enhance the bioavailability of poorly water soluble drugs, solid dispersions have become one of the most active areas of research in the pharmaceutical industry.

2.4.1. Classification of solid dispersion

Based on molecular arrangements, solid dispersions can be broadly classified into the following types; simple eutectic mixtures, amorphous precipitations in crystalline matrices, solid solutions, glass solutions, complex formations of drug and matrices and amorphous precipitations, as shown in table 2.2.

Table 2.2 Types of solid dispersion (Adapted from Singh et al., 2011)

	Type	Matrix *	Drug **	Remark	No. phases
1.	**Eutectic**	C	C	The first type of prepared solid dispersion	2
2.	**Amorphous precipitation in crystalline matrix**	C	A	Rarely encountered	2
3	**Solid solution**				
	Continuous solid solution	C	M	Miscible at all compositions, never prepared	1
	Discontinuous solid solution	C	M	Partially miscible, 2 phases even though drug is molecularly dispersed	2
	Substitutional solution	C	M	Molecular diameter of drug differs than 15%	1 or 2

				from the matrix diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinuous 2 phases even though drug is molecularly dispersed.	
	Interstitial solid solutions	C	M	Drug molecular diameter less than 59% of matrix diameter. Usually limited miscibility, discontinuous.	2
4	**Glass suspension**	A	C	Particle size of dispersed phase dependent on cooling rate. Obtained after crystallisation of drug in amorphous matrix.	2
5	**Glass suspension**	A	A	Particle size of dispersed phase dependent on cooling rate. Obtained after crystallisation of drug in amorphous matrix.	2
6	**Glass solution**	A	M	Requires miscibility or solid solubility, complex formation or upon fast cooling, evaporation during preparation.	1

*A: matrix in amorphous state, C: matrix in crystalline state

**A: drug dispersed as amorphous cluster in the matrix, C: drug dispersed as crystalline particles in the matrix, M: drug molecularly dispersed throughout the matrix

2.4.1.1. Simple eutectic mixture

A simple eutectic mixture involves two compounds which are completely miscible in the liquid state with limited distribution in the solid state. Generally differential scanning calorimetry of two compounds shows two endothermic peaks but in the case of a eutectic mixture, produces a single endothermic peak that lowers the melting point in comparison with the individual compound. This simple eutectic mixture can be prepared by various methods such as solvent, physical (grinding or mixing), solvent fusion and fusion methods.

If a mixture consists of a slightly soluble drug and a highly soluble carrier in an aqueous media, the carrier will dissolve quickly resulting in the release of very fine drug particles (Tiwari *et al*., 2009).

2.4.1.2. Solid solution

A solid solution contains dissolved solid solute in a solvent. Two components crystallise together in one homogenous phase to form a mixed crystal (Dokoumetzidis *et al*., 2006). In solid solutions, the particle size is reduced to a molecular level to achieve higher dissolution than from a simple eutectic mixture. In accordance with Mohammed, in a binary system in which the formation of a solid solution is specious, the phase diagram is defined by the disappearance of a thaw point at a temperature higher than the eutectic point (Mohammed *et al*., 2001). Depending upon their miscibility, solid solutions are classified into continuous and discontinuous solid solutions and are based upon the solvate distribution in the solvent. Solid solutions are divided into amorphous substitutional and interstitial.

2.4.1.3. Continuous solid solution

In continuous solutions, all components are miscible in all proportions. To date, no continuous solid dispersion has been reported in the pharmaceutical industry. Theoretically it represents that the bonding strength between two constituents is stronger than the bonding capacity of the individual components.

2.4.1.4. Discontinuous solid solutions

Here, the solubility of the two components is restricted in each other. In a particular composition and temperature region, one component is completely soluble in the other component. Below a certain temperature, the mutual solubility of the two constituents begins to decrease. As per practical consideration, Goldberg et al. suggested that the term 'solid solution' should be applicable when the mutual solubility exceeds 5% (Goldberg *et al*., 1965).

2.4.1.5. Glass solution or suspension

This concept was applied for the first time by Chiou and Riegelman for enhancing dissolution. It is a homogeneous system in which the solute dissolves in a glassy carrier (Chiou and Riegelman, 1969). The term ‘glassy’ describes materials which are transparent and brittle below the glass transition temperature (Fernandez *et al*., 1992). It is obtained by a rapid quench of the melt. On heating, glass softens gradually and continuously without a sharp melting endotherm.

2.4.1.6. Amorphous precipitation

An amorphous precipitate forms when a drug precipitates as an amorphous form in an inert matrix. It is similar to a simple eutectic mixture. In an

amorphous precipitation the higher energy state of the drug leads to improved dissolution compared to the crystalline form of the drug.

2.4.2. Advantages of solid dispersion

A solid dispersion is useful to enhance the solubility and bioavailability of a poorly soluble drug**.** It leads to an increase in the degree and rate of absorption of a drug. Various parameters such as molecular weight, particle porosity, wettability and composition can be controlled, resulting in enhancement of the bioavailability of poorly water soluble drugs. The bitter taste of some drugs can be masked using this approach (Singh *et al*., 2011).

2.4.3. Marketed solid dispersion products

The commercial application of solid dispersions has so far been relatively limited, to date only a few formulations have been marketed which are displayed in table 2.3.

Table 2.3 Marketed solid dispersion products

Drug	Trade Name	Formulation Composition
Ritonavir /Lipnovir	Kaletra®	Copovidone, sorbitan monolaurate, colloidal silicon dioxide and sodium stearyl fumarate
Ritonavir	Norvir®	Copovidone, anhydrous dibasic calcium phosphate, sorbitan monolaurate, colloidal silicon dioxide and sodium stearyl fumarate
Itraconazole	Sporanox®	Sugar spheres, hydropropyl methyl cellulose, gelatine, polyethylene glycol
Etravirine	Intelence®	Hypromellose, silicified microcrystalline cellulose, croscarmellose sodium, lactose monohydrate

Tacrolimus	Prograf®	Lactose, hydropropyl methyl cellulose, croscarmellose sodium
Rosuvastatin	Crestor®	Hypromellose, crospovidone, lactose, microcrystalline cellulose
Griseofulvin	Gris-PEG®	Colloidal silicon dioxide, lactose, magnesium stearate, methylcellulose, methylparaben, polyethylene glycol 8000, povidone
Nabilone	Cesamet®	Povidone and corn starch
Ibuprofen	Solufen®	Gelucire 44/14
Vemurafenib	Zelboraf®	Hypromellose acetate succinate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and hydroxypropyl cellulose
Telaprevir	Incivek®	Hypromellose acetate succinate, croscarmellose sodium, colloidal silicon dioxide, dibasic calcium phosphate (anhydrous), microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sodium lauryl sulfate and sodium stearyl fumarate

2.4.4. Current trends in solid dispersion technology

Innovative manufacturing processes to prepare solid dispersions have been developed to overcome drawbacks of traditional techniques. Solid dispersions can be categorised based on the implementation and recent development (Vasconcelos *et al*., 2007):

2.4.4.1. First generation solid dispersions

In 1961, Sekiguchi and Obi developed a eutectic mixture to enhance the rate of drug release which consequently increased the bioavailability of poorly

water soluble drugs (Sekiguchi and Obi, 1964). Later, Levy and Kaning prepared solid dispersions using mannitol as a carrier through molecular dispersions as an alternative to eutectic mixtures (Levy and Kaning, 1963). Crystalline solid dispersions were formed which are thermodynamically stable but did not release drug as the fast as amorphous form.

2.4.4.2. Second generation solid dispersions

In the late sixties, it was noted that solid dispersions with crystalline drugs were not effective as they were thermodynamically more stable. Hence, a second generation of solid dispersions was developed containing amorphous matrices (Singh *et al*., 2011).

2.4.4.3. Third generation solid dispersions

Recently, it has been illustrated that the rate of dissolution can be improved if the carrier has self emulsifying properties or surface activity, therefore the third generation of solid dispersions evolved. These involve using a surfactant as a carrier which enhances the bioavailability of the poorly soluble API; reducing recrystallisation and increasing the stability of the formulation (Singh *et al*., 2011).

Table 2.4 Carriers used in different generations

Generations	Carriers
First	Sugar, organic acids, urea
Second	Starch derivatives such as cyclodextrin, cellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and completely synthetic polymers like polyethylene glycols, povidone, polymethacrylates

Third	Tween 80, poloxamer 408, Gelucire 44/14

2.4.5. Preparation of solid dispersions

A number of methods have been developed to prepare solid dispersions (figure 2.7), details of which are provided below:

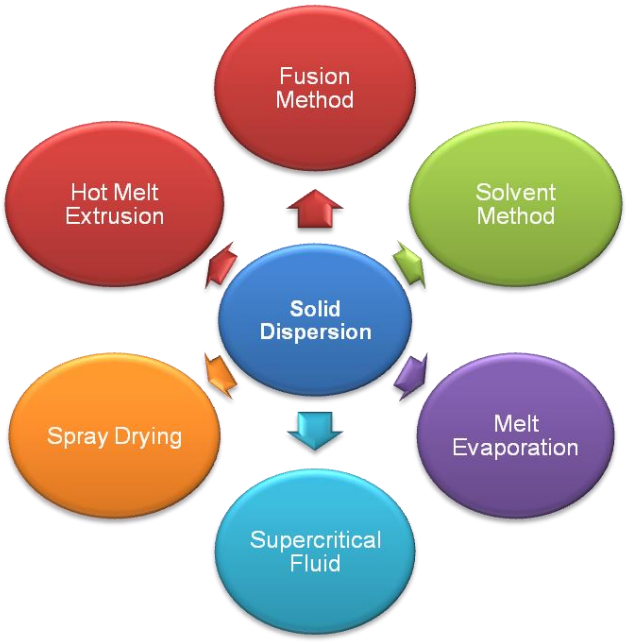


Figure 2.7 Methods for preparation of solid dispersion

2.4.5.1. Fusion method

Sekiguchi and Obi introduced a fusion method to prepare solid dispersion where two components are mixed in the molten state achieved by heating (Sekiguchi and Obi, 1964). The first solid dispersion of sulfathiazole and urea were prepared using this technique. At high temperature, several drugs or carriers may frequently evaporate and can decompose. To avoid this problem, physical mixtures should be heated in a sealed container or in the presence of an inert gas such as nitrogen. Hence, a high processing temperature is a downside of this technique (Drooge *et al*., 2006).

2.4.5.2. Solvent method

An elementary technique which consists of two steps; the first step is the preparation of a solution containing a drug and carrier and the second stage includes the removal of the solvent to form a solid dispersion. This method requires the use of elevated temperature and a vacuum to remove the solvent, followed by drying the precipitate under a vacuum (Hem *et al*., 1967). Various limitations are associated with this method; the main disadvantage is the use of organic solvents. It is difficult to choose and remove all of the solvent from the precipitate. As a result, solvent traces can cause adverse effects and affect the stability of the components. Also the high preparation cost, selection of common organic solvents and difficulties in reproducing crystal forms are drawbacks linked with the solvent method.

2.4.5.3. Melt solvent method or melt evaporation

In this method a minimum amount of suitable organic solvent is used to dissolve the drug and then this solution is directly incorporated into a molten polymer such as polyethylene glycol followed by evaporation to obtain a solvent free and clear dispersion. The solid dispersion is then dried further to achieve a constant weight. Several disadvantages are connected with this method; it is not applicable to heat sensitive materials, and the solvent used may affect the polymorphic form of the drug (Fernandez *et al.,* 1992).

2.4.5.4. Super critical fluid (SCF) technology

During the late 1980's, SCF technology was first introduced into particle engineering. This technology encompasses the use of supercritical CO_2 under a specific temperature and pressure followed by rapid

depressurisation. For engineering of APIs various SCF techniques are available such as Rapid Expansion of a Supercritical Solution (RESS), Rapid Expansion of a Supercritical Solution into a Liquid Solvent (RESOLV), Gaseous Anti Solvent (GAS), Particles by Compressed Antisolvent (PCA), Supercritical Antisolvent (SAS), Aerosol Solvent Extraction System (ASES) and Solution Enhanced Dispersion by Supercritical Fluids (SEDS). These techniques deliver advantages such as the generation of high purity products, good control over crystal polymorphism, single step process green chemistry principles and high yields (Gentile *et al*., 2007). However, the use of supercritical CO_2 solves problems associated with non-polar materials, but the co-solvent solubility effect of polar materials can be increased so it is a selective method. It may be disadvantageous to use supercritical solvents rather than organic solvents because of their lower effectiveness. Additionally, the scale up of this process is practically difficult.

2.4.5.5. Spray drying

This is a widely used technique to prepare solid dispersions. In this method, the drug and carrier are dissolved and then the solvent is removed by spraying it into a stream of heated air. It is cost effective and a simple technique.

2.4.5.6. Hot melt extrusion (HME)

HME has been used in the pharmaceutical industry mainly to prepare solid dispersions for improving the solubility of poorly water soluble drugs. Extrusion is a process whereby a mixture of drug and polymer is processed using a twin screw extruder. This technology is suitable for high doses as

well as for potent compounds. Solid dispersions prepared by HME can allow controlled release and provide improvements in dissolution behaviour. Furthermore, HME offers many advantages over traditional pharmaceutical operations; such as enhancing the bioavailability of poor water soluble drugs, solvent free processing, cost saving by reducing production time, capability of producing sustained, targeted and modified drug release, better content uniformity with different size ranges and uniform molecular dispersion. It is applicable to wide range of dosage forms and products have good stability. Additionally HME can be used for formulating clinically advantageous dosage forms for combating drug abuse and acting as a dose dumping deterrent. There are several pharmaceutical companies applying HME as a drug delivery technique including Soliqs, Germany and PharmaForm, USA. The use of HME is building rapidly and the technique is gaining significant attention within the pharmaceutical industry. However, High temperature processing is a major concern due to the thermal sensitivity of many drugs.

A crystal engineering approach can be potentially used for a wide range of crystalline APIs. It has been reported that crystal engineering approaches served as a potential alternative for traditional solubility enhancement techniques. In fact, crystalline forms are recommended as they tend to be more reproducible, stable and amenable to purification than amorphous solids (Shan *et al*., 2008). However, polymorphs provide an opportunity to improve solid state properties without interrupting the molecules involved (Beyer *et al*., 2001 and Terada *et al*., 2000).

2.5. Polymorphs

Engineering crystal properties by a choice of adequate molecular building blocks has to deal with the fact that a given API can be isolated in many solid forms such as single entity crystals, solvates, salts, co-crystals and their polymorphs each with its own characteristics and properties. Figure 2.8 indicates schematic of the section.

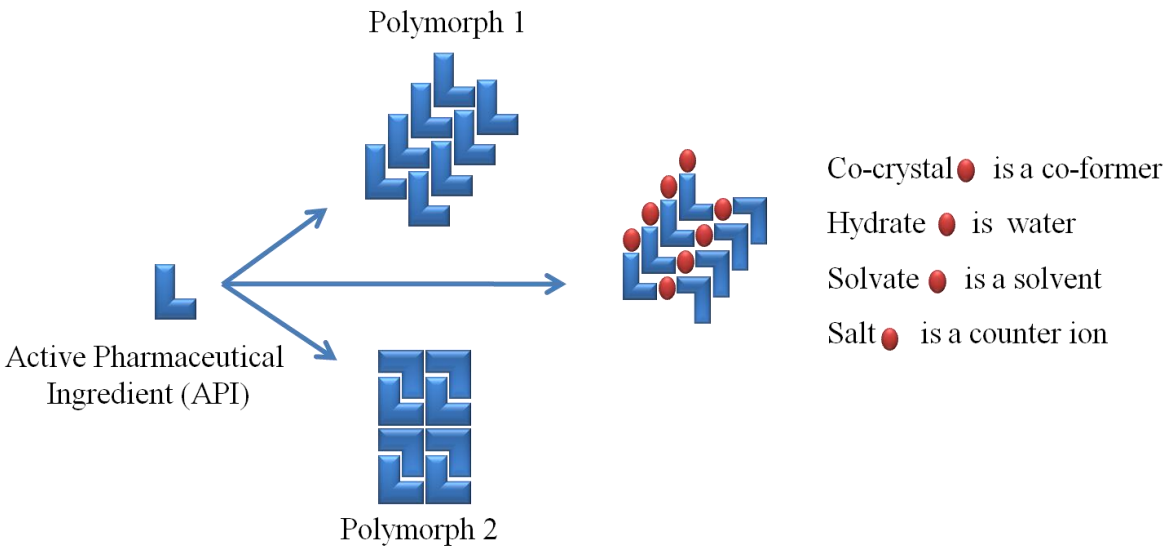


Figure 2.8 Solid forms of API

Polymorphism is the tendency of a molecule to adopt more than one crystalline phase. The significance of this phenomenon has been well studied in the past decade and it has gained fundamental, practical and legal interest from a range of industries including agricultural, pharmaceutical, food, explosives, pigments and dyestuffs (Day *et al.,* 2005). Polymorphs and allotropes are closely related; polymorphism is the structural diversity of compounds whereas allotropy is used in general to refer to elements. For example, the gross property difference between diamond and graphite is well known (shown in figure 2.9) and this is a good example of how structure can affect properties. The carbon atom is the same in both the crystals however the arrangement of atoms is different in the different crystal structures which subsequently leads to the change in properties such as hardness and conductivity. In polymorphs, molecules exist in different patterns such as packaging, conformation and supramolecular synthons in the crystal lattice (Aceves-Hernandez *et al.,* 2009).

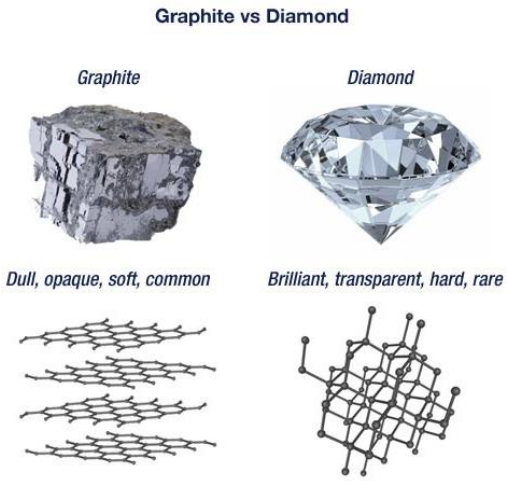


Figure 2.9 Allotropes of carbon; graphite and diamond (Adapted from Wikipedia http://en.wikipedia.org/wiki/Allotropy**)**

During crystallisation various forms may emerge depending on process parameters such as solvent type, temperature, additives and method of preparation. The polymorphs can be customised by solvent dependent processes, thermal or mechanical stress. Polymorph screening may be used, which combines the creative use of process variables with high throughput. In addition, advanced computational approaches to crystal structure prediction add a new tool to the anticipation and understanding of polymorphism. Therefore, it is a critical step to accurately assess polymorph properties and indentify the correct form of the API in the early stage of a drug's development. The famous assertion by the late Walter McCrone in 1965, "the number of forms of a molecule is proportional to the time, money and experiments invested on that compound" has gained credence in recent years; as displayed by a significant increase in publications (McCrone, 1965). Figure 2.10 shows flow chart for polymorphs.

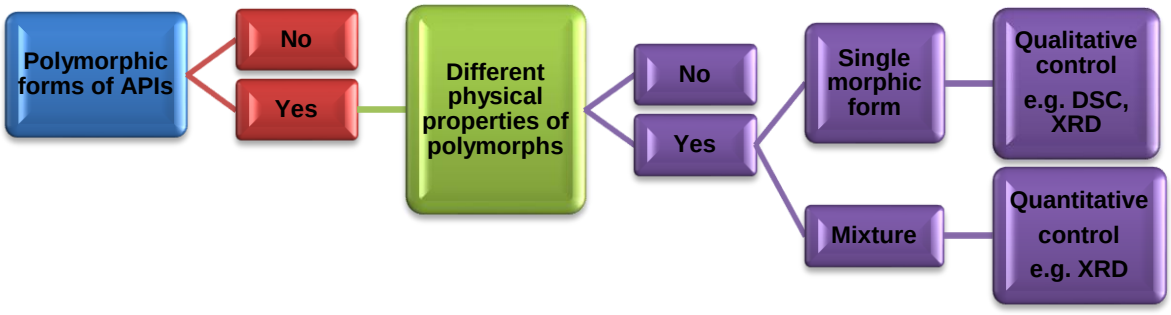


Figure 2.10 Flow chart or decision tree for polymorphs (Adapted from ICH guideline for polymorphism)

2.5.1. Industrial significance

Polymorphs may undergo interconversion as a result of external influences such as processing, crystallisation or storage conditions (Spruijtenburg *et al.,* 2000). The appearance of a novel crystal form at the early stages of

development may be useful, and is therefore classed as 'enabling'. At a later stage, the occurrence of a new form, especially a stable one which is not bioequivalent, may have catastrophic consequences on product performance and regulatory acquiescence. This issue is highlighted by 'disappearing polymorphs' i.e. the sudden appearance of a new crystal form (Davey *et al*., 1997 and Bernstein, 2002). In unfortunate cases, important forms may not be discovered during initial screening. A high profile case was Ritonavir (Norvir) semi-solid capsules (Chemburkar *et al*., 2000). When Ritonavir was developed only form I was known. Two years after market introduction in 1996, it started to precipitate in the capsule and in some capsules failed to pass dissolution tests due to formation of the thermodynamically stable form II. Ritonavir forms I and II have a high solubility difference and the solubility differences in polymorphs can alter the rate of dissolution and bioavailability. As a result the original Ritonavir product had to be taken off from the market and a novel formulation of soft-gel capsules had to be created with extensive effort and investment. This polymorphic transformation during storage resulted in great market interruption of the product. The new Ritonavir formulation has made over $ 1 billion sales in five years and in 2003 the price of Ritonavir was increased by 400%.

Polymorphism plays a pivotal role from the patent perspective in the pharmaceutical industry. This issue is highlighted by the Zantac patent case; GlaxoSmithKline's blockbuster histamine H_2 receptor antagonist: ranitidine hydrochloride. This involved a legal battle between major generic companies concerning the solid-state generation of Form I of ranitidine hydrochloride without concomitant crystallization of Form II (Davey *et al*., 2003).

The generation of undesired polymorphs may occur through solvent mediated transformation during the crystallisation process (Tian *et al*., 2008; Sanphui *et al.,* 2011 and Maruyama *et al.,* 2001). In contrast, an understanding of these processes can lead to the desired crystal form being achieved. For example, L-glutamic acid, a naturally occurring amino acid essential for building protein blocks, adopts two crystal structures; the metastable α form and the stable β form (Ferrari *et al*., 2004). L-glutamic acid is used as a food additive and flavour enhancer in the form of salt known as monosodium glutamate in the food industry. It is crucial to isolate the α form rather than form β; the major challenge being to prevent its transformation. Polymorphic transformation of L-glutamic acid from α and β form is shown in figure 2.11. The stable β polymorph causes a situation whereby the crystallising slurry coagulates into a gel and cannot be processed further (Sugita et al., 1988). Garti et al. demonstrated that the addition of surface active agents lead to the favoured crystallisation of the α form (Garti *et al*., 1997). Trimesic acid and transglutonic acid act as a conformational mimic of the α form which selectively inhibit nucleation of the β form and stabilise the α form.

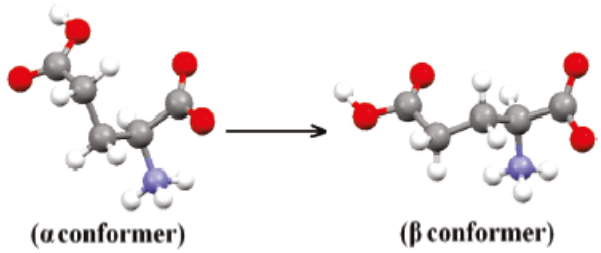


Figure 2.11 Polymorphic transformation of L- glutamic acid from α and β form

Obtaining the right polymorph is important in the pharmaceutical industry; for example the broad spectrum anthelminthic drug mebendazole crystallizes in

three forms namely A, B and C (Brits *et al*., 2010). The commercially available form A is the most stable form whereas forms B and C are metastable forms. The solubility order for mebendazole polymorphs are B > C > A. Therefore form C is pharmaceutically preferred as its solubility is enough to ensure optimal bioavailability without showing the toxicity associated with form B. Many researchers pointed out that form A has no pharmacological activity either alone or when present in more than 30% in a polymorphic mixture. However, form C has a tendency to transform to the inactive form A; so it is desirable to stabilize form C by adding a surfactant, polymer or co-former (Kumar *et al*., 2008).

The crystal tendency can have an impact on processing parameters such as bulk density, flowability and filterability. For example, theophylline exists in four polymorphic forms. It has been reported by Suihko et al. that all four forms of theophylline have different processing characteristics (Suihko *et al.,* 2001). Another example is paracetamol; many pharmaceutical companies are interested in paracetamol polymorphs. Manufacturing analgesic paracetamol tablets requires a compaction process. Commercially available form I exhibits poor compressibility, so a time consuming and expensive wet granulation step is required. Alternatively, Form II is more suitable for direct compression (Martino *et al.,* 1997).

These examples highlight the practical importance and consequences of polymorphism. It is therefore very important to identify different polymorphs of a substance, and to have control over the formation of different polymorphs at all stages of production to ensure product quality.

2.5.2. Thermodynamic and thermokinetic relationships

The crystallisation of polymorphs involves a number of steps such as nucleation, crystal growth and transformation from the metastable to the stable form. In order to achieve selective crystallisation, a mechanical understanding of each stage and process dependant factors need to be clear. Wilhelm Ostwald stated that a system moves from a high energy state to an equilibrium without significant change in the free energy (Ostwald *et al*., 1897). Therefore, the crystal that crystallises out first has the lowest energy barrier i.e. high energy level (kinetically metastable form). This form would then transform to the relatively low energy level until the lowest energy state (thermodynamically stable form) is reached. This is known as 'Ostwald's rule of stages'. Hence, a polymorphic system would shift through each possible crystal form until it reaches the most stable phase.

From a thermodynamic point of view, under constant pressure polymorphic systems are categorised as monotropic and enantiotropic systems (Burger *et al.,* 1979). The process involving the transition of one form into another form is called a phase transition and this may occur at constant pressure by changing the temperature according to the phase rule. In enantiotropic systems, the phase transition is reversible and the transition energy is endothermic on heating. In contrast, if the phase transition is irreversible the two polymorphs are monotropically related. In this case only one form is stable compared to the others regardless of temperature. The heat of fusion rule states that in a monotropic system the higher melting point polymorph will have a higher heat of fusion. If a high melting point polymorph has a lower heat of fusion then the two forms are enantiotropically related.

A number of analytical techniques are used to understand the thermodynamic relationship between polymorphs such as Hot Stage Microscopy (HSM) and Differential Scanning Calorimetry (DSC). DSC can be used to provide quantitative information about the relative stability of polymorphs, the energy involved in the phase transition and the enatiotroopic or monotropic behaviour of these transitions. However, HSM can serve as a qualitative tool to visualise morphological changes during phase transition under optical microscopy.

2.5.3. Regulatory aspects

Regulatory concerns can be classed as purity, stability, strength, bioequivalence, quality, toxicity, safety and efficacy of the drug molecule and the drug formulation (Vippagunta *et al*., 2001). As polymorphs differ in their dissolution profile and stability, there are regulatory concerns over the characterisation of reproducible forms to ensure the original properties. Preferably, one should select a commercially accepted form. However if current marketed drugs are under patent, one can use a newly invented form. Regarding regulatory guidelines, the discovery of a new polymorph offers an opportunity to generic manufacturers to introduce innovative products. The FDA and European regulatory authorities require the solid state properties of molecules to be analysed from safety and efficacy perspectives with respect to the drug product (Vippagunta *et al*., 2001).

2.6. Hot melt extrusion

Hot melt extrusion (HME) - melting a physical mixture and forcing it through an orifice under a controlled set of conditions to prepare a contemporary material is a promising pharmaceutical technology for the preparation of different dosage forms and drug delivery systems. Extruders for pharmaceutical use have been specially designed and adapted for mixing drugs with carriers in various dosage forms. This section is primarily focused on equipment design, principles, applications and limitations of HME. A schematic presentation of HME process and solid dispersions are displayed in figure 2.

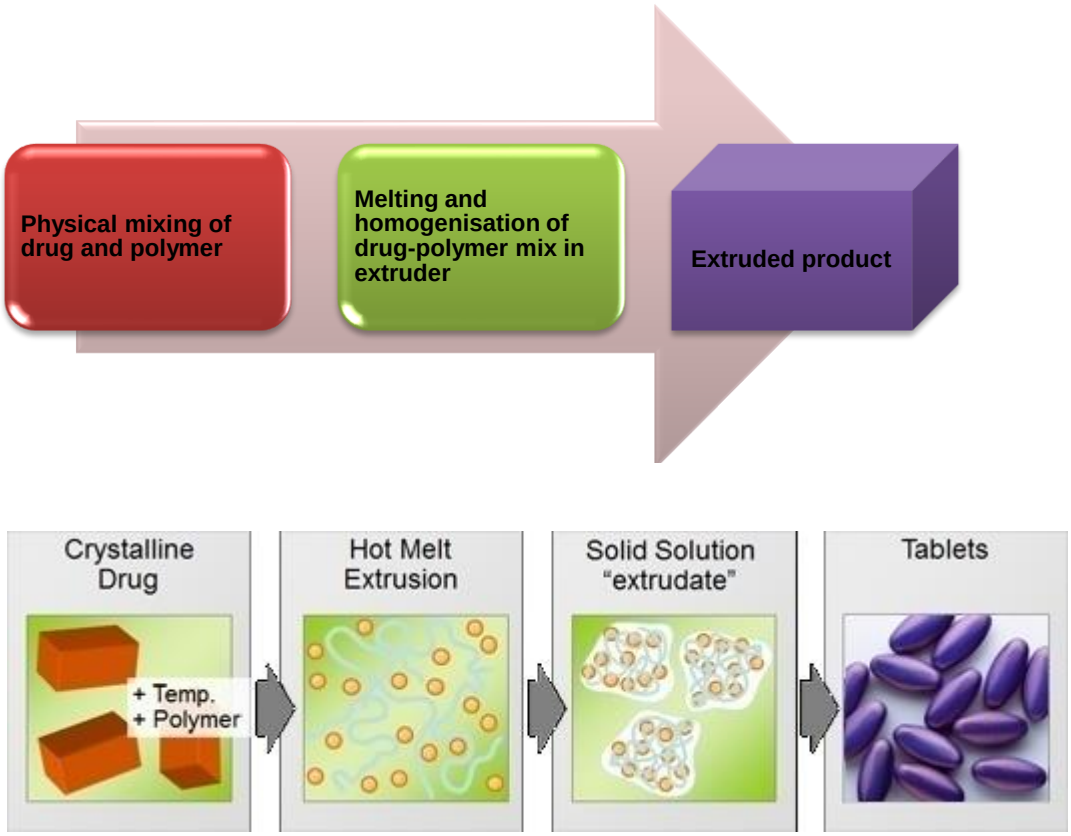


Figure 2.12 A schematic presentation of HME process and solid dispersions (Adapted from Ali *et al*., 2012)

Extrusion dates from the 1930s as a process used for producing polymeric coatings for wire insulation. In 1940, extrusion was used for the first time in the plastics industry for bulk manufacturing. Currently, extrusion is one of the most widely used processing techniques in the plastics, rubber and food industries. Extrusion is the process of converting raw material into a uniform shaped product by pushing it through a die under controlled conditions. Recently, this technique has been successfully applied to the pharmaceutical industry by scaling down. Furthermore, it is a solvent free technique and the availability of a broad variety of pharmaceutical excipients and polymers is advantageous for this hot melt extrusion technique. HME is considered to be an efficient technique with particular benefits over solvent based processes such as co-precipitation (Breitenbach *et al*., 2002). HME is a continuous technique that allows for the preparation of desired formulations in a single step with pharmaceutical as well as economic advantages. The number of patents issued related to HME in the pharmaceutical industry has been increasing continuously (figure 2.13). This technique has been widely used in the pharmaceutical industry for preparing solid dispersions; it is a process where drug and excipients are melted and then forced through a die and, depending upon the purpose, shaped into granules, pellets, tablets, film or milled into powder (Rauwendaal *et al*., 1986).

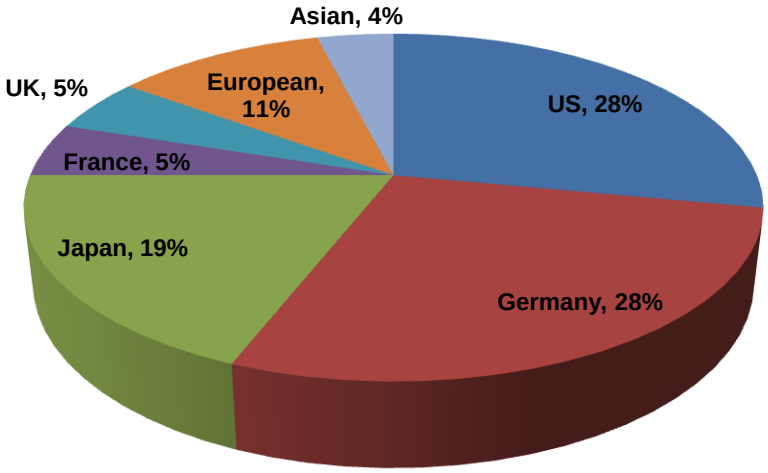


Figure 2.13 Use of hot melt extrusion for pharmaceutical applications by country (adapted from Zang *et al.* 2007)

Published literature concerning HME has shown an increased interest of this technique within the pharmaceutical industry. It can provide novel and innovative drug delivery approaches such as solid dispersions, effervescent granules, transdermal films, complex formations, co-crystal formations and sustained release formulations.

2.6.1. Equipment

Figure 2.14 Thermo Pharmalab hot melt extruder

Hot melt extruders such as the example (shown in figure 2.14) come with downstream processing auxiliary equipment and monitoring tools for

evaluating performance and product quality such as temperature gauges, screw-speed controller, extrusion torque monitor and pressure gauges (Kruder *et al.,* 1985). Typically, the extruder is composed of a feeder, a hopper, a barrel, single or twin screws, a die and a screw drive unit. The auxiliary unit is composed of heating and cooling devices for the barrel, conveyor belt for cooling down the product and a solvent injection pump. Inside a stationary cylindrical barrel, the extruder consists of one or two rotating screws; this cylindrical barrel is manufactured from a single piece or from separate sections and clamped together. At the end of the barrel an end plate or die is connected which determines the shape of the extrudate.

2.6.2. Types of hot melt extruder

Based on operating principles hot melt extruders may be broadly classified into ram and screw extruders. The classification of extruder is shown in figure 2.15.

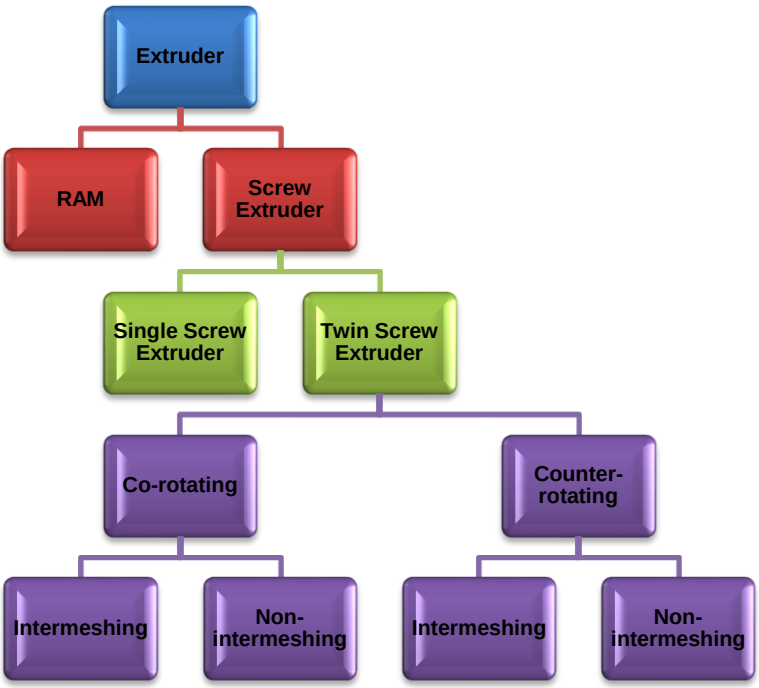


Figure 2.15 Types of extruder

2.6.2.1. Ram extruder

High pressure is the operational principle of ram extrusion. This high pressure is generated through the positive displacement of a ram. During ram extrusion, materials are introduced into a heated cylinder, then the softened material is forced through a die under pressure and converted into the desired shape (Perdikoulias *et al.,* 2003). Ram extrusion has a limited heating ability which can cause variances in temperature distribution. In comparison with screw extruders, ram extruders produce products with limited homogeneity and have high residence times.

2.6.2.2. Screw extruder

Screw extruders are further categorised into single screw and twin screw. The major differences are the methods of conveying or transporting the material (Rauwendaal *et al.,* 1984). A schematic presentation of single and twin screw extruders is displayed in figure 2.16.

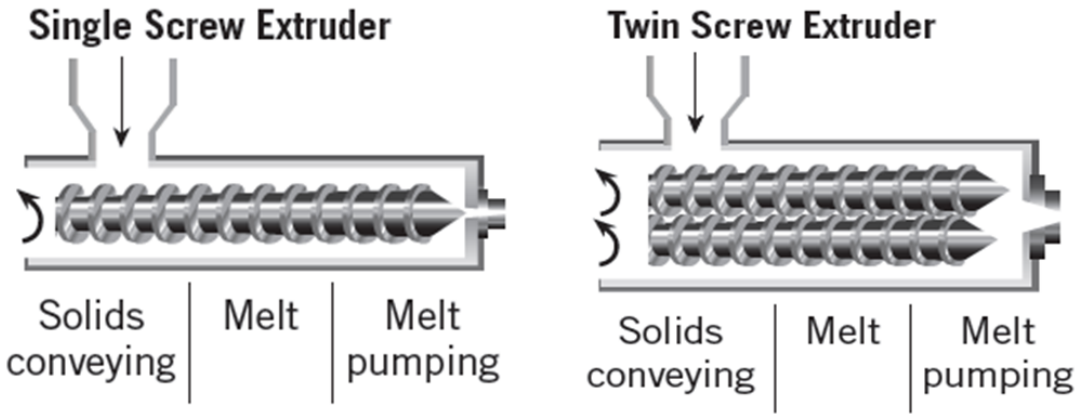


Figure 2.16 Cross-section of single and twin screw extruder barrel (Adapted from Particle sciences drug delivery services, Technical Brief 2011, vol. 3)

Single screw extruder

Single screw extruders (displayed in figure 2.17) are the most widely used types of extruder. A single screw in a heated barrel rotates and is responsible for a number of processes such as material conveying or transporting, melting, devolatilising and pumping.

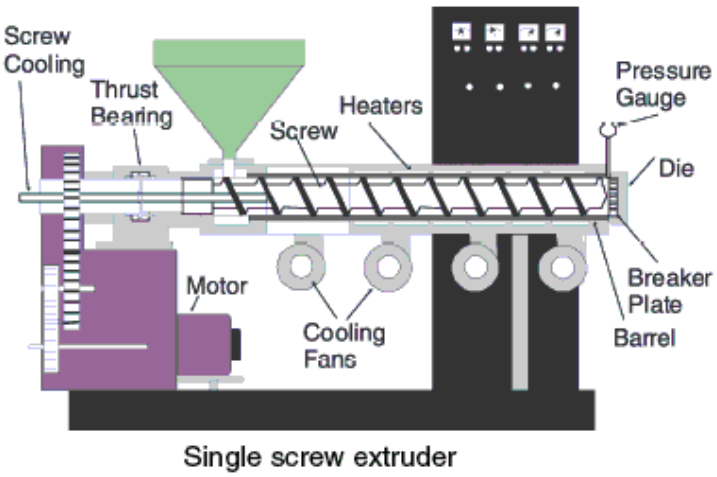


Figure 2.17 Single screw extruder (Adapted from plastics.com)

The operating principle of single screw extrusion is based on frictional forces and viscous forces in the conveying zone. Hence, extrusion is significantly dependent on the frictional and viscous properties of materials being processed. The mass flow is set by the feed system and is dependent on the screw rotation speed. Generally the screw is driven from the hopper end, and if the screw diameter is less than 18 mm, it becomes weak and some variation may occur. To overcome these associated problems, a vertical screw may be used driven from the discharge end (Luker *et al.,* 2003). Single screw extrusion offers a high efficiency to investment ratio. Though it has a simple mechanism, it is simple to operate, has a relatively low cost and has a limited mixing capability. A comparison of mixing capacities of single and

twin screw extruders was made by Ferns by adding coloured dye to the material being processing. Extrudates obtained from a single screw extruder had bands with several shades but extrudates from the twin screw extruder had uniform colour distribution (Ferns, 1974).

Twin screw extruder

As the name suggests, twin screw extruders incorporate two screws which are located side by side inside the barrel. During the late 1930's the first twin screw extruder was developed in Italy. It is a more efficient process than single screw extrusion because in the twin screw extruder mixing occurs at a macroscopic as well as microscopic level. At The macroscopic level, the material is exchanged between two screws and at the microscopic level, mixing occurs at high shear regions of the screw element interaction. Different twin screw elements are displayed in figure 2.18.

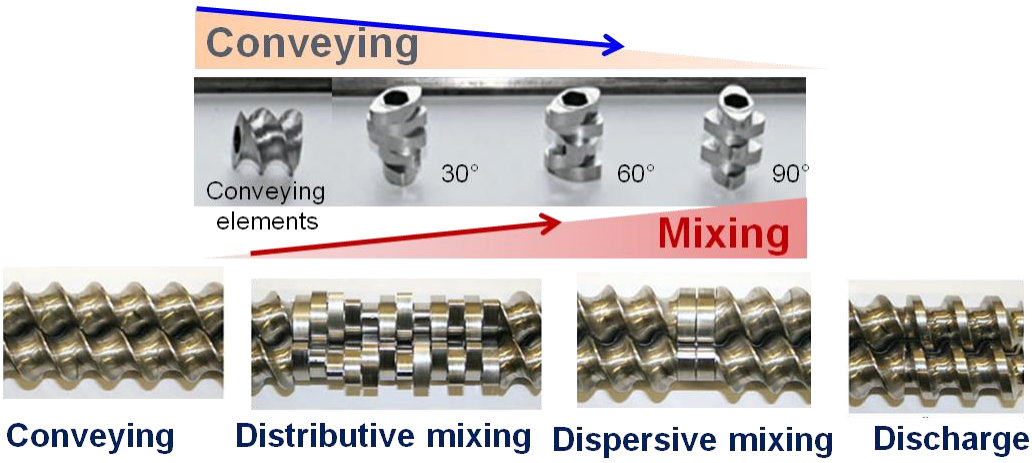


Figure 2.18 Twin screw elements

The twin screw extruder is characterised by the following features:

- **Short residence time**: In a typical extrusion process, residence time is up to 2 min.

- **Self-wiping**: Extruder screws are self-wiping and ensure the emptying of the barrel and minimum wastage during shutdown.
- **Minimum inventory**: This is significant when processing hazardous materials.
- **Versatility**: Processing parameters can be modified continuously and it is relatively easy to change the degree of mixing. Modular screw elements allow different screw configurations to be used to achieve high or low shear for the respective application (Whelan *et al.,* 1996). These screws are interchangeable and can be swapped to suit each application. Dies can also be exchangeable therefore it allows a variety of formulation processes in a single piece of equipment. It is applicable for a wide range of polymers with low viscosity and fine powders can be processed directly through the system.

2.6.3. Extruder design

Commercially available twin screw extruders have a modular design to aid screw alternation. The screw design has a major impact on the extrusion process and can be designed to achieve particular shear intensities and residence times. Whelan et al. studied various available screw designs (Whelan *et al.* 1996). In HME, screw dimensions are usually specified in terms of their length/diameter ratio (L/D). For example, a screw with length of 1000 mm and diameter of 25 mm indicates a 40:1 L/D ratio. Typically, extruder screw dimensions vary from 25:1 to 40:1. For a single screw extruder, this should be 36:1 or less, for intermeshing twin screw extruders it can be 60:1 or shorter and for non-intermeshing twin screw extruders the L: D ratio may be 100:1 or higher due to the intermesh clearance restriction

(Steiner *et al.* 2003). Another common term is 'screw diameter' e.g. 20 mm screw diameter indicates the diameter of a single screw or the diameter of each screw in a twin screw extruder. The OD/ID (outer diameter / inner diameter) determines the available free volume. There are two types of free volume gaps; flight gap and intermesh gap. The flight gap is the gap between the OD and the barrel while the intermesh gap is the gap between two screws in the case of a twin screw extruder. Channel or flight depth is an important extruder design factor because torque is directly proportional to the channel depth (Chokshi *et al.* 2004). In extruder design, it is necessary to find out the most favourable equilibrium between the free volume and the torque to achieve the maximum throughput.

2.6.4. Process

Theoretically the extrusion process (displayed in figure 2.19) is divided into four parts (Breitenbach *et al.,* 2002).

1. Feeding
2. Conveying
3. Flow through die
4. Exit from die and down-stream processing

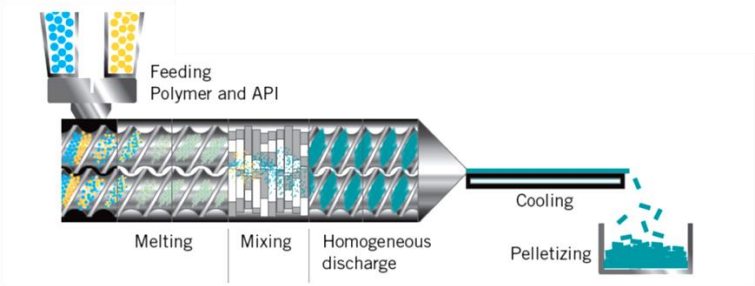


Figure 2.19 Hot melt extrusion process (Adapted from Particle sciences drug delivery services, Technical Brief 2011, vol. 3)

Material is fed from a hopper to the feeding section which has a deeper channel depth. This configuration facilitates the feed material to drop easily into the screws for transporting along the barrel. At a steady screw speed, the helix angle and pitch control the throughput. The solid plug of material is conveyed to the transition zone for mixing, compressing, melting and plasticizing (Breitenbach *et al.,* 2002). Once the material enters into the compression zone, the polymer begins to melt. The temperature of the compression section is usually set above the glass transition temperature of the polymer (McGinity *et al.,* 2007). Compression is achieved by reducing the thread pitch without controlling a constant flight depth or by reducing flight depth with controlling a constant thread pitch (Johnson *et al.,* 1982). An increase in pressure occurs in both processes as the material shifts along the barrel. Molten material moves in a helical path due to the pressure flow, transverse flow, leakage and drag flow. The gap between the barrel width and the screw diameter is in the range of 0.1 to 0.2 mm (Martin *et al.,* 2001). The material reaches the metering zone in a homogeneous plastic form which is ideal for extrusion through a die. The metering zone is responsible for lowering the pulsating flow of the material and for ensuring uniform release through the die plate (Breitenbach *et al.,* 2002).

The monitoring and understanding of several parameters is necessary for successful extrusion. Barrel temperature, screw speed and feed rate are controlling parameters while melt pressure and motor load are parameters which can be monitored to provide a valuable indication of the state of the process.

- **Barrel temperature:** The glass transition temperature, melting and degradation temperature of polymer and drug determines the barrel temperature.
- **Screw speed and feed rate**: Screw speed and feed rate have a great influence on the extrusion process. It is essential to manage the balance between strong and weak mass transfer. Constant screw speed and feed rate assures a constant amount of material in the extruder and therefore the shear intensity and residence time remains constant (Martin, 2001).
- **Die melt pressure**: The screw speed, feed rate and melt viscosity determines the melt pressure. Screw speed and feed rate parameters are set based on the properties of the polymer and drug e.g. molecular weight, miscibility capacity (Breitenbach *et al.,* 2002).

2.6.5. Materials used in HME processing

The materials used in the HME must meet the same guidelines for purity and safety as those used in conventional methods. HME has been widely used for the preparation of solid dosage forms such as tablets, granules, pellets, powder and transdermal patches. The materials employed for HME processing must display, to some extent, thermal stability with an accepted degree of physical and chemical stability. The thermal stability of each component and mixture should be enough to endure the preparation process (James, 2004).

Extrudates are complex mixtures of APIs and functional excipients. Excipients can be broadly categorised into polymers, plasticisers, release modifying agents, bulking agents and other additives (Chokshi *et al*., 2004).

The excipients can convey a particular property to the extrudates as similar to those dosage forms prepared by traditional methods (Follonier *et al.,* 1995).

2.6.5.1. Active Pharmaceutical Ingredients (APIs)

The properties of APIs can often limit the available options of formulations and preparation methods, in preparing an acceptable dosage form. HME is a comparatively new technique to the pharmaceutical industry which offers several advantages. This is an anhydrous method, therefore it can prevent the degradation of the potential candidates because no hydrolysis can take place. Additionally, poorly compressible materials can be integrated into tablets prepared by cutting an extruded rod, reducing the problem usually seen in traditional methods. APIs should be stable in the extrusion process, this is very important to access the thermal, physical and chemical properties. Depending on the distinctive properties of the drug and other excipients, the drug may be present in undissolved particles or in a solid solution. The state of drug in the formulation stage may have an influence on the stability and processibility (James, 2004).

2.6.5.2. Polymers

In HME, the API is embedded in a carrier matrix containing one or more meltable compounds and other additives. The meltable compounds can be polymeric materials (Zhang *et al.,* 1998) or low melting waxes (Miyagawa *et al*., 1996).

The selection of polymers for the HME process primarily depends on polymer stablity, drug-polymer miscibility and the purpose of the desired

dosage form. A number of carrier systems have been used in the pharmaceutical industry for the extruded dosage forms.

Such polymer systems comprise of polyvinylpyrrolidone (PVP) (Tantishaiyakul *et al.,* 1999) and its co-polymers such poly(ethylene-co-vinyl acetate) (Follonier *et al.,* 1995), polyvinylpyrrolidone-vinyl acetate (Zingone *et al.,* 1992), a variety of polyethylene glycols grades, acrylates (Abd *et al.,* 1998) and cellulose ethers (Yano *et al.,* 1997), different molecular weight polyethylene oxides (Zhang *et al.,* 1998), poly methacrylate derivatives and poloxamers. Along with different classes of biodegradable polymers, the thermoplastic aliphatic poly (esters) such as poly (lactide) (PLA), poly (glycolide) (PGA) and copolymer of lactide and glycolide, poly (lactide-co-glycolide) (PLGA) have been exploited in extrusion. Starch and starch derivatives have been applied along with low molecular weight excipients like sugars and sugar alcohols and waxes (Ndindayino *et al*., 2002). For HME use, the basic requirement is the thermo plastic properties of the polymer.

2.6.5.3. Plasticisers

Polymeric carriers may require the incorporation of the additional plasticiser into the system in order to improve the processability and the physical and the mechanical properties of the extrudates (James 2004). Plasticisers are added during manufacturing of the extruded dosage forms to facilitate the extrusion of the material and to amplify the flexibility of the extruded material. This approach may allow for the processing of heat sensitive drugs or polymers by reducing the processing temperature (Karen *et al*., 2006). The selection of a suitable plasticizer is based on the polymer-plasticiser compatibility and the stability of plasticiser. A varity of plasticisers are

available such as triacetin (Follonier *et al.,* 1995), citrate esters (Aitken-Nicho *et al.,* 1996), and low molecular weight polyethylene glycols (Follonier *et al.,* 1995).

Plasticisers lower the glass transition temperature (Tg) of the polymer, thus improving the stability profile of the API and polymer. A drop in Tg depends on the category and the level of the plasticiser (James, 2004). Plasticizers reduce the shear forces required to extrude a polymer, by this means, one can improve the processing of the high molecular weight polymers (Zhang *et al*., 1998). As an assessment, the themo-chemical stability and volatility of the plasticiser throughout processing and storage should be considered (Repka *et al.,* 1999).

2.6.5.4. Other additives

The dissolution rate of an API from the extrudates can be increased or decreased by incorporating rate modifying agents. For a mixture that undergoes degradation by oxidation or free-radical degradation during processing and storage, the addition of antioxidants and light absorbers or acid acceptors is recommended (James, 2004). Generally antioxidants are divided as preventive antioxidants or chain breaking antioxidants. Preventive antioxidants avoid the generation of free radical chain reactions. Preventive agents such as ascorbic acid, can interfere with auto-oxidation in a preventative way since they preferentially undergo oxidation. These agents protect APIs and polymers from an oxygen molecule attack and can be known as oxygen scavengers. They are mainly efficient when employed in a closed system where oxygen cannot be replaced once it is consumed.

Chelating agents are another type of preventive antioxidant that reduce the free radical formation rate by forming a stable complex with metal ions which catalyse these types of reduction reactions e.g. edetate disodium (EDTA) and citric acid. Waxy materials such as glyceryl monostearate are used to function as a thermal lubricant during hot-melt processing (Crowley *et al*., 2007).

2.6.6. Applications of HME

2.6.6.1. General applications

Extrusion has wide range of applications in the plastics and rubber industry, it is used for the production of pipes, sheets, hoses, insulated wires and cables and polystyrene tiles. Common polymers such as acrylic, polyethylene, polypropylene, nylon, polyvinyl chloride, polystyrene and polycarbonate are used for plastic manufacturing. Profile extrusion describes a process where the die determines the shape of the extrudate e.g. a tube or more complex shape. The extruded profiles are further processed horizontally; their length controlled by cut off equipment. These profiles can be processed further, for example, by orientation in film or blow moulding (Schott, 1983). Since the 1930s, extrusion has also been utilized in the food industry for the production of pastas and cereals. This versatile process combines mixing with cooking (Senouci, 1985).

2.6.6.2. Pharmaceutical applications

The dissolution profile of an orally administered formulation is highly dependent on the solubility and permeability of the drug. It has been estimated that approximately 40% of innovative molecular entities have poor

aqueous solubility and hence low bioavailability. This proportion is increasing because of the introduction of combinational chemistry and the significance of lipophilic receptors (Kerns, 2001). Formulation scientists are trying to concentrate on the solubility issues caused by assorted pharmaceutical interferences. Currently, researchers are attracted towards solid dispersions to improve the dissolution and bioavailability of poorly water soluble drugs. HME is a convenient technology to prepare solid dispersions. Implants, oral dosage forms, stents, topical films, bioadhesive ophthalmic inserts, effervescent tablets and implants have all been prepared using this technology (Repka *et al.,* 2007).

Over the last two decades the importance of 'continuous processing' has been recognised by the pharmaceutical industry. HME is an efficient technique for preparing drug delivery systems. Comparatively lower capital investment and labour costs are key advantages of HME apart from it being a solvent free technology (Gamlen, 1986).

Research in this area is growing and published literature exposes many novel and innovative aspects. Pharmaceutical applications of this technology include sustained release systems, films for transdermal delivery, taste masking and crystal engineering (schematic is shown in figure 2.20). Some key developments in HME are discussed below.

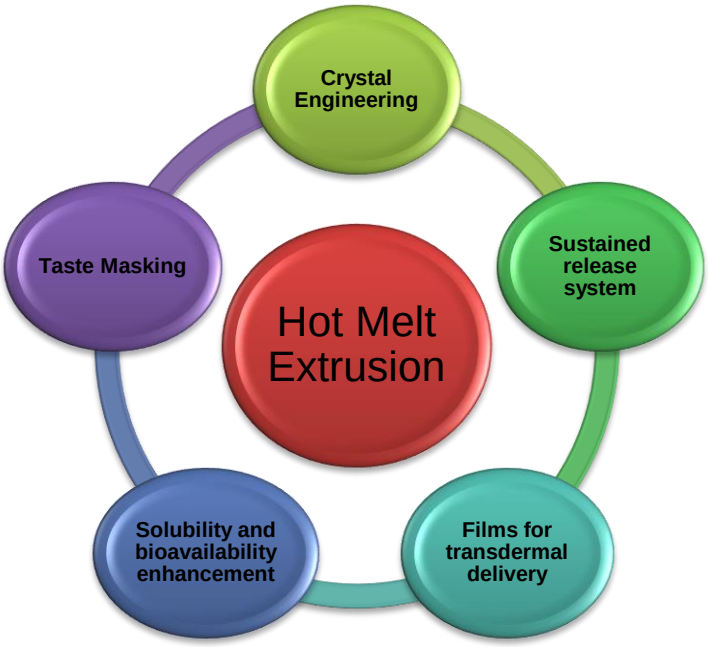


Figure 2.20 Variety of applications of HME

Sustained released systems

In 1990, Mank *et al*. studied extrusion of various thermoplastic polymers to prepare sustained release pellets. In 1994, Follonier *et al*. produced sustained release pellets containing the freely water soluble drug diltiazem hydrochloride using HME. The influence of polymers, polymer to drug ratio and the size of pellets on drug release were examined (Follonier *et al.,* 1995). Examples of different polymers include ethyl cellulose, cellulose acetate butyrate, polyethyl acrylate/methyl methacrylate/trimethyl ammonio ethyl methacrylate chloride and polyethylene-co-vinyl acetate (EVAC). Triacetin and diethyl phthalate were employed as the plasticisers. The pellets showed a smooth surface, low porosity and slow drug release.

Theophylline pellets for controlled release were prepared by hot melt extrusion method using Eudragit and poly ethylene glycol 8000 polymers. *In-vitro* studies showed a controlled release pattern which was influenced by pH

dependent dissolution and polymer swelling (Shaikh *et al*., 1987 and Young *et al*., 2005).

Miyagawa et al. produced controlled release diclofenac granules using twin screw extrusion and proved that good mechanical strength wax matrix granules could be achieved at a temperature below the melting point of wax (Miyagawa *et al.,* 1996). Shimpi et al. discovered the application of Gelucire 43/01, a hydrophobic lipid for designing a multi-unit floating drug delivery system of a highly water API such as diltiazem HCl using a melt granulation technique. Approximately 65% to 80% drug release was achieved over 6 hours with an initial fast release from the surface (Shimpi *et al*., 2004). Mehuys et al. developed alternative techniques for preparing an enteric coating system, offering continuous and rapid processing using polyvinyl acetate phthalate and hydroxyl methyl cellulose as a means of HME (Mehuys *et al*. 2005). Similarly, gastro-resistant matrix tablets were successfully prepared using HME containing acrylate polymer Eudragit® L100-55. The presence of plasticiser triethyl acetate, an acidity modifier (citric acid) and hydrophilic polymers (Kollidon 30 and Carbopol 971), significantly enhanced the drug release. Moreover drug release was dependent on the concentration of triethyl acetate and the pH of the media (Andrews et al., 2008).

The thermal stability of Poly(ethylene Oxide) (PEO) in SR released tablets was studied and it was found that chemical stability of PEO was dependent on the storage conditions, processing parameters and the molecular weight of the polymer (Crowley *et al.,* 2002). Oshlack et al. patented a melt extruded, orally administrable, opioid formulation containing a plurality of

multiparticulates (Oshlack *et al*., 2004). Fukuda et al. studied the influence of pH, selected buffer and the ionic strength on chlorpheniramine maleate release and the release mechanism from sustained release tablets containing chitosan and xanthan gum produced by HME. The extruded tablets showed pH and buffer independent sustained release (Fukuda *et al.,* 2006).

Vervaet et al. manufactured sustained release ibuprofen and metoprolol tartrate using ethylcellulose as a carrier (Verhoeven *et al*., 2008). Vasanthavada *et al*. explored the application of HME for melt granulation to develop a high dose, modified release tablet formulation (Vasanthavada *et al.,* 2011). Melt granulation technology using HME has emerged as a robust and significantly useful technique for generating modified release oral formulations with high dose.

Films for transdermal delivery

The application of HME for preparing elastic and thin acrylic films for transdermal delivery was investigated by Aitken-Nichol et al. This study involved a comparison between cast films using various methods and found that HME was a practically feasible technology for preparing acrylic resin films (Aitken-Nichol *et al*., 1996). Traditionally, cast films were produced using aqueous or organic solvents for transdermal and transmucosal delivery systems. Repka et al. reviewed several drawbacks of these solvent based methods such as time consuming, expensive and environmental damage (Repka *et al.,* 1999). They prepared hot melt extruded bioadhesive films containing ketoconazole and Carbopol 974P NF for topical onychomycosis therapies (Repka *et al*., 2004). Muco-adhesive matrix films of clotrimazole

(10% w/w) were developed for local drug delivery for oral candidiasis. The formulation contained polymer carriers such as hydroxypropyl cellulose and poly(ethylene oxide), bio-adhesive polycarbophil and excipients (Repka *et al*., 2003). The effect of tartaric acid on the bioadhesive, moisture sorption and mechanical properties of extruded hydroxypropyl cellulose and polymer additives were investigated (Mididoddi *et al.,* 2006). The added tartaric acid significantly influenced the bio-adhesive and mechanical properties of the film.

Mididoddi et al. studied the physicochemical properties of melt extruded bio-adhesive films for onychomycosis treatment and successfully determined the stability of the antifungal drug incorporated in these films. The thermal behaviour, surface morphology and crystalline properties were investigated by DSC, SME and PXRD respectively. The obtained data demonstrated that the melt cooled mixture of API and polymers reached an amorphous state (Mididoddi *et al*., 2006).

Thin films containing the model drug clotrimazole and two different molecular weights of poly(ethylene) oxide (PEO) were prepared using HME and their solid state, bio-adhesive and mechanical properties were studied (Prodduturi *et al*., 2005). PXRD patterns showed the recrystallisation of the drug after storage for 3 months at 25°C / 60% Relative Humidity (RH). The inadequate physical stability of the drug and PEO system may be due to the low glass transition of PEO and its tendency to fold upon cooling from the melt.

Oral, muco-adhesive thin films of the cellulosic polymers such as hydroxypropyl cellulose (HPC) and hydroxypropyl methyl cellulose (HPMC) loading, with a topical anaesthetic lidocaine were produced using HME

(Rekpa *et al*., 2005). Two formulations were prepared, one containing only HPMC and the drug and the other containing the drug and HPC:HPMC (80:20). Both formulations showed sustained release and the mechanism was mainly diffusion of lidocaine through the carrier matrix. Incorporation of HPMC delayed the drug release and enhanced adhesive properties. These types of films would be advantageous for dental procedures and topical applications.

Cilurzo et al. reported that oral, fast dissolving films of maltodextrins with piroxicam can be prepared using HME (Cilurzo *et al.,* 2008).

Solubility or bioavailability enhancement

A solid dispersion can be prepared to enhance the solubility of poorly soluble APIs. Different techniques are used to produce solid dispersions such as melting method, solvent method, melting solvent method (melt evaporation), lyophilization techniques, melt agglomeration process, the use of surfactant, electrospinning and Super Critical Fluid. Karanth et al., stated the use of HME as an alternative feasible approach in the field of solid dispersion (Karanth *et al*., 2006). In 1969, cellulose acetate phthalate pellets were prepared using a rudimentary ram extruder and their dissolution rate with respect to pellet geometry was studied (Rippie *et al*., 1969).

De Brabander et al. suggested the use of HME for manufacturing matrix mini tablets that minimised the risk of dose dumping, reduced inter and intra-subject variability and offered highly dispersive formulations within the gastrointestinal tract (De Brabander *et al.,* 2003). The capability of HME for wettability to improve the drug release pattern of engineered particles was demonstrated by Miller et al. (Miller *et al.,* 2007). The dissolution and the

bioavailability of a poorly soluble BCS class II drug felodipine was significantly enhanced by preparing its solid dispersion with Kollidon® VA64. The amorphous state of the extrudates were confirmed by PXRD and (13) C CP/MAS nuclear magnetic resonance (NMR) analysis. The molecular level mixing prevented the drug from recrystallisation when stored even at 40°C / 75% RH for almost 2 months (Song *et al*., 2013).

Fukuda et al. investigated the influence of sulfobutyl ether beta-cyclodextrin (SBE(7)-beta-CD; Captisol on the dissolution rate of ketoprofen. Extrusion was performed at 100°C, near to the melting temperature of ketoprofen. The physicochemical properties and drug release were studied and compared with samples obtained from co-grinding, heat treatment, freeze drying and physical mixture. The extruded sample showed a significantly faster dissolution rate and was least affected by the moisture (Fukuda *et al*., 2008).

Tang *et al*. demonstrated that HME is a useful technique to prepare solid dispersions of fenofibrate with Eudragit E100 and polyvinylpyrrolidone vinyl acetate copolymer S600 and is a remarkable tool for enhancing the solubility and bioavailability of finofibrate (He *et al*., 2010). Nano or micro dispersions of ritonavir were prepared by dispersion of ritonavir melt extrudates in an aqueous media. The dissolution rate was significantly improved in the melt extrudates in comparison with the crystalline API (Tho *et al.,* 2010). Perissutti et al. used HME to enhance the dissolution rate of carbamazepine (Perissutti *et al.,* 2002).

In 2010, DiNunzio et al. reported the application of appropriate formulation techniques and novel manufacturing processes such as Kinetisol® dispersing for preparing solid dispersions without adding any solvent or

plasticiser. This technique can be used to improve the physicochemical properties, homogeneity and solid state stability of the solid dispersion. It is an innovative, high energy process which utilises a combination of shear and frictional energies to rapidly prepare hydrophilic and plasticiser-free solid dispersions. In this study, an example of itraconazole - Eudragit L 100 was demonstrated (DiNunzio *et al*., 2010). Tho et al. discussed the preparation of a nano or micro dispersion of a protease inhibitor, an anti-HIV drug ritonavir melt extrudate in aqueous media (Tho *et al.,* 2010). The system was formed by dissolving the extrudate in a hydrophilic carrier containing a surfactant and this was dispersed in an aqueous medium. The dissolution profile and drug release was improved in comparison with pure crystalline drug.

HME has been widely used to increase the bioavailability of a poorly soluble drug by forming a molecular dispersion (Breitenbach *et al.,* 2003). This application can be explained from the example of Kaletra®, a combination of lopinavir and ritonavir as mentioned by Rosenberg et al. in the US patent (Rosenberg *et al*., 2005 and Rosenberg *et al*. 2007). Before, the combination of lopinavir and ritonavir was marketed for oral delivery as soft gel capsules since both the APIs are insoluble in water. The dosage was three capsules twice a day with food to maximise the bioavailability of lopinavir and these capsules require refrigerated storage to prevent degradation. However, the tablet formulation prepared using HME reduced the number of dosage units taken per day and simplified the storage conditions.

The coating of hot melt extruded tablets with suitable polymers has been shown to extensively delay the onset of crystallisation during dissolution and storage (Bruce *et al*., 2010).

Taste masking

The taste masking of bitter drugs is one of the major challenges, particularly for the preparation of orally disintegrating tablets. HME has proved to be an efficient and effective technique to mask the bitter taste of APIs by preparing solid dispersions using taste masking drug carriers. Eudragit EPO has been used to mask the taste of ibuprofen and granules were prepared by HME. The taste masking principle is based on the ionic interactions of complimentary ionic groups. The anionic polymer interacts with the cationic drug or vice-versa to mask the taste. These types of interactions give rise to hydrogen bonding and subsequently mask the bitter taste of APIs. (Gryczke *et al*., 2011). Maniruzzaman *et al.* have achieved taste masking of paracetamol through intermolecular forces between the drug and polymer by processing oppositely charged components (Maniruzzaman *et al*., 2012).

Crystal engineering

Patent GB2009/050924 by Paradkar *et al*., discloses the use of extrusion for Solvent-Free Continuous Co-crystallisation (SFCC) technology. The patent claims that extrusion is an excellent technique for generating co-crystals whilst at the same time being easily amendable to a quality by design (QbD) approach, a new paradigm in the pharmaceutical industry.

Dhumal et al. produced agglomerated cocrystals of ibuprofen- nicotinamide using the HME technique. This technology offers tight control over the process parameters with the flexibility for modifying the purity of the co-

crystal. It also allows online monitoring by adapting process analytical techniques such as NIR and Raman spectroscopy (Dhumal *et al*., 2010).

2.6.7. Marketed formulations using HME technology

Various pharmaceutical companies across the globe are currently using HME as a drug delivery technique. Melt extrusion has also been confirmed to be a suitable method for the production of controlled release reservoir systems containing polyethylene vinylacetate (EVA) co-polymers. Implanon® and Nuvaring®, two controlled release systems have been developed based on this technology. Some of the formulations prepared by hot melt extrusion are shown in table 2.5.

Table 2.5 Marketed formulations using HME

Formulation with specification	Company
Kaletra (For HIV treatment)	SOLIQS, Germany
Verapamil (Isoptin SRE)	SOLIQS, Germany
Ibuprofen fast onset	SOLIQS, Germany

PharmaForm has developed an extrusion based technique: PharmaForm Abuse Deterrent Technology (PADT), to prevent and deter drug abuse. This technique requires HME to create a drug delivery platform which facilitates rapid drug absorption and the desired adverse effect. They have launched dosage forms which provide a solution to this problem. In addition, PADT technology prevents alcohol-induced dose dumping and alcohol extraction by maintaining sustained release characteristics in 40% alcohol, in comparison to the release in water or normal dissolution medium for more than 3 hrs (Andrews *et al*., 2009).

2.6.8. Regulatory concern

Pharmaceutical formulations prepared using HME have been approved in the USA, Europe and Asia (Breitenbach *et al*., 2002). HME is a mature engineering technique which has full documentation to execute regulatory expectations. HME also provides information regarding different parameters such as torque, feed rate, pressure, segmental temperature, screw speed and melt pressure. These parameters can be monitored with probes and local sensors during processing. Enabled process analytical techniques (PAT) allow the in-line monitoring using different analytical techniques e.g. UV-Visible, Raman and N-IR. Such data can ensure the quality of a product and can simplify quality control.

2.6.9. Advantages and limitations of HME

2.6.9.1. Advantages

Continuous process: Being a single step continuous technique, extrusion overcomes the problems associated with batch processes such as batch variability, wastage, time consuming and complicated processes.

Solvent free: The technique is independent of water or solvent so it is an environmentally friendly and anhydrous method.

High yield: The process has a high yield capacity and less wastage is associated with processing.

Easily scalable: HME can be readily scaled from laboratory (bench top) to manufacturing scale.

PAT: Extrusion facilitates PAT to monitor in-line processing to maintain quality of product.

Table 2.6 Advantages of HME

Features	Benefits
Solvent free	Environmentally friendly; economical; no residue in the final product
Continuous process	Fewer unit batches required; efficient scale-up from laboratory to large scale production
Intense mixing and agitation achieved	Improved content uniformity
Compressibility not required	Useful for powder with low compressibility index
Polymers serve multiple purposes	Less number of excipients required; cost effective
Versatility	Sustained, modified, controlled and targeted release formulations
Greater thermodynamic stability than that produced by other hot melt methods	Less tendency towards recrystallisation

2.6.9.2. Limitations

The application of high temperature and shear can be major drawbacks in HME.

A limited number of FDA approved polymers, flow properties of polymers and high energy requirements are limitations of the technique. However, these challenges can be overcome by engineering and formulation approaches. The selection of suitable polymers and the use of plasticizers can allow processing to be carried out at low temperatures. Appropriate control of parameters such as applied shear, temperature, residence time and screw

design can reduce the possibility of drug or polymer degradation by lowering the mixing intensity.

2.6.10. Summary

HME is a moderately innovative technology in the pharmaceutical industry. There are some concerns associated with HME such as high processing temperatures and high plasticiser load adversely affecting the stability of thermolabile drugs during processing. HME may offer intellectual property benefits and opportunities in the fields of sustained release formulations, bioavailability and solubility enhancement, taste masking and crystal engineering. This technology certainly appears to have an immense potential to transform the development and manufacturing of many new dosage forms and novel drug delivery systems.

HME was selected for investigation during this research due to its versatility and potential usage with a wide range of pharmaceutical applications. Its use in forming polymeric formulations will be explored, together with novel solid state transformation.

3. Materials and Methods

In this chapter, the materials, experimental procedures and characterisation methods used throughout the research are described in detail. The methods section is subdivided into two parts; methods used for processing thermolabile drugs using hot melt extrusion and those used for the generation of polymorphs using high temperature extrusion. The computational methodology adapted to investigate the stability of prepared crystal forms is also described. PCP Disso software, developed at Poona College of Pharmacy, Pune, India was used to analyse the dissolution results. The pharmacokinetic study was performed at C U Shah College of Pharmacy, SNDT University, Mumbai, India by me. The computational studies were perfomed with the help of Dr. John Kendrick. A schematic presentation of the chapter is shown in figure 3.1.

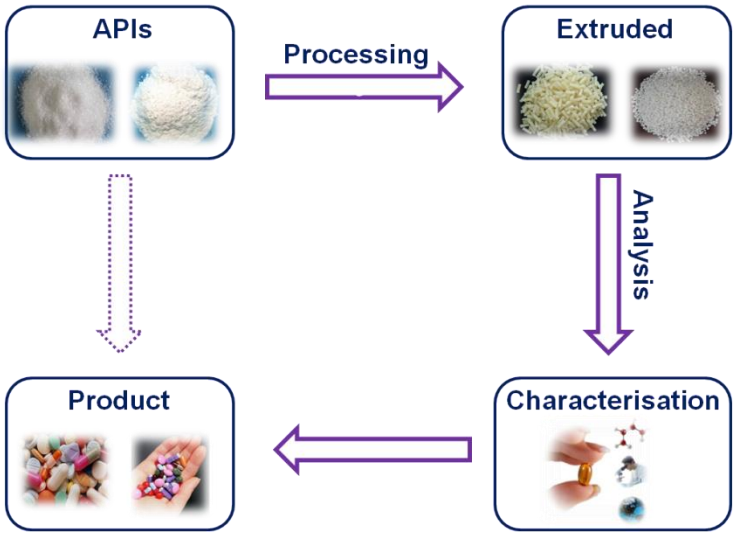


Figure 3.1 A schematic presentation of the chapter

3. 1. Materials

A description of important equipment and materials used for this research is provided in this section. These include

3.1.1. Drugs

Artemisinin, piracetam, chlorpropamide, carbamazepine, paracetamol and theophylline (All sources and lot numbers are lised in Table 3.1).

Table 3.1 List of APIs, sources and their lot numbers

APIs	Source	Lot no.
Artemisinin	Cipla Pharmaceuticals	ART25062007
Piracetam	Sigma Aldrich	P5295
Chlorpropamide	Sigma Aldrich	C1290
Carmabazepine	Sigma Aldrich	C4024
Paracetamol	Sigma Aldrich	A3035
Theophylline	Sigma Aldrich	T1633

3.1.2. Polymers

Soluplus®

3.1.3. Chemicals and solvents

Specifications of all the chemicals and solvents are summarised in Table 3.2.

Table 3.2 Specification of drug, chemicals and solvents

Drug/ Chemical/ Solvent	Supplier	Grade	Lot Number
Soluplus®	BASF, Germany	-	HJ076
Sodium lauryl sulphate	Fluka	99.0%+	71727

Ethanol	Fisher Chemicals	HPLC grade	724798, 856783
Carboxymethyl cellulose	Sigma Aldrich	-	F5832
Acetonitrile	Fisher Chemicals	HPLC grade	1376894
Methanol	Fisher Chemicals	HPLC grade	1758328
Sodium hydroxide	Sigma Aldrich	ACS 97.0%+	221465

3.1.4. Equipments

Specifications of all the equipment used in this research work are listed in Table 3.3.

Table 3.3 Specification of equipments

Equipments	Make	Specifications
Twin screw extruder	Thermo Scientific, UK	Pharmalab 16 mm co-rotating
Scanning electron microscopy	FEI (Cambridge, UK)	Quanta 400 SEM
DSC	TA Instruments (Crawley, UK)	Q2000
PXRD	Bruker (Billerica, USA)	D8 powder diffractometer
TGA	TA Instruments (Crawley, UK)	Q 5000IR
Helium pycnometer	Micromeritics (Atlanta, USA)	AccuPyc 1330
HPLC	Agilent technologies (Wokingham , UK)	1100 series
HPLC-MS	WatersAlliance (Milford, USA)	separation module 2695
GC-MS	Agilent technologies (Wokingham , UK)	7890A GC system
Dissolution apparatus	Copley Scientific (Nottingham, UK)	USP-XXVI type 2 paddle test apparatus
Hot stage microscope	Linkam, (Tadworth, UK)	Zeiss Axioplan-2 microscope using a

		Linkam 44 hot stage (THMS600)
Shear cell	Linkam, (Tadworth, UK)	CSS450 optical rheology system
FTIR	Digilab (Randolph, USA)	FTS 2000 spectrometer
UV	Agilent technologies (Wokingham , UK)	Cary 50 Varian probe
Rotational rheometer	Anton Paar (Graz, Austria)	Physica MCR 501
Feeder	Brabender technologies (Duisburg, Germany)	Brabender Gravimetric Feeders

3.1.5. Software

The following table (Table 3.4.) details the software used in this work

Table 3.4 List of all software used in the work

Software	Purpose
TA universal analysis	Thermal analysis
PowDLL converter	PXRD pattern analysis
PCP Disso V3	Dissolution data
Cary Win UV scan application version 02.00(25)	UV spectra
Material Studio software 4.1.0	Computational predictions

3.2. Methods used for the processing of a thermolabile drug using hot melt extrusion

The following techniques were used for the physicochemical characterisation of pure artemisinin and prepared solid dispersions.

3.2.1. Characterisation of pure drug and polymer

3.2.1.1. Fourier transform infrared spectroscopy

Samples for FTIR analysis were prepared by using the KBr disc method (1% samples). The prepared discs were analyzed at 25°C using a Digilab FTS 2000 spectrometer (Randolph, USA) equipped with a deuterated triglycine

sulphate (DTGS) detector. A total of 128 scans were measured and an average spectra was recorded between 4000 to 600 cm^{-1} at a resolution rate of 4 cm^{-1}.

3.2.1.2. Thermo-gravimetric analysis

The onset of thermal degradation was analysed using a TA Instruments Q5000 Thermo Gravimetric Analyser (Crawley, UK) equipped with a RSC90 cooling unit. Each aluminium pan was calibrated before loading. Approximately 5 mg of sample was loaded into each aluminium pan and the pans were heated at a rate of 10°C/ min over the temperature range of 25 to 200°C. An inert atmosphere was maintained by purging with nitrogen gas at a flow rate of 30 ml/min.

3.2.1.3. Differential scanning calorimetry

Differential Scanning Calorimetry (DSC) studies were carried out using a TA Instruments Q2000 (Crawley, UK) equipped with an RSC90 cooling unit. Indium standards were used to calibrate the DSC temperature and enthalpy scales. Approximately 4 mg of samples were hermetically sealed in an aluminium pan and a similar empty pan was used as a reference. The pans were heated at a constant rate of 10°C/ min over a temperature range of 25 to 200°C. The inert atmosphere was maintained by purging with nitrogen at a flow rate of 50 ml/min.

3.2.1.4. Powder X-ray diffractometry

PXRD patterns were recorded using a Bruker D8 X-ray powder diffractometer with an X-ray wavelength of 0.154 nm, Cu source, 40 keV voltage and a filament emission of 40 mA. Samples were scanned from 2 to

30° (2θ) using a 0.01° step width and a 1s time count. The scatter slit was 0.2° and the receiving slit was 1°.

3.2.1.5. Ultra-Violet visible spectrophotometry

The UV absorption spectrum of artemisinin was measured using a Cary 50 Varian probe UV visible spectrophotometer (Wokingham, UK). Samples were prepared in ethanolic solution and the spectra were recorded with the range of 200 to 500 nm. Cary Win UV scan application version 02.00(25) software was used to record the spectra. A calibration curve for artemisinin was obtained using 10% (v/v) ethanolic water and 0.1% (w/v) sodium lauryl sulphate as a solvent. 5, 10, 15, 20, 25 and 30 µg/ml standard artemisinin solutions were prepared. One ml of artemisinin solution was treated with alkali by adding 2 ml of 0.2% (w/v) NaOH solution. All the mixtures were kept in a water bath at 50°C for 30 mins and the UV absorbance was recorded at 290 nm. The absorbance was then plotted against the respective concentrations in order to produce a calibration curve.

3.2.1.6. Rotational rheometry

The rheological behaviour of artemisinin, Soluplus® and physical mixtures in different ratios was studied using an Anton Paar Physica MCR 501, rotational rheometer (Graz, Austria), equipped with a temperature controlled furnace. Physical mixtures of artemisinin and Soluplus® were prepared in 1:1, 1:3 and 1:5 ratios (w/w) (50, 33.3 and 16.7% (w/w) respectively) by blending in a Turbula mixer for 10 min. Parallel plates of diameter 25 mm were used for rheological characterisation with the distance between the plates set to 1 mm. The polymer or physical mixture was added to the bottom

plate after the set temperature had been achieved. Upon melting, separation between the plates was reduced to the set experimental distance. The time dependent stability of melts were measured using a time-temperature sweep test. The test was performed at temperatures of 100, 110 and 130°C, at a fixed strain of 1% and a fixed frequency of 10 Hz for 30 minutes. The complex viscosity was measured every 5 seconds. During rheological measurement, it was observed that there was some discolouration in the mixture after melting. The colour intensity increased with increasing concentration of artemisinin in the mixture. Therefore physical mixture containing 50% (w/w) artemisinin was only investigated for extrusion and product optimisation.

3.2.2. Preparation of Solid Dispersions by Extrusion

Extrusion was carried out using a co-rotating twin screw extruder (Pharmalab, Thermo Scientific, UK) with a screw diameter of 16 mm and a screw length to diameter ratio of 40:1. An extruder temperature profile of T110 was used (T110, as detailed in table 3.13) at a constant screw rotation speed of 50 rpm. The powder blend (10 g) was fed into the extruder at a rate of 0.12 kg/h using a gravimetric twin screw feeder (Brabender, Germany). Following extrusion, the extruded strand was air cooled and pelletised. The experimental set up is shown in figure 3.2.

Figure 3.2 Different views of Pharmalab co-rotating 16 mm twin screw extruder

3.2.2.1. Extruder Screw Configurations

Residence time has a significant impact on the quality of the extruded material, therefore two different screw configurations were employed. The following table (Table 3.5) describes the two different configurations employed in this experiment (figure 3.3).

Table 3.5 Screw configurations
(a: in terms of diameter ID: 16 mm)

A		B	
Length (D)[a]	Element	Length (D)[a]	Element
8	Forwarding	28	Forwarding
2.25	30°	2.25	30°
1.25	60°	1.25	60°
1	90°	1	90°
6	Forwarding	6	Forwarding
1.5	Discharge	1.5	Discharge
20	**Total length**	**40**	**Total Length**

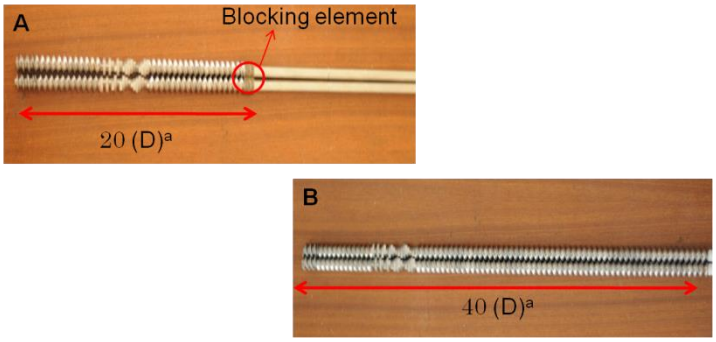


Figure 3.3 Extruder screw configurations

3.2.2.2. Temperature Profiles

In this study, extrusion was carried out using the optimum T110 temperature profile. This profile was selected from data obtained from rotational rheometry. The extruder barrel is divided into 9 different zones and the highest temperature was maintained at zone 7 as it encompasses the mixing section. The set temperature profiles are shown in Table 3.6.

Table 3.6 Diagrammatic presentation of temperature profiles

Temperature Profile	Zone 2	3	4	5	6	7	8	9	Die
T110 A	-	-	-	-	25	25	110	110	110
T110 B	20	25	80	90	100	110	110	110	110

3.2.3. Characterisation of extruded materials

Extrudates were characterised using DSC and X-Ray diffractometry (as described above).

3.2.3.1. Assay

Solid dispersions equivalent to 20 mg of artemisinin were weighed accurately and dissolved in a suitable quantity of medium containing 10% (v/v) ethanolic water and 0.1% (w/v) sodium lauryl sulphate. An appropriate quantity was treated with alkali using 0.2% (w/v) NaOH. The drug content was measured

at 290 nm using a UV spectrophotometer. Analysis of data was performed using PCP-Disso software (Poona College of Pharmacy, PCP Disso V3, Pune, India).

3.2.3.2. *In-vitro* Dissolution

In-vitro dissolution studies were performed using a USP-XXVI type 2 paddle test apparatus (Copley Scientific, Nottingham, UK). Powder samples equivalent to 20 mg of artemisinin were placed in dissolution vessels containing 600 ml of dissolution medium maintained at 37°C ± 0.1°C and stirred at 100 rpm. The dissolution medium consisted of ethanol 10% ethanolic water and sodium lauryl sulphate (0.1% w/v). Samples were collected periodically and replaced with fresh dissolution medium. The collected sample was filtered using a cellulose acetate filter and treated with alkali. The concentration of artemisinin was determined spectrorphotometrically at 290 nm. The dissolution profiles were generated using PCP Disso software V3 (Poona College of Pharmacy, Pune, India).

3.2.3.3. Pharmacokinetic Study

Study protocol

A study was performed with prior approval from the IAEC of C U Shah College of Pharmacy, whose guidelines were followed throughout the studies. 36 healthy albino wistar rats with a weight 180-200 g were taken and divided into three groups; control, pure drug and solid dispersion. A sparse technique was used to collect blood samples (n=6). The animals were housed in standard metabolism cages and fasted for 12 hours before dosing but allowed free movement and access to water throughout the experiment.

100 mg of artemisinin was dispersed in 0.5% (w/v) aqueous CMC solution and the oral dose (equivalent to 100 mg of artemisinin) was administered using an oral syringe. At predetermined time intervals, blood samples were obtained by the retro orbital technique and collected in EDTA tubes.

Sample analysis

Plasma was obtained by centrifugation of the blood sample at 3500 rpm for 15 mins. A volume of 200 µl plasma was pipetted into Eppendorf tubes and 100 µl of internal standard (artemether solution 1000 µl/ml) and 700 µl methanol were added. The solution was vortexed for 2 minutes and the organic phase was separated by centrifugation. The collected sample was then subjected to analysis by HPLC (Agilent technologies, 1100 series, Wokingham, UK). The plasma level of artemisinin was analysed by HPLC using 65% acetonitrile and 35% water as the mobile phase. The HPLC system consisted of an Agilent 1200 series, UV detector set at 210 nm and a C18 column (250 x 4.6 mm). Artemisinin exhibits a maximum UV absorption at 210 nm. The limits of detection and quantification were 1.01 and 3.06 µg/ml, respectively. The concentration against peak area graph plot was found to be linear ($r^2 = 0.998$).

3.2.3.4. Stability

All extruded materials were stored at room temperature and their stability was studied at intervals of 1 month, 3 months, 6 months, 9 months and 12 months by PXRD and dissolution using the above methods.

3.3. Methods used for polymorphic transformation

3.3.1. High temperature extrusion

The commercially available forms of drugs were processed in a twin screw extruder (Pharmalab, ThermoScientific, UK with screw diameter 16 mm and length to diameter ration 40:1) at different set temperatures, below the melting point of the respective drugs. Screw rotation speeds of 10, 20 and 30 rpm were used to investigate the effect of shear and residence time on the product. The screws were configured to produce low, medium and high shear intensity. Full details of the screw configurations, temperature profiles and screw speed are displayed in Table 3.7.

Table 3.7 Full details of extrusion experiments with different applied parameters

Drug	Temperature Profiles	Screw Speed	Configuration
Artemisinin	T130, T140	20 and 30 rpm	A, B, C
Piracetam	T130	10 rpm	C
Chlorpropamide	T115	10 rpm	C
Carbamazepine	T145	10 rpm	C
Theophylline	T120, T150	10 and 30 rpm	A, B, C
Paracetamol	T130, T150	10 and 30 rpm	A, B, C
Glycine	T115, T130	10 and 30 rpm	A, B, C

3.3.1.1. Extrusion Temperature profiles

Full details of temperature profiles are illustrated in Table 3.8.

Table 3.8 Details of temperature profiles

Profile	Zone 2	3	4	5	6	7	8	9	10
T130	20	60	80	120	120	125	125	130	130
T140	20	60	80	140	140	140	140	140	140
T115	20	60	80	100	110	115	115	115	115
T145	20	60	80	145	145	145	145	145	145

T130	20	60	80	130	130	130	130	130	130
T120	20	60	80	120	120	120	120	120	120
T150	20	60	80	150	150	150	150	150	150

3.3.1.2. Screw configurations

Full details of screw configurations A (low shear intensity), B (medium shear intensity) and C (high shear intensity) are displayed in table 3.9.

Table 3.9 Extruder Screw configurations

A		**B**		**C**	
Length (D)[a]	Element	**Length (D)[a]**	Element	**Length (D)[a]**	Element
28	Forwarding	11	Forwarding	6	Forwarding
2.25	30°	1	30	2	90°
1.25	60°	1	60	1	60°
1	90°	1	90	6	Forwarding
6	Forwarding	6	Forwarding	1.25	60°
1.50	Discharge	1.5	30	4	Forwarding
40	**Total Length**	8	Forwarding	1	90°
		1	60	1	60°
		2	90	1.25	30°
		6	Forwarding	4	Forwarding
		1.5	Discharge	1	60°
		40	**Total Length**	1	30°
				9	Forwarding
				1.50	Discharge
				40	**Total Length**

3.3.2. Crystallisation of artemisinin polymorph

A re-crystallisation technique was used to prepare the triclinic form of artemisinin (Chan et al., 1997). It was performed in a 500 ml conical flask. The temperature of the reaction vessel was maintained at 80°C by recirculating water. The orthorhombic form of artemisinin (20g) was added in 50 ml of cyclohexane. The supersaturated mixture was then heated for 1 hr at 80°C along with continuous stirring. The temperature was decreased by 10°C every 30 minutes until the solution temperature reached 30°C. After a few minutes, stirring was stopped and the triclinic form was isolated, vacuum dried and stored in an air tight container. The determined recovery was approximately 13g.

3.3.2.1. Characterisation of the prepared crystals

The prepared crystals were characterised using DSC, FTIR and X-Ray diffractometry (as described above).

Gas Chromatography- Mass Spectrometry (GCMS)

GC-MS was performed to calculate the amount of residual solvent using Agilent technologies 7890A GC system and the following method was used.

Preparation of stock solution

Cyclohexane (200 mg) was weighed accurately and transferred to 100 ml volumetric flask. This was mixed with 15 ml dimethylformamide (DMF) and diluted to the volume with DMF. 1 ml of above stock solution was transferred to 50 ml volumetric flask and dissolved in 25 ml DMF and further diluted with DMF.

Preparation of sample solution

Samples (500 mg) were accurately weighed and transferred to a 50 ml volumetric flask. They were then dissolved in 30 ml of DMF and were further diluted with DMF.

Chromatographic conditions are listed in Table 3.10.

Table 3.10 Chromatographic conditions

Gas Chromatograph	
Column	Rtx®-624, 30 m, 0.32 mm ID, 1.80 µm (cat.# 10970)
Injector Temperature	150°C
Carrier gas	Helium
Detector Temperature	240° C
Injector Mode	Split less
Split Ratio	NA
Oven Temperature	40° C
Initial Time	10 min
Rate	10 °C
Final Temperature	240 ° C
Final Time	10 min
Injection volume	1µl
Carrier Gas	He, constant flow
Flow Rate	2.16 mL/min
Linear Velocity	35.3 cm/sec
Detector	FID @ 260°C

3.3.3. Characterisation of extruded samples

Extruded samples were analysed by DSC and PXRD as described above.

3.3.3.1. High Performance Liquid Chromatography - Mass Spectrometry (HPLC-MS)

HPLC was performed using a WatersAlliance separation module 2695 (Milford, USA). Column C18, 3 x 100 mm, 1.8 um particle size was used and 1ul of artemisinin was loaded. 50% acetonitrile, 50% water, 0.09% formic acid and 0.01% trifluroacetic acid was used as a mobile phase.

3.3.3.2. Density measurement

True density of the samples was measured using a Micromeritics AccuPyc 1330 Helium Pycnometer (USA). An empty cup of volume 10 cm^3 was initially analysed to confirm that the value of the average volume was zero; the error was found to be less than 0.05%. The instrument was calibrated using a calibration standard metal ball with a known volume of 6.372882 cm^3. Helium gas (99.995% pure) was passed under a pressure of 20 psig with an equilibrium rate of 0.005 psig/ min at a temperature of 25°C $\pm$ 2°. Following the calibration, a known mass of sample was added to the cup. Samples were analysed in triplicate and an average density was calculated.

3.3.3.3. Scanning electron microscopy (SEM)

Samples were mounted on aluminium pin-stubs (Agar Scientific, Stansted, U.K.) for SEM using self-adhesive carbon mounts (Agar Scientific). Scanning electron microscopy was performed using a Quanta 400 SEM (FEI Company, Cambridge, UK) in a high vacuum operated at an acceleration

voltage of 20 kV. XTM Microscope control software version 2.3 was used for imaging.

3.3.3.4. Pharmacokinetic study

The same pharmacokinetic study was performed for the prepared polymorph as described previously (3.2.3.3.).

3.3.3.5. Mechanical understanding of high temperature extrusion process

Hot stage microscopy and shear were used to illustrate the mechanism of polymorphic transformation during the high temperature process.

Hot stage microscopy (HSM)

Microscopy was performed using a Zeiss Axioplan-2 microscope equipped with a Linkam 44 hot stage (THMS600) (Tadworth, UK). The data was visualised using Axiovision (4.5) software with the linksys 32 patch for hot stage control. The sample was isothermally treated at 140°C for 90 min at a heating rate of 10°C/min. Images were captured at different intervals.

Shear Cell

Shear cell microscopy (displayed in figure 3.4) was performed using a Linkam shear cell (CSS450) coupled with a polarised light microscope connected to a video capture system. The sample was loaded between the top and bottom of highly polished quartz windows of the shear cell and the gap between the two plates was reduced to 30 µm by slowly lowering the upper glass plate of the Linkam device. The sample was isothermally heated at 140°C for 15 min and the steady shear rate was maintained at 0.5 s^{-1}. Images were captured using a digital camera.

Figure 3.4 A model shear cell

3.3.4. Computational Techniques

Computational chemistry is able to generate complementary data to experiments, based upon the structures, properties and reactions of materials. It involves the application of mathematical, computing and chemical skills to solve interesting chemical problems. It can assist the experimental chemist to predict the results before running the actual experiment or it can challenge the experimental chemist to find entirely new chemical entities. It can also be a useful tool to investigate compounds which are very difficult to generate and expensive to purchase. The increasing interest in computational techniques for structure and physicochemical property prediction of molecules has become a vital tool in chemical research. Recently the pharmaceutical industry has been attracted to these computational techniques because drug discovery and efficacy depends on the surface activity of active pharmaceutical ingredients and excipients.

Quantum mechanics and molecular mechanics are the foundation of most computational techniques. Quantum mechanical theory is commonly used for

accurate simulations of atomic and molecular systems. It can be based on the time dependant Schrödinger equation associated with the molecular Hamilton. Although this technique describes molecular structure very accurately, it is computationally very expensive therefore is applicable only to the smallest systems or to small molecules. Even with the most powerful computers available today, calculations on large systems are beyond the reach of quantum mechanics. Another major limitation of quantum mechanics is the calculation of the electronic energy for a given nuclear configuration.

Molecular mechanics describes the total energy of the system as a sum of analytical terms representing bonding and non-bonding interactions. The advantage of molecular mechanics is that it allows for the modelling of a wide range of molecules including segments of DNA and proteins; making it a primary tool for a computational biochemist. The main benefit of molecular mechanics is the speed at which modelling or calculations can be performed.

Molecular mechanics depends on the accuracy of the force field. A force field is a description of the potential energy surface, which is a function of the geometry of the molecule or set of the molecules. Various force fields have been developed over the years for modelling purposes. Some force fields account for coupling between bending and stretching in adjacent bonds in order to improve the accuracy of the mechanical model. A force field for molecular mechanics is designed from the following principles:

- Nuclei and electrons are lumped into atom-like particles
- Atom-like particles are spherical and have a net charge

- Interactions are based on springs and classical potentials
- Interactions are pre-assigned to specific atom types
- Interactions determine the spatial distribution of atom-like particles and their energies

The quality of a force field calculation relies on the suitability of the mathematical form of the energy expression and the accuracy of the parameters. Force field methods are investigated mainly to predict geometries and relative energies of the molecules. For systems where accurate parameters are available, it is possible to make a very good prediction of geometries and relative energies of a large number of molecules in a short space of time (Goodman, 1998 and Jensen, 1999). In general, structural features are relatively easier to predict compared to relative energies. Validation of a force field is commonly made by proving how accurately it reproduces reference data that may or may not have been employed in the actual parameterisation.

Different molecular modelling software packages are commercially available. Materials Studio is an example of such software. It comprises a suite of molecular modelling software packages from Accelrys Inc., San Diego, CA. designed to allow researchers in the field of material science and chemistry to predict and understand the correlation between the atomic and molecular structure of a material with its physicochemical properties. It has been widely used in various industries such as pharmaceutical, polymer, metal, composites, catalysts, fuel and batteries. The 'Visualiser' is a graphical user environment in which the researcher can construct, manipulate and view models of molecular structures. It offers different modelling modules and the

researcher has to pick a specific module for a desired requirement, combining it with the Visualiser.

In this work, Material Studio software was used to understand the stability of the prepared polymorphs computationally.

3.3.4.1. Crystal structures

3D crystal structures of both polymorphs were obtained from the Cambridge Structural Database (CDS) with codes QNGHSU (orthorhombic) and QNGHSU01 (triclinic). These structures were used to develop and validate the force field which was used for further calculations of the morphology prediction and the adsorption energies using the morphology and the sorption modules in Material Studio software 4.1.0.

3.3.4.2. Geometry optimisation

Geometry optimisation refines the geometry of a structure until it satisfies specific criteria. It is an interactive practice in which the atomic synchronises and the cell parameters are customised until the total energy of the structure is minimised. Hence, the optimised structure relates to a minimum in the potential energy surface. Geometry optimisation was performed using Universal, CVFF, PCFF and Dreiding force fields with built in and equilibrated charges (QeQ) from a Forcite module. Calculated values were then compared with experimental values. Forcite is a classical molecular mechanics module that allows fast energy calculations and reliable geometry optimisation of the molecules. Forcite is designed to work with a wide range of forcefields, and provide easy and flexible access to the associated parameter options.

3.3.4.3. Morphology prediction

The Morphology module predicts the external morphology of a crystal from the atomic structure of a crystal. The crystal habit is critically important for the pharmaceutical and industrial processing of solids. There are different examples in the pharmaceutical and chemical industries where the crystal shape may have influenced the dissolution rate and bioavailability of the drug stability, density and processability. Therefore chemists, chemical and process engineers are interested in crystal morphology and its relation to the internal atomic arrangement. This relationship enables prediction of crystal shape and the effect of different solvents and additives. This tool has significant applications in the pharmaceutical, food science, cement, agrochemical, commodity and petrochemical industries. There are many methods to deduce a crystal habit, such as Bravais - Freidel - Donnay - Harker (BDTH), Growth morphology and Equilibrium morphology.

Table 3.11 Principle of different morphology modules

Morphology	Principle
Bravais - Freidel - Donnay - Harker (BDTH) theory	The BDTH method is a geometrical calculation which uses the crystal lattice and symmetry to generate a list of possible growth faces and their relative growth rates.
Growth Morphology	The Growth morphology presumes that the growth rate of a crystal face is proportional to its attachment energy.
Equilibrium Morphology	The equilibrium morphology of a crystal is calculated by the minimum of the surface energies for all relevant crystal faces.

The BDTH, Growth morphology and Equilibrium morphology method within Material Studio Software 4.1.0 was used to predict the crystal morphology.

3.3.4.4. Sorption

The sorption module offers a solution for the prediction of molecular adsorption on the surface of crystalline material. Molecular adsorption into microporous structures such as zeolites, alumino hosphates, or polymers is essential in several applications including hydrocarbon cracking, air separation, ion exchange and gas sensors. The sorption module simulates a pure adsorbate in a sorbent framework by using the Metropolis Monte Carlo method.

4. Processing of a thermolabile drug using hot melt extrusion

Pharmaceutical hot melt extrusion involves the processing of a drug and polymer in a molten state under shear applied by rotating screws. High processing temperatures can limit its application for some thermolabile APIs. Processing temperature can be reduced using plasticisers, but this can significantly increase the bulk of the formulation. Here, Soluplus®, a polyvinyl caprolactum-polyvinyl acetate-polyethylene glycol graft co-polymer which has low Tg and good extrudability, was selected. Artemisinin, a keystone of malaria treatment recommended by the World Health Organisation (WHO) was used as a model thermolabile API. The well-known problem associated with artemisinin is its poor aqueous solubility. In addition, it provides a processing challenge due to its thermolabile nature. The lactone ring of artemisinin degrades in basic pH, thus a weak acid (citric acid) was used to maintain a neutral pH. A schematic presentation of the chapter is shown in figure 4.1.

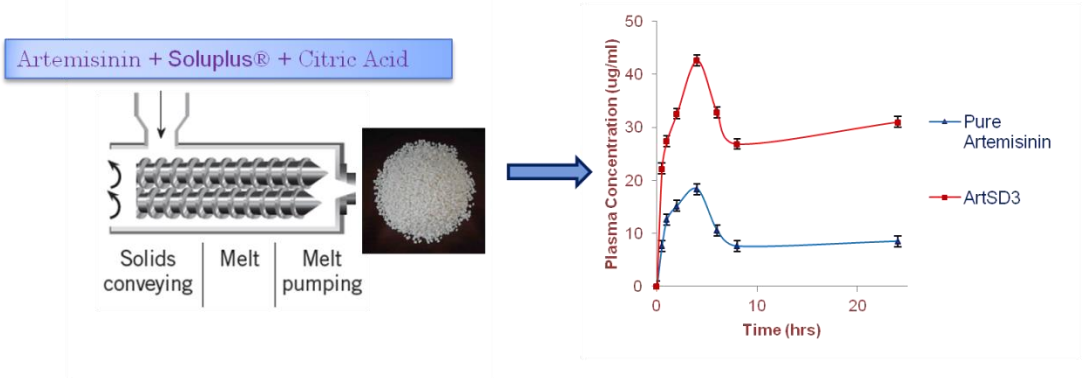


Figure 4.1 A schematic presentation of the chapter

4.1. Introduction

Hot melt extrusion (HME) has been widely used in the pharmaceutical industry to prepare solid dispersions with the aim of improving the bioavailability of poorly water soluble drugs (Luener *et al*., 2000). During the processing of solid dispersions by HME, the hydrophobic drug is processed with a thermoplastic polymer in a molten state to obtain a stabilised amorphous form to achieve enhanced aqueous solubility. In HME, the selection of a suitable polymer plays a vital role in the formulation as well as in setting extrusion conditions. Typically the extrusion process should be carried out at 20-40°C above the glass transition temperature (Tg) of the polymer. The 'extrudability' of a polymer can be determined by its glass transition and its rheology (Chokshi *et al*., 2005). Exposure of material to high temperatures is one of the major concerns during HME, as this may adversely affect the drug stability especially for thermolabile drugs. High processing temperatures can limit the processing of thermolabile drugs (Thumma *et al.,* 2005) and high temperature HME processing is not suitable for a number of APIs due to thermal decomposition which may result in the loss of pharmacological activity (Follonier *et al*., 1994). In such cases, plasticisers may be added to the pure polymer in order to lower the Tg and melt viscosity, allowing extrusion to be performed at lower temperatures (Ghebremeskel *et al*., 2007 and Repka *et al*., 2008). Lowering the processing temperature reduces drug degradation and facilitates drug stability in pharmaceutical formulations. Repka et al. formed films containing the thermolabile drug hydrocortisone in hydroxypropyl cellulose by incorporating high levels of plasticisers during melt extrusion (Repka *et al*., 1999).

Generally, plasticisers are used in a concentration range of 5-30 % w/w of the extrudate. The use of plasticisers in pharmaceutical formulations has some disadvantages, such as plasticisers with low molecular weight may volatilise and contribute to internal pollution; this phenomenon is known as 'sick house syndrome'. Plasticisers contribute to the bulk of the dosage form and therefore lower the adhesive strength of the product. They can also adversely affect the mechanical properties, drug release and stability of the product as well as cause bubble formation. In the last 10 years, a new technique was adapted from the polymer industry using a combination of pressurised gases with processing (Tomasko *et al*., 2003). The injection of supercritical CO_2 leads to the swelling and modifying of the polymer's mechanical and physical properties. In addition, the carbon dioxide acts as a plasticiser and reduces the glass transition temperature. Verreck *et al*. investigated the use of CO_2 as a foaming and reversible plasticiser, through its reducing chain-chain interactions and increasing the inter-chain distance, and its effect on thermal properties and performance of an itraconazole solid dispersion (Verreck *et al*., 2007). However, the application of supercritical CO_2 in HME increases the cost of production in comparison with the conventional method.

Therefore, there exists a requirement for development of a more suitable approach to facilitate the processing of heat sensitive drugs which is one of the main objectives of this work.

Artemisinin, a keystone of malaria treatment, is isolated from the Chinese herb Artemisia annua L. and is recommended by the World Health

Organisation (WHO) as part of a combination therapy. Artemisinin has low bioavailability and poor water solubility. Artemisinin is a widely used antimalarial drug which has poor water solubility and a thermolabile nature. It exhibits two crystal forms; a commercially available orthorhombic form and a less stable triclinic form. Therefore artemisinin has been selected as a model drug to explore the application of hot melt extrusion to prepare solid dispersions of thermolabile drugs and cause solid state polymorphic transformation.

Artemisinin was extracted from the herb *Artemisia annua L.* and analysed by Chinese scientists in 1972. It was proven to be effective against plasmodium falciparum as well as cerebral malaria (Charles *et al*., 1990). Artemisinin is a polycyclic sesquiterpeneendoperoxide. The peroxide group within it is fundamental for anti-malarial activity. It blocks a free heme released by the parasite and converts it into hemozoin which helps to create proteins to kill the parasite (Eckstein *et al*., 2003 and Kannan *et al.,* 2002). Additionally, it has a very low toxicity in the standard therapeutic dose (Koch *et al*., 1981 and Luo *et al*., 1987). The molecular structure of artemisinin is displayed in figure 4.2 and a detailed profile of artemisinin is displayed in Table 4.1.

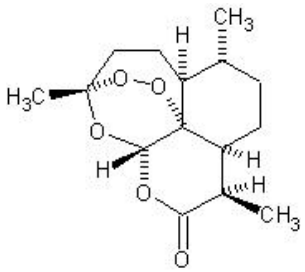


Figure 4.2 Molecular structure of artemisinin

Table 4.1 Physicochemical properties of artemisinin

Chemical Name	(3R,5aS,6R,8aS,9R,12S,12aR)-Octahydro-3,6,9-trimethyl-3,12-epoxy-12H- pyrano[4.3-j]-1,2-benzodioxepin-10(3H)-one
Molecular Formula	$C_{15}H_{22}O_5$
Molecular weight	282.3 g
Melting Point	152-157°C
Description	White crystalline powder or colourless needles
Solubility	Practically insoluble in water, very soluble in dichloromethane, freely soluble in acetone, soluble in ethanol and methanol
Storage	0-5°C

Artemisinin has poor aqueous solubility, which results in low and unpredictable absorption after oral administration; thus limiting its therapeutic applications. Moreover, it has a short half life and a high first pass metabolism which often leads to incomplete parasite clearance (Titulaer *et.al*., 1991).

In the present study, artemisinin was selected as a model drug due to its thermolabile nature. This poses significant processing challenges for the formation of solid dispersions (Chen *et al*., 2008).

A novel amphiphilic copolymer, Soluplus® (polyvinyl caprolactum polyvinyl acetate polyethylene glycol) was chosen to form solid dispersions with artemisinin, as it has the ability to enhance the solubility of poorly water soluble drugs and is suitable for melt extrusion below 120°C without the need for the incorporation of an additional plasticiser (Ali, 2010).

Soluplus®, a commercially available copolymer developed by BASF, is a polyvinyl caprolactum polyvinyl acetate polyethylene glycol in the form of white to yellowish free flowing granules with a slight characteristic odour. Because of its amphiphillic behaviour, it can either act as a carrier to form solid dispersions or solid solutions. The molecular structure of soluplus® is displayed in figure 4.3.

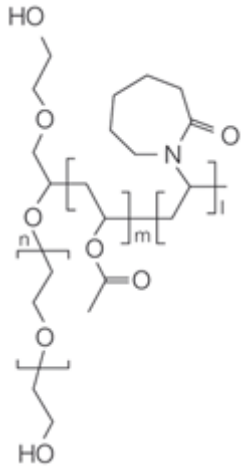


Figure 4.3 Structure of Soluplus® Polymer

Soluplus® is freely soluble in water. The following table (Table 4.2) indicates the solubility of Soluplus® in different solvents:

Table 4.2 Solubility of Soluplus® in different solvents

Solvent	Ratio
Water	Any
Acetone	Up to 50%
Methanol	Up to 45%
Ethanol	Up to 25%
Dimethylformamide	Up to 50%

Applications

Recommended for Extrusion

Soluplus® has a glass transition temperature of 70° C. It is suitable for extrusion and can be used in the processing range of 120 to 180°C without any additional plasticizer. It is reported that, a solid dispersion of fenofibrate and itraconazole can be made with Soluplus® at 100°C and 150°C respectively, keeping screw speed at 200 rpm, feed rate at 1kg/hr using a 16 mm twin screw extruder.

Features of Soluplus®

- General: It can be used as an emulsifying agent or binding agent for wet granulation and act as a dry binder for direct compression.
- Solubility enhancer: It can act as a solubility enhancing hydrophilic polymer for poor aqueous soluble drugs.
- Drug loading onto nonpareils: A solution of drug and Soluplus® into organic solvents such as ethanol or acetone is able to form layering on sugar strand or nonpareil by spraying.

The aim of this work was to investigate solid dispersion formulations of artemisinin and Soluplus® using HME, with a focus on processing challenges, product stability and biopharmaceutical performance.

4.2. Result and discussion

4.2.1. Material characterisation

Materials were analysed using FTIR, TGA and DSC.

4.2.1.1. Fourier Transform Infrared Spectroscopy (FTIR)

The structural determination and confirmation of an API is an important part of raw material analysis. The infrared absorption spectrum of artemisinin was obtained using an infrared spectrometer.

Artemisinin is a complex molecule resulting from the fusion of rings, which are, apart the methyl substituents, bicycle, lactone and cyclohexane, for a total number of 42 atoms (Moroni *et al*., 2008). Artemisinins shows standard FTIR peaks (displayed in figure 4.3) at 928 cm^{-1}, 1137$cm^{-1}$and a strong band at 1760 cm^{-1} (lactone ring C=O) (Lin *et al*., 1985).

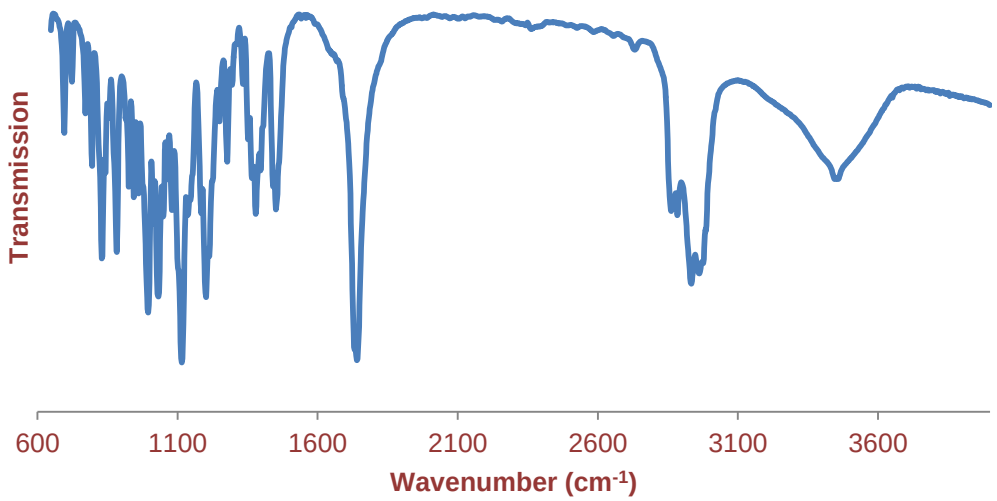


Figure 4.4 FTIR spectra of pure artemisinin

4.2.1.2. Thermo Gravimetric Analysis (TGA)

In extrusion, processing is performed at an elevated temperature and therefore, it is necessary to determine the onset of degradation of the API and polymer. Thermo-gravimetric analysis was carried out to determine the onset of degradation of pure artemisinin and Soluplus® (shown in figure 4.5).

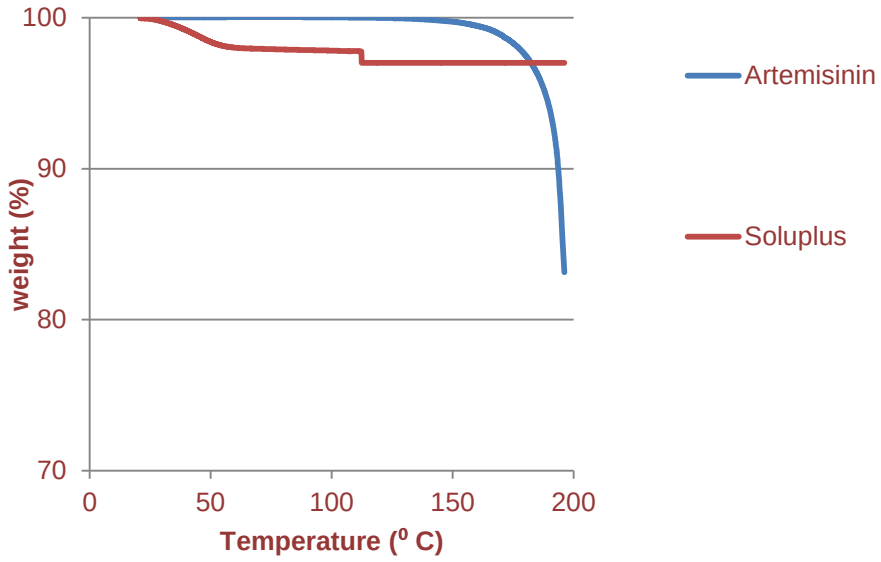


Figure 4.5 Thermo-gravimetric analysis of artemisinin and Soluplus®

The above thermogram illustrates that the onset of degradation of pure artemisinin started at 160°C. Above 170°C, rapid degradation of artemisinin was observed which is represented by rapid weight loss. The degradation of artemisinin was found to be 15.73% from 170°C to 200°C whereas Soluplus® demonstrated thermal stability up to 200°C. Soluplus® showed the presence of moisture at a level of 2-5% (w/w).

4.2.1.3. Differential scanning calorimetry (DSC)

DSC thermograms of artemisinin, Soluplus® and their physical mixtures are shown in figure 4.6. Artemisinin exhibited a major endotherm at 154.81°C and Soluplus® exhibited a Tg at 70°C whereas the physical mixture showed a Tg at 80°C with a sharp endotherm at 154.75°C. From the DSC screening, temperatures of 100, 110 and 130°C were selected for rheology testing.

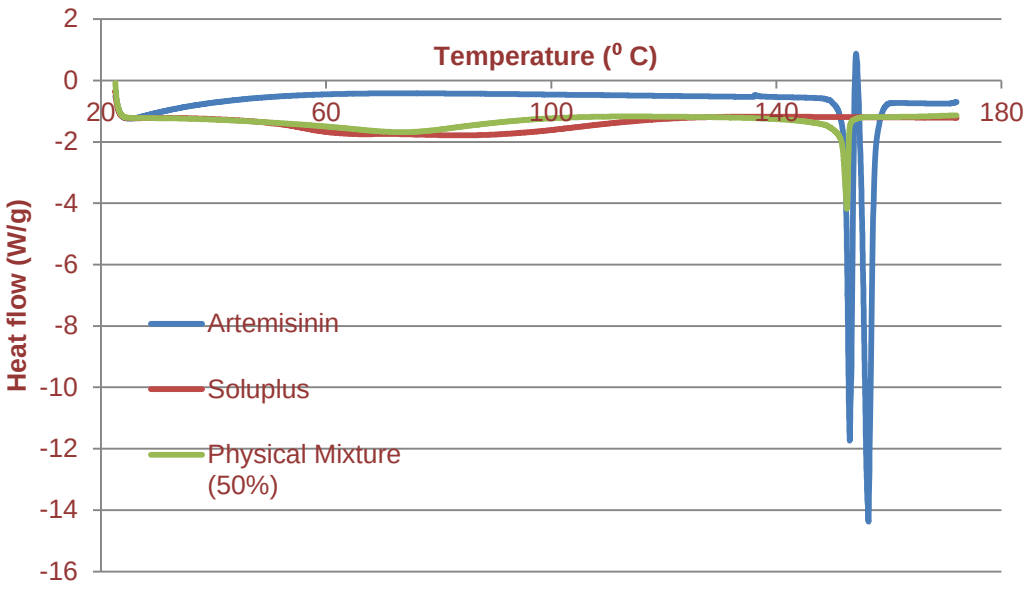


Figure 4.6 DSC thermograms of Soluplus (a), artemisinin (b) and physical mixture (c).

4.2.1.4. Rotational rheology

At a preformulation stage, the polymer is selected on the basis of drug-polymer miscibility, glass transition temperature and the rheology of the mixture in its molten state. These properties may be tailored by the addition of a plasticiser, or by designing novel polymers of an amphiphillic nature and suitable extrudability such as Soluplus®. Screening at the preformulation level generally involves thermal analysis, rheological testing, miscibility predictions using a Flory–Huggins approach and hot stage microscopy (Tian *et al*., 2013 and Lakshman *et al*., 2008).

The rotational rheometer is a device which can be used for studying the thermal compatibility of a drug and a polymer under controlled shear. It has been widely used in polymer research to study polymer flow. It enables the structural dynamics of complex fluids to be directly monitored at the same time as they are under precisely controlled temperature and a variety of

shear modes. In this project, a rotational rheometer was used as a screening tool for optimising processing temperatures, drug loadings and to understand the effect of additives under shear.

API and polymer interaction was also evaluated using rotational rheometry. Samples may undergo structural changes when subjected to high temperature and shear with respect to time. This may affect the viscosity of the formulation and these changes can be monitored using a 'time sweep' test. Furthermore, the polymer and API may undergo time dependent degradation at high temperatures, therefore the data obtained from this test can be correlated with typical HME residence times. Ideally, the viscosity of the polymer should remain constant at low shear rates for a given temperature; changes in viscosity may indicate structural changes in the material.

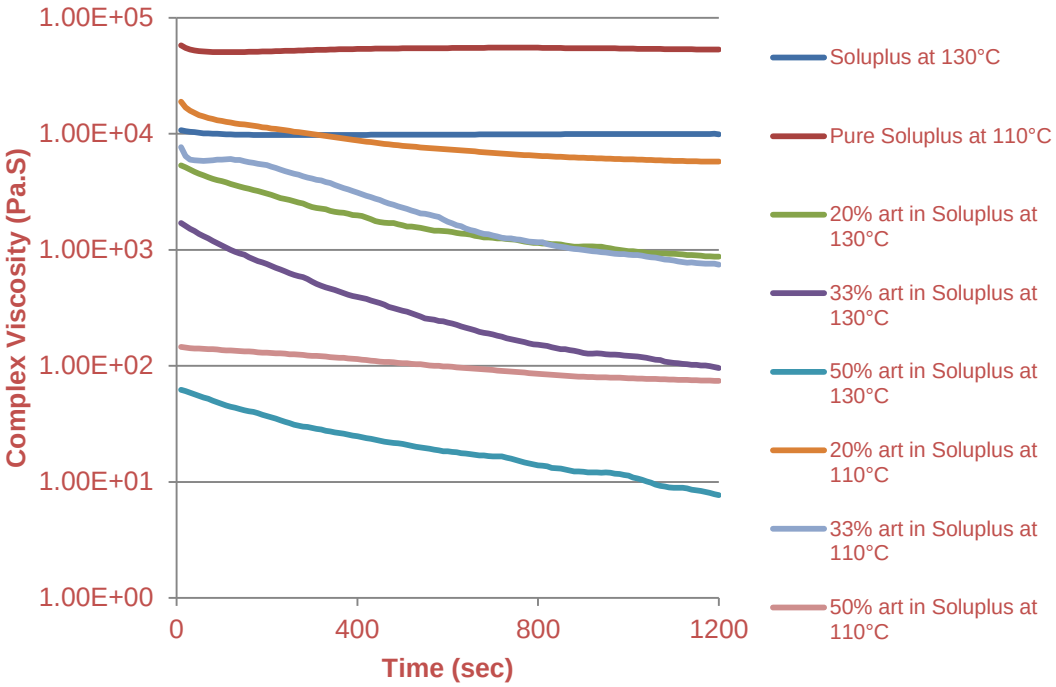


Figure 4.7 Time dependent complex viscosity

From the DSC data, three temperatures were selected for the shearing experiments: 100, 110 and 130°C. However, the experiment could not be performed below 110°C as the material would not flow in the rheometer. The complex viscosity of the polymer with different drug loadings for time dependent tests at 110° C and 130°C are shown in figure 4.7. For pure Soluplus®, the viscosity is seen to be stable for 20 minutes at 110°C and 130°C. The plasticising effect of artemisinin can be clearly observed as a drop in the complex viscosity with increasing drug loading. At a high drug loading of 50%, a drop in viscosity at these low angular frequencies combined with the visual observation of the treated material suggests that degradation had occurred. No discolouration was observed when Soluplus® and artemisinin were separately subjected to rotational rheometry tests at a temperature of 130°C. This indicates that an interaction between Soluplus® and artemisinin leads to the observed degradation during shearing at 130°C. The level of applied shear was found not to influence the discolouration.

Thermal and rheological studies of artemisinin and Soluplus® provided some insight into artemisinin - Soluplus® compatibility issues which have been taken into consideration for further experiments. The important information is sumerised below:

a. Pure Soluplus® does not show any discolouration at 130°C. Thermal analysis has shown that artemisinin is stable up to 160°C, and the treated sample in the TGA pan did not show any colour change. Therefore, there is an interaction between Soluplus® and artemisinin when subjected to high temperature. The DSC thermogram of the

physical mixture did not show any thermal events. Similarly, the TGA thermogram of the physical mixture containing 50% drug loading between the temperature range of 20-50°C, and isothermal TGA carried out at 110°C and 120°C for 30 minutes, did not show any significant weight loss other than moisture loss (shown in figure 4.8 and 4.9) respectively. The TGA sample of the physical mixture (1:1) after heating upto 200°C showed slight discolouration. It is important to understand if shear has enhanced this discolouration process.

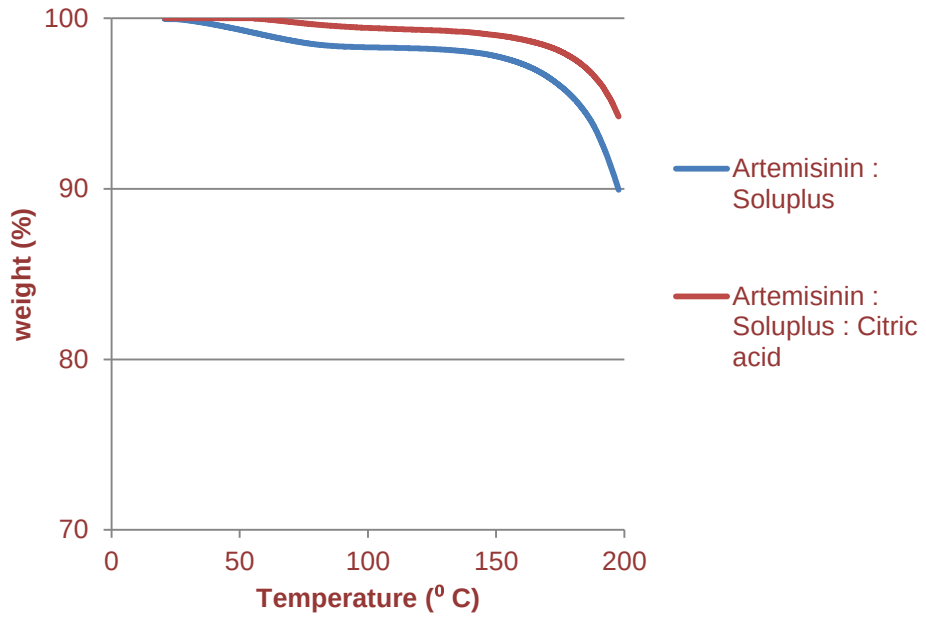


Figure 4.8 Thermo-gravimetric analysis of physical mixtures

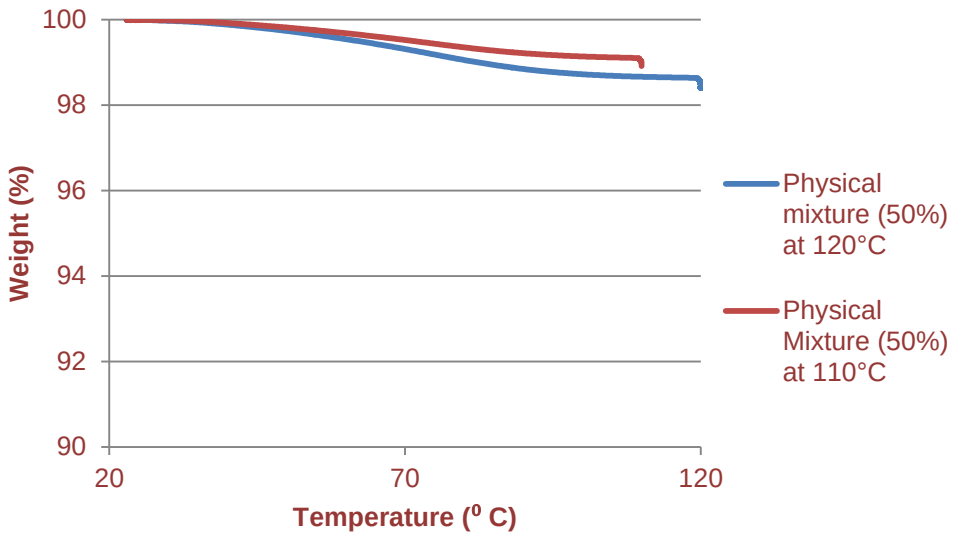


Figure 4.9 Isothermal thermo-gravimetric curves for 50% physical mixtures at 110º C and 120º C for 30 minutes

b. The rheological measurements involved heating pure Soluplus® and physical mixtures of Soluplus® and artemisinin to high temperatures under different shear conditions. This study was used to investigate discolouration separately from rheological measurements. It was observed that the Soluplus® sample did not show any discolouration whereas the physical mixture samples showed a change in colour in all cases during rheological measurements. The samples measured at 110°C were less intense in colour as those samples processed at 130°C. The shear intensity did not have any significant effect on the colour and the colour intensity of the samples increased with an increase in drug loadings. The colour change was found to occur approximately after 10 minutes of shear application. This clearly indicates that there is some interaction between the drug and polymer which causes discolouration. It also suggests that the intensity of

discolouration increases with temperature and may increase with time too.

c. It is reported that even though artemisinin itself is acidic in nature, it contains a sesquiterpene lactone ring with an unusual peroxide bridge (Eckstein *et al*., 2003). The sesquiterpene lactone ring undergoes electrochemical reduction at a basic pH. It was necessary to check if the moisture present in the polymer was producing a microenvironment with a basic pH which may cause degradation. The pH of the pure Soluplus® slurry was found to be 7.5. Soluplus® contains 2-5% (w/w) moisture which may provide an alkaline microenvironment, caused by the Soluplus® dissolving, leading to degradation. Therefore, it was decided that adding citric acid to the drug and polymer mixture may reduce the pH and reduce the number of heavy metal ions which could also potentially be responsible for the discolouration.

d. Rheology experiments were carried out with the addition of 2-5% (w/w) citric acid to the 1:1 physical mixture with the highest colour intensity. It was observed that there was no discolouration for the samples containing 5% citric acid but discolouration was not prevented by 2% (w/w) citric acid. This indicates that citric acid could have prevented discolouration by avoiding the exposure of artemisinin to an alkaline microenvironment. When the physical mixture (1:1), containing 5% citric acid, was processed at 110°C, there was a decrease in the complex viscosity for the initial 3 minutes, followed by the viscosity remaining constant (shown in figure 4.10). An attempt

was made to record the spectrum of the coloured sample in water and in ethanol separately over the UV and visible range but it did not exhibit any absorption.

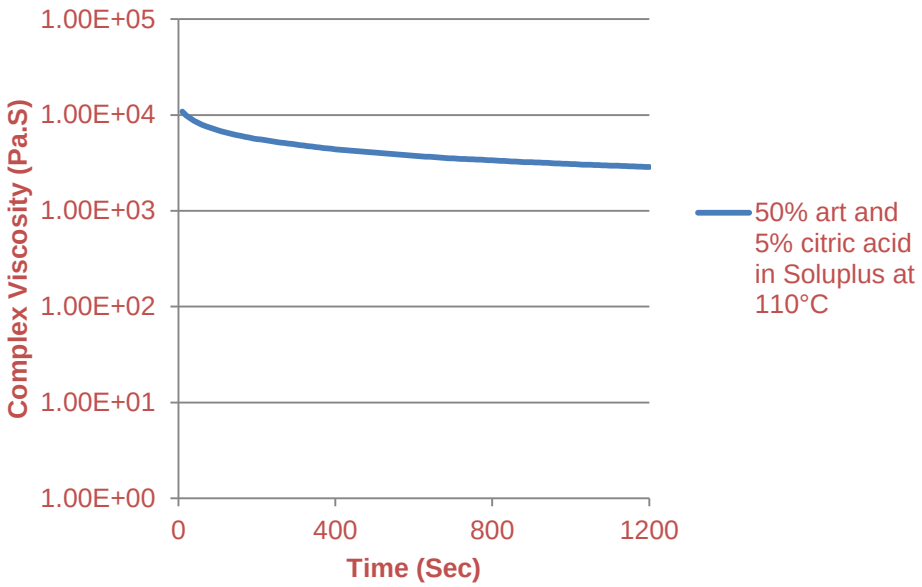


Figure 4.10 Time dependent complex viscosity of physical mixture containing 5% citric acid

e. Another approach which was adapted during extrusion was to reduce the screw length which automatically reduce the residence time and shear applied during processing. The results from this study are discussed in the next sections. The extrusion studies were conducted at 110°C, with a 1:1 (w/w) artemisinin : Soluplus® composition

f. It was important to study if there is a significant reduction in drug content as a result of processing. Artemisinin does not contain a chromophore, hence it was difficult to select a sensitive and appropriate analytical method. A UV method was selected which involved the post derivatisation. The details of the calibration curve development are as follows:

The UV method was based on the formation of an alkali salt of artemisinin (Q292) (shown in figure 4.11) formed by treatment with 0.2% NaOH at 40°C, however the product was not coloured (Wright, 2002).

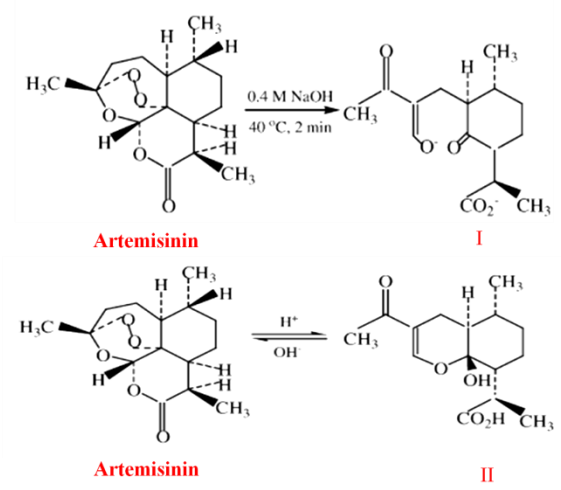


Figure 4.11 Interaction of artemisinin with NaOH

Artemisinin is highly reactive with alkalis such as NaOH and KOH, it reacts with 0.2% NaOH and forms an alkali salt (Q292) which is stable for up to 5 hours. This method is specific for artemisinin and it does not react to other artemisinin derivatives such as dihydroartemisinin, artemether and artisunate. Artemisinin was heated with the alkali at 100°C for 10 minutes which resulted in discolouration. The coloured compound has not yet been identified but it is apparent that subjecting artemisinin to an alkaline material at high temperatures may be responsible for this discolouration.

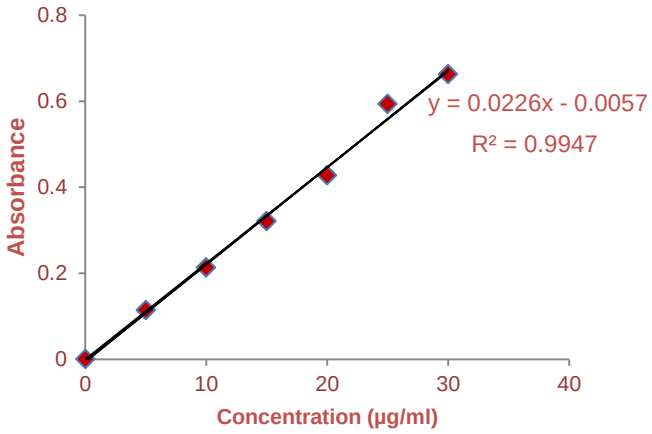


Figure 4.12 Calibration curve of artemisinin

A calibration curve was obtained using standard solutions of artemisinin (5, 10. 15, 20, 25 and 30 µg/mL) as shown in figure 4.12. This calibration curve was used to calculate the artemisinin content from the produced extrudates.

4.2.2. Preparation of solid dispersion

From the rheology experiments, non-linear data was obtained from the 50% artemisinin loaded sample, therefore a 1:1 (w/w) artemisinin: Soluplus® ratio was selected. DSC and rotational rheology can serve as simple techniques for selecting temperature profiles and extrusion was carried out at T110. The temperature profile of T110 was considered as the optimum setting, exhibiting moderate levels of torque and suitable extrudate consistency. Three extrusion batches were carried out: ArtSD1, ArtSD2 and ArtSD3. Details of these batches are summarised in Table 4.3.

Table 4.3 Summary of extruded materials

Batches	Screw configuration (shown in Table 3.3)	Proportion			Temperature Profiles (shown in Table 3.4)	Visual Observation
		Drug	Polymer	Citric acid		
ArtSD1	A (Half screw length)	1	1	-	T110A	
ArtSD2	B (Full screw length)	1	1	-	T110B	
ArtSD3	B (Full screw length)	1	0.95	0.05	T110	

4.2.3. Characterisation of extrudates

4.2.3.1. Assay

From a visual observation, it was found that ArtSD2 was darker in colour when compared to ArtSD1. However, the assay of the product was in the range of 80 to 85% and 75 to 80% for ArtSD1and ArtSD2 respectively. Therefore, the physical mixture (1:1) containing 5 % citric acid was extruded and the assay of the modified formulation ArtSD3 was found to be 103%.

Assay results are shown in Table 4.4. As ArtSD3 showed a higher drug content, this formulation was used for further characterisation.

Table 4.4 Assay results of extrudates

Batches	Average Purity (%)	Standard deviation
ArtSD1	83.30	1.85
ArtSD2	78.65	2.79
ArtSD3	103.20	3.54
Extruded artemisinin	99.33	0.57

crystals (neat)		
Extruded Soluplus® (neat)	-	-

4.2.3.2. Differential Scanning Calorimetry

The thermogram of ArtSD3 (figure 4.13) showed an exotherm at 180°C, representing the liberation of formic acid; however the material did not exhibit a melting endotherm corresponding to that of artemisinin, indicating that an amorphous state of the solid dispersion had been achieved.

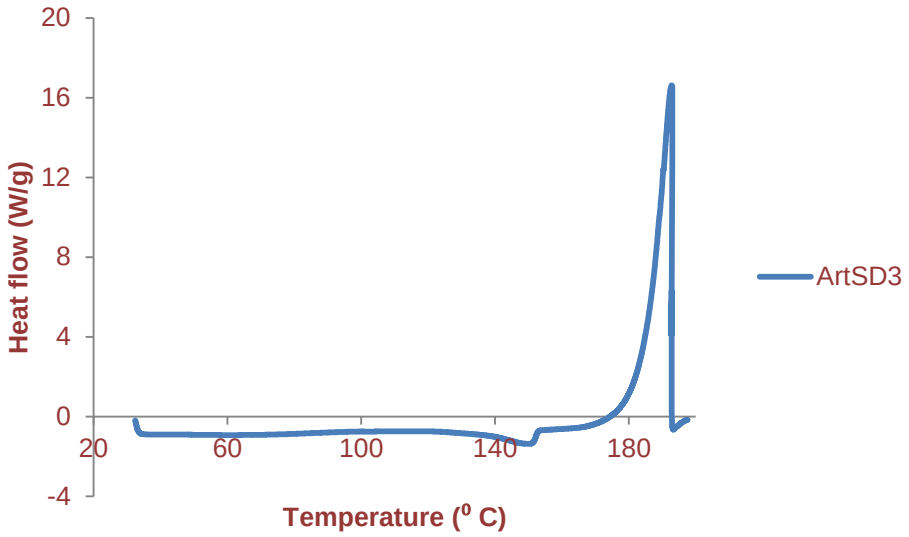


Figure 4.13 DSC curve for ArtSD3.

4.2.3.3. Powder X-ray diffraction

The effect of the processing parameters on the materials' physical properties was examined by comparing the X-ray diffraction patterns of ArtSD3 with artemisinin, Soluplus® and physical mixtures as shown in figure 4.14.

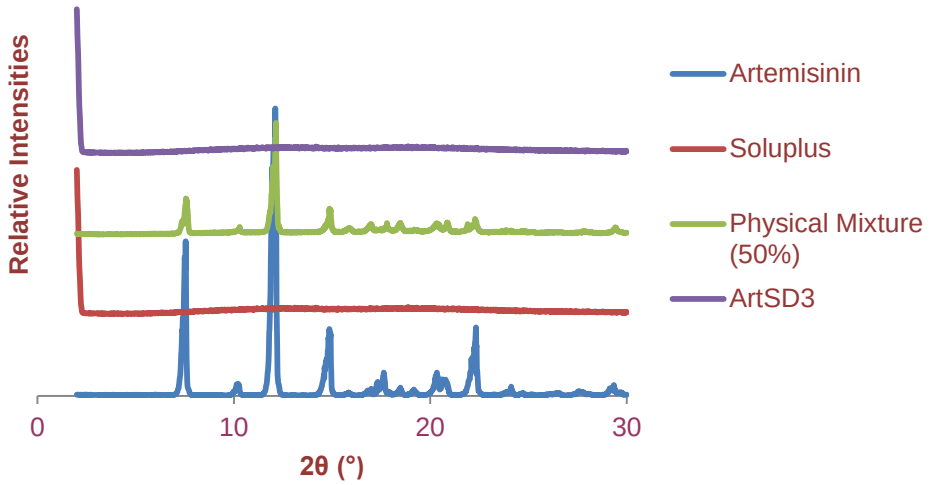


Figure 4.14 Experimental PXRD patterns of pure artemisinin, physical mixture and ArtSD3

Artemisinin exhibited characteristic peaks at 2θ of 7.5, 12, 14.5, 20.2 and 21.9 degrees, while Soluplus®, being amorphous in nature, did not show any crystalline peaks. For the physical mixture, the crystalline peaks of artemisinin were clearly observed. The complete disappearance of crystalline peaks in ArtSD3 ilustrated that the prepared solid dispersion using Soluplus® was transformed into an amorphous state. The intensity of the crystalline peaks was low for the physical mixture when compared to those for pure artemisinin. This signifies that the presence of Soluplus® had no influence on the physical state of artemisinin.

4.2.3.4. In-vitro dissolution study

The pharmaceutical performance of the extrudates was investigated by *in-vitro* dissolution tests and compared with the pure drug and physical mixture, as shown in figure 4.15.

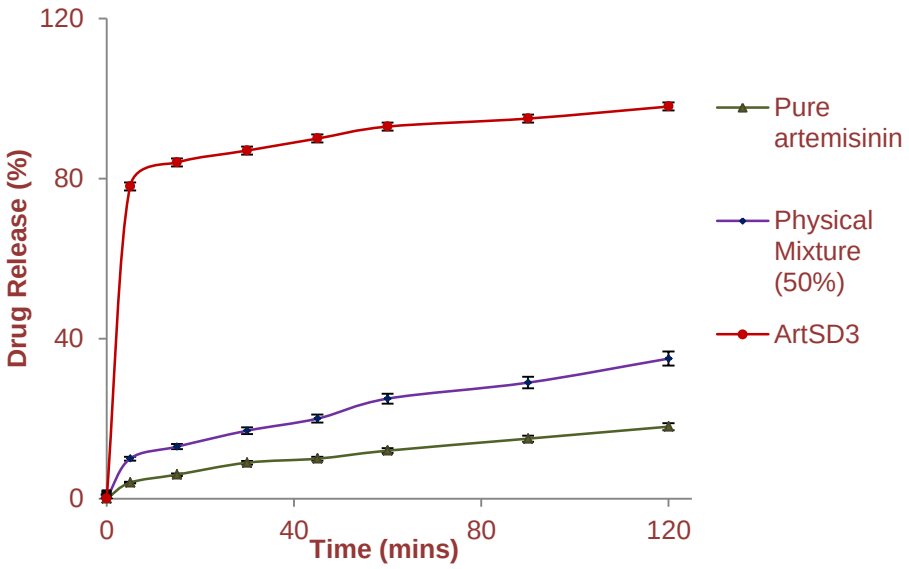


Figure 4.15 Drug release rates from pure drug, physical mixture of drug and polymer and ArtSD3

The dissolution profile of ArtSD3 was approximately five times higher compared to that of the pure drug. The dissolution rate of the physical mixture was greater than that of pure artemisinin, although not considerably. In the first 45 minutes, 92% of the drug was released from ArtSD3 which is presumably due to transferring the crystalline state to the amorphous state resulting in a higher dissolution rate. In 60 minutes, 75% drug release was achieved from the solid dispersions of artemisinin with PVP (1:5 ratio), prepared by supercritical fluid technology (Nijlen *et al*., 2003). Niijlen *et al*. prepared solid dispersions of artemisinin in a polyvinylpyrrolidone(PVP) K25 polymer carrier using a solvent evaporation method. This experiment was performed in dichloromethane and the solvent was removed by rapid evaporation at 45°C under low pressure. As a solvent based technique, this batch process was complicated to scale up. Therefore, Soluplus® can be said to be equally effective in improving the dissolution rate of artemisinin.

4.2.3.5. Pharmacokinetic study

To validate the *in-vitro* results, *in-vivo* experiments were performed. The bioavailability of pure artemisinin and ArtSD3 were studied in Albino rats.This was done to verify the correlation between the *in-vivo* data and the data obtained by the *in vitro* dissolution method.

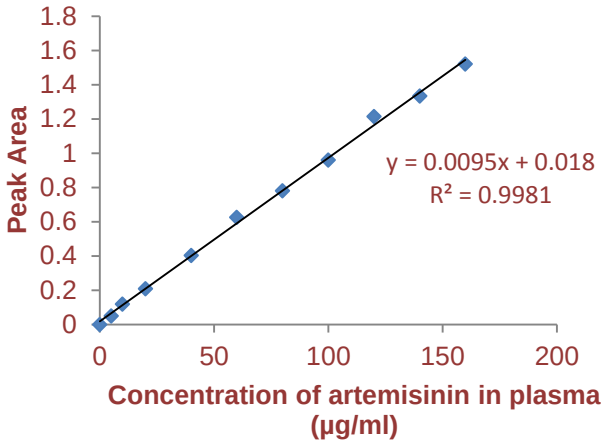


Figure 4.16 Artemisinin calibration curve in plasma

A calibration curve was obtained using standard solutions of artemisinin in plasma (5, 10, 20, 40, 60, 80, 100, 120, 140 and 160 µg/ml). Figure 4.16 shows the calibration curve, the equation for the best-fit line and regression coefficient value. This calibration curve was used to calculate the amount of artemisinin present in plasma.

Twelve rats were used for each formulation and samples were analysed once. The plasma concentration against time curve was obtained after the oral administration of the formulations. The plasma concentrations for pure artemisinin and ArtSD3 are displayed in Table 4.5 and 4.6 respectively. The plasma concentration of artemisinin and ArtSD3 were 18.33 µg/ml and 42.59

µg/ml. The plasma concentration of ArtSD3 clearly shows the enhanced bioavailability of ArtSD3 compared to that of the pure drug.

The maximum artemisinin concentration in the plasma reached by ArtSD3 demonstrated a better release in the amorphous state (shown in figure 4.17). A typical chromatogram of a rat plasma sample spiked with 120 µg/ml artemisinin, with a retention time of (RT) 9.96 and an internal standard artemether RT of 16.68 is shown in Figure 4.18. The areas under the curves for both pure artemisinin and ArtSD3 are shown in table 4.7.

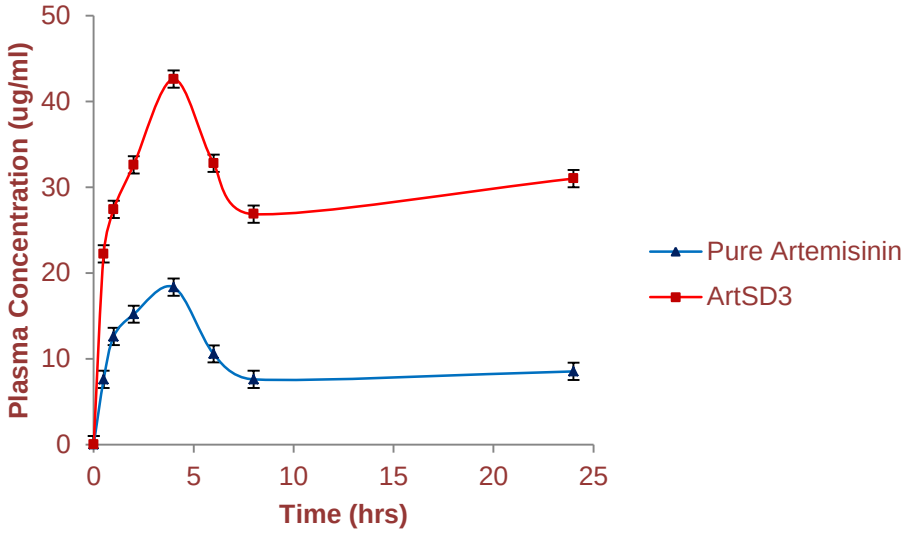


Figure 4.17 Plasma concentration after oral administrating pure artemisinin and ArtSD3

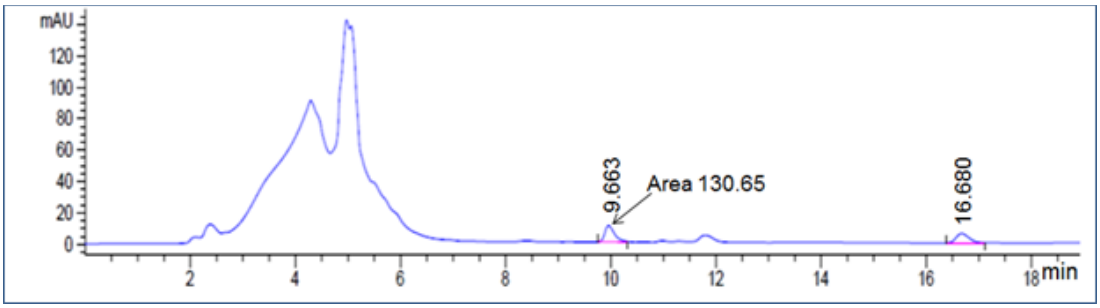


Figure 4.18 A typical chromatogram of a rat plasma sample spiked with 120 µg/mlartemisinin RT 9.96 and internal standard artemether RT 16.68

Artemisinin is a Biopharmaceutical classification system (BCS) class II drug meaning that it has low solubility and high permeability. It has been reported that artemisinin has only 8-10% bioavailability (Balint *et al*., 2001), a short half-life and a high first pass metabolism. These properties contribute to partial parasite removal, resulting in artemisinin recrudescences (Titulaer *et al*., 1991).

Table 4.5 Plasma concentration of pure artemisinin

Plasma Concentration of pure artemisinin(µg/ml)							
Time(h)	Rat 1	Rat 2	Rat 3	Rat 4	Rat 5	Rat 6	Mean
0	0	0	0	0	0	0	0
0.5	7.78	6.67	7.78	7.78	8.89	6.67	7.59
1	15.56	8.89	10	11.11	12.22	17.78	12.59
2	31.11	8.89	10	11.11	12.22	17.78	15.18
4	18.89	17.78	20	18.89	17.78	16.67	18.33
6	16.67	12.22	10	8.89	7.78	7.78	10.55
8	10	7.78	7.78	6.67	6.67	6.67	7.59
24	8.89	10	8.89	6.67	7.78	8.89	8.51

Table 4.6 Plasma concentration of ArtSD3

Plasma Concentration of ArtSD3 (µg/ml)							
Time(h)	Rat 1	Rat 2	Rat 3	Rat 4	Rat 5	Rat 6	Mean
0	0	0	0	0	0	0	0
0.5	22.22	24.44	21.11	22.22	23.33	20.00	22.22
1	27.78	26.67	26.67	26.67	28.89	27.78	27.41
2	33.33	31.11	28.89	34.44	32.22	35.56	32.59
4	43.33	41.11	45.56	41.11	42.22	42.22	42.59
6	26.67	33.33	35.56	32.22	33.33	35.56	32.78
8	20.00	23.33	28.89	27.78	30.00	31.11	26.85
24	13.33	18.89	20.00	18.89	20.00	17.78	18.15

Jinadasa et al. have observed that the absorption of artemisinin is poor and negligible when it reaches the lower gastrointestinal (GI) tract; specifically the

colon (Jinadasa *et al*., 1996). Thus, enhancing the solubility of artemisinin could ensure better drug dissolution in the upper GI tract, greater bioavailability and in turn, reduced chances of recrudescence. A rapid dissolution rate and hence absorption could lead to enzyme saturation during the first pass in the liver, resulting in a higher fraction of unmetabolised drug entering the systemic circulation, compared to a slower rate of drug dissolution. Many attempts have been made to improve the dissolution rate of artemisinin but ultimately these have not been successful due to process complexity and cost constraints. Though cyclodextrin complexation resulted in a threefold improvement in solubility which doubled the bioavailability (Titulaer *et al*., 1991), the proposed formulation was 'bulky' because a 1:1 molar ratio was used.

Table 4.7 Area under curves for pure artemisinin and ArtSD3

Rats	Pure artemisinin (µg.hr/ml)	ArtSD3 (µg.hr/ml)
Rat 1	47.01	127.15
Rat 2	58.33	147.22
Rat 3	37.77	164.03
Rat 4	32.56	157.64
Rat 5	34.65	165.49
Rat 6	55.83	165.49

ArtSD3 showed a three-fold increase in AUC compared to pure artemisinin. The average C_{max} concentration (maximum plasma concentration) for artemisinin and the ArtSD3 were 16µg/ml and 40µg/ml respectively, whereas T_{max} (Time to reach C_{max}) was 4 hours for both.

4.2.3.6. Stability study

Although an interest in solid dispersions is growing rapidly, the commercialisation of solid dispersions in the pharmaceutical industry is limited. In three decades, only two solid dispersion formulations have been marketed: griseofulvin with polyethylene glycol and nabilon with polyvinylpyrrolidone (Serajuddin *et al.,* 1999). The formulation stability is a major issue for solid dispersions owing to phase separation. There are also chances of crystallisation occurring during storage as the drug is molecularly dispersed (Ford *et al.,* 1986). Shibata et al. proposed that moisture might affect the physical stability of solid dispersions due to the crystallisation of the amorphous drug (Shibata *et al.,* 2013). In addition, some carriers can exist in thermodynamically unstable states in solid dispersion forms and hence suffer from stability problems (Serajuddin *et al*., 1999).

The obtained solid dispersion (ArtSD3) was stored at room temperature and a stability study was performed at various intervals immediately after extrusion: 1 day, 1 week, 1 month, 3 months, 6 months, 9 months, 12 months and 24 months by DSC, PXRD and *in-vitro* dissolution. The DSC thermograms, PXRD patterns and *in-vitro* dissolution profiles of the respective extrudates were similar to the original data. The PXRD patterns of ArtSD3 at 1 month, 3 months, 6 months, 9 months, 12 months and 24 months are shown in figure 4.19. There was no variation in the result due to time, which proves that the stability of the HME prepared artemisinin: Soluplus® solid dispersions.

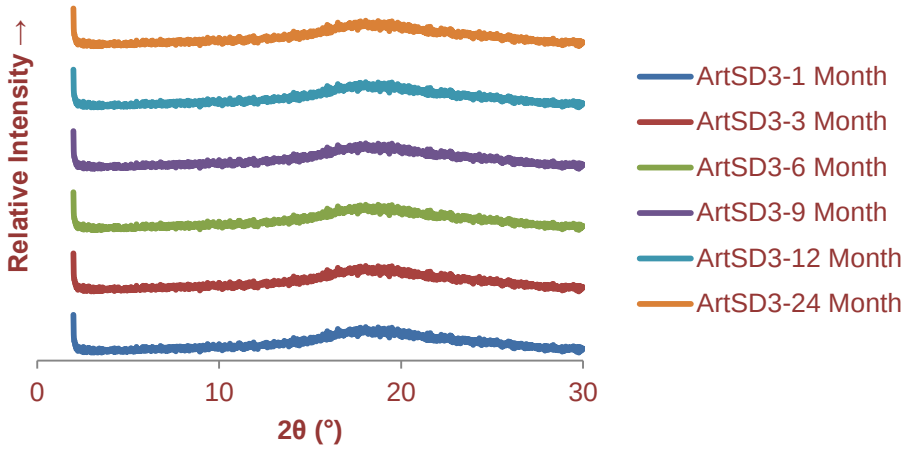


Figure 4.19 PXRD patterns of ArtSD3 at different time intervals

4.2.4. Summary of chapter

It is clear that the processing of thermolabile drugs is one of the most challenging and convoluted aspects of HME. Intensive shear and high temperatures are potential drawbacks of HME, but the introduction of twin screw extruders allows different screw designs for various pharmaceutical applications and the availability of wide range of polymers can help to overcome the problem. Polymer selection and screw geometry have been considered as the primary parameters for the extrusion experiments carried out. The compatibility of artemisinin and Soluplus® was initially studied using rotational rheology. These primary studies formed the background set conditions for the processing of artemisinin. However, the batch processed using a half length screw (ArtSD1), exhibited only 87% drug content and it was difficult to quantify the degradation in the ArtSD1 and ArtSD2. Citric acid was found to suppress the degradation of the drug at the processing temperature by maintaining a neutral microenvironment.

The release rates of the drug were significantly improved compared to the pure drug and the physical mixture or drug and polymer, in both *in-vitro* and *in-vivo* studies. The system was shown to be stable up to at least 24 months, highlighting the potential for the enhancement in delivery of this important but difficult API.

This work has demonstrated that the extrusion of a thermolabile drug, with the amphiphilic polymer Soluplus® and a small amount of citric acid, can lead to a stable and soluble solid dispersion.

5. Polymorphic transformation using high temperature extrusion

This chapter reports a novel solvent free method to generate and stabilise metastable forms of APIs. The stability of the metastable form obtained by high temperature extrusion is greater than that of polymorph prepared using a solvent based technique. A schematic presentation of the chapter is shown in figure 5.1.

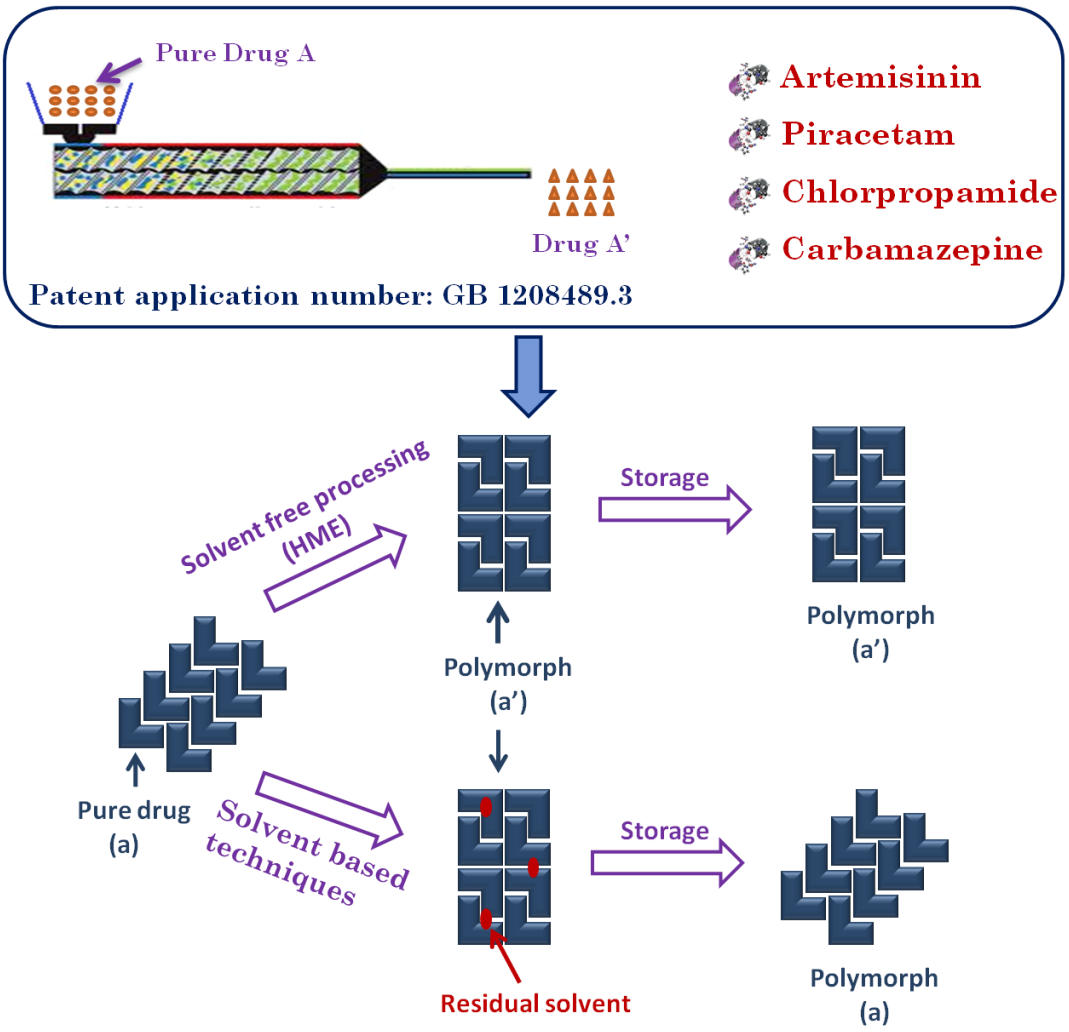


Figure 5.1 A schematic presentation of the chapter

5.1. Introduction

There is a drive within the pharmaceutical industry to explore the use of metastable polymorphs of drugs whose most stable form has low solubility, low bioavailability, intellectual property (IP) issues, manufacturing difficulties or chemical instability (Hilfiker *et al*., 2006). However, it is known that in solution, although the less stable forms nucleate first due to a higher nucleation rate, they transform through any available pathways to more energetically stable forms (Davey *et al*., 1997; Schroer *et al*., 2003 and Zhang *et al*., 2004). The presence of solvent often enables such transformations and consequently, it may be difficult to isolate the metastable polymorph before it undergoes solvent mediated transformation. Various attempts have been made to disrupt the growth of the stable form using additives (Gu *et al*., 2002) or structurally similar substrates (Mitchell *et al*., 2001). Such methods raise additional issues as they are inherently time consuming, expensive and restricted to small scale screening applications.

Seeding a solution is a well known approach to crystallise a metastable form (Beckmann *et al*., 2000). Even so, some associated concerns must be considered such as the selection of a reliable method for generating seed crystals, the temperature range of the metastable zone for harvesting, and the requirement for thorough drying (Deegan *et al*., 1997). Another approach is contact line crystallisation, which Capes et al., employed to produce the metastable polymorph of paracetamol (Form II) (Capes *et al*., 2007). Although Form II had been previously grown by several routes, the method of Capes et al. generated crystals of Form II which remained stable and did not revert to the most stable polymorph, Form I. In this method,

crystallisation takes place on the receding miniscus of an evaporating solution. The conditions reduce the possibility of solvent mediated transformation since the crystals are continually removed from solution and the amount of solvent is lowered by evaporation. These findings suggest that metastable forms may be produced in a solvent free environment, since kinetic pathways to the stable form are unavailable. This potentially useful method of forming metastable crystals is however, difficult to scale up.

Here, application of high temperature extrusion (HTE) was explored to produce solvent-free metastable drug forms. Though the HTE technique is similar to hot melt extrusion, it operates below the melting point of the API. This is the first application of such a method to the control of polymorphic transformation. Different APIs such as artemisinin, piracetam, carbamazepine, chlorpropamide, paracetamol and theophylline were processed using this method. From these, successful polymorphic transformation was achieved in artemisinin, piracetam, chlorpropamide and carbamazepine. The major focus of the work presented in this chapter is the polymorphic transformation of artemisinin; however transformations of a wider range of APIs have also been included as part of the investigation of the HTE process.

Artemisinin exhibits two polymorphic forms; orthorhombic and triclinic, as shown in figure 5.2. The commercially available orthorhombic form is considered to be thermodynamically more stable and has lower water solubility whilst the metastable triclinic form has a higher dissolution rate and has a tendency to undergo solvent mediated transformation (Chan *et al*., 1997).

The HTE process has been used to produce crystals of the triclinic form of artemisinin which remained stable for over two years, by applying a combination of controlled temperature and shear. Attempts have also been made to understand the mechanisms causing this transformation.

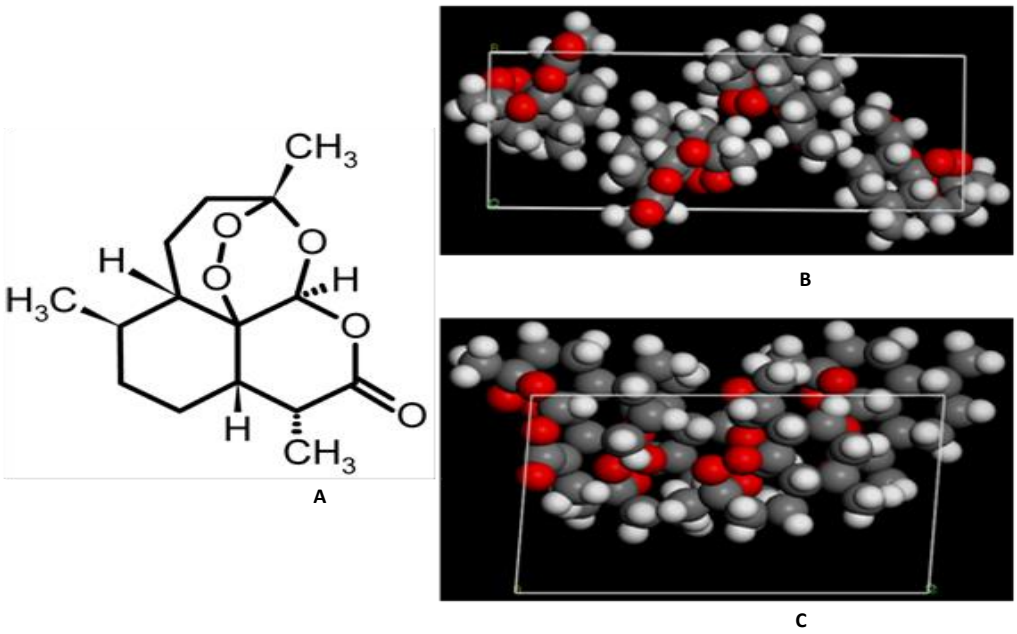


Figure 5.2 A shows the molecular structure of artemisinin, B the orthorhombic form of artemisinin (space group $P2_12_12_1$) and C the triclinic form (space group P^1).
Crystal data for artemisinin
Orthorhombic: $P2_12_12_1/n$, a = 24.08Å, b = 9.44Å, c = 6.36Å and R- *factor* = 0.075
Triclinic: $P1/n$, a = 9.89 Å, b = 15.34 Å, c = 9.88 Å, α = 90.92, β = 102.99, γ = 93.24 and R *factor* = 0.052

5.2. Result and discussion

As reported in the previous chapter, the stability of artemisinin at high temperature and shear was a potential issue during HME and as such was the subject of further investigation. Whilst addressing this discolouration issue in solid dispersions, extrusion of artemisinin crystals and physical mixtures were performed at 130ºC. It was observed that one of the extruded materials showed an additional PXRD peak at 2θ:7.89 (displayed in figure 5.3) which was found to be a characteristic peak of the triclinic form of

artemisinin. This surprising observation acted as a seed for further investigations and the subsequent development of HTE for polymorphic transformations.

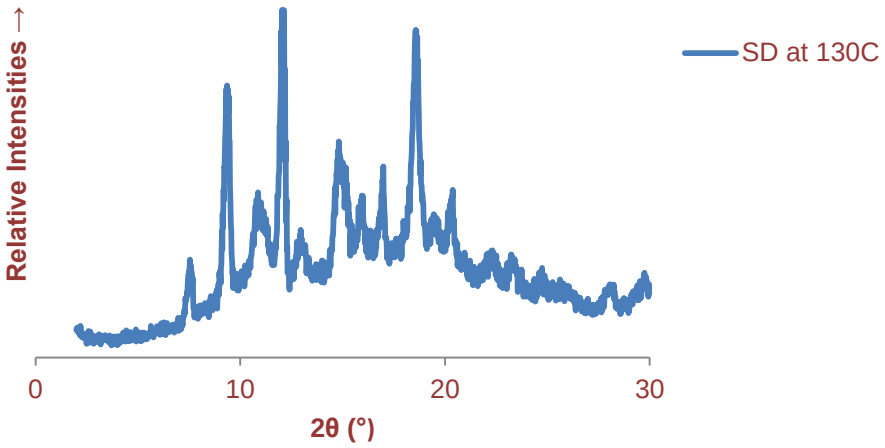


Figure 5.3 Experimental PXRD patterns of extruded artemisinin and Soluplus® at 130º C. Red arrow indicates the characteristic peak of the triclinic form of artemisinin 2θ: 7.89

5.2.1. Preliminary screening

Preliminary screening was performed using hot stage microscopy and a model shear cell.

5.2.1.1. Hot Stage Microscopy

Isothermal hot stage microscopy experiments were performed to determine whether thermal treatment alone was able to cause complete polymorphic transformation of artemisinin crystals. Orthorhombic crystals of artemisinin were subjected to isothermal heating at 140°C on a hot stage for 90 min and changes in form were recorded. Images were collected periodically and the product at the end of the experiment was collected and characterised by PXRD (shown in figure 5.4). PXRD results for the orthorhombic and triclinic

polymorphs indicated the ratio of the peak intensities at 2θ=9.95 and 7.80 respectively can be used to estimate the fraction of triclinic polymorph present. The PXRD pattern of the product showed a small peak at 2θ=9.95; characteristic of the triclinic form dominated by the orthorhombic peaks.

The orthorhombic to triclinic phase transformation was observed to occur slowly on a hot stage when isothermal conditions were maintained at 140°C. Fine orthorhombic crystals were seen to disappear gradually while thicker, plate-shaped crystals started to appear during polymorphic transformation. After a longer period at 140°C the orthorhombic crystals underwent sublimation. Recorded images are shown in figure 5.5 (a), (b) and (c). During this process of transformation an intermediate vapour phase was observed as the triclinic plates were growing at the expense of contracting orthorhombic fine crystals. Similar vapour phase polymorphic transformation has been observed in the case of venlafaxine hydrochloride (Roy *et al.,* 2007). The intensity of the thick, plate-like crystals increased and there was a partial transformation into the triclinic form. Complete polymorphic transformation was not achieved at high temperature; in fact many pharmaceutical materials subjected to higher temperatures over a long period of time are likely to suffer degradation.

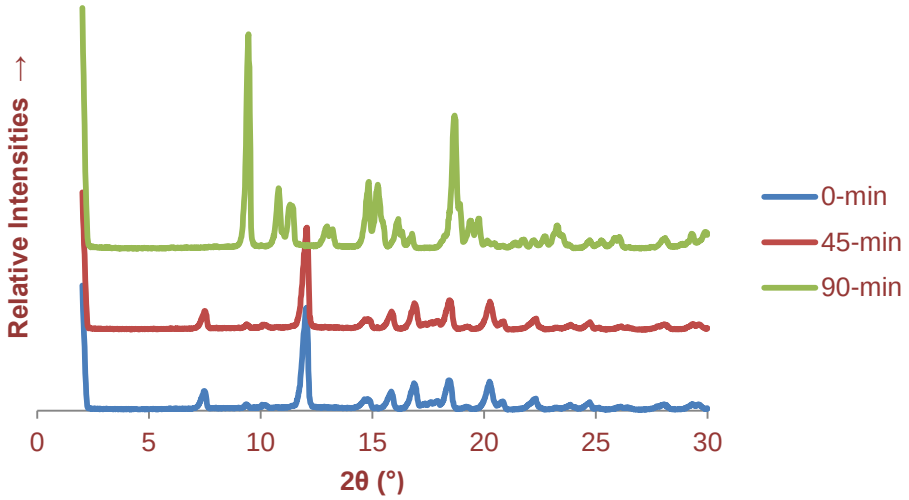


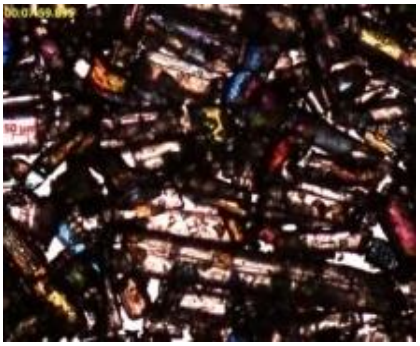
Figure 5.4 Experimental PXRD patterns of thermally treated material at different intervals

A

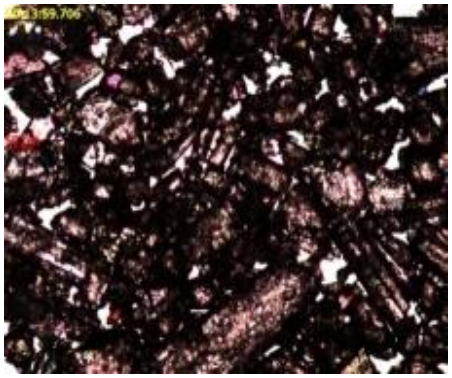
B

C

D



E



F

Figure 5.5 Microscopy images during isothermal heating of orthorhombic crystals at 140°C (A) 0 min, (B) 45 min and (C) 90 min; during isothermal heating of orthorhombic crystals at 140°C and with 0.5 s^{-1} shear rate (D) 0 min, (E) 8 min and (F) 15 min.

In order to confirm that polymorphic transformation was taking place through vapor phase sublimation, experiments were carried out using a sublimation unit. Orthorhombic crystals were heated at 145°C. After 90 minutes a new crystal phase started growing on the condensing surface (shown in figure 5.6). The PXRD patterns confirmed that the collected sublimed crystals were the triclinic form. The PXRD pattern of the powder collected from the lower vessel showed partial transformation to the triclinic form (figure 5.7).

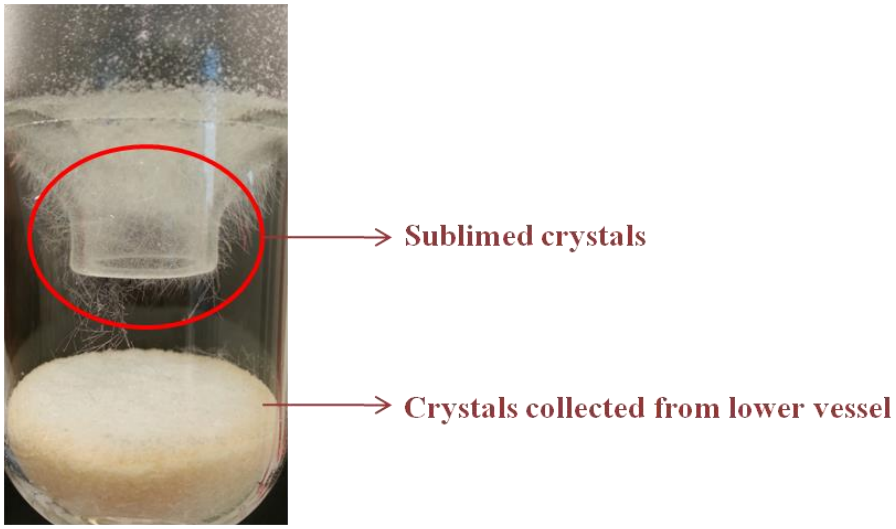


Figure 5.6 Polymorphic transformation of artemisinin crystals by sublimation

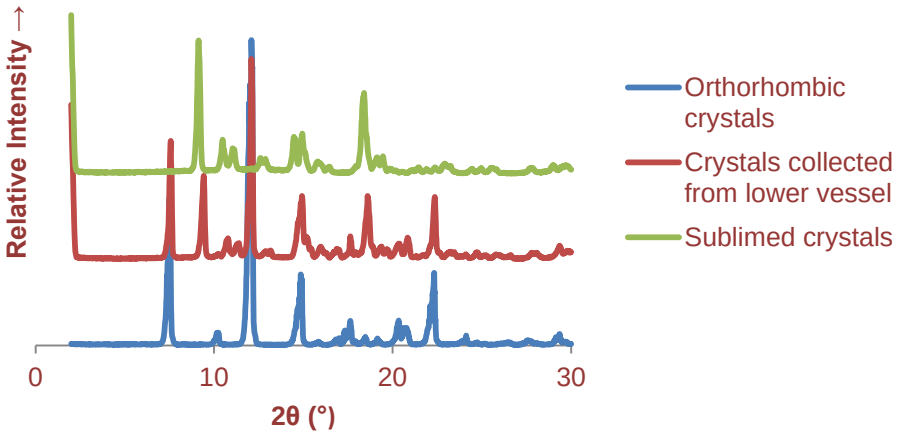


Figure 5.7 Experimental PXRD patterns of orthorhombic form, sublimed crystals and crystals collected from lower vessel

Therefore, a combination of shear and temperature was applied in order to achieve complete polymorphic transformation.

5.2.1.2. Shear Cell

The next experiment was performed to investigate the effect of temperature and shear using a shear cell. Initial results indicated that transformation was not complete when artemisinin was exposed to high temperature alone. The shear cell provided an opportunity to study material state under model shear

conditions and has been widely used in polymer research to study flow and shear enhanced crystallisation. The structural dynamics of complex fluids can be directly monitored via a standard optical microscope while subject to precisely controlled temperature and various shear modes. Shear cell microscopy was performed using a Linkam shear cell (CSS450) coupled with a polarised light microscope connected to a video capture system. The orthorhombic form of artemisinin was loaded between the top and bottom of highly polished quartz windows of the shear cell and the gap between the two plates was reduced to 30µm by slowly lowering the upper glass plate of the Linkam device. The sample was isothermally heated at 140° C for 15 min and a steady shear rate of 0.5 s^{-1} maintained. Treated samples were collected periodically and analysed by PXRD (shown in figure 5.8). Interestingly, complete transformation to the triclinic form was observed after only 13 minutes. The captured images are shown in figure 5.5 (d), (e) and (f). No polymorphic transformation was observed at lower shear rates. It was not possible to track individual crystals of artemisinin since during continuous shear the breakdown of crystals and vapour phase transformation occurred simultaneously. In this process the applied mechanical shear stress continually disrupts the crystalline structure which leads to the formation of new surfaces being continuously exposed to high temperatures. The process of transformation is therefore accelerated under high temperature and shear.

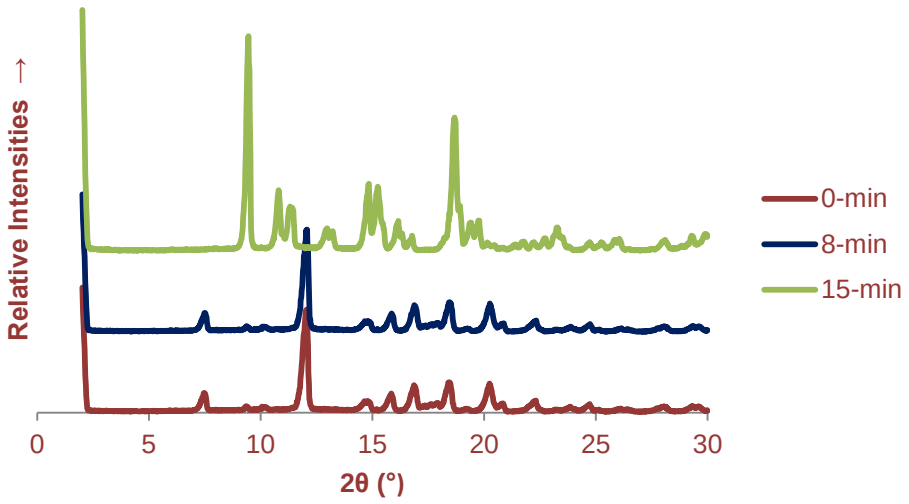


Figure 5.8 Experimental PXRD patterns of the material treated in shear cell

5.2.2. High temperature extrusion of artemisinin

For high temperature extrusion, temperatures of 120 and 140°C were selected to avoid melting or degradation because of any rise in temperature in the extrusion process due to viscous shearing. The product of a series of extrusion experiments were analysed using PXRD. Results are summarised in figure 5.9 which shows that the temperature profile T140, screw rotation speed of 20 rpm and a high shear intensity screw configuration caused almost total conversion to the triclinic form. The residence time during extrusion was generally 10 – 15 minutes depending on the screw geometry and set screw rotation speed. Generally speaking both higher shear intensity and higher set temperature resulted in improved conversion levels. Precise levels of shear intensity provided by HTE could not be quantified, although different intensities were achieved by modification of extruder screw geometry.

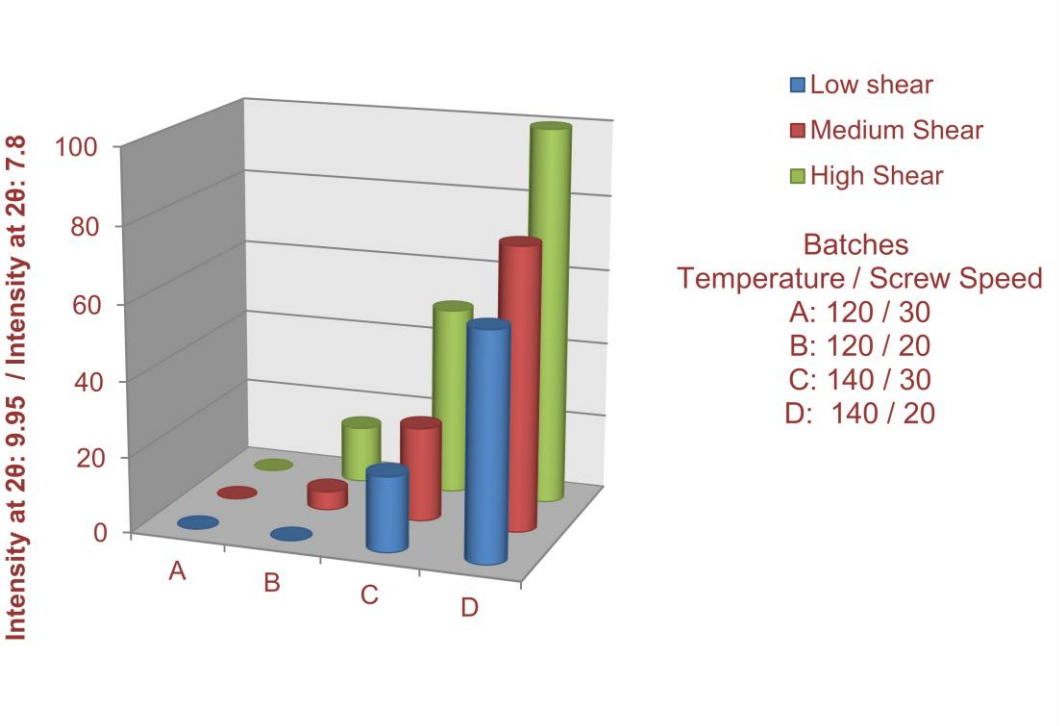


Figure 5.9 Effect of temperature and shear on residual polymorph

5.2.3. Characterisation of the extruded products

5.2.3.1. Powder X-ray diffraction

The generation of a triclinic polymorph was confirmed by PXRD analysis. The PXRD pattern of orthorhombic form exhibited peaks at 2θ: 9.45, 2 θ: 18.5, 20: 14.95 and 20: 15.09 whereas the triclinic form exhibited peaks at 2θ:7.89, 20: 12.1 and 20: 15.34. These PXRD patterns were confirmed from the Cambridge Crystallographic Database as corresponding to orthorhombic and triclinic form respectively (shown in figure 5.10).

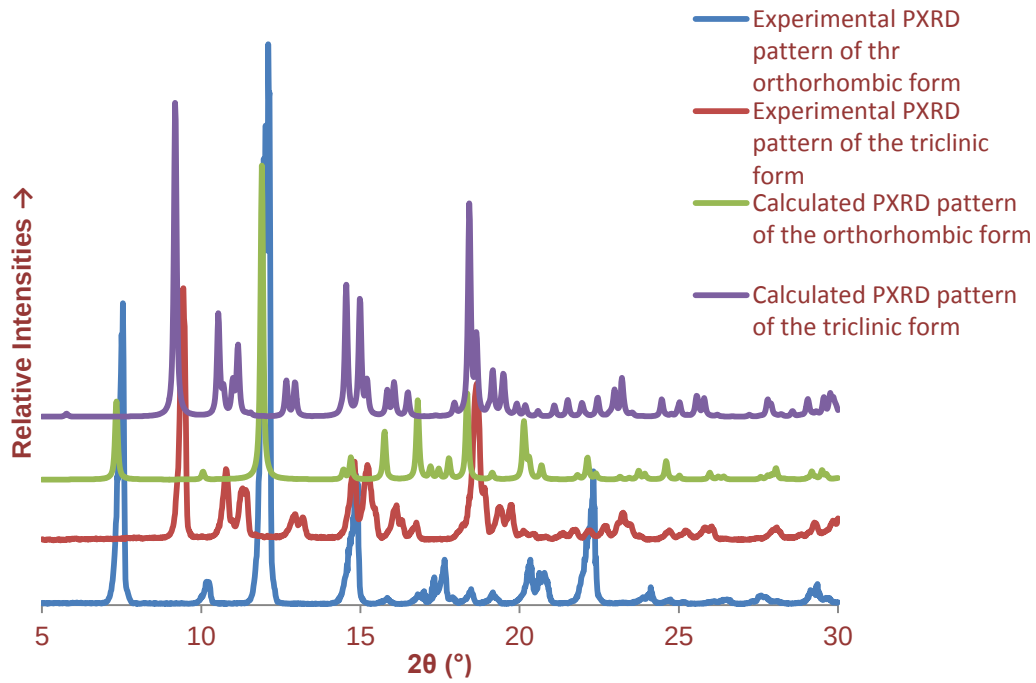


Figure 5.10 Experimental and calculated PXRD patterns of orthorhombic and triclinic polymorphs of artemisinin

5.2.3.2. Differential scanning calorimetry

DSC analysis of the orthorhombic form of artemisinin showed two melting endotherms sharp peak at 154.81°C while the processed artemisinin showed only one melting endotherm at 154.75°C corresponding to the triclinic form (displayed in figure 5.11).

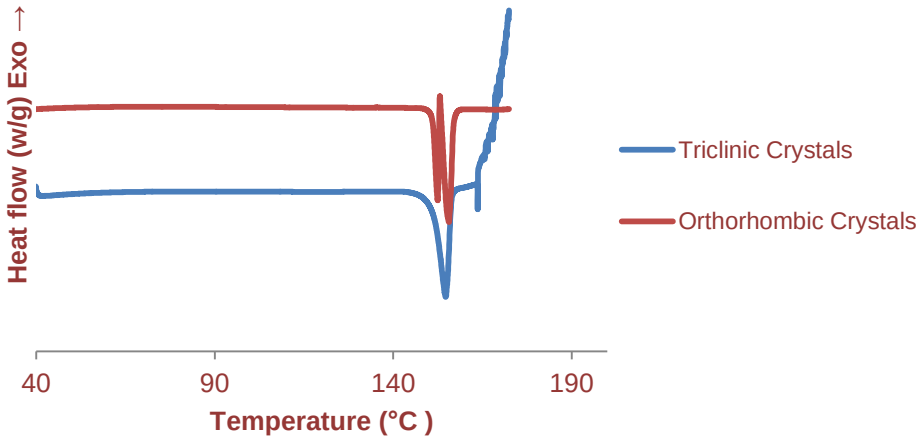


Figure 5.11 DSC curves of triclinic and orthorhombic artemisinin

The enthalpy for melting of the triclinic form was 82.85 J g^{-1} and for the orthorhombic form 82.91 J g^{-1}. The thermal data did not provide any information about stability of two polymorphs.

5.2.3.3. Fourier Transform Infrared Spectroscopy

FTIR spectra for both unprocessed and processed artemisinin were similar (shown in figure 5.12). The spectra for triclinic crystals were broader than the orthorhombic crystals in the range between 2845 to 3000 cm^{-1} and 1300 to 1500 cm^{-1}. This observation is also similar with a report by Chan *et al*. (Chan *et al*., 1997).

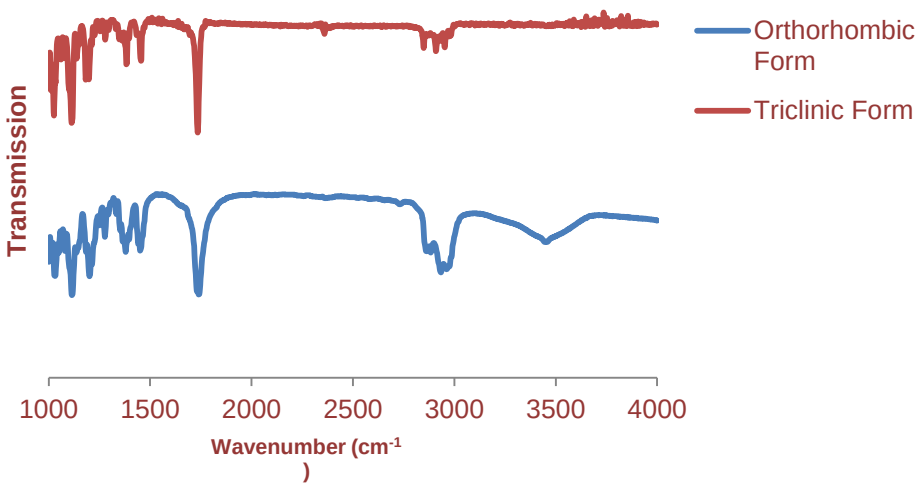


Figure 5.12 FTIR spectra of the orthorhombic and triclinic forms of artemisinin

5.2.3.4. High performance liquid chromatography: Mass Spectrometry

The HPLC method using a UV detector was described in an artemisinin monograph without any derivatisation but has limited sensitivity. HPLC-MS is a sensitive technique which is capable of detecting impurities which were not observed in HPLC-UV method. The use of mass spectroscopy permitted an accurate detection of molecular formula. For orthorhombic artemisinin, the

chromatogram showed a high resolution of mass spectrum at 283.2 ion corresponding to the molecular formula $C_{15}H_{23}O_5$. Additional peaks were obtained at 324.4, 265.1, 237.1 and 300.3 related to [M+Na], loss of water, loss of water and CO and loss of water and two CO respectively (Stringham *et al*., 2009). The mass spectra obtained for the triclinic form was identical to the orthorhombic form. The retention time for the orthorhombic form was the same as the retention time of the triclinic form i.e. 8.23 and 8.24 minutes respectively with a well-shaped peak, this result demonstrated the purity of extruded artemisinin (displayed in figure 5.13). Lin *et al*. has reported that artemisinin degrades when exposed to temperatures of 150°C for approximately 15 minutes and this thermally decomposed artemisinin shows numerous additional peaks of $C_{14}H_{21}O_3$ ion. In this decomposed product, the spectrum at 283.2 disappears and shows a largest peak at 237.15 but artemisinin shows both spectra. It is also stated that retention time shifts from 6.5 to 7.3 minutes for thermally degraded artemisinin (Lin *et al*., 1985). These two observations are indicative of the formation of 100% triclinic artemisinin without any degradation.

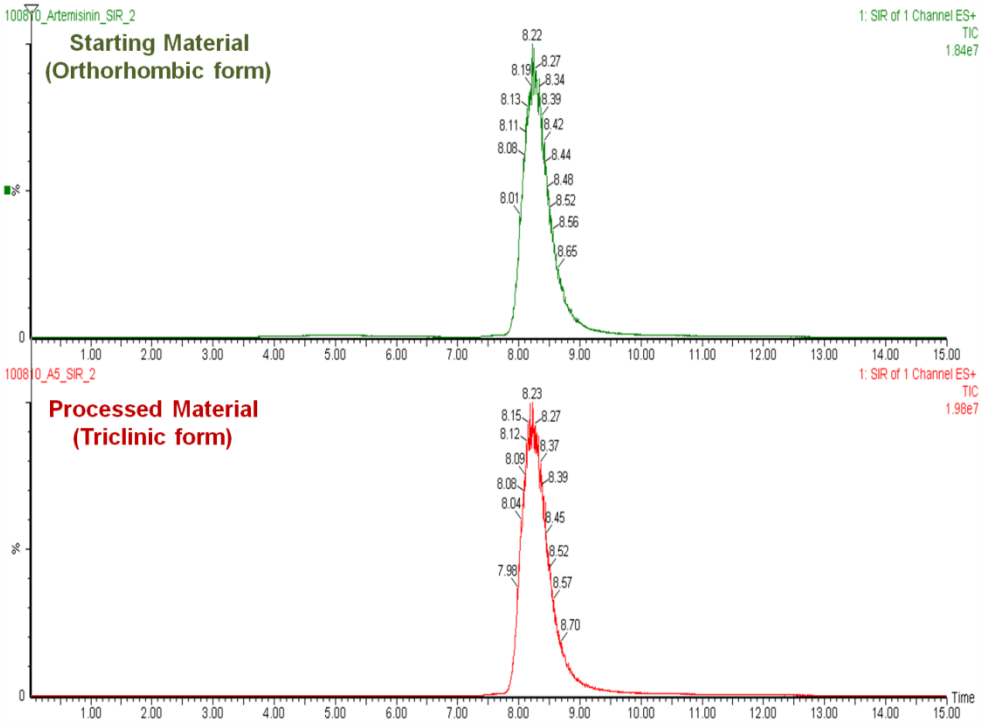


Figure 5.13 LCMS spectrum for orthorhombic and triclinic artemisinin

5.2.3.5. Density Determination

True density was measured for artemisinin polymorphs using helium pycnometry in triplicate and an average was calculated. True density for the orthorhombic and the triclinic forms were found to be 1.298 gm/ml and 1.286 gm/ml respectively. These values were similar to the densities reported by Chan et al (Chan *et al.*, 1997) as summarised in Table 5.1. The measured true density correlates with Burger and Ramberger who stated that a solid form with higher density will be more stable at 0 K, compared to the solid form with the lower density (Burger *et al.,* 1979).

Table 5.1 Densities of artemisinin polymorphs

Forms	True Density (gm/ml) (Measured)	True Density (gm/ml) (Reported)
Orthorhombic	1.298	1.294
Triclinic	1.286	1.286

5.2.4. Stability of the triclinic crystals

The stability of crystals of the triclinic form produced by extrusion was compared to those produced by recrystallisation. Orthorhombic crystals were recrystallised from cyclohexane at 80°C and the triclinic crystals were obtained by vacuum drying. PXRD was used to monitor transformation to the orthorhombic form. It was observed that the triclinic form obtained by the solvent method transformed into the orthorhombic form within a week when stored at room temperature (PXRD patterns are shown in figure 5.14). To obtain further insight, traces of solvent in the crystal were measured by gas chromatography. The residual solvent of cyclohexane was found to be 1.25% by volume. This suggests that even minor traces of a solvent may be enough to cause solvent mediated transformation. In contrast the triclinic form obtained from the solvent free extrusion method was found to be stable for more than two years.

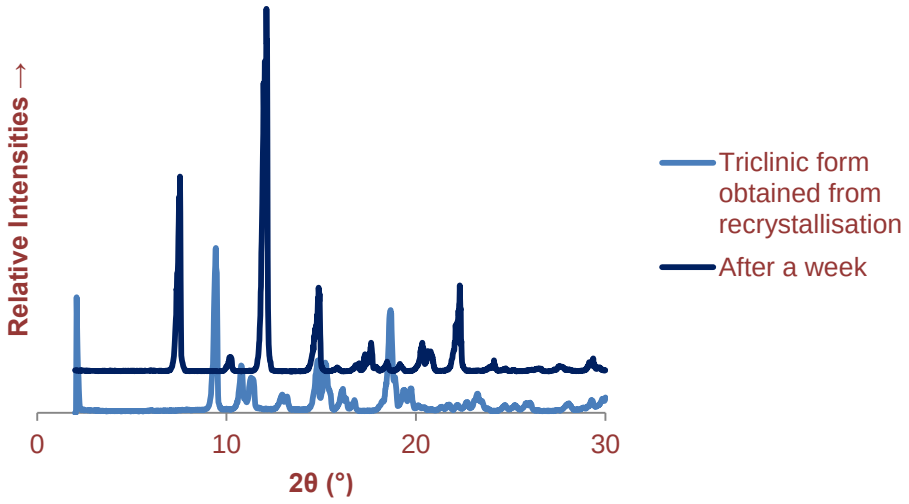


Figure 5.14 Experimental PXRD patterns of the triclinic form obtained from recrystallisation

The impact of different solvents; acetone, ethanol, methanol and water on the extruded triclinic form were studied. 0.1ml of solvent was mixed with 3g of extruded triclinic material. PXRD patterns were recorded every day for a month and then once a month for a period of 15 months. PXRD patterns of each sample showed rapid transformation to the orthorhombic form, except for the sample with water as a solvent (shown in figure 5.15).

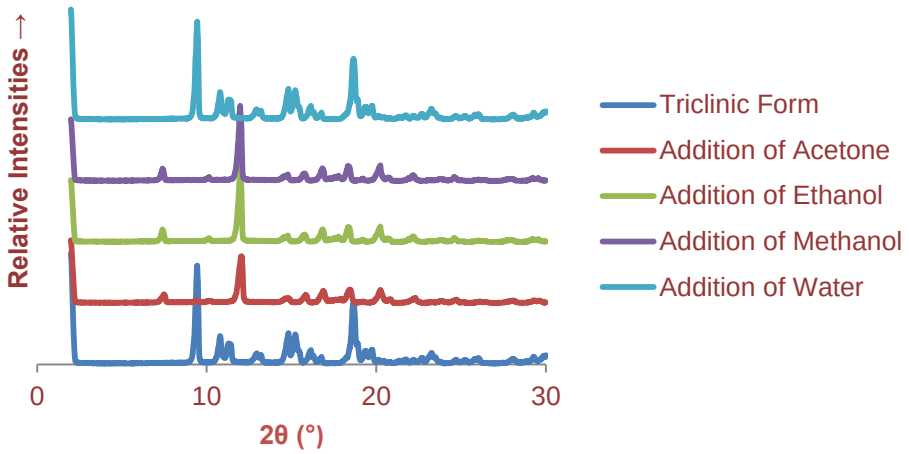


Figure 5.15 Transformation of the triclinic to the orthorhombic form in presence of different solvents

The solubility of artemisinin in different solvents was measured at 20°C using a gravimetric method and after saturation solubility was monitored for 6hrs. The experiment was repeated three times and an average was calculated. The triclinic form showed slightly higher solubility than the orthorhombic form in all solvents except water. In the case of water the triclinic form is five times more soluble than the orthorhombic form. In the light of this significant difference in solubility, rapid transformation of the triclinic form to the orthorhombic may be expected, but surprisingly the triclinic form remained stable in the presence of water. This may be due to the low solubility of both

forms in water and generally speaking the transformation rate appeared to correlate well with the solubility of the triclinic form in the solvent (Table 5.2).

Table 5.2 Solubility of art in different solvents and transformation duration

Solvent	Solubility orthorhombic (mmol/L)	Solubility triclinic (mmol/L)	Transformation duration
Acetone	850.06	927.99	Immediate
Ethanol	92.10	113.34	3 days
Methanol	138.13	159.39	3 days
Water	0.22	1.11	No transformation observed in15 months

5.2.5. Computational studies

To understand stability and solvent mediated transformation of artemisinin polymorphs**,** a computational analysis using the Morphology and Sorption modules of Material Studio Software 4.1.0 (Accelrys, 2006) was performed.

5.2.5.1. Geometry Optimisation

The 3D crystal structures of both polymorphs were obtained from the Cambridge Structural Database (CSD) with codes QNGHSU (orthorhombic) and QNGHSU01 (triclinic). Geometry optimisation was performed using Universal, CVFF, PCFF and Dreiding force fields with built in and equilibrated charges (QeQ) and the calculated values were compared with the experimental values. The force field results are shown in Table 5.3. The PCFF force field (Hill *et al.,* 1995) with QEq charges (Rap *et al.,* 1991) was found to calculate lattice parameters in closest agreement with experimental data and therefore this force field was used in all further calculations. A further check on the quality of the force field was performed by comparing

the energy difference between the calculated lattice energies of the two geometry optimised crystals. The PCFF force field with QEq charges predicted the orthorhombic form to be more stable than the triclinic form by 0.14kcal/mol. This compares well with 0.06 kcal/mol found from the enthalpies of the melting transitions from DSC measurements. It was noted however that the calculated energies take no account of temperature. The agreement between the calculated and experimental geometries and energies gives some confidence in the calculations of crystal habit reported below, although it must be emphasised that such calculations are only indicative of the likely significant surfaces to be found in these crystals.

Table 5.3 Geometry optimisation calculation for orthorhombic and triclinic forms of artemisinin

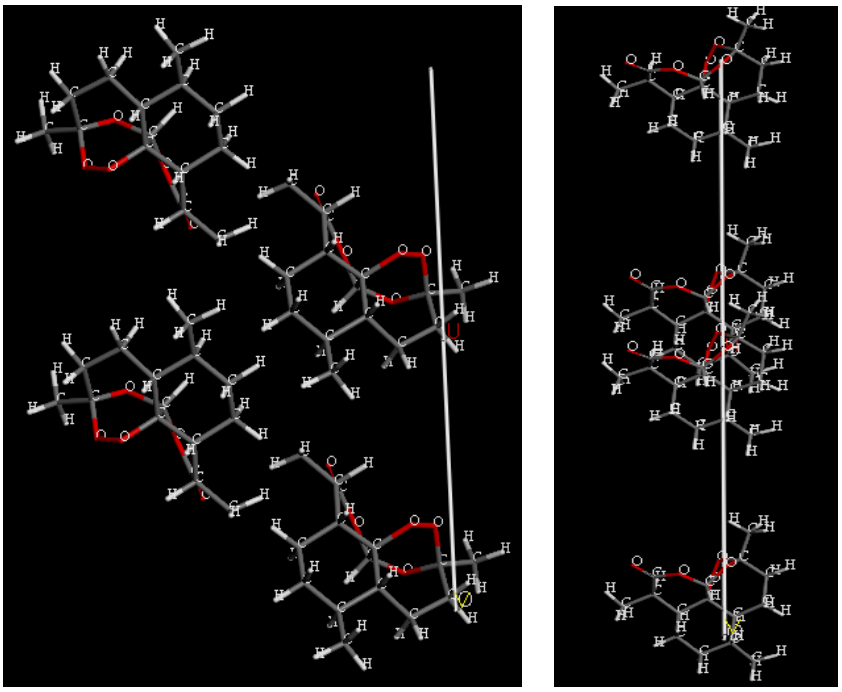
Force fields	**Orthorhombic**			**Triclinic**						**Average error (%)**
	a	b	c	a	b	c	α	β	γ	
Experimental	24.0	9.4	6.4	9.9	15.3	9.9	90.9	103.9	93.2	
Dreiding + QeQ	24.2	9.5	6.5	9.8	16.2	10.0	89.8	102.0	90.0	
Mean error	0.8	1.0	2.9	-0.6	5.7	1.5	-1.2	-0.9	-3.2	2.5
Universal + QeQ	24.1	9.1	6.4	9.7	15.1	9.9	90.3	103.2	96.9	
Mean error	0.2	-3.3	0.8	-1.2	-1.3	0.9	-0.7	0.2	4.0	1.9
CVFF (Built in charge)	25.8	8.8	6.4	10.0	14.5	10.1	90.0	105.4	90.1	
Mean error	7.3	-6.0	1.1	2.1	-4.8	3.0	-1.0	2.4	-3.3	4.0
PCFF (Built in charge)	25.7	8.8	6.2	9.9	14.7	10.0	89.8	103.6	91.8	
Mean error	6.8	-5.8	-1.1	0.9	-4.1	1.4	-1.2	0.7	-1.5	3.4
CVFF + QeQ	25.0	9.0	6.4	9.7	15.3	9.9	89.9	102.4	97.7	
Mean error	3.9	-4.6	0.9	-1.5	0.3	0.6	-1.1	-0.5	4.8	2.7
PCFF + QeQ	24.1	9.5	6.4	9.6	15.4	9.8	90.3	100.9	90.2	
Mean error	0.1	0.5	1.0	-3.0	0.6	-0.4	-0.7	-2.0	-3.2	1.7

*** The average error is calculated by taking the square root of sum of the squared error and dividing by 9.**

5.2.5.2. Morphology Prediction

BFDH, Growth and Equilibrium morphologies of both polymorphs were calculated using the Morphology modules and results are summarised in Table 5.4. The predicted growth and equilibrium morphologies were similar, with the {200} and {100} faces dominating the morphologies of the orthorhombic and triclinic faces respectively.

The cohesive strength of crystal planes is related to their attachment energies (Wildfong *et al*., 2007). Therefore, growth morphologies of the polymorph were calculated using the Morphology module, during which attachment energies of all low index faces were calculated. The calculated crystal habit was dominated by, the {200} faces for the orthorhombic form and {100} for the triclinic form with percentage areas of 58.3% and 55.4% respectively (Table 2). The molecular arrangement at the possible slip planes of the orthorhombic and triclinic forms are shown in figure 5.16. It clearly shows the molecular density is higher on the (100) surface of the triclinic form compared to the (200) surface of the orthorhombic crystal. In contrast the slip plane surfaces of chlropropamide demonstrated significant similarity in the molecular arrangement at the slip plane of two polymorphs which was considered to be responsible for interconversion of these polymorphs (Wildfong *et al*., 2007). The difference in molecular arrangements of surfaces may have been responsible for transformation of orthorhombic to triclinic rather than interconversion under applied shear.



a b

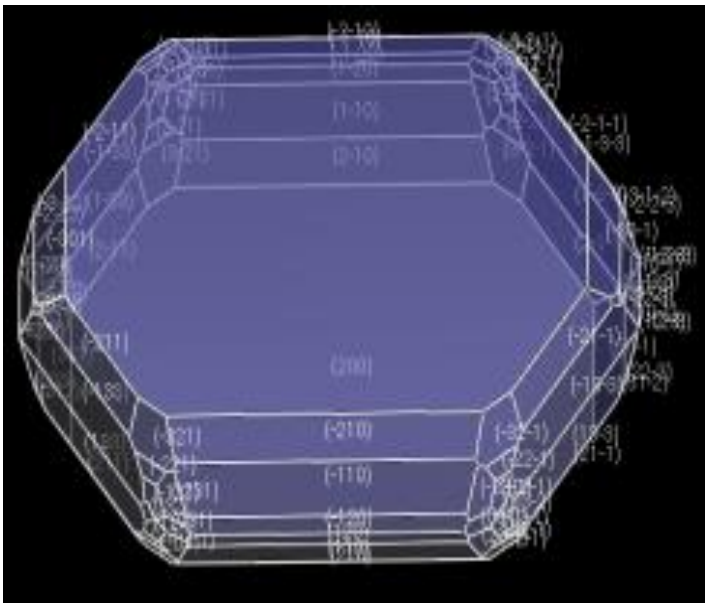
Figure 5.16 Orthorhombic and triclinic crystal structures, viewed in the (a) (200) plane and (b) (100) plane respectively

Equilibrium morphology was used for further computational analysis because it the surface energy of each surface. After analysing the surface area of the predicted morphology it was found that the {200} faces for the orthorhombic form and the {100} faces for triclinic form, with percentage areas of 88% and 37% respectively had the maximum surface area as shown in figure 5.17.

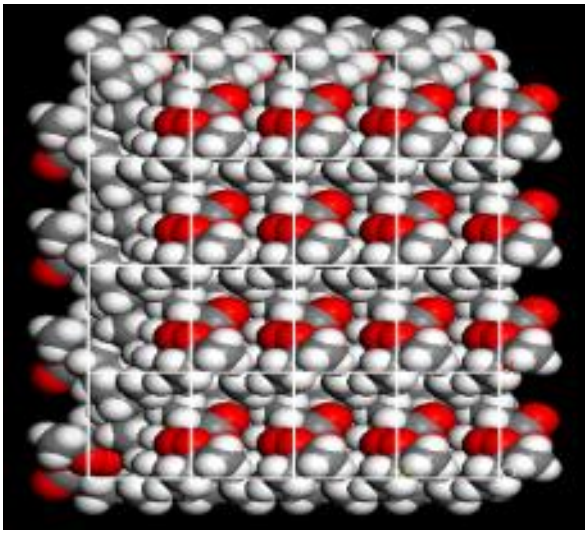
Table 5.4 Results of morphology calculations using different methods

Orthorhombic		Triclinic	
BFDH			
hkl	Total facet area (%)	**hkl**	Total facet area (%)
200	36.6	**010**	21.9
110	37.8	**001**	11.2
101	23.4	**100**	10.6
Growth Morphology			
hkl	Total facet area (%)	**hkl**	Total facet area (%)
200	29.2	**100**	27.7
110	23.7	**001**	10.9
101	10.0		
Equilibrium morphology			
hkl	Total facet area (%)	**hkl**	Total facet area (%)
200	44.1	**100**	18.8

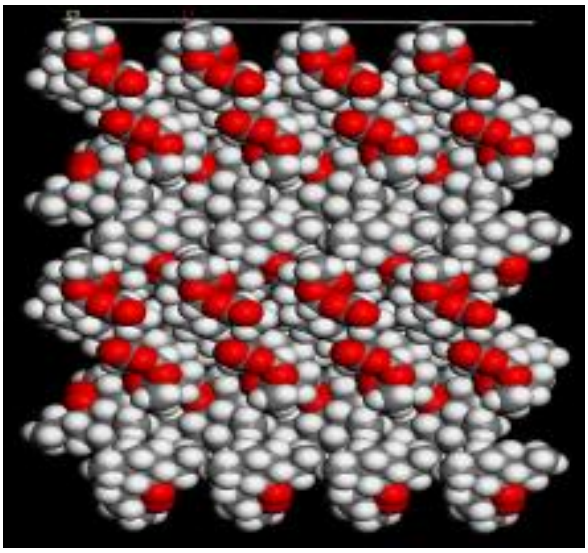
The molecular arrangement of these two faces will have significant influence on the properties of the crystal. The oxygen atoms of the orthorhombic polymorph are exposed in the channels of the {200} surface resulting in a more hydrophilic surface than the triclinic form (shown in figure 5.13).



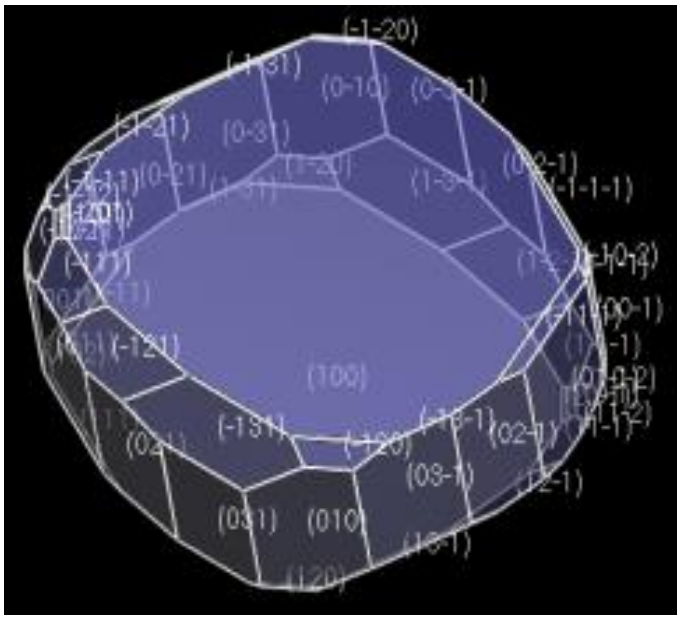
A



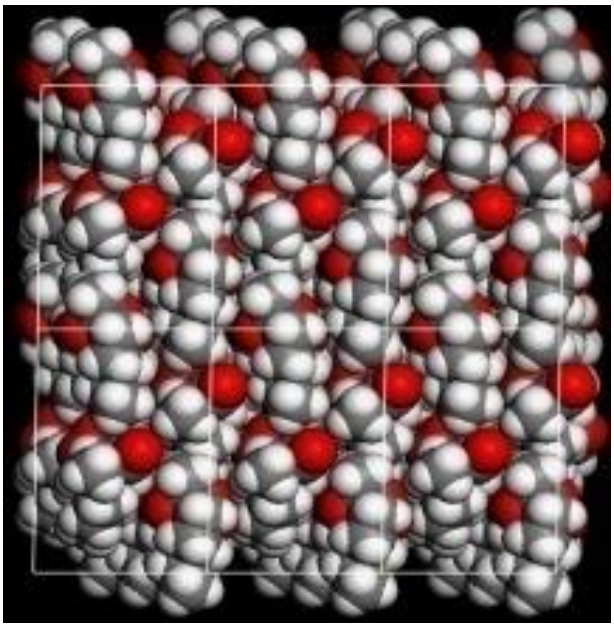
B



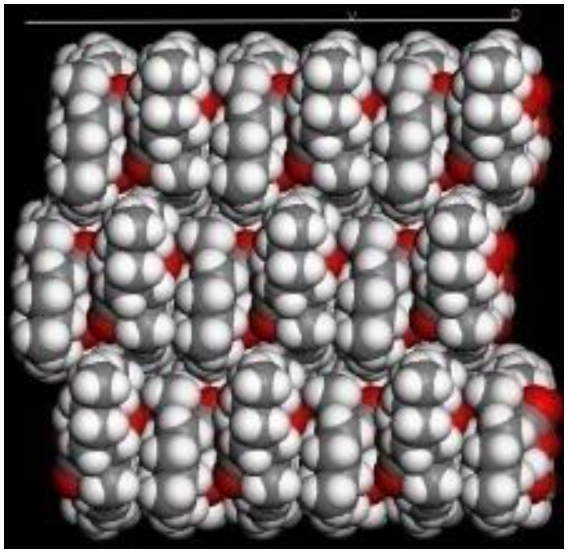
C



D



E



F

Figure 5.17 Predicted habit of the orthorhombic form (A) and its (200) surface, top view (B) and side view (C). Predicted habit of the triclinic crystal form (D) and its (100) surface, top view (E) and side view (F)

5.2.5.3. Sorption Studies

To investigate the effect of solvents such as acetone ethanol, methanol and water on the surface of the crystals, the sorption module was used to calculate adsorption energy. The sorption module simulates a pure adsorbate in a sorbent framework by using the Metropolis Monte Carlo

method. The calculated adsorption energy for different solvents on the {100} surface of the triclinic form and the {200} surface of the orthorhombic form are shown in Table 5.5. The adsorption energies are larger on the orthorhombic {200} surface, which may be due to adsorption into a channel which will provide a large contribution from van der Waals interactions. This is supported by the fact that the strength of adsorption on the {200} surface is proportional to the size of the molecule. Adsorption on the triclinic {100} surface shows little differentiation between the four solvents studied and these results are not able to explain the difference in stabilities of the triclinic crystals in acetone (which rapidly convert to the orthorhombic form) and in water (which are stable for more the 15 months). As mentioned previously, the reason for the stability of the triclinic crystals is most likely to be due to their low solubility. The aqueous solubility of the triclinic form is only 0.312 mg/ml.

Table 5.5 Adsorption energies of solvents on the orthorhombic (200) and triclinic (100) surfaces of artemisinin

Solvents	Adsorption energy for the orthorhombic (200) surface (kcal/mol)	Adsorption energy for the triclinic (100) surface (kcal/mol)
Acetone	-16.30	-7.10
Ethanol	-15.75	-6.27
Methanol	-14.27	-5.68
Water	-11.76	-5.97

5.2.6. Mechanism of polymorphic transformation during HTE

Pharmaceutical processing has the potential to disrupt the crystal lattice of APIs and has thus gained considerable attention (Gerhardt *et al.,* 1994 and Phadnis *et al.,* 1997). Different molecular arrangements can provide diverse physical and chemical properties in pharmaceutical substances thus altering solubility, density, stability and bioavailability (Modi *et al.,* 2013). Several unit operations employed to prepare solid dosage forms, such as grinding, milling, drying and compression may induce solid state polymorphic transformation (Morris *et al.,* 2001). Some elegant examples which utilise such process induced transformation have been described in pharmaceutical research. Tablet compression has been reported to cause a polymorphic transition in drugs, such as acetaminophen, piroxicam, carbamazepine, phenylbutazone and chlorpropamide, which alters the physicochemical properties of these drugs and finally influences the dissolution rate and bioavailability of the final products (Lin, 2007). Grinding can also induce polymorphic transitions in caffeine, theophylline and famotidine (Cheng *et al*., 2008). Recently some solvent free technologies have been investigated which cause complete polymorphic transformations. Trask et al. demonstrated the application of solvent assisted grinding to achieve polymorphic transformation in anthranillic acid and succinic acid (Trask *et al.,* 2007).

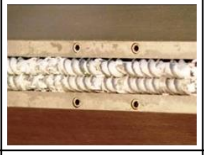
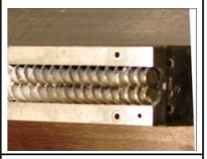
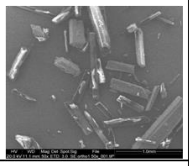
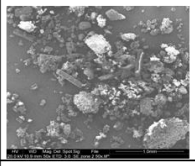
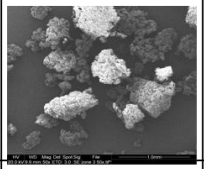
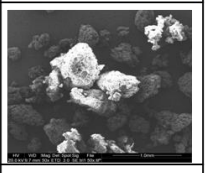
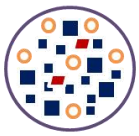
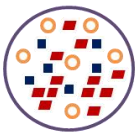
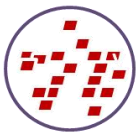
The two primary factors responsible for causing this transformation in HTE are temperature and shear. Polymorphic transformations induced by high temperature or pressure are well known. Louer et al. generated metastable piracetam polymorph at room temperature. Form I of piracetam was formed

by heating form III to 410K at ambient pressure for 30 min in a glass capillary followed by quenching to room temperature (Louer *et al.,* 1995). Boldyreva et al. demonstrated pressure induced transformation of paracetamol. The study was carried out in a diamond anvil cell and there was no change in a single monoclinic form crystal until the pressure was increased up to 4.5 GPa (Boldyreva *et al.,* 2002). Sometimes the transformation was observed when the pressure was slowly decreased after an initial increase. This transformation is dependent on the API and the procedure of increasing/decreasing pressure. Cheng *et al.* discussed the role of mechanical stress and rise in temperature during processing in polymorphic transformation using a grinding method (Cheng *et al.,* 2007).

5.2.6.1. Polymorphic Transformation in HTE

Here, the concept of providing a combination of controlled temperature and shear was explored through the application of HTE to induce polymorphic transformation. The commercially available orthorhombic form of artemisinin was processed in a twin screw extruder. To examine the transformation mechanism further, artemisinin from different zones along the extruder barrel was collected and characterised by SEM and PXRD. Results are shown in Table 5.6 and Figure 5.18. Observation of the collected samples revealed that agglomerated material occurred in the later section of the process**.**

Table 5.6 SEM images of the samples collected from different zones of extrusion and schematic presentation of the predicted mechanism.

Zone	2-4	4-6	6-8	8-10
Extruder				
SEM				
Observations (Size)	Orthorhombic crystals (150-200 µm)	Preheating, conveying and size reduction (100-150 µm)	Vapour phase transformation and agglomeration (200-250 µm)	Continuous transformation and agglomeration (200-250 µm)
Schematic				
Orthorhombic crystals : ■ ▪ Triclinic crystals: ▪ ▪ Vapour phase : ○				

Within the extruder barrel, material passes through three phases; preheating which occurs when the material passes through initial conveying zones and its temperature is raised to 100°C. During this phase no significant decrease in particle size or change in crystal form was observed. In the next zone, mixing paddles in the extruder screws were set up to impart high shear and the set temperature was raised to 140°C. Also in this region, forward conveying of the material is slowed by the mixing elements so the residence time is increased. It is assumed that artemisinin in this region of the extruder undergoes vapour phase transformation and a significant reduction in size due to the high shearing stresses imparted by the screws. Samples taken

from this zone did not show complete transformation to the triclinic form, although a considerable portion of orthorhombic API had been converted. Complete transformation was observed in the next zones (6-8) where the high shearing configuration caused further densification of the material forming slightly larger agglomerates. Agglomerates conveyed into the final zone (8-10) were observed to break down into smaller agglomerates which may be due to shearing between the screw and barrel wall. This study has provided an understanding of polymorphic transformation of artemisinin through the vapour phase which occurs in high temperature extrusion and a complex process of agglomeration and de-agglomeration. In a previous study concerning the formation of co-crystals in extrusion, similar observations were made where by co-crystallisation occurred via melt and eutectic phase assisted agglomeration induced by high shear stress (Dhumal *et al.,* 2010). The suitability of solid state polymorphic transformation by melt extrusion is currently being explored for a range of pharmaceutical applications.

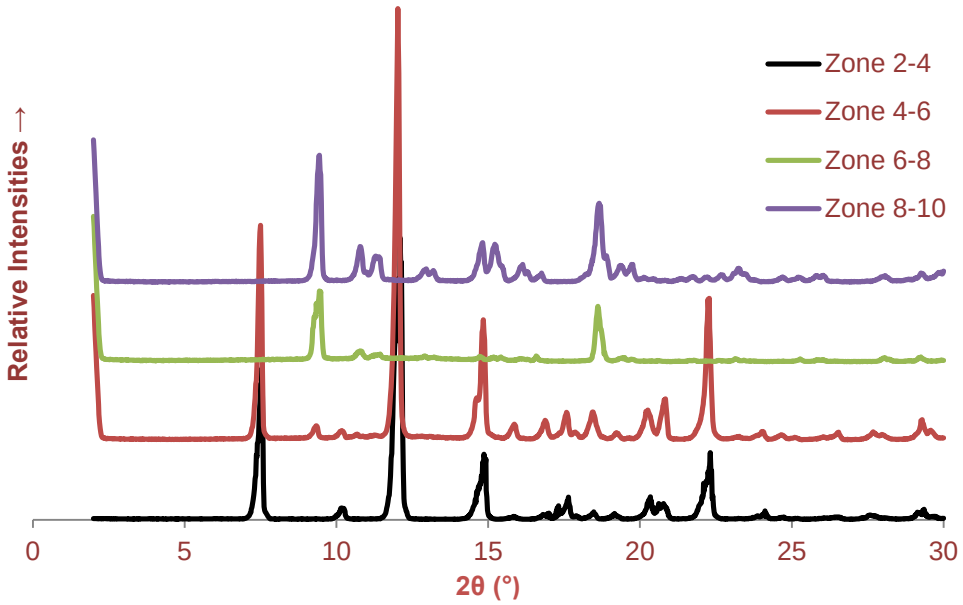


Figure 5.18 Experimental PXRD patterns of the material collected from different zones of extruder

5.2.7. Performance evaluation

5.2.7.1. In-vitro dissolution study

According to Chan, the orthorhombic form of artemisinin has a high density and low water solubility compared to the triclinic form (Chan *et al.,* 1997). This solubility difference between the orthorhombic form and triclinic form was verified by *in-vitro* dissolution studies. The dissolution test was carried out for 10 hours using water as a dissolution medium. The dissolution profile of triclinic polymorph was enhanced when compared to the orthorhombic form. In 10 hours 25% of artemisinin was released from the orthorhombic form while 90% of artemisinin was released from the triclinic form as displayed in figure 5.19. This data is in conformation with a work from a Malaysian group.

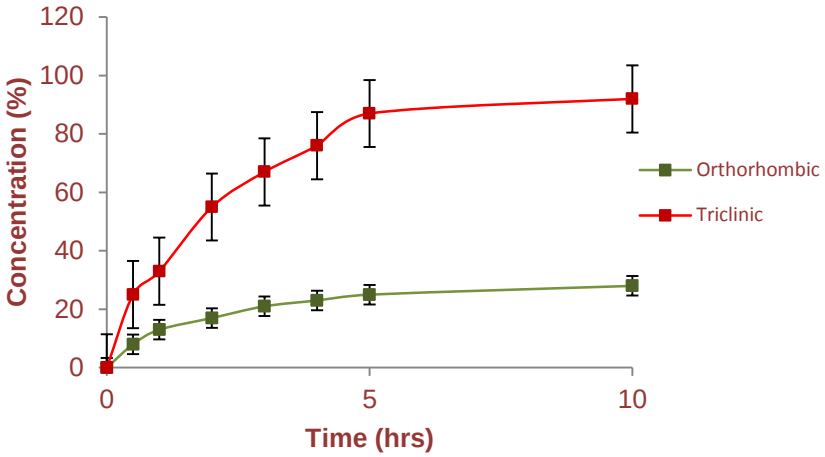


Figure 5.19 Dissolution profile of orthorhombic and triclinic artemisinin

5.2.7.2. Pharmacokinetic Study

To correlate *in-vitro* dissolution data, a pharmacokinetic study was performed. The HPLC calibration curve is shown in Figure 5.20. The artemisinin plasma concentrations achieved at different time after administration of the orthorhombic and triclinic forms are given in Tables 5.7 and 5.8 respectively. The plasma concentration-time profiles were plotted and Areas Under Curve (AUC) were calculated (shown in Figure 5.21) using a Trapezoidal rule. The AUCs obtained for orthorhombic and triclinic forms are shown in Table 5.9.

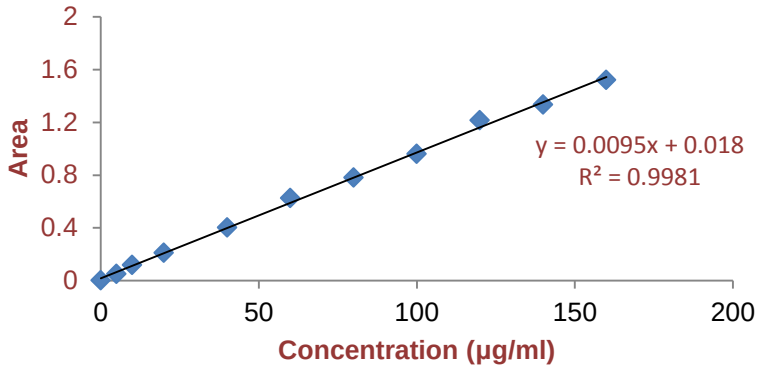


Figure 5.20 Calibration curve for artemisinin in plasma samples

Table 5.7 Plasma concentration of orthorhombic form of artemisinin

Plasma Concentration (µg/ml)							
Time(h)	**Rat 1**	**Rat 2**	**Rat 3**	**Rat 4**	**Rat 5**	**Rat 6**	**Mean**
0	0	0	0	0	0	0	0
0.5	7.78	6.67	7.78	7.78	8.89	6.67	7.59
1	15.56	8.89	10	11.11	12.22	17.78	12.59
2	31.11	8.89	10	11.11	12.22	17.78	15.18
4	18.89	17.78	20	18.89	17.78	16.67	18.33
6	16.67	12.22	10	8.89	7.78	7.78	10.55
8	10	7.78	7.78	6.67	6.67	6.67	7.59
24	8.89	10	8.89	6.67	7.78	8.89	8.51

Table 5.8 Plasma concentration of triclinic form of artemisinin

Plasma Concentration (µg/ml)							
Time(h)	**Rat 1**	**Rat 2**	**Rat 3**	**Rat 4**	**Rat 5**	**Rat 6**	**Mean**
0	0	0	0	0	0	0	0
0.5	14.44	13.33	10	8.89	8.89	6.67	10.37
1	10	7.78	16.67	14.44	25.56	27.78	17.03
2	13.33	12.22	20	21.11	15.56	11.11	15.55
4	22.22	21.11	16.67	15.56	17.78	16.67	18.33
6	24.44	31.11	27.78	31.11	26.67	28.89	28.33
8	16.67	11.11	17.78	16.67	18.89	20	16.85
24	8.89	7.78	8.89	7.78	8.89	6.67	8.14

Table 5.9 Comparison of Area Under Curve (AUC) of artemisinin polymorphs

	Orthorhombic (µg.hr/ml)	Triclinic (µg.hr/ml)
Rat 1	188.06	349.17
Rat 2	233.33	297.50
Rat 3	151.11	367.5
Rat 4	130.28	352.5
Rat 5	138.61	376.94
Rat 6	223.33	365.28
Mean	177.45	351.48
Standard Deviation	44.20	28.34

The triclinic form showed a two fold increase in AUC compared to the orthorhombic form. The average C_{max} for the orthorhombic form and the triclinic forms were 16 µg/ml and 31 µg/ml respectively whereas T_{max} were 4 hrs and 5 hrs for the orthorhombic and the triclinic forms respectively.

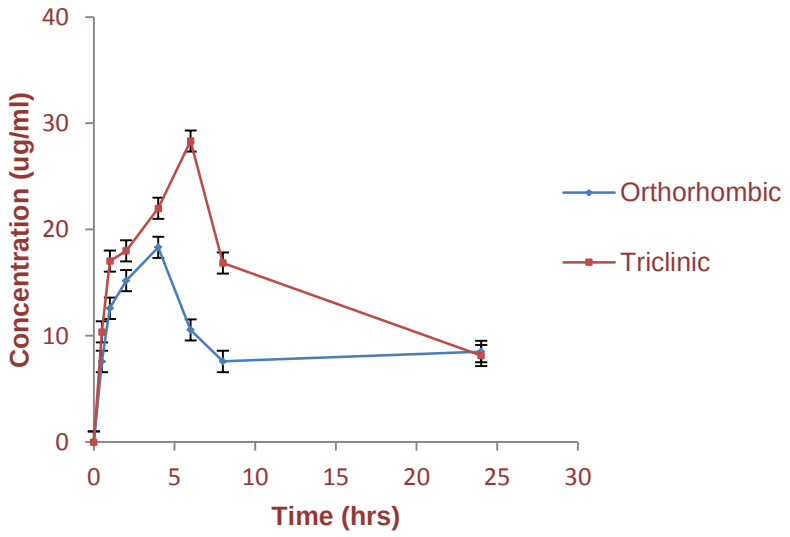


Figure 5.21 Plasma concentration profiles of the orthorhombic and the triclinic forms of artemisinin

5.2.3. Summary

It has been shown that it is possible to manufacture high purity, metastable, triclinic crystals of artemisinin using high temperature extrusion. The extruder

screw configuration and processing parameters such as temperature and screw speed can be optimised in order to produce the desired polymorph and level of purity. Shelf-life of the product has been shown to be significantly longer than for the triclinic crystals formed by solvent based methods, with crystals of the triclinic form still stable after one year. The prepared triclinic form also showed an increase in bioavailability.

5.3. Additional API Case Studies

High temperature extrusion is a continuous process which can potentially be scaled-up to achieve higher throughputs and the method is not limited to transformation of artemisinin. In the following section a range of APIs are investigated for use with the HTE technique for solid state phase transformation.

5.3.1. Piracetam

Piracetam is a noortropic agent recently marketed by UCB Pharma as a Nootropil®. It is used to treat age associated mental decline and disorders linked with the nervous system. Three polymorphs of piracetam have been identified and structurally characterised. Form III is the stable form of piracetam. Form I is a metastable form and undergoes solution mediated transformation, therefore this drug has been selected as a model drug for polymorphic transformation. The molecular structure and physicochemical properties of piracetam are displayed in figure 5.22 and Table 5.10 respectively.

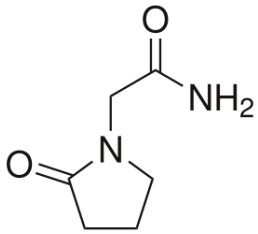


Figure 5.22 Molecular Structure of Piracetam

Table 5.10 Physicochemical properties of piracetam

Chemical Name	**2-(2-Oxopyrrolidin-1-yl)acetamide**
Molecular Formula	$C_6H_{10}N_2O_2$
Molecular weight	142.2 g
Melting Point	152°C
Description	White powder
Solubility	Freely soluble in water and soluble in alcohol.
Storage	In dry container and cool place

Piracetam occurs in four different enantiometric polymorphic forms namely forms I, II, III and IV (Fabbiani *et al*., 2005) shown in Figure 5.18. The crystal structures of form II (triclinic) and form III (monoclinic) are known, however no crystallographic exploration of form I and its crystal structure has been reported. Form III is a commercially available most stable form whilst forms II and I are metastable forms. Form II and III can be prepared by solvent crystallisation using various solvents such as methanol and propan-2-ol. Both forms convert to form I at high temperature (above 400K). Also form I can be prepared at room temperature by quenching the stable form, however, it is not stable at room temperature and within few hours transforms it transforms to form II. Therefore, form I is a high temperature

phase and has a narrow thermal stability range. The molecular confirmation of piracetam polymorphs are shown in figure 5.23.

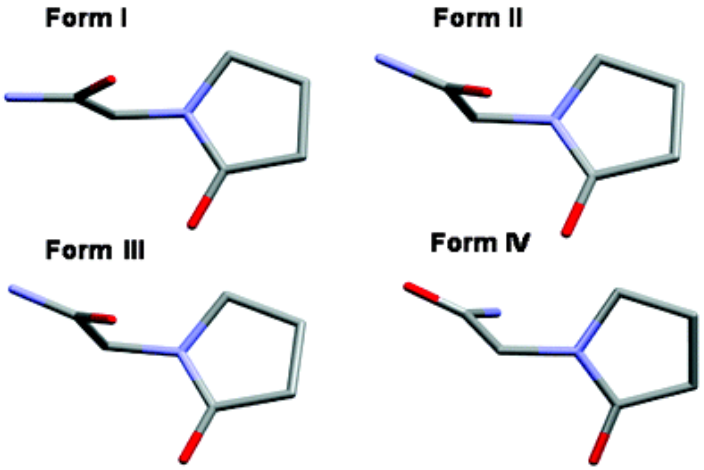


Figure 5.23 Conformation of piracetam molecule in different polymorphic form (Fabbiani *et al*., 2005)

Here, form III piracetam was processed in a twin screw extruder at a temperature profile of T130 and screw rotation speed of 10 rpm. The obtained product showed a PXRD pattern which belongs to form I. This form I then transformed to form II after 2 weeks. Interestingly, the obtained form II was found to be stable for more than a year. All PXRD patterns are shown in figure 5.24.

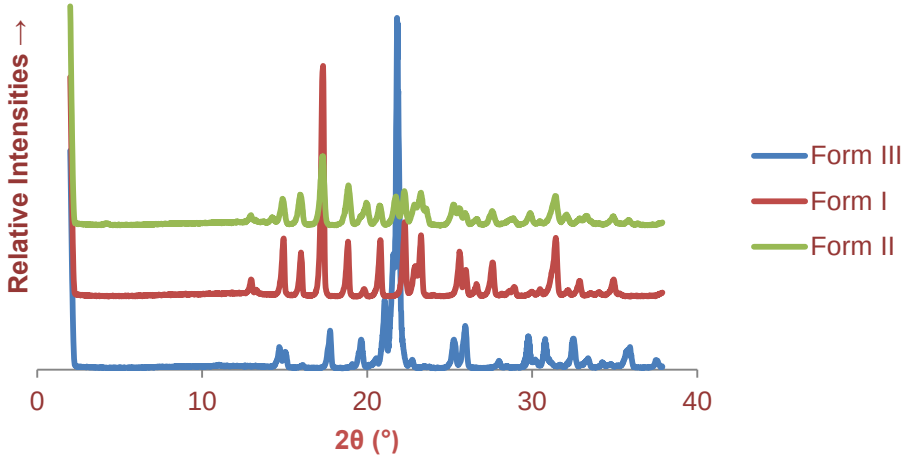


Figure 5.24 Experimental PXRD patterns of piracetam polymorphs

5.3.2. Carbamazepine

The anticonvulsant drug, carbamazepine has been widely used for over 30 years to treat epilepsy and trigeminal neuralgia. The P-monoclinic form has the lowest free energy of all the forms at room temperature. It possesses challenges such as a narrow therapeutic window, autoinduction of metabolism and dissolution dependent bioavailability (Bertilson *et al.,* 1986). Carbamazepine crystallises in four anhydrous polymorphs and one hydrate. Many attempts have been made to improve the solubility of carbamazepine, such as preparing a solid dispersion, complexation or co-crystal. The molecular structure and physicochemical properties of carbamazepine are displayed in figure 5.25 and Table 5.11 respectively.

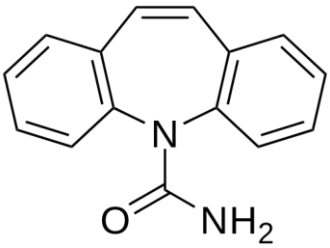


Figure 5.25 Molecular structure of carbamazepine

Table 5.11 Physicochemical properties of carbamazepine

Chemical Name	**5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide**
Molecular Formula	$C_{15}H_{12}N_2O$
Molecular weight	236.269 g/mol
Melting Point	189-192 °C
Description	White powder
Solubility	Practically insoluble in water, slightly soluble in ethanol and soluble in chloroform
Storage	In dry container and cool place

Carbamazepine is known to crystallise in four anhydrous polymorphs form I (triclinic), form II trigonal, form III (p-monoclinic) and form IV (c-monoclinic) (Krahn *et al*., 1987). Form III is the most stable polymorph of carbamazepine at room temperature. There is much confusion between the naming of carbamazepine polymorphs in literature. Specifically, the morphologically similar triclinic and trigonal forms are difficult to differentiate without the use of PXRD. The trigonal form shows the highest free energy hence it is the least stable crystal form of carbamazepine. The optimised structure of carbamazipne and packing diagram of carbamazepine polymorphs are shown in Figure 5.26.

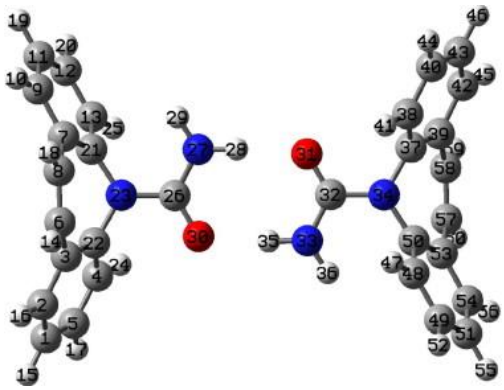


Figure 5.26 Optimised geometry of carbamazepine dimer (Adapted from Czernicki *et al*., 2013)

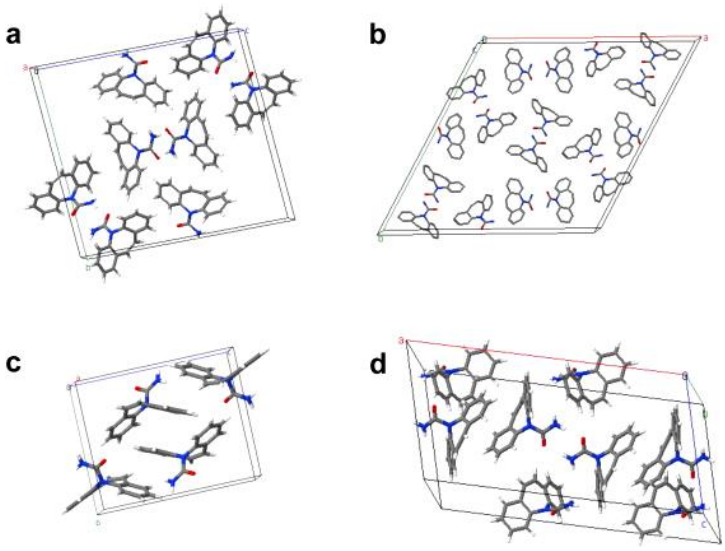


Figure 5.27 Packing diagrams of carbamazepine polymorphs: (a) form I, (b) form II, (c) form III, and (d) form IV (Cambridge Crystallographic Data Centre) (Adapted from Czernicki *et al.,* 2013)

Grzesiak et al. has reported that all four form are close in energy and their stability order is III > I > IV > II at room temperature (Grzesiak *et al*., 2003). All polymorphs of carbamazepine share a common hydrogen bonding motif resulting in a dimer with two amide–amide hydrogen bonds. The phase transformation between these polymorphs can be induced in the presence of solvent or mechanical or thermal stress. It is reported that form III transforms to form I upon heating at 150°C for two weeks (Ceolin *et al*., 1997).

During twin screw extrusion, form III was converted to form I at a temperature profile of T140 and screw rotation speed of 10 rpm. Formation of the triclinic crystals was confirmed by PXRD (shown in figure 5.28.). Form III shows characteristic peaks at 2θ: 15.36, 19.56, 25.00 and 27.47 whereas form I shows indicative peaks at 2θ: 7.92, 9.37, 12.28 and 19.99.

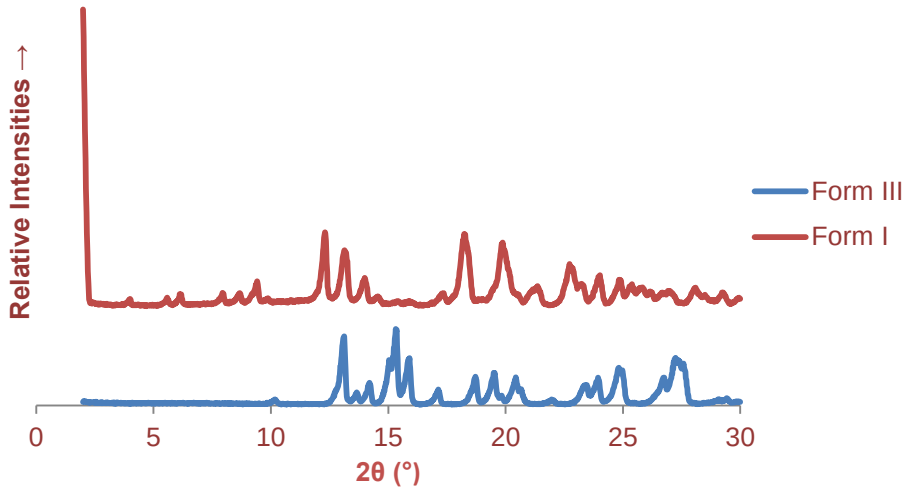


Figure 5.28 Experimental PXRD patterns of carbamzepine polymorphs

5.3.3. Chlorpropamide

In the beginning of the 1950s sulfonyl urea therapy was introduced to treat type II diabetes mellitus. Chlorpropamide is one of the first generation sulfonyl urea derivatives offering prolonged pharmacological action. It is a Biopharmaceutical Classification System (BCS) class II drug which has solubility issues causing problems for absorption. Chlorpropamide has been known for its polymorphic versatility for a long time. According to the Burger nomenclature, the polymorphs are identified as form I, II, III, IV and V; form III is commercially available (Ayala *et al.,* 2011). Form III has the aforementioned solubility and stability issues. The molecular structure and physicochemical properties of chlorpropamide are displayed in figure 5.29 and Table 5.12 respectively.

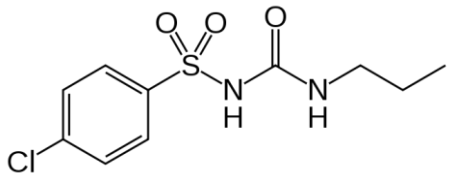


Figure 5.29 Molecular structure of chlorpropamide

Table 5.12 Physicochemical properties of chlorpropamide

Chemical Name	**4-chloro-*N*-(propylcarbamoyl)benzenesulfonamide**
Molecular Formula	$C_{10}H_{13}ClN_2O_3S$
Molecular weight	276.74 g/mol
Melting Point	126–130 °C
Description	White powder
Solubility	Practically insoluble in water, moderately soluble in chloroform and soluble in alcohol
Storage	In dry container and cool place

Chlorpropamide exists in five crystal forms and has been known for its polymorphic flexibility for a long time. Simmon reported polymorphic behaviour of chlorpropamide for the first form, whilst a careful screening and identification of each crystal form was performed by Burger (form I, II, III, IV and V) (Ayala et al., 2012). Recently, Chesalov *et al.* anticipated a new nomenclature based on the order in which the crystal structures were elucidated. The proposed notation uses Greek characters as follows: *α* (III), *β* (II), *γ* (IV), *δ* (VI), and *ε* (I) (Chesalov *et al.,* 2008). Form I, II and III are generally referred as form C, B and A. All these forms show complex thermodynamic relationships and phase transformation under temperature, kinetic and pressure. It is often considered as a model API which undergoes phase transition during tabletting, the detailed mechanism of these

transformations has been investigated (Ayala *et al.,* 2012). Otsuka et al. has reported the partial transformation of form A to C on tabletting. The density of form C is less than the density of form A which led to the conclusion that the increase in pressure during tabletting cannot account for the A to C phase transition (Otsuka *et al.,* 1989). The polymorphism of chlorpropamide is a good case of study to demonstrate the sensitivity of Raman spectroscopy to conformational and packing changes.

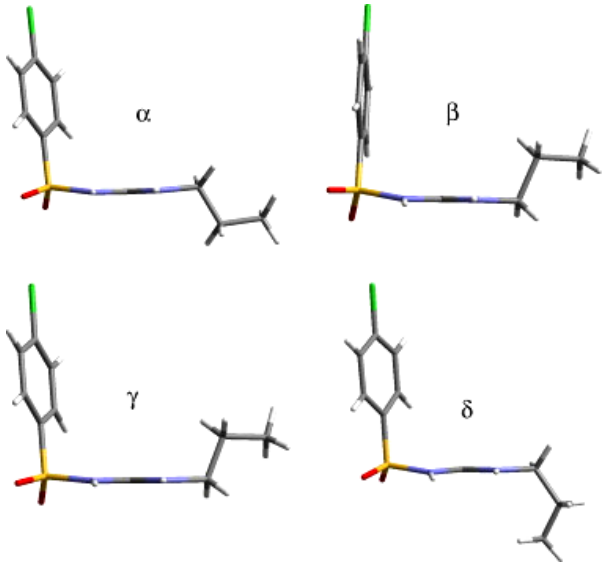


Figure 5.30 Molecular confirmations of chlorpropamide polymorphs (Adapted from Chesalov et al., 2008)

Form A of chlorpropamide is commercially available (Figure 5.30) and considered as the most stable form whereas form C is metastable at room temperature and exhibits a greater dissolution rate. Form C has been known to generate from heating of any other crystal phase to 115°C for about 1hr (Ayala *et al.,* 2012).

Using the HTE method, commercially available form C was extruded in a twin screw extruder using the temperature profile T115 at a screw rotation speed of 10 rpm. Details of these experiments were reported earlier in

Chapter 3. Surprisingly, here the residence time was 10 min and complete transformation was achieved. This transformation was confirmed by PXRD (as shown in Figure 5.31).

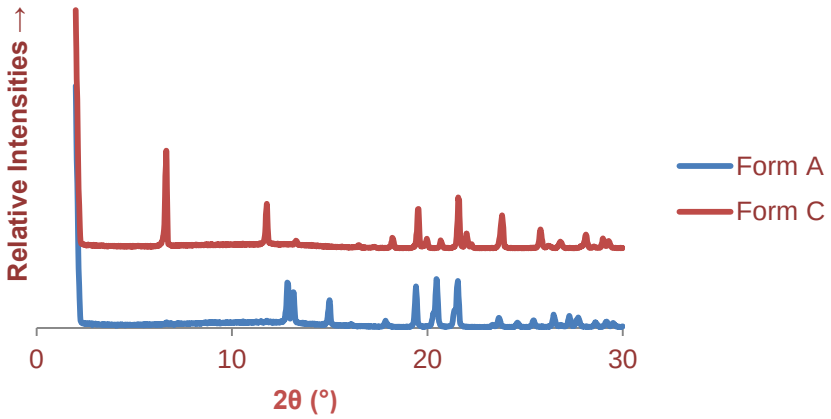


Figure 5.31 Experimental PXRD patterns of chlorpropamide polymorphs

Form A exhibits characteristic peak area at 2θ: 6.6, 11.7 and 19.5 while form C shows a distinct peak at 2θ: 15.

5.3.4. Paracetamol

Paracetamol is a para-aminophenol derivative with anti-inflammatory and anti-pyretic effects. It has been widely used to treat mild to moderate pain and fever. Though it is safe in a normal therapeutic dose, an overdose may cause heptic necrosis (Campanero *et al.,* 1999). As it has a good toleratability profile, it is preferred in patients in whom salicylates and other non-steroidal anti-inflammatory drugs are contraindicated. It has a short half life of 2-3 hours, therefore frequent dosing is required (Coulthard *et al.,* 2001). Paracetamol shows three polymorphic structures: form I (monoclinic), form II (orthorhombic) and form III respectively. The monoclinic form of paracetamol is thermodynamically more stable and available in the market

than form II and form III. The monoclinic form has low solubility and processability. The molecular structure and physicochemical properties of paracetamol are displayed in figure 5.32 and Table 5.13 respectively.

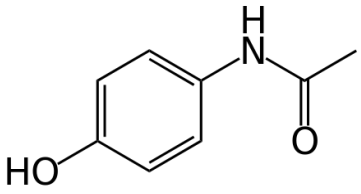


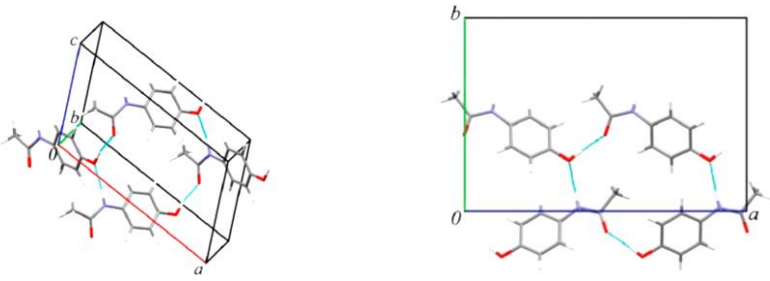
Figure 5.32 Molecular structure of paracetamol

Table 5.13 Physicochemical properties of paracetamol

Chemical Name	**N-(4-hydroxyphenyl)acetamide**
Mlecular Formula	$C_8H_9NO_2$
Molecular weight	151.16
Melting Point	169-172°C
Description	White, crystalline powder.
Solubility	Miscible in water
Storage	Room temperature

Paracetamol crystals adapt two polymorphic structures, namely monoclinic and orthorhombic (as shown in Figure 5.33). The monoclinic form of paracetamol is the thermodynamically stable form in comparison with orthorhombic crystals. Although the monoclinic form is the marketed solid phase it has poor compressibility because it does not have slip planes in its crystal structure. Therefore a time consuming wet granulation process is generally required. In contrast, the orthorhombic form possesses a processing advantage; it undergoes plastic deformation during compression as it has well developed slip planes in its crystal structure (Martino *et al.,* 1996). However the orthorhombic form is metastable and offers more

solubility than the monoclinic form. Recently, a third form of paracetamol was generated in fusion experiments but this form has reported stability issues and therefore no data has been reported relating to its crystal structure and physicochemical properties.



A **B**

Figure 5.33 The fragments of crystal structures of the two polymorphs of paracetamol (A) the monoclinic and (B) the orthorhombic (Adapted from Kolesov *et al.,* 2011)

The orthorhombic form of paracetamol can be obtained by solvent crystallisation, under pressure or thermal stress. Boldyreva *et al.,* demonstrated pressure induced transformation of paracetamol. This study was carried out in a diamond anvil cell (Boldyreva *et al.,* 2002). There was no change in a single monoclinic form crystal until pressure was increased up to about 4.5 GPa. Sometimes the transformation was observed when the pressure was slowly decreased after initial increase. Overall this transformation was found to exhibit poor reproducibility and depended strongly on the sample and on the procedure of increasing/decreasing pressure.

Paracetamol was processed using HTE method at different sets of temperature profiles and screw speeds (details are provided in Chapter 3). The PXRD pattern of the monoclinic form is displayed in Figure 5.34.

Although paracetamol undergoes phase transformation by thermal or mechanical stress surprisingly no transformation was observed during the extrusion experiments. This requires further investigation with computational support to fully understand the reasons why transformation was not achieved; however this study is considered to be outside the scope of this thesis.

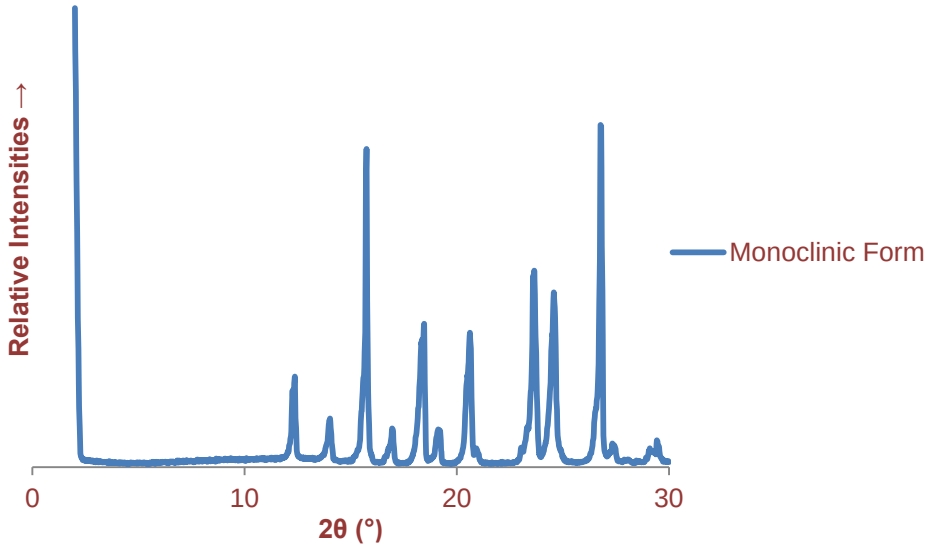


Figure 5.34 Experimental PXRD pattern of the monoclinic form of the paracetamol crystal

5.3.5. Theophylline

Theophylline is a methylxanthine derivative widely used to treat asthma and pulmonary diseases for its bronchodilator action. Depending on the storage conditions, it exists in either anhydrous or in hydrous forms. Anhydrous theophylline exhibits three polymorphic forms: I, II and III. Form II is currently commercially available, has a low solubility in water and shows dose dependant pharmacokinetics (Parvez *et al.,* 2004). It has a very narrow therapeutic range (10-20 µg/ml) and there is a very small difference between the therapeutic and toxic effect (Mengozzi *et al*., 1998). A 20-30 µg/ml serum

concentration of theophylline resulted in toxicity in more than 80% of individuals (Gohel *et al.,* 1997). However, the efficacy and toxicity can be modified by applying different formulation approaches. The molecular structure and physicochemical properties of theophylline are displayed in figure 5.35 and Table 5.14 respectively.

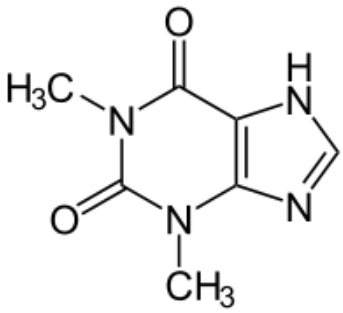


Figure 5.35 Molecular structure of theophylline

Table 5.14 Physicochemical properties of theophylline

Chemical Name	**1,3-dimethyl-7H-purine-2,6-dione**
Molecular Formula	$C_7H_8N_4O_2$
Molecular weight	180.164 g/mol
Melting Point	270-274°C
Description	White, odourless, crystalline powder with a bitter taste
Solubility	Soluble in water (8.3 g/l) at 20 °C, 0.1 M NaOH, 0.1 M HCl, ethanol (moderately), DMSO, alkali hydroxides, ammonia, dilute hyrochloric acid, nitric acid, dilute aqueous acid, and dilute aqueous base.
Storage	Room temperature

Three anhydrous forms of theophylline exist, namely forms I, II and III. Form II of theophylline is commercially used and has an orthorhombic structure. This form is prepared by dehydrating the monohydrate of theophylline. Form

I can be generated by evaporating an aqueous solution of theophylline at a temperature of 95°C for a period of 24 hr (Otsuka *et al.,* 1990). Szterner et al. reported preparation of form I by a thermal method that involved heating form II in a glass vial at 110°C for 14 hr under vacuum 0.02 Pa (Szterner *et al*., 2010).

When theophylline form II was processed in a twin screw extruder using different temperature profiles, different intensities of shear and screw speed form I could not be generated. The PXRD patterns of theophylline polymorphs shows same peak positions but with different patterns of intensities. It exhibits three characteristic peaks at 2θ: 7.22, 12.7 and 14.4; form I shows high intensity of peak 1 and 3, and form II shows peak 2 with high intensity. The PXRD pattern of form II is shown in figures 5.36. This experiment also requires further investigation to fully understand the reasons why transformation could not be achieved.

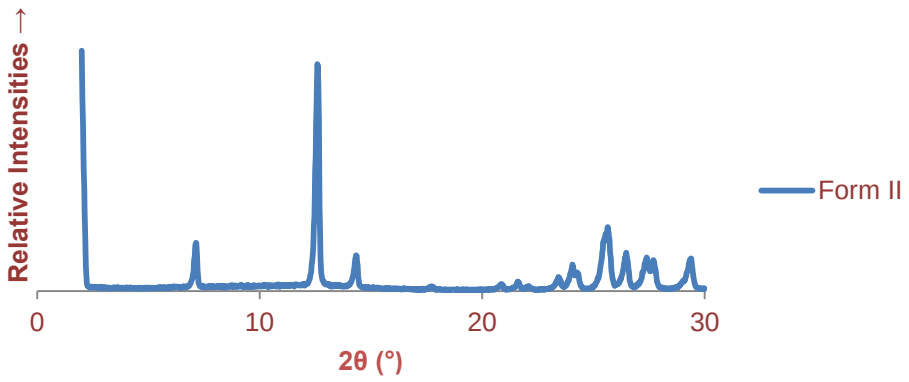


Figure 5.36 Experimental PXRD pattern of theophylline form II

5.4. Summary of chapter

HTE is a potentially commercially viable technology to induce polymorphic transformation under the action of high temperature and shear to obtain

stabilised metastable polymorphs of. Several examples have been demonstrated such as artemisinin, piracetam, chlorpropamide and carbamazepine. This method may be applicable for other pharmaceutical drugs where the metastable form is more efficient.

The method involves processing of commercially available stable polymorphic forms using a heated screw extruder with suitable screw configuration at a suitable temperature either, below, above or at the melting point of the drug (all current examples have been processed at least 10°C below the melting point). Extruder screw configuration can be optimised in order to achieve the desired polymorph with high purity and stability. For example length to diameter ratio, type and level of mixing can be configured to achieve optimum shear conditions, temperature and residence time within the process. The processing temperature also plays an important role in achieving the desired form and purity. The obtained polymorphic form has been characterised and confirmed by DSC, XRPD and FTIR. Chemical purity was analysed using HPLC-MS. The performance was characterised using various studies including dissolution, pharmacokinetic and physical stability etc.

This method provides a solvent free continuous route to producing stabilised metastable polymorph without need of any additional stabiliser. Being a solvent free process the instability associated with the residual solvent is overcome. This is a simple, continuous, reproducible, scalable process yielding product with high purity and stability compared to the conventional techniques. Moreover, the product obtained is in agglomerated form which reduces several unit operations in downstream processing.

6. Conclusion and Recommended Future Work

As detailed in chapter 1, the primary aim of this research was to explore novel pharmaceutical applications of hot melt extrusion technology. Specific objectives included the investigation of HME to form polymeric solid dispersions of thermolabile drugs and an exploration of extrusion to achieve polymorphic transformation into more desirable forms of APIs. This section lists the main conclusions drawn throughout the studies and highlights the most significant achievements of the work, which include enhancement of the physicochemical properties of artemisinin via two distinct processing routes.

6.1. Conclusions

The following conclusions summarise the most important findings drawn from the experimental results detailed in chapters 4 and 5:

- Soluplus® was shown to be an effective polymer for producing an amorphous formulation of artemisinin by hot melt extrusion, as confirmed by the lack of evidence of crystalline artemisinin in DSC and PXRD results. Extrusion set temperature, residence time and screw configuration were found to be important factors which influenced the properties of the amorphous formulation.

- Incompatibility between Artemisinin and Soluplus® was observed during rheological measurements and hot melt extrusion. Samples containing polymer alone did not show any discolouration whereas the

physical mixtures of drug and API exhibited a discolouration from white to yellow or brown.

- Applied shear intensity in rheology experiments did not have a significant effect on the resultant colour of the amorphous formulation; however the colour intensity of the samples increased with increasing drug loading.

- Citric acid was found to suppress degradation of the drug by maintaining a neutral microenvironment. Superior quality of artemisinin - Soluplus® solid dispersions was achieved by incorporating relatively low amounts of citric acid into the formulation prior to hot melt extrusion.

- The optimised solid dispersion of artemisinin showed significant enhancement in the dissolution profile compared to the pure drug. In 45 minutes, 92% drug was released from the solid dispersion (ArtSD3) which increased from 22% for pure artemisinin.

- Comparative *in-vivo* pharmacokinetic studies performed in Albino rats using the optimised formulation (ArtSD3) and pure drug indicated a 2.5 fold increase in C_{max} and bioavailability.

- The developed amorphous formulation of artermisinin was found to be stable for a period of 24 months under accelerated studies as per ICH guidelines.

- Partial polymorphic transformation from orthorhombic to triclinic crystals of artemisinin was observed at high temperature. This was found to occur during experiments through a vapour phase.

- Under a combination of imposed shear stress and raised temperature the polymorphic transformation rate of artemisinin was found to accelerate; this was attributed to the crystalline structure being disrupted continuously thus exposing new surfaces.

- The hot melt extrusion process was adapted to achieve complete polymorphic transformation from the orthorhombic to triclinic form of artemisinin. Polymorphic transformation was confirmed using PXRD, DSC and FTIR.

- The prepared triclinic crystals of artemisinin significantly improved stability when compared to those obtained by solvent crystallisation. Residual solvent traces were found to affect the stability of the triclinic form.

- In 10 hours 25% of artemisinin was released from the orthorhombic form while 90% of artemisinin was released from the triclinic form. The triclinic form showed a four times greater dissolution rate and two fold increase in bioavailability in Albino rats than the orthorhombic form.

- Computational analysis suggested that adsorption on the triclinic {100} surface of artemisinin was comparable with all four of the solvents studied and these results were unable to explain the observed differences in stability of the triclinic crystals in acetone (rapid

conversion to the orthorhombic form) and in water (stable for more than 15 months). However, the transformation rate of the triclinic to orthorhombic form correlated well with the solubility of the triclinic form in each solvent.

- Successful transformation of other APIs such as piracetam, chlorpropamide and carbamazepine using hot melt extrusion were also demonstrated.

The key achievements of this research have been to improve the properties of artemisinin, an important drug in global healthcare, by two different extrusion based routes. A stabilised amorphous system was developed which demonstrated significantly improved properties over the pure API. Additionally a novel extrusion based process was developed to generate a stabilised metastable polymorph without incarporating any additional stabiliser. A patent application (PCT/GB/1208489.3) surrounding this invention has been submitted as a direct outcome of this research.

This research has confirmed that hot melt extrusion is an attractive, solvent-free, continuous technology which can provide significant advantages in commercialisation of novel pharmaceutical formulations. The high temperature and shearing forces encountered during extrusion can restrict the processing of thermolabile drugs and therefore a detailed understanding of the relationship between the extrusion process and material properties is vital. Successful processing of a thermolabile material is dependent on the selection of a suitable polymer and an appropriate control of the process parameters.

6.2. Recommended Future Work

In order to gain improved understanding of the processes and formulations developed during this work, the following further work is recommended:

- Developed artemisinin solid dispersion (ArtSd3) formulations can be suitably converted to patient compliant oral dosage form such as pellets, tablets and or capsules and or sachets etc.

- Quantification of the mechanical properties of the prepared triclinic form of artemisnin would useful to gain further insight into the extrusion process.

- In this thesis, only a single API, artemisinin, was investiaged in detail. It is therefore suggested that other examples would be interesting to study in detail. In the case of piracetam, form I is difficult to isolate as it transforms to form II within a few hours using traditional methods but form I prepared by applying the HTE technique was stable up to one month. Therefore a study of the solubility of form I in different solvents is recommended.

- Chlorpropamide polymorphs are sensitive to Raman spectroscopy and therefore it is suggested that this could be used as a good example to apply PAT during extrusion processing. The generated form C has a greater dissolution rate and therefore the biovailability of the metastable form C could be enhanced.

- Paracetamol and theophylline undergo polymorphic transformation under thermal and mechanical stress but surprisingly did not exhibit

phase transformation during high temperature extrusion. Further investigation of these examples using computational modelling is recommended.

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7.3. Output

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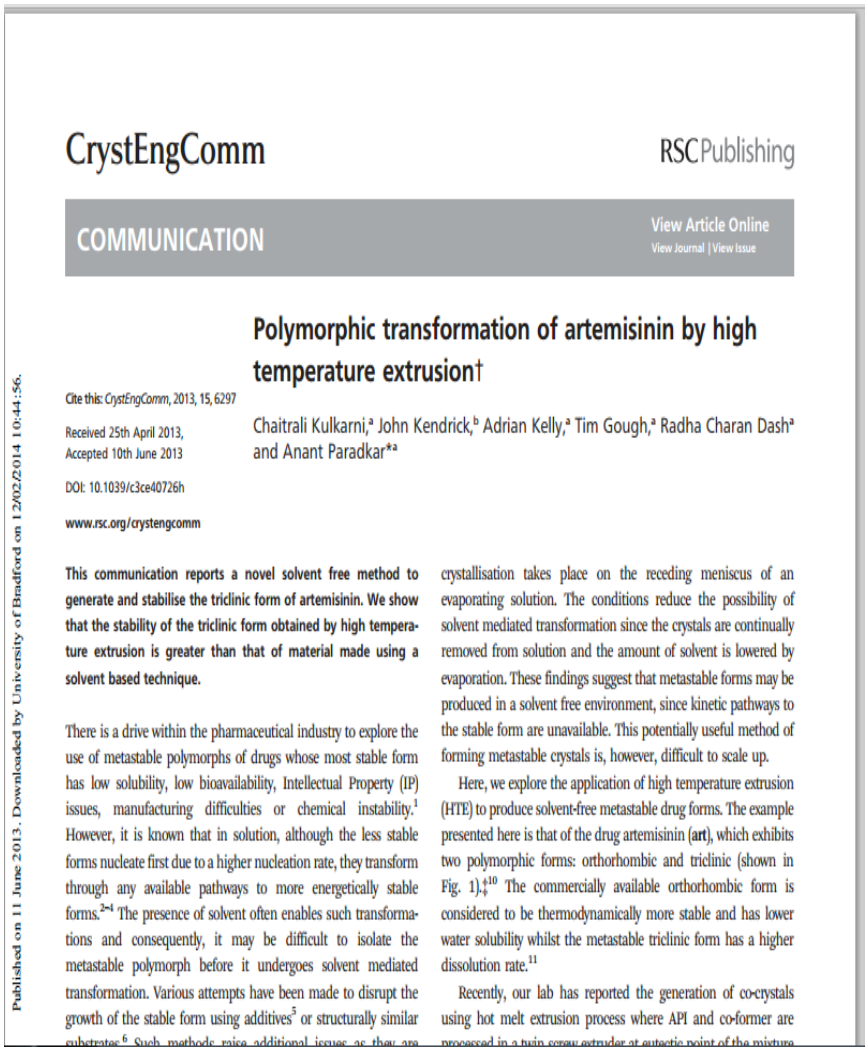
- Polymorphic transformation of artemisinin by high temperature extrusion



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This communication reports a novel solvent free method to generate and stabilise the triclinic form of artemisinin. We show that the stability of the triclinic form obtained by high temperature extrusion is greater than that of material made using a solvent based technique.

There is a drive within the pharmaceutical industry to explore the use of metastable polymorphs of drugs whose most stable form has low solubility, low bioavailability, Intellectual Property (IP) issues, manufacturing difficulties or chemical instability.[1] However, it is known that in solution, although the less stable forms nucleate first due to a higher nucleation rate, they transform through any available pathways to more energetically stable forms.[2–4] The presence of solvent often enables such transformations and consequently, it may be difficult to isolate the metastable polymorph before it undergoes solvent mediated transformation. Various attempts have been made to disrupt the growth of the stable form using additives[5] or structurally similar substrates.[6] Such methods raise additional issues as they are crystallisation takes place on the receding meniscus of an evaporating solution. The conditions reduce the possibility of solvent mediated transformation since the crystals are continually removed from solution and the amount of solvent is lowered by evaporation. These findings suggest that metastable forms may be produced in a solvent free environment, since kinetic pathways to the stable form are unavailable. This potentially useful method of forming metastable crystals is, however, difficult to scale up.

Here, we explore the application of high temperature extrusion (HTE) to produce solvent-free metastable drug forms. The example presented here is that of the drug artemisinin (**art**), which exhibits two polymorphic forms: orthorhombic and triclinic (shown in Fig. 1).‡[10] The commercially available orthorhombic form is considered to be thermodynamically more stable and has lower water solubility whilst the metastable triclinic form has a higher dissolution rate.[11]

Recently, our lab has reported the generation of co-crystals using hot melt extrusion process where API and co-former are processed in a twin screw extruder at eutectic point of the mixture

- Mechanism for polymorphic transformation of artemisinin during high temperature extrusion

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Mechanism for Polymorphic Transformation of Artemisinin during High Temperature Extrusion

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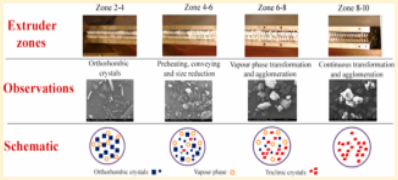
Supporting Information

ABSTRACT: A novel, green, and continuous method for solid-state polymorphic transformation of artemisinin by high temperature extrusion has recently been demonstrated. This communication describes attempts to understand the mechanisms causing phase transformation during the extrusion process. Polymorphic transformation was investigated using hot stage microscopy and a model shear cell. At high temperature, phase transformation from orthorhombic to the triclinic crystals was observed through a vapor phase. Under mechanical stress, the crystalline structure was disrupted continuously, exposing new surfaces and accelerating the transformation process.



Pharmaceutical processing has the potential to disrupt the crystal lattice of APIs and has thus gained considerable attention.[1,2] Different molecular arrangements can provide diverse physical and chemical properties in pharmaceutical substances, thus altering solubility, density, stability, and bioavailability.[3] Several unit operations employed to prepare solid dosage forms, such as grinding, milling, drying, and compression may induce solid-state polymorphic transforma-

conveying material along the barrel; the extent of shear and residence time in the process depends on the screw configuration, screw speed, set temperature, and properties of the material. The barrel is divided into several zones and the temperature of each zone can be independently controlled.[10] The extruder has been used as a reactor to cause grafting of the polymers. Solvent-free cocrystallization (SFCC) using a melt extruder involves processing of stoichiometric amounts of