

# **READ ONLINE PHARMACEUTICAL AMORPHOUS SOLID DISPERSIONS**

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## **Pharmaceutical Amorphous Solid Dispersions Introduction**

### **Amorphous Solid Dispersions**

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.

### **Pharmaceutical Amorphous Solid Dispersions**

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 solid dispersion approach • Addresses global regulatory issues including US regulations, ICH guidelines, and patent concerns around the world

### **Amorphous Drugs**

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-founded 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.

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

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.

## **Recent Progress in Solid Dispersion Technology**

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.

## **Pharmaceutical Solid Dispersion Technology**

Presents a detailed discussion of important solid-state properties, methods, and applications of solid-state analysis Illustrates the various phases or forms that solids can assume and discusses various issues related to the relative stability of solid forms and tendencies to undergo transformation Covers key methods of solid state analysis including X-ray powder diffraction, thermal analysis, microscopy, spectroscopy, and solid state NMR Reviews critical physical attributes of pharmaceutical materials, mainly related to drug substances, including particle size/surface area, hygroscopicity, mechanical properties, solubility, and physical and chemical stability Showcases the application of solid state material science in rational selection of drug solid forms, analysis of various solid forms within drug substance and the drug product, and pharmaceutical product development Introduces appropriate manufacturing and control procedures using Quality by Design, and other strategies that lead to safe and effective products with a minimum of resources and time

## **Solid-State Properties of Pharmaceutical Materials**

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.

## **Melt Extrusion**

This volume is intended to provide the reader with a breadth of understanding regarding the many challenges faced with the formulation of poorly water-soluble drugs as well as in-depth knowledge in the critical areas of development with these compounds. Further, this book is designed to provide practical guidance for overcoming formulation challenges toward the end goal of improving drug therapies with poorly water-soluble drugs. Enhancing solubility via formulation intervention is a unique opportunity in which formulation scientists can enable drug therapies by creating viable medicines from seemingly undeliverable molecules. With the ever increasing number of poorly water-soluble compounds entering development, the role of the formulation scientist is growing in importance. Also, knowledge of the advanced analytical, formulation, and process technologies as well as specific regulatory considerations related to the formulation of these compounds is increasing in value. Ideally, this book will serve as a useful tool in the education of current and future generations of scientists, and in this context contribute toward providing patients with new and better medicines.

## **Formulating Poorly Water Soluble Drugs**

*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

## **Developing Solid Oral Dosage Forms**

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.

## **Chemical Engineering in the Pharmaceutical Industry**

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](#).

## **Hot-Melt Extrusion**

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 30 new 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.

## **Chemical Engineering in the Pharmaceutical Industry**

The objective of this third edition is to consolidate within a single text the most current knowledge, practical methods, and regulatory considerations pertaining to formulations development with poorly water-soluble molecules. A pharmaceutical scientist's approach toward solubility enhancement of a poorly water-soluble molecule typically includes detailed characterization of the compound's physicochemical properties, solid-state modifications, advanced formulation design, non-conventional process technologies, advanced analytical characterization, and specialized product performance analysis techniques. The scientist must also be aware of the unique regulatory considerations pertaining to the non-conventional approaches often utilized for poorly water-soluble drugs. One faced with the challenge of developing a drug product from a poorly soluble compound must possess at a minimum a working knowledge of each of the above mentioned facets and detailed knowledge of most. In light of the magnitude of the growing solubility problem to drug development, this is a significant burden especially when considering that knowledge in most of these areas is relatively new and continues to develop.

## **Formulating Poorly Water Soluble Drugs**

Amorphous solid dispersion is one of the techniques used for enhancing dissolution rate of drugs with low aqueous solubility. The physical stability of the amorphous solid dispersion is the main challenge for their formulation development and commercialisation by pharmaceutical industry. The aims of the project were to prepare amorphous solid solution of a poorly aqueous soluble drug using different molecular weight mixtures of PEG and PEG mixed with other polymers such as PVP and poloxamers, the formulations were prepared using melt method, solvent evaporation and quench cooled from melt method. Also, to find a system with controlled instability to study the impact of various features on the stability of the formulation. A series of physicochemical characterisation techniques were used to evaluate the different formulations such as XRPD, VT XRPD, DSC, dissolution and microscopy. The cooling temperature of the formulation from melt has a great impact on forming amorphous CBZ in PEG mixture. PEG 300 did show the ability to reduce the crystallinity in the other PEG used and to reduce the enthalpy of CBZ recrystallisation which indicates that less crystals been formed. The higher the PEG concentration in the formulation, the more stable the CBZ amorphous form. The best performing formulations in terms of controlling the recrystallisation of the CBZ from melt were the PEG 4000 and 6000 mixed with PEG 300, but their dissolution profile was not as good as the formulations with one PEG. The substitution of just 5% of PEG weight with PVP did show an increase in CBZ amorphous form stability. The quench cooling method did not show any decomposition of CBZ and that was proven by the HPLC method used. CBZ amorphous solid solution can be achieved by formulating the drug with PEG using melt method and the addition of secondary polymer such as PVP to the formulation at low concentration can inhibit the CBZ recrystallisation from the glassy/ liquid state and increases CBZ physical stability.

## **Physical Analysis of Solid Solution Formulations**

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

## **Developing Solid Oral Dosage Forms**

Since their first application in the improvement of solubility of orally delivered drugs, applications of solid dispersions have considerably expanded to include cancer, infections, and inflammatory conditions. This book presents recent advancements in the development and use of solid dispersions for different therapeutic applications. This book can be particularly useful for researchers as well as postgraduate students in formulation sciences and drug delivery. Undergraduate students will also find elements of this book very relevant to scientific fundamentals such as solubility and crystallization of amorphous materials as well as drug delivery challenges.

## **Solid Dispersions for Drug Delivery**

Teaches future and current drug developers the latest innovations in drug formulation design and optimization This highly accessible, practice-oriented book examines current approaches in the development of drug formulations for preclinical and clinical studies, including the use of functional excipients to enhance solubility and stability. It covers oral, intravenous, topical, and parenteral administration routes. The book also discusses safety aspects of drugs and excipients, as well as regulatory issues relevant to formulation. Innovative Dosage Forms: Design and Development at Early Stage starts with a look at the impact of the polymorphic form of drugs on the preformulation and formulation development. It then offers readers reliable strategies for the formulation development of poorly soluble drugs. The book also studies the role of reactive impurities from the excipients on the formulation shelf life; preclinical formulation assessment of new chemical entities; and regulatory aspects for formulation design. Other chapters cover innovative formulations for special indications, including oncology injectables, delayed release and depot formulations; accessing pharmacokinetics of various dosage forms; physical characterization techniques to assess amorphous nature; novel formulations for protein oral dosage; and more. -Provides information that is essential for the drug development effort -Presents the latest advances in the field and describes in detail innovative formulations, such as nanosuspensions, micelles, and cocrystals -Describes current approaches in early pre-formulation to achieve the best in vivo results -Addresses regulatory and safety aspects, which are key considerations for pharmaceutical companies -Includes case studies from recent drug development programs to illustrate the practical challenges of preformulation design Innovative Dosage Forms: Design and Development at Early Stage provides valuable benefits to interdisciplinary drug discovery teams working in industry and academia and will appeal to medicinal chemists, pharmaceutical chemists, and pharmacologists.

## **Innovative Dosage Forms**

Metastable Liquids provides a comprehensive treatment of the properties of liquids under conditions where the stable state is a vapor, a solid, or a liquid mixture of different composition. It examines the fundamental principles that govern the equilibrium properties, stability, relaxation mechanisms, and relaxation rates of metastable liquids. Building on the interplay of kinetics and thermodynamics that determines the thermophysical properties and structural relaxation of metastable liquids, it offers an in-depth treatment of thermodynamic stability theory, the statistical mechanics of metastability, nucleation, spinodal decomposition, supercooled liquids, and the glass transition. Both traditional topics--such as stability theory--and modern developments--including modern theories of nucleation and the properties of supercooled and

glassy water--are treated in detail. An introductory chapter illustrates, with numerous examples, the importance and ubiquity of metastable liquids. Examples include the ascent of sap in plants, the strategies adopted by many living organisms to survive prolonged exposure to sub-freezing conditions, the behavior of proteins at low temperatures, metastability in mineral inclusions, ozone depletion, the preservation and storage of labile biochemicals, and the prevention of natural gas clathrate hydrate formation. All mathematical symbols are defined in the text and key equations are clearly explained. More complex mathematical explanations are available in the appendixes.

## **Metastable Liquids**

This research is focussed on investigating the effect of structural relaxation on the dissolution of amorphous solid dispersions, produced via spray drying and ball milling at a 1:1 drug to polymer ratio. -- Structural relaxation (SR) is a multi-exponential decay process in which metastable amorphous materials gradually evolve towards the more thermodynamically stable crystalline state. This process is characterised by a decrease in energy and free volume and a concomitant increase in structural order. The importance of SR studies stems from the direct link between the physical changes induced by SR and the consequent therapeutic implications for the amorphous material. SR causes a decline in drug solubility leading to decreased drug dissolution profile and subsequently a lower bioavailability. -- The drug of interest within this study is griseofulvin, an antifungal drug, which according to the British Pharmacopoeia is classified as practically insoluble in water (Ph Eur monograph 0182; British Pharmacopoeia 2010. I and II. 2010). The polymer Hypermellose acetate succinate NF (HPMCAS; grade ASMF) is utilised due to its hydrophilic and amorphous nature. The influence of the manufacturing process on the production of amorphous griseofulvin was evaluated via DSC, XRPD and FTIR. -- Results demonstrate a significant enhancement in the dissolution profile of griseofulvin, by solid dispersions prepared via both spray drying and ball milling. Statistical analysis was performed via 1-way ANOVA ( $P=0.05$ ,  $V_1=2$ ,  $V_2=3$ ). However, the dissolution profile of spray dried (SD) samples was generally faster than the ball milled sample. This was attributed to the totally amorphous nature of the SD sample as illustrated by DSC and XRPD, in comparison to the ball milled (BM) sample. DSC thermograms and XRPD scans of BM sample (1: 1 drug to polymer ratio) showed partial crystallinity.

## **The Effect of Relaxation Rate on the Dissolution of Amorphous Griseofulvin Solid Dispersions**

Oral lipid-based formulations are attracting considerable attention due to their capacity to facilitate gastrointestinal absorption and reduce or eliminate the effect of food on the absorption of poorly water-soluble, lipophilic drugs. Despite the obvious and demonstrated utility of these formulations for addressing a persistent and growing problem

## **Oral Lipid-Based Formulations**

Nowadays, the pharmaceutical industry is seeking manufacturing processes that enable the delivery of high quality medicines with less cost and delivery time. The introduction of flexible manufacturing equipment such as twin-screw equipment can be used for these purposes and be part of a continuous manufacturing platform. Hot-Melt Extrusion (HME) and Twin-Screw Granulation (TSG) are two applications that can be used with the same processing equipment and reduce the number of stages involved in the manufacturing process. In this thesis the use of HME to produce amorphous solid dispersions of the poorly water soluble drug albendazole is investigated. HME enabled the transformation of the drug solid state from crystalline to amorphous by optimised processing parameters and the use of two suitable hydrophilic polymers as carriers. Amorphous solid dispersions showed an increase of albendazole dissolution properties. Differences in drug release rate indicated possible molecular interactions between the drug molecule and one of the polymers studied. Further studies are required to investigate the type of possible interactions. Computed tomography was used to determine the density differences and the internal structure properties of the extruded materials.

This thesis studied the impact of screw element design, processing parameters and mechanism behind granule formation in twin-screw wet granulation. The use of conveying elements only achieved a poor liquid distribution due to the low shear applied. Combined screw configurations of mixing and conveying elements resulted in better liquid distribution properties. Excess of fines production was attributed to a breakage mechanism caused by the use of the distributive feed screw. These results can contribute towards the design of space of TSG processes. Overall, this thesis showed that the optimisation of processing parameters in HME and TSG can lead to the enhancement of product properties which would be beneficial for continuous manufacturing platforms.

## **Development and Control of Pharmaceutical Solids Using Extrusion and Granulation**

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  $c_{max}$ . 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 oxeglitzazar 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 oxeglitzazar which shows a substance-specific super-additive effect. In contrast to the other extrudates, the formulation of PVCL-PVAc-PEG and oxeglitzazar 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 Freisetzungverhalten werden mit den physikalischen Mischungen der Komponenten verglichen, um den Einfluss der Formulierung zu bestimmen. Durch USAC wird die initiale Freisetzungsrates 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, molekularisperse feste Lösungen vor. Abhängig von der Trägersubstanz wird die initiale Freisetzungsrates 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 Freisetzungsrates 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 molekularisperse 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 molekularisperse Systeme vorliegen. Von den beiden untersuchten Technologien ist lediglich die Schmelzextrusion geeignet, um feste Dispersionen mit einem verbesserten Freisetzungverhalten 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.

## **Solubility enhancement of poorly water-soluble drugs by solid dispersion**

"Pharmaceutics is the art of pharmaceutical preparations. It encompasses design of drugs, their manufacture and the elimination of micro-organisms from the products. This book encompasses all of these areas."--  
Provided by publisher.

### **Aulton's Pharmaceutics**

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

### **Polymorphism in Pharmaceutical Solids**

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 solid dispersion approach • Addresses global regulatory issues including USA regulations, ICH guidelines, and patent concerns around the world

### **Pharmaceutical Amorphous Solid Dispersions**

A one-stop resource for researchers, developers, and post graduate students in pharmaceutical science. This handbook and ready reference provides detailed, but not overloaded information -- presenting the topic without unnecessarily complex formalism. As such, it gives a systematic and coherent overview of disordered materials for pharmaceutical applications, covering fundamental aspects, as well as preparation and characterization techniques for the target-oriented development of drug delivery systems based on disordered crystals and amorphous solids. Special attention is paid to examine the different facets and levels of disorder in their structural and dynamic aspects as well as the effect of disorder on dissolution and stability. Chapters on processing induced disorder and on patenting issues round off the book. As a result the book helps overcoming the challenges of using these materials in the pharmaceutical industry. For pharmaceutical and medicinal chemists, materials scientists, clinical physicists, and pharmaceutical laboratories looking to make better and more potent pharmaceuticals.

### **Disordered Pharmaceutical Materials**

The aim of this project is to find out a NIF/PVP formulation in capsule which has enhanced dissolution rate and stability. Amorphous solid dispersions can be used to enhance the solubility and dissolution rate of poorly soluble drug. Freeze drying technique is able to remove the solvent inside and therefore increase the

T<sub>g</sub> value of the mixtures and stabilize the formulation. This technique is also known to increase the wettability and surface area of insoluble drug. Solid dispersions of nifedipine (NIF) having varying concentrations of polyvinylpyrrolidone (PVP K10 and K30) in tertiary butyl alcohol (TBA) were prepared and then freeze dried. Physical mixture of NIF/PVP was also prepared using two types of PVP: K10 and K30. The appearance of PVP K30 freeze dried cake was not pharmaceutical elegant, collapse will easily occur, thus for NIF formulations that are needed to freeze dried, PVP K10 is a better option. Thermal analysis of freeze dried NIF/PVP K10 samples showed a single glass transition temperature and there was no melting peak found during first heat of heat-cool-heat cycle, suggestive of a miscible dispersion and amorphous nature. While in thermograms of physical mixture samples, melting peak was observed in most of them, which indicated that NIF in the mixture was crystalline. Dissolution test suggested that the freeze dried sample had an enhanced dissolution rate compared to physical mixtures. Thus freeze drying technique is more desired. Dissolution study on freeze dried NIF/PVP K10 samples suggested that 1:2 NIF/PVP K10 reached nearly full recovery at about 15 minutes. Thus freeze dried NIF/PVP K10 formulation with ratio of 1:2 is the best formulation which has a good dissolution rate and a high T<sub>g</sub> value (116.30±0.74 °C).

## **Investigation and Characterization of Freeze-dried Solid Dispersion Based on Poorly Soluble Drug and Polyvinylpyrrolidone**

This comprehensive up-to-date guide and information source is an instructive companion for all scientists involved in research and development of drugs and, in particular, of pharmaceutical dosage forms. The editors have taken care to address every conceivable aspect of the preparation of pharmaceutical salts and present the necessary theoretical foundations as well as a wealth of detailed practical experience in the choice of pharmaceutically active salts. Altogether, the contributions reflect the multidisciplinary nature of the science involved in selection of suitable salt forms for new drug products.

## **Handbook of Pharmaceutical Salts Properties, Selection, and Use**

Properties and Formulation: From Theory to Real-World Application 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 the much-needed reformulation of currently marketed products can be significantly affected by these challenges. More recently it was reported that the percentage increased to 90% for the candidates of new chemical entities in the discovery stage and 75% for compounds under development. In the most comprehensive resource on the topic, this third 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 the detailed discussion on solubility theories, solubility prediction models, the aspects of preformulation, biopharmaceutics, pharmacokinetics, regulatory, and discovery support of water-insoluble drugs to various techniques used in developing delivery systems for water-insoluble drugs. This book includes more than 15 water-insoluble drug delivery systems or technologies, illustrated with case studies and 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. The aim of this book is to provide a handy reference for pharmaceutical scientists in the handling of formulation issues related to water-insoluble drugs. In addition, this book may be useful to pharmacy and chemistry undergraduate students and pharmaceutical and biopharmaceutical graduate students to enhance their knowledge in the techniques of drug solubilization and dissolution enhancement.

## **Water-Insoluble Drug Formulation**

Many newly proposed drugs suffer from poor water solubility, thus presenting major hurdles in the design of suitable formulations for administration to patients. Consequently, the development of techniques and materials to overcome these hurdles is a major area of research in pharmaceutical companies. Drug Delivery

Strategies for Poorly Water-Soluble Drugs provides a comprehensive overview of currently used formulation strategies for hydrophobic drugs, including liposome formulation, cyclodextrin drug carriers, solid lipid nanoparticles, polymeric drug encapsulation delivery systems, self-microemulsifying drug delivery systems, nanocrystals, hydrosol colloidal dispersions, microemulsions, solid dispersions, cosolvent use, dendrimers, polymer-drug conjugates, polymeric micelles, and mesoporous silica nanoparticles. For each approach the book discusses the main instrumentation, operation principles and theoretical background, with a focus on critical formulation features and clinical studies. Finally, the book includes some recent and novel applications, scale-up considerations and regulatory issues. Drug Delivery Strategies for Poorly Water-Soluble Drugs is an essential multidisciplinary guide to this important area of drug formulation for researchers in industry and academia working in drug delivery, polymers and biomaterials.

## **Drug Delivery Strategies for Poorly Water-Soluble Drugs**

An important resource that puts the focus on understanding and handling of organic crystals in drug development. Since a majority of pharmaceutical solid-state materials are organic crystals, their handling and processing are critical aspects of drug development. Pharmaceutical Crystals: Science and Engineering offers an introduction to and thorough coverage of organic crystals, and explores the essential role they play in drug development and manufacturing. Written contributions from leading researchers and practitioners in the field, this vital resource provides the fundamental knowledge and explains the connection between pharmaceutically relevant properties and the structure of a crystal. Comprehensive in scope, the text covers a range of topics including: crystallization, molecular interactions, polymorphism, analytical methods, processing, and chemical stability. The authors clearly show how to find solutions for pharmaceutical form selection and crystallization processes. Designed to be an accessible guide, this book represents a valuable resource for improving the drug development process of small drug molecules. This important text: Includes the most important aspects of solid-state organic chemistry and its role in drug development. Offers solutions for pharmaceutical form selection and crystallization processes. Contains a balance between the scientific fundamental and pharmaceutical applications. Presents coverage of crystallography, molecular interactions, polymorphism, analytical methods, processing, and chemical stability. Written for both practicing pharmaceutical scientists, engineers, and senior undergraduate and graduate students studying pharmaceutical solid-state materials, Pharmaceutical Crystals: Science and Engineering is a reference and textbook for understanding, producing, analyzing, and designing organic crystals which is an imperative skill to master for anyone working in the field.

## **Pharmaceutical Crystals**

Amorphous, polymer, supersaturation, solubility, Biopharmaceutical Classification System, hot-melt extrusion, spray-drying.

## **Characterization of Amorphous Solid Dispersions**

Solid State Development and Processing of Pharmaceutical Molecules A guide to the latest industry principles for optimizing the production of solid state active pharmaceutical ingredients. Solid State Development and Processing of Pharmaceutical Molecules is an authoritative guide that covers the entire pharmaceutical value chain. The authors—noted experts on the topic—examine the importance of the solid state form of chemical and biological drugs and review the development, production, quality control, formulation, and stability of medicines. The book explores the most recent trends in the digitization and automation of the pharmaceutical production processes that reflect the need for consistent high quality. It also includes information on relevant regulatory and intellectual property considerations. This resource is aimed at professionals in the pharmaceutical industry and offers an in-depth examination of the commercially relevant issues facing developers, producers and distributors of drug substances. This important book: Provides a guide for the effective development of solid drug forms. Compares different characterization methods for solid state APIs. Offers a resource for understanding efficient production methods for solid state forms of

chemical and biological drugs Includes information on automation, process control, and machine learning as an integral part of the development and production workflows Covers in detail the regulatory and quality control aspects of drug development Written for medicinal chemists, pharmaceutical industry professionals, pharma engineers, solid state chemists, chemical engineers, Solid State Development and Processing of Pharmaceutical Molecules reviews information on the solid state of active pharmaceutical ingredients for their efficient development and production.

## **Solid State Development and Processing of Pharmaceutical Molecules**

This is truly an exciting time to be in the field of polymer science. Advances in polymerization methods are providing polymer scientists with the ability to specify and control polymer composition, structure, architecture, and molecular weight to a degree that was not possible just a decade ago. This, in turn, is resulting in many novel application possibilities of polymers ranging from drug delivery systems and nanolithography to stimuli-responsive materials and many others. In addition, many of the application areas of polymers – such as coatings, adhesives, thermoplastics, composites, and personal care – are also taking advantage of the ability to design polymers during their development efforts. Not to forget, many of these applications of polymers involve mixing polymers with solvents, catalysts, colorants, and many other ingredients to prepare a formulated product. However, the tuning of polymer composition and structure as well as polymer formulations to optimize the final performance properties can be challenging, especially since in many cases several interacting variables need to be optimized simultaneously. This is where the methodologies and techniques of combinatorial and high-throughput experimentation to synthesize and characterize polymer libraries can be an invaluable approach. Simply put, a polymer library is a collection of multiple polymer samples having a systematic variation in one or more variables related to composition, structure, or process. Various methods and strategies have been explored to efficiently prepare a large number of polymer samples and also to screen these samples for key properties of interest.

## **Polymer Libraries**

A little over 7ve years have passed since the first edition of this book appeared in print. Seems like an instant but also eternity, especially considering numerous developments in the hardware and software that have made it from the laboratory test beds into the real world of powder diffraction. This prompted a revision, which had to be beyond cosmetic limits. The book was, and remains focused on standard laboratory powder diffractometry. It is still meant to be used as a text for teaching students about the capabilities and limitations of the powder diffraction method. We also hope that it goes beyond a simple text, and therefore, is useful as a reference to practitioners of the technique. The original book had seven long chapters that may have made its use as a text - convenient. So the second edition is broken down into 25 shorter chapters. The first 7teen are concerned with the fundamentals of powder diffraction, which makes it much more logical, considering a typical 16-week long semester. The last ten chapters are concerned with practical examples of structure solution and refinement, which were preserved from the first edition and expanded by another example – R solving the crystal structure of Tylenol .

## **Fundamentals of Powder Diffraction and Structural Characterization of Materials, Second Edition**

"This edition reflects the changes which have occurred in spray drying technology and plant design since the publication of the fourth edition. The author argues that spray drying will remain the most important dehydration technique available to convert pumpable fluid feedstocks into powders. Topics covered include the drying principles, a survey of auxiliary equipment and the applications of spray drying in industry. There is a new chapter on spray drying in environmental control and there is a list of spray drying patents issued within the last five years. This edition also contains more data and tables that cover operation and design information for a wide range of products."--Provided by the publisher.

## Spray Drying Handbook

"Polymorphism in the Pharmaceutical Industry - Solid Form and Drug Development" highlights the relevance of polymorphism in modern pharmaceutical chemistry, with a focus on quality by design (QbD) concepts. It covers all important issues by way of case studies, ranging from properties and crystallization, via thermodynamics, analytics and theoretical modelling right up to patent issues. As such, the book underscores the importance of solid-state chemistry within chemical and pharmaceutical development. It emphasizes why solid-state issues are important, the approaches needed to avoid problems and the opportunities offered by solid-state properties. The authors include true polymorphs as well as solvates and hydrates, while providing information on physicochemical properties, crystallization thermodynamics, quantum-mechanical modelling, and up-scaling. Important analytical tools to characterize solid-state forms and to quantify mixtures are summarized, and case studies on solid-state development processes in industry are also provided. Written by acknowledged experts in the field, this is a high-quality reference for researchers, project managers and quality assurance managers in pharmaceutical, agrochemical and fine chemical companies as well as for academics and newcomers to organic solid-state chemistry.

## Polymorphism in the Pharmaceutical Industry

Molecular modeling techniques have been widely used in drug discovery fields for rational drug design and compound screening. Now these techniques are used to model or mimic the behavior of molecules, and help us study formulation at the molecular level. Computational pharmaceutics enables us to understand the mechanism of drug delivery, and to develop new drug delivery systems. The book discusses the modeling of different drug delivery systems, including cyclodextrins, solid dispersions, polymorphism prediction, dendrimer-based delivery systems, surfactant-based micelle, polymeric drug delivery systems, liposome, protein/peptide formulations, non-viral gene delivery systems, drug-protein binding, silica nanoparticles, carbon nanotube-based drug delivery systems, diamond nanoparticles and layered double hydroxides (LDHs) drug delivery systems. Although there are a number of existing books about rational drug design with molecular modeling techniques, these techniques still look mysterious and daunting for pharmaceutical scientists. This book fills the gap between pharmaceutics and molecular modeling, and presents a systematic and overall introduction to computational pharmaceutics. It covers all introductory, advanced and specialist levels. It provides a totally different perspective to pharmaceutical scientists, and will greatly facilitate the development of pharmaceutics. It also helps computational chemists to look for the important questions in the drug delivery field. This book is included in the Advances in Pharmaceutical Technology book series.

## Computational Pharmaceutics

The book describes the properties, analytical methods and the applications of different polyvinylpyrrolidone excipients (povidone, crospovidone, copovidone etc.) for use in pharmaceutical preparations. This group of excipients is one of the most important excipients used in modern technology to produce drugs. The book is intended for all persons working in the research, development and quality control of drugs. It gives a survey of all applications in solid, liquid and semisolid dosage forms including many drug formulation examples and more than 600 references to the literature.

## Polyvinylpyrrolidone Excipients for Pharmaceuticals

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