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Pharmaceutical Amorphous Solid Dispersions

John Wiley & Sons Providing a roadmap from early to late stages of drug development, this book overviews amorphous solid dispersion technology – a leading platform to deliver poorly water soluble drugs, a major hurdle in today’s pharmaceutical industry. • Helps readers understand amorphous solid dispersions and apply techniques to particular pharmaceutical systems • Covers physical and chemical properties, screening, scale-up, formulation, drug product manufacture, intellectual property, and regulatory considerations • Has an appendix with structure and property information for polymers commonly used in drug development and with marketed drugs developed using the amorphous sold dispersion approach • Addresses global regulatory issues including USA regulations, ICH guidelines, and patent concerns around the world

Amorphous Solid Dispersions

Theory and Practice

Springer This volume offers a comprehensive guide on the theory and practice of amorphous solid dispersions (ASD) for handling challenges associated with poorly soluble drugs. In twenty-three inclusive chapters, the book examines thermodynamics and kinetics of the amorphous state and amorphous solid dispersions, ASD technologies, excipients for stabilizing amorphous solid dispersions such as polymers, and ASD manufacturing technologies, including spray drying, hot melt extrusion, fluid bed layering and solvent-controlled micro-precipitation technology (MBP). Each technology is illustrated by specific case studies. In addition, dedicated sections cover analytical tools and technologies for characterization of amorphous solid dispersions, the prediction of long-term stability, and the development of suitable dissolution methods and regulatory aspects. The book also highlights future technologies on the horizon, such as supercritical fluid processing, mesoporous silica, KinetiSol®, and the use of non-salt-forming organic acids and amino acids for the stabilization of amorphous systems. Amorphous Solid Dispersions: Theory and Practice is a valuable reference to pharmaceutical scientists interested in developing bioavailable and therapeutically effective formulations of poorly soluble molecules in order to advance these technologies and develop better medicines for the future.

Investigation of Amorphous Solid Dispersions for Solubility Enhancement of Poorly Water-soluble Drugs

Understanding the Effect of Material Properties on Amorphous Drug Crystallization and the Impact on Formulation Performance

The preparation of amorphous solid dispersions (ASDs) has enabled the development of oral dosage forms for many poorly water-soluble compounds. The aim of the work presented in this dissertation is to advance our understanding of ASDs, specifically their long-term stability with respect to crystallization and the implications of instability on product performance. Advancing knowledge in these areas is pivotal for the pharmaceutical industry and its efforts in drug discovery. Much of our understanding of ASD stability results from empirical or extrapolative models that have been applied to describe stability. Their application has been limited and they do not provide fundamental insights into the recrystallization process to aid in the rationale development in ASDs. Notably, they fail to consider supersaturation as the driving force for crystallization, diffusivity in viscous systems, and interfacial effects. The works presented in this dissertation model the mechanisms of crystal nucleation and growth in ASDs by incorporating these concepts, develop and apply characterization tools to determine critical model parameters, and study the effects of crystallization on product performance.

The Development of Sulfadoxine and Nevirapine Pharmaceutical Amorphous Solid Dispersions

Sulfadoxine -- Nevirapine -- Pharmaceutical amorphous solid dispersion (PhASD) -- Nanocrystalline solid dispersion -- Polymers -- PVP25 -- Solvent evaporation -- Spray-dry -- Dissolution -- Solubility -- Accelerated stability studies.

Solid-State Properties of Pharmaceutical Materials

John Wiley & Sons Solid-State Properties of Pharmaceutical Materials -- Contents -- Preface -- Acknowledgments -- 1 Solid-State Properties and Pharmaceutical Development -- 1.1 Introduction -- 1.2 Solid-State Forms -- 1.3 ICH Q6A Decision Trees -- 1.4 "Big Questions" for Drug Development -- 1.5 Accelerating Drug Development -- 1.6 Solid-State Chemistry in Preformulation and Formulation -- 1.7 Learning Before Doing and Quality by Design -- 1.8 Performance and Stability in Pharmaceutical Development -- 1.9 Moisture Uptake -- 1.10 Solid-State Reactions -- 1.11 Noninteracting Formulations: Physical Characterizations -- References -- 2 Polymorphs -- 2.1 Introduction -- 2.2 How Are Polymorphs Formed? -- 2.3 Structural Aspect of Polymorphs -- 2.3.1 Configurational Polymorphs -- 2.3.2 Conformational Polymorphs -- 2.4 Physical, Chemical, and Mechanical Properties -- 2.4.1 Solubility -- 2.4.2 Chemical Stability -- 2.4.3 Mechanical Properties -- 2.5 Thermodynamic Stability of Polymorphs -- 2.5.1 Monotropy and Enantiotropy -- 2.5.2 Burger and Rambergers Rules -- 2.5.3 vant Hoff Plot -- 2.5.4 DG/Temperature Diagram -- 2.6 Polymorph Conversion -- 2.6.1 Solution-Mediated Transformation -- 2.6.2 Solid-State Conversion -- 2.7 Control of Polymorphs -- 2.8 Polymorph Screening -- 2.9 Polymorph Prediction -- References -- 3 Solvates and Hydrates -- 3.1 Introduction -- 3.2 Pharmaceutical Importance of Hydrates -- 3.3 Classification of Pharmaceutical Hydrates -- 3.4 Water Activity -- 3.5 Stoichiometric Hydrates -- 3.6 Nonstoichiometric Hydrates -- 3.7 Hydration/Dehydration -- 3.8 Preparation and Characterization of Hydrates and Solvates -- References -- 4 Pharmaceutical Salts -- 4.1 Introduction -- 4.2 Importance of Pharmaceutical Salts -- 4.3 Weak Acid, Weak Base, and Salt -- 4.4 pH-Solubility Profiles of Ionizable Compounds

Understanding the Thermodynamics and Oral Absorption Potential of Pharmaceutical Amorphous Solid Dispersions

Recent Progress in Solid Dispersion Technology

MDPI Amorphous solid dispersion (ASD) is a powerful formulation technology to improve oral absorption of poorly soluble drugs. Despite their being in existence for more than half a century, controlling ASD performance is still regarded as difficult because of ASD's natural non-equilibrium. However, recent significant advances in ASD knowledge and technology may enable a much broader use of ASD technology. This Special Issue, which includes 3 reviews and 6 original articles, focuses on recent progresses in ASD technology in hopes of helping to accelerate developmental studies in the pharmaceutical industry. In striving for a deep understanding of ASD non-equilibrium behavior, the Special issue also delves into and makes progress in the theory of soft-matter dynamics.

Preparation and Characterization of Carvedilol and Indomethacin Amorphous Solid Dispersions

Amorphous solid dispersions provide one of the few approaches available for improving the solubility of poorly water-soluble active pharmaceutical ingredients. They are mainly 2-component systems consisting of drug and polymer, where the amorphous drug is molecularly dispersed in an amorphous polymer matrix. The presence of polymer helps to maintain the drug in an amorphous state, which is thermodynamically unstable due to the possession of excess Gibbs free energy, enthalpy and entropy. To delay or prevent crystallization, the molecular mobility of the amorphous glass should be sufficiently low to avoid nuclei formation and crystal growth and is achieved by the maintaining the amorphous solid dispersion at a specific storage temperature and conditions, together with strong drug-polymer interactions. One of the major preparation processes for amorphous solid dispersions involves hot melt extrusion, producing solid dispersions at elevated temperatures without solvents. Four amorphous solid dispersions of 20% and 40% (w/w) carvedilol and indomethacin were manufactured using HPMC-AS as a polymeric carrier. Solid dispersions were characterized as freshly manufactured powders, as they were during a 1-month stability study using various analytical methods. Attention was paid to the molecular interactions in solid dispersions, miscibility, phase separation, crystallinity and molecular mobility. Solid dispersions of carvedilol exhibited satisfactory stability, which was reflected in preservation of amorphous carvedilol due to the sufficiently high glass transition temperature of the solid dispersions and the drug-polymer interactions. Indomethacin solid dispersions demonstrated the importance of drug loading in solid dispersions, together with the moderate or weak intermolecular interactions between drug and polymer. The enthalpy relaxation provides information regarding the lower molecular mobility of carvedilol in solid dispersions, indicating sufficient stabilization of amorphous drug by the selected polymer. Moreover, the intermolecular interactions were studied below and higher than the glass transition of the mixtures with different drug loadings, using temperature-dependent infrared spectroscopy. During this experiment, it was found that the intermolecular hydrogen bonds varied with the composition and measured temperature, resulting in disruption of intermolecular hydrogen bonds after passing the glass transition temperature.

Generation of High Drug Loading Amorphous Solid Dispersions by Different Manufacturing Processes

The main difficulty when an Active Pharmaceutical Ingredient (API) is orally administered is to guarantee that the clinical dose of the API will be dissolved in the available volume of gastrointestinal fluids. However, about 40% of APIs with market approval and nearly 90% of molecules in the discovery pipeline are poorly water-soluble and exhibits a poor oral absorption, which leads to a weak bioavailability. Amorphous solid dispersions (ASD) are considered as one of the most effective strategies to solve solubility limitations of poorly-water soluble compounds and hence, enhance their oral bioavailability. Despite their introduction as technical strategy to enhance oral APIs bioavailability more than 50 years ago, ASD formation and physical stability remains a subject of intense research. Indeed, several factors can influence the physical storage stability of ASD, among them, the glass transition temperature of the API-carrier binary mixture, the apparent solubility of the API in the carrier, interactions between API and carrier, and the manufacturing process. This thesis consisted of two parts that aim on developing new formulations of ASD of an antiretroviral API, Efavirenz (EFV), dispersed in an amphiphilic polymer, Soluplus, by using two different processes, Spray-drying (SD) and Hot-melt extrusion (HME). EFV is the class II BCS API of our choice because it is a challenging API for new formulations. It needs higher-dosed ASDs, for which chemical and physical stability during storage and dissolution will be critical. Aiming a rational development of high-loaded EFV-Soluplus ASDs, the first part focused on the construction of a temperature- composition EFV-Soluplus phase diagram. The phase-diagram was constructed from a thermal study of recrystallization of a supersaturated ASD (85 wt% in EFV), generated by spray drying. To our knowledge, this is the first study reporting a phase-diagram for this binary system. This phase-diagram is very useful and demonstrated that the EFV solubility in Soluplus ranges from 20 wt% (25 °C) to 30 wt% (40 °C). ASD of EFV in Soluplus containing more than 30 wt% of EFV should be monitored over storage under typical temperature conditions. This phase-diagram might be considered as a preformulation tool for researchers studying novel ASD of EFV in Soluplus, to predict (thermodynamic and kinetic) stability. ASD prepared by different techniques can display differences in their physicochemical properties. The second part of this thesis focused on the manufacturing of ASD by HME or SD processes. This study clearly shows that ASD is a useful formulation strategy to improve the aqueous solubility and the dissolution rate of EFV from EFV-Soluplus binary mixtures. HME and SD manufacturing processes demonstrated to be efficient to generate ASDs in a large range of compositions and loads of EFV. The optimization of EFV to Soluplus ratio can be used to tailor the release kinetics from ASD. The choice of a high EFV load exceeding the thermodynamic solid solubility in Soluplus is possible but it needs the consideration of its kinetic stability over time.

Pharmaceutical Solid Dispersion Technology

CRC Press There has not, until now, been a single up-to-date volume to provide those in drug R&D with practical information on all aspects of solid dispersion technology for drugs. This forthcoming volume finally provides such a guide and reference. The unified presentation by a team of specialists in this field is designed for practical application. Theoretical concepts are covered for a fuller understanding of current techniques. All significant recent developments are included.

Developing Solid Oral Dosage Forms

Pharmaceutical Theory and Practice

Academic Press Developing Solid Oral Dosage Forms: Pharmaceutical Theory and Practice, Second Edition illustrates how to develop high-quality, safe, and effective pharmaceutical products by discussing the latest techniques, tools, and scientific advances in preformulation investigation, formulation, process design, characterization, scale-up, and production operations. This book covers the essential principles of physical pharmacy, biopharmaceutics, and industrial pharmacy, and their application to the research and development process of oral dosage forms. Chapters have been added, combined, deleted, and completely revised as necessary to produce a comprehensive, well-organized, valuable reference for industry professionals and academics engaged in all aspects of the development process. New and important topics include spray drying, amorphous solid dispersion using hot-melt extrusion, modeling and simulation, bioequivalence of complex modified-released dosage forms, biowaivers, and much more. Written and edited by an international team of leading experts with experience and knowledge across industry, academia, and regulatory settings Includes new chapters covering the pharmaceutical applications of surface phenomenon, predictive biopharmaceutics and pharmacokinetics, the development of formulations for drug discovery support, and much more Presents new case studies throughout, and a section completely devoted to regulatory aspects, including global product regulation and international perspectives

Thermokinetic Processing of Supersaturating and Mucoadhesive Amorphous Solid Dispersions

Thermal processing of amorphous solid dispersions continues to gain interest in the pharmaceutical industry, as evident by several recently approved commercial products. Still, a number of pharmaceutical polymer carriers exhibit thermal or viscoelastic limitations in thermal processing, especially at smaller scales. Additionally, active pharmaceutical ingredients with high melting points and /or that are thermally labile present their own specific challenges. A number of formulation and process driven strategies to enable thermal processing of challenging compositions have been adopted including the use of traditional plasticizers and surfactants, temporary plasticizers utilizing sub- or supercritical carbon dioxide, designer polymers tailored for hot melt extrusion processing, and KinetiSol® Dispersing technology. The objective of the first study was to compare and contrast two thermal processing methods, HME and KinetiSol® Dispersing (KSD), and investigate the influence of polymer type, polymer molecular weight, and drug loading on the ability to produce amorphous solid dispersions (ASDs) containing the model compound griseofulvin (GRIS). Dispersions were analyzed by a variety of imaging, solid-state, thermal, and solution-state techniques. Dispersions were prepared by both HME and KSD using polyvinylpyrrolidone (PVP) K17 or hydroxypropyl methylcellulose (HPMC) E5. Dispersions were only prepared by KSD using higher molecular weight grades of HPMC and PVP, as these could not be extruded under the conditions selected. PXRD analysis showed that

dispersions prepared by HME were amorphous at 10 and 20% drug load; however, showed significant crystallinity at 40% drug load. PXRD analysis of KSD samples showed all formulations and drug loads to be amorphous with the exception of trace crystallinity seen in PVP K17 and PVP K30 samples at 40% drug load. These results were further supported by other analytical techniques. KSD produced amorphous dispersions at higher drug loads than could be prepared by HME, as well as with higher molecular weight polymers that were not processable by HME, due to its higher rate of shear and torque output. The purpose of the second study was to evaluate the feasibility of processing polyvinyl alcohol amorphous solid dispersions utilizing the model compound ritonavir with KinetiSol® Dispersing (KSD) technology. Polyvinyl alcohol has received little attention as a matrix polymer in amorphous solid dispersions (ASDs) due to its thermal and rheological limitations in extrusion processing and limited organic solubility in spray drying applications. Additionally, in extrusion processing, the high temperatures required to process often exclude thermally labile APIs. The effects of KSD rotor speed and ejection temperature on the physicochemical properties of the processed material were evaluated. Powder X-ray diffraction and modulated differential scanning calorimetry were used to confirm amorphous conversion. Liquid chromatography-mass spectroscopy was used to characterize and identify degradation pathways of ritonavir during KSD processing and 13C nuclear magnetic resonance spectroscopy was used to investigate polymer stability. An optimal range of processing conditions was found that resulted in amorphous product and minimal to no drug and polymer degradation. Drug release of the ASD produced from the optimal processing conditions was evaluated using a non-sink, pH-shift dissolution test. The ability to process amorphous solid dispersions with polyvinyl alcohol as a matrix polymer will enable further investigations of the polymer's performance in amorphous systems for poorly water-soluble compounds. The oral delivery of mucoadhesive patches has been shown to enhance the absorption of large molecules such as peptides. In this study, we hypothesized that this mechanism could have utility for poorly soluble small molecules by utilizing a mucoadhesive polymer as the matrix for an amorphous solid dispersion. Binary dispersions of itraconazole and Carbopol 71G were prepared utilizing a thermokinetic mixing process (KinetiSol Dispersing) and the physicochemical properties were investigated by powder x-ray diffraction, calorimetry, and liquid chromatography. Adhesion of the dispersions to freshly excised porcine intestine was investigated with a texture analyzer. Minitablets were compressed from the optimal dispersion and further investigated in vitro and in vivo in rats. Thermokinetic mixing successfully processed amorphous dispersions up to 30% drug loading and each dispersion exhibited works of adhesion that were approximately an order of magnitude greater than a negative control in vitro. Ethylcellulose (EC) coated and uncoated minitablets prepared with the 30% drug load dispersion were delivered orally to rats and exhibited sustained release characteristics, with overall bioavailability greater for the uncoated minitablets compared to the EC-coated minitablets, similar to the rank order observed in our in vitro dissolution experiments. Necropsy studies showed that minitablets delivered with enteric-coated capsules targeted release to the distal small intestine and adhered to the intestinal mucosa, but the rat model presented limitations with respect to evaluating the overall performance. Based on the in vitro and in vivo results, further investigations in larger animals are a logical next step where fluid volumes, pH, and transit times are more favorable for the evaluated dosage forms.

Amorphous Drugs

Benefits and Challenges

Springer This book explains theoretical and technological aspects of amorphous drug formulations. It is intended for all those wishing to increase their knowledge in the field of amorphous pharmaceuticals. Conversion of crystalline material into the amorphous state, as described in this book, is a way to overcome limited water solubility of drug formulations, in this way enhancing the chemical activity and bioavailability inside the body. Written by experts from various fields and backgrounds, the book introduces to fundamental physical aspects (explaining differences between the ordered and the disordered solid states, the enhancement of solubility resulting from drugs amorphization, physical instability and how it can be overcome) as well as preparation and formulation procedures to produce and stabilize amorphous pharmaceuticals. Readers will thus gain a well-funded understanding and find a multi-faceted discussion of the properties and advantages of amorphous drugs and of the challenges in producing and stabilizing them. The book is an ideal source of information for researchers and students as well as professionals engaged in research and development of amorphous pharmaceutical products.

Pharmaceutical Technologies for Improving Drug Loading in the Formulation of Solid Dispersions

It is estimated that 90% of new chemical entities in development pipelines exhibit poor aqueous solubility. For compounds not limited by biological membrane permeability, this poor aqueous solubility is the limiting factor in bioavailability. Therefore, the formulation of such drugs has primarily been centered on improving dissolution properties. Traditional approaches for overcoming poor aqueous solubility include salt formation of the active ingredient, complexation, the use of surface active agents, formulation into oil based systems, particle size reduction, or a combination of these methods. More recently amorphous solid dispersions have been explored. Currently, the drug loading within solid dispersions is limited resulting in large quantities of the formulation being required for a therapeutically relevant dose. In the frame of the work herein, Thin Film Freezing was utilized to generate high drug loaded amorphous solid dispersions of the poorly water soluble drug phenytoin utilizing a hydrophilic polymer or an amphiphilic graft copolymer for system stabilization. Additionally a new solvent removal technique, atmospheric freeze drying, was investigated for removal of the solvents used during Thin Film Freezing. The Thin Film Freezing materials were subsequently incorporated into a polymeric carrier for solid dispersion formulation by a novel fusion production technique termed Kinetisol® dispersing. Studies of the solid dispersions produced by Thin Film Freezing revealed an amorphous system had been obtained for both stabilizing polymers. The formulation containing a hydrophilic carrier was capable of achieving supersaturation. Conversely, the amphiphilic graft copolymer demonstrated a phenytoin-polymer interaction resulting in poor dissolution. Atmospheric freeze drying of the Thin Film Freezing product demonstrated that the alternative drying technique generated powders with significantly improved handling properties as a result of reduced electrostatic interactions due to the increased pore size, reduced surface area, larger particle size, and higher, though acceptable, residual solvent levels. The use of Thin Film Freezing powders during Kinetisol Dispersing resulted in a single phase amorphous system while solid dispersions produced from physical mixtures of bulk materials were amorphous two-phase systems. This indicates that the use of amorphous drug compositions during solid dispersion production may increase drug loading in the final system while remaining single phase in nature.

Investigation of Dissolution and Dispersion Behavior of Ritonavir from Amorphous Solid Dispersion

The aim of this study was to develop ritonavir amorphous solid dispersion (ASD) formulation, investigate its aqueous dissolution and dispersion behavior, and predict potential pharmacokinetic parameters by in-silico modeling. The binary/ternary ASDs of ritonavir with PVPVA or HPMCAS-MG in the absence or presence of surfactants were prepared by using the hot-melt extrusion method. The amount of ritonavir was fixed at 20 %w/w, while amount of polymer and surfactant in the formulation was varied. The film-casting technique was used to confirm the miscibility of drug and polymer in the absence and presence of surfactant in different formulations. PXRD and DSC analyze were carried out to determine solid state properties of the neat ritonavir and solid dispersion formulations prior to conducting dissolution and dispersion testing. All in-vitro dissolution and dispersion studies were performed under non-sink condition at pH 2 (0.01N HCl), pH 4.5 (acetate buffer), and pH 6.8 (phosphate buffer), as well as in a biorelevant medium (FeSSIF-V2). Particle size analysis of the dispersed phase after dispersion of the extrudates in aqueous media was carried out in-line using a particle size analyzer. Raman spectroscopy coupling with chemometrics method was used to identify the polymorphic form of the precipitates from the extrudates after exposing to dissolution medium. The software simulation was then carried out to predict the oral absorption based on in-vitro studies. Stability studies of the ASDs were carried out at 25°C/60%RH for 1 year and 40°C/75%RH for 1 month. Ritonavir, 20%w/w, was found to be miscible with various ratios of polymers and surfactants used. Supersaturated solutions were formed and the supersaturation was maintained throughout 2 h of dissolution testing. However, above certain concentration in dissolution media, ritonavir phase separated and formed milky dispersions. Particle size analysis of the dispersed phase revealed that nano/micro particles were generated by all ASD formulations. The biorelevant media provided much higher drug dissolution as compared to that in standard phosphate buffer medium. The slurries from the extrudates containing ritonavir:PVPVA:sorbitan monolaurate at 20:70:10 % w/w revealed that mixtures of amorphous and crystalline of ritonavir were present. The predicted fraction absorbed ranged from 65 to 90%. In the solid state, all ASDs did not show any ritonavir crystallization under both the stability testing conditions. In the present study, various factors influencing formulations, physical stability and drug release of ASDs of ritonavir were studied. It was observed that there was a good correlation between in-vitro dissolution, in-line particle size monitoring and in-silico modeling which can served as a predictive tool in pharmaceutical development of the ASD for ritonavir as well as other poorly water-soluble drugs. The dissolution and dispersion testing using biorelevant media provided more accurate results on the behavior of the drug formulation than only the result from dissolution testing in standard buffers.

Hot-Melt Extrusion

Pharmaceutical Applications

John Wiley & Sons Hot-melt extrusion (HME) - melting a substance and forcing it through an orifice under controlled conditions to form a new material - is an emerging processing technology in the pharmaceutical industry for the preparation of various dosage forms and drug delivery systems, for example granules and sustained release tablets. Hot-Melt Extrusion: Pharmaceutical Applications covers the main instrumentation, operation principles and theoretical background of HME. It then focuses on HME drug delivery systems, dosage forms and clinical studies (including pharmacokinetics and bioavailability) of HME products. Finally, the book includes some recent and novel HME applications, scale -up considerations and regulatory issues. Topics covered include: principles and die design of single screw extrusion twin screw extrusion techniques and practices in the laboratory and on production scale HME developments for the pharmaceutical industry solubility parameters for prediction of drug/polymer miscibility in HME formulations the influence of plasticizers in HME applications of polymethacrylate polymers in HME HME of ethylcellulose, hypromellose, and polyethylene oxide bioadhesion properties of polymeric films produced by HME taste masking using HME clinical studies, bioavailability and pharmacokinetics of HME products injection moulding and HME processing for pharmaceutical materials laminar dispersive & distributive mixing with dissolution and applications to HME technological considerations related to scale-up of HME processes devices and implant systems by HME an FDA perspective on HME product and process understanding improved process understanding and control of an HME process with near-infrared spectroscopy Hot-Melt Extrusion: Pharmaceutical Applications is an essential multidisciplinary guide to the emerging pharmaceutical uses of this processing technology for researchers in academia and industry working in drug formulation and delivery, pharmaceutical engineering and processing, and polymers and materials science. This is the first book from our brand new series Advances in Pharmaceutical Technology. Find out more about the series here.

Processing Impact on the Performance of Amorphous Solid Dispersions

The level of understanding of amorphous solid dispersions has grown significantly in the last two decades. A number of commercial amorphous solid dispersions have been approved and they have become the industry norm for overcoming poor water-solubility when an enabling technology is necessary. Despite their success, there are still challenges in developing high performing amorphous solid dispersions. The impact of processing technique on the quality of the resultant amorphous solid dispersion is an area that is not well understood. Spray drying and melt extrusion are the two dominant manufacturing techniques for preparing amorphous solid dispersions. The mechanism for the formation of an amorphous solid dispersion from each process is very different. Therefore, the resulting material can have different properties which contribute to the overall performance of the amorphous solid dispersions. A better understanding of processing impact is necessary. Another challenge in the development of amorphous solid dispersions is the limitation to process high melting point drug substances that also have limited organic solvent solubility. For these substances, spray drying cannot be used, and at the high temperatures required to dissolve the drug in the polymer carrier, there is significant degradation during melt extrusion. Strategies such as plasticizer, supercritical fluids, and polymer selection for melting point suppression have been used in the past but have limitations. This research focuses on the impact of the processing technique on the physical and chemical stability of the resultant amorphous solid dispersions as well as the resultant dissolution performance. This work showed that based on its mechanism of formation, melt extrusion can have an advantage when preparing a high potency amorphous solid dispersion with a fast crystallizing drug. Due to the high level of mixing in the extruder and higher temperature, a more homogeneous and thermodynamically stable amorphous solid dispersion can be prepared. Spray drying, in contrast, can produce a higher drug loading amorphous solid dispersion, however, the material is less homogeneous and physically unstable. Additionally, through process and formulation understanding, a previously deemed “un-extrudable” drug substance was successfully processed by melt extrusion. This process was also successfully scaled from lab to pilot scale equipment.

Rationalising the Selection of Pharmaceutical Excipients for the Formulation of Amorphous Solid Dispersions

Novel Uses of Pharmaceutical Polymers as Enabled by KinetiSol® Dispersing

Poor water-solubility is a common characteristic of drug candidates in pharmaceutical development pipelines today. Various processes have been developed to increase the solubility, dissolution rate and bioavailability of these active ingredients belonging to BCSII and IV classifications. Over the last decade, nano-crystal delivery forms and amorphous solid dispersions have become well established in commercially available products and industry literature. Chapter 1 is a comparative analysis of these two methodologies primarily for orally delivered medicaments. The thermodynamic and kinetic theories relative to these technologies are presented along with a survey of commercial relevant scientific literature. Marketed products from both technologies are presented, but there appears to be more amorphous dispersion products on the U.S. market today and current development trends are showing an industry preference for amorphous solid dispersions. Many pharmaceutical polymers have been investigated as the primary component in amorphous solid dispersions for their ability to increase the apparent water solubility of poorly water-soluble drugs. Polyvinyl alcohol (PVAL) has not been investigated as a concentration enhancing polymer owing to its high melting point/high viscosity and poor organic solubility. Due to the unique attributes of the KinetiSol® Dispersing (KSD) technology, PVAL has been enabled for this application and Chapter 2 contains an initial investigation into various grades for improvement of the solubility and bioavailability of the poorly water-soluble model drug, itraconazole (ITZ). Polymer grades were chosen with variation in molecular weight and degree of hydroxylation to determine the effects on performance. Differential scanning calorimetry, powder x-ray diffraction, polarized light microscopy, size exclusion chromatography and dissolution testing were used to characterize the amorphous dispersions. An in vivo pharmacokinetic study in rats was also conducted to compare the selected formulation to current market formulations of ITZ. Chapter 3 continues the investigation into the use of PVAL as a concentration enhancing polymer for amorphous solid dispersion. The previous chapter revealed that the 88% hydrolyzed grade was optimal for ITZ compositions with regard to solid-state properties, non-sink dissolution performance and bioavailability enhancement. This chapter explores the influence of molecular weight for the 88% hydrolyzed grade in the range of 4 to 8 mPa·s with the top performing grade from both chapters emerging as PVAL 4-88. Amorphous dispersions at 10, 20, 30, 40 and 50% ITZ drug loads in PVAL 4-88 were compared by dissolution performance. Analytical tools of diffusion-ordered spectroscopy and Fourier transform infrared spectroscopy were employed to understand the interaction between drug and polymer. Finally, results from a 30 month stability test of a 30% drug loaded ITZ:PVAL 4-88 composition shows that stable amorphous dispersions can be achieved. The KinetiSol® Dispersing (KSD) technology has been shown to create solid dispersion systems from challenging drugs and highly viscous polymers. The focus has been primarily using this technology for solubility enhancement, but it can be advantageous for other obstacles facing the pharmaceutical development industry. Chapter 4 contains an investigation into the use of the technology for producing abuse deterrent formulations for the drug, theophylline, which is used as a model for oxycodone. Various high molecular weight polymers are combined with plasticizers to produce mechanical and chemical properties sufficient to resist alcohol dose dumping, size reduction for immediate release and syringeability for injection. Thus, the KinetiSol® Dispersing (KSD) technology can be used as a formulation platform for creating abuse deterrent delivery forms in addition to solid amorphous dispersions for solubility enhancement.

Application of Hot-melt Extrusion in the Manufacturing of Amorphous Solid Dispersions Containing Thermally Labile Drugs

Hot-melt extrusion has gained favor over traditional pharmaceutical formulation techniques in bioavailability/solubility enhancement because it is a solvent-free and continuous operation process that does not require major downstream processing. However, the thermal and mechanical energy applied during the extrusion process can cause chemical degradation of drugs and polymeric carriers In Chapter 1, different methods of preparing amorphous solid dispersions were reviewed. The amorphous solid dispersions generated by different methodologies were compared in terms of physical stability, chemical stability, and the in vivo/in vitro performance. In Chapter 2, the solubility advantage of amorphous solid dispersions was investigated through the heterogeneous phase equilibria analysis. A thermodynamic model for the quantitative assessment of solubility advantage of amorphous solid dispersions was then presented. The thermodynamic model accounted for the chemical potential change as a result of (a) amorphization, (b) ASD formation, and (c) water partition. Experimental solubility advantages of amorphous solid dispersions containing indomethacin was studied by means of intrinsic dissolution measurement. The thermodynamic model allowed predicting the solubility advantage of amorphous solid dispersions. In Chapters 3 and 4, the strategies used in hot-melt extrusion to facilitate manufacture of amorphous solid dispersions containing thermally labile drugs were investigated. Formulation screening based on Flory-Huggins theory, and the utilization of polymer designed for the extrusion process was evaluated in Chapter 3. With the selection of proper formulations, amorphous solid dispersions containing 30% (w/w) carbamazepine were manufactured without any degradation. Improved dissolution properties were also revealed with the final formulations. In Chapter 4, gliclazide was identified as a thermally labile drug with severe degradation by hydrolysis at elevated temperatures, especially when it existed in amorphous or solution form. After optimization of the hot-melt extrusion process, including improved screw design, machine setup, and processing conditions, gliclazide amorphous solid dispersion with ~95% drug recovery was achieved. This study demonstrated the importance of the following factors on drug degradation: (a)

changing screw design to facilitate shorter amorphous (melt) residence time, (b) lowering processing temperature to avoid excess thermal exposure, and (c) minimizing processing parameters to reduce unnecessary mechanical energy input.

Processing Challenging Active Pharmaceutical Ingredients and Polymers by Kinetisol to Produce Amorphous Solid Dispersions with Improved In-vitro and In-vivo Performance

KinetiSol processing is an emerging technology for processing amorphous solid dispersions for pharmaceutical delivery of poorly water soluble drugs. Chapter 1 reviews the current literate around the application of this technology and provides insights into its benefits to pharmaceutical product development for poorly water soluble drugs. In Chapter 2, KinetiSol processing was used to render amorphous the poorly water soluble drug vemurafenib. Vemurafenib was challenging because conventional processes of pharmaceutical amorphous dispersions (hot melt extrusion and spray drying) were unable to render formulations containing this molecule amorphous and a non-ideal solvent-controlled coprecipitation process was utilized in production of its commercial product. Material generated by the KinetiSol process had particle morphology that differentiated it from the commercial particles. In-vitro and in-vivo performance analysis of the KinetiSol and commercial materials demonstrated enhanced product performance and drug exposure for the materials processed by KinetiSol. In Chapter 3, KinetiSol processing produced a high drug load formulation of the anti-viral and pharmacokinetic boosting drug, ritonavir. The amorphous solid dispersion of ritonavir was demonstrated as amorphous and intimately mixed by sensitive analysis such as solid state nuclear magnetic resonance. During comparison to the commercial product for ritonavir, transmembrane flux analysis revealed similar permeation rates for both dosages. Subsequent in-vivo pharmacokinetic analysis in dogs resulted in equivalent exposure for the test and reference products with a small reduction in maximum plasma concentration. It was concluded that the tablet generated in the study could serve as a pharmacokinetic booster with tablet mass reduced by approximately half. In Chapter 4, the extent of a surprising pharmacokinetic result with a lubricant was investigated. The result was surprising as lubricants such as magnesium stearate are typically understood to hinder performance in dosage forms containing poorly soluble drugs and are typically avoided, but the original result showed a significant increase in exposure. The study evaluated several additional cases and demonstrated positive effects of lubricant inclusion for weak acid, neutral, and weak base example compounds. Additionally, the study evaluated additional components not classified as pharmaceutical lubricants but with similar physiochemical properties to magnesium stearate and demonstrated similar positive benefits for these additional compounds

Investigation of Amorphous Solid Dispersions of Poorly Water-soluble Drugs in Poly (2-hydroxyethyl Methacrylate) Hydrogels for Enhanced Solubility and Controlled Release

BIOMIMETIC DISSOLUTION

A TOOL TO EVALUATE AMORPHOUS SOLID DISPERSION PERFORMANCE

The pharmaceutical industry is at a critical juncture. With little remnants of the "Golden Age of the Pharmaceuticals" and applied pressure from large companies experiencing a dissipation of proprietary compounds, trends indicate a transition from a decade of stagnant productivity to one in which high throughput screening technologies and computational chemistry have diversified the discovery of new chemical entities (NCE). Despite these advances, drug discovery has been challenged by chemical entities that present delivery limitations due to the properties of their molecular structure. A recent evaluation of development pipelines indicated that approximately 70% of drug candidates exhibit poor aqueous solubility; thereby, resulting in erratic dissolution and insufficient bioavailability. Due to intrinsic physical properties, these compounds are known by the biopharmaceutics classification system (BCS) as class II compounds and are amendable to solubility and bioavailability enhancement platforms. Approaches such as pH adjustment, micronization, nanosuspensions, co-solvent solubilization, cyclodextrin inclusion complexation, salt formation, emulsified drug formulations and amorphous solid dispersions (ASD) are commonly utilized to maximize bioavailability and enrich in vivo absorption by prolonging exposure to high concentrations of dissolved drug in the gastrointestinal tract (GIT). Single-phase amorphous systems, such as solid dispersions, have been the focal point of the aforementioned practices as a result of their ability to promote a state of drug supersaturation over an extended duration of time. Within the structure of this dissertation, the application of concentration enhancing polymers for bioavailability enhancement of low solubility compounds was evaluated using solvent and fusion-based solid dispersion technologies. Exploiting a variety of analytical methodologies and tools, formulations produced by spray drying and hot melt extrusion (HME) techniques were investigated for sufficient dissolution enhancement. Studies revealed the selected formulation approaches provided a viable platform for manufacturing solid dispersions by illustrating systems that offered rapid and prolonged periods of supersaturation. While of the applications of single-phase amorphous solid dispersions are continuously expanding, their dissolution behavior is not as well understood. The overarching objective of dissolution testing during formulation development is to achieve biological relevance and predict in vivo performance. Proper in vitro dissolution testing can convey the influence of key in vivo performance parameters and be implemented for assessment and comparison of ASD formulations. Studies suggest that existing research fails to accurately address the intricacies associated with the supersaturated state. Upon solvation and during transit in the GIT, several high-energy drug-containing species are present in addition to free drug. Although these species are not absorbed in vivo, they play a pivotal role in generating and maintaining the supersaturation of a drug substance and function to replenish the supply of free drug as it permeates across the gastrointestinal membrane. Established dissolution apparatuses and methodologies in the United States Pharmacopeia (USP) focus on evaluation of total dissolved drug and may not be physiologically relevant for determining the amount of drug absorbed in vivo. Within the framework of this dissertation, a dissolution methodology was designed to reflect the physiochemical, physiological and hydrodynamic conditions that transpire throughout dissolution and absorption of an ASD during transit in the GIT. The apparatus and model present the ability to understand the kinetics and mechanisms of dissolution, supersaturation and nucleation. To support this hypothesis, analytical methods including high pressure liquid chromatography (HPLC) with ultraviolet (UV) detection were developed and fully validated. In parallel, a novel plasma membrane treatment was established to fabricate biomimetic membranes that possessed a hydrophilic and hydrophobic surface. The treated membranes are comprised of applied surface chemistries that emulate the unstirred aqueous layer created by microvilli protruding from the intestinal epithelial membrane as well as lipophilic constituents corresponding to the epithelial lipid membrane. Calculated in vitro similarity (f2) and difference (f1) factors support the hypotheses that plasma treated microporous polymer membranes exhibit biorelevant properties and demonstrate adequate biorelevance for in vitro dissolution studies. The described dissolution methodology has been applied as a tool for selection of candidates to move forward to pharmacokinetic studies. In a culminating study, in vitro - in vivo correlations (IVIVC) were performed employing the universal membrane-permeation non-sink dissolution method for formulations of Carbamazepine. To demonstrate the utility of the methodology, multiple level C correlations were established. The membrane-permeation model enables quantitative assessment of drug dissolution and absorption and offers a means to predict the relative in vivo performance of amorphous solid dispersions for BCS class II drug substances.

Preformulation Studies for the Preparation of Amorphous Solid Dispersions

The major challenges in the formulation of amorphous solid dispersions (ASDs) using hot-melt extrusion (HME) are the selection of an ideal polymeric carrier, optimization of HME processing conditions, and screening of the physical stability of the ASDs. Addressing these challenges using traditional approaches require extensive experimentation and large amounts of active pharmaceutical ingredients (API) which may not be feasible during the initial stages of product development. Therefore, there is a need to develop material-sparing techniques for the successful formulation of ASDs. The objective of the present study was to develop material-sparing techniques that can be used as pre-formulation tool during the formulation of ASDs. For this purpose, mefenamic acid (MFA) was used as a model drug and four chemically distinct polymers with close values of the solubility parameters, viz. Kollidon® VA64, Soluplus®, Pluronic® F68, and Eudragit® EPO, were used as polymeric carriers. The selection of an ideal polymer was carried out based on the solubility parameter approach, melting point depression method, thermodynamic phase diagrams, and Gibbs free energy plots. Then the HME processing conditions were determined based on a material-sparing technique using differential scanning calorimeter (DSC). The physical stability of the ASDs was estimated using the modified Avarami equation. Based on the results of the melting point depression, thermodynamic phase diagrams and Gibbs free energy plots, Eudragit® EPO was found to be an ideal polymer for the preparation of amorphous solid dispersion formulation of mefenamic acid. The design space for HME determined using DSC method showed that when 20% drug loaded MFA-EPO blends was heated at a rate of 5.5 °C/min to a temperature of 146 °C, the resulting ASD

contained a residual crystallinity of 13.6% and drug degradation of 3.8%. The physical stability of the MFA-EPO ASDs determined using a modified Avarami equation showed that the rate of recrystallization changed significantly with the change in process temperature as compared to the change in the relative humidity. The study results show that the time frame and experiments required in the formulation of ASDs can be significantly reduced by using the materialsparing techniques developed based on the theoretical and experimental approaches.

Melt Extrusion

Materials, Technology and Drug Product Design

Springer Science & Business Media This volume provides readers with the basic principles and fundamentals of extrusion technology and a detailed description of the practical applications of a variety of extrusion processes, including various pharma grade extruders. In addition, the downstream production of films, pellets and tablets, for example, for oral and other delivery routes, are presented and discussed utilizing melt extrusion. This book is the first of its kind that discusses extensively the well-developed science of extrusion technology as applied to pharmaceutical drug product development and manufacturing. By covering a wide range of relevant topics, the text brings together all technical information necessary to develop and market pharmaceutical dosage forms that meet current quality and regulatory requirements. As extrusion technology continues to be refined further, usage of extruder systems and the array of applications will continue to expand, but the core technologies will remain the same.

Chemical Engineering in the Pharmaceutical Industry

Drug Product Design, Development, and Modeling

John Wiley & Sons A guide to the important chemical engineering concepts for the development of new drugs, revised second edition The revised and updated second edition of Chemical Engineering in the Pharmaceutical Industry offers a guide to the experimental and computational methods related to drug product design and development. The second edition has been greatly expanded and covers a range of topics related to formulation design and process development of drug products. The authors review basic analytics for quantitation of drug product quality attributes, such as potency, purity, content uniformity, and dissolution, that are addressed with consideration of the applied statistics, process analytical technology, and process control. The 2nd Edition is divided into two separate books: 1) Active Pharmaceutical Ingredients (API's) and 2) Drug Product Design, Development and Modeling. The contributors explore technology transfer and scale-up of batch processes that are exemplified experimentally and computationally. Written for engineers working in the field, the book examines in-silico process modeling tools that streamline experimental screening approaches. In addition, the authors discuss the emerging field of continuous drug product manufacturing. This revised second edition: Contains 21 new or revised chapters, including chapters on quality by design, computational approaches for drug product modeling, process design with PAT and process control, engineering challenges and solutions Covers chemistry and engineering activities related to dosage form design, and process development, and scale-up Offers analytical methods and applied statistics that highlight drug product quality attributes as design features Presents updated and new example calculations and associated solutions Includes contributions from leading experts in the field Written for pharmaceutical engineers, chemical engineers, undergraduate and graduation students, and professionals in the field of pharmaceutical sciences and manufacturing, Chemical Engineering in the Pharmaceutical Industry, Second Edition contains information designed to be of use from the engineer's perspective and spans information from solid to semi-solid to lyophilized drug products.

Enhancing Delivery of Poorly Water-soluble Drugs by Innovative Amorphous Solid Dispersions

Poorly water-soluble drugs continue to dominate today's drug development pipelines, and thus a multitude of technologies and solubility-enhancing methodologies have been commercialized to address this issue. One-such methodology to enhance the solubility of poorly water-soluble drugs is the development of amorphous solid dispersions. What was once considered a risky method of drug delivery (due to lack of drug kinetic stability in its amorphous state), formulating drugs as amorphous solid dispersions has grown significantly over the past two decades. Two amorphous solid dispersion-producing technologies have become well-understood for the development and successful delivery of poorly water-soluble drugs, and thus an overwhelming majority of commercialized amorphous solid dispersion products are processed by these two technologies; hot melt extrusion and spray drying. Each technology has distinct advantages and disadvantages, and thus many poorly water-soluble drugs are unable to process by either technology using conventional techniques. Thus, novel utilization of excipients and processing methods is necessary to continually expand the formulation design space. Furthermore, the development and commercialization of novel amorphous solid dispersion-producing technologies is necessary to further-expand the formulation design space. Therefore, the following research is an effort to expand the formulation design space of poorly water-soluble drugs while forming amorphous solid dispersions. The following research focuses on continued innovation in the field of amorphous solid dispersions to enhance the bioavailability of poorly water-soluble drugs. These research directions demonstrate innovative use of an ordinary excipient to enhance delivery of amorphous solid dispersions processed by hot melt extrusion. Additionally, these studies demonstrate the use (and further understanding) of a novel technology, KinetiSol, that allows for processing amorphous solid dispersions without the necessity of external thermal input or solvent(s). KinetiSol-processed materials are compared with spray dried materials to evaluate the kinetics behind drug release of a weakly basic drug processed with an ionic polymer, and findings from this study will be essential for future delivery of amorphous solid dispersions of weakly basic drugs in ionic polymers

Assessment of Nanocomposites Vs. Amorphous Solid Dispersions for Dissolution Enhancement of Bcs Class Ii Drugs

Nanoparticle-based formulations (nanocomposites) and amorphous solid dispersions, shortly ASDs, are two major pharmaceutical formulation platforms used for the bioavailability enhancement of poorly water-soluble drugs. While they both have several advantages-disadvantages, a scientific comparative assessment of their drug release performance and dissolution mechanisms at different drug doses is not available. With the goal of addressing this issue, the dissertation aims to achieve three major objectives: (1) develop a processing-formulation understanding of wet media milling process for fast-efficient production of drug nanoparticles in stable nanosuspension form, (2) elucidate the impact of various classes dispersants on drug release rate and mechanisms during the redispersion-dissolution of nanocomposites prepared via dying of the drug nanosuspensions, and (3) assess the dissolution enhancement imparted by drug nanocomposites vs. ASDs prepared via drying of drug nanosuspensions by a novel nanoextrusion process, which allows for a scientific, head-to-head assessment of the two formulation platforms at various drug doses.

The Development of Ritonavir and Pyrimethamine Amorphous Solid Dispersions

Ritonavir -- Pyrimethamine -- Polymer -- Amorphous solid dispersion (ASD) -- Screen polymers for amorphous drug stabilisation (SPADS) -- Solubility -- Dissolution -- UV analysis -- HPLC -- Stability

Chemical Engineering in the Pharmaceutical Industry, Active Pharmaceutical Ingredients

Wiley A guide to the development and manufacturing of pharmaceutical products written for professionals in the industry, revised second edition The revised and updated second edition of Chemical Engineering in the Pharmaceutical Industry is a practical book that highlights chemistry and chemical engineering. The book's regulatory quality strategies target the development and manufacturing of pharmaceutically active ingredients of pharmaceutical products. The expanded second edition contains revised content with many new case studies and additional example calculations that are of interest to chemical engineers. The 2nd Edition is divided into two separate books: 1) Active Pharmaceutical Ingredients (API's) and 2) Drug Product Design, Development and Modeling. The active pharmaceutical ingredients book puts the focus on the chemistry, chemical engineering, and unit operations specific to development and manufacturing of the active ingredients of the pharmaceutical product. The drug substance operations section includes

information on chemical reactions, mixing, distillations, extractions, crystallizations, filtration, drying, and wet and dry milling. In addition, the book includes many applications of process modeling and modern software tools that are geared toward batch-scale and continuous drug substance pharmaceutical operations. This updated second edition: • Contains 30new chapters or revised chapters specific to API, covering topics including: manufacturing quality by design, computational approaches, continuous manufacturing, crystallization and final form, process safety • Expanded topics of scale-up, continuous processing, applications of thermodynamics and thermodynamic modeling, filtration and drying • Presents updated and expanded example calculations • Includes contributions from noted experts in the field Written for pharmaceutical engineers, chemical engineers, undergraduate and graduate students, and professionals in the field of pharmaceutical sciences and manufacturing, the second edition of Chemical Engineering in the Pharmaceutical Industry focuses on the development and chemical engineering as well as operations specific to the design, formulation, and manufacture of drug substance and products.

The Development of Paracetamol and Dapsone Amorphous Solid Dispersions

Amorphous solid dispersion (ASD) -- Screen polymers for amorphous drug stabilisation (SPADS) -- Nanocrystalline solid dispersion (NSD) -- Solubility -- Dissolution -- Stability -- Polymer -- Dapsone -- Paracetamol -- Solvent evaporation.

Solubility enhancement of poorly water-soluble drugs by solid dispersion

a comparison of two manufacturing methods

Cuvillier Verlag Summary Solid dispersions are a promising approach for controlled release drug delivery systems as both the bioavailability enhancement of poorly water-soluble drugs as well as the sustained release of water-soluble drugs are possible to optimize their in vivo performance. Different methods for the manufacture of solid dispersion systems have been introduced in literature. In the present work, two methods are compared: hot-melt extrusion and ultrasound-assisted compaction technique. Various carrier systems and drugs with different physicochemical properties are applied to investigate the feasibility of the technologies for pharmaceutical formulation. The formulations are compared to the corresponding untreated physical blends of the components regarding their solid state structure and dissolution behavior to assess the effect of the manufacturing technique. Ultrasound-assisted compaction technique improves the initial dissolution rate of fenofibrate, a poorly water-soluble model drug. The crystalline API is partially converted into its amorphous state. As equivalent results can be achieved if the polymers are added directly to the dissolution medium, the dissolution enhancement is attributed to an improved wettability of the drug. A statistical design of experiments is employed to investigate the effect of the process parameters on the results. Difficulties are encountered in the determination of process parameters which result in an optimal outcome. The process is very sensitive to the smallest changes of settings, for example of the position of the sonotrode. Additionally, the delivery of ultrasound energy is inhomogeneous. There is no or only insufficient user control of these parameters available. Furthermore, the duration of ultrasound energy delivery which is identified as a crucial parameter cannot be set by the user. The variable factors ultrasound energy, pressure of the lower piston and pressure of the upper piston affect the defined responses in the opposite direction. Hence, there are no settings which result in a satisfactory outcome. A strong influence of the material characteristics on the process is observed leading to a batch to batch variability. Due to an insufficient reproducibility of results, the application of the technology cannot be recommended in its current state in the pharmaceutical formulation development and/or production. Improvements in homogeneity of energy delivery, process monitoring, user control and amount of leakage are mandatory for an acceptable performance and a future application in the pharmaceutical sector. The polymers COP, HPMC and PVCL-PVAc-PEG are well suitable as carriers for hot-melt extruded formulations of fenofibrate. All three extrudates are amorphous one-phase systems with the drug molecularly dispersed in the polymer. The enhancement of the initial dissolution rate and the maximum concentration level achieved are dependent on the applied carrier system. Supersaturation levels of up to 12.1 times are reached which are not stable due to recrystallization processes. The application of blends of polymers as carriers reduces the decrease rate after cmax. Because of water absorption and polymer relaxation, the overall dissolution performance decreases with increasing storage times which can be avoided through an optimization of the packaging. If oxeglitazar is used as API, the initial dissolution rate of the extrudates is below that of the untreated drug, with the exception of the ternary blend of COP, HPMC and oxeglitazar which shows a substance-specific super-additive effect. In contrast to the other extrudates, the formulation of PVCL-PVAc-PEG and oxeglitazar does not form a molecularly dispersed solid solution of the drug in the carrier. Instead, an amorphous two-phase system is present. No changes are observed after storage, presumably due to higher glass transition temperatures of the hot-melt extruded systems which are considerably above those of the corresponding fenofibrate extrudates. With felodipine as API, the dissolution profile is enhanced with COP as single carrier. If HPMC or PVCL-PVAc-PEG is used as single or additional polymeric carriers, the dissolution is equivalent (HPMC) or lower (PVCL-PVAc-PEG) than that of the pure drug although molecularly disperse systems are present in all cases. Out of the two investigated methods only hot-melt extrusion is a suitable technology to manufacture solid dispersions with an improved dissolution behavior. The dissolution profile of the extrudates can be influenced by adding polymers with differing physicochemical characteristics. Predictions on the dissolution behavior of the extrudates with polymeric blends as carriers can be made if there is knowledge on the dissolution profiles of the corresponding single polymeric extrudates. Due to substance-specific effects, the results are not transferable from drug to drug. Even so, the data are promising as the release behavior of the manufactured extrudates can be easily modified and readily adapted to one's needs. Further research will have to be conducted to verify the concept and the relevance of the results in vivo. Zusammenfassung Feste Dispersionen sind ein vielversprechender Ansatz zur Herstellung von Drug Delivery-Systemen mit kontrollierter Wirkstofffreisetzung, da sie sowohl die Bioverfügbarkeit schlecht wasserlöslicher Arzneistoffe verbessern als auch die Freisetzung gut wasserlöslicher Arzneistoffe verzögern können und so deren in vivo Verhalten optimieren. Verschiedene Herstellungsmethoden wurden in der Literatur vorgestellt. In der vorliegenden Arbeit werden zwei Technologien miteinander verglichen: Schmelzextrusion und Ultraschall gestützte Verpressung (USAC). Verschiedene Trägersysteme und Arzneistoffe mit unterschiedlichen physikochemischen Eigenschaften werden untersucht, um die Einsatzmöglichkeit im pharmazeutischen Bereich zu überprüfen. Die Struktur der hergestellten Systeme und deren Freisetzungsverhalten werden mit den physikalischen Mischungen der Komponenten verglichen, um den Einfluss der Formulierung zu bestimmen. Durch USAC wird die initiale Freisetzungsrate von Fenofibrat, einem schlecht wasserlöslichen Modellarzneistoff, verbessert. Eine teilweise Umwandlung vom kristallinen in den amorphen Zustand tritt auf. Vergleichbare Ergebnisse werden bei einer Polymerzugabe zum Freisetzungsmedium erreicht; daher wird davon ausgegangen, dass vor allem eine verbesserte Benetzbarkeit des Arzneistoffs eine Rolle spielt. Mittels statistischer Versuchsplanung wird der Einfluss der verschiedenen Prozessparameter untersucht. Die Einstellung der Prozessparameter, um ein optimales Ergebnis zu erhalten, gestaltet sich schwierig. Der Prozess reagiert auf kleinste Veränderungen, zum Beispiel der Position der Sonotrode, überaus sensitiv. Außerdem wird die Ultraschallenergie nicht homogen übertragen. Die Kontrolle dieser Parameter durch den Anwender ist nicht oder nur unzureichend möglich. Ebenso kann die Dauer der Ultraschallapplizierung, die essentiell für den Prozess ist, nicht eingestellt werden. Die Prozessparameter Ultraschallenergie, Unterstempeldruck und Sonotrodendruck beeinflussen die Zielgrößen in entgegengesetzter Richtung. Daher gibt es keine Einstellung, die für alle Zielgrößen optimale Ergebnisse liefert. Zusätzlich ist der Prozess stark abhängig von den Eigenschaften des verwendeten Materials: Die Verwendung unterschiedlicher Polymerchargen macht eine Anpassung der Prozessparameter notwendig, um vergleichbare Ergebnisse zu erhalten. Eine ausreichende Reproduzierbarkeit der Ergebnisse für einen Einsatz dieser Technologie in Formulierungsentwicklung oder Produktion ist nicht gegeben. Eine homogene Ultraschallenergiezufuhr sowie Verbesserungen der Prozessüberwachung, der Benutzerkontrolle und eine Verminderung der austretenden Materialmenge sind für eine akzeptable Leistung und eine zukünftige Anwendung im pharmazeutischen Bereich zwingend erforderlich. Die Polymere COP, HPMC, PVCL-PVAc-PEG sind für eine Freisetzungsverbesserung von Fenofibrat mittels Schmelzextrusion geeignet. Es liegen einphasige, molekulardisperse feste Lösungen vor. Abhängig von der Trägersubstanz wird die initiale Freisetzungsrate unterschiedlich stark erhöht, ebenso die maximale Konzentration des Arzneistoffes in Lösung. Eine bis zu 12.1-fache Übersättigung wird erreicht, die aufgrund von Rekristallisationsprozessen nicht stabil ist. Der Einsatz von polymeren Mischungen reduziert die Geschwindigkeit des Konzentrationsabfalls. Die Absorption von Wasser und Relaxationseffekte vermindern die Freisetzungserhöhung mit zunehmender Lagerdauer; dieser Entwicklung kann durch eine Optimierung des Packmittels entgegengewirkt werden. Wird der ebenfalls schwer wasserlösliche Arzneistoff Oxeglitazar verwendet, so ist die initiale Freisetzungsrate der Extrudate der des reinen Arzneistoffs unterlegen, mit Ausnahme der ternären Mischung von COP, HPMC und Oxeglitazar, die einen substanzspezifischen überadditiven Effekt aufweist. PVCL-PVAc-PEG-Oxeglitazar-Extrudate bilden im Gegensatz zu den übrigen Formulierungen keine molekulardisperse feste Lösung, sondern ein amorphes Zwei-Phasen-System. Eine Veränderung während der Lagerzeit wird nicht beobachtet, vermutlich aufgrund der höheren Glasübergangstemperaturen dieser Systeme. Lediglich das Freisetzungsprofil von COP-Felodipin-Extrudaten ist verbessert. Gegenüber dem reinen Arzneistoff ist die Freisetzung der übrigen Extrudate vergleichbar (HPMC) oder verringert (PVCL-PVAc-PEG), obwohl auch hier molekulardisperse Systeme vorliegen. Von den beiden untersuchten Technologien ist lediglich die Schmelzextrusion geeignet, um feste Dispersionen mit einem verbesserten Freisetzungsverhalten herzustellen. Das Freisetzungsprofil der Extrudate kann durch den Zusatz von Polymeren mit unterschiedlichen Eigenschaften optimiert und vorhergesagt werden, wenn das Freisetzungsprofil der Einzelpolymer-Extrudate bekannt ist. Die Ergebnisse sind aufgrund von substanzspezifischen Effekten nicht von Arzneistoff auf Arzneistoff übertragbar. Nichtsdestotrotz sind die Erkenntnisse dieser Arbeit vielversprechend, da gezeigt wird, dass das Freisetzungsprofil der Extrudate leicht beeinflusst und an spezifische Anforderungen angepasst werden kann. Weitere Untersuchungen sind notwendig, um das Konzept und die Relevanz der Ergebnisse in vivo zu überprüfen.

Nuclear Magnetic Resonance for the Characterisation of Hot-melt Extruded Pharmaceutical Amorphous Solid Dispersions

Developing Solid Oral Dosage Forms

Pharmaceutical Theory and Practice

Academic Press Developing Solid Oral Dosage Forms is intended for pharmaceutical professionals engaged in research and development of oral dosage forms. It covers essential principles of physical pharmacy, biopharmaceutics and industrial pharmacy as well as various aspects of state-of-the-art techniques and approaches in pharmaceutical sciences and technologies along with examples and/or case studies in product development. The objective of this book is to offer updated (or current) knowledge and skills required for rational oral product design and development. The specific goals are to provide readers with: Basics of modern theories of physical pharmacy, biopharmaceutics and industrial pharmacy and their applications throughout the entire process of research and development of oral dosage forms Tools and approaches of preformulation investigation, formulation/process design, characterization and scale-up in pharmaceutical sciences and technologies New developments, challenges, trends, opportunities, intellectual property issues and regulations in solid product development The first book (ever) that provides comprehensive and in-depth coverage of what's required for developing high quality pharmaceutical products to meet international standards It covers a broad scope of topics that encompass the entire spectrum of solid dosage form development for the global market, including the most updated science and technologies, practice, applications, regulation, intellectual property protection and new development trends with case studies in every chapter A strong team of more than 50 well-established authors/co-authors of diverse background, knowledge, skills and experience from industry, academia and regulatory agencies

The Characterization of Cannabidiol Amorphous Solid Dispersions

Generating amorphous solid dispersions (ASDs) containing active pharmaceutical ingredients has become a favorable technique of emerging prominence to improve drug solubility and overall bioavailability. Cannabidiol (CBD) has now become a major focus in cannabinoid research due to its ability to serve as an anti-inflammatory agent, showing promising results in treating a wide array of debilitating diseases and pathologies. The following work provides evidence for generating homogenous glass phase amorphous solid dispersions containing 50% (w/w) up to 75% (w/w) CBD concentrations in the domain size of 2 – 5 nm. Concentrations up to 85% (w/w) CBD were concluded homogenous in the supercooled liquid phase in domain sizes of 20 – 30 nm. The results were obtained from polarized light microscopy (PLM), differential scanning calorimetry (DSC), as well as solution and solid-state NMR spectroscopy.

Polymorphism in Pharmaceutical Solids

CRC Press Using clear and practical examples, Polymorphism of Pharmaceutical Solids, Second Edition presents a comprehensive examination of polymorphic behavior in pharmaceutical development that is ideal for pharmaceutical development scientists and graduate students in pharmaceutical science. This edition focuses on pharmaceutical aspects of polymorphism a

Discovering and Developing Molecules with Optimal Drug-Like Properties

Springer This authoritative volume provides a contemporary view on the latest research in molecules with optimal drug-like properties. It is a valuable source to access current best practices as well as new research techniques and strategies. Written by leading scientists in their fields, the text consists of fourteen chapters with an underlying theme of early collaborative opportunities between pharmaceutical and discovery sciences. The book explores the practical realities of performing physical pharmaceutical and biopharmaceutical research in the context of drug discovery with short timelines and low compound availability. Chapters cover strategies and tactics to enable discovery as well as predictive approaches to establish, understand and communicate risks in early development. It also examines the detection, characterization, and assessment of risks on the solid state properties of advanced discovery and early development candidates, highlighting the link between solid state properties and critical development parameters such as solubility and stability. Final chapters center on techniques to improve molecular solubilization and prevent precipitation, with particularly emphasis on linking physiochemical properties of molecules to formulation selection in preclinical and clinical settings.

THE RELATIONSHIPS AMONG FLORY-HUGGINS SPECIFIC INTERACTION PARAMETERS, MAXIMUM AMORPHOUS CAPACITY, SOLID-STATE INTERACTIONS, EQUILIBRIUM SOLUBILITY, AND DISSOLUTION OF SPRAY DRIED AMORPHOUS DRUG DISPERSIONS

The aim of this study is to evaluate the specific interactions, solid-state, and solution-state interactions between drug and polymers in amorphous spray dried dispersions and evaluate the subsequent impact on drug dissolution in non-sink media. This is intended to be used as a screening tool for dosage-form development. Formulations with specific theoretical and observed interactions between drug and polymer may exhibit improved dissolution rate, increased absorption rate, increased capacity for drug loading and improved physical stability. Four BCS II class drugs were evaluated: ibuprofen, ketoprofen, nifedipine, and itraconazole. Binary and ternary spray dried dispersions were manufactured with conventional polymers and arabinogalactan. Specific interaction parameters between each drug and polymer were determined using theoretical group contribution calculations and DSC data. Solid-state interactions were evaluated using modulated DSC and FTIR, and solution-state interactions were evaluated using 1H-NMR. The maximum amorphous content for each formulation was calculated from the enthalpy of melting point peaks using DSC. Flory-Huggins Specific Interaction Parameters were calculated and show that a negative specific parameter was associated with increased solid-state interactions and improved capacity to contain drug in the amorphous state. Correlations between Flory-Huggins specific interaction parameter, amorphous drug loading, and equilibrium solubility were established. Ternary spray-dried dispersions containing drug, conventional polymer, and arabinogalactan displayed similar hydrogen bonding as was observed with binary spray-dried dispersions. Solid and solution-state interactions observed in binary systems may be incorporated into ternary systems with arabinogalactan to both maintain amorphous drug capacity and improve dissolution rate compared to the binary. Supersaturation of amorphous binary and ternary dispersions was attained as compared to the crystalline drug. Mechanical properties of polymers as related to dissolution rate were investigated, and ternary systems containing to rapidly swelling and dissolving arabinogalactan had more pronounced erosion properties as compared to binary drug : HPMC dispersions. The resultant ternary systems are an improvement over binary drug polymer systems.

Effect of Molecular Interactions on Properties of Amorphous Solid Dispersions

Amorphous solid dispersions have been widely applied to improve the oral bioavailability of BCS Class II and Class IV compounds by increasing their kinetic solubility and dissolution rate. However, maintaining the amorphous state of drug substances in amorphous solid dispersions is a challenge, whereby intermolecular interactions formed between the drug molecule and the polymer are thought to be of critical importance. A number of studies have been published to demonstrate the effect of drug-polymer intermolecular interaction on physicochemical properties of amorphous solid dispersions. In most of the cases, stronger drug-polymer interactions can more effectively disrupt molecular self-assembly of the drug in the dispersion and therefore lead to a relatively more stable amorphous solid dispersion system with a higher drug loading. Despite their success, there are still essential needs to mechanistically understand the role of all kinds of molecular interactions in amorphous solid dispersion systems. Within the scope of this dissertation, three types of molecular interactions including drug-drug interaction, drug-polymer interaction and polymer-polymer interaction in amorphous solid dispersion systems were studied. In Chapter 1, the molecular interactions in amorphous solid dispersions were discussed from thermodynamic perspective. The current understanding of the impact of molecular interactions on process conditions and amorphous solid dispersion properties was also reviewed. In Chapter 2, we demonstrated the molecular level mechanism of rafoxanide self-

association in aqueous media. The effect of self-association on physichochemical properties of rafoxanide was thoroughly investigated. In Chapter 3, we studied the molecular interactions between rafoxanide and povidone in different co-solvents. The difference in molecular interaction in different co-solvents is critical to the solvent selection of spray drying process. We also illustrated the impact of rafoxanide self-association on rafoxanide-povidone interaction in different environments. In Chapter 4, we compared the solid-state properties, dissolution behavior and physical stability of rafoxanide-povidone amorphous solid dispersions with different level of molecular interactions. The differences were further explained. In Chapter 5, we claimed a novel pH mediated control-precipitation method based on interpolymer complexation. The effect of interpolymer complexation on properties of itraconazole amorphous solid dispersions was also investigated. In Appendix A, we studied the effect of surfactant on drug-polymer miscibility, drug dissolution and physical stability of celecoxib amorphous solid dispersion. This study provides supplemental information on surfactant self-association during dissolution and its impact on drug release

Water-Insoluble Drug Formulation

CRC Press Scientists have attributed more than 40 percent of the failures in new drug development to poor biopharmaceutical properties, particularly water insolubility. Issues surrounding water insolubility can postpone, or completely derail, important new drug development. Even much-needed reformulation of currently marketed products can be significantly affected by these challenges. Water Insolubility is the Primary Culprit in over 40% of New Drug Development Failures The most comprehensive resource on the topic, this second edition of Water Insoluble Drug Formulation brings together a distinguished team of experts to provide the scientific background and step-by-step guidance needed to deal with solubility issues in drug development. Twenty-three chapters systematically describe solubility properties and their impact on formulation, from theory to industrial practice. With detailed discussion on how these properties contribute to solubilization and dissolution, the text also features six brand new chapters on water-insoluble drugs, exploring regulatory aspects, pharmacokinetic behavior, early phase formulation strategies, lipid based systems for oral delivery, modified release of insoluble drugs, and scalable manufacturing aspects. The book includes more than 15 water-insoluble drug delivery systems or technologies, illustrated with case studies featuring oral and parenteral applications. Highlighting the most current information and data available, this seminal volume reflects the significant progress that has been made in nearly all aspects of this field.