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POLYMERIC DOSAGE FORMS WITH IMPROVED RELEASE KINETICS FOR KETOPROFEN AND FENOFIBRATE

FORMES GALENIQUES POLYMERIQUES AVEC CINETIQUES DE LIBERATION AMELIOREE POUR LE KETOPROFENE ET LE FENOFIBRATE

THESE

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List of abbreviations

A:	Specific Area
AFM:	Atomic Force Microscopy
AP:	Absorption Potential
API:	Active Pharmaceutical Ingredient
BA:	Bioavailability
BCS:	Biopharmaceutics Classification System
CD:	Cyclodextrin
Cs:	Concentration saturation
D:	Diffusion coefficient
DCS:	Developability Classification System
DSC:	Differential Scanning Calorimetry
FDA:	Food and Drug Administration
FIP:	Fédération Internationale Pharmaceutique
FTIR:	Fourier Transformed Infra-Red spectroscopy
GIT:	Gastro-Intestinal Tract
GMP	Good Manufacturing Practice
GRAS:	Generally Regarded As Safe
HCl:	Hydrochloric Acid
HLB:	Hydrophile lipophile balance
HME:	Hot-Melt Extrusion
HPC:	Hydroxypropylcellulose
HPLC:	High Performance Liquid Chromatography
HPMC:	Hydroxypropylmethylcellulose
HSM:	Hot-stage microscopy
HTS:	High Throughput Screening
IC:	Isothermal microcalorimetry
ICH:	International Conference of Harmoinzation
IR:	Immediate Release
L:	Thickness of the diffusion layer

LFCS:	Lipid Formulation Classification System
MC:	Methylcellulose
MEC:	Minimum Effective Concentration
MTC:	Minimum Toxic Concentration
Mw:	Molecular weight
NF:	National Formulary
NIR:	Near-Infrared spectroscopy
NME:	New Molecular Entities
NMR:	Nuclear Magnetic Resonance
NSAI:	Non Steroidal Anti-Inflammatory
OMS:	Ordered Mesoporous Silica
PAT:	Process Analytical Technology
PCA:	Precipitation with Compressed fluid Anti-solvent
PEG:	Polyethylène glycol
PEO:	Polyethylène Oxide
PVP:	Polyvinylpyrrolidone
PVP-CL:	Crospovidone
PVP-VA:	Vinylpyrrolidone-vinyl acetate copolymer
PWSD:	Poorly water soluble drug
RESAS:	Rapid Expansion from Supercritical to Aqueous Solution
RESS:	Rapid Expansion of Supercritical Solution
SAS:	Supercritical Anti-solvent
SD:	Solid Dispersion
SEDDS:	Self-Emulsifying Drug Delivery System
SEDS:	Solution Enhanced Dispersion by the Supercritical fluids
SEM:	Scanning electron microscopy
SFL:	Spray Freezing into Liquid
SLS:	Sodium lauryl sulfate
SMEDDS:	Self-MicroEmulsifying Drug Delivery System
T_g:	Glass transition temperature
TPGS:	d-α-tocopherol polyethylene glycol 1000 succinate

TPS:	Teraherttz pulsed spectroscopy
TSE:	Twin-Screw Extruder
USP:	United States Pharmacopeia
UV:	Ultra-Violet spectroscopy
XRPD:	X-Ray Pattern Diffraction

Table of contents

RÉSUMÉ DÉTAILLÉ 1

CHAPTER I. INTRODUCTION 16

I. DISSOLUTION AND SOLUBILITY 17

I.1. Background 17

I.2. Observations 19

I.3. Ways to enhance drug solubility 21

I.3.1. Structure modification 21

I.3.2. Formulation strategies 22

II. AMORPHOUS DRUGS IN PHARMACEUTICAL FORMS 25

II.1.1. Generation and properties 25

II.1.2. Stabilization of the amorphous drugs 27

II.1.2.1. Binary co-amorphous mixtures 28

II.1.2.2. Mesoporous systems 28

III. SOLID DISPERSIONS 30

III.1. Background 31

III.2. Classification and definitions 32

III.3. Advantages and drawbacks 35

III.4. Drug release mechanisms from solid dispersions 36

III.5. Formulation of solid dispersions 40

III.5.1. Preparation methods 40

III.5.2. Selection and type of carriers 42

III.5.3. Characterization of solid dispersions 47

III.6. Hot-Melt-Extrusion 49

III.6.1. Equipment 51

III.6.1.1. Co-rotating twin screw extruders 52

III.6.1.2. Downstream processing equipment 53
III.6.2. HME processing 54
III.6.2.1. Screw design and configuration 54
III.6.2.2. Processing parameters and scale-up 55
III.6.2.3. Process analytical technology 55
III.6.3. Materials 56
III.6.3.1. Carriers 56
III.6.3.2. Plasticizers 58
III.6.3.3. Other processing aids 58
III.7. Spray-drying 59
III.7.1. Equipment and process 59
III.7.1.1. Atomization 60
III.7.1.2. Drying chambers 61
III.7.1.3. Collecting systems 63
III.7.2. Materials 63
III.7.2.1. Carriers 64
III.7.2.2. Solvent system 65
III.7.3. Process parameters 66
III.7.3.1. Feed flow rate 66
III.7.3.2. Inlet temperature 66
III.7.3.3. Spray flow rate 68
III.7.4. Pharmaceutical applications 68
III.7.4.1. Excipients and co-spray dried composites 68
III.7.4.2. Solubility improvement 69
III.7.4.3. Other applications 70
IV. RESEARCH OBJECTIVES 71
V. REFERENCES 73

CHAPTER II. ACCELERATED KETOPROFEN RELEASE FROM POLYMERIC MATRICES: IMPORTANCE OF THE HOMOGENEITY/HETEROGENEITY OF EXCIPIENT DISTRIBUTION 94

I. INTRODUCTION 96

II. MATERIALS AND METHODS 97

II.1. Materials 97

II.2. Preparation of physical mixtures 97

II.3. Preparation of hot-melt extrudates 98

II.4. Preparation of spray-dried powders 98

II.5. In vitro drug release measurements 99

II.6. Equilibrium solubility measurements 99

II.7. mDSC analysis 99

II.8. X-ray diffraction studies 100

II.9. Scanning electron microscopy and optical macro/microscopy 100

III. RESULTS AND DISCUSSION 101

III.1. Ketoprofen-Eudragit® E hot-melt extrudates 101

III.2. Spray-dried and hot-melt extruded ternary combinations 107

III.3. Ketoprofen:Eudragit® E:PVP combinations 113

III.4. Ketoprofen:Eudragit® E:PVPVA combinations 114

III.5. Ketoprofen:Eudragit® E:HPMC combinations 115

IV. CONCLUSION 117

V. REFERENCES 117

CHAPTER III. ACCELERATED KETOPROFEN RELEASE FROM SPRAY-DRIED POLYMERIC PARTICLES: IMPORTANCE OF PHASE TRANSITIONS AND EXCIPIENT DISTRIBUTION 120

I. INTRODUCTION 122

II. MATERIALS AND METHODS 123

II.1. Materials 123

II.2. Preparation of physical mixtures 123

II.3. Preparation of spray-dried powders 124

II.4. In vitro drug release measurements 125

II.5. Equilibrium solubility measurements 125

II.6. mDSC analysis 125

II.7. Particle size measurements 126

II.8. X-ray diffraction studies 126

II.9. Scanning electron microscopy 126

III. RESULTS AND DISCUSSION 127

III.1. Impact of the type of polymer 127

III.2. Impact of the processing conditions 136

III.3. Drug suspension versus drug solution used for spray-drying. 141

IV. CONCLUSION 146

V. REFERENCES 146

CHAPTER IV. ACCELERATED FENOFIBRATE RELEASE FROM SPRAY-DRIED MICROPARTICLES BASED ON POLYMER BLENDS 149

I. INTRODUCTION 151

II. MATERIALS AND METHODS 152

II.1. Materials 152
II.2. Preparation of physical mixtures 153
II.3. Preparation of spray-dried microparticles.....153
II.4. In vitro drug release measurements.....153
II.5. Determination of equilibrium solubility 154
II.6. X-ray diffraction studies.....155
II.7. Particle size measurements 155
III. RESULTS AND DISCUSSION 155
III.1. PVP/Eudragit® E blends 155
III.2. HPMC/Eudragit® E blends.....163
IV. CONCLUSION 169
V. REFERENCES 169
GENERAL CONCLUSION 172
SUMMARY 176
RESUME 178

RESUME DETAILLE

Depuis plus d'un siècle, l'administration de médicaments par voie orale est la voie la plus employée, du fait de la simplicité et de la facilité de prendre un comprimé. Cependant, la réussite thérapeutique d'un traitement médicamenteux dépend de la biodisponibilité et par conséquent de la solubilité du principe actif en milieu aqueux. Cette dernière est l'un des plus importants paramètres permettant d'atteindre la concentration minimale effective dans la circulation systémique et d'obtenir une réponse pharmacologique. De nos jours, de plus en plus de principes actifs sont peu solubles en milieu aqueux impliquant des faibles taux de dissolution et une faible absorption. Cette dernière pouvant aussi être limitée par une étroite fenêtre d'absorption dans le tractus gastro-intestinal comme c'est le cas pour de nombreux principes actifs qui voient leur absorption limitée au début de l'intestin grêle. En conséquence, pour obtenir une concentration effective dans la circulation sanguine et ainsi une réponse pharmacologique, les doses et fréquences d'administration doivent être augmentées. Ceci, peut alors induire une augmentation des effets secondaires et un dépassement de la concentration minimale toxique conduisant à la non observance du patient et donc à un échec thérapeutique. Il devient alors essentiel d'améliorer la solubilité de ces composés peu solubles et par conséquence leur taux de dissolution, leur biodisponibilité et finalement l'efficacité du principe actif à un dosage et une fréquence d'administration réduite. C'est pourquoi, il est nécessaire et essentiel d'améliorer la solubilité des principes actifs pour obtenir et commercialiser des produits biodisponibles et efficaces.

La biodisponibilité par voie orale d'un principe actif est déterminée par deux facteurs clés : la perméabilité et la solubilité. A partir de ces deux facteurs, le « Biopharmaceutics Classification System » a été crée (Table 1). Pour réaliser cette classification il a, au préalable, été nécessaire de définir les différents termes:

- ✓ Un principe actif est considéré comme hautement soluble quand sa dose maximale est soluble dans 250 mL ou moins de milieu aqueux sur une gamme de pH allant de 1 à 7,5 ;
- ✓ Un principe actif est considéré comme hautement perméable quand son absorption représente 90% ou plus de la dose administrée.

Table 1 : Classification BCS [d'après (Amidon et al., 1995)]

	Haute perméabilité	Faible perméabilité
Haute solubilité	Classe I	Classe III
Faible solubilité	Classe II	Classe IV

En 2003, la biodisponibilité d'un principe actif administré par voie orale a été définie par la « Food and Drug Administration » comme étant: « le taux et la quantité à laquelle le principe actif ou la partie active est absorbée à partir d'un médicament et devient disponible sur son site d'action. Pour les médicaments qui ne sont pas destinés à être absorbés dans la circulation sanguine, la biodisponibilité peut-être évaluée par des mesures visant à refléter le taux et la quantité de principe actif à laquelle le principe actif ou la partie active devient disponible sur son site d'action » (FDA, 2003a).

Historiquement la principale source utilisée pour découvrir de nouveaux composés biologiquement actifs était des produits naturels isolés de plantes (digoxine), d'animaux (insuline du porc) ou de produits de fermentation (pénicilline). Cependant pour réduire le temps et les coûts engendrés par la production de nouvelles molécules compétitives et efficaces, les chercheurs ont développé durant les années 1980, de nouvelles technologies : la chimie combinatoire et le criblage haut débit, « High Throughput Screening » (HTS). La première permet de synthétiser des centaines voire des milliers de molécules en un temps limité. Quant au criblage haut-débit il permet aux chercheurs de conduire rapidement des milliers de tests biochimiques, génétiques et pharmacologiques. La combinaison de ces deux techniques permet alors d'obtenir un très grand nombre de candidats potentiels en un minimum de temps. Cependant l'application de ces techniques a conduit à l'obtention de candidats possédant des propriétés physico-chimiques, pharmacocinétiques et pharmacodynamiques qui sont loin d'être optimales. En effet, leurs structures sont de plus en plus complexes, ils sont le plus souvent lipophiles et ont une masse moléculaire importante. Il résulte de ces caractéristiques une solubilité en milieu aqueux et une absorption par voie orale limitée. Par conséquent, de profonds changements ont pu être observés dans la répartition des molécules entre les différentes classes du BCS (Figure 1).

Pour appuyer ces observations, un « état des lieux » a été réalisé en 2006 sur le « top 200 » des principes actifs commercialisés aux États-Unis. Il a été montré que 40% des molécules présentes sur le marché font partie des classes II et IV du BCS, c'est-à dire qu'elles ont une faible biodisponibilité principalement due à leur faible solubilité en milieu aqueux (*Figure 1A*). Pour les nouvelles molécules en cours de développement, ce n'est pas 40% mais 90% qui font partie des classes II et IV de cette classification (*Figure 1B*). Il apparaît donc comme nécessaire et primordial d'optimiser les caractéristiques de ces molécules pour obtenir une solubilité et par conséquent une biodisponibilité acceptable pour qu'elles soient mises sur le marché.

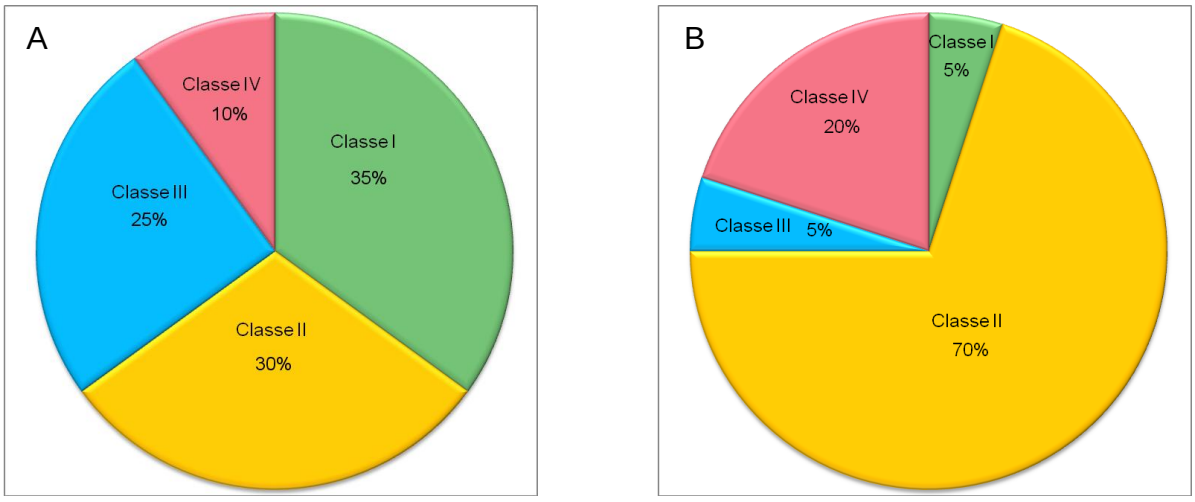


Figure 1 : Répartition des PA en fonction de la classification BCS. A : Molécules commercialisées, B : Molécules en développement [d'après (Benet et al, 2006)]

Depuis de nombreuses années, l'amélioration de la solubilité des principes actifs peu solubles est devenue l'un des principaux challenges de l'industrie pharmaceutique. Bien que présentant une structure chimique potentiellement idéale pour interagir avec la cible, elles échouent dans l'efficacité in vivo : après administration, elles ne peuvent se dissoudre dans les milieux aqueux biologiques et par conséquent ne peuvent être transportées sur leur site d'action pour atteindre la concentration efficace, amenant à un échec thérapeutique. De nombreuses stratégies ont alors été envisagées pour surmonter ce sérieux obstacle incluant des stratégies (Figure 2):

- chimiques : les prodrogues, les sels, les co-cristaux, les nano-cristaux ;
- galéniques : les formulations lipidiques, les micelles polymériques, les cyclodextrines, les systèmes mésoporeux et les dispersions solides.

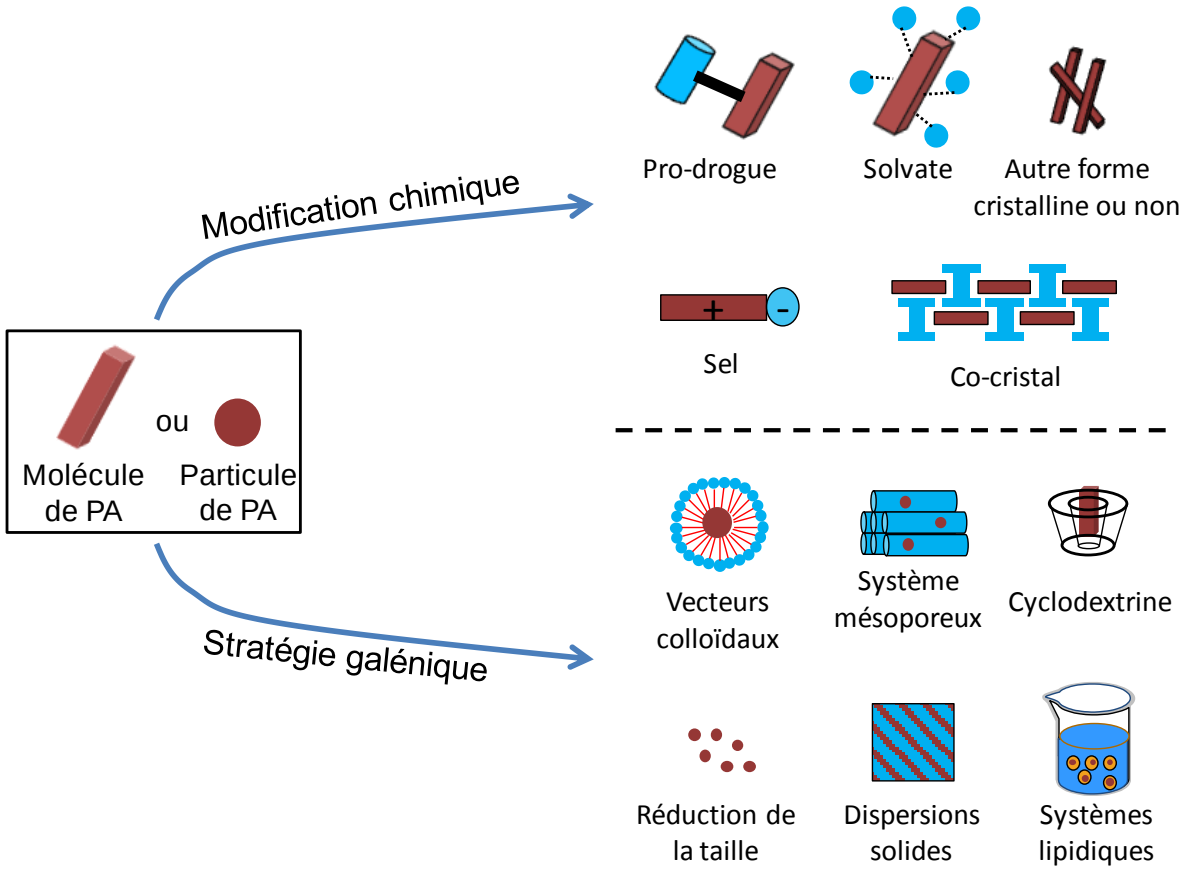


Figure 2 : Différentes stratégies utilisées pour l'amélioration de la solubilité des principes actifs faiblement solubles

Les dispersions solides ont déjà été intensément étudiées mais du fait de leur instabilité principalement due à la forme amorphe du principe actif au sein de celle-ci, seulement une vingtaine de spécialités ont été commercialisées en plus de 50 ans de recherche.

La forme amorphe des principes actifs est de plus en plus utilisée pour l'amélioration de la solubilité des principes actifs, principalement pour former des dispersions solides amorphes. Cependant, la stabilisation de cette forme reste encore aujourd'hui un véritable challenge expliquant le peu de spécialités commercialisées à l'heure actuelle. Cette forme peut-être obtenue de différentes manières dont les plus fréquentes sont :

- ✓ le broyage permettant son obtention directement à partir du solide cristallin ;

- ✓ le « quench-cooling » et la précipitation à partir d'une solution où le principe actif est préalablement transformé en une forme non-cristalline thermodynamiquement stable (liquide ou en solution) puis rapidement transformée en un solide par refroidissement ou évaporation du solvant.

Alors que la forme cristalline (Figure 3A) présente un ordre à longue distance et est la forme la plus stable d'un composé donné, l'état amorphe (Figure 3B) est l'état le moins stable d'un solide, typiquement caractérisé par un ordre à très faible distance (quelques liaisons hydrogènes) et une température de transition vitreuse. Au-dessus de celle-ci le solide est dans un état « caoutchouteux » et en-dessous dans un état « vitreux ».

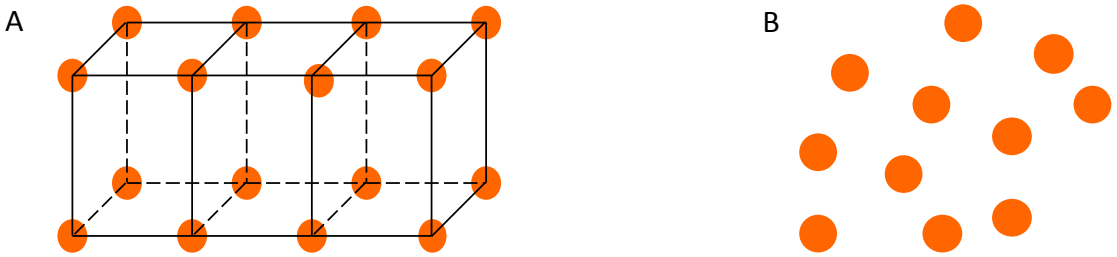


Figure 3: Représentation schématique de la forme cristalline (A) et amorphe (B) d'un composé

Ce problème de stabilité est principalement dû à la haute énergie de cet état qui conduit à une plus grande mobilité moléculaire et est donc responsable de la haute réactivité chimique mais aussi de la tendance à la recristallisation qui peut survenir durant le procédé de fabrication, le stockage ou la dissolution. Cependant, cet état présente plusieurs propriétés très intéressantes également liées à ce haut niveau d'énergie qui sont principalement une solubilité apparente et un taux de dissolution augmenté. Ces propriétés sont dues à l'amélioration des propriétés thermodynamiques et à l'absence de maille cristalline à rompre. Pour limiter la perte de ces avantageuses propriétés, de nombreux efforts ont été mis dans la compréhension des facteurs critiques conduisant à la recristallisation et au dépassement de ceux-ci en trouvant des méthodes de stabilisation de cette forme. Du fait de la complexité du phénomène de recristallisation et des nombreux facteurs impliqués, leur importance relative est aujourd'hui encore floue. C'est pour cela que très peu de méthodes sont disponibles en vue de la stabilisation de la forme amorphe : les dispersions solides, les systèmes mésoporeux et les co-amorphes.

Comme expliqué précédemment, la formation de dispersion solide est l'une des techniques les plus utilisées et faisant l'objet de très nombreuses recherches par leurs nombreux avantages, cependant le problème crucial pour qu'elles soient couramment appliquées dans le développement pharmaceutique reste et restera encore pour quelques années la stabilisation de la forme amorphe.

C'est en 1961 que Sekiguchi et Obi développe une nouvelle méthode pour contrer le problème de solubilité des principes actifs peu solubles par la formation d'un mélange eutectique entre un PA peu ou pas hydrosoluble et un ou plusieurs vecteurs hydrosolubles par la fusion de leur mélange physique. Ils ont alors émis l'hypothèse que le PA était présent à l'état microcristallin dans ce mélange (Sekiguchi and Obi, 1961). Cinq ans plus tard, Goldberg a démontré que tout le principe actif n'était pas forcément dans un état microcristallin. Une certaine fraction du PA pouvait être dispersée à l'état moléculaire dans la matrice, formant une solution solide (Goldberg et al., 1966a). Quelques années plus tard le terme dispersion solide a été défini par Chiou et Riegelman comme étant : « la dispersion à l'état solide d'un ou plusieurs principes actifs dans un vecteur inerte préparé par des méthodes à base de solvants, de fusion ou une combinaison des deux » (Chiou and Riegelman, 1971). En 1985, Corrigan a suggéré la définition comme étant : « un produit formé en convertissant un mélange principe actif – vecteur de l'état fluide à l'état solide » (Corrigan, 1985). Aujourd'hui le terme de dispersions solides est le plus souvent lié aux solutions solides dans lesquelles le principe actif est dissous (solution solide amorphe) ou dispersé à l'état moléculaire (suspension solide amorphe) ou cristallin (suspension solide cristalline) du fait de leurs nombreux avantages comparés aux autres méthodes :

- ✓ Le principe actif peut-être neutre ;
- ✓ La réduction de la taille des particules à l'état moléculaire avec la possibilité de le présenter sous sa forme amorphe ;
- ✓ La simplicité des procédés ;
- ✓ Une meilleure mouillabilité ;
- ✓ Une plus grande porosité et une agglomération réduite des particules obtenues.

Cependant, elles restent peu commercialisées principalement à cause de problèmes liés à leur fabrication et leur stabilité. Une autre raison majeure est le manque de prédictibilité du comportement des dispersions solides à cause d'un manque de connaissances de base sur leurs propriétés physico-chimiques. Certains de ces problèmes sont :

- ✓ La possibilité de recristallisation de la phase amorphe durant la fabrication (stress mécanique) ou le stockage (température et humidité) ;
- ✓ Sa méthode de préparation avec potentiellement une dégradation due à la chaleur ou aux solvants résiduels ;
- ✓ La reproductibilité de ces propriétés physico-chimiques principalement due à la variation de la vitesse de refroidissement ou d'autres conditions de fabrication ;
- ✓ La difficulté de les incorporer dans des formes galéniques comme les capsules ou les comprimés à cause d'une diminution de la compressibilité et un comportement collant sur les poinçons ;
- ✓ La transposition d'échelle du procédé de fabrication qui peut être délicat.

Aujourd'hui de nouvelles méthodes optimisées et plus facilement transposables ont été mises au point et plusieurs stratégies pour limiter la recristallisation durant le stockage ont été étudiées, cependant cela dépend principalement des propriétés du principe actif et la meilleure issue pour stabiliser le système est de combiner plusieurs approches et surtout de comprendre le comportement physico-chimique de ces systèmes. Le choix du procédé de fabrication et des excipients est alors primordial pour obtenir les propriétés physico-chimiques souhaitées.

La sélection du vecteur est l'un des facteurs clés dans le succès des dispersions solides. Le vecteur doit posséder certaines propriétés essentielles présentées dans le tableau suivant (Table 2) afin de former un système physico-chimiquement stable lors du stockage avec un profil de libération du principe actif rapide. De très nombreux matériaux cristallins ou amorphes sont utilisés comme vecteurs pour former des dispersions solides et tous les polymères cités sont bien connus et approuvés par l'industrie pharmaceutique. Les plus fréquemment utilisés sont: les polyéthylènes-glycol (PEG), les poloxamères, la

polyvinylpyrrolidone (PVP), la crospovidone (PVP-CL), le copolymère de vinylpyrrolidone – vinyl acétate (PVPVA), les dérivés cellulosiques, les dérivés acryliques, l'urée, les polyols, les émulsifiants, les acides organiques. Durant ce travail quatre polymères ont été utilisés : la PVP K30, la PVPVA, l'HPMC et un dérivé acrylique : l'Eudragit® E.

Table 2 : Propriétés recherchées dans les vecteurs pour la formation de dispersions solides

Propriétés	**Caractéristiques souhaitées**
Sécurité	Inerte, généralement reconnu sans danger (GRAS)
Préparation	Thermiquement stable et thermoplastique (méthodes de fusion)
	Soluble dans les solvants organiques (méthodes à base de solvants)
Libération	Soluble dans l'eau avec des propriétés solubilisantes et stabilisantes
Stabilité	Fragilité et transition vitreuse élevée
	Accepteurs/Donneurs d'hydrogène

De nombreuses techniques ont été développées pour formuler les dispersions solides pouvant être séparées en deux groupes : les méthodes basées sur la fusion du vecteur et/ou du principe actif et celles basées sur l'évaporation de solvants.

Les méthodes basées sur la fusion du vecteur et/ou du principe actif ont été les premières utilisées et comprennent aujourd'hui de nombreuses variantes. L'utilisation de températures élevées pour ces méthodes traditionnelles pose problème pour les PA thermolabiles. De plus dans le cas d'un vecteur ayant un point de fusion ou une température de transition vitreuse trop élevée, le principe actif peut ne pas être complètement miscible dans le vecteur. Pour éviter ces différents problèmes, des modifications ont été apportées aboutissant aux méthodes optimisées :

- ✓ La fusion du mélange au-dessus du point eutectique avant un refroidissement rapide par divers moyens ;

- ✓ L'atomisation d'un mélange fondu directement suivie par la congélation des gouttelettes ;
- ✓ L'injection sous pression d'un mélange thermoplastique fondu dans un moule de forme définie ;
- ✓ L'extrusion en phase chauffante, utilisée au cours de ce travail et expliquée par la suite.

Jusqu'à l'arrivée des méthodes à base de solvants, les dispersions solides étaient exclusivement préparées par la méthode de fusion. Le principe de ces méthodes est de solubiliser le principe actif et le vecteur dans un même solvant puis de l'évaporer pour conduire à la formation de particules solides. La différence réside dans le moyen utilisé pour faire évaporer le solvant. Les principales méthodes utilisées sont :

- ✓ La co-précipitation du PA et du vecteur lors de l'ajout d'un anti-solvant. Les particules seront ensuite filtrées et séchées ;
- ✓ L'utilisation d'évaporateur rotatif permettant une évaporation du solvant sous pression réduite et placé dans un bain-marie ;
- ✓ L'utilisation de fluides supercritiques ;
- ✓ La congélation-séchage (« freeze-drying ») qui consiste à congeler la solution par immersion dans de l'azote liquide puis d'évaporer le solvant par sublimation ;
- ✓ Par atomisation-séchage (« spray-drying »), qui a également été utilisée et sera détaillée un peu plus loin dans ce résumé.

Les deux méthodes les plus utilisées à l'heure actuelle sont celles employées lors de ce travail à savoir : l'extrusion en phase chauffante et l'atomisation-séchage.

Après obtention de ces dispersions solides, la caractérisation physico-chimique ainsi que les tests de dissolution in vitro sont nécessaires pour déterminer l'état physique dans lequel se trouve le principe actif, le type de dispersion solide obtenu et les performances pharmaceutiques de cette dernière. Pour cela de nombreuses techniques thermiques, spectroscopiques, microscopiques et différents tests de dissolution sont disponibles.

La première technique utilisée lors de ce travail est l'extrusion en phase chauffante ou « Hot Melt Extrusion » (HME). C'est une technique bien connue et utilisée depuis le milieu du 19ème siècle dans l'industrie agro-alimentaire (pâtes) et plastique pour préparer les gaines des fils électriques. De nos jours, elle est toujours très utilisée dans l'industrie plastique pour préparer des produits comme : les sacs plastique, des plaques et des tuyaux. Elle a également été adaptée à un usage pharmaceutique et l'intérêt pour cette technique a rapidement progressé avec de nombreux articles et brevets. Elle est utilisée pour de très nombreuses applications incluant : les médicaments à libération immédiate, prolongée et contrôlée pour la voie orale, les systèmes transdermiques, transmuqueux et transunguéaux mais aussi les implants et les anneaux vaginaux.

Les extrudeurs co-rotatif bi-vis sont les plus utilisés dans le domaine pharmaceutique et sont composés : d'un système d'alimentation, d'un fourreau contenant les vis, d'unités de dégazage, de plusieurs capteurs de pression et de température et d'une filière donnant la forme à l'extrudat comme présenté en Figure 4. A ceci, un procédé en aval peut être ajouté permettant un procédé en une seule étape tel que : un pelletiseur permettant l'obtention de cylindres de dimensions souhaitées, des rouleaux compacteurs pour former des films d'épaisseurs contrôlées ou encore l'injection dans un moule de formes variées pour répondre à différentes demandes comme des formes pédiatriques attrayantes, des inserts auriculaires….

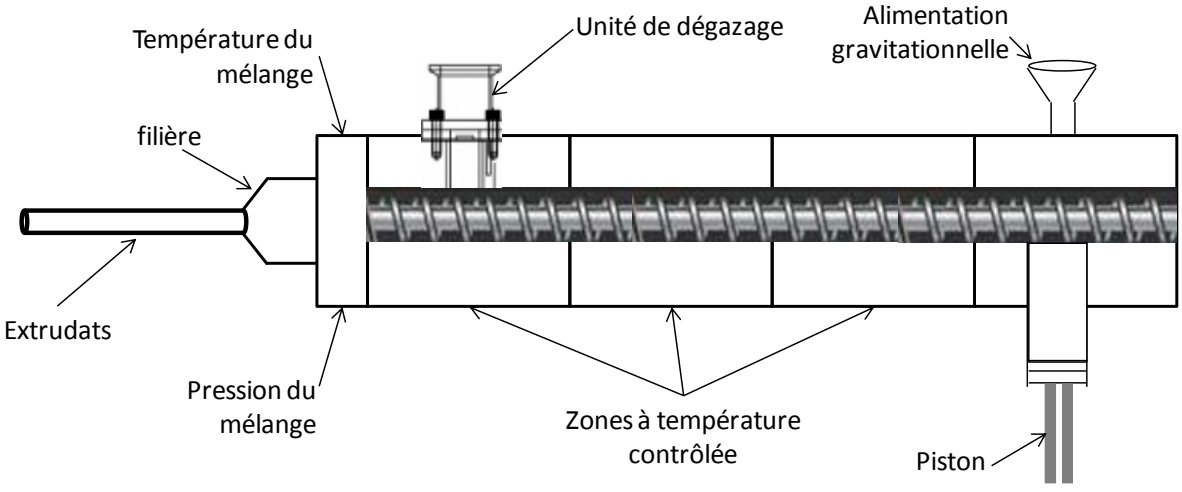


Figure 4 : Représentation schématique d'un HME

Il s'agit d'un procédé continu ou le mélange est simultanément fondu, mixé, homogénéisé tout au long des vis puis extrudé en fonction de la forme de la filière. Par la suite les extrudats obtenus pourront être mis sous la forme souhaitée en fonction des besoins : comprimés, gélules, sticks, poudre, etc. Le principal avantage de cette technique est le faible temps de résidence du mélange dans l'extrudeuse permettant l'utilisation de principes actifs thermolabiles. Différents paramètres auront une influence non négligeable sur le produit final tels que : la configuration des vis (éléments convoyeurs et de broyage), la vitesse de rotation des vis, le taux d'alimentation, les températures appliquées aux différentes zones de l'extrudeur qui représentent les paramètres les plus fréquemment étudiés et ont un impact direct sur le taux de cisaillement et le temps de résidence du mélange dans l'extrudeur. Pour contrôler au mieux le procédé, les technologies analytiques de procédés (« Process Analytical Technology ») ont été développées et adaptées à l'extrusion.

La seconde technique employée est l'atomisation-séchage ou « spray-drying ». D'abord utilisée pour produire le lait en poudre dans les années 1920, elle reste aujourd'hui l'une des principales applications de ce procédé dans l'industrie agro-alimentaire. L'utilisation de cette technique a explosé lors de la 2nde guerre mondiale avec les besoins en grande quantité de nourriture, le poids et la taille ont donc été réduits par cette technique facilitant le transport et la conservation des aliments. C'est également à cette période que l'industrie pharmaceutique s'y est intéressée pour faciliter le transport de plasma et de sérum afin de soigner les blessés. Après plus de 150 ans de recherche, c'est aujourd'hui encore l'une des techniques de séchage les plus utilisées et servant de très nombreuses applications dans l'industrie pharmaceutique dont : la production d'excipients pour améliorer leurs propriétés de compression, la fabrication de mélanges prêts à l'emploi pour la compression directe, l'amélioration de la solubilité de nombreux principes actifs par la formation de dispersions solides, le séchage d'émulsions pour augmenter leur stabilité physico-chimique, le masquage de goût, le séchage de protéines, de vaccins, d'organismes viables et la production de poudres inhalables.

Cette technique requiert un équipement assez simple comprenant : un système d'atomisation, une chambre de séchage et un système collecteur (Figure 5). Chacun de ces éléments peut avoir un énorme impact sur les caractéristiques du produit obtenu et ils sont

donc choisis en fonction de l'application souhaitée. Pour cela, une solution contenant le principe actif et le polymère est vaporisée dans la chambre de séchage, formant un aérosol. Il entre alors en contact avec un courant d'air chaud permettant une évaporation rapide du solvant et l'obtention de microparticules solides. La poudre ainsi formée passe dans un cyclone et est récupérée dans un collecteur.

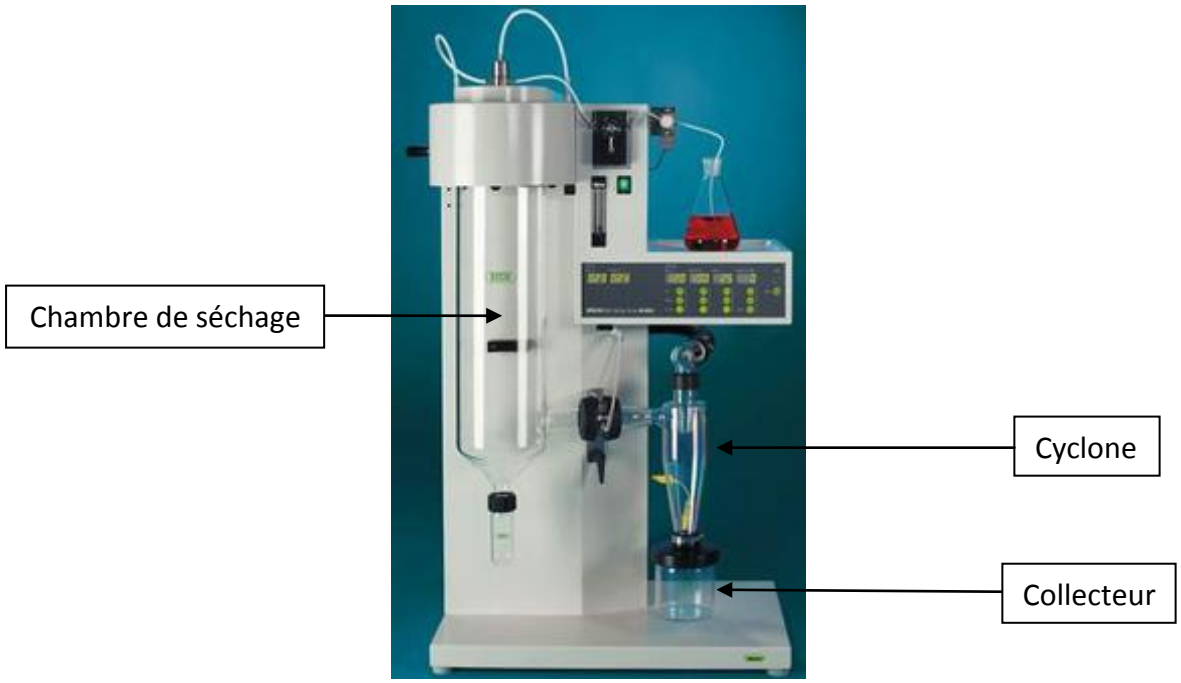


Figure 5 : Büchi B-290

Dans cette technique, comme pour l'extrusion en phase chauffante, plusieurs paramètres peuvent avoir une grande importance et doivent être sélectionnés avec attention. Les principaux paramètres étant : la température d'entrée, le taux d'alimentation et le taux d'atomisation du gaz.

Les dispersions solides amorphes représentent aujourd'hui une solution attractive pour améliorer la solubilité des principes actifs peu solubles, assurant une meilleure observance du traitement par le patient due à la diminution des doses administrées ainsi qu'à la réduction des effets secondaires. Aujourd'hui, l'extrusion en phase chauffante et l'atomisation séchage représentent les deux techniques les plus fréquemment utilisées pour préparer ce type de systèmes. Cependant malgré des recherches approfondies dans

ce domaine depuis plus de 50 ans, seulement quelques produits ont atteint le marché pharmaceutique, principalement à cause de problèmes de stabilité physico-chimique de l'état amorphe.

Le principal objectif de ce travail a été d'améliorer la solubilité des principes actifs peu solubles par formation de dispersions solides utilisant les deux techniques les plus utilisées : l'extrusion en phase chauffante et l'atomisation-séchage. Dans cette étude, le kétoprofène a été incorporé dans des matrices polymériques hydrophiles pour augmenter sa solubilité apparente. Les deux techniques ont été employées et l'Eudragit® E a été considéré comme une matrice intéressante pour plusieurs raisons : c'est un polymère thermoplastique, offrant une stabilité thermique suffisante pour l'extrusion en phase chauffante, il se dissout rapidement en milieu acide et peut interagir avec les groupements acides de par ses nombreux azotes ternaires. Des mélanges binaires « principe actif – Eudragit®E » ainsi que des mélanges ternaires « principe actif – Eudragit®E - PVP », « principe actif – Eudragit®E - PVPVA », « principe actif – Eudragit®E - HPMC » ont été étudiés et caractérisés Les systèmes obtenus ont été caractérisés par macro/microscopie optique, microscopie électronique à balayage, diffraction laser, analyse calorimétrique différentielle modulée, diffraction des rayons X et l'étude du profil de libération in vitro en milieu acide (HCl 0.1M). Les libérations ont été intentionnellement réalisées en condition « non sink » afin d'évaluer le potentiel des formulations à produire des solutions sur-saturées et la durée de ces dernières. Tous les systèmes présentent un profil de libération du kétoprofène beaucoup plus rapide comparé au produit commercial et à la dissolution du principe actif pur. De plus, des solutions sur-saturées peuvent être obtenues et restent stables au moins 2 h. Cependant, en fonction des polymères utilisés, différents profils de libération ont été obtenus indiquant que l'utilisation de matrices polymériques pour l'accélération de la libération de principes actifs peu solubles peut être très complexe puisqu'elle n'est pas seulement influencée par la composition du système mais aussi potentiellement par leur structure interne et notamment par l'homogénéité/hétérogénéité de la distribution des excipients. Par la suite, pour mieux comprendre comment les paramètres du procédé et de formulation affectent la libération du kétoprofène dans l'HCl 0.1 M à partir de microparticules obtenues par atomisation-séchage basées sur l'HPMC, la PVP ou la PVPVA, des poudres binaires atomisées-séchées chargées à 30% de kétoprofène

ont été préparées. Le principal objectif a été d'essayer d'élucider l'impact de différents paramètres sur la microstructure résultante et les conditions pour la dissolution du principe actif. Cette étude a été menée en trois étapes : l'impact du type de polymère, l'impact des différents paramètres du procédé avec le polymère sélectionné et suspension versus solution pour préparer la poudre atomisée-séchée. Les systèmes obtenus ont été caractérisés par microscopie électronique à balayage, diffraction laser, analyse calorimétrique différentielle modulée, diffraction des rayons X et l'étude du profil de libération in vitro en milieu acide (HCl 0.1M). Des microparticules polymériques hydrophiles préparées par atomisation-séchage offre un potentiel majeur pour l'amélioration du taux de libération des principes actifs peu solubles. Cependant, malgré leur éventuelle composition plutôt simple (e.g. mélange binaire principe actif:polymère), ces formulations peuvent être très complexes, puisqu'il n'y a pas seulement l'état physique dans lequel se trouvent le principe actif et le polymère mais aussi leur distribution spatiale qui peut fortement impacter la libération du principe actif.

Dans une dernière partie, le but a été de déterminer et de mieux comprendre l'impact du ratio du mélange ainsi que du taux de charge en principe actif sur les caractéristiques clés du système, principalement le taux de libération du principe actif. En conséquence, différents types de microparticules basées sur des mélanges de polymères : HPMC, PVP et Eudragit®E ont été préparées par atomisation-séchage. Le fénofibrate a été choisi comme principe actif modèle puisqu'il est pratiquement insoluble en milieu aqueux (0.23 mg/L, 37°C), il ne présente pas de groupement carboxylique et seulement quelques possibilités de liaisons hydrogène, recristallise très facilement du fait de sa très faible température de transition vitreuse (≈ -20°C) et présente une solubilité limitée dans les matrices polymériques. Des microparticules chargées en kétoprofène et basées sur des mélanges PVP/Eudragit®E et HPMC/Eudragit®E ont été préparées par atomisation-séchage. La composition des systèmes et en particulier le ratio polymère : polymère : principe actif ainsi que le taux de charge ont été étudiées et les propriétés clés déterminées. Cela inclut les études de libération du principe actif dans l'HCl 0.1 M, la diffraction des rayons X, les mesures de solubilités et l'analyse de la taille des particules. Avec toutes les formulations des solutions hautement sur-saturées ont été obtenues après mise en contact des microparticules avec le milieu de dissolution, contrairement aux différentes références. De

plus, la présence d'Eudragit®E co-dissous conduit à une augmentation significative de la solubilité du fénofibrate. Les mélanges de polymères offre un potentiel intéressant pour augmenter la solubilité apparente des principes actifs faiblement solubles, puisque les propriétés avantageuses peuvent être combinées. Cependant, il n'y a pas de systèmes simples et il faut être prudent dans l'optimisation de tels systèmes. Idéalement, leur optimisation devrait se faire au moyen d'une compréhension mécanistique de la libération du principe actif.

Chapter I. INTRODUCTION

For almost a century, oral drug delivery is the preferred and the most employed way to administer drugs as it's easy and simple to take pills, tablets and solutions. However, clinical effectiveness depends on the bioavailability (BA) of the drug and ultimately on the drug solubility (Dokoumetzidis and Macheras, 2006). The latter is one of the most important parameters to reach the minimum effective concentration (MEC) in the systemic circulation and to obtain a pharmacological response. Nowadays, more and more active pharmaceutical ingredients (API) are poorly-water soluble implying poor dissolution rates and poor absorption which may also be complicated by site specificity permeability along the gastrointestinal tract (GIT) as many drugs have a reduced absorption window limited to the upper small intestine (Davis, 2005; Streubel et al., 2006). Consequently, to obtain an effective concentration in the systemic circulation and thus a pharmacological response, doses and administration frequency need to be increased. This can induce more side effects while exceeding the minimum toxic concentration (MTC) and the non observance of the patient can lead to a failure of the treatment. It's therewith essential to improve solubility of poorly water soluble drugs (PWSD) and by consequence dissolution rates, bioavailability and finally the effectiveness of the drug at a lower drug loading of the dosage form (Figure I.1). In this context, it's necessary and essential to improve drug solubility in order to obtain bioavailable and efficient products.

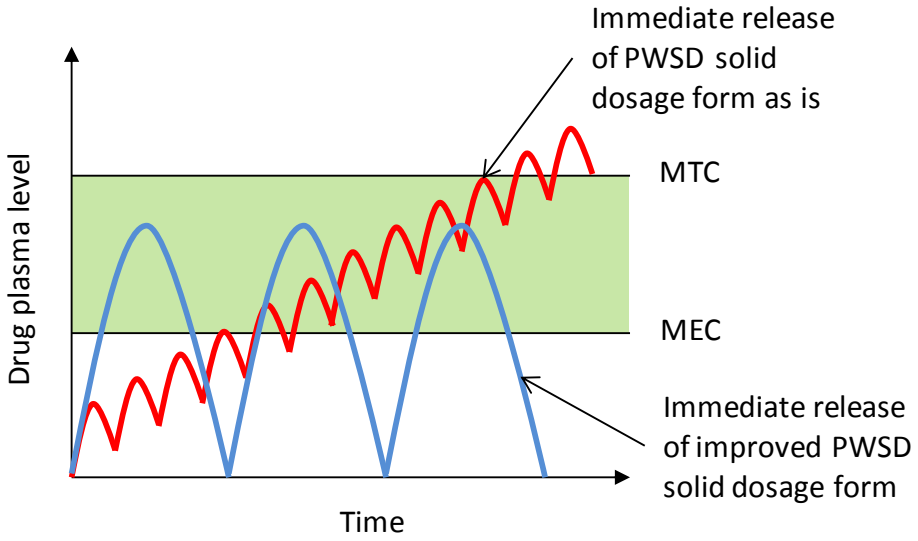


Figure I.1: Schematic representation of drug blood level of a PWSD solid dosage form as is and a PWSD solid dosage form with improved solubility.

I. Dissolution and solubility

I.1. Background

The first dissolution experiments have been conducted and published in 1897 by Noyes and Whitney (Noyes and Whitney, 1897). In this study they established the well-known equation which demonstrates that the rate of dissolution acts proportionality to the difference between concentration at time *t* (C) and saturation concentration (C_s). Its mathematical expression is:

$$\frac{dM}{dt} = \frac{D\,A\,(Cs - C)}{L}$$

Dissolution mechanism is attributed to the diffusion of molecules through a thin solvation layer formed around the solid surface. Until today, this equation is still the reference concerning rate of dissolution and depends on the specific area (A), the diffusion coefficient (D) and the thickness of the diffusion layer (L) of the device.

In 1951, Edwards has been the first to appreciate and postulate that dissolution of a tablet in the gastrointestinal tract might be the step controlling absorption in the bloodstream (Edwards, 1951). Nelson confirmed this basic premise and explicitly established a relation between in vitro dissolution rates and blood levels of a drug orally administered (Nelson, 1957). Later on, in the 1960's, several studies have demonstrated the importance of dissolution on the bioavailability of drugs. A slight change in the formulation has induced large differences in the drug response and might have caused toxic doses within the patients. The most dramatic examples have occurred with phenytoin in Australia (Tyrer et al., 1970) and digoxin in the UK and the USA (Lindenbaum et al., 1971).

Subsequently the needs of dissolution requirements in the different pharmacopeias have been highlighted. In 1970, the first official dissolution test was the basket-stirred-flask test (USP 1) and has been adopted in 6 monographs of the United States Pharmacopeia (USP) and National Formulary (Bruce et al., 2005). In the next editions of the USP, the

number of monographs on dissolution requirements has exploded. The paddle method has been adopted in 1978, the first chapter on drug release appears within the USP 21 (1985) and the first guidelines has been published in 1981 by the "Fédération Internationale Pharmaceutique" (FIP) (Dokoumetzidis and Macheras, 2006).

From the 50's to the end of the 70's intensive research has been done on factors affecting the dissolution rate. Three main factors have been highlighted: the degree of agitation, the solubility and finally the surface of the device exposed to the dissolution medium. Two of three factors capitulate directly from the Noyes-Whitney equation (Dokoumetzidis and Macheras, 2006).

Since 1980, various approaches have been proposed for the estimation of oral drug absorption. In 1985, Amidon and co-workers estimated the absorption potential of a drug using the water-solubility and the administered dose of the drug (Papadopoulou et al., 2008). That's an important step to theoretically analyze oral drug absorption (Dressman et al., 1985). An important work in the history of oral drug absorption has been published by Oh et al. in 1993. The model is based on mass balance considerations and takes into account dissolution, absorption and dose numbers, the three fundamental parameters which control the extent of oral drug absorption (Oh et al., 1993). Based on this work, it has been recognized that drug solubility and the gastrointestinal permeability are the two key factors to control oral bioavailability of a drug. Consequently, the "Biopharmaceutical Classification System" (BCS) has been created (Table I.1) which has had a significant impact on the development of immediate release (IR) oral dosage forms. It enables *in vitro* data using instead of *in vivo* human studies to check the bioequivalence of low risk compounds (BCS class I). To classify drugs, the following terms have been defined (Amidon et al., 1995):

- ✓ A drug is considered highly soluble when the maximum of its therapeutic dose is soluble in 250 mL or less of aqueous medium on a pH range from 1 to 7.5;
- ✓ A drug is considered highly permeable when its gastrointestinal absorption represents at least 90% of the administered dose.

Table I.1: BCS classification [from (Amidon et al., 1995)]

Permeability / Solubility	High	Low
High	Class I	Class III
Low	Class II	Class IV

In 2003, the bioavailability of an orally administered drug has been defined by the Food and Drug Administration (FDA) as "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action." (FDA, 2003a).

I.2. Observations

Historically, new active compounds were principally natural products isolated from plants (digoxin), animals (insulin) or fermentation products (penicillin). Since 1980's, to reduce time and costs generated by the production of efficient and competitive drugs, new drug design techniques have been developed: combinatorial chemistry and "High Throughput Screening" (HTS). The first one allows to synthesize thousands molecules in a reduced time and the latter one conducts rapidly thousands biochemical, genetic and pharmacological tests. A combination of these two techniques permits to obtain thousands potential candidates rapidly. However, physico-chemical, pharmacodynamic and pharmacokinetic properties of those candidates are not ideal. The chemical structures are often complex and the drugs are most of the time lipophilic with a high molecular weight. In this context the number of poorly water-soluble drugs has dramatically increased (Lipinski et al., 2001).

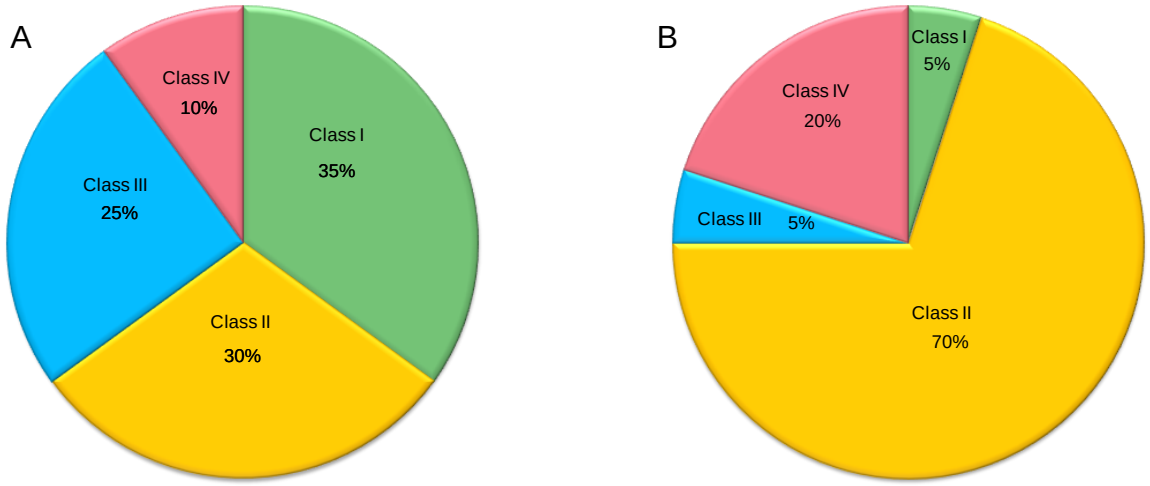


Figure I.2: Drug distribution according to the BCS. A: marketed drugs, B: drugs in development [from (Benet et al., 2006)]

In 2006, the characteristics of the top 200 drugs on the U.S market have been reviewed by Benet. He notices that 40% of those drugs are considered as poorly-water soluble (Figure I.2A). Regarding new molecular entities (NME), this percentage has increased to approximately 90% (Figure I.2B) (Benet et al., 2006).

Today, many studies question the too strict definition in terms of the BCS, especially concerning the solubility term (Benet et al., 2006; Lindenberg et al., 2004; Papadopoulou et al., 2008; Yu et al., 2002). Butler has recently revised the BCS focusing towards the feasibility of the development of a drug. In this revised classification the Developability Classification System (DCS) has been designated, new parameters have been taken into account: intestinal solubility of the drug, compensatory nature of solubility and permeability in the small intestine and an estimate of the particle size needed to overcome dissolution rate limited absorption (Butler and Dressman, 2010). I won't refer deeper into this subject as it isn't within the scope of this work.

Development and formulation of poorly-water soluble drugs is, today, one of the most challenging subjects for scientists. Researchers have developed many ways to overcome this problem.

I.3. Ways to enhance drug solubility

There are both "structure modification" and "formulation strategy" approaches to enhance drug solubility (Figure I.3). The two ways will be briefly described.

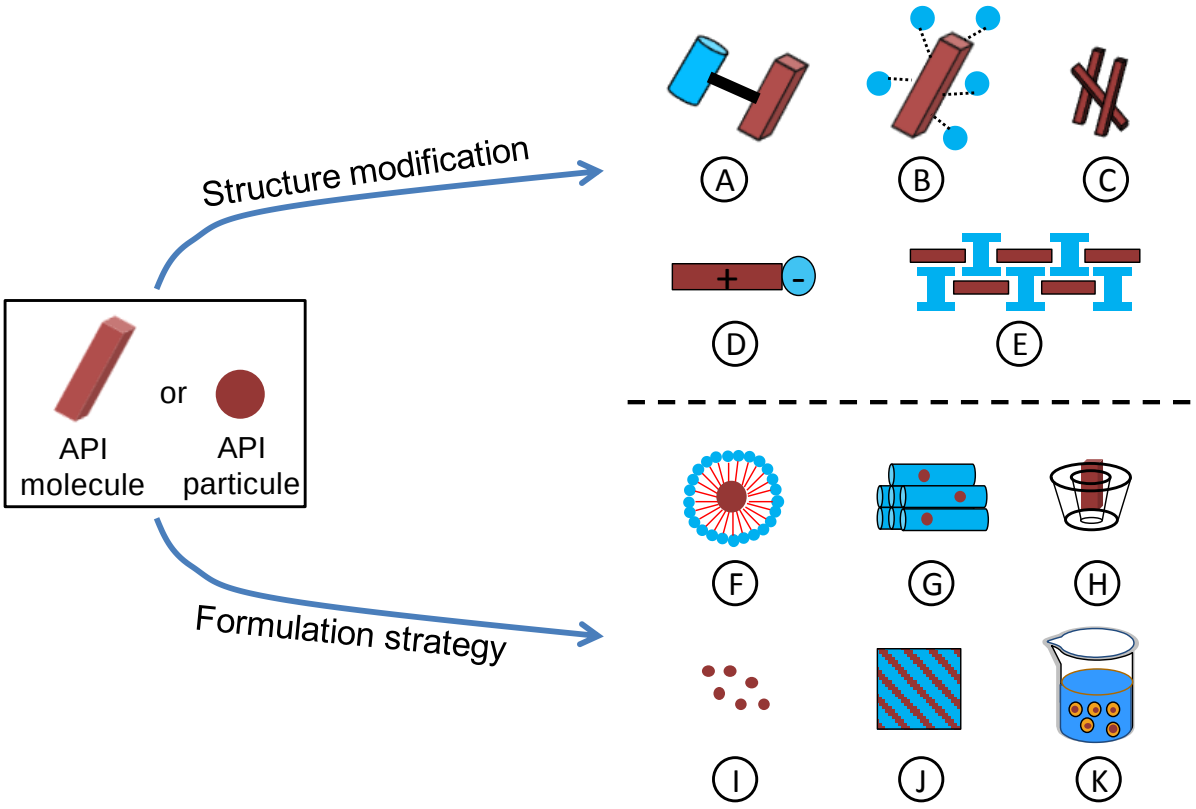


Figure I.3: Various ways to enhance drug solubility. A: Prodrug, B: Solvate, C: Other crystalline or amorphous form, D: Salt, E: Co-crystal, F: Colloidal carrier, G: Ordered mesoporous silica, H: Cyclodextrin inclusion, I: Particle size reduction, J: Solid dispersions, K: Lipid based delivery system

I.3.1. Structure modification

Changing its crystal habit, chemical structure or adding a pro-group can improve drug solubility. Two approaches exist:

✓ **The crystal engineering** which allows to handle solubility or dissolution rate of the parent compound by modifying its solid state (Aaltonen et al., 2009; Blagden et al., 2007) into an amorphous form, a polymorph, a solvate, a salt (Serajuddin, 2007) and more recently co-crystals (Almarsson and Zaworotko, 2004; Elder et al., 2013; Friscic

and Jones, 2010; Liu et al., 2012b; Thakuria et al., 2013), thanks to the composition of the crystallization medium and the process used to generate the oversaturation;

- ✓ The addition of a pro-group leads to a **prodrug** formation which necessitates a biotransformation in order to obtain a biologically active compound (Müller, 2009; Rautio et al., 2008; Stella and Nti-Addae, 2007).

With the HTS methods, the chemical way can be investigated very early in the drug development as only few milligrams of an active compound are necessary to screen all forms of this API. In this context, pharmaceutical industry, firstly investigates this way in order to select the "hits of candidates". Either these hits can be formulated as is or, most of the time, a way to formulate needs to be found in order to better improve the drug's solubility of the hit or to stabilize a highly soluble but thermodynamically unstable form.

I.3.2. Formulation strategies

Concerning the formulation ways, the improvement of the drug's solubility occurs without chemical modification. Numerous approaches have been studied and applied (Singh et al., 2011):

- ✓ **The particle size reduction** (micronisation and nanonisation) which ensues directly from the Noyes-Whitney equation. Further processes, divided in "bottom-up" and "top-down" methods are available. The "bottom-up" methods such as precipitation or crystallization consist in building nano- or microcrystals from the drug molecules. In contrast to the "top-down" methods where the starting point is the crystalline form, whose size needs to be decreased. Therefore, milling is one of the most used methods since many years, there also are high pressure homogenization and spraying methods (Gao et al., 2008; Merisko-Liversidge and Liversidge, 2008; Möschwitzer, 2013; Shegokar and Müller, 2010; Sinha et al., 2013);
- ✓ **The soluble cyclodextrin (CD) complexes:** Those amphiphilic molecules can increase the solubility, bioavailability and stability of API by their hydrophobic cavity which can encage the PWSD, forming the inclusion complex. Drug molecules can also form non inclusion complexes by hydrogen bonding with external hydroxyl groups of the

CD (Brewster and Loftsson, 2007; Del Valle, 2004; Kurkov and Loftsson, 2013; Loftsson et al., 2005; Zhang and Ma, 2013);

- ✓ **The lipid based delivery systems:** These systems are classified into four groups predominantly based on their composition forming the Lipid Formulation Classification System (LFCS). Among these exist the self-emulsifying drug delivery systems (SEDDS) and self-microemulsifying drug delivery systems (SMEDDS) which correspond to the type II and III of the LFCS (Mu et al., 2013; Müllertz et al, 2010; Pouton, 2006);
- ✓ **The colloidal carriers,** which are polymeric micelles, microspheres or nanoparticles and liposomes. The first one is rather new for oral drug delivery of PWSD and only few systems have been studied (Gaucher et al., 2010; Malzert-Fréon et al., 2006, 2010; Repka et al., 2012; Tomasina et al., 2013a, 2013b). The latter one is mainly used for intravenous applications and in cosmetic products. Its use for oral drug delivery is fairly difficult due to the low gastric stability (Fricker et al., 2010);
- ✓ **The ordered mesoporous silica**, the emerging one: Due to its specific characteristics such as high porosity, large surface area and uniform pore shape and dimensions, OMS should give high dissolution rates of the PWSD. Adsorption of the API occurs by Van der Waals interactions with the carrier allowed by the high surface area and depends on many variables such as the pore diameter and volume, the surface area and the OMS particle size and functionalization (Chen et al., 2013; Mamaeva et al., 2013; Manzano and Vallet-Regi, 2010; Qian and Bogner, 2012; Simovic et al., 2011; Xu et al., 2013).
- ✓ **The solid dispersions** in which the drug is dispersed or dissolved within a carrier, most of the time a polymer. It allows to present the drug to the medium as small-sized particles inducing enhanced wetting and reduced agglomeration. In the case of solid solutions and glass solutions the drug is in the molecular state hence the crystal lattice is already disrupt which triggers the dissolution process (Brough and Williams III, 2013; Crowley et al., 2007; Janssens and Van den Mooter, 2009; Leuner and Dressman, 2000; Serajuddin, 1999; Srinarong et al., 2011; Van den Mooter, 2012; Vasconcelos et al., 2007; Zhao et al., 2012).

These formulation options lead to some marketed products, however further investigations on all approaches need to be done to improve the number of successes of the overall drug development process. Solid dispersions have already been extensively studied but due to its instability, only few products have already reached the market. In the next chapter detailed information on solid dispersions and how to obtain them will be given, the stabilization of the amorphous state in a pharmaceutical dosage form will also be discussed.

II. Amorphous drugs in pharmaceutical forms

As it will be presented in the third part of this introduction, amorphous drugs are more and more used to improve drug solubility especially by forming amorphous solid dispersions as it has been shown just above (Brough and Williams III, 2013; Van den Mooter, 2012). However, until today their stabilization is still a challenge and this explains the few marketed products based on this form (Table I.2). In this part generation of the amorphous state and its properties will be shortly described followed by discussion concerning the stability and the stabilization of these form.

II.1.1. Generation and properties

An amorphous form can be obtained by several methods and the most commonly used are presented in Figure I.4. In the case of the milling the amorphous form is directly obtained from the solid whereas for the two others methods, the solid is previously converted into a thermodynamically stable non-crystalline form (melt or solution) (Craig et al., 1999; Hancock and Zografi, 1997; Laitinen et al., 2013; Yu, 2001).

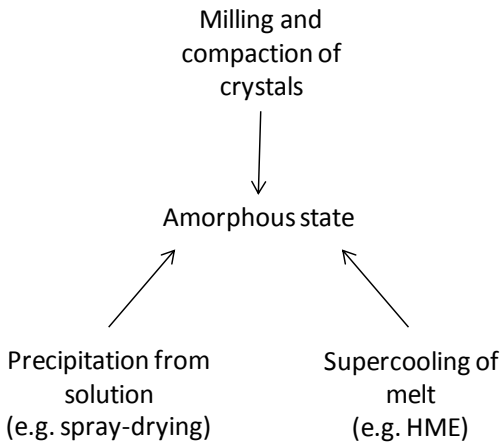


Figure I.4: Schematic diagram of the most common ways to obtain amorphous form of a pharmaceutical compound [adapted from (Hancock and Zografi, 1997)]

For simplicity, I'll only describe glass formation from the super-cooling from the melt which is depicted in Figure I.5. It can be observed that until the melting point of the compound is reached, no major changes in volume and enthalpy occur whilst at the Tm a discontinuity appears due to the transition from the solid to the liquid state. From this

state, if the cooling rate is sufficiently high, recrystallization can't take place and the volume and enthalpy value might follow the equilibrium line of the liquid leading to the "super-cooled liquid" also called "rubbery state". Further cooling of the material will result in a deviation from the equilibrium line. This one occurs at a specific temperature, which is known as the glass transition temperature (Tg) and the properties of the compound also changes giving a non-equilibrium state where the material becomes "frozen", the "glassy state" (Craig et al., 1999; Hancock and Zografi, 1997).

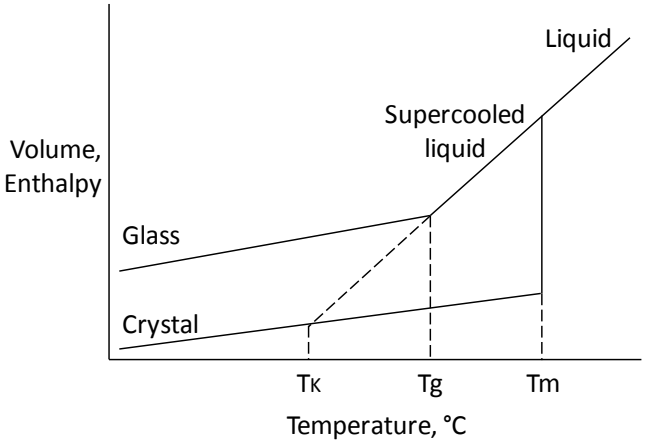


Figure I.5: Schematic illustration of the variation of enthalpy (or volume) with temperature [adapted from (Hancock and Zografi, 1997)

While the crystalline form (Figure I.6A) presents long-range order and is the most stable form of a given compound, the amorphous state (Figure I.6B) is the less stable form of a solid typically with a short-range order (e.g. via hydrogen bonding) and characterized by its glass transition temperature.

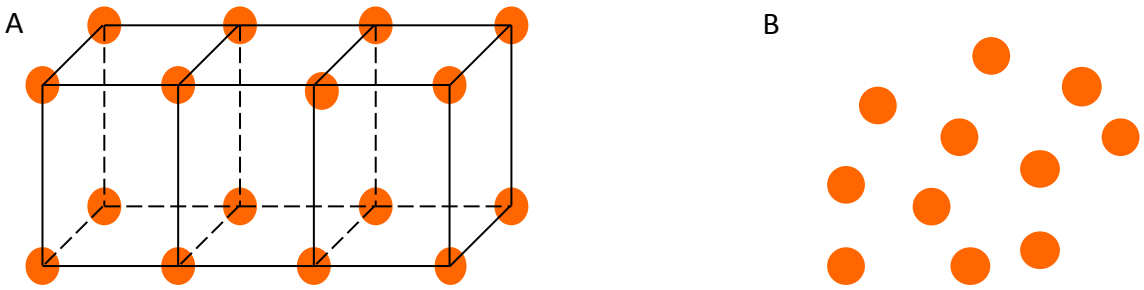


Figure I.6: Schematic representation of the crystalline (A) and amorphous (B) form of a compound

This stability problem is mainly due to the high energy of this state leading to higher molecular mobility and responsible for the high chemical reactivity but also for the recrystallization tendency which can occur during process, storage or dissolution. However, it presents very interesting properties also linked with this high level of energy, especially higher apparent solubility and dissolution rate due to enhanced thermodynamic properties and the absence of crystal lattice to disrupt. To limit the lost of these advantageous properties numerous efforts have been put into understanding the critical factors in recrystallization and then overcoming them by finding stabilization methods which are presented right after.

II.1.2. Stabilization of the amorphous drugs

Until today relative importance of each factor affecting crystallization of the amorphous state is still unclear due to the complexity of this phenomenon. Only few methods are available to improve its stability mainly by incorporating excipients acting as stabilizers.

Solid dispersion is one of the first and most commonly used technique to tackle poor aqueous solubility and to stabilize the amorphous drug. It consists in combining one or more excipients with a drug which will be transformed into its amorphous form during the manufacturing process. This will be detailed in the next part as it has been the employed strategy during this work (Brough and Williams III, 2013; Janssens and Van den Mooter, 2009; Leuner and Dressman, 2000; Serajuddin, 1999; Srinarong et al., 2011; Van den Mooter, 2012; Vasconcelos et al., 2007).

More recently, other techniques aimed for stabilization of the amorphous form have been investigated: the binary co-amorphous mixtures and the mesoporous systems (Laitinen et al., 2013).

II.1.2.1. Binary co-amorphous mixtures

While solid dispersions are mainly prepared with polymers, the co-amorphous systems consists on the association of two small molecules via milling or melt-quenching them together. Some used small molecules such as citric acid, sugars and urea have been used in the first years of research on solid dispersions before being replaced by polymers. Today, they're celebrating a comeback within the formation of co-amorphous systems (Masuda et al., 2012). For example, paracetamol has been melt-quenched with citric acid leading to a physically stable system even if Tg of room temperature or lower were noticed. With the 1:1 (w:w) ratio, system remains stable upon storage at 25°C in dry conditions at least two years. Stability was explained by hydrogen-bonds interaction between the two components as indicated by the ^{13}C NMR (Hoppu et al., 2007, 2008, 2009).

Instead of using a small molecule and a drug, it can be possible to combine two drugs leading to amorphous binary drug mixtures with further advantages:

- ✓ Formation of a stable system
- ✓ Combination therapy
- ✓ Simultaneous improvement of drugs solubility

Although presenting numerous advantages, research on such system is still quite new and some cloudy zones remain especially concerning a relation between these systems and co-crystals but also concerning their ability to form pharmaceutical products have not yet been shown.

II.1.2.2. Mesoporous systems

As presented above, OMS has recently shown growing interest in solubility enhancement to produce stable amorphous drug delivery systems (Chen et al., 2013; Mamaeva et al., 2013; Manzano and Vallet-Regi, 2010; Qian and Bogner, 2012; Simovic et al., 2011; Xu et al., 2013). Incorporation of the drug can be obtained by mechanical activation (Limnell et al., 2011), solvent deposition methods (Kinnari et al., 2011) or vapor-phase mediated mass transfer (Qian et al., 2011). Amorphization of the drug occurs due to

the spatial limitation as critical nuclei size is larger than pore diameter. In these systems, further mechanisms are responsible for the stability of the amorphous drug (Qian and Bogner, 2012):

- ✓ Spatial constraints,
- ✓ Decreased molecular mobility depending on interactions between drug and silica but also on the pore size,
- ✓ Decreased Gibbs free energy upon drug adsorption.

However, until today even if amorphization of the drug is obtained, stability of the systems still present some problems under stressed conditions either by chemical degradation of the drug (Kinnari et al., 2011; Limnell et al., 2011) or recrystallization (Miura et al., 2011). Understanding of the interaction mechanisms is still required for these systems.

III. Solid dispersions

As explained above, solid dispersions have widely been considered to enhance drug solubility as a strategy to tackle the dissolution rate and limited oral absorption, but until today only a few products have reached the market either aiming immediate or sustained release (Table I.2) (Janssens and Van den Mooter, 2009; Vasconcelos et al., 2007).

Table I.2: Examples of commercially available solid dispersions (non exhaustive list) [adapted from (Brough and Williams III, 2013; Kawabata et al., 2011; Shah et al., 2013)]

Trade name	Drug	Processing technology	Company	FDA approval[a]
Gris-PEG®	Griseofulvin		Pedinol	1975
Cesamet®	Nabilone	Solvent evaporation	Valeant pharma	1985
Nimotop®	Nimodipine		Bayer	1988
Nivadil®	Nivaldipine		Astellas	1989[b]
Sporanox®	Itraconazole	Fluid bed bead layering	Janssen	1992
Prograf®	Tacrolimus	Spray drying	Astellas pharma	1994
Crestor®	Rosuvastatin		Astrazeneca	2003
Fenoglide™	Fenofibrate	MeltDose®	Life Cycle Pharma	2007
Kaletra®	Lopinavir, Ritonavir	Melt-extrusion	AbbVie	2007
Intelence®	Etravirine	Spray drying	Janssen	2008
Certican® / Zortress®	Everolimus	Spray drying	Novartis	2010
Norvir	Ritonavir	Melt extrusion	AbbVie	2010
Onmel	Itraconazole	Melt extrusion	Merz pharma	2010
Incivek	Telaprevir	Spray drying	Vertex	2011
Zelboraf	Vemurafenib	Solvent/anti-solvent precipitation	Roche	2011
Kalydeco	Ivacaftor	Spray drying	Vertex	2012

[a] Dates taken from FDA website

[b] Approval date in Japan

III.1. Background

In 1961, Sekiguchi and Obi developed a new method to overcome the problem with drug solubility by the formation of eutectic mixtures via melting a physical mixture of a drug and a water soluble carrier (Sekiguchi and Obi, 1961). In a second part of their study, they noticed that the rate of drug release and, consequently, the BA of the PWSD was improved and have suggested that the drug is dispersed in a microcrystalline state within the matrix (Sekiguchi et al., 1964). Based on this suggestion, Goldberg and co-workers established that a fraction of the drug could be molecularly dispersed in the matrix, forming as a result a solid solution. When this system is exposed to an aqueous medium, the carrier dissolves immediately, releasing the drug as very fine particles. In this case the increase in the surface area of the drug particles increases the dissolution rate and the BA of PWSD (Goldberg et al., 1966b, 1966c). Few years later, the term solid dispersion is defined by Chiou and Riegelman in the first review on these systems as "a dispersion of one or more active ingredients in an inert carrier in the solid state prepared by solvent, melting or solvent-melting methods" (Chiou and Riegelman, 1971). More than ten years later, in 1985, Corrigan has suggested the definition of being a "product formed by converting a fluid drug-carrier combination to the solid state" (Corrigan, 1985).

Since that, intensive research has been done on solid dispersions but during three decades after the work of Sekiguchi, only two products have been marketed: a solid dispersion of nabilone in povidone (Cesamet®, Lilly) and a griseofulvin in poly(ethylene glycol) (Gris-PEG®, Novartis) (Li et al., 2009). As presented in Table 2, some others solid dispersions have been marketed during the two last decades but this number stays very limited regarding the intensive research and the number of papers and reviews (Craig, 2002; Janssens and Van den Mooter, 2009; Leuner and Dressman, 2000; Serajuddin, 1999; Srinarong et al., 2011; Van den Mooter, 2012; Vasconcelos et al., 2007) published on these systems.

Nowadays, research in this field is still a challenge for scientists and the availability of new carriers and new technologies and a better understanding of what happens within the system could change the situation.

III.2. Classification and definitions

Solid dispersion is the general terms for several types which can be distinguished as follows: (Table I.3):

Table I.3: classification of solid dispersions [adapted from (Janssens and Van den Mooter, 2009)]

Type	Eutectic mixtures	Solid solution	Glass solutions		
Sub-type	X	X	Glassy or amorphous solid solution	Glass suspension	
Phases	2	1	1	2	2
Drug	crystalline	molecularly dissolved	molecularly dissolved	crystalline	amorphous
Carrier	crystalline	crystalline	amorphous	amorphous	amorphous
A DSC will find	2 Mp	1 Mp	1 Tg	Mp + Tg	2 Tg
Stability of the system	Very stable	Stable (drug below saturation solubility	Stable (drug below saturation solubility	Very stable	Only kinetically stabilized (oversaturation)

The first classification has been introduced by Chiou and Riegelman in 1971 including simple eutectic mixtures, solid solutions and glass solutions (Chiou and Riegelman, 1971).

Eutectic mixtures are the cornerstone of solid dispersions. It consists of two crystalline components which are completely miscible in the liquid state but limited in the eutectic composition and at the eutectic temperature in the solid state. If the composition is different from the eutectic one, one of the components begins to crystallize before the eutectic temperature (Figure I.7) (Janssens and Van den Mooter, 2009; Leuner and Dressman, 2000).

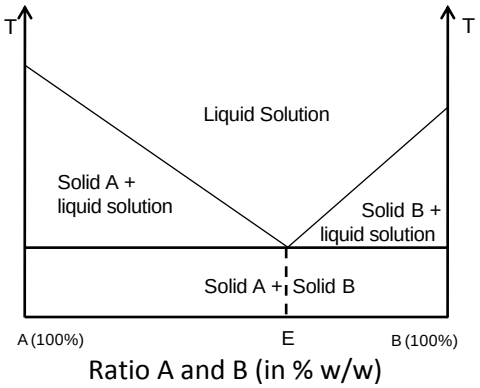


Figure I.7: Phase diagram of an eutectic system (from (Leuner and Dressman, 2000))

For certain compositions of a drug and a crystalline carrier it has been noticed that solid solubility of a compound in another isn't always limited to a precise composition and temperature as reported in the case of eutectic mixtures. These systems are called "**solid solutions**" and can be classified either according to their miscibility (continuous and discontinuous) or to the way in which drug molecules are distributed within the crystalline carrier (interstitial and substitutional) (Janssens and Van den Mooter, 2009; Leuner and Dressman, 2000):

- ✓ Continuous solid solutions if the two solids are miscible at any composition ratio;
- ✓ Discontinuous solid solutions when the solubility of a compound into another one is limited;
- ✓ Interstitial crystalline solid solutions if the active molecule has a diameter that is no greater than 0.59 of the carrier molecule and if the volume of active compound molecules is less than 20% of the solvent (Figure I.8A);
- ✓ Substitutional crystalline solid solutions in the case where the two components have similar molecular size (Figure I.8B).

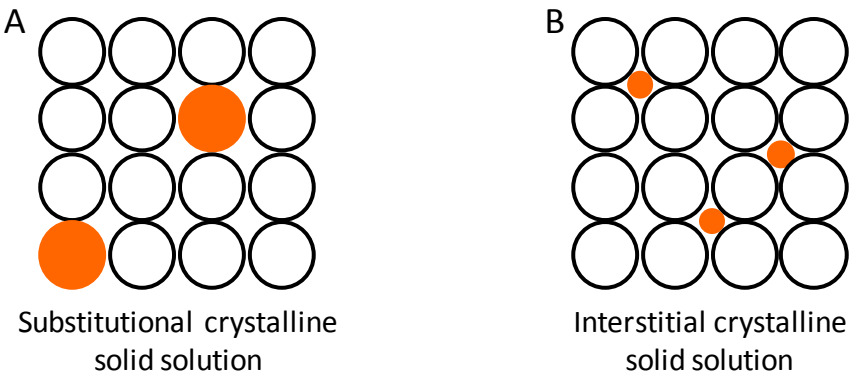


Figure I.8: Schematic representation of solid solutions as a function of the repartition of the drug molecules (orange) within the carrier molecules (white) [adapted from (Leuner and Dressman, 2000)].

Last but not least is the group of the **glass solutions**. In this type of solid dispersions the carrier is amorphous and the drug is either molecularly dissolved (glassy or amorphous solid solution) (Figure I.9A) or is not totally soluble within the matrix and two phases are present (glass suspension) (Figure I.9B). This group is the most studied and applied as the amorphous form of a drug is potentially the most soluble but the most thermodynamically unstable, that's why until today only few products of this type reach the market.

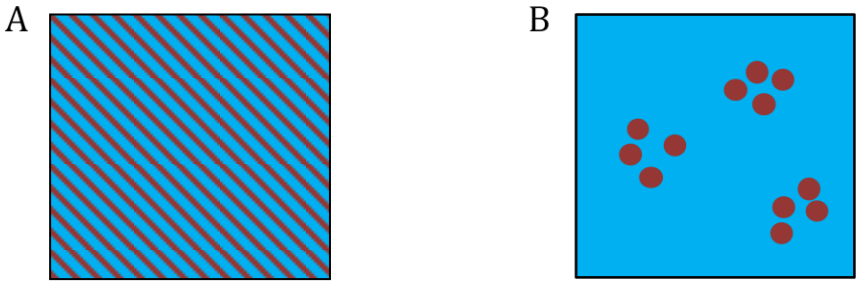


Figure I.9: Schematic representation of A: glassy solid solution and B: glass suspension

During more than 40 years, intensive research has been conducted on solid dispersions, beginning with crystalline drugs and carriers and evolving towards amorphous drugs and/or carriers. This evolution led to systems with increased solubility whereas stability was decreased. Nowadays, the term solid dispersion is mostly linked to amorphous solid dispersions (glass solution) and research mainly focuses on the stabilization of these improved systems and rests one of the main challenges for scientists, which will be reported into detail within the last chapter of this introduction.

III.3. Advantages and drawbacks

As shown in Figure I.3, various methods to improve drug solubility and in consequence drug bioavailability are possible. A solid dispersion is one of the possibilities in formulation and presents some advantages over the other strategies which are (Serajuddin, 1999; Vasconcelos et al., 2007):

- ✓ The drug can be neutral and no more clinical trials need to be performed as it's not a NME;
- ✓ In contrast to the particle size reduction technique, which is limited to 2 – 5 µm what is not sufficient to improve considerably drug solubility it offers an alternative;
- ✓ Particle size reduction to the last state with a molecularly dispersed drug;
- ✓ Simplicity of the manufacturing;
- ✓ Improved wetting even with carriers without any surface activity;
- ✓ The obtained particles present a higher porosity;
- ✓ Reduced agglomeration of the obtained particles;
- ✓ The drug can be present in its amorphous state which allows a faster release as no energy to break up the crystal lattice is necessary.

Despite extensive research, solid dispersions are not broadly used in commercial products mainly due to manufacturing and stability consideration. Another reason is that predictability of the behavior of a solid dispersion is poor because of the lack of a basic understanding of their physico-chemical properties. Some of these reasons are as follows: (Karanth et al., 2006; Serajuddin., 1999; Vasconcelos et al., 2007):

- ✓ The possibility of recrystallization of the amorphous phase during processing (mechanical stress) or storage (temperature and humidity stress) (Pokharkar et al., 2006; Vasanthavada et al., 2004, 2005);
- ✓ Its method of preparation with potential drug degradation upon heating or the presence of residual solvents;

- ✓ The reproducibility of its physico-chemical properties mainly due to variation of the cooling rate or some other manufacturing conditions;
- ✓ Difficulty to be incorporated into formulations of dosage forms such as capsules or tablets as a decrease in compressibility and a sticky behavior on the punches frequently occurred;
- ✓ The scale-up of manufacturing processes can be tricky.

Today some new, optimized and easily up-scalable methods are on their way and various strategies to limit drug recristallization upon storage have been studied, however they mainly depend on the drug properties and the best way to stabilize the system is to combine different approaches and to understand the fundamental physico-chemical behavior of these systems.

III.4. Drug release mechanisms from solid dispersions

Solid dispersions are generally regarded as systems to enhance the *in vitro* drug release compared to conventional forms with concomitant implications for the *in vivo* release. Most of the time, an enhancement of the dissolution rate becomes significant when an increase of up to four hundred fold is present as reported by Said *et al.* (Said et al., 1974). However, until today, despite numerous reviews and approximately 500 original research articles on solid dispersions, mechanisms supporting the observed enhancement in dissolution rate are still not well understood and only three reviews have been published within four decades (Chiou and Riegelman, 1971; Corrigan, 1985; Craig, 2002).

In those reviews, two apparently conflicting mechanisms are argued to be in charge of the drug dissolution behavior from solid solutions and dispersions: drug release is controlled either by the carrier or by the drug. Improvement of the dissolution in the case of solid dispersions was also attributed to the reduced particle size of the drug. All the possible well accepted mechanisms occurring with enhanced dissolution devices still derive from the well-known review by Chiou and Riegelman (Chiou and Riegelman, 1971) with complementary explanations in the most recent review (Craig, 2002).

Two mechanisms which seem to be opposed are debated. In some papers from Corrigan, Dubois, Ford, Craig and Newton, it has been reported that the drug release is controlled by the carrier. In these studies, Corrigan showed that the dissolution of the solid dispersions and of the polymer alone (PEG) were similar, implying that the dissolution rate of the drug is controlled by the inert carrier (Corrigan, 1985, 1986). In the same time, a comparative study of solid dispersions containing PEG and various drugs which have been prepared under comparable conditions have mainly showed equivalent dissolution rates and have confirmed the work of Corrigan (Dubois and Ford, 1985). Few years later, Craig and Newton found a logarithmic linear relationship between the dissolution rate and the molecular weight (Pokharkar et al., 2006) of the PEG, leading once again to the conclusion that the carrier properties govern (Craig and Newton, 1992). Corrigan also suggests that the carrier-controlled dissolution might be modeled regarding the approach outlined by Higuchi (Higuchi, 1967; Higuchi et al., 1965). In this model, there would be a surface layer rich in the major component (A) through which the minor component (B), most of the time, the drug, has to diffuse before reaching the dissolution medium (Figure I.10).

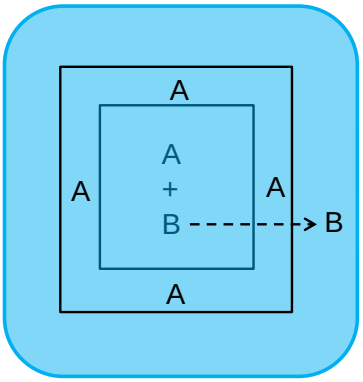


Figure I.10: Schematic model of the dissolution model for a two component system [adapted from (Higuchi et al., 1965)].

Considering that, Lloyd *et al.* have claimed that the physical form of the drug had no influence on the release rate in the case of a carrier-controlled dissolution (Lloyd et al., 1999). To study this hypothesis, they prepared solid dispersions based on PEG 4000 via heating in a stainless steel cylinders, containing different paracetamol particle size fractions. After that, drug release has been investigated and surprisingly, they firstly noticed that the fastest release was obtained with the largest particles. After further

analysis and an assessment of the drug concentration within the dissolving surface, they found out that's due to the occurrence of a local settling during the solidification process when cooling from the melt. Finally they found the dissolution rate to be independent of the preparation method or initial particle size (Lloyd et al., 1997).

However, in 1988, Sjökvist have shown that improvement in the dissolution rate of griseofulvin was directly linked to the size of the released particles (Sjökvist and Nyström, 1988). To conciliate these opposing results, a study has been realized by Sjökvist-Saers and Craig and they came to the conclusion that a linear relationship exists between the intrinsic dissolution rate of the model drugs in dispersion and the aqueous solubility of the drug. In this context, properties of drugs are clearly linked to the dissolution rate leading to a drug-controlled dissolution rate (Sjökvist-Saers and Craig, 1982). In 2003, Shin and Kim have proposed that an improvement in the dissolution rate was due to the amorphous form of the drug confirming the fact that properties of the drug are as important as carrier properties (Shin and Kim, 2003).

Since 1971, further mechanisms seem to be responsible for improvement in the drug dissolution rate from solid dispersions depending on numerous factors such as the model drug, the carrier, the ratio of the components but also the physico-chemical properties and interactions which can occur during the formation of the solid dispersions. However, despite the fact that some mechanisms and factors have been highlighted, some questions remain unanswered, for example which factors determine whether the dissolution is carrier- or drug- controlled and what are the implications to understand the mechanisms in order to design the dosage form?

In the review done by Craig, he proposes a model (Figure I.11) giving an explanation of the behavior of the drug particles during the dissolution process. This model is based on the theory of Higuchi with its polymer-rich layer at the dissolving surface.

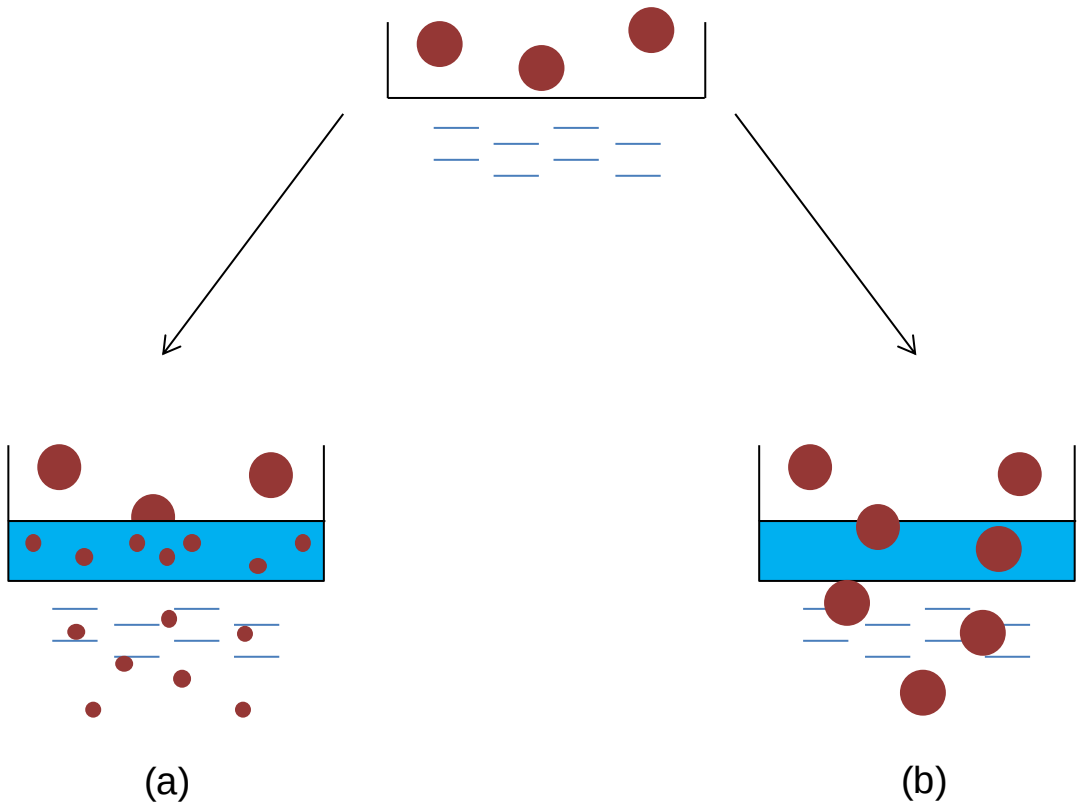


Figure I.11: Schematic diagram showing the fate of drug particles during the dissolution process. (a) carrier-controlled dissolution and (b) drug-controlled dissolution. Large spheres represent un-dissolved drug particles, small spheres partially dissolved drug particles, blue regions correspond to hydrated material. [from (Craig, 2002)]

In Figure I.11a, the process associated with the carrier-controlled release where the drug dissolves within the polymer rich layer and is released depending on the dissolution release of the polymer. Considering water soluble polymers, the model becomes more complicated and leads to a gradual decrease in polymer concentration between the solid surface and the release medium. For the drug-controlled process (Figure I.11b), the drug is released unchanged into the release medium due to a too slow dissolution within the rich polymer layer. Dissolution rate is directly linked to the drug properties (size, physical form, etc.), implying that an improvement in dissolution rate can occur by an increase in the specific surface area and the possibility of an improved wetting and a lower agglomeration (Craig, 2002).

However, even if the two mechanisms have been described separately, there are probably many cases where both take place. In this context, the choice of the manufacture

method and the excipients in order to formulate the solid dispersions seems to be a critical step.

III.5. Formulation of solid dispersions

III.5.1. Preparation methods

Three ways have been developed to form solid dispersions, in this part only the methods applied to improve drug solubility and consequently the BA are briefly described:

- ✓ Melting methods including (Keen et al., 2013):
  - **Melt mixing**, one of the simplest methods as it consists of melting the physical mixture above the eutectic point before cooling and solidifying it. The main drawback is that the use of high Mw polymers has to be avoided due to their too high viscosity (Kolasinac et al., 2012);
  - **Spray congealing** directly ensues from the melt mixing. It consists of atomizing a molten mixture, subsequently followed by a congealing of the droplets. In contrast to the melt mixing the cooling rate is more controlled and similar for each microsphere. It can be a downstream process of further thermal processes such as the melt mixing in order to reduce the thermal exposure of the API (Passerini et al., 2006, 2012);
  - **Melt granulation**: This process is based on the agglomeration of powders by the application of heat. The binder is either pre-melted and sprayed into the granulator or mixed with other powders and melting during the process (Passerini et al., 2006; Van Melkebeke et al., 2006);
  - **Hot-melt-extrusion:** The physical mixture is fed via a hopper into the barrel and then by means of the screws, the mixture is conveyed, melted and mixed until the die giving the shape to the hot-melt extrudates. This method is further explained into more details (Kalivoda et al., 2012);
  - **Injection-molding**: A melt of thermoplastic materials is pushed by high pressure into a close mold, giving the shape;

- **Kinetisol® dispersing:** This system is composed of a cylindrical chamber in which paddles rapidly rotate. Heating is generated by a combination of friction and shear;

- **Hot-spin-melting**: In a high speed mixer, drug and carrier are molten for an extremely short time and dispersed within a cooling tower by air or an inert gas.

✓ Solvent methods, with various processes to remove residues:

- Two main methods using **supercritical fluids** have been developed to improve drug solubility: "Rapid Expansion of Supercritical Solution" (RESS) and "Precipitation with Compressed fluid Anti-solvent" (PCA). Some others methods exist with some changes from the initial methods: "Rapid Expansion from Supercritical to Aqueous Solution" (RESAS), "Supercritical Anti-Solvent" (SAS) and "Solution Enhanced Dispersion by the Supercritical fluids" (SEDS) (Banchero et al., 2009; Fages et al., 2004; Pasquali et al., 2008; Sethia and Squillante, 2004; Won et al., 2005);

- **"Evaporative Precipitation into Aqueous Solution"** (EPAS), a relatively new process patented in 2002 where the drug is previously dissolved within an organic solvent having a low boiling point. This solution is pumped through a heated pipe under vacuum and sprayed within a stabilized aqueous solution. Rapid solvent evaporation leads to a rapid precipitation of the drug particles (Chen et al., 2002);

- **Rotary-evaporation**, the simplest method, in which the solution is placed in an evaporation flask, the solvent is then rapidly removed under reduced pressure in a heated bath, forming a thin film around on the flask's wall.

- **Spray-drying**: Powder blends are previously dissolved or dispersed within solvents. Then this solution/suspension is atomized through a nozzle in a drying chamber to quickly evaporate the solvent and the spray-dried powder is collected as a fine powder in the collector vial. This method will be explained in details later on.

- **Freeze-drying or lyophilization**: In this method, the solution/suspension is frozen and the solvent is sublimated under reduced pressure to form a solid dispersion.

✓ Combination of melting and solvent method

All these methods serve to obtain solid dispersions, improving solubility and finally the bioavailability of the drug. The two most applied manufacturing methods are hot-melt extrusion and spray-drying which have been used in this thesis and will be explained in more details in chapter II.6 and II.7 respectively.

III.5.2. Selection and type of carriers

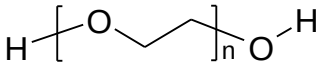
The selection of the carrier is one of the key factors in the success of solid dispersions. The carrier has to possess most of the properties cited in table I.4 in order to form a physico-chemically stable system upon storage with a fast drug release profile.

Table I.4: Desired carrier properties for solid dispersion formulation [from (Janssens and Van den Mooter, 2009)]

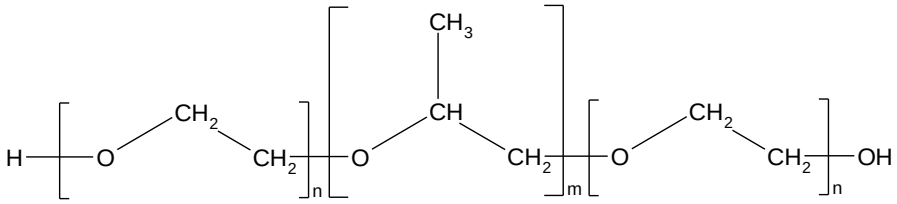
Properties	Desired characteristic
Safety	Inert, Generally Recognized As Safe (GRAS)
Preparation	Thermally stable and thermoplastic (melting methods)
	Soluble in organic solvents (solvent methods)
Release	Water soluble with solubilizing and stabilizing properties
Stability	High Tg and fragility
	Hydrogen donors/acceptors

Numerous crystalline or amorphous materials are used as carriers to form solid dispersions and all the presented polymers are approved by the pharmaceutical industry and well-known. Mainly used are (Leuner and Dressman, 2000):

- ✓ **Polyethylene glycol (PEG):** different types of PEG present some advantages such as a low melting point, a low toxicity, a good solubility in water which isn't dependent of the pH and in many organic solvents; they're able to solubilize some compounds and also to improve compound wettability. The molecular weight, the chain length and the drug/PEG ratio influence the drug release rate. However, PEG presents also some problems such as instability during the process and formulation problems into acceptable dosage form if the solid dispersion is too soft;

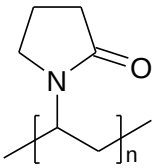


- ✓ **Pluronic block co-polymers** : They are commercially introduced by BASF in the early 1950s and are composed of ethylene oxide and propylene oxide. The two most used are the poloxamer 188 and 407. They have been firstly used as solubilizing agents before becoming a carrier to form solid dispersions. These carriers present some advantages such as a low melting point, a good solubility in common organic solvents and a non-toxicity;



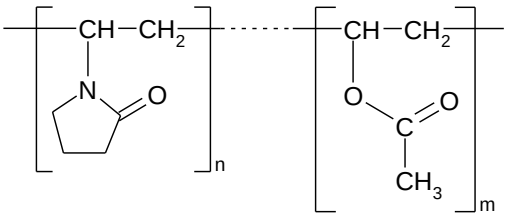
- ✓ **Polyvinylpyrrolidone (PVP)**: It is widely used as an excipient in the pharmaceutical industry and was first applied as a plasma expander in the 1940s. Various types of PVP exist depending on the length of the molecular chain. On one hand, the Tg is high which limits the use of this polymer with the melting method, except with drug showing a plasticizer effect. On the other hand, they present a pH independent water miscibility and a good miscibility in the most common organic solvent allowing the use for solvent methods. In many cases they improve the wettability of the dispersed compound, they show a high solubilisation tendency and a high compatibility with numerous drug substances. The chain length has a significant influence on the drug release rate as higher Mw of PVP implies a lower aqueous solubility and a higher viscosity. Similarly to PEG, a higher drug release rate can be

obtained with higher PVP contents which can be explained by a better miscibility of the drug within the matrix. Given orally, PVP is regarded as non-toxic, principally due to a too high Mw to be absorbed from the GIT. In this thesis, PVP K30 has been used either by hot-melt extrusion or by spray-drying. This type presents a Tg of around 160°C and is recognized to stabilize the amorphous form of drugs and lowering the re-precipitation of the latter within the dissolution medium;



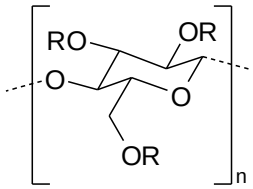
- ✓ **Crospovidone (PVP-CL)**: In contact with water, this polymer doesn't dissolve but swell. However, this polymer is also used to improve drug solubility by improving drug wettability;

- ✓ **Polyvinylpyrrolidone-vinylacetate copolymer (PVPVA)**: As PVP, PVPVA shows a high solubilisation tendency and a high compatibility with numerous drug substances The use of PVPVA copolymers to form solid dispersions results into a significant increase in the drug release rate and also an increase of the bioavailability but a too high content can lead to a decrease in the drug release rate, probably due to a too high viscosity of the diffusion layer. For this polymer, the drug/carrier ratio seems to be a very important criterion. The Kollidon VA 64 which is composed of poly(vinylpyrrolidone-co-vinyl acetate) in a ratio of 6:4 m:m is also used in this manuscript to form solid dispersions via the two cited techniques;



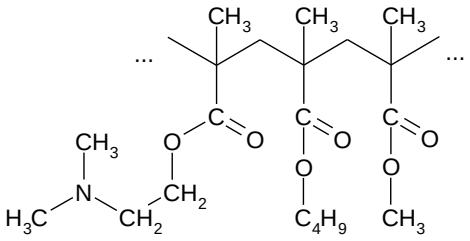
- ✓ **Cellulose derivatives**: These polymers are composed of saccharide units which are linked by β-1,4-glycoside bonds forming un-branched chains with a high molecular weight. Various types exist by alkylation leading to methyl- (MC), hydroxypropyl- (HPC), hydroxypropylmethyl- (HPMC) and many other semi-synthetic types of

cellulose. These polymers belong to the group of amorphous polymers with generally a high Tg of around 160°C. Because of this, their use with the melting method is quite limited but possible. As well as the PEGs, PVPs and PVPVA, HPMC show good drug solubilization. HPMCs consist of ethers of cellulose in which 16.5 to 30% of the hydroxyl groups are methylated and 4 to 32% are derivatized with hydroxypropyl groups which are soluble in water and aqueous mixtures with ethanol, methanol or dichloromethanol. The type used in this thesis is the type 2910 which had an average methoxy content of 29% and a hydroxypropyl content of 10%. It presents a Tg of around 155°C and was also recognized to stabilize an amorphous form of a drug and to lower the re-precipitation of the latter within the dissolution medium;

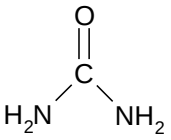


$R = CH_2CH(OH)CH_3$

- ✓ **Polyacrylates and polymethacrylates**: The main use of these polymers is the coating of dosage forms in order to modify the drug release and they're commonly referred to by the trade name Eudragit®. These polymers also belong to the group of amorphous polymers. Nowadays, some Eudragits® are also used to improve drug solubility, especially the Eudragit® E as it is soluble in acidic medium at pH up to 5.5 and swells at higher pH values. This polymer presents some advantages such as a thermal stability, a thermoplastic behavior (Tg ~ 48°C), a cationic nature which facilitates drug-polymer interaction, low hygroscopicity and it rapidly dissolves at acidic pH due to its multiple tertiary amines (pKa = 8-9). The Eudragit® E PO has been used as the main polymer during this thesis and has shown very interesting results which are mentioned in more detail in this manuscript later on. Despite of the low glass transition of this polymer it is also recognized to stabilize amorphous form of drugs and lowered reprecipitation in the dissolution medium and can be used either in HME or spray-drying;



- ✓ **Urea:** It was one of the first carriers used to form solid dispersions. It presents a good solubility in water and in many common solvents and is regarded as non-toxic. Nowadays this carrier is not often used but it still shows an improvement in dissolution rate of PWSD as mentioned quite recently (Okonogi et al., 1997);



- ✓ **Sugar, polyols and their polymers:** Despite a very good solubility in water and no toxicity they are less used than others mainly due to their high melting points combined with a poor solubility in most of organic solvents. However, some of them such as mannitol, sorbitol, and chitosan are the most commonly used sugars to form solid dispersions and to improve the drug dissolution rate. Others sugars which have been used are dextrose, galactose, sucrose, xylitol and maltose;

- ✓ **Emulsifiers**: This type of carrier have shown only little improvement in the drug release rate and presents a toxicity problem, in this context they're mainly used in combination with another carrier. They increase drug release rates by an improvement of the wetting and a solubilization effect on the drug. Two emulsifiers are mainly used: sodium lauryl sulfate (SLS) and polysorbate 80. Further examples of frequently used emulsifiers are the Gelucires®, which is a group of glycerides-based excipients and are classified by two numbers, the first corresponds to the approximate melting point and the second to the hydrophilic-lipophilic balance (HLB) value;

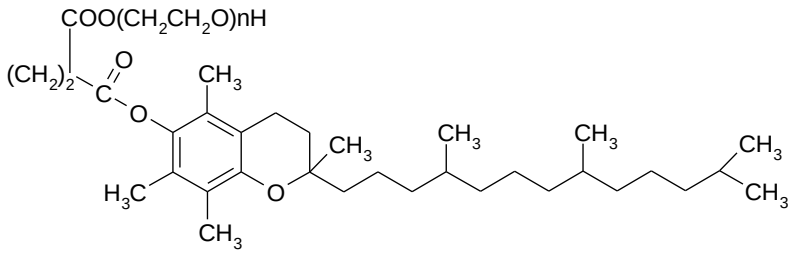
- ✓ **Organic acids and derivates**: They have been used in the first years of research on this topic. No further important studies have been published in recently;

- ✓ **Alternative carriers**:

  - Cyclodextrins can be used to form solid dispersions by freeze-drying or co-precipitation;

  - Gelita® collagel which is a hydrolysis product of collagen and has been reported to improve the drug solubility by the spray-drying technique;

  - The D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) has been reported in the literature to improve the dissolution and the solubility of PWSD. It's a water-soluble and natural product derived from the vitamin E, which is composed of hydrophilic and hydrophobic moiety making it similar to surface active agent with some possibilities of stabilizer, emulsifier and absorption enhancer. This compound also presents a low melting point (38°C) with a high degradation temperature (199°C).



As it is shown, there are many potential carriers to form solid dispersions and each of them present advantages and drawbacks leading to a combination of carriers to obtain stable and highly soluble products. Four of these carriers (PVP K30, PVPVA, HPMC E5 and Eudragit® E PO) have been used during this work either alone or in combination to reach the desired drug release profiles with a good storage stability.

III.5.3. Characterization of solid dispersions

After manufacturing the solid dispersions, physico-chemical characterizations as well as in vitro dissolution are necessary to determine the physical state of the drug (especially the degree of cristallinity of the drug), the type of solid dispersion and the pharmaceutical performance of the system and to make sure of the stability of the system. To do this, further techniques has been used and summarized in table I.5.

Drug dissolution in conjunction with physico-chemical characteristics might provide evidence for the formation of molecularly or nearly molecularly dispersed systems. Solid dispersions are frequently made to improve dissolution characteristics of drugs and in consequence *in vitro* test dissolution are of prime importance. The aim of those tests is to show the capability of systems to enhance solubility, dissolution rate but also if supersaturated solution is stable or tends to rapidly crystallize. Results are compared to those of pure drug and physical blends potentially allowing identification of mechanism by which the carrier improve the solubility: solubilization, wetting or formation of solid dispersion/solution (Leuner and Dressman, 2000). Nowadays, numerous studies report on the supersaturating drug delivery systems, mainly based on amorphous solid dispersions with various carriers which potentially prevents drug precipitation (Bevernage et al., 2013; Xu and Dai, 2013).

Table I.5: Methods for physico-chemical characterization of the solid dispersions [from (Almeida et al., 2012b; Guo et al., 2013; Leuner and Dressman, 2000)]

Spectroscopic techniques	X-ray powder diffraction (XRPD) Near-Infrared spectroscopy (NIR) Infrared spectroscopy (IR) Fourier transformed infrared spectroscopy (FTIR) Raman spectroscopy Terahertz pulsed spectroscopy (TPS) Dielectric spectroscopy
Thermal techniques	Differential thermoanalysis (DSC) Isothermal microcalorimetry (IMC) Thermal Gravimetric Analysis (TGA) Microthermal analysis (Micro-TA)
Microscopic techniques	Polarization microscopy Hot-stage microscopy (HSM) Scanning electron microscopy (SEM) Atomic Force Microscopy (AFM)
Water vapor sorption	Dynamic Vapor Sorption analysis (DVS)
Dissolution testing	Agitated flasks USP apparatus Flow through cells

Today, the new drug delivery systems, e.g. solid dispersions, nano-based systems… bring new challenges to scientists, especially concerning physico-chemical stability. Their success depends on a thorough understanding of the structure of the solid dispersion, the underlying mechanisms and solid state characteristic mainly related to manufacturing process and storage conditions. The stabilization and use of amorphous form in pharmaceutical field will be discussed in the last part of this introduction.

III.6. Hot-Melt-Extrusion

It's a well-known technique which has been first introduced in the plastics industry in the mid-nineteenth to prepare polymeric insulation coatings to wires. Nowadays, it's still frequently used in plastics industry to prepare plastic products: plastic bags, sheets and pipes. It has also been introduced in the pharmaceutical field and interest for this technique has rapidly growing with numerous papers, patents and reviews which have been published within 15 years (Breitenbach, 2002; Crowley et al., 2007; Gryczke et al., 2011; Lu et al., 2013; Maniruzzaman et al., 2012; Repka et al., 2007, 2008, 2012; Shah et al., 2013; Williams et al., 2010; Wilson et al., 2012). This technology can be applied for a wide range of applications including (Almeida et al., 2012b; Repka et al., 2008):

- ✓ Oral drug delivery for:
  - Immediate release (Deng et al., 2013; Feng et al., 2012; Fu et al., 2010; Liu et al., 2012b; Maniruzzaman et al., 2013; Mohammed et al., 2012; Sakurai et al., 2012; Tho et al., 2010; Zhang et al., 2013),
  - Sustained release (Almeida et al., 2011, 2012a; Dierickx et al., 2013; Dierickx et al., 2012, 2013; Verhoeven et al., 2006, 2009; Vithani et al., 2013),
  - Enteric release (Andrews et al., 2008; Schilling and McGinity, 2010; Schilling et al., 2010), and
  - Targeted drug release (Bruce et al., 2005; Cassidy et al., 2011; Miller et al., 2008);
- ✓ Trans-drug delivery systems:
  - Transdermal (Prodduturi et al., 2005; Zepon et al., 2013),

- Transmucosal (Munjal et al., 2006; Palem et al., 2013; Prodduturi et al., 2005), and
- Transungual (Mididoddi and Repka, 2007; Trey et al., 2007);

- ✓ PLGA implants: (Ghalanbor et al., 2010; Li et al., 2013a, 2013b)
- ✓ Intravaginal rings (Clark et al., 2012; Johnson et al., 2010)

On all these interesting applications drug solubility enhancement is, today, one of the most applied due to the dramatically high number of PWSD. It has been made possible by the use of the glass solutions (table I.3). The three sub-types can be used, even if, the crystalline glass suspension is mainly used for highly soluble drugs to obtain a controlled-drug release. However, micro- or nano-crystalline glass suspensions can also find application in solubility enhancement. In 2011, Thommes et al prepared extrudates based on mannitol as rapidly recrystallizing carrier and three different PWSD. This resulted in higher dissolution rates compared to pure drug and physical blends explainable by an increase in wettability. Moreover, the presence of cristallinity doesn't raise the problem of physical stability compared to amorphous one (Thommes et al., 2011). When cooling is too fast to allow drug recrystallization with a limited solubility of the drug within the carrier an amorphous glass suspension is obtained, however these systems tend to crystallize within time. The preferred system is the glassy solid solution where the drug is molecularly dissolved within the carrier and the system present a single glass transition temperature (Claeys et al., 2013; Shah et al., 2013).

Since 20 years, research on HME has led to numerous articles and patents, however only few products have reached the market due to three main hurdles:

- ✓ Difficulty to obtain robust process with reproducible physico-chemical properties.
- ✓ Thermal degradation of heat-sensitive drug,
- ✓ Recristallization of amorphous drug during storage and dissolution, and

Many efforts have been put in to understand mechanism underlying these obstacles and then to overcome them by means of:

- ✓ Process analytical technology (PAT) to control, analyze and optimize the manufacturing process (Saerens et al., 2013), and

- ✓ Use of crystallization inhibitors which prevent or reduce drug recristallization (Xu and Dai, 2013)

In this part the major aspects of melt extrusion technology will be discussed by means of: equipment (extruders, downstream processing equipment), processing (screw design, PAT, processing parameters and scale-up) and materials used in HME (carriers, plasticizers, functional excipients and other processing aids).

III.6.1. Equipment

Although extremely important, I should like to go rapidly through because it is already reviewed in sufficient details and during this work, equipment has stayed the same (Breitenbach, 2002; Crowley et al., 2007; Repka et al., 2012).

Firstly developed for the plastic industry, manufacturers have been able to adapt to pharmaceutical's industry needs with smaller equipment requiring lower amount of material and in accordance with the current Good Manufacturing Practice (cGMP) standards. Another important requirement is that the building material has to be non-reactive, non-absorptive and non-toxic. (Figure I.12).

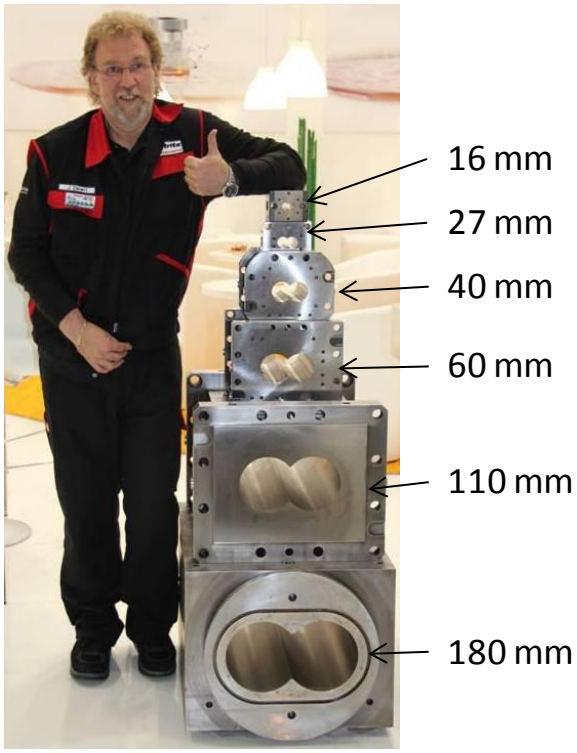


Figure I.12: From plastic to pharmaceutical industries extruders

An extruder is composed of a feeder (gravitational or by plunger system), barrel with screws or ram, torque sensors, heating/cooling device, venting port, die and potentially a downstream processing machinery (Figure I.13). Further types of screw-extruders exist depending on: number of screws (single, twin or multiple), direction of rotation of the screw for twin- and multiple-screw extruder (co- or counter-rotating) (Crowley et al., 2007; Repka et al, 2012; Shah et al., 2013). In the pharmaceutical field, the most applied are the co-rotating twin-screw extruders, which are briefly present right after.

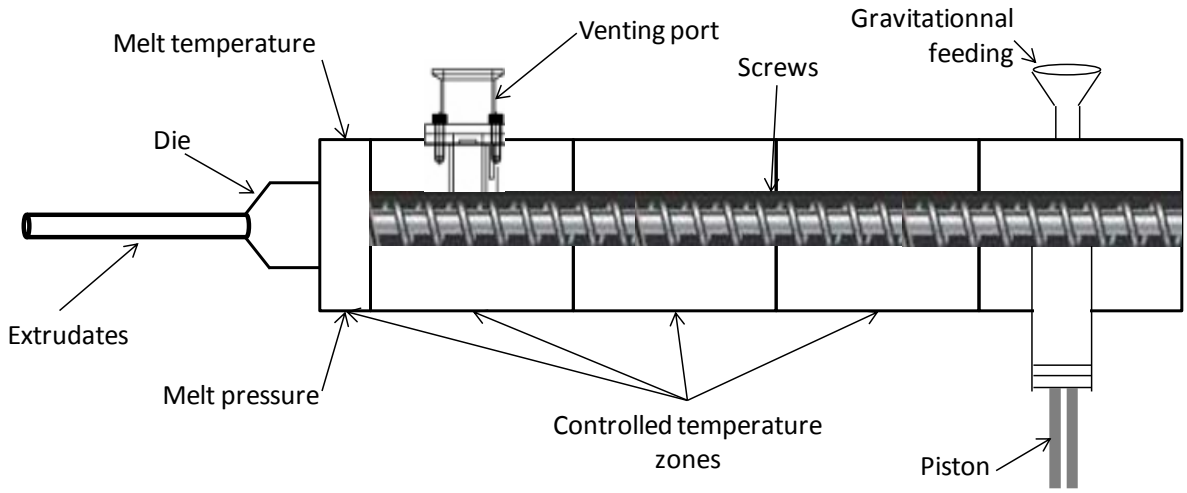


Figure I.13: Schematic representation of a hot-melt extruder

III.6.1.1. Co-rotating twin screw extruders

Co-rotating twin-screw extruders (TSE) are industrially the most important type used in the pharmaceutical field as they present several advantages compared to single-screw extruder especially a better mixing of the components as it has been shown by Ferns (Ferns, 1974) but also to counter-rotating twin-screw extruder as screws are normally composed of individual elements possessing various properties and allowing a very flexible option to arrange transport, mixing and degassing zones along the barrel while screw design is less flexible for the counter-rotating twin-screw extruders. The design of the screw has a significant impact on the process which will be detailed in section II.6.2.1 (Crowley et al., 2007; Gryczke et al., 2011; Repka et al., 2012; Shah et al., 2013). Dimensions of the screws are generally given by the L/D ratio which is the length of the screw divided by the diameter and the size of an extruder is mainly described based on the diameter of the

screw, i.e., 11-27 mm extruder (pilot scale) compared to 60 mm (production scale) (Steiner, 2003). For example the Leitritz Nano-16® that is 400 mm of length and 16 mm of diameter that exhibits a L/D ratio of 25:1 and is named a 16-mm extruder. At the end of the barrel, the die is attached giving the shape to the extrudates and helps to facilitate further downstream processing into the desired product (Crowley et al., 2007).

III.6.1.2. Downstream processing equipment

A wide range of downstream are available following the extrusion process in which the three most applied are (Leister et al., 2012):

- ✓ The strand pelletization where extrudates are cut into small cylinders in a strand pelletizer after cooling on conveyor belt (Figure I.14 A),
- ✓ The chill roll in which a belt of defined thickness is obtained after the passage of the melt between two chilled rolls. At the end of the unit, the resulting belt can be broken into small flakes (Figure I.14 B), and
- ✓ The injection molding by filling molds with the molten drug-polymer mixture. Manufacturers can develop a great number of molds from classic tablets to pediatric friendly designs or adapted to body cavities like ears or vagin (Figure I.14 C) (Claeys et al., 2012; Quinten et al., 2012; Repka et al., 2012),

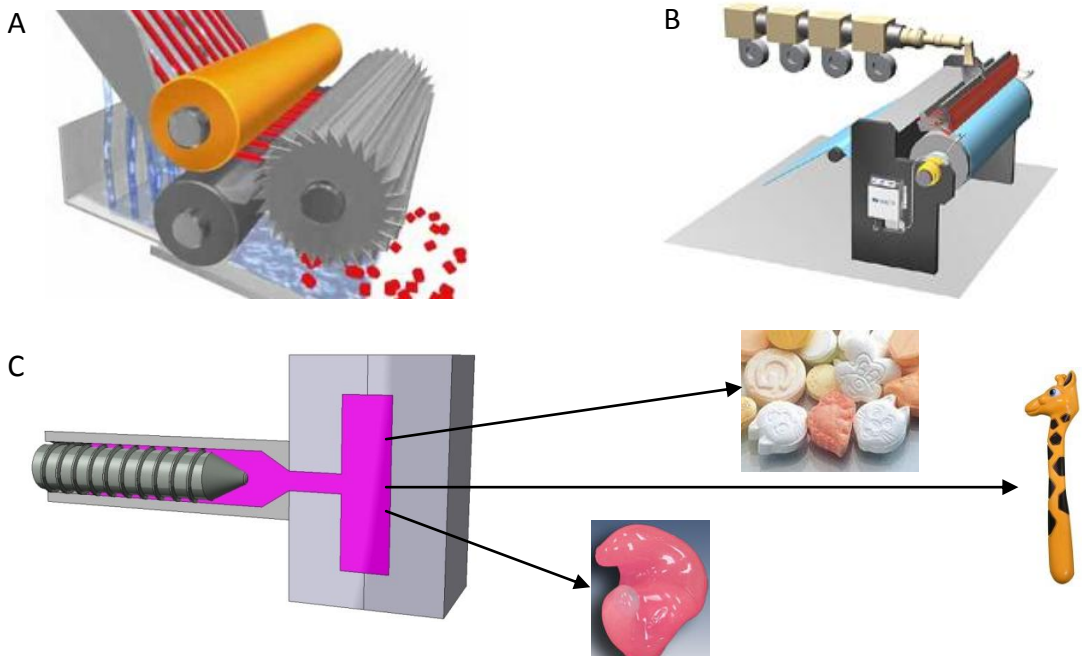


Figure I.14: Dowstream process: A Strand pelletization, B Chill roll, C Injection molding

III.6.2. HME processing

Hot-melt extrusion is a continuous process comprising five steps: feeding, melting/conveying, mixing, venting and extrusion. Each zone can be heated separately at the desired temperature, except the feeding zone which is generally kept at room temperature to avoid premature melting of the components and so blocking the inlet. Physical blend is fed into the barrel either by gravitational feeding or by a micro-plunger system (e.g. Leistritz nano16®) and is then melted and conveyed to soften the blend before mixing which allow homogenization and a well dispersion/dissolution of the drug within the carrier. Finally, at the end of the screw the molten drug/polymer blend is extruded through the die and can be further process depending on the needs (Breitenbach, 2002; Crowley et al., 2007; Shah et al., 2013). Depending on the screw design and the applied processing parameters, the final result can be very different and need to be taking into considerations as well as the behavior of the different components throughout the process helping by the process analytical technology (PAT).

III.6.2.1. Screw design and configuration

Individual elements are added on the screw shaft depending on the needs of scientist. Two main types of screw elements are available (Leister et al., 2012; Steiner, 2003):

- ✓ Conveying elements (Figure I.15) generally present in feeding, melting/conveying and venting zone, and
- ✓ Kneading/Mixing elements (Figure I.15) characterized by the angle (30°, 60° or 90°) between adjacent elements. The higher the angle the higher the mixing.

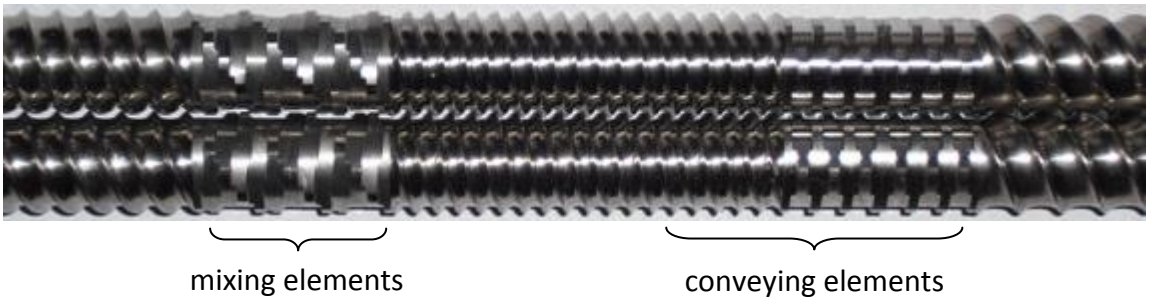


Figure I.15: Screw profile with the different types of elements

Depending on screw configuration, characteristics of the product will vary. Although that is potentially of crucial importance, only few papers have been published in this domain. Indeed, in 2002, Nakamichi and co-workers have shown the crucial role of the kneading elements in transforming the crystalline drug to its amorphous form within the solid dispersions (Nakamichi et al., 2002). Moreover, those elements also play a key role in drug dissolution within the matrix as it has been shown by Liu et al on blends of indomethacin and Eudragit® E PO (Liu et al., 2012a). However, as long as one mixing zone is included, the number and the position of these elements doesn't significantly affect the homogenization and drug dissolution rate (Verhoeven et al., 2008).

III.6.2.2. Processing parameters and scale-up

Some processing parameters can have important influence on the resulting products and have to be well controlled to obtain a robust process more easily scalable. Further studies have been conducted to identify and study the role and effect of the process parameters on the final product. Screw speed, feed rate and processing temperature represent the most commonly studied critical parameters and interplay with shear rate, shear stress and mean residence time (Liu et al., 2010; Shibata et al., 2009; Verreck et al., 2003).

A considerable advantage of the HME process is the relatively easy scaling-up from TSE possessing the same geometry and especially the same L/D ratio. However, any deviation of those parameters between two machines, directly result in changes in the HME process (Dreiblatt, 2012).

To better control the process, the PAT has been introduced and interest in applicable technology has rapidly increased.

III.6.2.3. Process analytical technology

Generally, during extrusion process, operators can follow basic information on zone temperature, melt temperature and pressure, torque, feed rate and screw speed for the main one. However, in many cases no sufficient informations are provided concerning products characteristics and stability throughout the process. In this context, the FDA has

published guidance on the PAT for the innovative pharmaceutical development and numerous investigations have been done in the last decade (Aksu et al., 2012; Burggraeve et al., 2013; De Beer et al., 2011; FDA, 2004; Read et al., 2010a, 2010b; Scott and Wilcock, 2006; Yu et al., 2004). This allows characterizing, analyzing and monitoring the chemical composition of the products in-line with the aim to obtain desired product attributes.

PAT comprises numerous analytical techniques that have been already used in pharmaceutical processes including: spectroscopic techniques (Raman, NIR, UV/visible, fluorescence, terahertz, NMR) (Bakeev, 2010; Saerens et al., 2011, 2012), ultrasound (Kazys and Rekuviené, 2011) and rheological techniques (Xie et al., 2012). However, until today, although reviews have been published on the different process analytical tools for pharmaceutical processes, only one review focused on the advantages and drawbacks of the different PAT already used for supervising HME process (Saerens et al., 2013). I won't refer deeper into this subject as it isn't within the scope of this work.

III.6.3. Materials

Materials used in HME need to meet some requirements such as the ability to deform easily upon heating without degradation following by a sufficiently quick solidification when exiting from the die and some others needs cited in Table I.4. Hot melt extruded dosage forms are frequently composed of the components already used in classic solid dosage forms. To facilitate processing, besides API and matrix carrier, others excipients can be added such as plasticizers, functional excipients and processing aids.

III.6.3.1. Carriers

The carrier is the major component entering in the hot-melt extruded dosage form and its selection is of crucial importance to obtain the desired physico-chemical properties, stability and drug release. They can be classified in polymeric and non-polymeric carriers, and the main carriers have been already presented in the part III.5.2.

In the aim of improving drug solubility, used carriers are most of time hydrophilic and belong to the polymeric ones. In this work, four polymers have been used and their

physico-chemical properties are briefly presented in table I.6. These polymers have already been successfully used in solubility enhancement of PWSD.

Table I.6: Physico-chemical properties of used carriers

Chemical name	Trade name	Tg (°C)
Polyvinylpyrrolidone	Kollidon® K30	160
Polyvinylpyrrolidone-co-vinyl acetate	Kollidon® VA64	101
Poly[butyl methacrylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate] 1:2:1	Eudragit® E PO	48
Hydroxypropyl methylcellulose	Methocel® LV E5	154

Recently, Eudragit® E PO has been widely used to improve drug solubility using hot-melt extrusion technique. In 2011, Gryczke et al. produced orally disintegrating tablets (ODT) based on Eudragit® E and ibuprofen using melt extrusion. They showed the potential of this polymer to improve drug release but also to mask the bitter-taste of the drug (Gryczke et al., 2011). At the same time, Kindermann et al. proved the formation of an electrolyte complex between acidic drugs and tertiary ammonium group of the Eudragit® E. Addition of an electrolyte in the dissolution medium allow an immediate drug release, attributed to the destabilization of the complex as no drug releases has been observed in demineralized water (Kindermann et al., 2011).

A growing interest in the use of polymer blends have also been noted as it allows to combine advantages of further polymers in the final dosage form but also to process difficult to handle interesting binary mixtures. In 2012, Sakurai et al. processed a low Tg BCS class II drug with polymer blends containing HPMC, PVPVA and PVP. They showed that combination of the stabilizing effect of the PVP and oral absorption enhancement effect of HPMC led to an increase in stability, solubility and bioavailability compared to drug-HPMC solid dispersion (Sakurai et al., 2012). Liu et al. prepared hot-melt extrudates based on a thermally unstable drug and showed that compared to single polymer a combination can lead to an improvement in drug solubility within the matrix but also to a decrease of the processing temperature. For instance a better in vitro dissolution and a physico-chemical stability at least 3 months has been obtained with hot-melt extrudates containing Eudragit® E:Soluplus® (1:1 w:w) (Liu et al., 2013).

Combining the craze for Eudragit® E and polymer blends, binary and ternary blends have been tested using the model drug ketoprofen and the results will be presented in chapter III.

III.6.3.2. Plasticizers

Sometimes to facilitate or to render extrusion process possible, a plasticizer had to be added. Generally, those molecules present a low Mw allowing a higher flexibility of the polymer. This result mainly in a lower glass transition temperature and melt viscosity due to the higher free volume existing between the polymer chains.

Further plasticizers have been already used in HME process such as vitamin E TPGS, surfactants (SLS, polysorbate 80), poloxamer, low-Mw PEG, citrate esters, triacetin, methylparaben. Depending on polymer-plasticizer compatibility and miscibility and on plasticizer stability, the most suitable will be selected. More recently, Verreck et al. demonstrates the double action: plasticizer and foaming effect of either pressurized or supercritical CO_2 (Verreck et al., 2006, 2007). Finally, it has been shown that some drugs can act as plasticizer in films (Siepmann et al., 2006) but also in hot-melt extruded dosage forms (Crowley et al., 2004).

In this work, no plasticizers had to be added as the two model drugs ketoprofen and fenofibrate present a plasticizing effect of the polymers used.

III.6.3.3. Other processing aids

This principally concerns protection from oxidative degradation which can occur within the HME due to the high temperature especially with cellulose-based polymers. To avoid this phenomenon, antioxidant agents: ascorbic acid or butylated hydroxytoluene need to be added.

III.7. Spray-drying

Spray-drying has been used for the first time in 1860 and in 1872 the first patent has been registered (Percy, 1872). However, due to efficiency, performance and safety problems, the evolution has stopped until the 1920s. At this time, the technique has been used to produce milk powder, and today it's still one of the main applications of this technique. Use of spray-drying technology has exploded during the 2nd world war due to the needs of large food quantities. Indeed, to reduce weight and volume and to gain in conservation of the food, spray-drying is the right technique. Moreover, many wounded persons needs plasma and serum transfusion, consequently to facilitate the transport they were dried and transported on the front (Wilkinson et al., 1942).

Growing interest in pharmaceutical industry has continued during the post-war period, with the drying of raw material extracts even the thermolabile one and until today plant extracts are still prepared by spray-drying as powders properties are better than those obtained with others drying techniques. After more than 150 years of research this technique is today a powerful and one of the most frequently used technology for drying and is used in the pharmaceutical industry for a wide range of applications which will be briefly presented later (Cal and Sollohub, 2010).

In this part the major aspects of the spray-drying technology will be discussed by means of: equipment and process, materials used, processing parameters and the pharmaceutical applications with a focus on the solubility enhancement.

III.7.1. Equipment and process

Spray-drying requires simple equipment composed of: an atomization device, a drying chamber and a collector system. Each of these elements will have a huge influence on the final product characteristics. However, as well as for HME equipment, no change occurred during this work. Consequently, the various parts and the basic principles of the process will be only briefly described.

III.7.1.1. Atomization

To transport the feed to the atomization device, a basic peristaltic pump is the most frequently used one. The only limitation is that the feed viscosity shouldn't be too high to allow a uniform and repeatable feeding and to avoid clogging within tube.

Atomization is one of the most important phases of the process as it leads to the formation of the droplets and thus causes the formation of large surface areas resulting in a rapid evaporation of the solvent. Further devices are available to create the atomization depending on the type of energy involved (Cal and Sollohub, 2010; Paudel et al., 2013):

- ✓ **Rotary atomizers**: It consists of a rotating disc on which the feed is brought on its center. Due to rotation, the feed is centrifugally spread out on the surface as a thin film, which is fragmented into droplets at the border of the rotating wheel (Figure I.16 A). Droplet size is dependent on the rotating speed. Although, it's the most effective atomizer, there are more wall deposits and consequently a lower yield.
- ✓ **Hydraulic (pressure) nozzles**: Using a high pressure pump, the feed is forced through tubing with decreasing diameter. When passing the nozzle a part of the energy is converted into kinetic energy leading to particle velocity allowing atomization (Figure I.16B). Main problem is when liquid has a too high viscosity to be pumped and frequently lead to clogging. Droplet size can be controlled by modifying pressure of the flow but also by modulating the spray angle. Those one are usually not use in pharmaceutical industry due to the wide range of size, the limited ability to control the properties of the obtained particles and the low efficiency limited industrial use.
- ✓ **Pneumatic nozzles or multiple-fluid nozzles:** Liquid feed is exposed to a gas stream causing its disintegration into droplets due to high frictional forces at the liquid surface (Figure I.16C). Droplet size can be controlled by further parameters: feed rate, gas flow rate and sometimes changing the orifice size. The two-fluid nozzles are the most commonly used for pharmaceutical application for some reasons: high efficiency, good dispersion of the liquid feed and further possibilities to modify the particles parameter can be done. As others device, nozzle can be clogged with too viscous liquid feed. However, in some spray-dryer an in-process cleaning is possible

with a needle driven by compressed air (Büchi B-290). To obtain narrower size distribution with enhanced pulmonary and oral absorption of PWSD, four-fluid nozzles can be used (Ozeki et al., 2012).

- ✓ **Ultrasonic nozzles**: Recently, this new atomizing device based on the vibration of a mesh has been developed by Büchi (Li et al., 2010b). A high frequency signal is applied on electrodes which are placed between two piezoelectric transducers. Then, the perforated thin membrane vibrates, expulsing numerous droplets with a narrower distribution size (Figure I.16D).

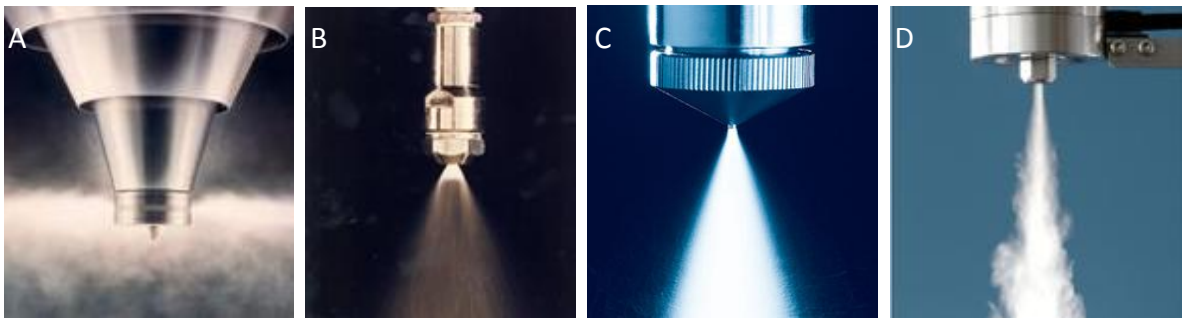


Figure I.16: Atomization devices: A: rotary atomizer, B: pressure nozzle, C: pneumatic nozzle, D: ultrasonic nozzle

III.7.1.2. Drying chambers

Right after atomization, droplets come into contact with the drying gas (air and nitrogen for the two most employed). Due to the non laminar flow, each droplet undergoes different air temperature and humidity conditions. Consequently, humidity of the atmospheric air has a huge impact on the drying process and depending on the seasons drying conditions are changed.

Based on the desired product properties and the selection of the atomizing device the shape of the chamber is determined. Most of the time, vertical chambers are used with a cylindrical shape ending by an inverted cone. Depending on the chamber height, tall and small drying chambers can be considered:

- ✓ **Tall** one corresponds to a ratio height to diameter > 5:1
- ✓ **Small** one which are the most frequently used, generally presents a ratio of 2:1 and can be used either with nozzle or rotating atomizers.

With equations, it's possible to determine the most suitable shape. However, their discussion isn't within the scope of this work and errors often occurred due to the complexity of interactions.

Afterward depending on the orientation of the liquid feed with regard to the drying gas, three configurations can be possible:

- ✓ **Concurrent**: atomizing device and air inlet are placed at the top of the drying chamber. The droplets will fall towards the outlet with the airflow. It's the most frequently used and the best known in terms of particles behavior (Figure I.17A),
- ✓ **Countercurrent**: In this case the air inlet is placed at the bottom of the drying chamber and the droplets will firstly hit cold air and finish to dry in the hot air at the bottom of the chamber. However, in food and pharmaceutical applications they are unsuitable as most of the products ares exposed to hot air leading to product parching (Figure I.17B),
- ✓ **Combined**: Here the feed is atomized from the bottom and the air flow from the top of the drying chamber. However, this leads to the mix of moist product with dry product which goes to the receptacle has to be thoroughly supervised. For thermostable products it's the most economic one. (Figure I.17C)

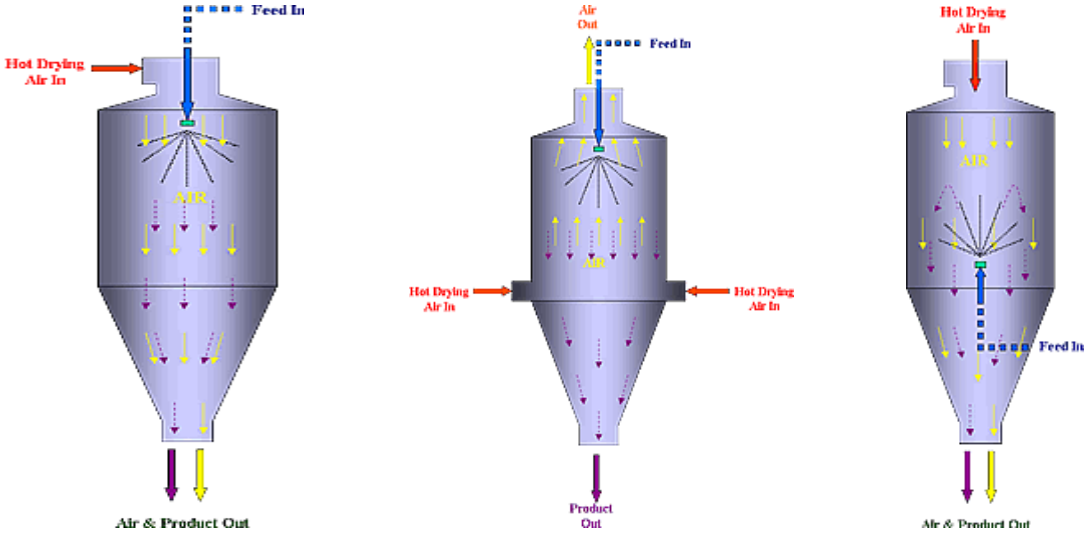


Figure I.17: Possible configurations of the spray-drying chamber. A: concurrent, B: counter-current, C: combined flow [from (Sakav, 2013)]

III.7.1.3. Collecting systems

Once dried, particles are collected either by settling on the bottom of the drying chamber or by leaving it with the air following by separation of the particles from the air.

For the former one if there is no cone-shape or if the angle doesn't allow a free flowing, a scraper device is required. Three main types are used: vibratory devices, mechanical brush and compressed-air stream. However, those systems might cause problems as the already dried product might meet some of the not completely dried product.

In the latter case, particles are transported to external separation devices. Typically, particles are separated from the drying air using cyclones and/or filter bags. In the cyclone a rotating vortex is created due to the high fluid velocity leading to the separation of the particles from the air as particles are drove on the walls. At the end of the conical part, a collector vial is placed to allow the reverse of the gas stream and particles to settle. Too fine particles might be collected on filter bags (Figure I.18).

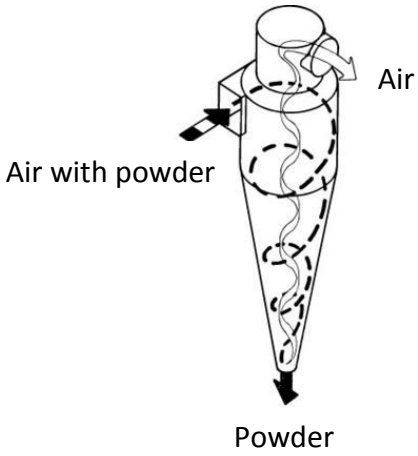


Figure I.18: Cyclone

III.7.2. Materials

As for HME, the used components of the formulation need to meet some requirements, especially a good solubility in the most commonly used solvents but also a sufficiently high Tg to avoid the formation of a continuous film on the wall of the cyclone. Basically, the spray-dry process requires only a solution or a suspension of the

drug/polymer blends. Carriers used in this work and choice of solvent system will be briefly discussed in regard to the spray-drying process.

III.7.2.1. Carriers

The idea is to select the right carrier, which primarily serves as a crystallization inhibitor by decreasing the molecular mobility of the amorphous form and thus can potentially maintain a supersaturation generated during in vitro dissolution and after oral administration in the gastrointestinal milieu (Bee and Rahman, 2010). As for HME, polymers which are used to improve drug solubility are mainly hydrophilic polymers and the same ones have been used for spray-drying. The selection of carriers has been based on the literature and their potential in increasing solubility of PWSD.

From the cellulosic derivatives, HPMC is the most frequently used as stabilizer for preparing spray-dried powders. The stabilizing effect has been attributed to the possibility of hydrogen bonding between hydroxyl group which can act as a H-bond donor and H-bond acceptor of the drug (Bee and Rahman, 2010). Boghra et al, showed that solubility enhancement of irbesartan can be attributed to crystallization inhibiting, anti-plasticizing and wetting properties (Boghra et al., 2011). Furthermore, Dahlberg and co-workers proved that interaction between drug and HPMC as well as the drug distribution within the polymeric matrix considerably influenced wettability of the system and that water penetration is of less importance compared to polymer mobilization (Dahlberg et al., 2010a, 2010b).

For the vinyl polymers, there are two commonly used for the formulation of spray-dried powders: a linear one (PVP) and a cross-linked one (PVP-VA). They both present miscibility in a wide range of solvents commonly used in spray-dry process, a good stability and the possibility to form H-bonding with H-bond donator drugs (Bee and Rahman, 2010). Numerous PWSD have shown improved in vitro drug release and/or in vivo performance using these two polymers (Al-Obaidi et al., 2011; Janssens et al., 2008a, 2008b, 2008c; Kim et al., 2013; Lee et al., 2013; Sahoo et al., 2010; Tung et al., 2011; Xu et al., 2007).

Concerning the poly(meth)acrylate polymers, as Eudragit® E presents a very interesting potential to improve drug solubility via HME (Gryczke et al., 2011; Kindermann

et al., 2011) and spray-drying with high melting point drug (Janssens et al., 2010; Nollenberger et al., 2009), it appears interesting to test this quite new polymer in spraying very low glass transition temperature drug. However, Eudragit® E which presents a quite low glass transition temperature (48°C) can't be processed alone with the two model drugs as they present very low Tg 0°C for the ketoprofen and – 20°C for the fenofibrate. Consequently, binary blends without Eudragit® E or ternary blends composed of drug, Eudragit® E and a second polymer presenting a higher Tg have been spray-dried.

III.7.2.2. Solvent system

A second important parameter to be taken into account with spray-dry formulations is the choice of the solvent system as it can have a huge impact on the physico-chemical properties and dissolution behavior of the obtained spray-dried powders. In general further conditions are required such as (Paudel et al., 2013):

- ✓ To find a common solvent for drug and carrier,
- ✓ To obtain an acceptable viscosity to allow the spray,
- ✓ To use solvents with low toxicity, a sufficiently high volatility, non combustive properties and allowing chemical stability of the feed components.

Although, dichloromethane is a class 2 solvent according to the International Conference of Harmonization (ICH), it's still often used in spray-drying processes as it solubilizes a wide range of chemical components and possesses a high volatility (Janssens et al., 2008a, 2008b, 2008c; Kim et al., 2011; Leane et al., 2013; Patel et al., 2012; Tung et al., 2011). However, today, due to (eco)-toxicological reasons more and more spray-drying trials are conducted with alcoholic or hydroalcoholic mixtures in combination with poorly-water soluble drugs to enhance the bioavailability even when starting from a fed suspension (Li et al., 2010a; Park et al., 2009, 2010; Paudel et al., 2013; Yan et al., 2012).

Nowadays, further studies have been conducted on the relation between the solvent system used and spray-dried powders properties of which the in vitro/in vivo performance and the stability of the obtained system (Al-Obaidi et al., 2009; Paudel et al., 2013).

III.7.3. Process parameters

After choosing the right carrier and solvent system, the processing has to be optimized, playing with the various process parameters which are: inlet temperature, spray and feed flow rate. Growing interest in quality by design (QbD) with the PAT offers ability to develop robust process allowing to obtain products with the desired properties (Nagy and Meszena, 2009). However, in the spray-drying technology, most of the obtained information by the use of QbD concern particle engineering and the bulk level properties of the final product (Chiou et al., 2007; Das et al., 2009; Langrish, 2007). Concerning the impact of the process parameters and interplay existing amongst them, there is only little information.

III.7.3.1. Feed flow rate

The feed rate firstly determines the time period which a particle spends in one of the various parts of the spray-dryer. It has also an impact on the outlet temperature and is responsible for the saturation degree of the exiting gas. A compromise need to be find to allow sufficient drying of particles before hitting the wall of the dryer while keeping the highest feed rate for time and cost saving (Vehring, 2008).

III.7.3.2. Inlet temperature

Which probably the most important factor as it affects the internal structure of the particles. Indeed; it directly impacts on further characteristics of the process and the product such as:

- ✓ The outlet temperature;
- ✓ The solvent evaporation kinetic which is responsible for the residual solvent content but also of the unique phase structure;
- ✓ Amorphicity, particle size, flowability, hygroscopicity… of the spray-dried powder.

However, this has mainly been studied for single components and some pure PWSD. In 1992, Matsuda et al., showed the influence of the inlet temperature on the amorphicity, intermolecular interactions and obtained glass transition temperature. Indeed, the lower the inlet temperature, the lower the Tg with complete absence of intermolecular interaction leading to lower physical stability of the amorphous form in contrast to higher inlet temperature which besides showed higher physical stability (Matsuda et al., 1992). However, depending on the PWSD, the opposite can be possible as it has been demonstrated by Ueno et al. with the ursodeoxycholic acid. In this case the highest temperature lead to the highest amorphization with the highest extent of H-bonding disruption (Ueno et al., 1998). Ohta et al. noticed that lower inlet temperature favored recristallization and water uptake with two different compounds, which (Ohta and Buckton, 2005). Those results clearly point out the fact that the inlet temperature probably influences the surface properties and the physical stability of the spray-dried solid dispersions.

Recently, Wu et al. prepared piroxicam-PVP films by casting to study the impact of solvent evaporation rate and temperature on the crystal nucleation. They noticed that the rate of evaporation and in consequence the temperature has a higher impact than the formulation composition on the films characteristics, especially on the crystal nucleation (Wu et al., 2011). However, depending on the spray-dried system, Duret et al. showed that crystallization of itraconazole increase with increasing of inlet temperature (Duret et al., 2012) while Sahoo et al. has demonstrated the opposite relation with artemisinin (Sahoo et al., 2009). Although, it's well known that a higher temperature results in larger particles with hollow cores, each system presents particular behavior and need to be optimized during the development with already developed methodology (Dobry et al., 2009). Moreover, the outlet temperature which is directly linked to the inlet temperature needs to be selected with care I order to avoid stickiness on the dryer walls (< Tg) (Patterson et al., 2007, 2008)

III.7.3.3. Spray flow rate

The selection of the drying gas is also important though the composition of the solution greatly influences this choice: dehumidified air for aqueous solutions and nitrogen for non-aqueous solutions.

Generally, it's not the gas flow rate but the ratio of the gas rate/feed rate which is taken into account as the idle parameter. Wang et al. studied the influence of the gas flow rate and noticed that the slower the flow rate the broader the particle size distribution and the lower the residual solvent content due to the slower movement of product throughout the system and consequently a longer action of the drying gas (Wang et al., 2009).

III.7.4. Pharmaceutical applications

Spray-drying is used in a wide range of applications in the pharmaceutical field. Here, I'll focused on the two applications in relation with this work and only cited some others very interesting applications (Sollohub and Cal, 2010).

III.7.4.1. Excipients and co-spray dried composites

As it has been shown just above, process parameters can have a huge influence on particles properties. For example spraying lactose lead to various compressive properties depending on spray process parameters which allow partial amorphization of the lactose as 55-76 % of the lactose remains crystalline (Chiou et al., 2008; Takeuchi et al., 1998). This type of lactose is widely used in compressive properties improvement of powders as it provides better plasticity and binding leading to hardness and lower friable tablets and is available as Tablettose®.

Furthermore, intensive research has also been done in spraying drug/excipients mixtures to allow direct tableting which is the preferred way for manufacturers to obtain tablets. For some compounds presenting very low Tg, avoiding film formation is very difficult as it's generally recognized that a drying temperature 10°C below the Tg seems to be safe (Bhandari and Howes, 1999). To avoid this phenomenon the addition of a second

compound with a high Tg is possible and predictable for binary mixtures and becomes very difficult for more complicated mixtures. Gonnissen et al. developed a one-step process leading to directly compressible powders by overcoming the difficulties linked with complex mixtures and low Tg compounds. Moreover, they're able to statistically optimize those powders. Following this, spray-drying was conducted at industrial scale with paracetamol or ibuprofen showing that powders can also be directly compressed. These results proves the scalability of the spray-drying process with popular drugs difficult to handle (Gonnissen et al., 2007, 2008a, 2008b, 2008c).

III.7.4.2. Solubility improvement

With the increasing number of PWSD, co-spray-drying of drug and excipients in the aim of increasing water solubility and BA of such compounds also presents very interesting opportunities. In 2009, Sahoo et al. sprayed artemisinin with various ratios of maltodextrin and under different process parameters. They've shown that the inlet temperature and the concentration in the feed and flow rate have a huge impact on the aqueous solubility especially due to particle size and cristallinity decrease (Sahoo et al., 2009).

Furthermore, addition of surfactants in spray-dry mixture, has pointed out that not only particle size and cristallinity affect the aqueous solubility but also the wettability of the particles (Chaubal and Popescu, 2008; Wong et al., 2006).

Another possibility to improve drug solubility via spray-drying is to spray mixture of PWSD with a water soluble substance such as hydrophilic polymer. Numerous studies have been published using this technique (Ozeki et al., 2006, 2012; Paradkar et al., 2004; Paudel et al., 2013; Piao et al., 2008).

SEDDS can also be obtained by spray-drying, leading to increase of solubility of various drugs allowing the use of smaller amounts of surfactants (Dollo et al., 2003; Kim et al., 2012; Yi et al., 2008).

III.7.4.3. Other applications

Spray-drying is also used in many others applications such as:

- ✓ **Modified drug release**: Playing with polymer type and drug/polymer ratio, allows to target the colon (Esposito et al., 2002; Shendge and Sayyad, 2013) or to modify the drug release (Beck-Broichsitter et al., 2012; Möbus et al., 2012a, 2012b),
- ✓ **Drying of proteins**: Mainly to improve stability and obtain fine and flowable powders. However, it still encounters some problems such a sticking of the protective agent on the wall of the dryer (Lee et al., 2011; Maury et al., 2005a, 2005b);
- ✓ **Inhalation powders and vaccines**: To facilitate administration via the respiratory tract (Hoang Thi et al., 2008; McAdams et al., 2012; Osman et al., 2013; Rodrigues et al., 2012; Saluja et al., 2010);
- ✓ **Taste masking**: To facilitate administration of bitter drugs (Hoang Thi et al., 2012, 2013).

IV. Research objectives

Amorphous solid dispersions represent an attractive way to improve drug solubility, while ensuring a better patient compliance due to a decrease of the administered dose but also of the side effects. Today, hot-melt extrusion and spray-drying techniques represent the two most used techniques to prepare this type of advanced drug delivery systems. However, despite intensive research in this field since 40 years, only few products have reached the market, principally caused by the physico-chemical stability problem of the amorphous state.

On one hand, this work consisted in increase the apparent solubility of the poorly-water soluble drug, ketoprofen by incorporating it into hydrophilic polymeric matrices using the two most employed techniques to form solid dispersions and the interesting matrix former: Eudragit®E.

The major aims of this study were:

(i) To prepare hot-melt extrudates and spray-dried powders based on various hydrophilic matrices in order to improve drug solubility and stabilize its amorphous form;

(ii) To physico-chemically characterize the obtained systems;

(iii) To study the impact of the matrix composition on the physico-chemical characteristic and in vitro drug release of the drug;

On the other hand, the impact of formulation and processing parameters on the key properties of spray-dried microparticles containing poorly-water soluble drugs has been extensively reported in the literature , as recently reviewed by Paudel et al. (Paudel et al., 2013). However, yet relatively little is known on the impact on the inner particles' structure but also on the use of polymer blends and the impact of simply varying the polymer:polymer blend ratio on the key properties of the systems.

In this matter the major objectives included:

(i) To prepare spray-dried powders based on various hydrophilic matrices in order to improve drug solubility and stabilize its amorphous form

(ii) To physico-chemically characterize the obtained spray-dried powder;

(iii) To study the impact of various formulation and processing parameters on the spray-dried powder characteristics and the resulting in vitro drug release;

The research objectives of this PhD thesis will be described within the three chapters:

(i) Accelerated Ketoprofen Release from Polymeric Matrices: Importance of the Homogeneity/Heterogeneity of Excipient Distribution [Chapter II]

(ii) Accelerated Ketoprofen Release from Spray-Dried Polymeric Particles: Importance of Phase Transitions and Excipient Distribution [Chapter III]

(iii) Accelerated Fenofibrate Release from Spray-Dried Microparticles Based on Polymer Blends [Chapter IV]

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Chapter II. ACCELERATED KETOPROFEN RELEASE FROM POLYMERIC MATRICES: IMPORTANCE OF THE HOMOGENEITY/HETEROGENEITY OF EXCIPIENT DISTRIBUTION

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Abstract

Polymeric matrices loaded with 10 to 50 % ketoprofen were prepared by hot-melt extrusion or spray-drying. Eudragit® E, PVP, PVPVA and HPMC were studied as matrix formers. Binary "drug-Eudragit® E" as well as ternary "drug-Eudragit® E-PVP", "drug-Eudragit® E-PVPVA" and "drug-Eudragit® E-HPMC" combinations were investigated and characterized by optical macro/microscopy, SEM, particle size measurements, mDSC, X-ray diffraction and in vitro drug release studies in 0.1 M HCl. In all cases ketoprofen release was much faster compared to a commercially available product and the dissolution of the drug powder (as received). Super-saturated solutions were obtained, which were stable during at least 2 h. Importantly, not only the composition of the systems, but also their inner structure potentially significantly affected the resulting ketoprofen release kinetics: For instance, spray-drying ternary ketoprofen:Eudragit® E:HPMC combinations led to a more homogenous HPMC distribution within the systems than hot-melt extrusion, as revealed by mDSC and X-ray diffraction. This more homogenous HPMC distribution resulted in more pronounced hindrance for water and drug diffusion and, thus, slower drug release from spray-dried powder compared to hot-melt extrudates of identical composition. This "homogeneity/heterogeneity effect" even overcompensated the "system size effect": the surface exposed to the release medium was much larger in the case of the spray-dried powder. All formulations were stable during storage at ambient conditions in open vials.

Keywords: poorly soluble drugs; hot-melt extrusion; spray-drying; ketoprofen, Eudragit® E

I. Introduction

Poor aqueous solubility has become a major concern for numerous new drug candidates. Despite a potentially ideal chemical structure allowing for interaction with the target, these substances fail to be effective in vivo: Upon administration they cannot dissolve in aqueous body fluids to a sufficient extent and, thus, cannot be transported to their site of action to reach therapeutically effective concentrations. Various interesting strategies have been proposed to overcome this crucial hurdle, including the use of lipid-based formulations (Mu et al., 2013), polymeric micelles (Repka et al., 2012), cyclodextrines (Fukuda et al., 2008; Kurkov and Loftsson, 2013), co-crystals (Elder et al., 2013; Thakuria et al., 2013), nanocrystals (Sinha et al., 2013), mesoporous systems (Xu et al., 2013), and amorphous systems (Brough and Williams III, 2013; Van den Mooter, 2012; Zhao et al., 2012). The overall aim is to increase the drug release/dissolution rate. This is often achieved via an increased apparent water solubility of the respective compound, even if super-saturation is achieved only for a limited time period: Once dissolved, the individualized drug molecules/ions/atoms might be rapidly transported away (e.g., by passive diffusion or active transport processes across the gastro intestinal mucosa). To prolong the life-time of super-saturated solutions, precipitation inhibitors have been proposed (Xu and Dai, 2013). Bevernage et al. recently published an excellent review on this topic (Bevernage et al., 2013). It has to be pointed out that upon oral administration, also bile salts can affect the absorption of poorly soluble drugs (Holm et al., 2013).

The aim of this study was to increase the apparent aqueous solubility of ketoprofen by incorporation into a hydrophilic polymeric matrix. The idea was to transform the crystalline raw material into a physical state with increased energy in order to increase the driving force for drug dissolution. At the same time, the system should be stable during long term storage, thus, re-crystallization or other system changes resulting in altered drug release rates were to be avoided. Different manufacturing techniques can be used to prepare such polymeric drug delivery systems, including hot-melt extrusion (Repka et al., 2012) and spray-drying (Paudel et al., 2013). Both techniques have been applied in this study. Eudragit® E, poly[butyl methacylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate] 1:2:1, was considered to be an interesting matrix former is this case,

since it is thermoplastic and provides sufficient thermal stability for hot-melt extrusion under appropriate conditions (Albers et al., 2009), rapidly dissolves at acidic pH and can interact with acidic drugs due to its multiple tertiary ammonium groups (Horisawa et al., 2000; Kindermann et al., 2011).

The obtained systems were thoroughly characterized using X-ray diffraction, mDSC, SEM, optical macro/microscopy, and drug release measurements in 0.1 M HCl before and after storage. Intentionally, drug release was monitored under non-sink conditions, in order to evaluate the potential of the formulations to provide super-saturated solutions and the life-time of the latter.

II. Materials and methods

II.1. Materials

Ketoprofen (Sigma-Aldrich, Steinheim, Germany); hydroxypropyl methylcellulose (HPMC, Methocel® E5; Colorcon, Dartford, UK); poly[butyl methacylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate] 1:2:1 (Eudragit® E, Eudragit® E 100 PO; Evonik, Essen, Germany); polyvinylpyrrolidone (PVP, Kollidon® K30) and poly(vinylpyrrolidone-co-vinyl acetate) (6:4 mass:mass, PVPVA, Kollidon® VA 64) (BASF, Ludwigshafen, Germany); Profenid® 100 mg (Sanofi, Paris, France); acetonitrile and sodium dihydrogen orthophosphate dihydrate (Fisher Scientific, Loughborough, UK); phosphoric acid 85 % (Sigma-Aldrich); ethanol 95 % (Brabant, Tressant, France).

II.2. Preparation of physical mixtures

Ketoprofen and one or more polymers (as indicated) were blended manually using a pestle and mortar for 10 min (100 g batch size). These blends were used for subsequent hot-melt extrusion or spray-drying.

II.3. Preparation of hot-melt extrudates

Drug-polymer blends were hot-melt extruded using a Leistritz "Nano 16" apparatus (Leistritz, Nurnberg, Germany), equipped with a co-rotating twin screw (diameter = 16 mm, 5 heating zones, kneading elements in zones 2 and 3, diameter of the die orifice = 1 mm). The screw speed and feeding rate were kept constant at 100 rpm and 4 cm^3/min, respectively. The feeding zone (zone 1) was kept at room temperature. Due to the different physicochemical properties of the investigated polymers (in particular different glass transition temperatures), the heating of zones 2-5 was optimized for each ketoprofen–polymer blend (Table II.1). The extrudates were air-cooled and manually cut into cylinders of 2 mm length.

Table II.1: Temperatures of the barrel zones during hot-melt extrusion of the ketoprofen-polymer blends. The feeding zone (zone 1) was kept at room temperature.

Polymer(s)	Drug loading, %	T, °C			
		Zone 2	Zone 3	Zone 4	Die
Eudragit® E	10	130	130	115	110
Eudragit® E	30	120	120	105	90
Eudragit® E	50	115	115	100	85
Eudragit® E:PVP 50:20	30	130	130	120	115
Eudragit® E:PVPVA 50:20	30	120	120	110	105
Eudragit® E:HPMC 50:20	30	130	130	120	120

II.4. Preparation of spray-dried powders

Drug-polymer blends were dissolved in 300 mL ethanol/water 85:15 (v:v). The liquids were spray-dried with a Buechi B-290 spray-dryer (Buechi, Basel, Switzerland), equipped with a 0.7 mm nozzle, using the following operating conditions: inlet temperature = 70°C; aspirator flow = 36 m^3/h; spray flow = 414 L/h; pump flow = 7.5 mL/min. The resulting outlet temperature was about 40-45°C.

II.5. In vitro drug release measurements

Appropriate amounts of formulations containing 60 mg ketoprofen were placed in 125 mL plastic flasks, filled with 100 mL 0.1 M HCl. The flasks were horizontally shaken (80 rpm, orbital movement) at 37 °C (GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). At predetermined time points, 3 mL samples were withdrawn, replaced with fresh medium, filtered through a 0.45 µm GF/PVDF filter (Whatman, GE Healthcare, Kent, UK) and subsequently diluted (1:30, v:v) with 0.1 M HCl. The drug content of the samples was determined by HPLC analysis (ProStar 230 pump, 410 autosampler, 325 UV–vis detector, Galaxie software; Varian Les Ulis, France). A reversed phase column C18 (Luna 5 µm; 110 Å; 150 mm × 4.6 mm; Phenomenex, Le Pecq, France) was used. The mobile phase was acetonitrile:phosphate buffer pH 3 (20 mM NaH_2PO_4) (45:55, v:v). The detection wavelength was 259 nm and the flow rate 1 mL/min. One hundred µL samples were injected. The elution time was around 9 min. Each experiment (drug release and drug detection) was conducted in triplicate.

II.6. Equilibrium solubility measurements

The equilibrium solubility of ketoprofen power (as received) was determined in agitated flasks in 0.1 M HCl, optionally containing 0.06, 0.14 or 0.54 % (w/v) Eudragit® E, or 0.14 % Eudragit® E:PVP, Eudragit® E:PVPVA or Eudragit E®:HPMC 5:2. An excess amount of ketoprofen was exposed to 20 mL medium at 37°C under horizontal, orbital shaking (80 rpm; GFL 3033). Every 24 h, samples were withdrawn, filtered and analyzed by HPLC for their drug content (as described above) until equilibrium was reached. Each experiment was conducted in triplicate.

II.7. mDSC analysis

Modulated Differential Scanning Calorimetry (mDSC) thermograms of the drug, polymers, hot-melt extrudates and spray-dried powders were recorded with a DSC1 Star System (Mettler Toledo, Greifensee, Switzerland). If not otherwise indicated, approximately

5 mg samples were heated in perforated aluminum pans from -30 to 170°C at 2°C/min with a modulation amplitude of ± 0.5 K. Only in the case of ketoprofen powder, two heating cycles were run (the aim was to transform the drug into an amorphous state during the cooling phase), under the following conditions: 1st heating: from 25 to 120°C at 2 °C/min, holding for 2 min; cooling: from 120 to -30 °C at 2 °C/min, holding for 2 min; 2nd heating: from -30 to 180 °C at 2 °C/min. The modulation amplitude was ± 0.5 K and the modulation period 15 to 30 s.

II.8. X-ray diffraction studies

X-ray powder diffraction patterns were recorded using a PANalytical X'Pert pro MPD powder diffractometer equipped with a Cu X-ray tube ($\lambda_{CuK\alpha}$ = 1,540Å) and the X'celerator detector. Powder samples were placed in a spinning flat sample holder, the measurements were performed in Bragg-Brentano θ-θ geometry.

II.9. Scanning electron microscopy and optical macro/microscopy

The morphology of spray-dried particles was studied using a Hitachi S4700 apparatus (Hitachi, Tokyo, Japan), operating at an accelerating voltage of 3 kV. The powder surfaces were coated with carbon. Hot-melt extrudates were observed with an optical image analysis system (Nikon SMZ-U; Nikon, Tokyo, Japan), equipped with a Zeiss camera (AxioCam ICc 1, Zeiss, Jena, Germany). Mean particle diameters were determined with an Axioscope microscope (Zeiss) and an optical imaging system (EasyMeasure; INTEQ, Berlin, Germany). Each measurement included 200 particles.

III. Results and discussion

III.1. Ketoprofen-Eudragit® E hot-melt extrudates

The open symbols in Figure II.1 illustrate ketoprofen release from Eudragit® E-based hot-melt extrudates in 0.1 M HCl. The initial drug loading was varied from 10 to 50 % (w:w), as indicated. For reasons of comparison, also drug release from the commercially available product Profenid® is shown (filled diamonds) and the dissolution of the ketoprofen powder (as received, mean particle diameter = 16 µm, filled squares). The dashed lines indicate the equilibrium solubility of the drug powder (as received) under the given conditions: Importantly, the presence of Eudragit® E increases the solubility of ketoprofen, which was determined to be equal to 0.18 ± 0.01, 0.23 ± 0.01, and 0.50 ± 0.01 mg/mL in 0.1 M HCl containing 0.06, 0.14 or 0.54 % w/v of this polymer. Clearly, ketoprofen release was significantly faster from all investigated extrudates compared to the commercially available product and the ketoprofen powder (as received). Remarkably, super-saturated solutions were obtained, which remained stable during the 2 h observation period. This fact can be of crucial importance in vivo, since dissolved drug might have sufficient time to be transported away from the site of release (e.g., absorbed into the blood stream).

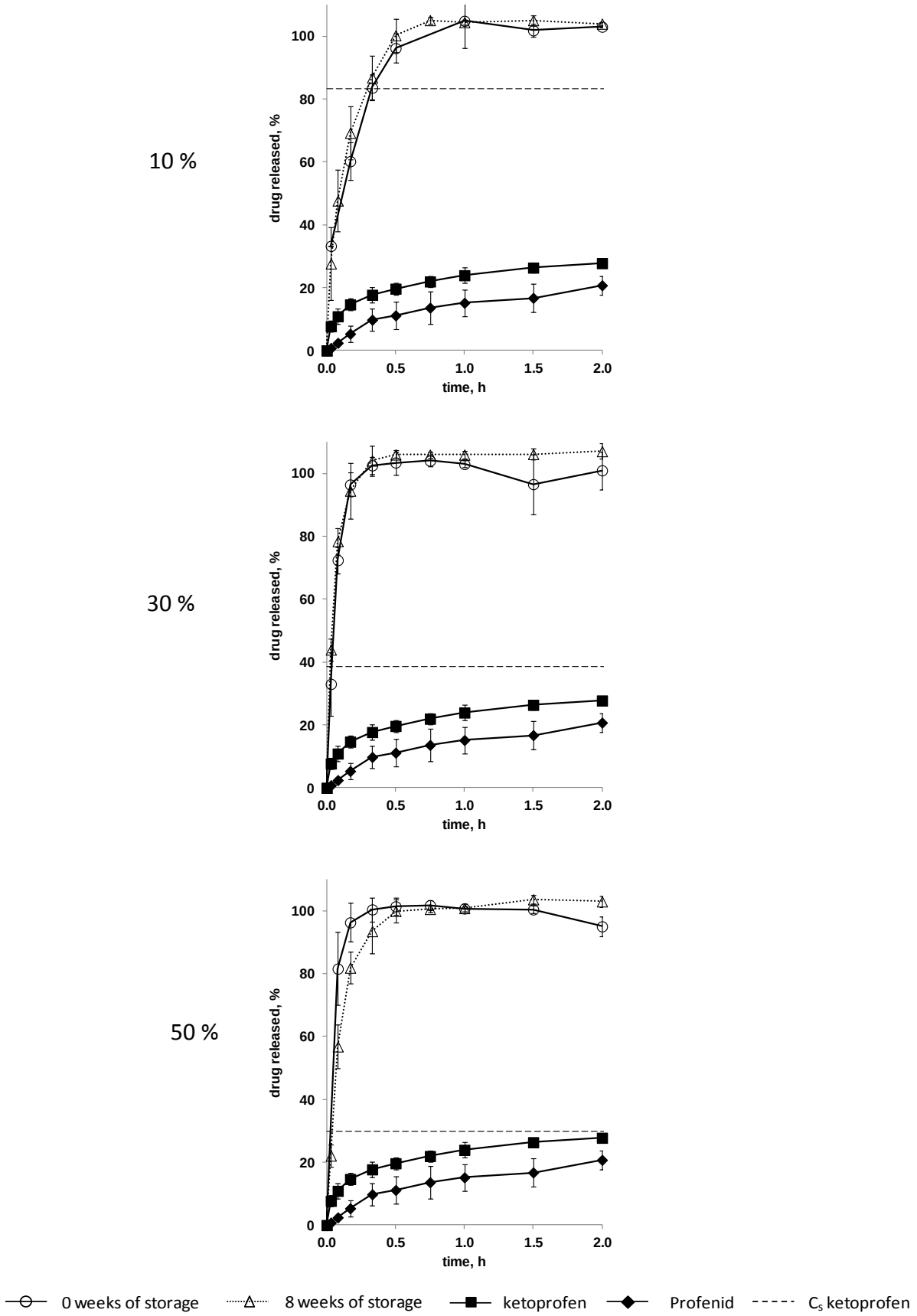

Figure II.1 Drug release from Eudragit® E-based hot-melt extrudates, loaded with 10, 30 or 50 % ketoprofen (as indicated) in 0.1 M HCl.

Optical macroscopy pictures showed *transparent* extrudates, irrespective of the investigated drug loading (Figure II.2).

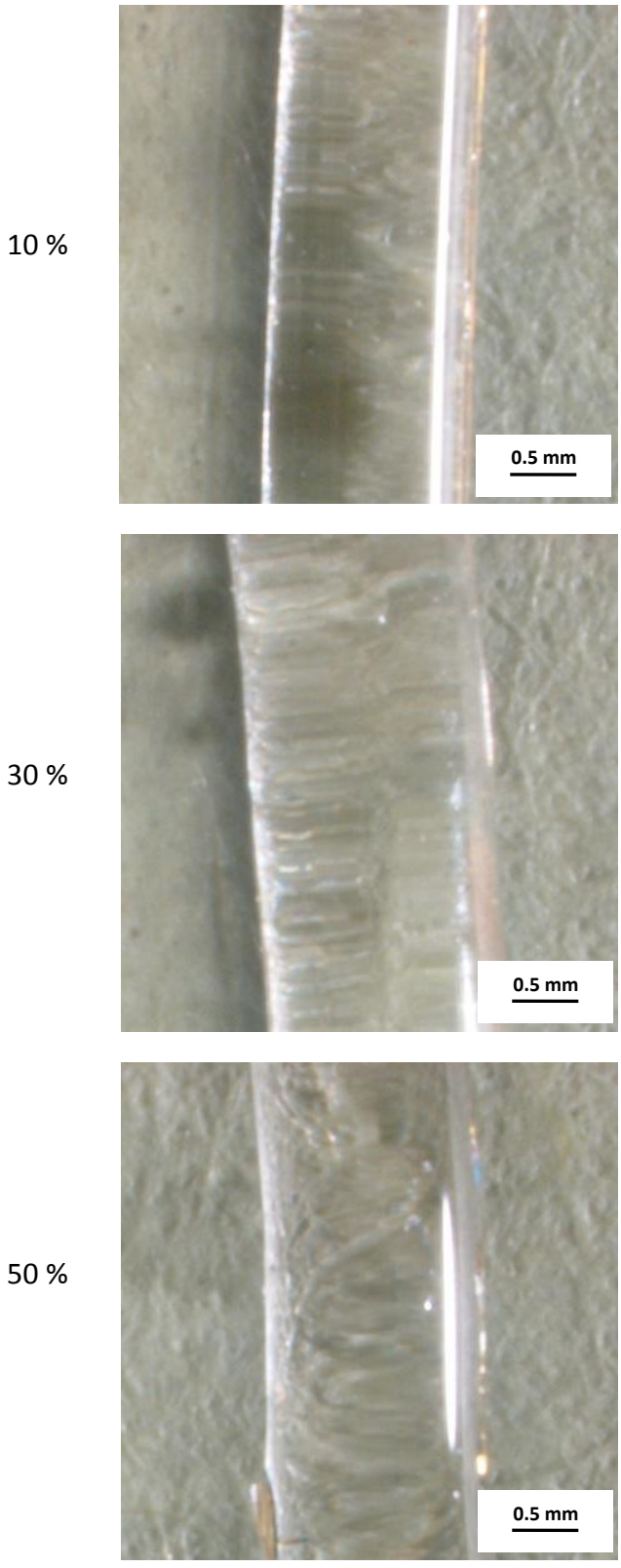

Figure II.2 Optical macroscopy pictures of Eudragit® E-based hot-melt extrudates, loaded with 10, 30 or 50 % ketoprofen (as indicated).

Also, no X-ray diffraction peaks were visible in these formulations, nor in the Eudragit® E raw material powder (Figure II.3). In contrast, the ketoprofen powder (as received) exhibited various sharp diffraction peaks, indicating its crystallinity.

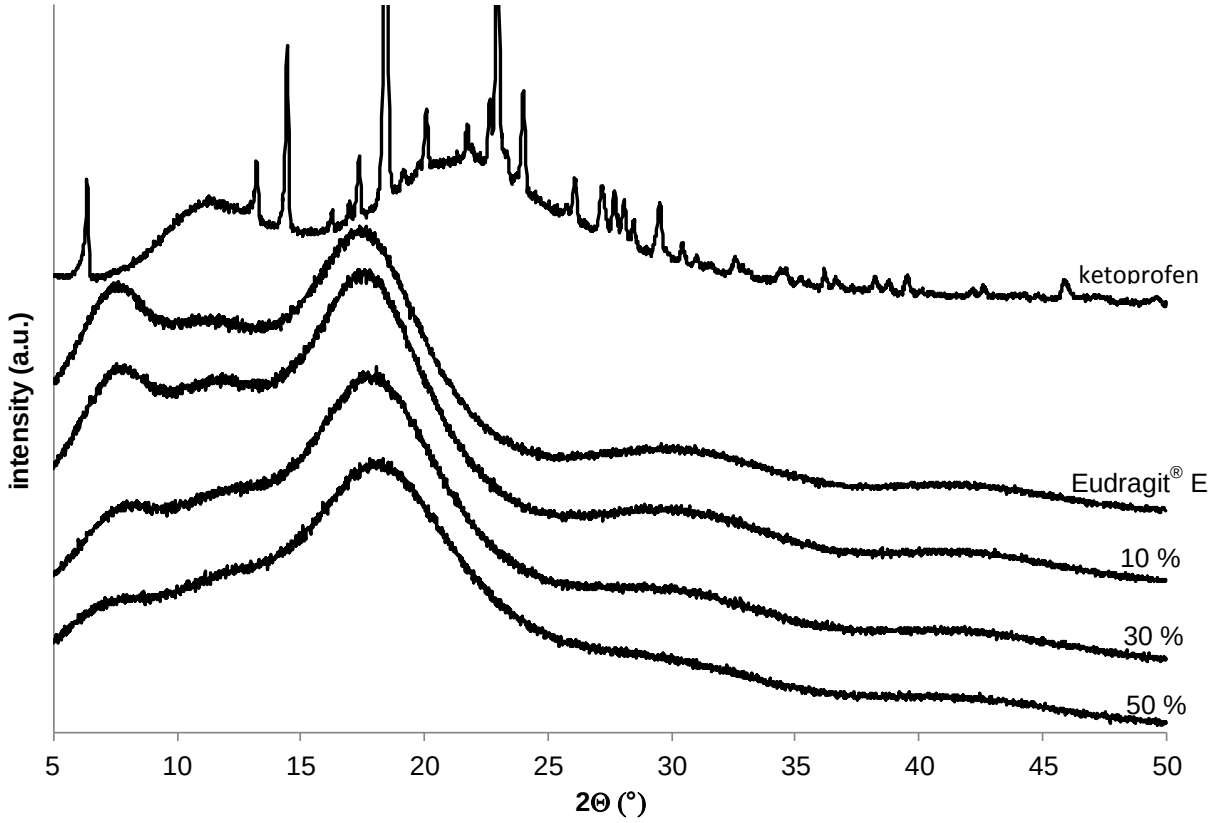

Figure II.3 X-ray diffraction patterns of ketoprofen powder (as received), Eudragit® E powder (as received), and ketoprofen-Eudragit® E hot-melt extrudates (the drug loading is indicated in the diagram).

Figure II.4 shows the mDSC thermograms of the three types of hot-melt extrudates. For reasons of comparison, also the thermograms of Eudragit® E powder and ketoprofen powder are shown. In the latter case, exceptionally two heating cycles were run, in-between which the samples were cooled to transform the ketoprofen from the molten state into an amorphous state. The arrows in Figure 4 indicate the glass transition temperatures (Tgs) of the systems. Importantly, all extrudates exhibited only one single Tg, which was located between the glass transition temperature of the amorphous Eudragit® E and the amorphous

ketoprofen. With increasing drug content, the Tg of the extrudates came closer to the Tg of the amorphous drug. Thus, homogeneous single-phase systems were probably obtained. Since the extrudates were transparent, did not exhibit clear X-ray diffraction peaks and only one single glass transition temperature, it can be hypothesized that the ketoprofen was *molecularly* dispersed within these polymeric systems.

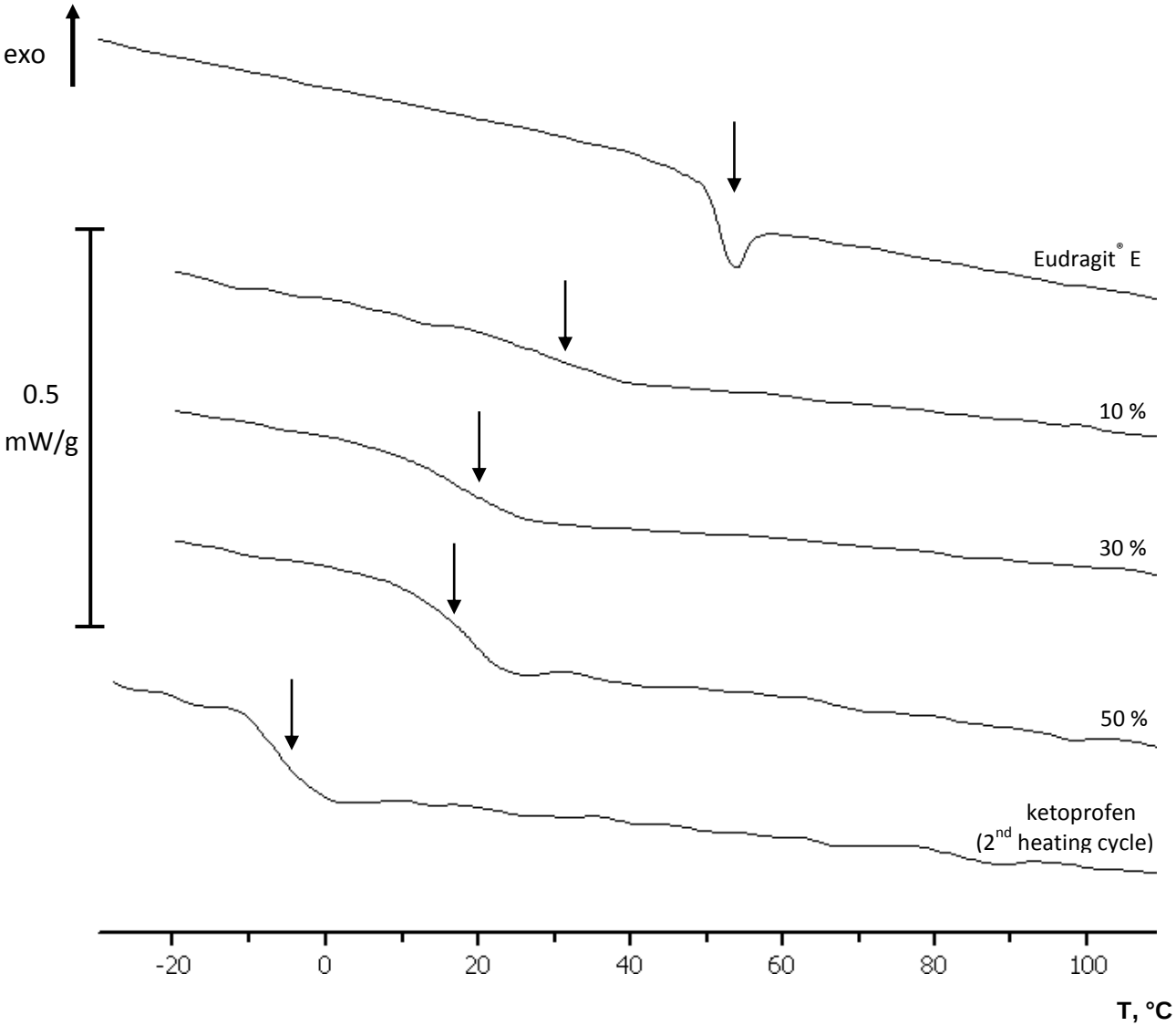

Figure II.4 mDSC thermograms of Eudragit® E powder (as received), ketoprofen-Eudragit® E hot-melt extrudates (the drug loading is indicated in the diagram) and ketoprofen powder (as received, 2nd heating cycle). The arrows mark glass transition temperatures.

Because ketoprofen is an acid (comprising –COOH groups) and Eudragit® E contains multiple basic tertiary ammonium groups, electrostatic interactions and salt formation during preparation and/or drug release might be of importance. Such interactions have been reported in the literature for other systems based on Eudragit® E and acidic drugs (Horisawa et al., 2000; Kindermann et al., 2011; Quinteros et al., 2008). To evaluate the importance of potential salt formation and the role of ion exchange during drug release, the respective extrudates were also released in *demineralized water*. Importantly, drug release was very slow from the extrudates under these conditions, e.g. < 5% release after 2 h exposure in the case of ketoprofen:Eudragit® E 30:70 hot-melt extrudates (data not shown). Thus, the observed significant increase in the drug release rate and formation of super-saturated solutions from the ketoprofen-Eudragit® E extrudates in 0.1 M HCl (Figure II.1) can most likely be attributed to a molecular dispersion of the drug within the polymeric system, forming one single phase, and in which interactions between the –COOH groups of the drug and the tertiary ammonium groups of the polymer are of fundamental importance.

The fact that the release *rate* of the drug (the slope of the curves in Figure II.1) from extrudates containing only 10 % ketoprofen was slightly slower compared to extrudates loaded with 50 % drug, might at least partially be explained by the higher polymer contents (binary systems were studied). With increasing Eudragit® E contents, denser polymer networks are formed, offering more resistance for water and drug diffusion (Siepmann and Siepmann, 2008, 2012). This is consistent with the observed increase in the glass transition temperature with increasing polymer content of the extrudates (Figure II.4). Interestingly, this “increased polymer network density effect” overcompensates the “increased drug solubility effect” with increasing Eudragit® E contents in the release medium (0.18 ± 0.01 versus 0.50 ± 0.01 mg/mL).

The *dotted* curves in Figure II.1 show the respective drug release profiles from the investigated extrudates after 8 weeks storage under ambient conditions (25 °C and 40 % relative humidity) in open vials. As it can be seen, drug release was unaltered. This is of great practical importance and in good agreement with reports in the literature (Kindermann et al., 2011): The good long term stability might at least partially be attributed to the significant electrostatic “drug-polymer” interactions discussed above.

Polymeric drug delivery systems for poorly water-soluble drugs are also frequently prepared by spray-drying. In this case, very small particles can be obtained, exhibiting a considerable surface, and thus, leading to a potential further increase in the drug release rate. However, when spray-drying the investigated ketoprofen-Eudragit® E formulations used for hot-melt extrusion upon dissolution in ethanol, a continuous film formed on the wall of the cyclone of the apparatus. Such film formation is favored by the low glass transition temperatures of these binary ketoprofen-Eudragit® E blends (Figure II.4). To overcome this restriction, a second polymer with a higher Tg was added to the system: PVP, PVPVA, or HPMC. Ternary "drug-polymer 1-polymer 2" systems can indeed offer an interesting potential to accelerate the release of poorly water soluble drugs (Janssens et al., 2008a, 2008b, 2008c, 2008d, 2008e).

III.2. Spray-dried and hot-melt extruded ternary combinations

The dotted curves in Figure II.5 show ketoprofen release from spray-dried ternary combinations consisting of 30 % drug, 50 % Eudragit® E and 20 % PVP, PVPAc, or HPMC (as indicated) in 0.1 M HCl. The left column illustrates drug release before storage, the right column after 8 weeks storage under ambient conditions (25 °C, 40 % relative humidity) in open vials. For reasons of comparison, also drug release from hot-melt extrudates of the same composition is shown (bold curves), as well as from the commercially available product Profenid® (filled diamonds). In addition, the dissolution of ketoprofen powder (as received) is illustrated (filled squares). The dashed lines indicate again the equilibrium solubility of the drug powder (as received) under the given conditions (in particular Eudragit® E concentration). Clearly, in all cases ketoprofen release from the spray-dried powders and hot-melt extrudates was much faster compared to drug release from the commercially available product and the dissolution of the drug powder (as received). Interestingly, ketoprofen release was:

(i) faster from spray-dried powders than from hot-melt extrudates in the case of PVP,

(ii) similar from spray-dried powders and hot-melt extrudates in the case of PVPVA, and

(iii) slower from spray-dried powders than from hot-melt extrudates in the case of HPMC.

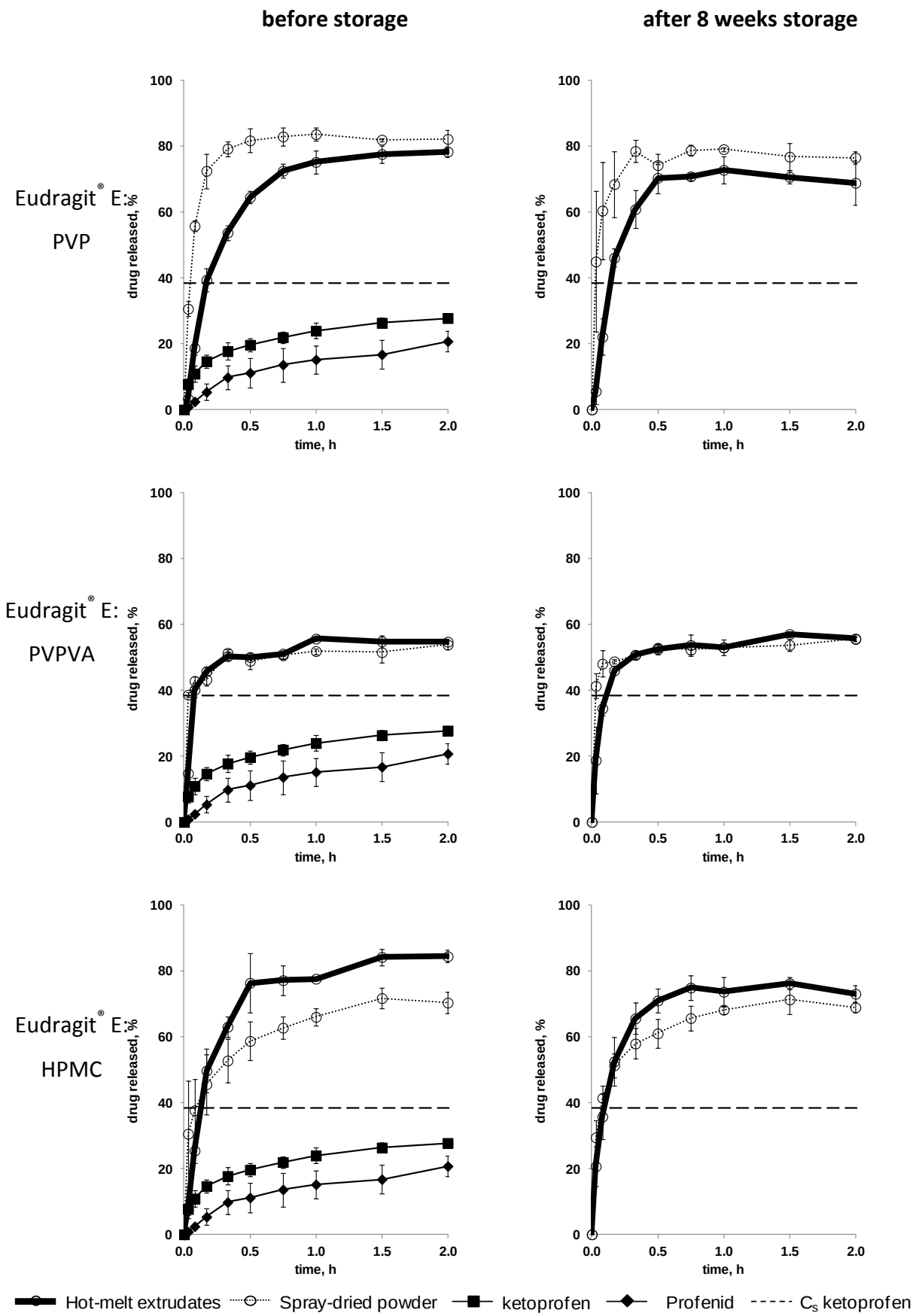

Figure II.5 Drug release in 0.1 M HCl from ternary blends: ketoprofen:Eudragit® E: PVP/PVPVA/HPMC (30:50:20, w:w:w) (as indicated).

To better understand these phenomena, the respective formulations were characterized by optical macro/microscopy, SEM, X-ray diffraction and mDSC. The optical macroscopy pictures in Figure II.6 (left hand side) show that ketoprofen:Eudragit® E:PVP and ketoprofen:Eudragit® E:HPMC hot-melt extrudates were opaque, whereas ketoprofen:Eudragit® E:PVPVA hot-melt extrudates were transparent. The mean particle sizes of the spray-dried formulations of identical composition were as follows: 6.9 ± 2.0, 9.3 ± 2.0 and 6.4 ± 2.7 µm for ketoprofen:Eudragit® E:PVP, ketoprofen:Eudragit® E:PVPVA, and ketoprofen:Eudragit® E: HPMC, respectively. Scanning electron microscopy revealed that aggregates were formed from smaller particles (Figure II.6, right hand side). X-ray diffraction did not indicate clear diffraction peaks in any of the investigated spray-dried powders and hot-melt extrudates, nor in PVP and PVPVA (Figure II.7). Only two smaller peaks were visible in HPMC powder (as received). The mDSC thermograms of all formulations and of the raw materials are shown in Figure II.8. The arrows indicate again glass transition temperatures (Tgs). Interestingly, two Tgs were observed in ketoprofen:Eudragit® E:PVP and ketoprofen:Eudragit® E:HPMC blends, irrespective of the type of preparation technique. In contrast, only one Tg was visible in the case of ketoprofen:Eudragit® E:PVPVA spray-dried powder and hot-melt extrudates.

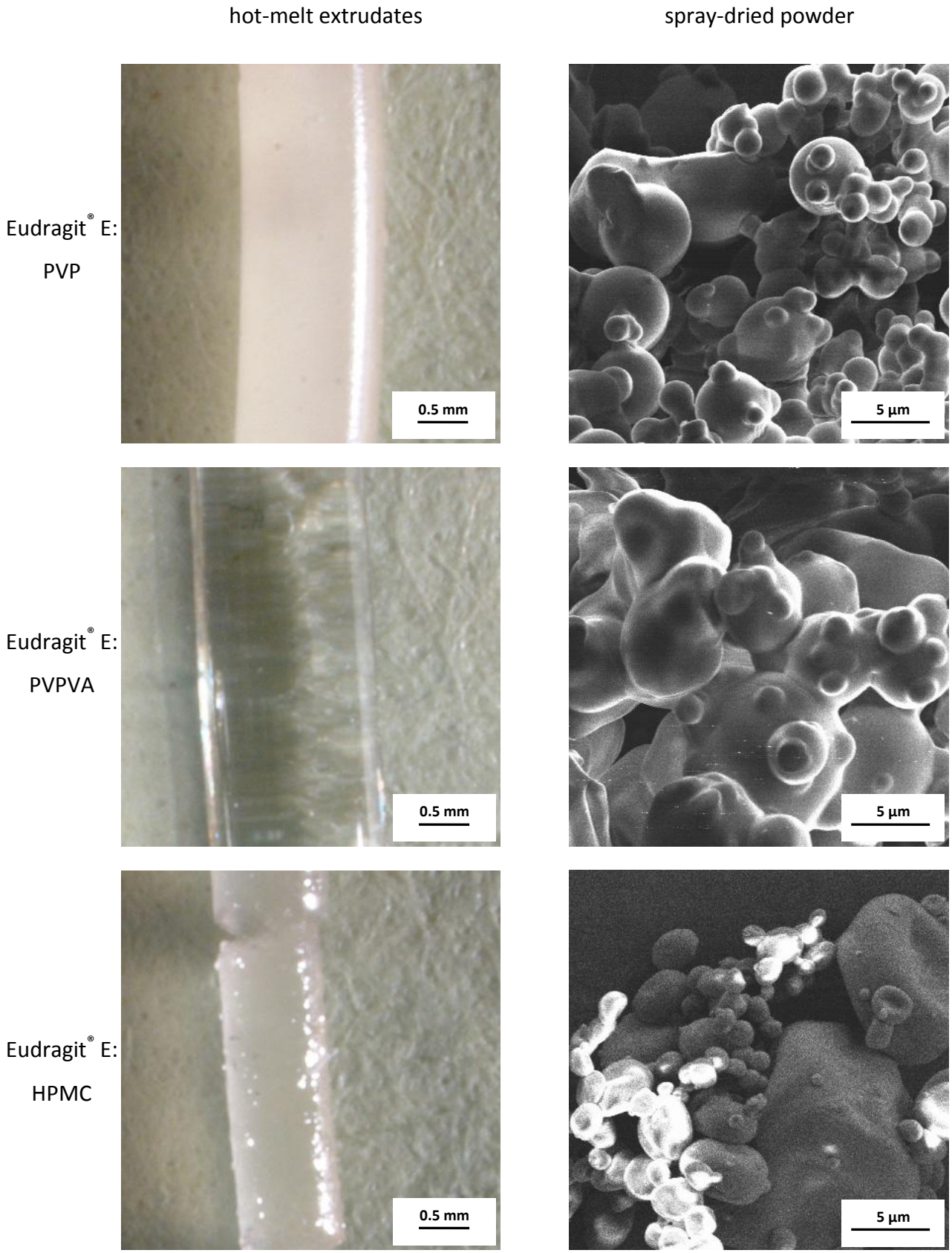

Figure II.6 Optical macroscopy pictures of hot-melt extrudates (left hand side) and SEM images of spray-dried powders (right hand side) of ternary (30:50:20, w:w:w) ketoprofen:Eudragit® E:PVP/PVPVA/HPMC blends (as indicated).

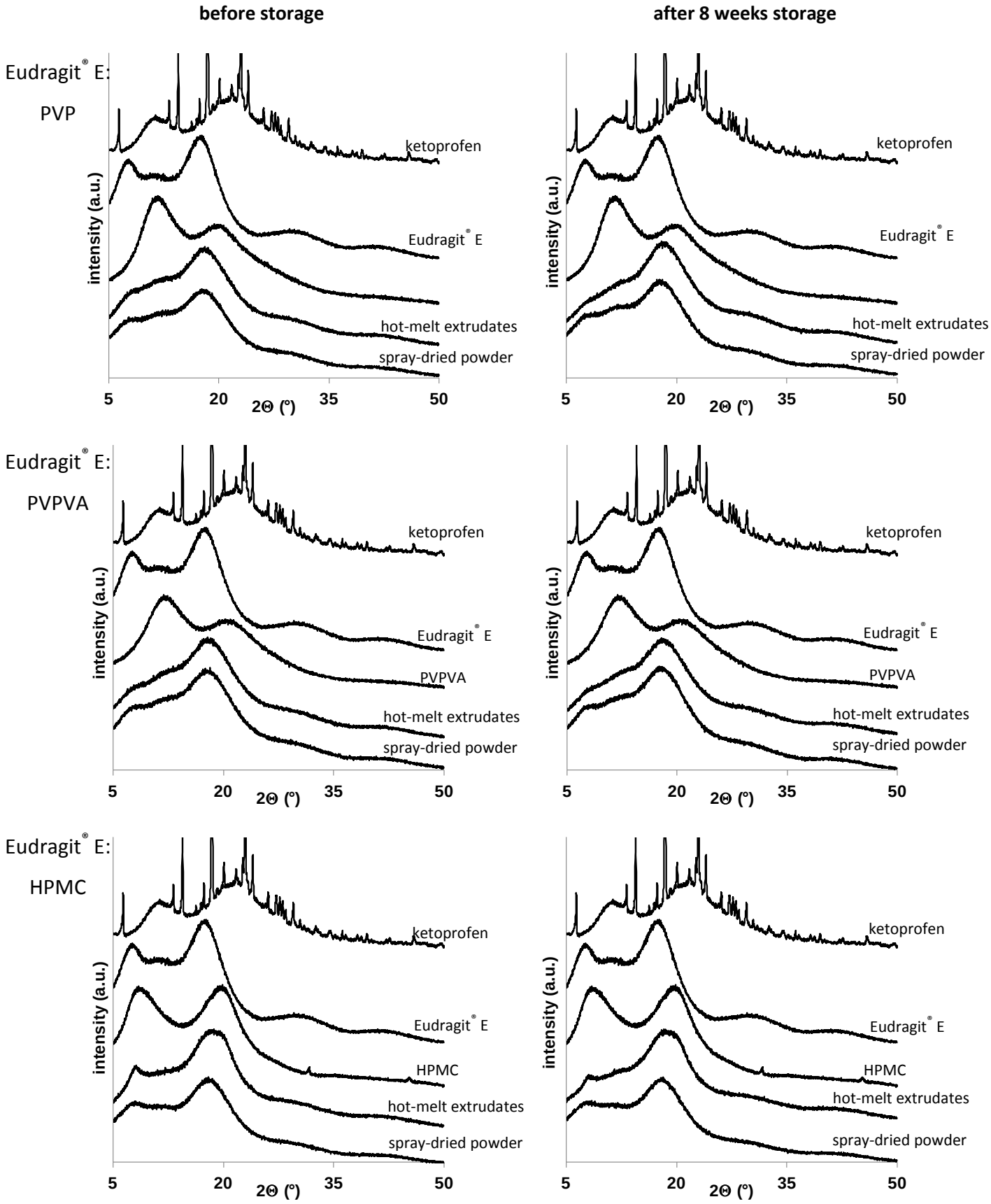

Figure II.7 X-ray diffraction patterns of hot-melt extrudates and spray-dried powders consisting of ternary ketoprofen:Eudragit® E: PVP/PVPVA/HPMC (30:50:20, w:w:w) blends (as indicated).

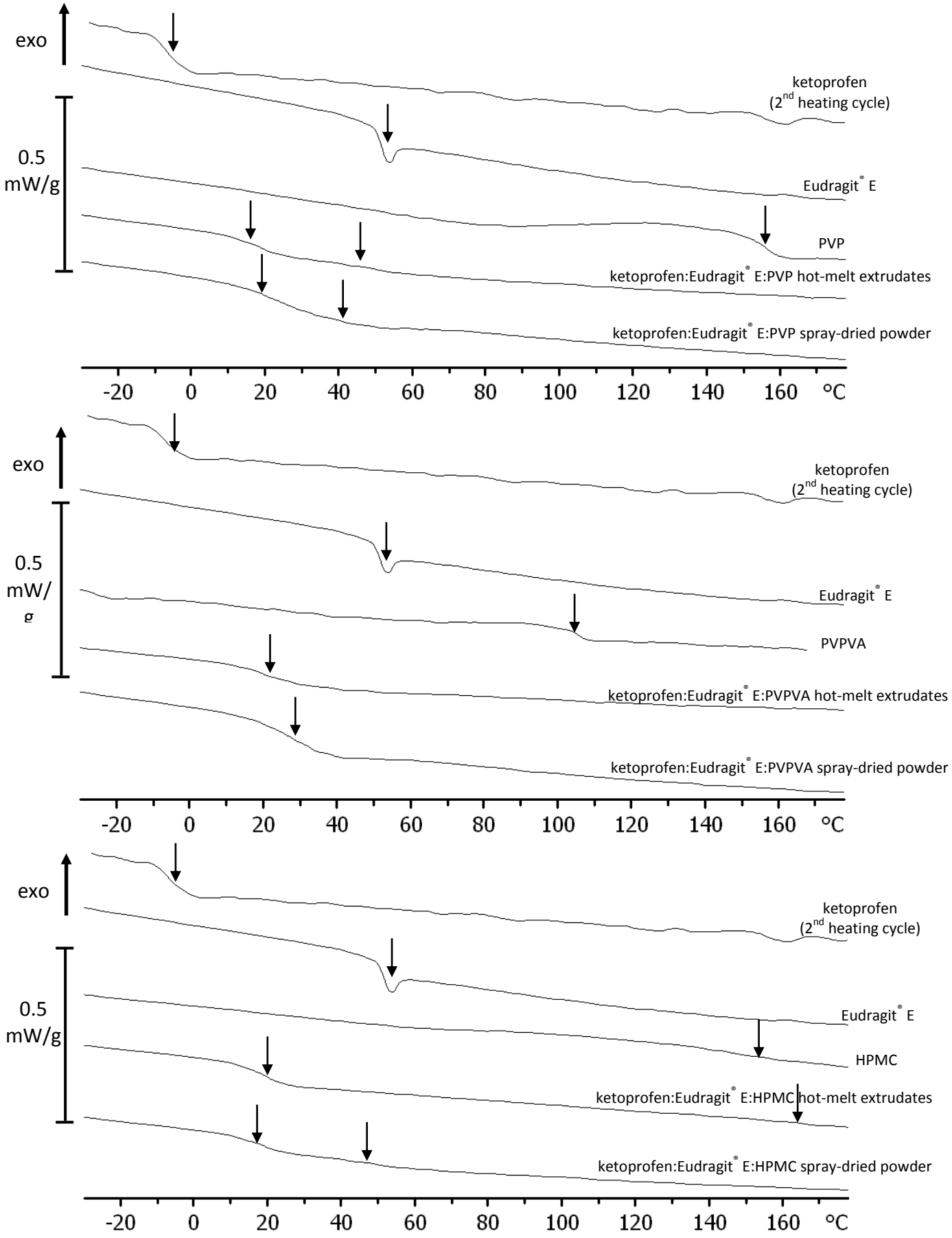

Figure II.8 mDSC thermograms of the ketoprofen powder (as received, 2nd heating cycle), polymer powders (as received), hot-melt extrudates and spray-dried powders consisting of ternary ketoprofen:Eudragit® E: PVP/PVPVA/HPMC (30:50:20, w:w:w) blends (as indicated).

III.3. Ketoprofen:Eudragit® E:PVP combinations

The fact that:

(i) *opaque* ketoprofen:Eudragit® E:PVP hot-melt extrudates were obtained (Figure II.6), and

(ii) two glass transition temperatures (located between the Tgs of amorphous drug and of PVP) were determined by mDSC in hot-melt extrudates and spray-dried powder (Figure II.8), can serve as indications for the existence of two separate amorphous phases. One phase can be expected to be rich in Eudragit® E and ketoprofen, because the lower Tgs of these ternary systems are in the range of the Tgs observed with binary ketoprofen-Eudragit® E hot-melt extrudates loaded with significant amounts of drug (Figure II.4). The other phase is likely to be rich in PVP and ketoprofen, since important interactions have also been reported in the literature for these two compounds: For instance, Di Martino et al. showed that ketoprofen dissolves easily in PVP upon heating and that its -COOH groups can interact with the ketonic parts of PVP via hydrogen bonding (as evidenced by NMR studies) (Di Martino et al., 2004). Furthermore, *binary* ketoprofen-Eudragit® E (Figure II.2) and *binary* ketoprofen-PVP (70:30) (data not shown) hot-melt extrudates were transparent, indicating an affinity of this drug to both types of polymers.

Importantly, ketoprofen release from these dispersions of the type “amorphous in amorphous” was rapid and super-saturated solutions were obtained, which remained stable during the observation period (Figure II.5), irrespective of the type of preparation method (spray-drying or hot-melt extrusion). The drug was dissolved in the two polymers, electrostatically bound to the tertiary ammonium groups of the Eudragit® E, and/or dispersed in an amorphous state within the non-homogeneous polymeric matrix, since no crystalline ketoprofen was observed by X-ray diffraction (Figure II.7), nor by mDSC (Figure II.8). Note that the leveling off of drug release below 100 % can be attributed to saturation effects: The dashed line indicates drug solubility under the given conditions. Increasing the volume of the release medium while keeping the amount of formulation constant led to more complete drug release in the observation period (data not shown).

The more rapid ketoprofen release from spray-dried powders compared to hot-melt extrudates of identical composition can at least partially be attributed to the smaller system size: the particles had a mean diameter of 6.9 ± 2.0 µm, while the cylinders were 2 mm in length and 1.4 mm in diameter. This results in a higher surface area exposed to the release medium and should, thus, lead to more rapid drug release (Siepmann and Siepmann, 2013). Importantly, ketoprofen release remained unaltered from the hot-melt extrudates and spray-dried powders upon storage at ambient conditions in open vials (Figure II.5, left versus right hand side). Also when comparing the X-ray diffraction patterns of the formulations before and after 8 weeks storage (Figure II.7 left versus right hand side), no significant changes can be seen. The slight decrease in the diffuse scattering bump of Eudragit® E at low angles during storage of hot-melt extrudates is consistent with the slightly lower first Tg of these systems compared to the respective spray-dried formulations of identical composition (Figure II.8): The lower the Tg of a polymeric system, the higher is the macromolecular mobility and the faster the system can homogenize. However, these only minor changes did not affect drug release (Figure II.5) and in no case evidence for drug re-crystallization was observed (Figures II.5, II.7 and II.8).

III.4. Ketoprofen:Eudragit® E:PVPVA combinations

Interestingly, ternary ketoprofen:Eudragit® E:PVPVA (30:50:20 w:w:w) combinations resulted in *transparent* hot-melt extrudates (Figure II.6), which showed only one single glass transition temperature (Figure II.8). The latter was also true for spray-dried powders of this composition. X-ray diffraction did not indicate any crystallinity (Figure II.7). Thus, one single homogeneous phase is likely to be formed, the drug being dissolved and/or electrostatically bound (to the ammonium groups of the Eudragit® E) in an intimate blend of the two amorphous polymers. This is consistent with the very fast drug release observed from ketoprofen:Eudragit® E:PVPVA (30:50:20 w:w:w) spray-dried powders and hot-melt extrudates (Figure II.5) (note that the *slope* of the curves is decisive for the release *rate*). The fact that no significant differences were observed between the release kinetics for the two types of preparation techniques can at least partially be explained by the fact that in both cases:

(i) “Chewing gum” like residues were rapidly formed upon exposure to the release medium. This is consistent with the relatively low Tgs of these formulations (around 20 to 25 °C, Figure 8). Thus, differences in the initial system size (as discussed above for ketoprofen:Eudragit® E:PVP combinations) are not of importance.

(ii) Highly homogenous one phase systems were obtained (Figures II.6, II.7 and II.8).

Interestingly, the degree of super-saturation is somewhat lower in the case of ketoprofen:Eudragit® E:PVPVA combinations than in the case of ketoprofen:Eudragit® E:PVP and ketoprofen:Eudragit® E:HPMC blends (Figure II.5). Eventually, the affinity of the ketoprofen to PVPVA is so high that the driving force for drug release is decreased. Importantly, no major changes were observed during 8 weeks storage in open vials with respect to the X-ray diffraction patterns (Figure II.7, left versus right hand side), and drug release remained unaltered (Figure II.5, left versus right hand side).

III.5. Ketoprofen:Eudragit® E:HPMC combinations

Surprisingly, ketoprofen release was faster from ketoprofen:Eudragit® E:HPMC (30:50:20 w:w:w) combinations prepared by *hot-melt extrusion* than from *spray-dried powders* of identical composition (bold versus dotted curves in Figure II.5). This was despite the much smaller system size, resulting in a much larger surface area: the spray-dried particle had a mean diameter of 6.4 ± 2.7 µm, while the extruded cylinders were 2 mm in length and 1.1 mm in diameter. The reason for this phenomenon is likely to be the different *internal structure* of the drug-polymer matrices, as revealed by X-ray diffraction and mDSC analysis: Two glass transition temperatures were observed in both cases (Figure II.8): The lower Tgs were relatively similar and close to 20 °C, whereas the higher Tgs were very different: about 160 °C in the case of hot-melt extrudates compared to about 50 °C in the case of spray-dried powders. Also, the X-ray diffraction patterns exhibited distinct differences: In hot-melt extrudates a diffuse scattering bump of HPMC was clearly visible, whereas in spray-dried powder of the same composition this was not the case (Figure II.7). Furthermore, the diffuse scattering bump of Eudragit® E was much more visible in hot-melt

extrudates than in spray-dried powders. Optical macroscopy pictures showed *opaque* hot-melt extrudates (Figure II.6).

Thus, two phases seem to co-exist in these systems, the degree of heterogeneity being dependent on the preparation technique. When prepared by hot-melt extrusion, pure HPMC domains (or domains being very rich in HPMC) seem to exist, as indicated by the high second Tg of the systems (Figure II.8). In contrast, this does not seem to be the case in spray-dried powders of the same composition: In this case, the second Tg is about 110 °C lower compared to the hot-melt extrudates. Thus, the HPMC seems to be more homogeneously dispersed in the spray-dried formulations. This can probably be attributed to the manufacturing procedure: in the case of spray-drying, the two polymers were dissolved in a common solvent. In the dissolved state, the macromolecules are highly mobile and can intensively mix. In contrast, during hot-melt extrusion (at least under the given conditions), pure HPMC domains (or domains very rich in HPMC) seem to remain "intact" during processing. The fact that binary Eudragit® E-HPMC and binary ketoprofen-HPMC hot-melt extrudates were *opaque* (data not shown) further confirmed the limited mutual miscibility of these compounds.

It can be expected that the more *homogeneous* distribution of the HPMC in the spray-dried ternary powders leads to more hindrance in water and drug diffusion within the formulation. In contrast, the more *heterogeneous* distribution of the HPMC in the hot-melt extrudates of identical composition is likely to limit water and drug transport mainly in the HPMC-rich domains. The Eudragit® E-rich and HPMC-poor domains can be expected to release the drug more rapidly, as indicated by the rapid release of ketoprofen from binary drug-Eudragit® E extrudates (Figure II.1). Thus, the degree of homogeneity of the distribution of the polymers can significantly affect the resulting drug release kinetics. It can even overcompensate particle size effects. Importantly, also in these cases drug release from the formulations did not change during 8 weeks open storage at ambient conditions (Figure II.5, left versus right hand side).

IV. Conclusion

Polymeric matrices aiming at accelerated release of poorly water-soluble drugs can be highly complex, since not only the composition of the systems, but also their inner structure can be of utmost importance.

Acknowledgements

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Chapter III. ACCELERATED KETOPROFEN RELEASE FROM SPRAY-DRIED POLYMERIC PARTICLES: IMPORTANCE OF PHASE TRANSITIONS AND EXCIPIENT DISTRIBUTION

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Abstract

HPMC-, PVPVA- and PVP-based microparticles loaded with 30 % ketoprofen were prepared by spray drying suspensions or solutions in various water:ethanol blends. The inlet temperature, drying gas and feed flow rates were varied. The resulting differences in the ketoprofen release rates in 0.1 M HCl could be explained based on X-ray diffraction, mDSC, SEM and particle size analysis. Importantly, some of the systems provided long term stable drug release, which was much faster than drug release from a commercially available product, the respective physical drug:polymer mixtures, as well as the dissolution of ketoprofen powder as received. Highly supersaturated release media were obtained, which did not show any sign for re-crystallization during the observation period. Interestingly, the processing conditions could fundamentally impact the physical state of the drug and the spatial distribution of the polymer, which are two of the key parameters determining the resulting drug release rate. Thus, even “relatively straightforward” formulations based on binary drug:polymer combinations can be highly complex.

Keywords: poorly soluble drugs; spray-drying; ketoprofen; HPMC; dissolution

I. Introduction

The poor aqueous solubility of many drugs and drug candidates has become a serious concern for the discovery of innovative therapeutic strategies. Even if a novel compound provides an ideal chemical structure to interact with its target (e.g., an enzyme or a receptor) and if it shows highly promising in vitro activity (e.g., in cell cultures), it fails in vivo, if it does not dissolve in aqueous body fluids to a sufficient extent. If the compound is not dissolved (molecularly dispersed) in water, it cannot be effectively be transported in the human body and reach its target site.

To overcome this fundamental hurdle, various interesting approaches have been described, including the use of cyclodextrins (Kurkov and Loftsson, 2013; Pathak et al., 2010; Yang et al., 2010), polymeric micelles (Dahmani et al., 2012; Lu and Park, 2013), nanocrystals (Sinha et al., 2013), formulations, in which the drug is in an amorphous state (Brough and Williams III, 2013; Laitinen et al., 2013; Van den Mooter, 2012), precipitation inhibitors (Bevernage et al., 2013; Xu and Dai, 2013), co-crystals (Elder et al., 2013), mesoporous systems (Van Speybroeck et al., 2009; Vialpando et al., 2011; Xu et al., 2013), microemulsions (Li et al., 2009), liposomes (Ali et al., 2013) and lipids (Lee et al., 2013; Mu et al., 2013; Qi et al., 2010). Various manufacturing procedures can be used to prepare these systems. Spray-drying and hot-melt extrusion have been shown to be particularly useful (Paudel et al., 2013; Shah et al., 2013). Spray-drying offers the advantage of obtaining small particles with a high total surface area, promoting drug release (Siepmann and Siepmann, 2013). Furthermore, since the drying times are short, drugs might be transformed into an amorphous state with increased apparent solubility. Often, polymers are added to provide long term stability, hindering the drug to re-crystallize. The presence of hydrophilic polymers can also facilitate particle wetting, which is a pre-requisite for drug dissolution. But also sugars, such as mannitol, can be used: An interesting study on solid dispersions based on itraconazole and mannitol was recently reported by Duret et al (Duret et al., 2012). Spray-drying hydro-alcoholic solutions of these compounds led to particles containing the drug in an amorphous state, while the sugar recrystallized.

The impact of formulation and processing parameters on the key properties of spray-dried microparticles containing poorly water-soluble drugs has been extensively

reported in the literature, as recently reviewed by Paudel et al. 2013 (Paudel et al., 2013). However, yet relatively little is known on the impact on the inner particles' structures (e.g., homogeneity of the polymer distribution) (Gué et al., 2013; Paudel et al., 2013). This is surprising, because the location of the drug and the polymer can be expected to be decisive for the resulting drug release kinetics (Siepmann and Siepmann, 2008).

The aim of this study was to better understand how formulation and processing parameters affect the release of ketoprofen in 0.1 M HCl from spray-dried microparticles based on HPMC (hydroxypropyl methylcellulose), PVPVA [poly(vinylpyrrolidone-co-vinyl acetate)], or PVP (polyvinylpyrrolidone). In particular, the impact on the resulting microstructure and conditions for drug dissolution and subsequent release were to be elucidated.

II. Materials and Methods

II.1. Materials

Ketoprofen (Sigma-Aldrich, Steinheim, Germany); hydroxypropyl methylcellulose (HPMC, Methocel® E5; Colorcon, Dartford, UK); polyvinylpyrrolidone (PVP, Kollidon® K30) and poly(vinylpyrrolidone-co-vinyl acetate) (6:4 mass:mass, PVPVA, Kollidon® VA 64) (BASF, Ludwigshafen, Germany); Profenid® 100 mg (Profenid®; Sanofi, Paris, France); acetonitrile and sodium dihydrogen orthophosphate dihydrate (Fisher Scientific, Loughborough, UK); phosphoric acid 85 % (Sigma-Aldrich); ethanol 95 % (Brabant, Tressant, France).

II.2. Preparation of physical mixtures

Ketoprofen and HPMC, PVPVA or PVP were blended manually using a pestle and mortar for 10 min (100 g batch size). These blends were used for the preparation of spray-dried microparticles and for in vitro drug release studies (for reasons of comparison).

II.3. Preparation of spray-dried powders

Appropriate amounts of PVPVA, PVP, or HPMC were dissolved in water in a beaker. Ketoprofen was dissolved in ethanol. Appropriate amounts of this ethanolic drug solution were added to the aqueous polymer solutions under magnetic stirring at 800 rpm. The drug content was 1 % (w:v) in all cases, the water:ethanol ratio was varied as indicated in Table III 1. Stirring was continued for 30 min. In the case of 90:10 and 80:20 water:ethanol mixtures, the ketoprofen re-precipitated, whereas it remained in solution in the case of 70:30 and 50:50 water:ethanol mixtures. The suspensions/solutions were spray-dried using a Buechi B-290 apparatus (Buechi, Basel, Switzerland), equipped with a 0.7 mm nozzle. The inlet temperature, drying gas flow and feed flow rates were varied as indicated in Table 1 and described in the text.

Table III.1: Formulation and processing parameters used for the preparation of the investigated spray-dried, ketoprofen-loaded microparticles. The aspirator flow rate was kept constant at 35 m^3/h, the nozzle diameter was 0.7 mm.

Polymer	Water:ethanol (% v:v)	Inlet temperature (°C)	Drying gas flow rate (L/h)	Feed flow rate (mL/min)
HPMC PVPVA PVP	90:10	110	414	7.5
HPMC	90:10	110	414	7.5
			414	10
			600	7.5
		90	414	7.5
			414	10
			600	7.5
	90:10 80:20 70:30 50:50	110	414	7.5

II.4. In vitro drug release measurements

Appropriate amounts of formulations containing 60 mg ketoprofen were placed in 125 mL plastic flasks, filled with 100 mL 0.1 M HCl. The flasks were horizontally shaken (80 rpm) at 37 °C (GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). At predetermined time points, 3 mL samples were withdrawn, replaced with fresh medium, filtered through a 0.45 µm GF/PVDF filter (Whatman, GE Healthcare, Kent, UK) and subsequently diluted (1:30, v:v) with 0.1 M HCl. The drug content of the samples was determined by HPLC analysis (ProStar 230 pump, 410 autosampler, 325 UV–vis detector, Galaxie software; Varian Les Ulis, France). A reversed phase column C18 (Luna 5 µm; 110 Å; 150 mm × 4.6 mm; Phenomenex, Le Pecq, France) was used. The mobile phase was acetonitrile:phosphate buffer pH 3 (20 mM NaH_2PO_4) (45:55, v:v). The detection wavelength was 259 nm and the flow rate 1 mL/min. One hundred µL samples were injected. The elution time was about 9 min. Drug release was measured before storage or after 8 weeks storage in open vials at ambient conditions (25 °C and 40 % relative humidity). Each experiment (drug release and drug detection) was conducted in triplicate.

II.5. Equilibrium solubility measurements

The equilibrium solubility of ketoprofen powder (as received) was determined in agitated flasks in 0.1 M HCl, optionally containing 0.14 % (w/v) HPMC, PVPVA or PVP. An excess amount of ketoprofen was exposed to 20 mL medium at 37°C under horizontal shaking (80 rpm; GFL 3033). Every 24 h, samples were withdrawn, filtered and analyzed by HPLC for their drug content (as described above) until equilibrium was reached. Each experiment was conducted in triplicate.

II.6. mDSC analysis

Modulated Differential Scanning Calorimetry (mDSC) thermograms of ketoprofen, HPMC, PVPVA, PVP, and spray-dried powders were recorded with a DSC1 Star System (Mettler Toledo, Greifensee, Switzerland). Approximately 5 mg samples were heated in perforated aluminum pans from -30 to 170°C at 2°C/min with a modulation amplitude of

± 0.5 K and a modulation period of 15 to 30 s. Only in the case of ketoprofen powder, two heating cycles were run (the aim was to transform the drug into an amorphous state during the cooling phase), under the following conditions: 1st heating: from 25 to 120°C at 2 °C/min, holding for 2 min; cooling: from 120 to -30 °C at 2 °C/min, holding for 2 min; 2nd heating: from -30 to 180 °C at 2 °C/min. The modulation amplitude was ± 0.5 K and the modulation period 15 to 30 s.

II.7. Particle size measurements

The sizes and size distributions of the spray-dried microparticles were determined with a Mastersizer S (Malvern, Orsay, France) (300 mm lens, dry powder modus). Each experiment was conducted in triplicate.

II.8. X-ray diffraction studies

X-ray powder diffraction patterns were recorded using a PANalytical X'Pert pro MPD powder diffractometer equipped with a Cu X-ray tube ($\lambda_{CuK\alpha}$ = 1,540Å) and the X'celerator detector. Powder samples were placed in a spinning flat sample holder, the measurements were performed in Bragg-Brentano θ-θ geometry.

II.9. Scanning electron microscopy

The morphology of the spray-dried particles was studied using a Hitachi S4700 apparatus (Hitachi, Tokyo, Japan), operating at an accelerating voltage of 3 kV. The powder surfaces were coated with carbon.

III. Results and Discussion

III.1. Impact of the type of polymer

The open circles in Figure III.1 illustrate ketoprofen release in 0.1 M HCl from microparticles obtained by spray-drying dispersions of 30:70 (w:w) drug:HPMC, drug:PVPVA or drug:PVP blends (as indicated) in 90:10 water:ethanol. The polymers were dissolved, whereas the drug was suspended (and dissolved) in the liquids, which were fed into the spray-dryer. The processing conditions are given in Table III 1. The solid curves indicate drug release before storage, the dotted curves after 8 weeks open storage at ambient conditions. The dashed straight lines illustrate the equilibrium solubility of ketoprofen powder (as received) under the given conditions. Importantly, the presence of the different types of polymers did not significantly affect the equilibrium solubility of ketoprofen, which was determined to be equal to 0.16 ± 0.00 mg/mL 0.1 M HCl at 37 °C (in the absence of polymer), and equal to 0.17 ± 0.01, 0.17 ± 0.01 and 0.16 ± 0.01 mg/mL upon addition of 0.14 % (w:v) HPMC, PVPVA or PVP, respectively. For reasons of comparison, also drug release from the respective physical mixtures (open squares) and from the commercially available product Profenid® (filled squares) is illustrated. In addition, the dissolution kinetics of ketoprofen powder (as received) under the given conditions is shown (filled diamonds). In all cases, the amount of formulation exposed to the release medium contained 60 mg drug.

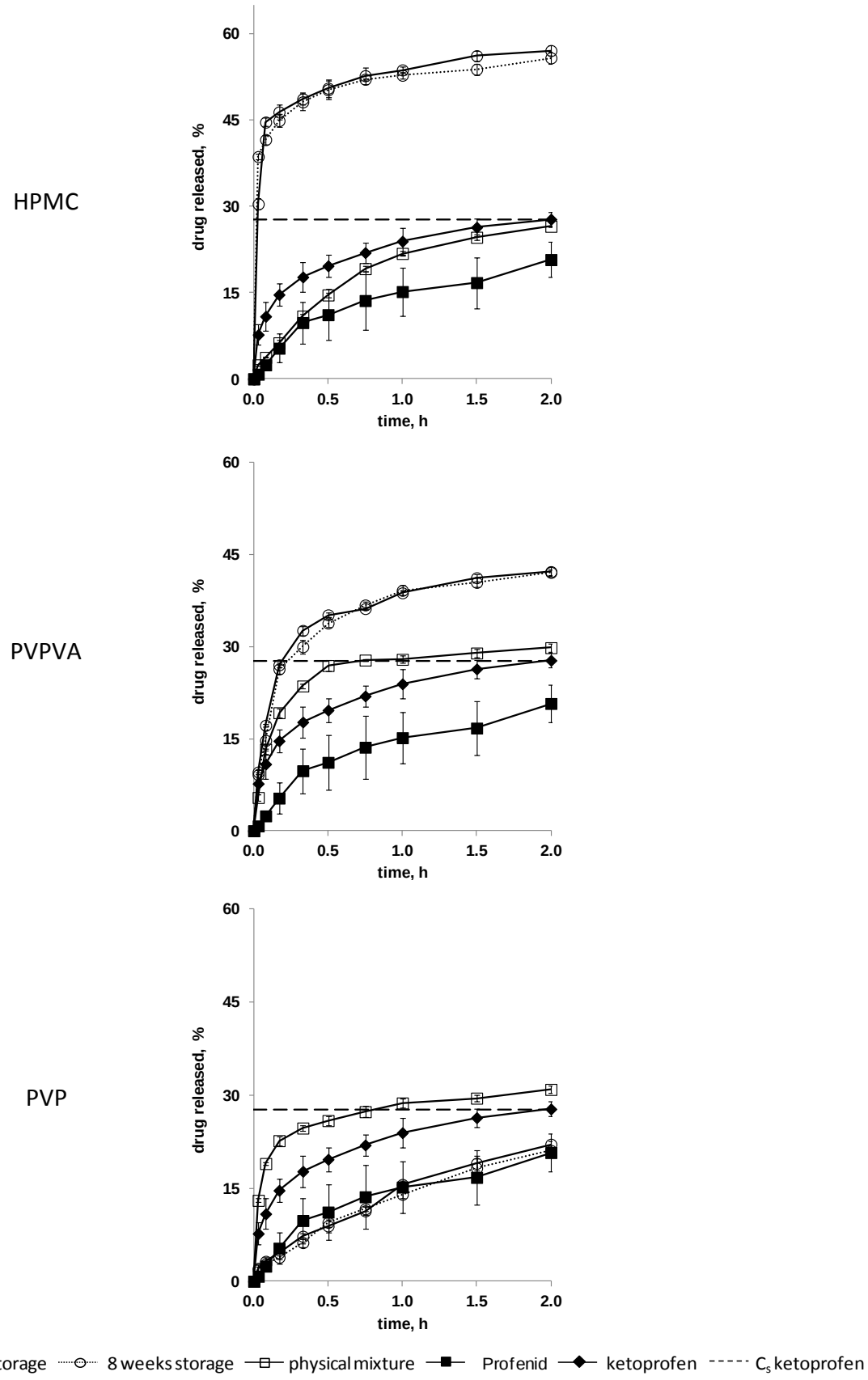

Figure III.1 Ketoprofen release from spray-dried microparticles based on drug:HPMC, drug:PVPVA or drug:PVP (30:70 w:w) in 0.1 M HCl (as indicated). The processing conditions are given in Table III 1.

Clearly, the type of polymer used for microparticle preparation strongly affected the resulting ketoprofen release kinetics: In the case of HPMC and PVPVA, much faster release was observed from the microparticles compared to the drug powder (as received), the respective physical mixtures and the commercial product. In contrast, ketoprofen release from drug:PVP-based microparticles was slower than from the corresponding physical mixture and the drug powder (as received). This is rather surprising, since the ketoprofen:PVP-based microparticles were much smaller than the ketoprofen:PVPVA- and ketoprofen:HPMC-based microparticles (Figure III 2).

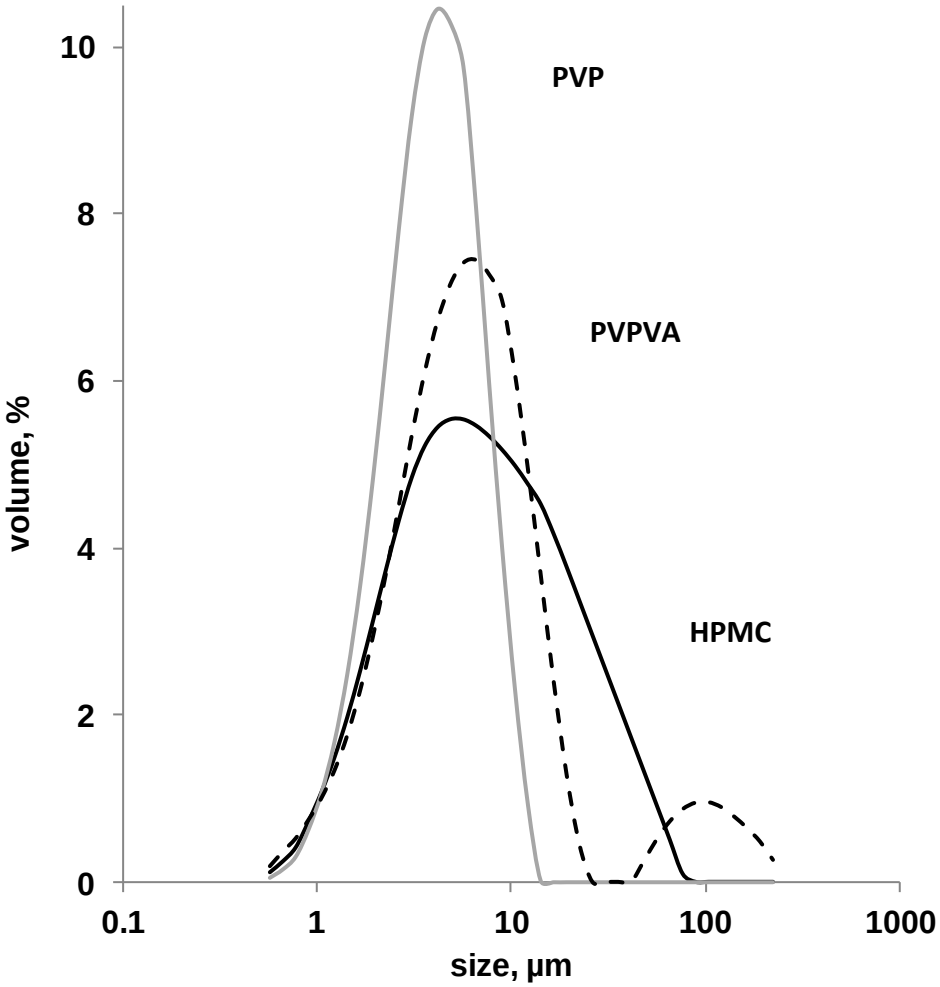

Figure III.2 Particle size distributions of spray-dried microparticles obtained with ketoprofen:HPMC, ketoprofen:PVPVA and ketoprofen:PVP (30:70 w:w) blends. The processing conditions are indicated in Table III. 1.

Smaller particles offer higher surface areas available for drug release and the lengths of the pathways to be overcome is shorter. Thus, higher (and not lower) drug

release rates could have been expected, if diffusional mass transport plays a major role (Siepmann and Siepmann, 2008, 2012). Importantly, the release medium became supersaturated in the case of ketoprofen:HPMC- and ketoprofen:PVPVA-based microparticles, and no sign for drug re-precipitation in the surrounding bulk fluid was visible during the observation period. In vivo, such supersaturated systems can be expected to allow for increased drug absorption (due to higher drug concentration gradients) and, hence, improved drug availability. Drug release was fastest and the degree of supersaturation was highest in the case of HPMC-based microparticles. In contrast to the *microparticles*, ketoprofen release from *physical mixtures* was much slower in the case of HPMC compared to PVPVA and PVP. Furthermore, in the case of physical mixtures, none of the systems led to significant supersaturation. To better understand these phenomena, the respective formulations were characterized by X-ray diffraction (Figure III.3) and mDSC analysis (Figure III.4).

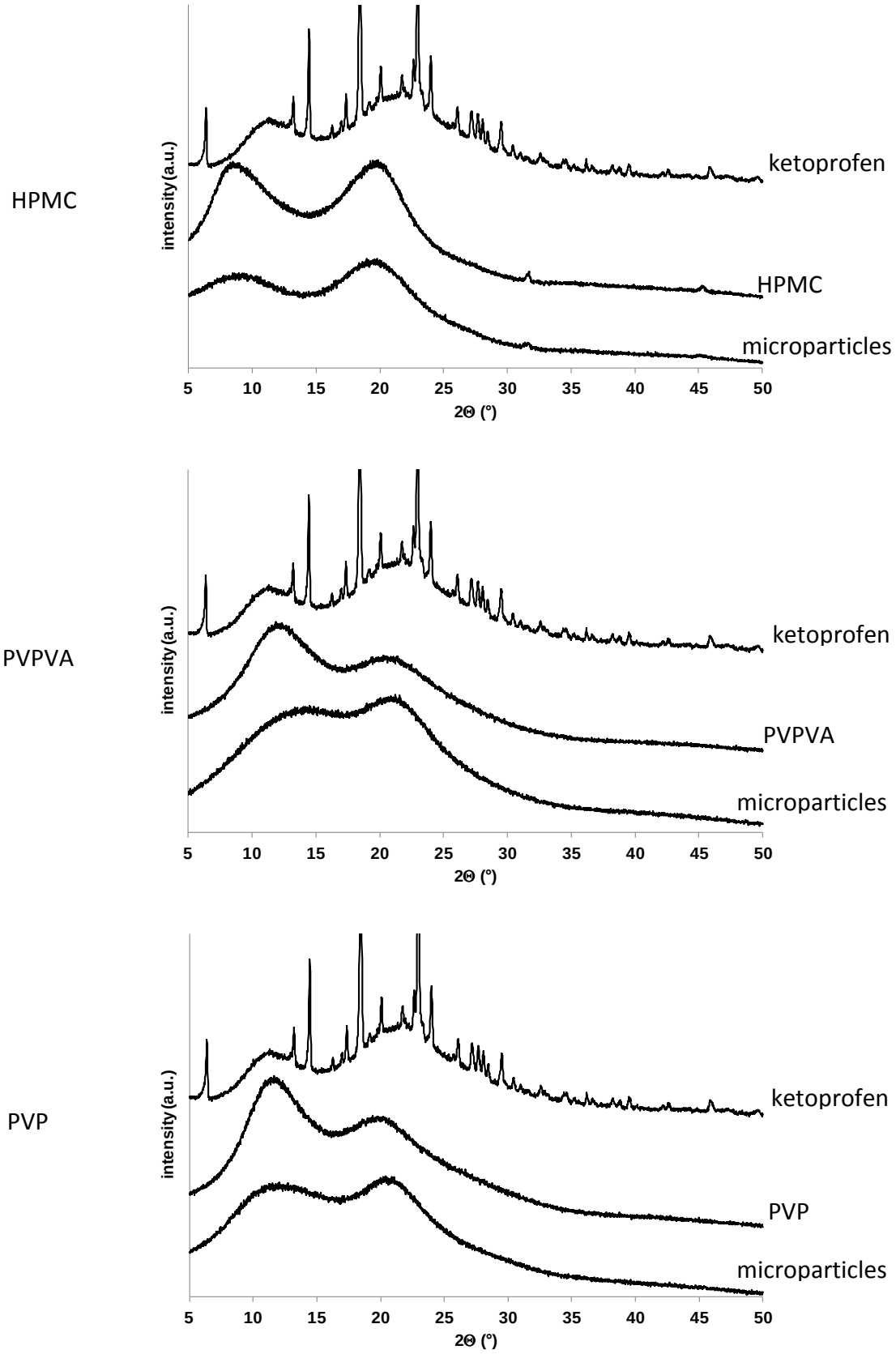

Figure III.3 X-ray diffraction patterns of ketoprofen powder (as received), polymer powder (as received, the type of polymer is indicated in the diagram) and ketoprofen-HPMC, PVPVA or PVP spray-dried microparticles loaded with 30 % ketoprofen.

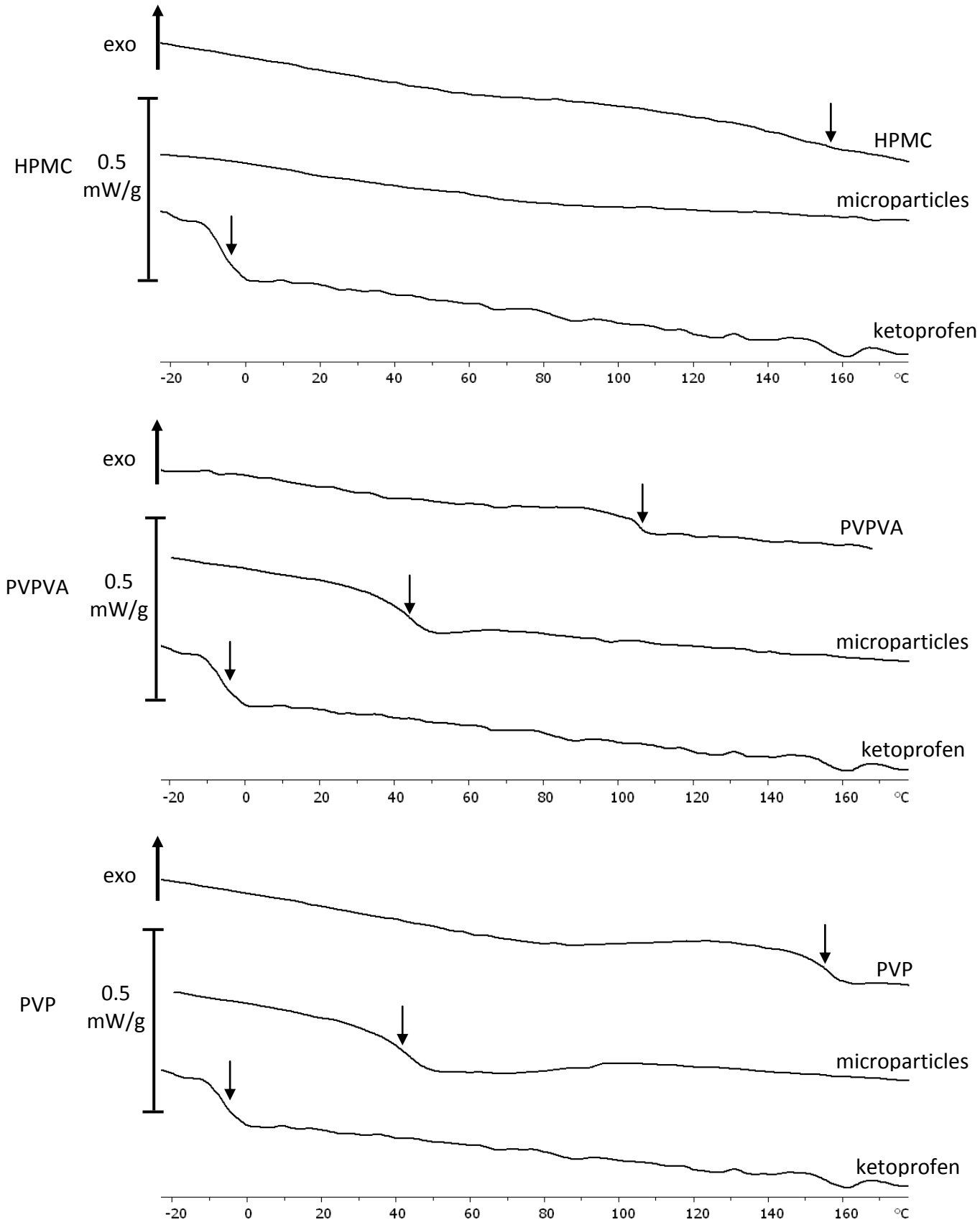

Figure III.4 mDSC thermograms of polymer powders (as received), spray-dried ketoprofen:polymer microparticles (the type of polymer is indicated in the diagram) and of ketoprofen powder as received (in the latter case exceptionally to heating cycles were run, the 2nd heating cycle being illustrated). The arrows mark glass transition temperatures.

Importantly, no X-ray diffraction peaks indicating crystalline ketoprofen were visible with any of the microparticle formulations, whereas the drug powder (as received) was highly crystalline (Figure III.3). Also the three polymer powders (as received) did not exhibit any X-ray diffraction peaks indicating crystallinity (except for two small peaks in the case of HPMC). Figure III.4 shows the mDSC thermograms of the three types of spray-dried microparticles. For reasons of comparison, also the thermograms of HPMC, PVPVA and PVP powders (as received) and of ketoprofen powder (as received) are shown. In the latter case, exceptionally two heating cycles were run in order to transform the crystalline drug into an amorphous state (the first heating cycle resulted in drug melting, during the cooling phase drug re-crystallization was to be avoided). Interestingly, the spray-dried ketoprofen:PVPVA- and ketoprofen:PVP-based microparticles exhibited only one single glass transition temperature (Tg), which was located between the Tgs of amorphous ketoprofen and the respective amorphous polymer: at 44 and 41 °C. In the case of ketoprofen:HPMC-based microparticles, the obtained signal did not allow a reliable detection of one or more Tgs. This is consistent with reports in the literature, highlighting the challenge to measure the Tg even in pure HPMC systems (McPhillips et al., 1999). Importantly, visual observation revealed that the ketoprofen-PVPVA- and the ketoprofen-PVP-based microparticles rapidly formed a (chewing gum like) lump upon exposure to the release medium, whereas ketoprofen-HPMC-based microparticles did not. Based on these observations, the observed ketoprofen release kinetics might be explained as follows:

- When adding the ethanolic solution of ketoprofen to the aqueous solutions of the polymers during the preparation of the liquids, which were fed into the spray-dryer, the drug precipitated as nanoparticles (water:ethanol ratio = 90:10): An opaque suspension was obtained, optical microscopy revealed particles in the sub-micrometer range. X-ray diffraction of the suspension did not show any diffraction peaks (Figure III.5). Thus, the nanoparticles were probably in an amorphous state, or crystalline regions were so small that they were not detected. The system was only metastable, since –if filtrated- large, needle-shaped ketoprofen crystals were rapidly growing. Importantly, these nanoparticles are likely to melt during spray-drying, since the melting point of the crystalline powder (as received) was about 94 °C and the inlet temperature was 110 °C. During solvent evaporation the resulting rapid cooling leads to the re-precipitation in an amorphous form,

and/or extremely small crystals which are not visible in the X-ray diffraction patterns, nor in the DSC thermograms, and/or the drug is dissolved in the polymer (solid solution). The fact that only one single Tg was observed at 41 or 44 °C (and no Tg at around -5 °C as for pure amorphous ketoprofen), might indicate that all of the drug is dissolved in the polymer, and that a homogenous 1-phase system is formed. However, nano-sized heterogeneities might be difficult to detect. In any case, the apparent solubility of the ketoprofen can be expected to be higher than that of the crystalline drug powder (as received). This explains the higher drug release rates observed from HPMC- and PVPVA-based microparticles (compared to the respective physical mixtures). The fact that ketoprofen release was *slower* from drug:*PVP*-based microparticles (compared to the respective physical mixture), can be attributed to the superposition of another phenomenon (described in the following point).

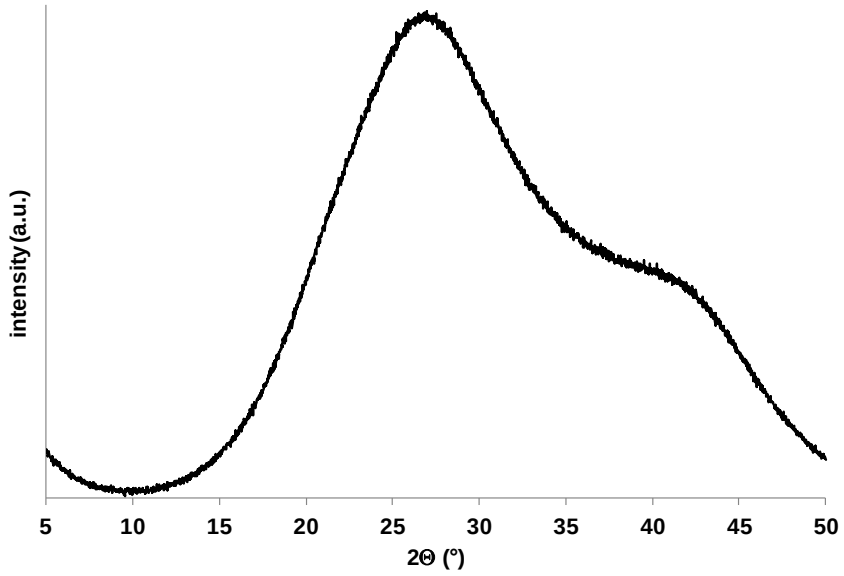

Figure III.5 X-ray diffraction patterns of the nanosuspension obtained upon mixing the ethanolic ketoprofen solution with the aqueous HPMC solution during the preparation of the liquid, which was fed into the spray-dryer for the manufacturing of ketoprofen-HPMC microparticles. The water:ethanol ratio was 90:10, the drug:polymer ratio 30:70.

- The glass transition temperatures (Tgs) of the microparticles were relatively close to 37 °C (the temperature of the release medium) in the case of PVPVA and PVP. Importantly, water is known to act as a plasticizer for many polymers (Faisant et al., 2002). Thus, the Tgs of the wetted microparticles are likely to decrease below 37 °C in the case of PVPVA and PVP. This results in the transition of the system from the glassy state into the rubbery state,

favoring particle sticking and lump formation. Indeed, rapid lump formation was visually observed upon exposure of ketoprofen:PVPVA- and ketoprofen:PVP-based microparticles to the release medium. This dramatically decreases the surface available for drug release and results in relatively low ketoprofen release rates. In the case of *PVPVA*, this "lump formation effect" results in a less pronounced increase in the ketoprofen release rate following the transformation of the drug into an amorphous and/or dissolved state. In the case of *PVP*, the "lump formation effect" even overcompensates the "phase transition effect" and leads to slower drug release from ketoprofen:PVP-based microparticles compared to the respective physical blends.

The fact that ketoprofen dissolution from physical mixtures was slightly faster than the dissolution of ketoprofen powder (as received) in the case of PVPVA and PVP can probably be attributed to the fact that the hydrophilic polymers facilitate drug particle wetting. As mentioned above, the presence of these polymers did not significantly affect the equilibrium solubility of ketoprofen. In contrast, in the case of HPMC, ketoprofen release from the physical mixture was slightly *slower* than the dissolution of the drug powder (as received). This can probably be attributed to the drug release retarding properties of the HPMC gel, which forms upon contact with water (Siepmann and Peppas, 2012). Importantly, the ketoprofen release kinetics did not change during 8 weeks open storage at ambient conditions, irrespective of the type of polymer (dotted versus solid curves in Figure III.1). This is very important from a practical point of view, since the increased drug release rates result from an energetically less favorable physical state of the drug. During storage the drug could potentially be transformed into an energetically more favorable state with a reduced apparent solubility. Also note that the leveling off of drug release below 100 % in Figure III.1 can be attributed to saturation effects: The dashed straight lines indicate ketoprofen solubility under the given conditions. Increasing the volume of the release medium, while keeping the amount of formulation constant led to more complete drug release (data not shown). Based on these results, HPMC was selected as the most promising carrier material and the impact of processing parameters and of the physical state of the drug in the liquid used for spray-drying was investigated.

III.2. Impact of the processing conditions

Figure III.6 shows the release of ketoprofen from microparticles prepared by spray-drying 30:70 (w:w) drug:HPMC blends dispersed in 90:10 water:ethanol mixtures using different processing parameters, namely: (i) inlet temperatures (110 versus 90 °C), (ii) drying gas flow rates (414 versus 600 L/h), and (iii) feed flow rates (7.5 versus 10 mL/min). Drug release is shown before storage (left hand side) and after 8 weeks open storage at ambient conditions (right hand side). Interestingly, varying the drying gas and feed flow rates within these ranges did not significantly affect drug release from microparticles prepared at 110 °C before storage, but led to a moderate decrease in the release rate when the inlet temperature was only 90 °C.

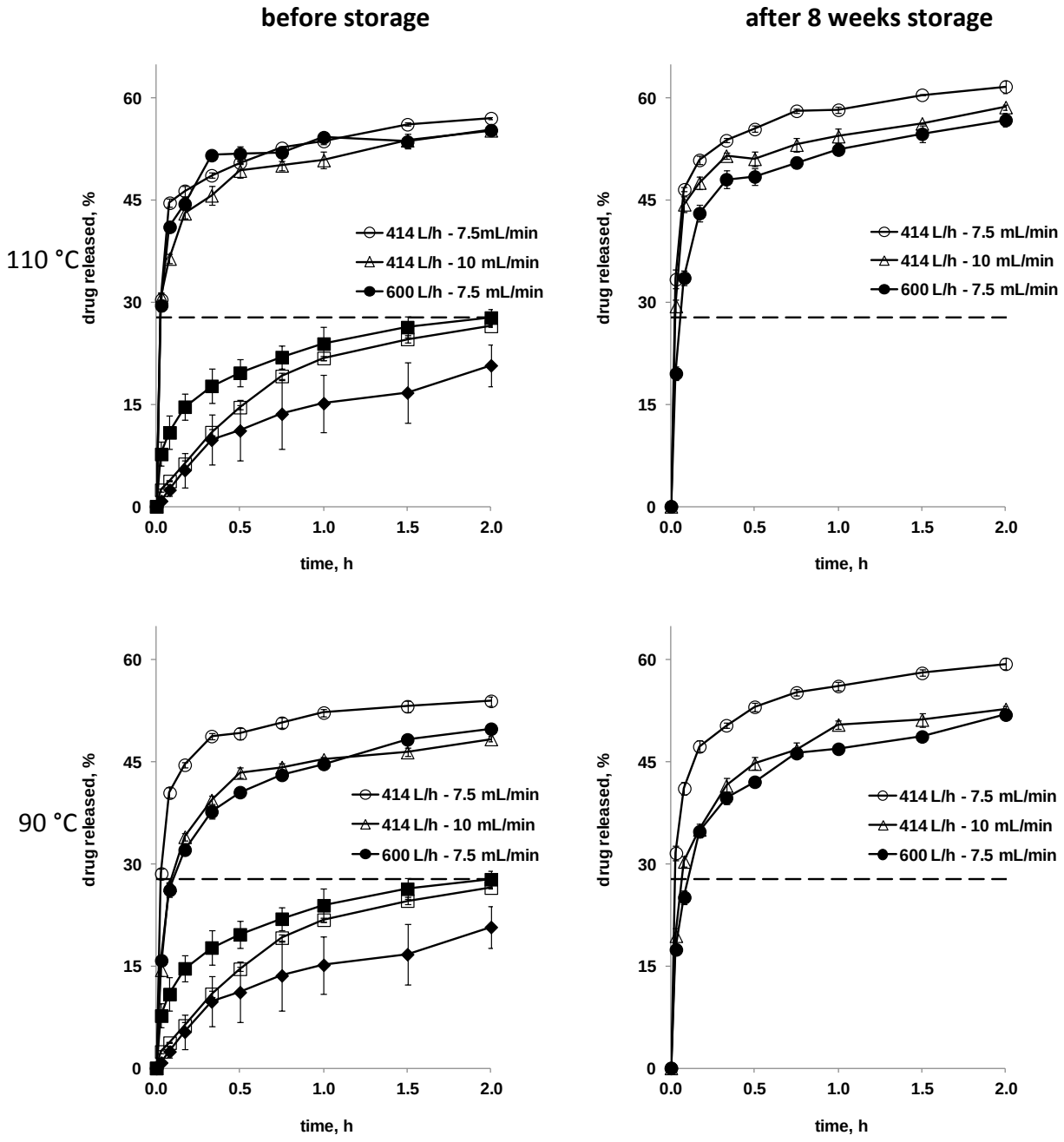

Figure III.6 Ketoprofen release in 0.1 M HCl from microparticles prepared by spray-drying drug:HPMC (30:70 w:w) blends using different processing conditions (Table III.1). The inlet temperature, drying gas and feed flow rates are indicated in the diagrams. For reasons of comparison, also drug release from the commercially available product Profenid® (filled diamonds), the dissolution of ketoprofen powder (as received, filled squares) and the dissolution of ketoprofen from a physical drug:HPMC blend (30:70 w:w, open squares) are illustrated. The dashed straight line indicates the equilibrium solubility of ketoprofen powder (as received) under the given conditions.

The microparticle size was reduced when increasing the drying gas flow rate from 414 to 600 L/h, irrespective of the inlet temperature (Figure III.7). This can be explained by the creation of smaller liquid droplets at the spraying nozzle with increasing drying gas flow rate. The investigated variation in the feed flow rate did not very much impact the resulting particle size, irrespective of the inlet temperature.

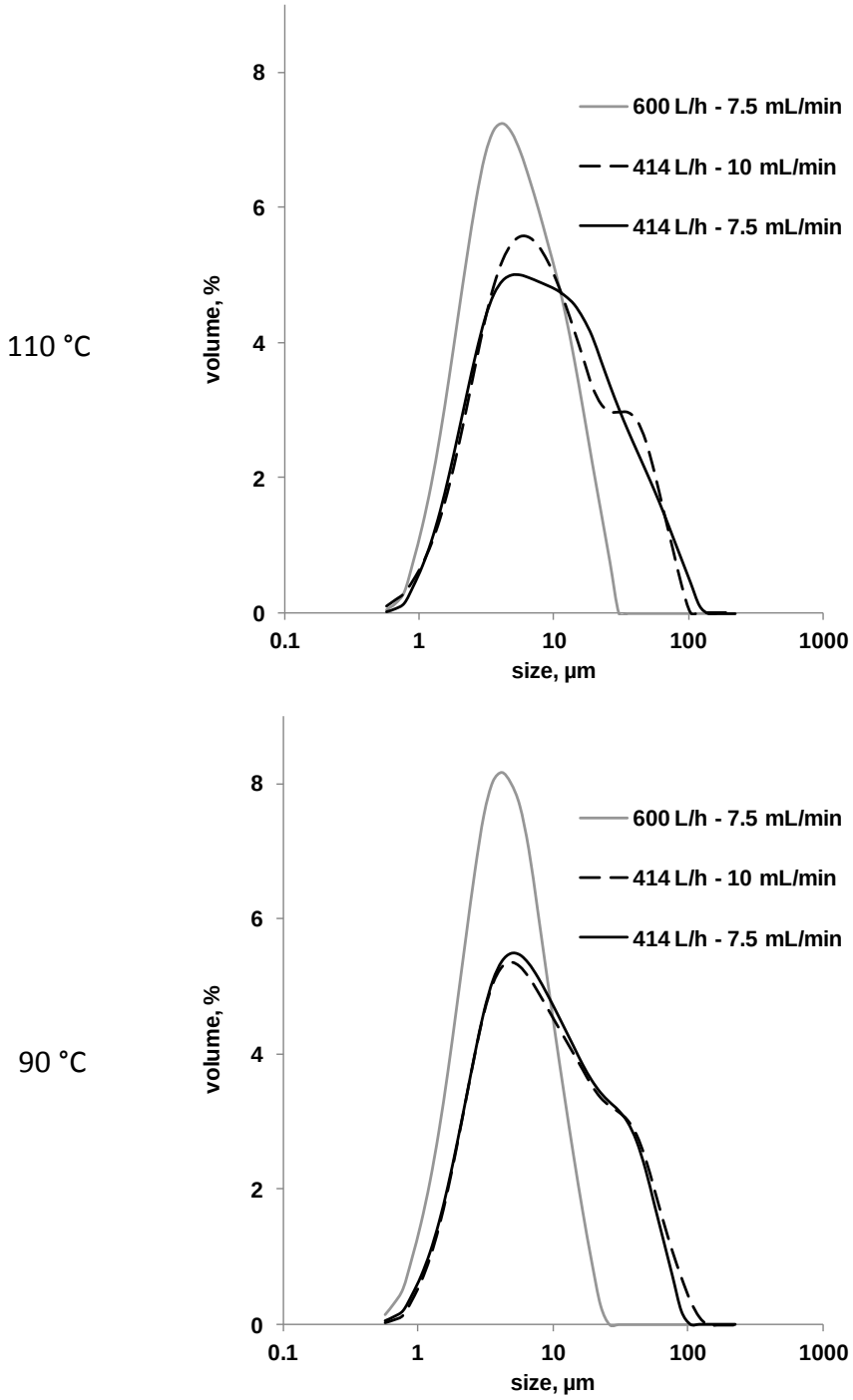

Figure III.7 Particle size distributions of spray-dried microparticles obtained with ketoprofen:HPMC (30:70 w:w) blends using a 90:10 (w:w) water:ethanol mixture. The applied inlet temperature, drying gas and feed flow rates are indicated in the diagrams.

The absence of a significant impact of varying the drying gas and feed flow rates at *110 °C* might be explained by the fact that under all investigated spraying and feeding conditions the majority of the ketoprofen nanoparticles had the time to melt during processing, re-solidifying in an amorphous state, and/or in very small (X-ray amorphous) crystals (Figure III.8) and/or dissolved in the polymer, exhibiting a high apparent drug solubility. The fact that at a drying gas flow rate of 600 L/h some small diffraction peaks were visible indicates that partially a few X-ray visible crystals also formed (eventually resulting from the phase transition of metastable amorphous ketoprofen), which did not have the time to melt during processing at this high drying gas flow rate). Importantly, the presence of these crystals did not impact drug release before storage (Figure III.6). However, they led to further crystal growth during storage (Figure III.8) and a decrease in the drug release rate (Figure III.6) (the larger drug crystals exhibiting a lower apparent solubility than the amorphous drug particles, or extremely small drug crystals, or ketoprofen dissolved in the polymer). At an inlet temperature of *90 °C*, this type of phase transition was more pronounced (Figure III.8), which is consistent with the hypothesis of incomplete ketoprofen melting at this temperature. Interestingly, this "phase transition effect" even overcompensated the "reduced particle size effect": The smaller particles obtained at 600 L/h and 7.5 mL/min exhibit slower drug release compared to the larger particles obtained at 414 L/h and 7.5 mL/min. At an inlet temperature of 90 °C, X-ray diffraction peaks were also visible at a drying gas flow rate of 414 L/h at a feed flow rate of 10 mL/min (Figure III.8). Again, the crystallinity of the systems increased upon storage. Importantly, at low drying gas and feed flow rates (414 L/h and 7.5 mL/min), X-ray amorphous microparticles were obtained, which did not show any sign for crystallization during 8 weeks open storage (Figure III.8) and exhibited similar release kinetics as microparticles prepared at 110 °C (being stable during storage). This can serve as an indication that under these conditions the time was sufficient for the ketoprofen nanoparticles to melt. Again, note that the partially observed leveling off of drug release below 100 % can be attributed to saturation effects. The dashed lines indicate drug solubility under the given conditions.

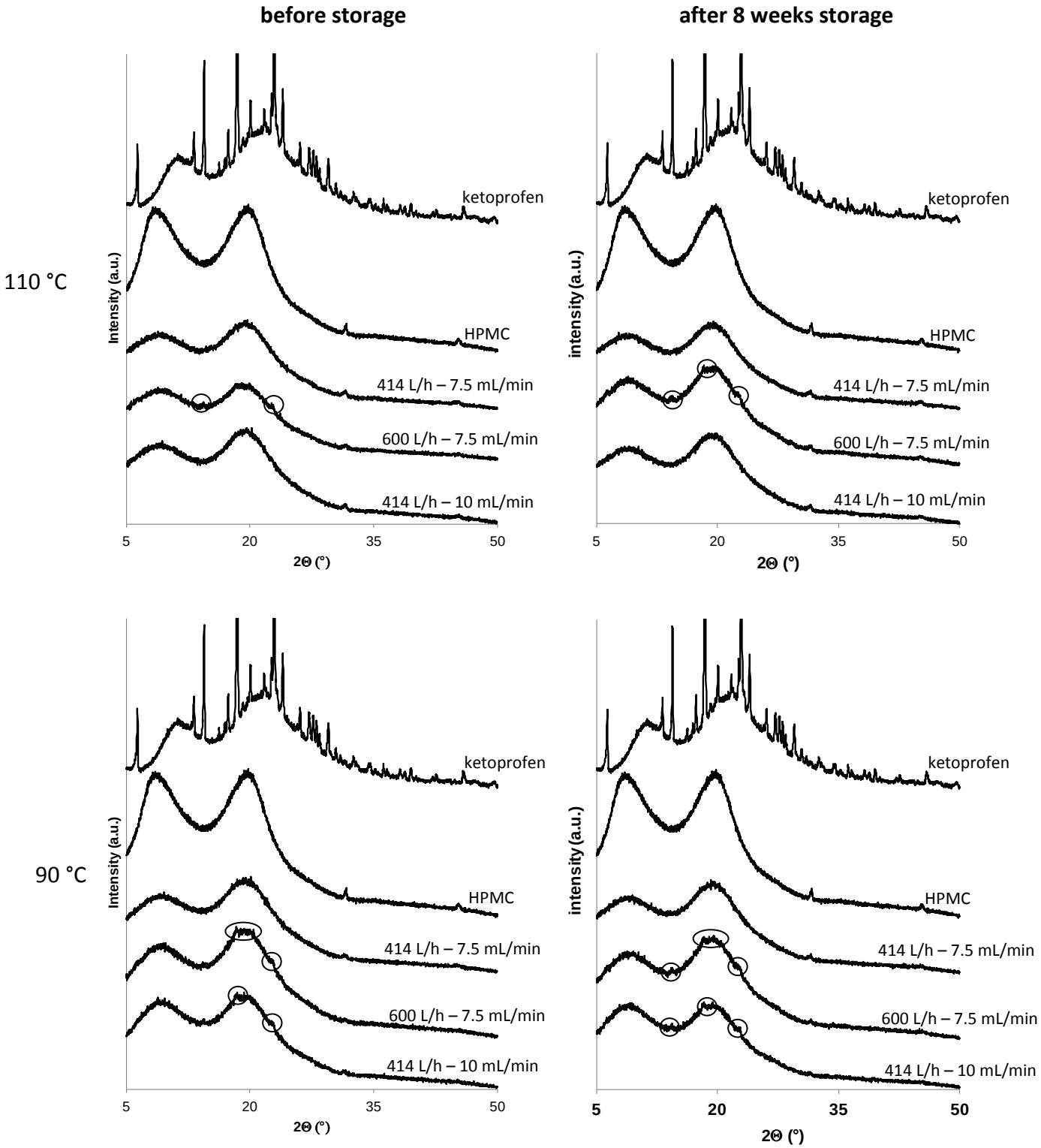

Figure III.8 X-ray diffraction patterns of ketoprofen powder (as received), HPMC powder (as received) and of microparticles obtained by spray-drying ketoprofen:HPMC 30:70 (w:w) blends using a 90:10 (w:w) water:ethanol mixture. The applied inlet temperature, drying gas and feed flow rates are indicated in the diagrams. In the case of microparticles, crystalline peaks of ketoprofen are highlighted.

III.3. Drug suspension versus drug solution used for spray-drying

In order to change the physical state of the drug in the liquid used for spray-drying, the blend ratio “water:ethanol” was varied as follows: 90:10, 80:20, 70:30 and 50:50. In the first two cases, the drug was at least partially suspended, in the latter two cases completely dissolved (at room temperature). The expectation was that a complete dissolution of the ketoprofen could lead to a finer (ideally molecular) dispersion of the drug within the resulting polymeric network and, thus, increased drug release rates. However, the opposite trend was observed, as illustrated in Figure III.9: Ketoprofen release from microparticles prepared with 70:30 and 50:50 water:ethanol mixtures (in which the drug is completely dissolved) (open and filled triangles) is much slower than from microparticles prepared with 90:10 and 80:20 water:ethanol mixtures (in which the drug is at least partially suspended) (open and filled circles). This was surprising, especially because in addition the size of the microparticles prepared with 70:30 and 50:50 water:ethanol mixtures was smaller than the size of the microparticles prepared with 90:10 and 80:20 blends (Figure III.10). As mentioned above, the drug release rate can be expected to increase with decreasing microparticle size, due to the increase in available surface area and shortened pathway lengths. Also, no lump formation was observed with any of these formulations upon exposure to the release medium. X-ray diffraction did not show any sign for drug crystals, irrespective of the water:ethanol blend ratio (Figure III.11). Thus, potential drug re-crystallization is unlikely to explain the observed differences between drug releases from microparticles prepared with drug “suspensions” versus “solutions”. The mDSC thermograms of the different types of microparticles and of HPMC and ketoprofen are illustrated in Figure III.12. No clear endothermic or exothermic events were visible in the investigated temperature range under the given conditions in the microparticles, for the reasons discussed above.

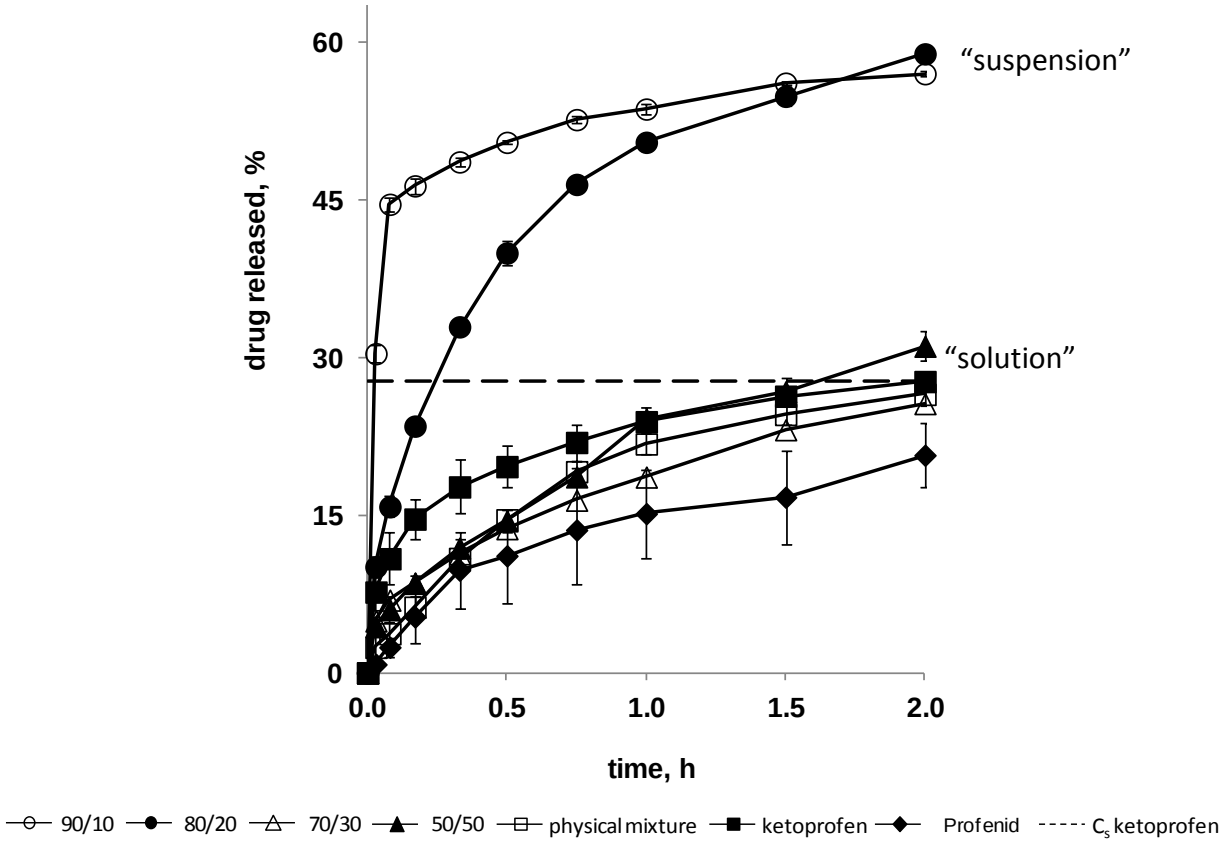

Figure III.9 Ketoprofen release in 0.1 M HCl from microparticles prepared by spray-drying drug:HPMC (30:70 w:w) blends, which were completely dissolved ("solution"), or at least partially suspended ("suspension") in different water:ethanol mixtures (w:w)

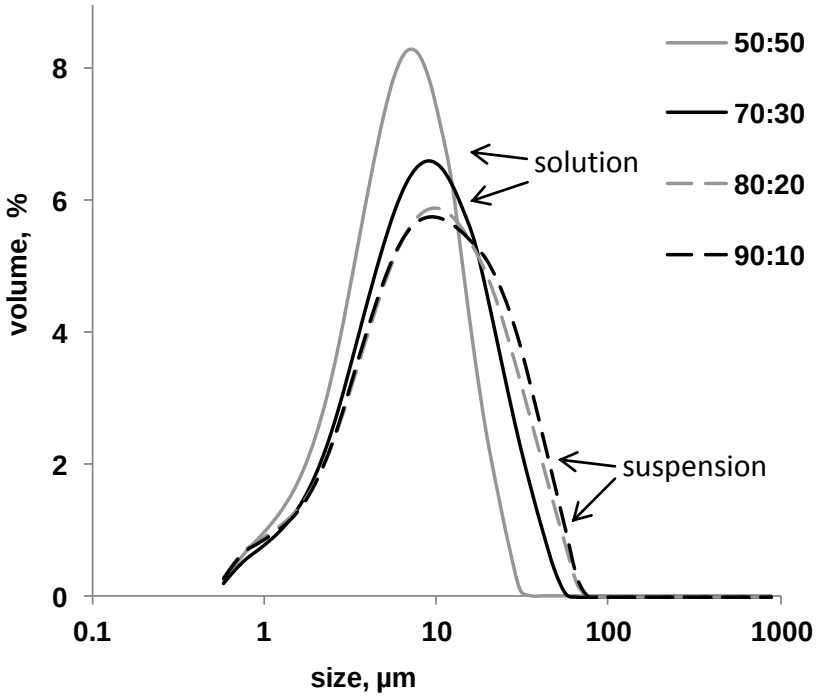

Figure III.10 Particle size distributions of spray-dried microparticles prepared with ketoprofen:HPMC (30:70 w:w) blends using different water:ethanol mixtures (w:w, as indicated in the diagram). The processing conditions are indicated in Table III.1

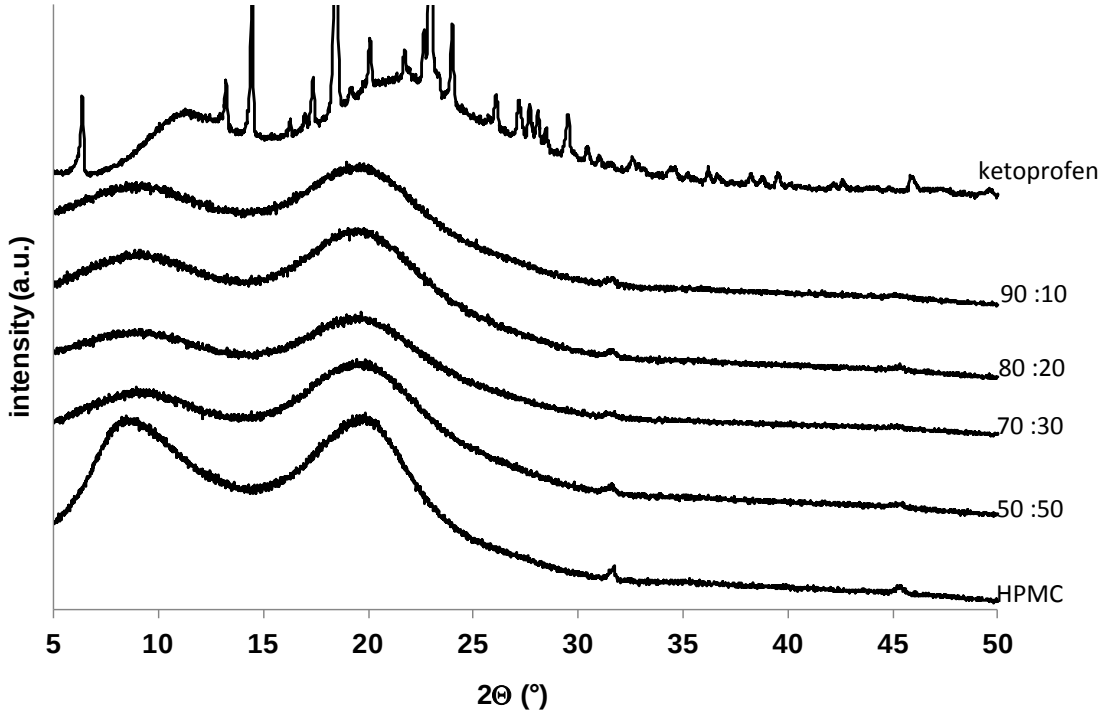

Figure III.11 X-ray diffraction patterns of ketoprofen powder (as received), microparticles obtained by spray-drying ketoprofen:HPMC 30:70 blends using different water:ethanol mixtures (the ratio is indicated in the diagram) and of HPMC powder (as received).

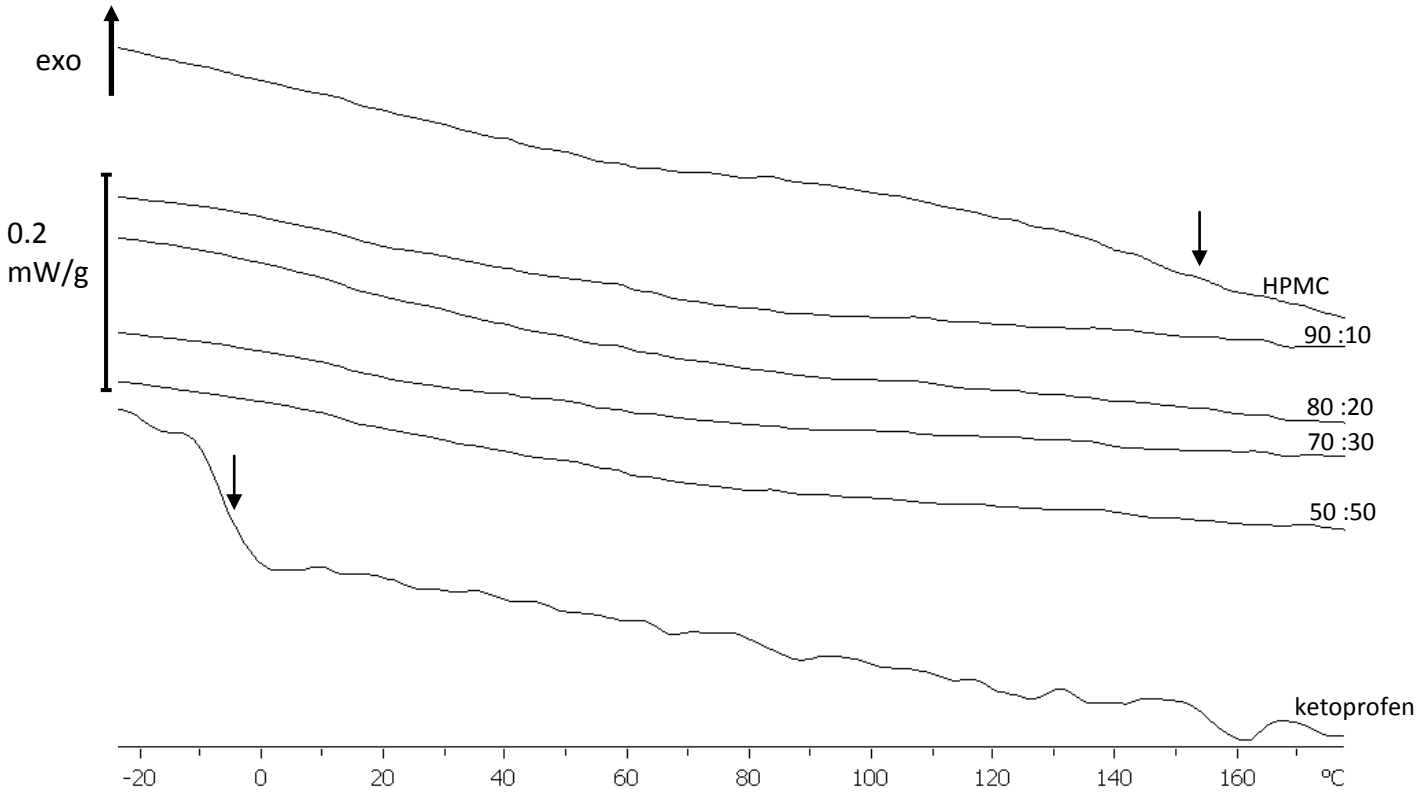

Figure III.12 mDSC thermograms of HPMC powder (as received), spray-dried microparticles prepared with 30:70 ketoprofen:HPMC blends and different water:ethanol ratios (indicated in the diagram) and of ketoprofen powder (in the latter case exceptionally 2nd heating cycle). The arrows mark glass transition temperatures.

Importantly, SEM pictures revealed that the surface of microparticles prepared with ketoprofen “suspensions” (90:10 and 80:20 water:ethanol mixtures) was somewhat heterogeneous, whereas the surface of microparticles prepared with ketoprofen “solutions” (70:30 and 50:50 water:ethanol mixtures) was smooth and homogeneous (Figure III.13). This might be explained by the fact that the HPMC is homogeneously distributed on the molecular level in the droplets consisting of drug-polymer solutions and forms a homogeneous and continuous network upon solidification. In contrast, in the case of ketoprofen “suspensions”, pure (under the given conditions molten) drug domains exist within the droplets created at the spraying nozzle and the HPMC chains are mainly present in the surrounding liquid. Thus, upon solvent evaporation, a more heterogeneous structure is obtained, consisting of HPMC-rich domains and HPMC-poor domains. Hence, upon exposure to the release medium it can be expected that the homogeneous HPMC distribution in microparticles prepared with ketoprofen “solutions” effectively hinders water penetration into the system, slowing down drug release. In contrast, the heterogeneous structure and presence of HPMC-poor domains in microparticles prepared with ketoprofen “suspensions” can be expected to facilitate water penetration, resulting in more rapid drug release. This is consistent with the observed drug release kinetics (Figure III.9). Again, note that the partially observed leveling off of drug release below 100 % can be attributed to saturation effects. The dashed line indicates drug solubility under the given conditions.

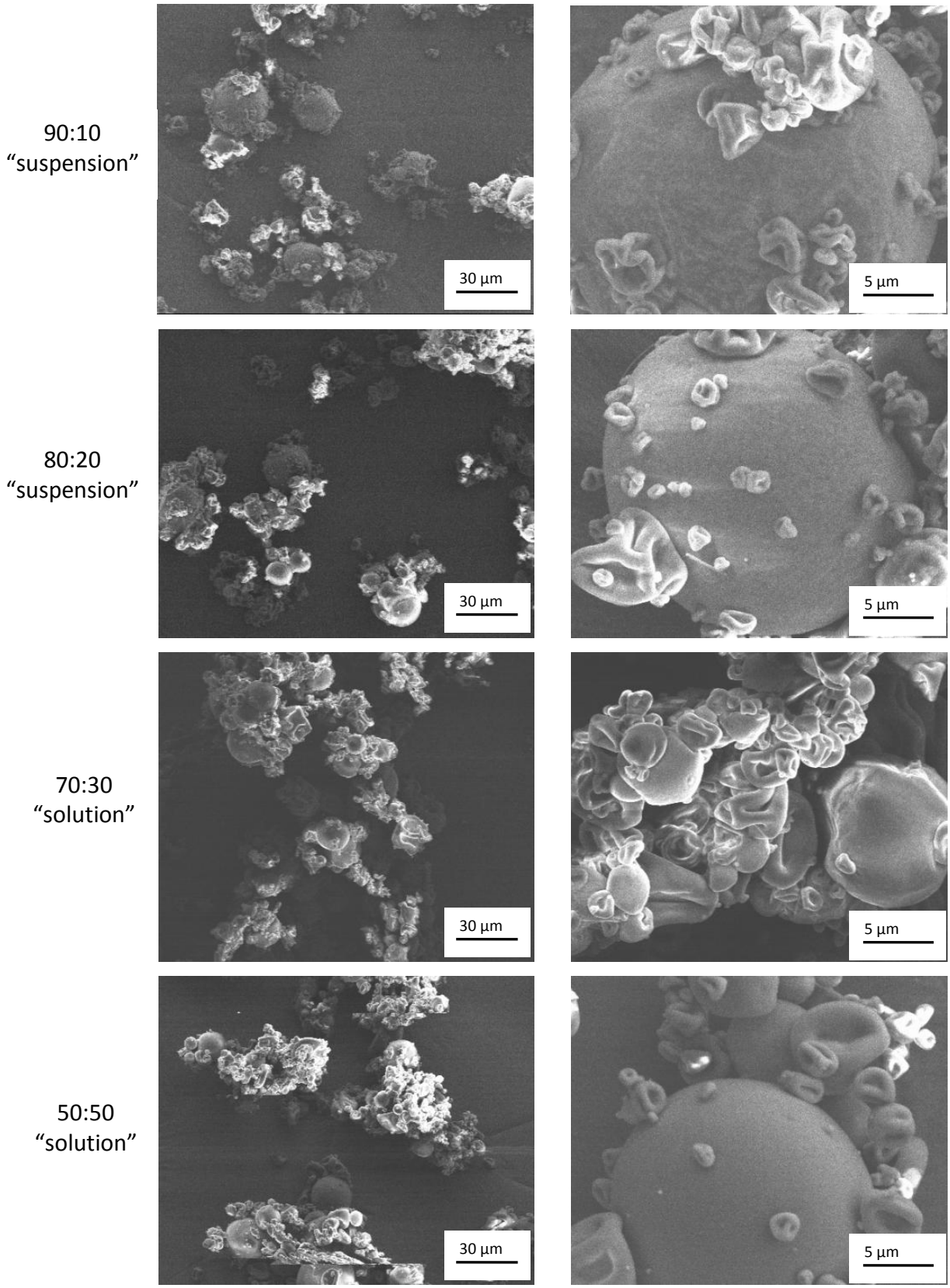

Figure III.13 SEM pictures of surfaces (lower and higher magnification) of microparticles prepared with 30:70 ketoprofen:HPMC blends and different water:ethanol ratios (indicated in the diagram). The processing conditions are indicated in Table III.1.

IV. Conclusion

Hydrophilic polymeric microparticles prepared by spray-drying offer a major potential to increase the release rate of poorly soluble drugs. However, despite of their eventually rather simple composition (e.g. binary drug:polymer blends), these formulations can be highly complex, because not only the physical states of the drug and polymer, but also their spatial distribution can strongly impact drug release.

Acknowledgements

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Chapter IV. ACCELERATED FENOFIBRATE RELEASE FROM SPRAY-DRIED MICROPARTICLES BASED ON POLYMER BLENDS

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[Submitted in *Journal of of Drug Delivery Sciences and Technology*]

Abstract

Fenofibrate-loaded microparticles based on PVP/Eudragit® E or HPMC/Eudragit® E blends were prepared by spray-drying. The composition of the systems (in particular the polymer/polymer blend ratio and the drug loading) were varied and the key properties determined. This includes drug release measurements in 0.1 M HCl, X-ray diffraction studies, solubility measurements and particle size analysis. For reasons of comparison, also the respective physical drug/polymer/polymer mixtures, microparticles based on binary drug/PVP and drug/HPMC blends, the fenofibrate powder as received and a commercially available drug product were investigated. Importantly, highly supersaturated fenofibrate solutions were created upon exposure of the different types of microparticles to the release medium, in contrast to any reference formulation. Also, the presence of co-dissolved Eudragit® E led to a significant increase in fenofibrate solubility. At 10 % drug loading, all microparticles were amorphous and drug release stable during 1 month open storage. However, at 30 % loading, HPMC containing microparticles showed storage instability, due to drug re-crystallization.

Keywords: Fenofibrate, Eudragit® E, PVP, spray-drying, solubility enhancement, supersaturation

I. Introduction

If a drug or drug candidate does not provide sufficient solubility in aqueous body fluids, it cannot reach its site of action in the living body and fails to show therapeutic efficacy in vivo, even if its chemical structure is ideal to interact with the target and in vitro studies show highly promising results. Formulators are more and more frequently confronted with this situation and a variety of strategies has been proposed to overcome the crucial hurdle of insufficient water-solubility. This includes the use of cyclodextrins (Kurkov and Loftsson, 2013), polymeric micelles (Sievens-Figueroa et al., 2012), the transformation of crystalline drugs into an amorphous state (Brough and Williams III, 2013; Van den Mooter, 2012; Zhao et al., 2012), lipid formulations (Mu et al., 2013), co-crystals (Elder et al., 2013; Thakuria et al., 2013), salt formation (Elder et al., 2013), particle size reduction (Ikeda et al., 2012; Sinha et al., 2013), mesoporous systems (Zhang et al., 2013), and amorphous systems (Brough and Williams III, 2013; Van den Mooter, 2012; Zhao et al., 2012). A comprehensive overview of the different strategies used to prolong the life-time of supersaturated solutions has been published by Bevernage et al. (Bevernage et al., 2012). Often, precipitation inhibitors are added (Xu and Dai, 2013). If the formulation is administered orally, the presence of bile salts might also affect the absorption of poorly soluble drugs (Holm et al., 2013).

The general aims of the various approaches are to accelerate the process of drug dissolution, increase the apparent drug solubility, eventually create supersaturated solutions and keep them sufficiently stable to allow for increased drug absorption/transport away from the administration site and to provide long term stable drug delivery systems. The mathematical description of the physical processes involved in drug dissolution has recently been reviewed (Siepmann and Siepmann, 2013). Different types of methods can be used to prepare such drug delivery systems with improved release of poorly water-soluble drugs, for example hot-melt extrusion (Repka et al., 2012; Shah et al., 2013), film-freezing (Zhang et al., 2012), and spray-drying (Paudel et al., 2013) (amongst many other techniques). And different types of polymers have been reported to be useful to facilitate the dissolution/release of poorly soluble drugs, for example hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and poly[butyl methacylate-co-(2-

dimethylaminoethyl) methacrylate-co-methyl methacrylate] 1/2/1 (Eudragit® E). However, yet relatively little is known on the use of polymer *blends* and the impact of simply varying the polymer/polymer blend ratio on the key properties of the systems. From other fields, it is well known that polymer/polymer blends can be highly useful, since the systems' performance can effectively be adjusted by simply varying the blend ratio (Lecomte et al., 2003, , 2004a, 2004b, , 2005).

The aim of this study was to prepare different types of microparticles based on polymer blends by spray-drying. The impact of the type of blend, blend ratio and drug loading on the key features of the systems (especially drug release rates) were to be determined and better understood, based on X-ray studies, particle size and solubility measurements. Fenofibrate was chosen as poorly water-soluble drug. For reasons of comparison, also the drug powder as received, physical blends of the drug and the respective polymers as well as a commercially available drug product were investigated. Intentionally, non-sink conditions were provided in order to more realistically simulate in vivo conditions.

II. Materials and Methods

II.1. Materials

Fenofibrate (Chemos, Regenstauf, Germany); hydroxypropyl methylcellulose (HPMC, Methocel® E5; Colorcon, Dartford, UK); poly[butyl methacylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate] 1/2/1 (Eudragit® E, Eudragit® E 100 PO; Evonik, Essen, Germany); polyvinylpyrrolidone (PVP, Kollidon® K30; BASF, Ludwigshafen, Germany); Lipanthyl® 145 mg (Abbott, Abbott Park, Illinois, USA); acetonitrile (HPLC Grade; Fisher Scientific, Loughborough, UK); phosphoric acid 85 % (Sigma-Aldrich, Steinheim, Germany); ethanol 95 % (Brabant, Tressant, France).

II.2. Preparation of physical mixtures

Fenofibrate and one or more polymers (as indicated) were blended manually using a pestle and mortar for 10 min (100 g batch size). These blends were used for subsequent spray-drying, mDSC analysis or for in vitro drug release measurements.

II.3. Preparation of spray-dried microparticles

Drug-polymer blends were dissolved in 600 mL ethanol/water 85/15 (v/v). The liquids were spray-dried with a Buechi B-290 apparatus (Buechi, Basel, Switzerland), equipped with a 0.7 mm nozzle, using the following operating conditions: inlet temperature = 70°C; aspirator flow rate = 36 m^3/h; drying gas flow rate = 414 L/h; feed flow rate = 7.5 mL/min. The resulting outlet temperature was about 40 to 45°C.

II.4. In vitro drug release measurements

Fenofibrate release studies were performed using the USP 35 paddle apparatus (Sotax, Basel, Switzerland) in 0.1 M HCl (500 mL; 37°C; 75 rpm; n = 3) with appropriate amounts of formulations containing 145 mg fenofibrate. At predetermined time points, 3 mL samples were withdrawn (replaced with fresh medium), filtered through an Acrodisc® (GxF/GHP 0.2µm, Pall, Port Washington, NY, USA), and subsequently diluted (1/1, v/v) with acetonitrile/water pH 2.5 (70/30, v/v) to prevent precipitation. The amount of fenofibrate in each sample was determined by HPLC analysis (ProStar 230 pump, 410 autosampler, 325 UV–Vis detector, and Galaxie software, Varian, Les Ulis, France). A reversed phase column C18 (Gemini 5 µm; 110 Å; 150 mm × 4.6 mm; Phenomenex, Le Pecq, France) was used. The mobile phase was acetonitrile/water pH 2.5 (70/30, v/v), the detection wavelength 258 nm and the flow rate 1 mL/min. One hundred µL samples were injected. The elution time was around 9 min. Each experiment (drug release and drug detection) was conducted in triplicate.

II.5. Determination of equilibrium solubility

The equilibrium solubility of fenofibrate powder (as received) was determined in agitated flasks in 0.1 M HCl, optionally containing different amounts of PVP, HPMC and/or Eudragit® E, as indicated in Table IV.1. An excess amount of fenofibrate was exposed to 20 mL bulk fluid, kept at 37°C under horizontal shaking (80 rpm; GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). Every 24 h, samples were withdrawn, filtered and analyzed by HPLC for their drug content (as described above) until equilibrium was reached. Each experiment was conducted in triplicate.

Table IV.1 Equilibrium solubility of fenofibrate determined in 0.1 M HCl containing different amounts of PVP, Eudragit® E and/or HPMC, at 37 °C.

Polymer(s)	**Solubility, µg/mL (mean ± SD)**
None	0.23 ± 0.03
0.26% w/v PVP	0.23 ± 0.03
0.17% w/v PVP + 0.09% w/v Eudragit® E	1.58 ± 0.07
0.15% w/v PVP + 0.11% w/v Eudragit® E	2.32 ± 0.03
0.11% w/v PVP + 0.15% w/v Eudragit® E	2.78 ± 0.04
0.07% w/v PVP	0.23 ± 0.05
0.04% w/v PVP + 0.03% w/v Eudragit® E	0.45 ± 0.13
0.26% w/v HPMC	0.52 ± 0.08
0.17% w/v HPMC + 0.09% w/v Eudragit® E	2.27 ± 0.10
0.15% w/v HPMC + 0.11% w/v Eudragit® E	2.81 ± 0.03
0.11% w/v HPMC + 0.15% w/v Eudragit® E	3.41 ± 0.01
0.07% w/v HPMC	0.46 ± 0.05
0.04% w/v HPMC + 0.03% w/v Eudragit® E	1.00 ± 0.07

II.6. X-ray diffraction studies

X-ray powder diffraction patterns were recorded using a PANalytical X'Pert pro MPD powder diffractometer equipped with a Cu X-ray tube ($\lambda_{CuK\alpha}$ = 1,540Å) and the X'celerator detector. Powder samples were placed in a spinning flat sample holder, the measurements were performed in Bragg-Brentano θ-θ geometry.

II.7. Particle size measurements

Mean particle diameters were determined with an Axioscope microscope (Zeiss, Jena, Germany) and an optical imaging system (EasyMeasure; INTEQ, Berlin, Germany). Each measurement included 200 particles.

III. Results and discussion

III.1. PVP/Eudragit® E blends

The open circles in Figure IV.1 show the dynamic changes in the concentrations of dissolved fenofibrate in the release medium upon exposure of spray-dried microparticles to 0.1 M HCl. The systems were based on different PVP/Eudragit® E/drug blends, as indicated. Microparticles free of PVP could not be prepared, due to the low glass transition temperature of Eudragit® E, resulting in intense sticking and film formation at the cyclone's wall (Gué et al., 2013). For reasons of comparison, also the resulting dissolved drug concentration time profiles measured after exposure of: (i) the respective physical blends (open squares), (ii) fenofibrate powder (as received, filled squares), and (iii) the commercially available product Lipanthyl® (filled diamonds), are illustrated in Figure IV.1. The dashed straight lines indicate the equilibrium solubility of fenofibrate powder (as received) in the presence of the respective amounts of Eudragit® E and/or PVP (as incorporated in the microparticles). Importantly, the presence of co-dissolved Eudragit® E led to increased fenofibrate solubility, whereas this was not the case for PVP (Table IV.1).

All spray-dried microparticles contained 10 % drug. In all cases, the amount of formulation exposed to the release medium contained 145 mg drug.

Importantly, highly supersaturated fenofibrate solutions were almost instantaneously formed upon contact of all types of microparticles with the release medium. The highest concentration was achieved with 60/30/10 PVP/Eudragit® E/fenofibrate blends. In all cases, the created solutions were metastable and the drug partially re-precipitated during the observation period. The concentration of dissolved fenofibrate asymptotically decreased towards its equilibrium solubility in the presence of the respective amounts of co-dissolved Eudragit® E. In vivo, drug transport away from the site of release might be rapid and the presence of various other compounds in the gastro intestinal tract might alter the re-precipitation periods. Thus, the observed re-precipitation under the given in vitro conditions might not be of relevance in vivo.

Interestingly, the concentrations of dissolved fenofibrate upon exposure of the drug powder (as received) and of the commercially available drug product to 0.1 M HCl (in the absence of polymers) were substantially lower compared to all Eudragit® E containing formulations. This clearly points out the impact of Eudragit® E as solubility enhancer. When comparing the different microparticle formulations and the respective physical mixtures, it becomes obvious that only microparticles are able to create supersaturated fenofibrate solutions. The reason for this phenomenon becomes evident in Figure IV.2: The X-ray diffraction patterns of the different types of spray-dried PVP/Eudragit® E/fenofibrate microparticles are illustrated. For reasons of comparison, also the diffraction patterns of fenofibrate, PVP and Eudragit® E powders (as received) are shown. Clearly, the drug powder was highly crystalline, whereas the polymers and all types of investigated microparticles did not show any sign for crystallinity. Thus, fenofibrate was transformed into an amorphous state and/or molecularly dispersed (= dissolved) in the polymer network (and/or eventually present as crystals, which were too small to show X-ray diffraction peaks). In these physical states of the drug, the inner energy is increased, resulting in increased apparent solubility and explaining the observed supersaturated solutions. The facts that: (i) all types of investigated microparticles (based on drug and PVP only, or on drug and PVP/Eudragit® E blends) led to the formation of supersaturated drug solutions (Figure IV.1), and (ii) only Eudragit® E, but not PVP, increases fenofibrate solubility (Table IV.1), indicates that the

solubility enhancing effect of Eudragit® E is not responsible for the observed supersaturation effects. The latter can be attributed to the altered physical state of the drug as discussed above. However, such energetically higher drug states might be transformed into energetically more favorable states during storage, resulting in decreasing drug release rates (risk of storage instability). Importantly, no sign for such solid-solid state transformations were visible with any of the investigated microparticles during 1 month storage in open vials at ambient conditions (25 °C, 40% relative humidity), and the resulting fenofibrate concentrations upon exposure to the release medium were similar before and after storage (solid versus dotted curves in Figure IV.1), irrespective of the type of formulation.

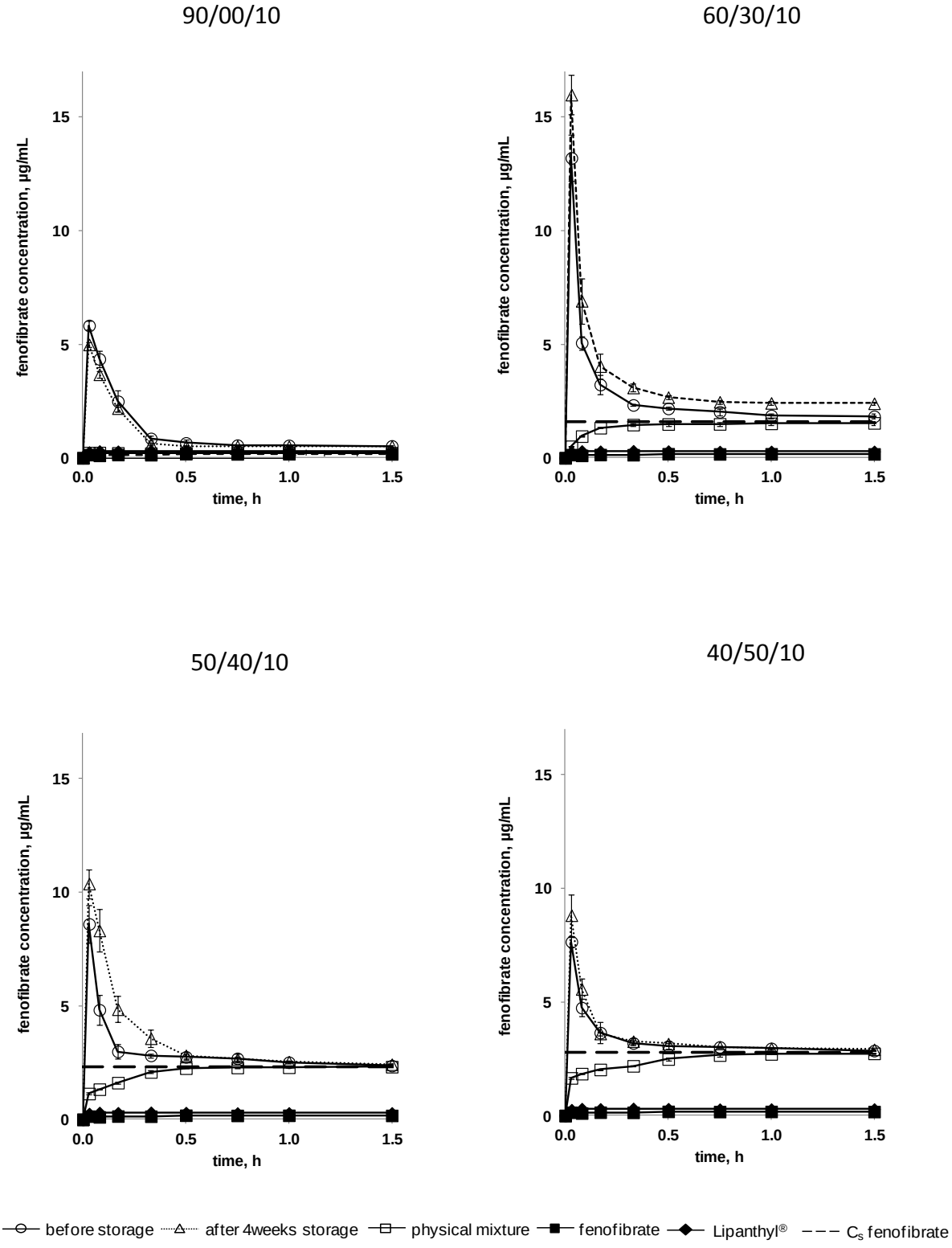

Figure IV.1 Dynamic changes in the concentration of dissolved fenofibrate in the release medium upon exposure of spray-dried microparticles to 0.1 M HCl. The particles consisted of different PVP/Eudragit® E/fenofibrate blends (the m/m/m ratios are indicated in the diagrams), all systems contained 10 % drug.

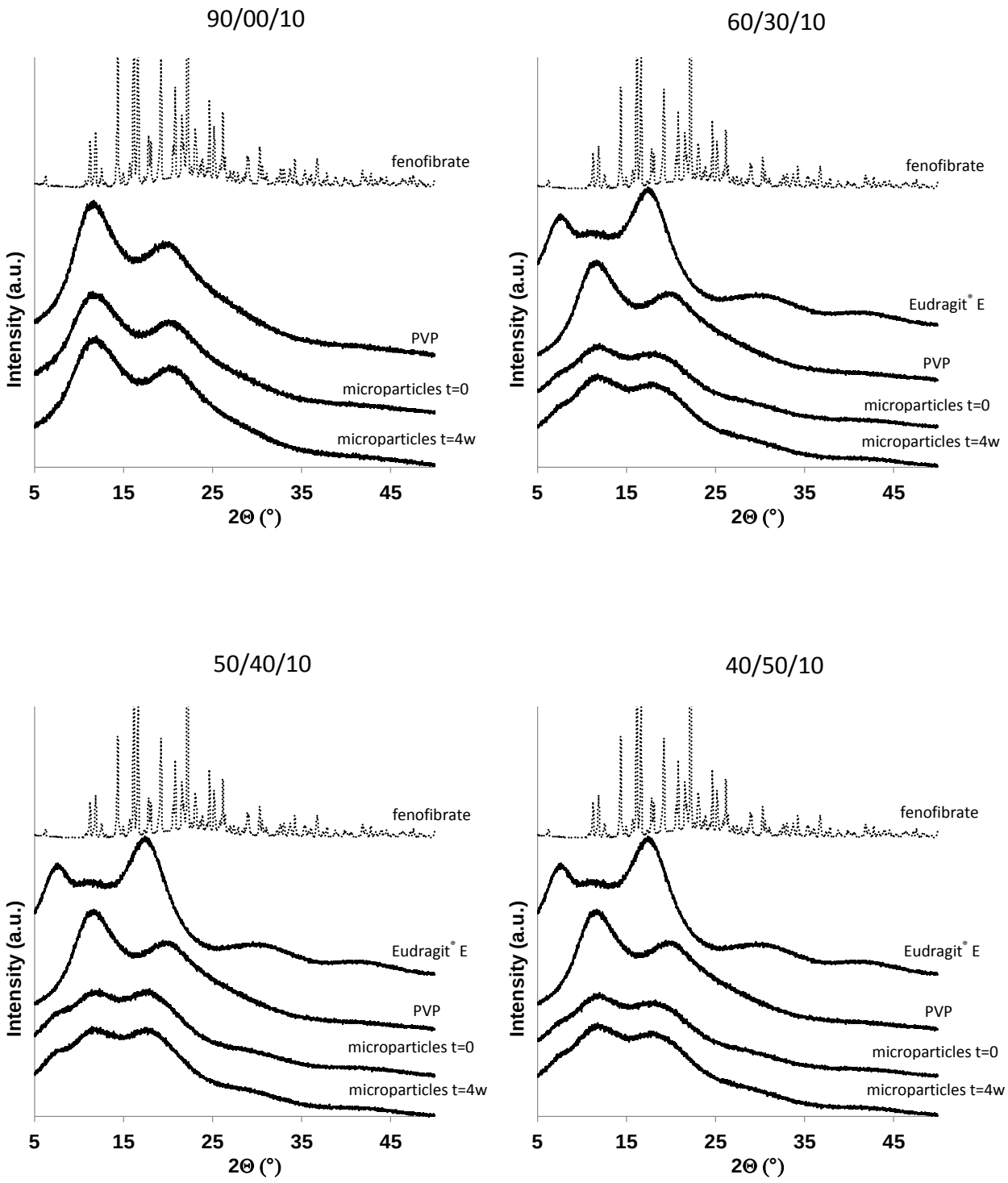

Figure IV.2 X-ray diffraction patterns of fenofibrate powder (as received), PVP powder (as received), Eudragit® E powder (as received), and PVP/Eudragit® E/fenofibrate microparticles containing 10 % drug (the composition is indicated in the diagrams) before and after storage (as indicated).

The open circles in Figure IV.3 illustrate the fenofibrate concentration time profiles measured upon exposure of 70/00/30 and 40/30/30 PVP/Eudragit® E/fenofibrate microparticles to 0.1 M HCl. In contrast to the systems described above, the drug loading was much higher: 30 versus 10 %. Again, the dissolution of drug powder (as received), and drug release from the respective physical mixtures and from the commercial product are shown for reasons of comparison. As at the lower drug loading, supersaturated solutions were obtained, which re-crystallized during the observation period. Also, the highest dissolved fenofibrate concentrations were observed with the Eudragit® E containing systems. The X-ray diffraction patterns of these microparticles (and of the reference substances) are plotted in Figure IV.4. As it can be seen, Eudragit® E containing systems did not show any sign for drug crystals, neither before, nor after storage. However, Eudragit® E free microparticles did, especially upon open storage for 1 month. This indicates that Eudragit® E is required to keep the entire fenofibrate amount in an energetically elevated state (dissolved in the polymer and/or in an amorphous state and/or in the form of extremely small crystals, which are not detectable under the given conditions) at 30 % drug loading. These findings are consistent with the observed drug release patterns after 1 month upon storage: The resulting fenofibrate release profiles remained unaltered in the case of Eudragit® E containing microparticles, but exhibited lower peak concentrations in the case of Eudragit® E free microparticles (dotted curves in Figure IV.3). Thus, the observed onset of re-crystallization in Eudragit® E free microparticles impacts fenofibrate release. It has to be pointed out that it can be expected that these solid-solid state transitions will continue upon further storage. Hence, it is likely that drug release further slows down with time in Eudragit® E free microparticles at high drug loadings. Note that the Eudragit® E-driven increase in fenofibrate solubility for microparticles containing the same relative amount of this polymer (30 %) is lower in Figure IV.3 (formulation 40/30/30 PVP/Eudragit® E/fenofibrate) compared to Figure. IV.1 (formulation 60/30/10 PVP/Eudragit® E/fenofibrate). This is due to the lower relative final Eudragit® E content in the bulk fluid: In all cases, formulations containing 145 mg fenofibrate were exposed to 500 mL medium. Thus, more microparticles loaded with only 10 % fenofibrate (and, thus, more Eudragit® E) were (was) exposed to the same liquid volume compared to microparticles loaded with 30 % drug.

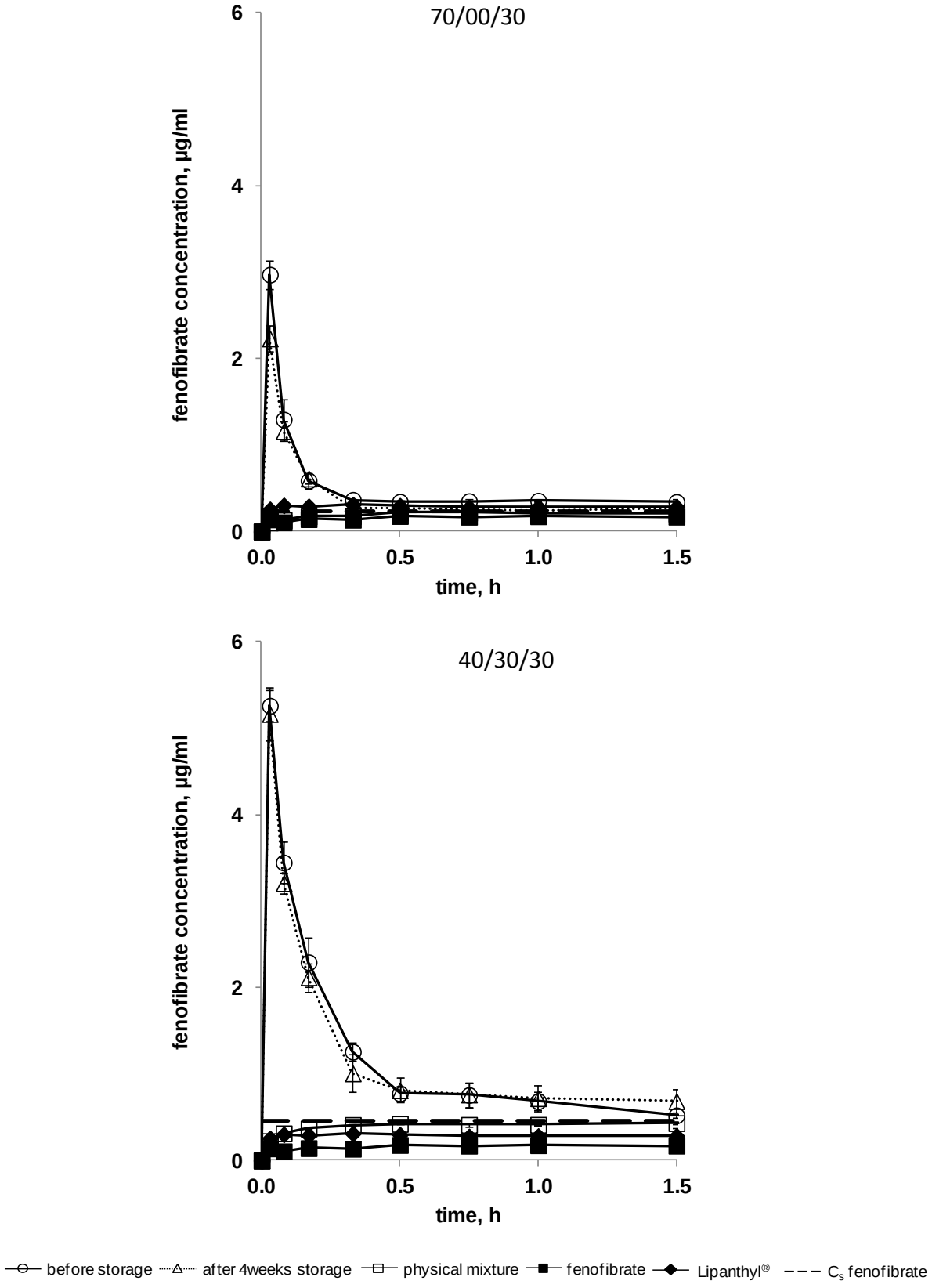

Figure IV.3 Dynamic changes in the concentration of dissolved fenofibrate in the release medium upon exposure of spray-dried microparticles to 0.1 M HCl. The particles consisted of different PVP/Eudragit® E/fenofibrate blends (the m/m/m ratios are indicated in the diagrams), all systems contained 30 % drug.

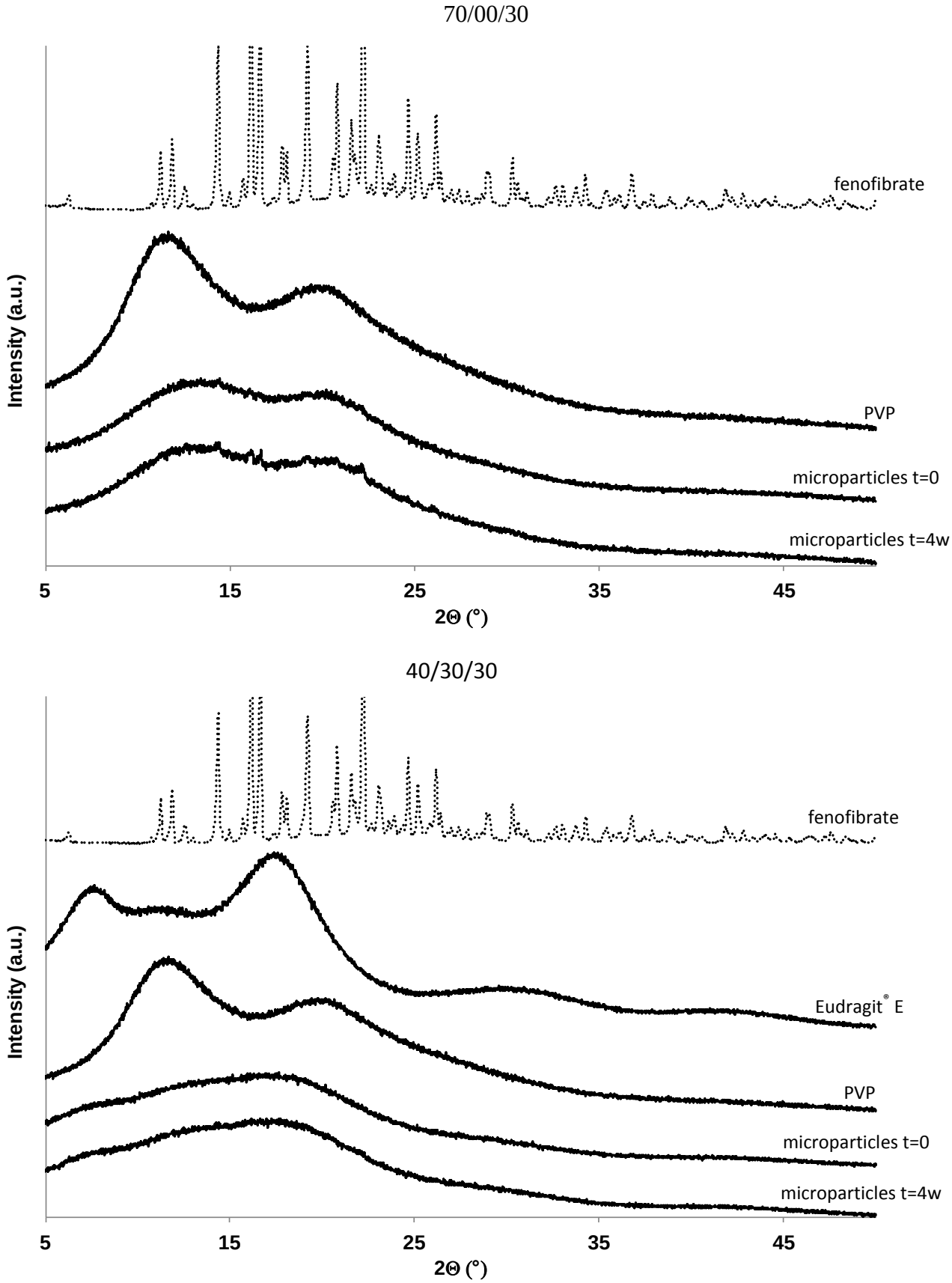

Figure IV.4 X-ray diffraction patterns of fenofibrate powder (as received), PVP powder (as received), Eudragit® E powder (as received), and PVP/Eudragit® E/fenofibrate microparticles containing 30 % drug (the composition is indicated in the diagrams) before and after storage (as indicated).

III.2. HPMC/Eudragit® E blends

The open circles in Figure IV.5 show the resulting concentration time profiles of dissolved fenofibrate upon exposure of microparticles based on different HPMC/Eudragit® E/drug blends to 0.1 M HCl. The drug loading was 10 % in all cases. Again, the behavior of the respective physical mixtures, drug powder (as received) and of the commercial drug product are illustrated for reasons of comparison and the dashed lines indicate fenofibrate solubility in the release medium containing the corresponding amounts of co-dissolved polymers. In contrast to PVP, the presence of co-dissolved HPMC increased fenofibrate solubility (Table IV.1), and the respective HPMC/Eudragit® E blends led to higher drug solubility values than the corresponding PVP/ Eudragit® E blends (2.27-3.41 µg/mL compared to 1.58-2.78 µg/mL at 37 °C, see also dashed straight lines in Figure IV.5 versus Figure IV.1). This explains the higher fenofibrate concentrations observed with the different physical blends and higher final plateau values observed with the microparticle formulations when comparing HPMC- and PVP-based systems (Figure IV.5 versus Figure IV.1). Importantly, again, supersaturated and metastable drug solutions were obtained with all types of microparticles (Figure IV.5). The X-ray diffraction patterns of the formulations (Figure IV.6) showed that this can again be attributed to the physical state of the fenofibrate in the microparticles: being dissolved in the polymer network and/or in an amorphous state and/or in the form of extremely small crystals, which are not detectable under the given conditions. Importantly, no changes were observed in the X-ray patterns upon 1 month open storage at ambient conditions for any formulation and the fenofibrate release kinetics remained unaltered (dotted versus solid curves in Figure IV.5). However, when increasing the drug loading from 10 to 30 % in HPMC containing microparticles, this behavior changed: As it can be seen in Figure IV.7, the drug release rate decreased upon 1 month open storage, irrespective of the presence or absence of Eudragit® E (dotted versus solid curves). This is because the drug re-crystallized during storage, as evidenced by X-ray diffraction (Figure IV.8). In the case of Eudragit® E free microparticles, fenofibrate crystals were present even before storage and their proportion increased with time. In the case of Eudragit® E containing microparticles, the system was initially X-ray amorphous, but clear diffraction peaks became visible upon storage. Thus, at high drug loadings, great caution should be paid.

Particle size effects are unlikely to play a major role for the above discussed differences between the release kinetics from the investigated microparticles, since the particle sizes of all systems were in the same order of magnitude (around 10 µm).

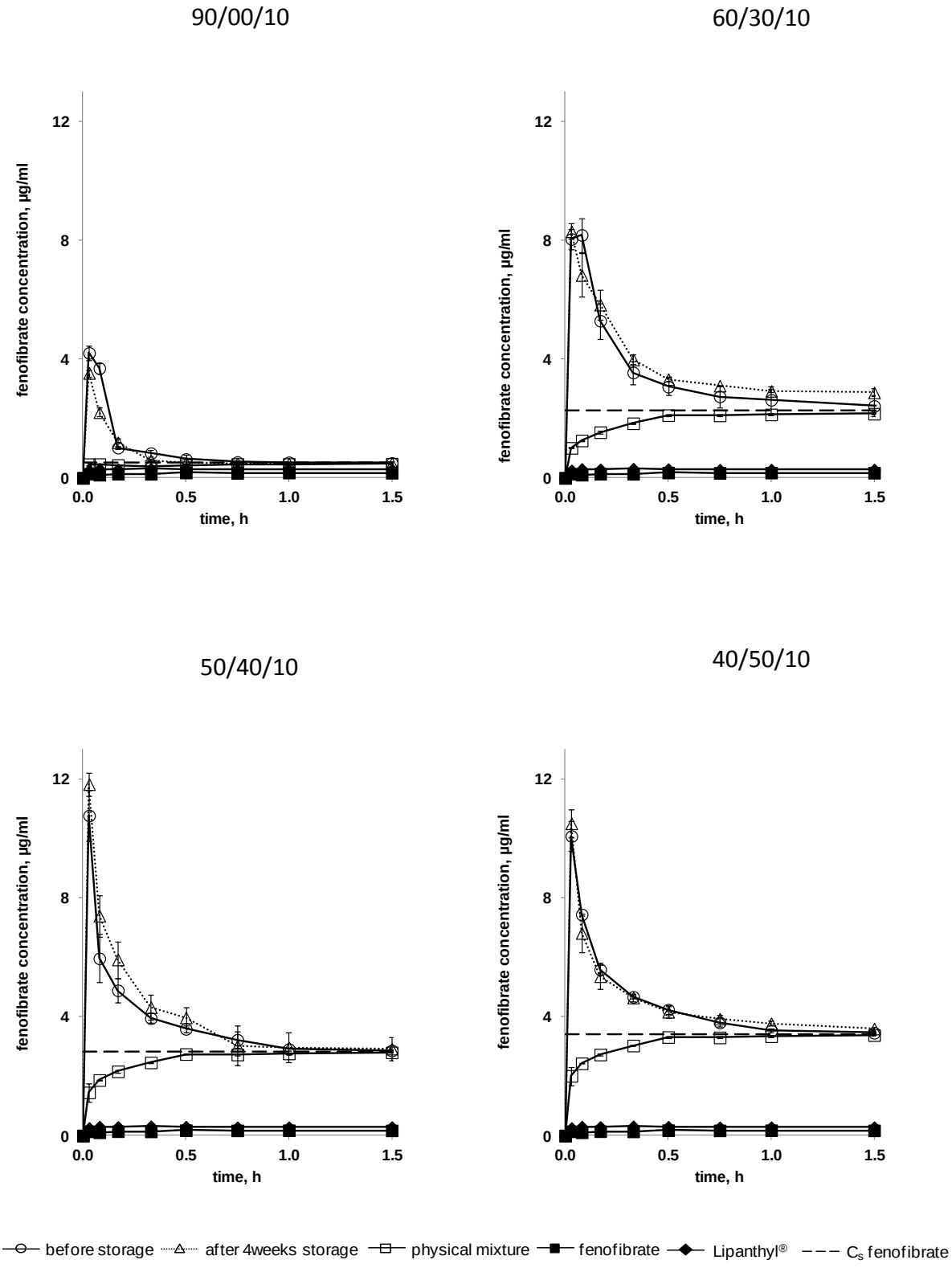

Figure IV.5 Dynamic changes in the concentration of dissolved fenofibrate in the release medium upon exposure of spray-dried microparticles to 0.1 M HCl. The particles consisted of different HPMC/Eudragit® E/fenofibrate blends (the m/m/m ratios are indicated in the diagrams), all systems contained 10 % drug.

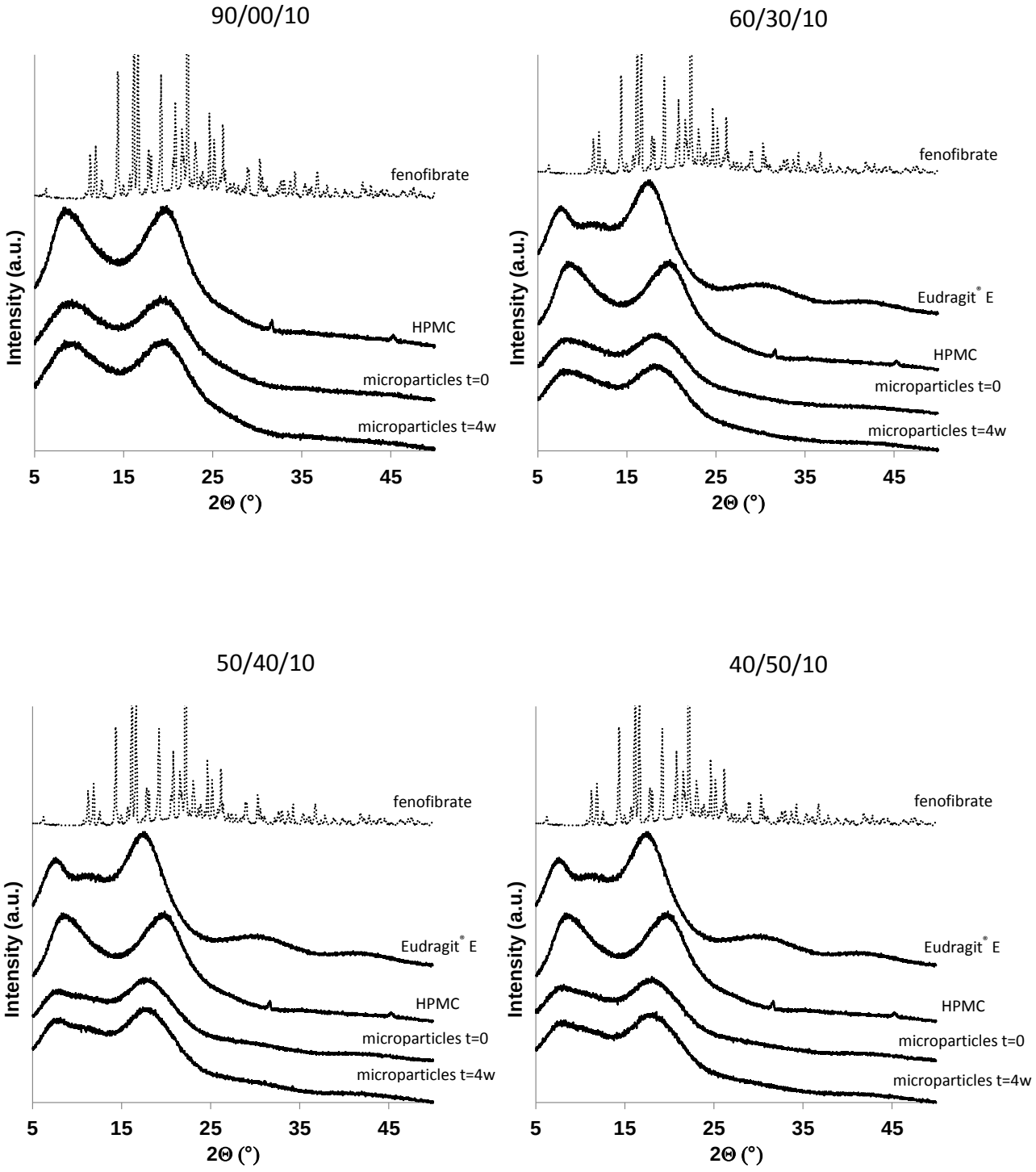

Figure IV.6 X-ray diffraction patterns of fenofibrate powder (as received), HPMC powder (as received), Eudragit® E powder (as received), and HPMC/Eudragit® E/fenofibrate microparticles containing 10 % drug (the composition is indicated in the diagrams) before and after storage (as indicated).

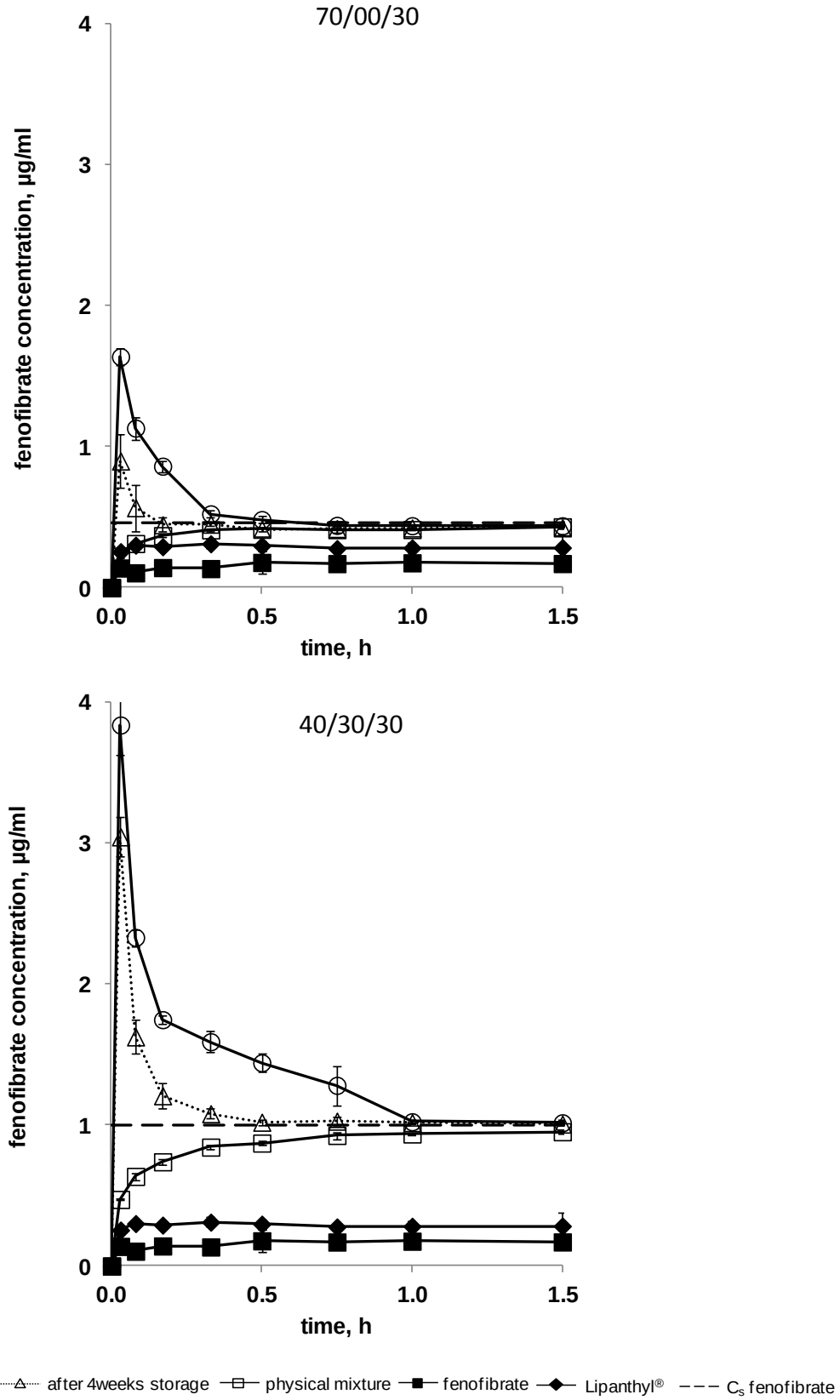

Figure IV.7 Dynamic changes in the concentration of dissolved fenofibrate in the release medium upon exposure of spray-dried microparticles to 0.1 M HCl. The particles consisted of different HPMC/Eudragit® E/fenofibrate blends (the m/m/m ratios are indicated in the diagrams), all systems contained 30 % drug.

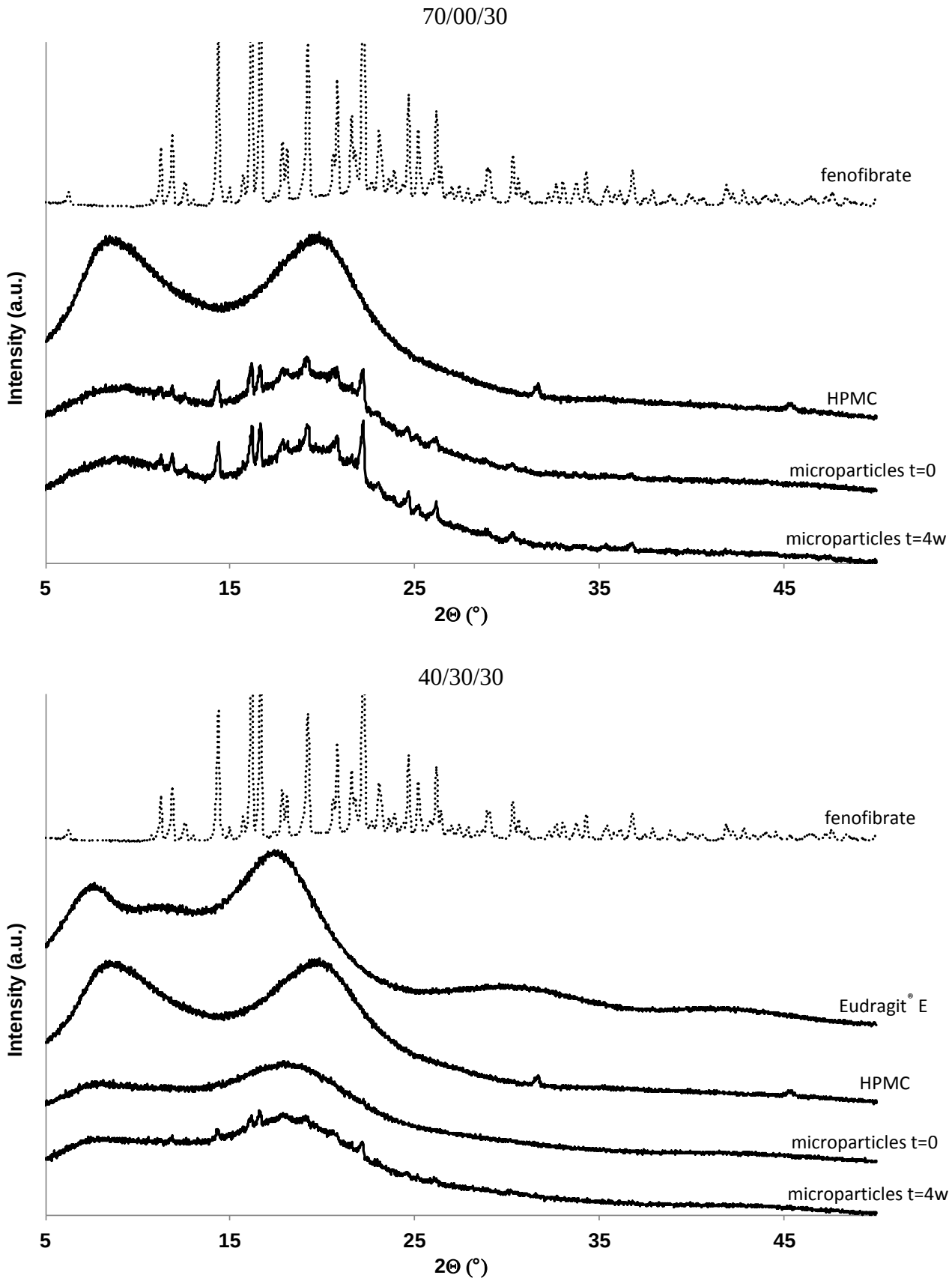

Figure IV.8 X-ray diffraction patterns of fenofibrate powder (as received), HPMC powder (as received), Eudragit® E powder (as received), and HPMC/Eudragit® E/fenofibrate microparticles containing 30 % drug (the composition is indicated in the diagrams) before *and after storage (as indicated).*

IV. Conclusion

Polymer blends offer an interesting potential to improve the release kinetics of poorly water-soluble drugs, since advantageous properties of the respective single polymers can be combined. However, such systems are not “simple” and care has to be taken when optimizing them. Ideally, system optimization is based on a mechanistic understanding of drug release.

Acknowledgements

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GENERAL CONCLUSION

Poor aqueous solubility has become a property of numerous new drug candidates causing major concern. Despite a potentially ideal chemical structure allowing for interaction with the target, these substances fail to be effective in vivo: upon administration, they cannot dissolve sufficiently in the aqueous fluids of the body and, thus, cannot be transported to their site of action to reach therapeutically effective concentrations. Various interesting strategies have been proposed to overcome this crucial hurdle, thus amorphous solid dispersions, which is one of the most promising ones. They present numerous advantages over the others ways such as an improved wetting, the particle size reduction to the last state with a molecularly dissolved/dispersed drug avoiding the required energy to break up the crystal lattice, simplicity of the manufacturing and a reduced agglomeration. However, although these systems have been widely and intensively studied since more than 50 years, only around twenty have reached the market since 1975. This is principally due to physico-chemical stability problem of such systems and some questions are still under investigation, especially concerning the stabilization of the amorphous form and the role of the various formulation and process parameters as well as the relationship existing between all the different implied mechanisms (Chapter I). This work has contributed to highlight the important points which have to be taken into account during development of such type of formulation.

Solid dispersions have been studied for more than 40 years and lead to numerous interesting research articles. However, today, only a few products have reached the market principally due to problems with the physico-chemical stability. The idea is to transform the crystalline raw material into a physical state having a greater energy in order to increase the driving force for drug dissolution. At the same time, the system should be stable during long term storage, thus, re-crystallization or other system changes, resulting in altered drug release rates, must be avoided. Different manufacturing techniques can be used to prepare such polymeric drug delivery systems, including hot-melt extrusion and spray-drying.

The main objective of this work has been to improve apparent drug solubility by forming solid dispersions using the two most employed techniques: hot-melt extrusion and spray-drying. In this study ketoprofen has been incorporated into hydrophilic polymeric

matrices to increase its apparent aqueous solubility. Both techniques have been applied and Eudragit® E has been considered to be an interesting matrix former in this case, as it is thermoplastic, provides sufficient thermal stability for hot-melt extrusion, rapidly dissolves at acidic pH and can interact with acidic drugs due to its multiple tertiary ammonium groups. Binary "drug-Eudragit®E" as well as ternary "drug-Eudragit®E-PVP", "drug-Eudragit®E-PVPVA", "drug-Eudragit®E-HPMC" combinations were investigated and characterized using X-ray diffraction, mDSC, SEM, optical macro/microscopy, and drug release measurements in 0.1 M HCl before and after storage. Drug release has been intentionally monitored under non-sink conditions, in order to evaluate the potential of the formulations to provide super-saturated solutions and the life-time of the latter. In all cases ketoprofen release was much faster compared to a commercially available product and the dissolution of the drug powder (as received). More important, super-saturated solutions could have been obtained, which were stable for at least 2 h. However, depending on the polymers used, different drug release behavior were obtained indicating that polymeric matrices aiming at accelerated release of poorly water-soluble drugs can be highly complex, since not only the composition of the systems, but also their inner structure can be of utmost importance, in particular the homogeneity/heterogeneity of excipients distribution. Subsequently, to better understand how formulation and processing parameters are affecting the release of ketoprofen in 0.1 M HCl from spray-dried microparticles based on HPMC (hydroxypropyl methylcellulose), PVPVA [poly(vinylpyrrolidone-co-vinyl acetate)], or PVP (polyvinylpyrrolidone), binary spray-dried powders loaded with 30% ketoprofen have been prepared. The main objective was to try to elucidate the impact on the resulting microstructure and conditions for drug dissolution and subsequent release. This study has been carried out in three steps: impact of the type of polymer, impact of the processing conditions with the selected polymer and drug suspension versus drug solution to prepare the spray-dried powders. The obtained systems have been thoroughly characterized using X-ray diffraction, mDSC, SEM, particle size analysis and drug release measurements in 0.1 M HCl before and after storage. Drug release has been intentionally monitored under non-sink conditions, in order to evaluate the potential of the formulations to provide super-saturated solutions and the life-time of the latter. Hydrophilic polymeric microparticles prepared by spray-drying offer a major potential to increase the release rate of poorly

soluble drugs. However, despite of their eventually rather simple composition (e.g. binary drug:polymer blends), these formulations can be highly complex, because not only the physical states of the drug and polymer, but also their spatial distribution can strongly impact drug release.

In a last part, the aim was to determine and better understood the impact of the blend ratio and drug loading on the key features of the systems, especially drug release rates. Consequently, different types of microparticles based on polymer blends, namely HPMC, PVP and Eudragit®E were prepared by spray-drying. Fenofibrate has been chosen as a model drug since it is practically insoluble in water (0.23 mg/L, 37°C), doesn't possess a carboxylic group and only few possibilities of hydrogen bonding, rapidly recrystallizes and presents a limited solubility in polymeric matrices. Fenofibrate-loaded microparticles based on PVP/Eudragit E or HPMC/Eudragit E blends were prepared by spray drying. The composition of the systems (in particular the polymer:polymer blend ratio and the drug loading) were varied and the key properties determined. This includes drug release measurements in 0.1 M HCl, X-ray diffraction studies, solubility measurements and particle size analysis. Importantly, highly supersaturated fenofibrate solutions were created upon exposure of the different types of microparticles to the release medium, in contrast to any reference formulation. Also, the presence of co-dissolved Eudragit E led to a significant increase in fenofibrate solubility. Polymer blends offer an interesting potential to increase the apparent solubility of poorly water-soluble drugs, since advantageous properties can be combined. However, these are no simple systems and care has to be taken when optimizing them. Ideally, such system optimization is based on a mechanistic understanding of drug release.

To conclude, this work highlighted the following points:

(i) Formulation and process parameters are of utmost importance in particular excipients distribution in designing amorphous solid dispersions;

(ii) Eudragit® E is a promising matrix former to improve drug solubility via further methods: HME and spray-drying but also to stabilize the amorphous form.

Perspectives:

In the view of the obtained results, the perspectives of research for this work can be attached to the following points:

(i) The more profound understanding of the factors either in the formualtion (e.g. excipients distribution, homogeneity/heterogeneity of the systems) or in the process (flow rate, solvents, temperature) which govern the drug release;

(ii) In vivo evaluation of the best systems in order to evaluate the efficiency of the solubility enhancement obtained in vitro;

(iii) Broaden the spectra of drugs which can be formulated as amorphous solid dispersions.

SUMMARY

Amorphous solid dispersions represent an attractive way to improve drug solubility, while ensuring a better patient compliance due to a decrease of the administered dose but also of the side effects. Today, hot-melt extrusion and spray-drying techniques represent the two most used techniques to prepare this type of advanced drug delivery systems.

The main objective of this work was to increase the apparent solubility of poorly-water soluble drug. In this study ketoprofen has been incorporated into various hydrophilic polymeric matrices. The intention was to transform the crystalline material into a physical state with a higher energy in order to increase the driving force for drug dissolution. However, at the time, the system should be stable during long term storage to avoid an alteration in the drug release rates. Various techniques can be used to prepare such polymeric drug delivery systems, of which hot-melt extrusion and spray-drying. Furthermore, Eudragit®E has been considered as an interesting matrix in this case, since it rapidly dissolves at acidic pH, can interact with acidic drugs due to its multiple tertiary ammonium groups and provides a sufficient thermal stability for hot-melt extrusion. Ketoprofen-loaded, Eudragit®E based hot-melt extrudates and spray-dried powders have been prepared. The obtained systems were characterized using various techniques (scanning electron microscopy, optical macro/microscopy). The physical state of the drug and the polymer was analyzed using X-ray diffraction and modulated differential scanning calorimetry (mDSC). The in vitro drug release measurement was studied using agitated flasks, intentionally monitored under non sink conditions. Irrespective of the polymer blends used, super-saturated solutions were obtained and remained stable throughout the observation period. Interestingly, polymeric matrices aiming at accelerated release of poorly water-soluble drugs can be highly complex, since not only the composition of the systems, but also their inner structure can be of utmost importance, in particular the spatial distribution of the excipients.

Furthermore, it’s well-known that formulation and processing parameters had a tremendous impact on the key properties of spray-dried microparticles containing poorly-water soluble drugs. However, yet relatively little is known on the impact on the inner particles’ structure. The main objective was to better understand how formulation and

processing parameters affect the release of ketoprofen in acidic media. In this matter, some formulation and process parameters were varied during the preparation of the spray-dried powders based on ketoprofen. Spray-drying offers a major potential to increase the release rate of poorly soluble drugs. However, despite of their eventually rather simple composition (e.g. binary drug:polymer blends), these formulations can be highly complex, because not only the physical states of the drug and polymer, but also their spatial distribution can strongly impact drug release. Subsequently, it's well-known from other fields that polymer:polymer blends can be highly useful, since the systems' performance can effectively be adjusted by simply varying the blend ratio. However, yet relatively little is known on the impact of the use of polymer blends and the impact of simply varying the polymer:polymer blend ratio on the key properties of the systems. Consequently, this work was intended to determine and try to understand the impact of the blend ratio and drug loading on the key features of the systems, in particular drug release rates. Fenofibrate loaded microparticles based on HPMC, PVP and Eudragit®E were prepared at different drug loading and different polymer blend ratios. To characterize the resulting formulations, X-ray studies, particle size and solubility measurements were done. Intentionally, non-sink conditions were provided in order to more realistically simulate in vivo conditions. These results showed that polymer blends offer an interesting potential to increase the apparent solubility of poorly water-soluble drugs, since advantageous properties can be combined. However, these are no simple systems and care has to be taken when optimizing them. Ideally, such system optimization is based on a mechanistic understanding of drug release.

Keywords: solid dispersions, poorly-water soluble drugs, amorphous form, solubility enhancement, hot-melt extrusion, spray-drying

RESUME

Les dispersions solides amorphes représentent une voie attractive pour l'amélioration de la solubilité des principes actifs tout en assurant une meilleure compliance du patient du fait de la réduction des doses administrées et des effets secondaires. Aujourd'hui l'extrusion en phase chauffante et l'atomisation-séchage représentent les deux techniques les plus utilisées pour préparer ce type de systèmes avancés.

Le principal objectif de travail a été d'améliorer la solubilité apparente de principes actifs peu hydrosolubles. Dans cette étude, le kétoprofène a été incorporé dans diverses matrices polymériques hydrophiles : l'idée étant de transformer le matériel cristallin en un état physique de plus haute énergie afin d'augmenter les forces régissant la dissolution de la substance active. Cependant, dans le même temps, le système doit rester stable durant le stockage à long terme pour éviter une altération du taux de libération du principe actif. Plusieurs techniques peuvent être utilisées pour préparer ce type de systèmes polymériques dont l'extrusion en phase chauffante et l'atomisation-séchage. De plus l'Eudragit®E a été considérée comme une matrice intéressante pour plusieurs raisons : il se dissout rapidement à pH acide, peut interagir avec les groupements acides grâce à ses multiples ammoniums ternaires et fournit une stabilité thermique suffisante pour l'extrusion en phase chauffante. Des extrudats et des microparticules comprenant de l'Eudragit®E et chargés en kétoprofène ont été préparés. Les systèmes obtenus ont été caractérisés au moyen de différentes techniques (microscopie électronique à balayage, macro/microscopie optique). L'état physique du principe actif et du polymère a été analysé par diffraction des rayons X et calorimétrie différentielle à balayage modulé (mDSC). Les libérations in vitro ont été réalisées en flacons agités et intentionnellement conduites en conditions « non sink ». Quels que soient les polymères utilisés, des solutions sur-saturées sont obtenues et restent stables durant toute la période d'observation. De manière intéressante, les matrices polymériques qui ont pour but d'accélérer la libération des principes actifs peu hydrosolubles peuvent être très complexes, puisqu'il n'y a pas seulement la composition du système mais aussi sa structure interne qui peuvent être d'une extrême importance, en particulier la distribution spatiale des excipients.

De plus, il est reconnu que les paramètres de formulation et de procédé ont un important impact sur les propriétés clés des microparticules atomisées-séchées contenant une substance peu hydrosoluble. Cependant, peu d'informations sont disponibles sur l'impact sur la structure interne des particules. Le principal objectif a été de mieux comprendre comment les paramètres de formulation et de procédé affectent la libération du kétoprofène en milieu acide. Dans cette optique, plusieurs paramètres de formulation et de procédé ont été modifiés durant la préparation des microparticules chargées en kétoprofène. L'atomisation-séchage offre un énorme potentiel dans l'augmentation du taux de libération du principe actif. Cependant, malgré leur éventuelle composition plutôt simple (e.g. mélange binaire principe actif:polymère), ces formulations peuvent être très complexes, puisqu'il n'y a pas seulement l'état physique dans lequel se trouvent le principe actif et le polymère mais aussi leur distribution spatiale qui peut fortement impacter la libération du principe actif. Par la suite, il est aussi reconnu que dans d'autres domaines d'applications pharmaceutiques les mélanges polymère: polymère peuvent être hautement utiles, puisque les performances du système peuvent être ajustées simplement par variation du ratio. Cependant, peu de choses sont encore connues sur l'impact de l'utilisation de mélanges de polymères et l'impact d'une simple variation du ratio des différents polymères sur les propriétés clés du système. Par conséquence, ce travail a voulu déterminer et essayer de comprendre l'impact du ratio des différents polymères et du taux de charge en principe actif sur les propriétés clés des systèmes, en particulier sur le taux de libération de la substance active. Des microparticules chargées en fénofibrate et basée sur l'HPMC, la PVP et l'Eudragit®E ont été préparées à différents taux de charge et différents ratios de mélanges de polymères. Pour caractériser les formulations résultantes, les études de libération du principe actif dans l'HCl 0.1 M, la diffraction des rayons X, les mesures de solubilités et l'analyse de la taille des particules ont été effectuées. Des conditions « non-sink » ont été intentionnellement utilisées pour simuler de façon plus réaliste les conditions in vivo. Les mélanges de polymères offrent un potentiel intéressant pour augmenter la solubilité apparente des principes actifs faiblement solubles, puisque les propriétés avantageuses peuvent être combinées. Cependant, il n'y a pas de systèmes simples et il faut être prudent dans l'optimisation de tels systèmes. Idéalement, leur optimisation

devrait se faire au moyen d'une compréhension mécanistique de la libération du principe actif.

Mots-clés : dispersions solides, principe actif faiblement soluble, amorphe, amélioration solubilité, extrusion en phase chauffante, atomisation-séchage