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Nanotechnologies for drug and contrast agents delivery

Elias Fattal

Univ Paris Sud, Institut Galien Paris-Sud, CNRS UMR 8612, Faculté de Pharmacie, F-92296 Châtenay-Malabry, France, elias.fattal@u-psud.fr

Nanoparticles have major potential biomedical applications. In most cases, these systems are made of polymers or lipids. These materials are biodegradable and degradation products should not be toxic and easily eliminated from the body. Applications of nanoparticles are based on the knowledge regarding their \emph{in vivo} fate following their administration facing two barriers: one that immunological consisting in their rapid uptake by the monocyte phagocytic system and the second that is cellular consisting in the endothelial barrier which cannot be crossed by nanoparticles unless it is leaky due to physiological or pathological conditions.

The knowledge about particle fate has allowed developing new nanomedicines for antiinfectious, anticancer drugs or nucleic acids. Nevertheless, we have shown that interactions of nanoparticles with the biological medium might also induce some deleterious effects such as inflammatory or oxidative response which should be taken into account in the development of these nanotechnologies. In our team, we have developed such strategies for local and systemic delivery of nucleic acids. Another way to improve drug efficiency is to combine molecularly targeted medical imaging and therapy. The principle is based on the detection of probes providing imaging contrast that can be targeted to specific molecular markers. The design of molecularly targeted contrast agents to elucidate molecular processes, to provide specific diagnosis and to help to target therapy is a major goal to achieve. In imaging techniques such as ultrasound and MRI, contrast agents are currently used to improve visualization of the microvasculature. Our goal is to design nanotechnologies containing these contrast agents for molecular imaging by ultrasound imaging and MRI using liquid perfluorocarbon, a compound that can provide dual imaging with these techniques. The aim of the presentation will consist in demonstrating our efforts in extending the possibilities and overcoming the limits in using nanotechnologies for the delivery of biotech drugs and contrast agents.
Perspectives on the crystal/amorphous duality of pharmaceuticals

M. Descamps, E. Dudognon, J.F. Willart

Unité Matériaux Et Transformations, (UMR CNRS 8207) MMT group.
University of Lille 1, Bât. P5, 59655 Villeneuve d'Ascq, France.
tel: 33 3 20 43 49 79 mail: marc.descamps@univ-lille1.fr

Most drugs are formulated in the solid state which may be either crystalline or amorphous (i.e. glassy). Disordered solids and amorphous materials are of interest, because they may have favorable biopharmaceutical properties e.g. enhanced solubility and dissolution capabilities. The drawback is their intrinsic physical and chemical instabilities since glassy materials are in a non-equilibrium state. As such their physical state depends on the way the amorphous states have been prepared. They also evolve upon aging. Manufacturing processes (quench cooling, milling, drying, extrusion…) impose very specific dynamical high stresses to the pharmaceutical compounds which may lead to a variety of amorphous physical states and physical state conversions.

In this presentation we consider two specific points of these issues:

(i) The metastability of the amorphous phase and its recrystallization. The question will be examined from the view point of the decoupling between the nucleation and growth processes, the interplay of polymorphism and the role of interfaces. Effects of confinement on the global kinetics will be briefly analyzed.

(ii) The possibility given by dynamical perturbations to create original amorphous states or (and) to modify their physical state and degree of stability. Consequences on formulation of amorphous drugs will be briefly raised.
Amorphous or nanocrystalline? Looking beyond the amorphous halo with the total scattering pair distribution function method

Simon J.L Billinge

Columbia University, USA, sb2896@columbia.edu

In the solid state, small molecules such as active pharmaceutical ingredient (API) molecules tend to pack in well defined arrangements leading to different crystalline polymorphs. An alternative solid form, increasingly of interest in the pharmaceutical industry, is the amorphous state. This state is characterized by a broad and largely featureless XRD pattern, the so-called “amorphous halo”, devoid of Bragg-peaks due to the lack of long-range order in the packing. A major challenge in bringing drugs to market in the amorphous form is the lack of a reliable method for fingerprinting, let alone carrying out a more complete structural characterization of, these materials. We have recently been exploring whether total scattering atomic pair distribution function methods (TSPDF) can alleviate this bottleneck. TSPDF uses short wavelength x-rays to obtain a scattering pattern of sufficient quality that it can be Fourier transformed to obtain a meaningful real-space pair distribution function that shows the distribution of atomic distances in the solid. We found that the approach is highly promising and provides additional information not available in a conventional XRD approach in the case of amorphous API’s. I will describe the method and show our results on a range of materials from more simple to more complex molecules. It is possible to differentiate truly amorphous from nanocrystalline forms and learn a surprising amount about the underlying molecular packing.
Synchrotron micro-XCT: A new non-destructive technique for imaging the 3D microstructure of pharmaceutical solid dosage forms at high resolution

J. Doucet, E. Leccia and B. Fayard
Novitom, 1, place Firmin Gautier F-38000 Grenoble (France), jean.doucet@novitom.com

The efficacy and safety of medicines both depend on the chemical nature of the drug and on the way the various ingredients are formulated together. The number of parameters to be controlled to reach the complex balance between all the ingredients in the final form is tremendous. It is necessary to take into account the various properties of the ingredients - physical, chemical, physico-chemical or mechanical. The micro-morphological parameters, like the size and distribution of the grains and the micro-defects, also play an important role in the bioavailability.

The drug formulation and manufacturing thus requires many efficient tools for the characterization and the control the products at all stages. Most techniques like optical microscopy, electron microscopy and FTIR spectro-microscopy, only provide results relative to a thin slice (2D), which limits the representativeness of the results. In addition, the sample preparation is generally invasive and/or destructive, which may cause artifacts.

During the last decade new 3D imaging techniques appeared, like confocal microscopy, optical coherent microscopy, acoustic microscopy, THz microscopy, NIR and H-NMR. The images they provide are interesting but generally difficult to interpret and to quantify. In addition, their lateral and in-depth spatial resolutions are generally different.

On the contrary, micro X-ray computed tomography (µXCT) is a non-invasive and non-destructive technique that overcomes most of the limitations of others 3D imaging techniques. It offers the best compromise between resolution, penetration depth and quantification. Its coupling with a synchrotron X-ray source (SR-µXCT) further enhances its performance in terms of spatial resolution, contrast and opportunity to track changes in real time.

µXCT consists in the reconstruction of three-dimensional objects from a series of radiographs obtained while rotating the object about an axis of rotation. The contrast of the images is due to differences of density between the various constituents of the object, like in medical radiography. The volumes are reconstructed in digital form. They can be graphically represented in different ways in order to highlight the structural detail of interest or the effects which are analyzed: series of virtual 2D sections or virtual sectional view of a cubic surface, either as a static image or animated form. The micro-morphological parameters of the constituents can be readily extracted from the quantitative analysis of the reconstructed volumes. The coupling of µXCT with a synchrotron X-ray source (SR-µXCT) further enhances its performance, leading to unprecedented performance in terms of image quality (contrast, sensitivity, resolution) and measurement time.

Our goal is to present here the unique capabilities of the SR-µXCT technique for the characterization and the analysis of solid dosage forms: 3D determination of grain morphology, volume distribution of grains and pores, micro-cracks, thickness and homogeneity of coatings, opportunity to track changes in real time in controlled environment (temperature, relative humidity and in liquid, under mechanical stress). Examples concerning semi-solid forms will be also presented.
Engineering Organic Glasses through Surface Mobility

Lian Yu

University of Wisconsin – Madison
School of Pharmacy and Department of Chemistry, USA, lyu@pharmacy.wisc.edu

Amorphous solids and glasses have important applications in bio-preservation, organic electronics, and the delivery of poorly soluble drugs. We report recent work that observed fast surface diffusion on organic glasses.¹ Surface diffusion is at least one million times faster than bulk diffusion, and remains fast despite significant bulk aging.² This high surface mobility is responsible for the fast surface crystal growth on organic glasses.³ Surface crystals rise above the glass surface as they grow laterally to exploit fast surface diffusion. Surface mobility is also responsible the formation of ultra-stable glasses by vapor deposition.³ Relying on rapid surface equilibration, vapor deposition can build glasses layer-by-layer to achieve exceptionally low energy and high density, as well as controlled anisotropy not present in liquid-cooled glasses.

REFERENCES:
Structural disorder, polymorphism and dynamics as seen by solid state NMR: the case of Ibuprofen

Marco Geppi¹, Elisa Carignani¹, Silvia Borsacchi², Marta Bonaccorsi¹, Lucia Calucci²

¹ Dipartimento di Chimica e Chimica Industriale, Università di Pisa, via Risorgimento 35, 56126 Pisa, Italy
email: marco.geppi@unipi.it
² ICCOM-CNR, via Moruzzi 1, 56124 Pisa, Italy

Ibuprofen (IB) is a drug used in many popular formulations. In spite of having been largely investigated, its structural and dynamic behaviour, as well as its polymorphism, show several still unknown aspects. Since several years our research group has been applying a variety of solid state NMR techniques to shed light on these properties for both the acidic and Na-salt forms of IB, either optically-pure and racemic [1-7].

The aspects that will be shown in this talk include:

(i) the polymorphism and pseudo-polymorphism of Na-IB studied by $^{13}$C CP-MAS spectra with the aid of X-ray and calorimetric data;
(ii) the detailed characterization of the molecular dynamic behaviour of acidic IB and the different forms of Na-IB, performed applying a variety of $^1$H and $^{13}$C spectral and relaxometric techniques over a very broad temperature range, and resulting in the quantitative determination of motional parameters for every individual molecular fragment;
(iii) the detection and distinction of either structural or dynamic disorder in the crystalline state and its detailed characterization with the aid of NMR measurements in the cryo regime and of DFT calculations.

The groups of M.H. Levitt (Southampton), P. Paoli (Florence), B. Mennucci and L. Bernazzani (Pisa) are greatly acknowledged.

REFERENCES

Nanoconfinement effects on ibuprofen based guests in mesoporous silica matrices

Madalena Dionísio¹, Ana Rita Brás², Isabel Fonseca¹, Gonçalo Brito Santos¹, Alexandra Costa¹,
Luís Branco¹, M. Teresa Viciosa³, Andreas Schoenhals⁴, Frédéric Affouard⁵ and Natália Correia¹,⁵

¹REQUIMTE/CQFB, Depto. de Química, FCT-UNL, 2829-516 Caparica, Portugal
madalena.dionisio@fct.unl.pt
²Forschungszentrum Juelich GmbH, 52425 Juelich, Germany
³CQFM-IN, IST-UTL, Avenida Rovisco Pais, 1049-001 Lisboa, Portugal
⁴BAM Federal Institute for Materials Research and Testing, D-12205 Berlin, Germany
⁵Unité Matériaux et Transformation (UMET), UMR CNRS 8207, UFR de Physique, BAT P5, Université Lille 1, 59655 Villeneuve d'Ascq, France

The molecular mobility and phase transformations of racemic ibuprofen based guests confined to nanostructured mesoporous silica, MCM-41 and SBA-15, with pore sizes ranging from 3.6 to 8.6 nm, were probed by Dielectric Relaxation Spectroscopy (DRS). Molecular dynamics was used to simulate racemic ibuprofen incorporated in MCM-41 (3.6 nm) pores.

It was confirmed that ibuprofen exists in the glass or supercooled state inside of pores, depending on the temperature. The molecular mobility of the guest revealed a multimodal character where three bulk-like relaxation processes: γ, β and α-process, the latter associated with the dynamic glass transition, and two additional ones were detected. With the exception of the highly local γ-process, the bulk-like processes emerged shifted to lower temperatures. The β-process for the confined guest was assigned to a Johari-Goldstein as found for bulk.¹ The mobility of the α-bulk-like relaxation is significantly enhanced inside pores undergoing a shift of ~ 20 and 30 K to lower temperatures for ibuprofen confined respectively, in, SBA-15 (8.6 nm)² and MCM-41 (3.6 nm).³ The respective relaxation time vs (1/T) dependencies change from VFTH in bulk, to Arrhenius-like inside pores, meaning that the scale of the confining media is interfering with the length scale of the cooperative motion underlying the glassy dynamics. The two additional processes are associated with the dynamics of the molecules anchored to the pore surface which mobility is highly slowed down. At the low-frequency flank of a dominant surface S-process, a Debye-like relaxation is found. The latter was attributed, with the help of MD simulations, to an internal conversion of the carboxylic groups between two conformations coupled to the fluctuations of the interfacial hydrogen-bonded structures, which are in the origin of the S process. It was demonstrate that ibuprofen is stabilized in the amorphous form over large periods of time (at least 2 years).

An additional strategy is reported where the ibuprofenate anion intrinsically combined with the cation of an ionic liquid was incorporated in SBA-15 with pore sizes of 4.5 and 5.7 nm being observed that the smaller pore size was efficient in avoiding crystallization.

REFERENCES

Solubility in polymers – an important parameter for the development of amorphous solid dispersions

Timo Rager

Solvias AG, Department for Solid-State Development, Römerpark 2, 4303 Kaiseraugst, Switzerland
timo.rager@SOLVIAS.com

New chemical entities for pharmaceutical or agricultural applications suffer increasingly from low solubility in aqueous systems, with the consequence that their bioavailability is poor. Essentially two approaches have been followed over the last decades to alleviate this problem: formation of co-crystals and formation of amorphous solid dispersions.

Amorphous solid dispersions consist of molecularly dispersed, i.e., dissolved, active ingredients in a glassy polymer. The idea behind this kind of formulation is that the active ingredient is kept in a highly soluble, quasi-amorphous state and prevented from crystallizing. Ideally, the solubility limit of the active ingredient in the polymer should not be exceeded in order to ensure unlimited stability of the formulation.

This raises the question of determining the solubility of a crystalline low molar mass compound in a polymer. Answering this question is far from trivial because of the inherent kinetic hindrance in highly viscous or even glassy polymeric systems.

Numerous methods have been proposed for this solubility determination in the past. A new approach, which is based on an evaluation of the melting enthalpies that are determined for mechanical mixtures of polymer and active ingredient, will be presented here. With the aid of an equation that is derived from the van't Hoff equation, these enthalpies are transformed into solubility curves, showing the solubility limit for the active ingredient as a function of temperature (see figure below).

Mechanochemistry: a versatile approach to materials synthesis and its specific role in pharmaceutical sciences

William JONES
University of Cambridge, UK, wj10@cam.ac.uk

Mechanochemistry deals with reactions induced by the input of mechanical energy – for example by impacts within a vibratory ball mill. The technique has seen application in a variety of areas of materials science including mechanical alloying in metallurgy, the synthesis of complex organic molecules and, more recently, the discovery and development of new solid forms of active pharmaceutical ingredients. Mechanochemistry has a long history with significant contributions from Ostwald, Carey Lea and notably Michael Faraday. My lecture will briefly overview the broad areas of application of mechanochemistry, with the major part being a focus on recent applications in the area of pharmaceuticals and its important role in exploring the rich variety of solid forms available for small, drug-like molecules.
Cocrystals and their shifting transition points

Nair Rodriguez-Hornedo

Department of Pharmaceutical Sciences, University of Michigan, Ann Arbor, Michigan 48109-1065, USA
e-mail: nrh@umich.edu

Pharmaceutical cocrystals are of great interest because of their potential to enhance solubility and bioavailability of poorly water-soluble drugs. Cocrystal development is however limited by their poor thermodynamic stability in aqueous environments. The work presented here will describe the mechanisms by which cocrystal stability can be fine-tuned via solution phase chemistry. Cocrystal thermodynamic stability is determined by the activities and chemical equilibria of cocrystal components in solution. As a result, the cocrystal to drug solubility advantage (Scocrystal/Scdrug) can be switched by changing the activities of dissolved cocrystal constituents. We have shown that moisture sorption by hygroscopic polymers or sugars [1] can generate cocrystals that are otherwise unstable in water. Moisture sorption and residual water content play an important role on cocrystal transformations where the stability range of cocrystals is determined by the solution composition of cocrystal components.

We have recently discovered that micellar surfactants can impart thermodynamic stability to intrinsically unstable cocrystals in aqueous media [2]. Cocrystals have a transition point at a specific surfactant concentration, such that a cocrystal more soluble than drug becomes equally soluble to drug, and on crossing the transition point the cocrystal becomes less soluble than drug. The mechanistic basis of such behavior is shown to be the asymmetric affinities of solubilizing agents for cocrystal constituents. Recognizing this property of cocrystals is critical for pharmaceutical development, as commonly used formulation additives can reduce and even switch the cocrystal solubility advantage over drug.

This talk will present the chemical basis and mathematical models that describe the sensitivity of cocrystal transition points and phase diagrams to solubilizing agents. An otherwise incongruently saturating cocrystal becomes congruently saturating by increasing the magnitude of drug solubilization over coformer. It will be shown that cocrystal transition points and critical stabilization concentrations (CSCs) of solubilizing agents can be predicted from the equilibrium constants associated with cocrystal dissolution and solubilization processes.

REFERENCES
Continuous cocrystallization of pharmaceutical products via Hot Melt Extrusion processing.

Dennis Douroumis

University Greenwich, UK, D.Douroumis@greenwich.ac.uk

Hot Melt Extrusion is an effective process technology for the development of pharmaceutical cocrystals in a continuous manner. This is an emerging area of development and has attracted industrial interest. HME processing is advantageous compared to traditional approaches as it can provide high quality (purity) of cocrystals with enhanced dissolution rates and excellent stability. Moreover, HME is coupled with Process Analytical Tools (PAT) such as NIR to monitor the manufacturing process to provide a better understanding and quality control.
Cocrystal Prediction: a reality for new drugs

Rafel Prohens\textsuperscript{1}, Christopher A. Hunter\textsuperscript{2}

\textsuperscript{1}Center for Intelligent Research in Crystal Engineering, Spain, rprohens@circecrystal.com
\textsuperscript{2}Department of Chemistry, University of Cambridge, ch664@cam.ac.uk

Formulation of drugs as cocrystals offers an opportunity to modulate physical properties, so identification of cocrystal formers for an active pharmaceutical ingredient is an area of great relevance to the pharmaceutical industry. Exhaustive experimental cocrystal screening is a very time-consuming task, but we have developed a computational method for identifying cocrystal formers that have a high probability of success based on calculated functional group interaction energies.\textsuperscript{[1]} The advantage of our approach is that it is sufficiently fast to be used as a high throughput method to screen very large numbers of potential coformers. The virtual screening tool has been applied to several APIs with a large coformer library in order to experimentally validate the method.\textsuperscript{[2],[3]}

Our results suggest that success rates in cocrystal screening can be significantly improved by application of computational filters to select the most appropriate coformers for experimental study.

REFERENCES

Advanced X-ray diffractometric techniques to characterize multicomponent pharmaceutical systems

Raj Suryanarayanan
University of Minnesota, College of Pharmacy, Minneapolis, MN, USA, surya001@umn.edu

Conventionally, powder X-ray diffractometry (XRD) has found widespread use for the identification of crystalline solid phases. Recent advances in instrumentation and software extend the utility of the technique to the study of multicomponent systems. Thus the active pharmaceutical ingredient in a complex dosage form, and more importantly, phase transitions induced during processing and storage can be characterized and quantified. The use of an X-ray microdiffractometer with an area detector enabled us to monitor phase transformations in tablets. The spatial information, gained by monitoring the tablet from the surface to the core (depth profiling), revealed progression of phase transformations from the surface to the tablet core as a function of storage time. Low temperature XRD enabled the physical characterization of solutes in frozen aqueous solutions. By attaching a vacuum pump to the low temperature stage of the diffractometer, it was possible to carry out the entire freeze-drying process in situ, in the sample chamber of the XRD. This enabled real time monitoring of phase transitions during all the stages of the freeze-drying process. The use of synchrotron radiation, by substantially enhancing the sensitivity of XRD, has extended the applications of XRD.
Tuning drugs release via multicomponent crystal forms

E. Dichiarante1, M. Curzi2, S. L. Giaffreda2, Genny Lamboglia2, D. Braga3, L. Chelazzi3, F. Grepioni3, M. R. Chierotti2 and R. Gobetto4

1PolyCrystalLine s.r.l., via F.S. Fabri 127/1, 40059 Medicina (BO), Italy; elena.dichiarante@polycrystalline.it
2PolyCrystalLine s.r.l., via F.S. Fabri 127/1, 40059 Medicina (BO), Italy
3Dipartimento di Chimica G. Ciamician, Università degli Studi di Bologna, Via Selmi 2, 40126 Bologna, Italy
4Dipartimento di Chimica I.F.M., Università di Torino, Via Giuria 7, 10125 Torino, Italy

A general strategy in the pharmaceutical industry is the selection of compounds free from physicochemical problems, and their developments using simple dosage forms.[1] For these reasons, but also for the considerable financial interest caused by legal ramifications, a constant screening for new drug solid forms and in particular multicomponent crystal forms is ongoing.[2] Multicomponent crystals can provide a different strategy to obtain new active pharmaceutical ingredients by altering the chemical and physical properties (solubility, stability, dissolution rate, etc) of molecular solid forms to improve crystal properties of API.[3]

In this work our Salt/Co-crystal screening protocol was applied to identify new multicomponent crystal forms of antidepressant Venlafaxine used as hydrochloride form in the treatment of major depressive disorder and anxiety disorder. The API was co-assembled, with different coformer pharmaceutically accepted, [4] by solid state techniques and crystallization from solution,[5] All new forms obtained were characterized by combined use of X-ray powder diffraction, differential scanning calorimetry, thermogravimetric analysis, FT-IR and Solid State NMR. Dissolution tests were also performed and compared to the value observed for the commercialized form that shows a high dissolution rate. In order to obtained an extended release the API is formulated in spheroids coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. The new multicomponent crystal forms obtained showed a decreased solubility with respect to that of venlafaxine HCl. Work is in progress to test the solubility of formulations prepared with the new multicomponent crystal forms.

REFERENCES

An Approach to the Measurement of Drug-Excipient Incompatibility

J. Loubens¹, S. Aubuchon² and L. Thomas³

¹TA Instruments France 5 rue Jacques Monod 78280 Guyancourt, France jloubens@tainstruments.com
²S. R. Aubuchon, Ph.D TA Instruments, 151 Lukens Drive, New Castle, DE 19720, USA
³L. C. Thomas DSC Solutions LLC, Smyrna, DE 19977, USA

Drug delivery systems or formulations typically consist of several ingredients, one of which is the actual drug or active pharmaceutical ingredient (API). Other components (excipients) in the formulation are added to improve manufacturability, stability or delivery of the drug to the patient. During development of an effective and reliable drug-delivery formulation, it is important to verify that none of the selected excipients has an adverse effect on drug efficacy. The pharmaceutical industry uses a variety of analytical techniques to evaluate drug-excipient interaction or incompatibility. However, these techniques are often applied after weeks and months of oven aging under varying conditions of temperatures and / or humidity. This delay in detecting drug-excipient incompatibility is expensive and can significantly impact commercialization of a beneficial drug. Our approach, using a combination of Thermogravimetric Analysis (TGA), Differential Scanning Calorimetry (DSC) and Temperature Modulated DSC, reduces the test time to one day and requires only a few milligrams of sample. Utility of this approach will be illustrated on mixtures of acetylsalicylic acid (aspirin) with magnesium stearate and crystalline sucrose.

Thermal analysis techniques such as TGA, DSC and Modulated DSC® should be the fastest and most reliable way to detect drug-excipient incompatibility because they have extremely high sensitivity for detecting changes in composition, thermal stability and structure. However, thermal analysis is seldom used for a variety of reasons including:

- Lack of a systematic approach; what time and temperature?
- Difficulty in relating room temperature stability to DSC results that are created at high temperatures, where the form of the drug is often amorphous
- Difficulty in interpreting DSC results

In this subject, we illustrate an approach fast and easy to use. Decisions about compatibility between the drug and excipient can typically be made in a day as compared to traditional oven and humidity aging, which can take months.

Experiments are carried over with Thermogravimetric analysis (TGA) and Differential Scanning Calorimetry (DSC and Modulated DSC®).

MDSC has much higher sensitivity than DSC for detection of drug-excipient interaction. This is due to the unique ability of MDSC to measure heat capacity under quasi-isothermal conditions. Since heat capacity is an absolute property, and not a rate like the heat flow signal of DSC, interaction can be measured even at low temperatures and low reaction rates. The change in heat capacity versus time at a constant temperature is a direct measurement of the compatibility or incompatibility inside a mixture of two components; It can be also compared to microcalorimetry measurements performed by high sensitivity instruments like TAM III Thermal Activity Monitor.

KEY WORDS
Drug Excipient compatibility, DSC, Modulated DSC®, Microcalorimetry
Small-volume and localized fields for nucleation understanding
CINaM-CNRS, Aix-Marseille Université, Campus de Luminy F-13288 Marseille, France
veesler@cinam.univ-mrs.fr

A better understanding of nucleation will open the way to new approaches to crystallization in production, for instance of pharmaceuticals and nanomaterials. In addition, we still lack a comprehensive theory of crystal nucleation from solution, mainly due to the fact that experiments on nucleation are generally of a stochastic nature: we do not know where and when an indefinite number of nucleation events will occur. A direct approach would consist in exploring the formation and the structure of the critical nuclei and then unravel the mechanisms of nucleation. Thus, we develop usual and unusual approach of crystallization. [1, 2]

First, to treat the stochastic nature of the nucleation, we use a recently developed universally solvent-compatible microfluidic device for crystallization studies in the nanoliter range. [3] This PEEK/Teflon microfluidic device is ideal for studying crystallization. It makes it possible to study crystallization of all solutes whatever the medium of crystallization: aqueous or organic solvents. The hundreds of droplets generated in the microfluidics setup yields a large sample of independent nucleation events.

Second, we propose a way of getting to the bottom of nucleation by controlling spatial and temporal location. We present experiments on the effective spatial and temporal control of nucleation in solution on biological and mineral molecules. [4] We developed 2 setups:
- A temperature-controlled setup for in-situ investigation of the effects of localized voltage on the nucleation and growth. [5]
- And, a simply-constructed and easy-to-use fluidic device that generates arrayed aqueous phase microdroplets in oil [6]. Up to thousands of microdroplets are generated, with volumes ranging from nanoliter to femtoliter, without surfactant.

We show how creating localized fields and fluxes [7], preventing convection and confining solutions led to a spatial control of the nucleation event. We confirm that miniaturization of crystallization tools offers interesting potentialities for the control and the study of crystallization processes.

REFERENCES
Crystal nucleation of poorly soluble drugs in aqueous solutions

Lennart Lindfors.

Pharmaceutical Development, AstraZeneca R&D Mölndal, SE-43183 Malmö, Sweden, Lennart.Lindfors@Astrazeneca.com

A significant proportion of drugs on the market are poorly soluble in water and it is expected that this will be even more pronounced in the future. Formulations of poorly water-soluble compounds offers a challenge to the formulation scientist, from the early discovery phase through the development to the launch of the pharmaceutical product. In formulations of poorly soluble compounds drug particle size are often reduced in order to facilitate drug dissolution. An interesting alternative are formulations where the API are in metastable state, for example in solid dispersions or when a salt of the API is used. The metastability offers an increased driving force for drug absorption. However, for the same reason crystallization to a less soluble state may occur.

In the presentation crystallization of a model compound, bicalutamide, in the absence and presence of a polymer polyvinylpyrrolidone (PVP) will be discussed. Results showed that PVP decreased the crystallization rate significantly in a system with PVP concentrations as low as 0.01 %(w/w), without changing the polymorph formed. Furthermore, in experiments designed to specifically study crystal nucleation, the same nucleation rate was found in the absence and presence of PVP. Instead, PVP adsorbs to the crystals formed in solution and by doing so, the crystal growth rate is reduced. This was confirmed in separate experiments using bicalutamide nanocrystals. By combining theories describing classical nucleation and crystal growth, with some modifications, a consistent description of several independent experiments performed in polymer-free systems was obtained. From these experiments a crystal-water interfacial tension of 22.1 mN/m was extracted.

REFERENCES

Crystallization kinetics and dynamics of amorphous pharmaceuticals under high pressure

S. Capaccioli¹, D. Prevosto², Wenkang Tu³ and Li-Min Wang³

¹Dipartimento di Fisica, Università di Pisa, Largo B. Pontecorvo 3, I-56127 Pisa, Italy, capacci@df.unipi.it
²Institute for Chemical and Physical Processes, CNR IPCF, I-56127 Pisa, Italy
³State Key Lab of Metastable Materials Science and Technology, College of Materials Science and Engineering, Yanshan University, Qinhuangdao, Hebei, 066004, China

The choice of the amorphous solid form for active pharmaceuticals ingredients (API) is often preferred for its improved solubility and bioavailability but its metastability entails the drawback of an enhanced tendency to crystallize, limiting broad applications. The recrystallization from the supercooled liquid form is a long studied phenomenon, rationalized taking into account both thermodynamic driving force and molecular mobility. Nevertheless, several recent studies reported unpredicted results showing fast mode of crystal growth (FCG) near and below the glass transition temperature, in a temperature range usually considered safe for the long term storage, since the molecular mobility is assumed to be arrested [1]. The origin of the fast crystal growth and the mechanism controlling the kinetics of recrystallization are still matter of debate [1,2]. Dynamics properties have been proposed to be important: in particular fast crystallizing systems have been often correlated to high fragility, strong translational/rotational decoupling, broadness of relaxation time distribution, while some studies report a peculiar role of the local secondary relaxations [3]. On the other hand, the importance of thermodynamic factors with respect of dynamic ones has been also suggested [4].

In this context, studies performed under pressure variations can be very useful. Usually pressure is a variable of interest in pharmaceuticals research to reveal polymorphism or to build the pressure-temperature phase diagram. Moreover, high pressure studies can be important to predict how tabletting can affect the API state. In principle high pressure paths could bring to glasses with higher stability, due to less excess of free energy, reduced fragility, less decoupling, and larger activation energy for local processes. The effect of density over the thermal fluctuations in favoring FCG has been also theorized [2], but experiments gave controversial results, with crystallization rate both strongly reduced [5] or enhanced [6] with increasing pressure. Actually, both thermodynamic and kinetic factor of the crystallization process should be taken into account [7]. We will present a study about the effect of temperature and pressure (up to 0.7 GPa) on (i) thermodynamic properties, (ii) dynamics and (iii) crystallization kinetics of a group of molecular pharmaceuticals, characterized by high (like ketoprofen) or low (like antipyrine) glass forming ability. We analyzed calorimetric and PVT (density) data to pursue goal (i), and broadband dielectric spectroscopy and iso-frequency dielectric monitoring, respectively, for goals (ii) and (iii).

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REFERENCES

Solubility and polymorph forms of paracetamol in supercritical CO₂

A. Idrissi, M. Kiselev, R. Oparin

Institute of solution chemistry of the RAS, Akademicheskaya st. 1, 153045, Ivanovo, Russia,
Laboratoire de Spectrochimie Infrarouge et Raman (UMR CNRS A8516), Université des Sciences et Technologies de Lille, 59655 Villeneuve d’Ascq Cedex, France, nacer.idrissi@univ-lille1.fr

Polymorphism of the drug compounds is one of the important problem in pharmaceutical science. As far as polymorphs have different physico-chemical properties, the study of nucleation process, re-crystallization, solubility, crystalline structure is crucial for the understanding of their bio-availability. There are two kind of polymorphism, which are discussed in the literature, depending on the type of nucleation process: namely packing or conformational ones. The packing nucleation means that molecules with almost uniform conformations are packed in different arrangement and therefore may form set of crystalline structures, while conformational polymorphism is defined as a possibility to form crystalline structures from different conformers. The screening of polymorphism is a hardly solving problem, because of so many control parameters. The conventional way to obtain polymorphs is crystallization of the most stable polymorph with later re-crystallization using In-situ heating, In-situ freeze drying, or crystallization from organic solvent etc. Recently there has been considerable interest to the new class of non-aqueous solvents which are the supercritical (SC) fluids (SCF). In the pharmaceutical industry the use of SCF and especially supercritical carbon dioxide is a promising alternative to replace processes such as extraction, drying and crystallization while more effectively controlling particle size and crystal polymorph. Carbon dioxide can replace environmentally toxic solvents as acetone, carbon tetrachloride, dimethylsulfoxide and so on, in process that although expensive purification procedure is used, the final product still contains low but still dangerous concentration of these toxic solvents. The use of supercritical fluids approach may help to control solubility and polymorph distribution functions for further nucleation of crystalline phase of certain polymorphic forms by varying the parameters of state rather then changing the solvents and the pH. In this presentation we will show the results of the investigation of solubility properties of a bioactive substance in Supercritical CO₂ (sCO₂). By using acetaminophen as a model compound we show that the IR spectroscopy can provide high sensitivity that makes it possible to study solubility at small concentrations, up to 10⁻⁶ mol.l⁻¹. Furthermore, the analysis of polymorph nucleation, using in situ IR spectroscopy at supercritical condition, will be discussed.

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Stabilization of Freeze Dried Disaccharide Based Formulations by Limited Addition of Polyols, Amino Acids, and Salts: What is (are) the Mechanisms

Michael J. Pikal

School of Pharmacy, University of Connecticut, Storrs, CT, USA
michael.pikal@uconn.edu

Some years ago Cicerone and Soles\(^1\) demonstrated that addition of small amounts of glycerol could improve stability of proteins in freeze dried trehalose based formulations. Similarly, we found that addition of small amounts of sorbitol could stabilize freeze-dried trehalose and sucrose formulations of a monoclonal antibody\(^2\). This stabilization did not correlate well with FTIR measures of the impact of sorbitol on protein structure or with the impact of sorbitol on the Tg or the enthalpy relaxation time (i.e., sorbitol addition decreases Tg and relaxation time). Recently, we have investigated the impact of addition of small amounts of amino acid and addition of small amounts of salts (alkali metal halides) on stability of proteins in disaccharide based formulations. Of the 15 amino acids investigated, all but two improved stability of the model proteins (rHSA and alpha chymotrypsin), with the degree of improvement depending on both the type and amount of amino acid used. Stability improvement approached a factor of five in several cases. We also find, that for BSA and rHSA formulated with sucrose (1:1 weight ratio), addition of LiCl and NaCl at moderate levels (≈9% of total solids) improved aggregation stability in the freeze dried solid by more than a factor of two. Finally, we note that protein stability in a given formulation is often optimal at an intermediate water content and suggest this observation may have it’s origin in the same physics that is driving the glycerol and sorbitol effects noted above.

The “mechanism” responsible for the stabilization produced by addition of small molecules was suggested\(^3\) to arise from the moderation of “fast dynamics” in these glassy systems by the glycerol, and presumably also by other “small molecules”. It was thought that the small molecule essentially fills “free volume holes” in the complex glass. Data for mean square amplitude of motion, \(<u^2>\), as measured by neutron backscattering, and high precision density measurements support this concept. Moreover, a number of studies have established an excellent correlation between stability and \(<u^2>\), even in cases where correlations between stability and protein structure, T\(_g\), or global dynamics, are poor. Thus, of the various physical parameters that might be expected to be predictive of stability, \(<u^2>\) data seem to correlate best with stability. However, with our amino acid data, correlation of stability enhancement with \(<u^2>\) is poor. Moreover, correlation with enthalpy relaxation times and correlations with free volume hole size evaluated by PALS were even worse. It seems that for modest ranges of stability and \(<u^2>\) other effects dominate. Perhaps the degree of coupling between protein and matrix as well as surface effects need to be seriously considered.

REFERENCES

Conformational disorder and atropisomerism in pharmaceutical compounds

A. Cesàro1,2, B. Bellich1, G. Giannini1, L. Fontanive1, S. Di Fonzo2, N. Masciocchi3 A. Maiocchi4 and F. Uggeri4

1Lab. Chimica Fisica e Macromolecolare, Dip. Scienze Chimiche e Farmaceutiche - Università di Trieste, Via Giorgieri 1 - 34127 Trieste e-mail cesaro@units.it
2Elettra-Sincrotrone Trieste,Italy, Strada Statale 14 km 163.5, Area Science Park, 34149 Trieste, Italy
3Dipartimento di Scienze e Alta Tecnologia, Università dell’Insubria, via Valleggio 11, 22100 Como, Italy
4Centro Ricerche Bracco, Bracco Imaging s.p.a., via Ribes 5, 10010 Collietta Giacosa (Torino), Italy

Many simple molecules of pharmaceutical relevance show complex conformational disorder in the liquid and solid states. Conformational disorder is a major hamper for crystallization and may favor the formation of amorphous materials. The obvious outcome is a substantial change in the material physico-chemical properties, in particular, in the equilibrium between solution saturation and solid state. The industrially relevant open issue deals with the fully understanding of crystallization conditions and the prediction of the polymorphic forms for new (and old) drugs. Attempt to analyze super-saturation and crystal growth during batch crystallization from solutions containing multiple conformers has been mechanistically presented in literature on the basis of the so-called approach of the single right conformer. Thus, strategies have been reported in controlling crystallization of conformationally flexible molecules. In addition, the relation between conformational disorder and crystal polymorphism is nowadays the specific goal of an extensive modelling with the use of hybrid ab-initio computer simulation. A particular category of conformational isomerism is that named “atropisomerism”, occurring in molecules with a topological chiral axis maintained by hindered rotation about single bonds. Thus, atropisomerism is a type of rotational isomerism in which the atropisomers can be experimentally separated if the barrier to rotation is large enough. The conventional energy barrier for atropisomers to be isolated at room temperature is approximately 25 kcal/mol [1,2]. The most important issue is that, when the barrier to rotation between the interconverting atropisomers is very high, the interconversion is hindered to the point that isomers can be considered as thermodynamically distinct molecules (as hexahelicene). The outcome for molecules with an intermediate barrier is that of an increasing apparent solubility of a crystalline form containing one atropisomer form only.

Examples of conformational polymorphism and its influence on crystallization will be given before outlining some properties of the tri-iodinated molecules [3], largely used as contrast agents, which show an extremely complicated pattern of conformational atropisomerism [4]. The success of these molecules will be shown to largely depend on the value of energy barrier that stabilizes a mixture of conformers.

REFERENCES

Structure formation in amorphous carbohydrates and proteins: phase behavior, barrier properties and relation to encapsulation performance.

Job Ubbink\textsuperscript{1,2}, Mina Roussenova\textsuperscript{2}, Concetta Tedeschi\textsuperscript{3}, Bruno Leuenberger\textsuperscript{2}, and Ashraf Alam\textsuperscript{2}

\textsuperscript{1}Food Concept & Physical Design “The Mill”, Mühleweg 10, CH-4112 Flüh, Switzerland, job.ubbink@themill.ch
\textsuperscript{2}DSM Nutritional Products AG, Wurmisweg 576, CH-4303 Kaiseraugst, Switzerland
\textsuperscript{3}H.H. Wills Physics Laboratory, University of Bristol, Tyndal Avenue, Bristol BS8 1TL, UK

Bioactive compounds in food, nutrition and pharmaceutics are often encapsulated in amorphous matrices principally consisting of mixtures of carbohydrates and biopolymers. In the glassy state at low water contents, such matrices have a number of functional properties, which render them useful in stabilizing and protecting sensitive bioactive compounds under adverse conditions. Specifically, glassy matrices based on carbohydrates and biopolymers constitute efficient barriers against the migration of oxygen and hydrophobic compounds. In addition, in the glassy state, they effectively form a scaffold stabilizing biomolecules and biomolecular complexes in low-moisture states by hydrogen bonding. The Achilles’ heel of encapsulation systems based on glassy carbohydrates and biopolymers is however their sensitivity to water. In particular for application in foods, which are often characterized by an elevated water activity, this constitutes an important limitation of the use of such encapsulation systems.

In this lecture, we will focus on the role of water in modulating the properties of carbohydrate- and protein-based encapsulation systems:

1. We will review recent results on the plasticization and anti-plasticization in amorphous carbohydrates and proteins, with as specific aim to demarcate the fundamental physical limits of application of such systems for the protection of sensitive bioactive compounds. In this context, we will report on our recent results on the interplay of hydrogen bonding and molecular packing in glassy carbohydrates \cite{1}.

2. We will discuss strategies to partially circumvent issues arising from the sensitivity of carbohydrate-biopolymer-based encapsulation systems to water. In particular, we will explore to which extent the formation of higher-order structures \cite{2,3} and micro-phase separation \cite{4} in essentially amorphous matrices consisting of a low molecular weight carbohydrate and a carbohydrate or protein-based biopolymer may help to increase the water activity range in which such systems can successfully be applied. We will present novel results of our recent investigation of the phase behavior of and structure formation in blends of hydrophobically modified starch and sucrose \cite{4}.

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\cite{4} C. Tedeschi, B. Leuenberger, J. Ubbink, Amorphous-amorphous phase separation in hydrophobically modified starch-sucrose blends I. Phase behavior and thermodynamic characterization (submitted, 2014).
Physical stability of amorphous molecular dispersions

J.F. Willart, E. Dudognon, A. Mahieu and M. Descamps

UMET (Unité Matériaux et Transformations) UMR CNRS 8207
University of Lille 1, Bât. P5, 59655 Villeneuve d’Ascq, France.
Jean-Francois.Willart@univ-lille1.fr

The molecular dispersion of a drug into a polymer is generally used to increase both its solubility and the physical stability of its amorphous form[1]. However, this formulation route requires a perfect knowledge of the solubility of the drug in the polymer. This property is in particular important for selecting appropriate polymers for formulations since it defines the maximal drug loading which prevents recrystallization. However, up to now, the determination of the solubility curve of drug/polymer systems is a long and tedious task. This situation is mainly due to the high viscosity of polymers which generally makes the equilibrium saturated states very difficult to reach[2].

We present here two original methods to determine faster the solubility of drugs into polymers[3]. The originality of the methods lies in the fact that the equilibrium saturated states are here reached by demixing of a supersaturated amorphous solid solution and not by the usual dissolution of a crystalline drug into an amorphous polymer. The equilibrium saturated states are thus much faster to reach due to the extra molecular mobility resulting from the strong plasticizing effect associated with the supersaturation conditions.

REFERENCES


Mark Shon¹, Beena Uchil ² and Dr. Philippe Lam ³

¹SP Scientific, Warminster, USA, PA, Mark.Shon@SPScientific.com
²Fresenius –Kabi, Skokie, IL
³Genentech, South San Francisco, CA,

In 2002, Dr. Michael Pikal in a paper published in American Pharmaceutical Review stated the following: “Control and Characterization of the Degree of Super-Cooling Can Provide a Solution to What is Perhaps the Biggest Freeze Drying Scale-Up Problem”. The ability to control nucleation during the freezing step of lyophilization has been considered to be one of the most significant developments in freeze drying in decades. A number of benefits have been demonstrated at the development scale including: Significant reduction in primary drying times, reduction in protein aggregation, improvement in cosmetic elegance of the cake, reduction in vial breakage, improved vial to vial uniformity and adherence to the FDA’s QbD initiative. In order for these advantages to have commercial benefits, controlled nucleation needs to be capable of being implemented in large production dryers. This presentation reviews the current state of commercialization and specifically details two collaborative studies where ControLyo™ Nucleation on Demand Technology was used to control nucleation in two different 28 square-meter production freeze dryers.
Local Controlled Drug Delivery to the Inner Ear

J. Siepmann\textsuperscript{1,2}, M. Gehrke\textsuperscript{1,2}, J. Sircoglou\textsuperscript{2,3}, C. Vincent\textsuperscript{2,3} and F. Siepmann\textsuperscript{1,2}

\textsuperscript{1}University of Lille, College of Pharmacy, 3 Rue du Prof. Laguesse, 59006 Lille, France
juergen.siepmann@univ-lille2.fr
\textsuperscript{2}INSERM U 1008, Controlled Drug Delivery Systems and Biomaterials, 3 Rue du Prof. Laguesse, 59006 Lille, France
\textsuperscript{3}University of Lille, School of Medicine, 1 Place de Verdun, 59000 Lille, France

Drug delivery to the inner ear is highly challenging due to the blood-cochlear barrier, which is anatomically and functionally similar to the blood-brain-barrier [1,2]. Upon drug administration via common routes (including oral, i.v., i.m. etc.) often only minor amounts of the active agent reach the target site (e.g. hair cells, lateral cochlear wall), because tight junctions effectively hinder the passage from the systemic circulation into the inner ear. Silicone-based cochlear implants allowing for local controlled drug delivery directly to the target site offer a great potential to overcome this crucial hurdle. However, the preparation and characterization of such systems is highly challenging, due to their small dimensions. Mathematical modeling can help facilitating the optimization of this type of advanced delivery systems: Mechanistically realistic mathematical theories can be used to allow for in silico simulations of the effects of key parameters of miniaturized implants (e.g., size and composition) on the resulting drug release kinetics. Importantly, such theoretical predictions do not require the knowledge of many system-specific parameters: Only the so-called “apparent” diffusion coefficient of the drug within the implant matrix is needed. This parameter can be easily determined via drug release measurements from thin, macroscopic films. The validity of the theoretical model predictions can be evaluated by comparison with independent experimental results obtained with cochlear implants. The latter consisted of miniaturized electrodes, which were embedded in silicone matrices loaded with various amounts of dexamethasone. Importantly, the experimental results confirmed the theoretical predictions. Thus, the presented theories can help to significantly speed up the optimization of this type of controlled drug delivery systems, especially if long release periods are targeted (e.g., several months or years).

REFERENCES
Cellulose derivatives for controlled release

Anette Larsson\textsuperscript{a,b}, Jurgita Kazlauske\textsuperscript{a,b}, Helene Andersson\textsuperscript{b,c}, Mariagrazia Marucci\textsuperscript{b,d}, Johan Hjärtstam\textsuperscript{b,d}, Mats Stading\textsuperscript{b,c}, Christian von Corswant\textsuperscript{b,d}

\textsuperscript{a} Pharmaceutical Technology, Applied Chemistry, Chemical and Biological Engineering, Chalmers University of Technology, Kemivägen 10, S-412 96 Gothenburg, Sweden, +46 31 772 2763, anette.larsson@chalmers.se

\textsuperscript{b} SuMo BIOMATERIALS, A VINNOVA VINV Excellent Center at Chalmers University of Technology

\textsuperscript{c} AstraZeneca R&D Mölndal, SE-431 83 Mölndal, Sweden

\textsuperscript{d} SIK – The Swedish Institute for Food and Biotechnology, Structure and Material Design, P.O. Box 5401, SE-402 29 Gothenburg, Sweden

Concepts for oral controlled drug release have been around since the 60’s, but still there is a need of understanding the release mechanism in order to develop formulations with improved drug release properties. This presentation will exemplify the effect of molecular weight on the drug release rate from pellet systems coated with cellulose derivatives ethyl cellulose, EC, and hydroxyl propy cellulose, HPC prepared from ethanol solutions. During the coating step, the ethanol will evaporate and the concentration of EC and HPC will increase. Due to the differences in molecular weight a phase separation will occur and create domains with high EC content or domains with high HPC content. Depending of the molecular weight, the phase separation will occur differently.\textsuperscript{1,2} Furthermore, since EC is water insoluble, whereas HPC dissolves in water, exposure to water of EC/HPC films will lead to dissolution and release of percolating HPC domains and formation a water filled pore structures. Since the phase separation depends on the molecular weight of the cellulose derivatives, different pore structures will be developed, resulting indifferent permeability of water and drugs through the coatings. Thus, by knowing how the films are formed one can predict the drug release rate. Coatings using water based EC coatings will have a complete other film formation mechanism. Here, EC particles with sizes around 100-150 nm are dispersed in water by using stabilizers, like surfactants. When the water evaporates during the coating step, the concentration of particles will increase and, if the conditions are correct, the EC particles will coalesce and form a coherent film. We have made our own EC dispersions and added HPC to the dispersions. Stability studies show that the addition of HPC introduces sedimentation of the dispersion. This may also influence the film structures.

Figure: CSLM images of EC/HPC ethanol solutions where the system is continuously evaporating and forming films. The images are for different molecular weight of EC.

New Nanofabrication Techniques for Drug Delivery
Duncan Q.M. Craig

UCL School of Pharmacy, 29-39 Brunswick Square, London WC1N 1AX, UK, duncan.craig@ucl.ac.uk

The development of new techniques for the manufacture of delivery systems remains a significant change, particularly for ‘difficult’ drugs which may have poor water solubility or need to be released in specific and inaccessible body sites.

Nanofabrication offers some potentially excited opportunities for delivery, including solid dispersion formation for poorly water soluble drugs, great structural flexibility, the possibility of compartmentalisation and considerable site flexibility in terms of insertion and administration. The presentation will outline some of the new methods for nanofabrication that are being explored at UCL, including the following:

- Nanofibre formation via electrospinning, including examples of the development of zein nanofibres for controlled delivery
- Bulk nanofibre manufacture using pressure gyration, a new technique developed within UCL Department of Mechanical Engineering
- Microbubble formation using pressure gyration for floating dosage forms and diagnostics
- High temperature spinning for sucrose-based systems

The possibilities and challenges of these approaches will be described, including feasibility of scale up, drug release, dosage form stability and dosage form development. Indeed, one of the major obstacles to nanofibre usage on the market is the tension between production speed, high value product development versus lower value higher output approaches, oral dosage form development in terms of capacity and suitable dosage form choice, realistic scale up and realistic cost. We argue that pressure gyration may well provide a realistic opportunity for bulk manufacture, given that kg level production is already possible.
Next generation solid dispersion design: engineering nanostructured materials

Sheng Qi

School of Pharmacy, University of East Anglia, Norwich Research Park, Norwich, UK
sheng.qi@uea.ac.uk

Solid dispersion technology has been widely researched for enhancing the delivery and bioavailability of poorly water-soluble drugs [1]. Amorphous molecular dispersions in which the drug is molecular dispersed in an amorphous polymeric matrix is considered to be an effective formulation approach for this purpose. Solid dispersions also have wide applications in controlled release drug delivery systems [2]. These different applications are largely controlled by the nanostructures of the solid dispersions used. In order to better ‘design’ the specific drug delivery functions of the desired formulations into the solid dispersions based delivery system, it is important to recognise the importance of material selection, the processing method and subsequent manipulation (e.g. milling) on the performance of the resulting solid dispersions. The engineering of next a new generation of solid dispersions to allowing highly sophisticated drug release patterns and physical stability profiles will require a fuller understanding of the impacts of processing and material aspects of the systems [3-6]. Examples of processing effects and material blending on the nanostructures of solid dispersions will be described in this presentation along with given future prospective of the designing offer the next generation of solid dispersions will be discussed.

REFERENCES

Continuous manufacturing of pharmaceuticals: wet granulation

J. Vercruysse¹, M. Toivainen², M. Fonteyne², N. Helkimo⁴, J. Ketolainen⁴, M. Juuti², U. Delaet⁵, I. Van Assche⁵, J.P. Remon¹, T. De Beer⁵, C. Vervaet¹

¹Department of Pharmaceutics, Ghent University, Belgium, Chris.Vervaet@UGent.be
²Optical Measurement Technologies, VTT Technical Research Centre, Kuopio, Finland
³Department of Pharmaceutical Analysis, Ghent University, Belgium
⁴School of Pharmacy, University of Eastern Finland, Kuopio, Finland
⁵Pharmaceutical Research and Development, Johnson & Johnson, Belgium

Over the last decade, there has been increased interest in the application of twin screw granulation as a continuous wet granulation technique for pharmaceutical drug formulations. However, the mixing of granulation liquid and powder material during the short residence time inside the screw chamber and the atypical particle size distribution (PSD) of granules produced by twin screw granulation is not yet fully understood. Therefore, this study aims at visualizing the granulation liquid mixing and distribution during continuous twin screw granulation using NIR chemical imaging. In first instance, the residence time of material inside the barrel was investigated followed by the visualization of the granulation liquid distribution as function of different formulation and process parameters (liquid feed rate, liquid addition method, screw configuration, moisture content and barrel filling degree). The link between moisture uniformity and granule size distributions was also studied.

α-Lactose monohydrate was granulated with distilled water using a twin screw granulator, being the granulation module of the ConsiGma™-25 system (GEA Pharma Systems, Collette, Wommelgem, Belgium), which is a continuous ‘from powder to tablet’ manufacturing system. For residence time analysis, theophylline anhydrate was used as a tracer molecule. During each granulation experiment, chemical imaging data of freshly produced granules were collected. Furthermore, granules were sampled and oven dried for PSD analysis. A two-level full factorial experimental design was performed to evaluate the influence of screw speed (600 - 900 rpm) and moisture content (2.3 – 6.7 % (w/w), based on wet mass) on the mean residence time and the residence time distribution. These parameters were inversely correlated with the screw speed. A lower moisture content resulted to a shorter mean residence time and narrower residence time distribution.

Granulation liquid distribution of granules was monitored and evaluated as function of liquid feed rate, liquid addition method and screw configuration. The distribution of granulation liquid was more homogenous at higher moisture content and with more kneading zones on the granulator screws. Different liquid addition methods (tubing configuration (independent vs. split tubing), number of liquid addition zones (1 vs. 2 zones), nozzle diameters (0.8, 1.6 and 2.4 mm) and pump type (peristaltic vs. piston pump)) did not influence the liquid distribution nor the granule size distribution. Only changing the pump orientation from in-phase to out-of-phase slightly increased the moisture uniformity. After optimization of the screw configuration, a two-level full factorial experimental design was performed to evaluate the influence of moisture content, screw speed and powder feed rate on the mixing efficiency of the powder and liquid phase. From these results, it was concluded that only increasing the moisture content significantly improved the granulation liquid distribution. Changing the filling degree of the screw chamber did not affect the moisture uniformity.

This study demonstrates that NIR chemical imaging is a fast and adequate measurement tool for allowing process visualization and hence for providing better process understanding of a continuous twin screw granulation system.
Phase transformation of APIs induced by various stresses analyzed in real time by Raman spectroscopy

Alain Hédoux1, Laurent Paccou2 and Yannick Guinet3

1 UMET UMR CNRS 8207, Université Lille 1, Villeneuve d’Ascq F-59560 France, alain.hedoux@univ-lille1.fr
2 UMET UMR CNRS 8207, Université Lille 1, Villeneuve d’Ascq F-59560 France, Laurent.paccou@univ-lille1.fr
3 UMET UMR CNRS 8207, Université Lille 1, Villeneuve d’Ascq F-59560 France, Yannick.guinet@univ-lille1.fr

Molecular organic compounds go through several stages of processing (milling, freeze-drying, spray-drying, tableting) for packaging as solid-dosage form. During their storage, drugs may be exposed to a wide range of temperatures and humidities which can lead to different kinds of phase transformations (between crystalline and amorphous states or crystal–crystal transitions). The aim of this presentation is to show the capabilities of Raman spectroscopy for the in-line monitoring of phase transformations of molecular systems during their exposition to various kinds of stresses corresponding to manufacturing processes or storage conditions. The contribution of simultaneous low- and high-frequency analyzes to the structural description of disordered systems and to the understanding of the transformation mechanism will be shown.
Strategies of modifications of implantable meshes for soft tissue reinforcement: Anti-infectious effect and MRI visibility

Xavier Garric1, Olivier Guillaume1, Vincent Letouzey2, Renaud De Tayrac2, Benjamin Nottelet1 and Jean Coudane1

1- Max Mousseron Institute of Biomolecules (IBMM), UMR CNRS 5247, Faculty of Pharmacy, Universities Montpellier-1, Montpellier-2, 15, avenue C.-Flahault, 34093 Montpellier, France
xavier.garric@univ-montp1.fr
2- Department of Gynecology, Caremeau Hospital, 30100 Nîmes, France

Surgical operations for soft tissue reinforcement (i.e. pelvic organs prolapse or abdominal hernias) are common procedures and require annually at least 1,200,000 of prostheses. Unfortunately, postoperative complications and reinterventions are still important, mainly due to infection, inflammation, erosion, exposition or meshes migration. We present here several strategies to bring to meshes anti-infective resistance and clinical follow-up capability through an MRI visible material. A coating of the mesh by degradable polymers (polyesters) trapping antibiotics was created using an airbrushing technique, without modifying dramatically the morphology and the mechanical properties of the meshes. This temporary drug reservoir-coating allows a sustained release of the drugs and hamper in vitro bacterial contamination and biofilm formation on the meshes, associated to a large periprosthetic microorganism growth inhibition for a minimum of three days. Simultaneously, magnetic resonance contrast agent was grafted onto the backbone of polymers and used as coating material in order to bring MRI visibility property to meshes. In vitro, polymers-contrast agent coating induce a significant signal in an experimental MRI (7 Tesla) and no contrast agent release was observed during the stability studies, whatever the sterilization procedures used.

REFERENCES

Functional Materials for Pharmaceutical and Medical Device Technologies prepared via Hot Melt-Extrusion

Tony McNally¹, Seong Y. Choi², Kayleen T. Campbell², Duncan Q.M. Craig³ and Robin D. Rogers⁴

¹INM, WMG, University of Warwick, CV4 7AL, UK (t.mcnally@warwick.ac.uk)
²School of Mechanical & Aerospace Engineering, Queen’s University Belfast, BT9 5AH, UK
³School of Pharmacy, University College London, WC1N 1AX, UK
⁴Department of Chemistry and Centre for Green Manufacturing, The University of Alabama, Tuscaloosca, AL 35487, USA

Abstract

There continues to be intense interest in the area of hot-melt extrusion as a method for the preparation of drug and other biomolecule loaded polymers. Moreover, extrusion technology has been employed for decades in the production of polymeric medical devices. The distinct advantage of the extrusion process is that it is a continuous process and as such it allows for consistent product flow at high throughput rates. This process also permits the drug/bio-molecule loaded polymer melt to be extruded into a sheet or thin film for patches, a tube for catheters or it can be pelletized and then via some secondary process be shaped in to a device or medical implant. In this presentation, we describe the preparation using hot melt extrusion of two functional materials, one for use in pharmaceutical, the other medical device applications. First, two ionic liquids (ILs) were designed and synthesized having both antibacterial and plasticizing efficacy when added to medical grade PVCs in a twin screw extruder [1,2]. Both ILs, 1-ethylpyridinium docusate and tributyl(2-hydroxyethyl) phosphonium docusate were effective plasticizers for PVC and exhibited antimicrobial activity to a range of Gram-positive bacteria including Meticillin resistant Staphylococcus aureus. Secondly, we describe the extrusion of composites of model drug loaded poly(ethylene glycol) and poly(ε-caprolactone) with modified layered silicates (nanoclays) [3-6]. The addition of nanoclays having very large aspect ratio (up to 600) and surface area can modify drug release in solid dispersion systems and can be used to manipulate the mechanical properties of these systems.

REFERENCES

Cyclodextrins modified biomaterials applied to the sustained delivery of drugs

B. Martel1,2, N. Tabary1,2, F. Chai1,3, N. Blanchemain1,3, S. Degoutin1,2, F. Cazaux1,2, L. Janus1,2, C. Neut1,3, J. Junthip1,2, S. Ouerghemmi1,2

1Université de Lille Nord de France 59000 Lille France, bernard.martel@univ-lille1.fr
2 UMERN CNRS8207- Lille 1 59655 Villeneuve d’Ascq France
3 INSERM U1008- Groupe Recherche Biométriaux, 59045 Lille France

Biomaterials are currently used in a wide range of surgical specialties. Their function consists of replacing, reinforcing or repairing failing organs. Despite of the biocompatibility of the base materials used for their manufacturing, secondary effects such as thrombosis, inflammation, restenosis or infections involve some long or short term post operatory complications that may prolong the healing period in the best cases, and the death of the patient in the worst cases. In the last two decades some efforts have been made by the researchers to find solutions in order to improve the in vivo integration of the medical implants. Among the most efficient solutions, one reported strategy consisted to transform the biomaterials into drug delivery systems capable of releasing the appropriate drugs. Naturally, cyclodextrins have presented the appropriate qualities for this purpose, due to their host-guest properties towards a large range of drugs. In particular, our team has developed in the last decade medical implants such as vascular prostheses, inguinal implants, periodontal devices, hydroxyapatite bone substitutes, and hydroxyapatite coated hip prostheses with prolonged drug delivery properties by using cyclodextrins. Through those applications, the present talk will first aim to describe our concept of biomaterials modification with cyclodextrins based on a crosslinking reaction, leading to the coating of the devices surface or bulk porosity by a cyclodextrin polymer (polyCD), recently extended to the Layer-by-Layer deposition technique. In addition, some preliminary results dealing with nanofibers membranes obtained by the electrospinning technique will be presented. An overview of the different processes and their parameters for the biomaterials functionalization will be displayed and the resulting sorption and sustained capacity of release towards drugs as antibiotic, antiseptics, antalgics will be presented.

To summarize, this presentation will aim to present the concept and the realization of applied research projects on cyclodextrins by showing the different steps and the different techniques used in order to respond to the very demanding specifications encountered in each of the above mentioned investigated applications.

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Exploring strategies for chitosan nanoparticles with improved mucoadhesive properties

Barbara Bellich1, Antonio Rampino2, Massimiliano Borgogna3, Paolo Blasi4 and Attilio Cesàro1

1 Lab. of Physical and Macromolecular Chemistry, Dept. of Chemical and Pharmaceutical Sciences - University of Trieste, Via Giorgieri 1 - 34127 Trieste, Italy, e-mail bbellich@units.it
2 Laboratorio Nazionale Consorzio Interuniversitario Biotecnologie (LNCIB), Area Science Park, Padriciano 99, Trieste, Italy. 3Dept. of Life Sciences - University of Trieste, Via Giorgieri 5 - 34127 Trieste 4Dept. of Chemistry and Technology of Drugs, University of Perugia, Via del Liceo 1, 06123 Perugia, Italy

INTRODUCTION. The advantages offered by the oral administration face, in the particular case of peptide drugs, the critical aspects of high susceptibility to digestive enzymes in the gastrointestinal tract, poor absorption, and their limited transport across the intestinal epithelial barrier. The drug loading in suitable carriers characterized by high mucoadhesive properties can in principle overcome some limits associated to their administration. Indeed, the ability to adhere to the mucosal surface promotes an increase of drug residence in the selected site. Chitosan peculiar characteristics, such as biodegradability, non-toxicity, tissue-adhesive activity and drug permeation enhancing capability, make it attractive for the preparation of biodegradable polymeric nanoparticles for the oral route [1, 2]. Chemical modification of chitosan or its association with other biopolymers is frequently suggested as a way to improve adhesion properties [3].

EXPERIMENTAL. Chitosan nanoparticles have been prepared by ionotropic gelation, via complexation with the anion triphosphate (TPP) [4]. With the specific aim of improving mucoadhesion, chitosan nanoparticles were also combined with negatively charged polyelectrolytes, such as pectins. In particular three pectins were considered: two commercial samples (from citrus fruit and from apples) and for comparison a model represented by polygalacturonic acid. Two different ways of preparation were followed. On one side (coating technique), chitosan nanoparticles were obtained with the standard optimized procedure and then coated with pectins. On the other side (blending technique), chitosan was added to the negative polyelectrolyte solution, in the presence of TPP. Both methods lead to the formation of negatively charged particles, thus proving the presence of pectin in the outer shell of particles. Nanoparticles size depended on the chitosan:pectin ratio.

In addition, several chitosan derivatives were investigated for their mucoadhesive properties and the possibility to obtain nanoparticles was explored. A trimethylated chitosan (TMC) and two glycosylated chitosans were synthesized from purified chitosan. Nanoparticles were prepared using different blends of chitosan and chitosan-galactose; their characterization in terms of size and surface charge revealed dimensions ranging from 140 to 360 nm and a positive surface charge. Polymers mucoadhesivity was tested with both in vitro and ex-vivo studies. Ex vivo evaluation revealed an increase of residence time, with respect to pure chitosan, for pectin from apple and for glycosylated chitosan. Cytotoxicity and biocompatibility of the polymers and the nanoparticles produced thereof was investigated both in vitro and in vivo, confirming their safety.

CONCLUSIONS. The mild complexation technique is very suitable for the preparation of nanocarriers of labile molecules, such as peptides and drugs active at low dosages. Exploitation of chitosan derivatives with a wide range of modification revealed a new tunable tool for improving mucoadhesive properties.

REFERENCES
Medical devices functionalized with Cyclodextrins: In vitro and in vivo evaluation

Nicolas Blanchemain¹, Feng Chai¹, Jonathan Sobocinski¹, Blandine Maurel¹, Elixène Jean-Baptiste¹, Joel Lyskawa², Christel Neut³, Bernard Martel²

¹INSERM U1008, Lille 2, Lille, France; ²UMET, Lille1, Villeneuve d’Ascq, France; ³INSERM U995, Lille 2, Lille, France (nicolas.blanchemain@univ-lille2.fr)

Biomaterials and Medical Devices were developed to preserve the integrity and life comfort of patients suffering from intense functional deficiencies. Though, implanted medical devices, may result in various issues such as restenosis (30% in cardiovascular surgery), thrombosis, infection (6% in cardiovascular surgery, 1-2% in orthopedic surgery), or pain (12% in visceral surgery) against which the systemic administration of drugs is not 100% efficient. Since 10 years, we have developed the surface modification of a wide range of medical devices with cyclodextrins aiming to promote the adsorption, the targeted and prolonged delivery of the active molecules. The aim of the present work is to evaluate the in vitro and in vivo efficacy of three different medical devices functionalized with CDs and loaded with active molecules used in three different surgical fields.

In the field of vascular surgery, the antibacterial activity of vascular prostheses functionalized with cyclodextrins (PLM-CD, Perouse Medical) has been evaluated in vitro and in vivo. The in vitro experiment showed a prolonged antibacterial activity of the PLM-CD loaded with three antibiotics (ciprofloxacin, rifampicin or vancomycin) against several bacteria stains. In most cases, a 5-7 days antibacterial activity was observed. The widest activity spectrum was obtained using the association ciprofloxacin / rifampicin. This association applied in in vivo experiments on rats showed an excellent effectiveness after 7 days of implantation of the PLM-CD loaded against 8 bacteria strains [1].

In the field of visceral surgery, the analgesic activity of a parietal implant functionalized with cyclodextrins (A1L-CD, Cousin Biotech) has been evaluated in vivo. A1L-CD have been impregnated in a ropivacaine solution and implanted in rats in the peritoneum. The colorectal distension experiment [2] was practiced to evaluate pain reduction that was significant at least for 7 days with A1L-CD loaded with ropivacaine.

In the field of coronary surgery, the anti-restenosis activity of a vascular stent functionalized with cyclodextrins (CoCr-CD, Abbott) has been evaluated in vitro and in vivo. The in vitro evaluation showed a selective effect of simvastatin to prevent the restenosis by limiting the proliferation of smooth muscle cells. The in vivo activity was performed by the follow-up the intra-stent restenosis in a rat model. 28 days after implantation, the CoCr-CD stent loaded with statin has clearly prevented the restenosis compared to a conventional drug eluting stent [3].

Finally, the in vivo evaluation have confirmed the in vitro models and highlighted the interest of the functionalization of various implantable medical devices with cyclodextrins as efficient tools for the improved delivery of a wide range of drugs and therapeutic effects.

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Hydrogel-mineral composites for bone regeneration

Timothy E.L. Douglas
Nano and Biophotonics Group, Department of Molecular Biotechnology, Faculty of Bioscience Engineering, Coupure Links 653, 9000 Gent, Belgium, Timothy.Douglas@UGent.be

Hydrogels are gaining interest as materials for tissue regeneration applications due to advantages including injectability and ease of incorporation of bioactive substances and micro- or nanoparticles. For bone regeneration applications, mineralization of hydrogels is considered desirable. This talk will present certain strategies to create a mineral phase within hydrogels form hydrogel-mineral composites. The resulting composites' physicochemical and biological properties, i.e. ability to support adhesion and proliferation of bone-forming cells and antibacterial activity, will be covered.
Self-Assembled Polymer-Protein Nanostructures: Protein–block copolymer biohybrids

Karen J. Edler¹, Amani El Fagui¹, Susanna Piluso², Heather C. Cassell³, Nick J. Plant³, Gabriel Cavalli²

¹Department of Chemistry, University of Bath, Claverton Down, BA2 7AY, UK; k.edler@bath.ac.uk
²Department of Biochemistry and Physiology, University of Surrey, Guildford, GU2 7XH, UK
³Department of Chemistry, University of Surrey, Guildford, GU2 7XH, UK

The combination of proteins and synthetic polymers is an appealing strategy to prepare biohybrid systems and address challenges in life sciences such as targeted drug delivery and nanotherapeutics [1]. In this collaborative study, Reversible Addition-Fragmentation chain Transfer (RAFT) polymerisation was used to prepare amphiphilic di and triblock copolymers based on poly(N-(2-hydroxypropyl) methacrylamide) (PHPMA) and poly(ε-caprolactone) (PCL) having a range of molecular weights and low polydispersity indices. Green fluorescent protein (eGFP) incorporating a unique sequence was prepared and, using transpeptidase Sortase A [2], site-specifically conjugated to the synthesized block copolymers to form protein–block copolymer biohybrids. Our approach allows the gradual increase of the length of the hydrophobic/hydrophilic segments in the biohybrids and thus enables progressive understanding of the complex relationship between polymer blocks and structural properties. Small-angle X-ray and neutron scattering, dynamic light scattering and cryo-transmission electron microscopy have been used to study the formation of structured nano-biohybrids, as polymer structure and molecular weight were changed.

SANS, DLS and cryo-TEM analyses of PHPMA-b-PCL-b-PHPMA triblock copolymer (left) and the corresponding eGFP-biohybrid (right).

REFERENCES

Numerical study of the interfacial free energy for model pharmaceutical systems.

J. Gerges1*, F. Affouard1

1 Unité Matériaux et Transformations (UMET), UMR CNRS 8207, UFR de physique – BAT P5
Université Lille 1, 59655 Villeneuve d’Ascq FRANCE
joseph.gerges@ed.univ-lille1.fr

Due to the increasing number of poorly water-soluble drugs, the interest of the amorphous state has emerged for formulation development. This state clearly presents some advantages to solve solubility problems. However, it is also intrinsically unstable compared to any crystalline forms. The development of amorphous pharmaceuticals is thus very challenging and particularly requires a fundamental physical understanding of the stability of amorphous state against crystallization.

One of the main parameters involved in nucleation and growth phenomena is the interfacial free energy $\gamma$ between the liquid and the crystalline state [1,2]. It is directly linked to the barrier for nucleation in the classical nucleation theory [3]. Despite its great importance, the determination of the interfacial free energy $\gamma$ remains a challenge from experiments. Turnbull [1] determined $\gamma$ from nucleation rates and found an empirical rule linking the enthalpy of melting $\Delta H_m$ to $\gamma$. These measurements show a lack of accuracy due to the classical nucleation theory approximations that are used to extract $\gamma$ from nucleation rates. Direct methods have been also used to measure $\gamma$ by examining the shape of the interface and determining the contact angle [4-7]. Both approaches also lack of precision concerning the anisotropy of $\gamma$ which is at the origin of the dendrite growth direction and its stability [8].

Numerical approaches via molecular dynamics simulations offer interesting opportunities to estimate the interfacial free energy $\gamma$. In the present study, the capillary fluctuation method has been successfully used to determine $\gamma$ of model pharmaceutical materials felodipine and nifedipine showing different crystallization and vitrification capabilities. These calculations required the simulation of the interface in equilibrium at the melting point and the calculation of the fluctuations of the position of the crystal-liquid interface. The calculations of $\gamma$ for different crystalline polymorphs of these materials well reproduced the experimental tendency of crystallization (Oswald rule of stage). This approach thus demonstrates that the capillary fluctuation method can be used as a tool for predicting crystallization behavior for pharmaceuticals products.

REFERENCES

Isocothermal calorimetric investigation of water release from thin hydrogel films

E. Elisei, E. Gurian, B. Bellich, A. Rampino, A. Cesàro, R. Heyd, and M.-L. Saboungi

1 Laboratory of Physical and Macromolecular Chemistry, University of Trieste, Via Giorgieri 1, I-34127 Trieste, Italy - elena.elisei@phd.units.it
2 LN-CIB Trieste, Area Science Park, Padriciano 99, I-34012 Trieste, Italy
3 Elettra Sincrotrone Trieste, Area Science Park, I-34149 Trieste, Italy
4 Centre de Recherche sur la Matière Divisée, University of Orleans & CNRS, rue de la Férollerie 1B,F-45071 Orléans Cedex 2, France
5 IMPMC-Sorbonne Univ & UPMC-Univ Paris 06, UMR CNRS 7590, 4 Place Jussieu, F-75005 Paris, France

The isothermal dehydration process of thin films of pure water and aqueous sugar solution has been investigated from both a theoretical (thermodynamics) and experimental (calorimetry) point of view [1]. In particular this combined treatment allowed to extract important physical and chemical parameter characteristic of the process (e.g. water activity) and to follow their behavior as function of the progress of the dehydration process. The film geometry has been reproduced by using a nano porous substrates (cellulose) that “forces” the solution in a planar geometry; this allows to work on low dimension surfaces, required for the calorimetric experiments, and then to well control many physical parameters (e.g. temperature and pressure) that characterize both the internal (film) and the external (environment) parts of the system.

Calorimetric experiments have been carried out in quasi-isothermal conditions; indeed it has been noted that the end of the process is not strictly isothermal, probably because of the interaction with the substrate’s nano-structure that influences the water diffusion. Moreover a thermodynamic approach has been developed in order to compare the results obtained. Simple water and aqueous sugar solutions have been chosen as the more general model systems to assess the feasibility of this kind of treatment to obtain the water activity and to follow its slowing down at the end of the process. This slowing down is directly related to a drastic change in the diffusion coefficient, characteristic of the solute-water molecules interaction for low-moisture systems.

This study has been now extended to more complex system as polymer solutions and mixed gels, to different geometries (bead, drop) and to different temperature conditions (heating scan) [2,3]. Moreover, this kind of study find applications in the field of cosmetics (e.g. hydration time ensured by a beauty cream), pharmaceutical (from a view point of both the active principle and the drug delivery), with the final goal to extend this study to biological systems (e.g. investigation of the internal structure of the cell by its dehydration).

REFERENCES

Molecular dynamics, physical stability and solubility advantage from amorphous ezetimibe drug

J. Knapik\textsuperscript{1,2}, Z. Wojnarowska\textsuperscript{1,2}, K. Grzybowska\textsuperscript{1,2}, W. Sawicki\textsuperscript{3}, K. Włodarski\textsuperscript{3}, M. Paluch\textsuperscript{1,2} \\

\textsuperscript{1}Institute of Physics, University of Silesia, Uniwersytecka 4, 40-007 Katowice, Poland, jknapik@us.edu.pl  
\textsuperscript{2}SMCEBI 75 Pułku Piechoty 1A, 41-500 Chorzów, Poland  
\textsuperscript{3}Department of Physical Chemistry, Medical University of Gdansk, 84-416 Gdansk, Poland \\

Ezetimibe (EZB) is a novel cholesterol-lowering drug, which acts at the small intestinal brush border membrane, where it selectively inhibits the absorption of dietary and biliary cholesterol. That is the reason why the EZB drug is extremely useful for the treatment or prevention hypercholesterolemia. It should be pointed out that the commercial form of this API available on the market exhibits low oral bioavailability (35%), which is attributed to its poor water solubility (8.4 mg/l). In order to increase the solubility and consequently bioavailability of EZB we have converted the crystalline drug to its amorphous counterpart. It should be stressed that the amorphous materials are usually unstable systems and may easily return to the crystalline form during the storage \cite{1,2}. Therefore, in this presentation we will thoroughly investigate the physical stability of amorphous EZB drug. As reported by many authors, the most important factor affecting recrystallization from the disordered state is the molecular mobility of the system \cite{3}. That is why, herein using the broadband dielectric spectroscopy (BDS) we described the molecular dynamics of EZB in a wide temperatures (153.15 K – 385.15 K) and pressure (0.1 MPa – 140 MPa) range. The dielectric as well as calorimetric data collected above the glass transition temperature (\textit{Tg} = 334 K) have indicated that the tested drug easily undergoes cold crystallization. In order to characterize this process we have studied the kinetics of isothermal recrystallization in terms of Avrami and Avramov model \cite{4}. Additionally, the Adam and Gibbs (AG) entropic model have been used to predict the physical stability of examined material at room temperature conditions i.e. below \textit{Tg} of EZB \cite{5}. As a final point, we have tried to stabilize the amorphous EZB by preparing the binary amorphous mixture ezetimibe + 20% wt. soluplus.

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Eudragit® E-Based Matrices for Accelerated Ketoprofen Release in Acidic Media


1 INSERM U 1008, University Lille Nord de France, Lille, France, susanne.muschert@univ-lille2.fr
2 University of Lille, USTL, UMET, 59655 Villeneuve d’Ascq, France,

Purpose: To increase the release rate of ketoprofen in acidic medium using matrices based on Eudragit® E.

Methods: Hot-melt extrusion and spray-drying were used to prepare polymeric matrices loaded with 10 to 50 % ketoprofen. Eudragit® E, optionally blended with PVP, PVPVA or HPMC was studied as matrix former. The obtained systems were characterized by optical microscopy, SEM, mDSC, X-ray diffraction and in vitro drug release studies in 0.1 M HCl.

Results: In all cases ketoprofen release was much faster compared to a commercially available product and the dissolution rate of the drug powder (as received). For example, 96% ketoprofen was released after 10 min, compared to 5 % in the case of the commercial reference product. Importantly, super-saturated solutions were obtained, which were stable for at least 2 h. When using ternary blends of ketoprofen, Eudragit E and HPMC E5, PVP or PVPVA, intermediate drug release profiles were observed. Spray-drying ternary ketoprofen:Eudragit® E:HPMC combinations led to a more homogenous HPMC distribution than hot-melt extrusion, as revealed by mDSC and X-ray diffraction. This more homogenous HPMC distribution resulted in more pronounced hindrance for water and drug diffusion and, thus, slower drug release from spray-dried powder compared to hot-melt extrudates of identical composition. This “homogeneity/heterogeneity effect” even overcompensated the “size effect” of the system. All formulations were stable during storage at ambient conditions in open vials.

Conclusion: Polymeric matrices aiming at accelerated release of poorly water-soluble drugs can be highly complex, since not only the composition of the systems, but also their inner structure can be of utmost importance.
Glass Forming Ability and Thermodynamics of Pharmaceuticals

Wenkang Tu12, Li-Min Wang1 and S. Capaccioli2

1 State Key Lab of Metastable Materials Science and Technology, College of Materials Science and Engineering, Yanshan University, Qinhuangdao, Hebei, 066004, China, wenkang_tu@gmail.com
2 Dipartimento di Fisica - Università di Pisa, Pisa, 56127, Italy

The vitrification or glass transition of conventional pharmaceuticals in the form of crystalline has attracted considerable interest in the last decade when the amorphous drugs are recognized to have remarkable advantages such as solubility, chemical activity and bioavailability.[1,2] However, the glass forming ability for pharmaceuticals usually differs much, and whereas drugs like probucol and ketoprofen are excellent glass-formers, the complete vitrification of antipyrene and indoprofen would, otherwise, require much higher cooling rates. The glass transition of materials is controlled in a comprehensive way imposed by the balance between the thermodynamic and kinetic factors, and we are expecting to get new understanding on the significance of the thermodynamic quantities on the glass formation of pharmaceuticals as well as the correlation between the thermodynamic and kinetic quantities. The thermodynamic and kinetic parameters involved in the glass transition and melting are experimentally measured in 14 pharmaceutical chemicals using a Perkin-Elmer calorimeter and a broad-band dielectric spectrometer. We found that, the glass forming ability of the pharmaceuticals strongly depends on the melting entropy and the ratio of the glass temperature to the melting point. Chemicals with high glass forming ability like probucol show low melting entropy, while drugs with marginal glass forming ability are of relatively higher melting entropy. Instead, the relationship between the glass forming ability and the kinetic fragility becomes not straightforward among the pharmaceuticals. For the majority of chemicals, the thermodynamic quantities involved in glass transition are found to be quantitatively correlated with the kinetic ones, as observed in the small molecule glass formers.

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The importance of HME parameters in the development of PEO extrudates with various molecular weights

O. Cantin\textsuperscript{1,2}, F. Siepmann\textsuperscript{1,2}, Y. Karrout\textsuperscript{1,2} and J. Siepmann\textsuperscript{1,2}

\textsuperscript{1}Univ. Lille 2, College of Pharmacy, 3 rue du Prof. Laguesse, 59006 Lille, France, cantin_oriane@yahoo.fr
\textsuperscript{2}INSERM U1008, 3 rue du Prof. Laguesse, 59006 Lille, France

Introduction
The application of Hot Melt Extrusion (HME) in pharmacy became increasingly interesting since 90’s. Among the thermoplastic polymers commonly used via HME (e.g. ethylcellulose, ethylene vinyl acetate, ammonium methacrylate copolymer, or some lipids \textsuperscript{[1]}), polyethylene oxide (PEO) is suitable to prepare sustained-release dosage forms. Different grades are available with molecular weight ranging from 100 kDa to 7,000 kDa. They have many advantages such as the extrudability at low temperature without adding plasticizer and the preparation of sustained-release twice daily dosage forms.

Purpose
The goal of this study was the modulation of the release kinetics due to the change of the molecular weight under appropriate extrusion conditions (e.g. extrusion temperature or screw speed).

Methods
All PEO grades available on the market were tested in order to determine the effect of the molecular weight on the drug release. PEO extrudates containing 10 \% of theophylline hydrate were prepared via HME. The drug and various PEO grades were blended for 10 min at 38 rpm and then extruded using a twin screw extruder (Nano 16, Leistritz) equipped with a 4 mm diameter die at different screw speeds (30 rpm, 60 rpm or 90 rpm) and temperatures (135-133-130-125 °C or 100-97-95-90 °C). Drug release measurements were UV spectrophotometrically conducted in phosphate buffer pH 7.4 (\( \lambda = 272 \) nm).

Results
Under these conditions all PEO grades can be easily extruded with respect to the torque value and extruder load limits. The results showed the strong impact of PEO molecular weight on theophylline release. The relative drug release decreased with increasing PEO molecular weight. For instance the entire drug content was released after 3 hours with PEO N10 (100 kDa) and over 12 hours with PEO 303 (7,000 kDa). Depending on the temperature, extrudates were either soft or showed some surface defects such as shark skinning or melt fracture. Importantly a decrease in temperature improved the extrudate appearance for almost all grades. However a yellow coloration was found with extrudates containing PEO of molecular weight less than 2,000 kDa contrary to extrudates with higher molecular weight that are white opaque. Grades with molecular weight less than 600 kDa showed an increase of the drug release when extruded at 135°C. This can be probably attributed to the fact that low molecular weights are thermally degraded during the extrusion which corresponds to the literature \textsuperscript{[2]}. Finally, no significant effect of the screw speed has been observed even for low molecular weights. Thus, it could be presumed that PEO grades are less sensible to mechanical degradation. Interestingly, all formulations remained stable after 1 month storage upon 25 °C and 60 \% relative humidity.

Conclusion
The good processability in the development of hot-melt extrudates can be achieved by the adjustment of the extrusion parameters. Moreover, appropriate PEO grades should be used to reach the desired drug release profile. Further studies should be conducted to investigate deeper the effect of the temperature on possible PEO degradation.

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The structure of the hydrogen-bonded complexes of salicylic acid in modified supercritical carbon dioxide

Darya L. Gurina, Marina L. Antipova and Valentina E. Petrenko

G.A.Krestov Institute of Solution Chemistry of the Russian Academy of Sciences, Russia, Ivanovo
gdi@isc-ras.ru

Salicylic acid or 2-Hydroxybenzoic acid (o-HBA) is one of the most widely used compounds in pharmaceutical industry. It also is used in the organic synthesis of many medicinal compounds including salicylates (its ester and salt derivatives) and acetylsalicylic acid [1,2]. Areas of application o-HBA imply a high quality requirements and purity of the product, which, in turn, is the motivation for using non-toxic solvents. The latter, for example, includes supercritical carbon dioxide (SC CO2). However, the solubility of polar organic compounds such as salicylic acid is rather low in the SC CO2. The simple way to overcome this limitation is to modify supercritical carbon dioxide with small amounts of co-solvents [3]. Despite of experimentally proven fact of increase the solubility of polar organic substances in SC CO2 with the addition of co-solvent the reasons of the phenomenon remain controversial. Majority of researchers suggest that intermolecular interactions between solute and co-solvent play the main role. In this context, the first goal of this work is to study the decay process of the hydrogen-bonded dimer of o-HBA in pure and modified by the addition of water, methanol and ethanol (up to 3.5mol.%) SC CO2 and the second task is to identify the nature of intermolecular interactions in the systems.

To achieve this goals the method of classical molecular dynamics implemented in the software package Gromacs-4.5.4 [4] was used. Simulation was carried out in NVT-ensemble in a cubic cell with periodic boundary conditions. Cell length in each case was corrected to maintain a constant density of 0.7 g/cm³. According to the analysis of the data it is shown that dimer decay process is faster in the modified solvent. In pure SC CO2 formation of solvation shells around the molecules of salicylic acid occurs due to weak hydrogen bonds and electron donor-acceptor (EDA) interactions with the solvent molecules and in the binary solvent the solvation shell includes co-solvent molecules. Besides strong hydrogen bonds are formed between hydrogen atom of the carboxyl group of o-HBA and oxygen atom of co-solvent. Furthermore, it was detected that local mole fraction of the co-solvent molecules around salicylic acid increase up to 0.12-0.17, while the mole fraction of the co-solvent in the bulk solvent is not greater than 0.035 in the case of methanol and ethanol, and 0.0079 - in case water. These results are in good agreement with the experimental ones obtained for Phenol Blue molecule dissolved in SC CO2 with acetone as co-solvent [5].

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New insights into the crystallisation behaviour of amorphous fenofibrate

Pratchaya Tipduangta, Laszlo Fabian, Sheng Qi

School of pharmacy, University of East Anglia, Norwich, Norfolk, UK NR4 7TJ, P.Tipduangta@uea.ac.uk

Fenofibrate has been mainly used for reducing cholesterol levels in patients with cardiovascular diseases. Although there are many commercial oral solid dosage forms for delivering fenofibrate, little is known in terms of the crystallisation behaviour of amorphous fenofibrate due to its high instable nature and low glass transition temperature (approximately -20°C). The purpose of this study is to fully characterize the crystallisation behaviour of amorphous fenofibrate by investigating the effect of processing methods (such as melting-quenching and hyper quenching via electrospraying) on the behaviour of amorphous fenofibrate, the triggers of crystallisation and the conversions between polymorphic forms. There are two polymorphic forms of fenofibrate have been reported [1,2]. The more stable form I has a melting point approximately 80°C and the meta-stable form II has a melting point at 74°C. Although the preparation of pure meta-stable form II is difficult, it has been reported the possibility of using melting-quenching method to obtain form II. Form II is highly instable and converts to the stable form I rapidly after preparation [1,2]. In this study, it was found that external crystallisation triggers such as surface disruption of amorphous fenofibrate and seeding could rapidly initiate the crystallization of both fenofibrate form I and II. The growth of the crystals occurred in two stages, rapid vertical upwards growth out of the surface of the amorphous drug followed by horizontal expansion of crystal growth in bulk. The crystallisation inhibition effect of polymer on amorphous fenofibrate was investigated using Poloxamer 407, a nonionic tri-block copolymer. Differential scanning calorimetry (DSC), attenuated total reflectant fourier transform infrared (ATR-FTIR) spectroscopy equipped temperature control stage, polarized light microscopy and powder X-ray diffractometry were used to characterize the dispersions containing fenofibrate. The dispersions containing less than 30% (w/w) poloxamer showed little inhabitation effect on fenofibrate crystallisation. As seen in Figure 1, the melting transitions of form I and II can be seen in the dispersions containing less than 30% poloxamer. Heating rate used in the DSC measurements showed significant effect on the conversion rate from form II to form I. Slower heating rate resulted more complete transformation from meta-stable form II to form I. This result was confirmed by variable temperature IR spectroscopic results. After isothermal treatment of fresh sample at 65°C for 20 min, the peak at 1716 cm⁻¹ which represents meta-stable fenofibrate shifted to 1727 cm⁻¹ which is the characteristic carbonyl stretching of the stable form I. The results of this study provide new understanding of the physical stability and crystallisation behaviour of amorphous fenofibrate.

Figure 1 DSC thermograms of crystalline fenofibrate form I fenofibrate and Poloxamer 407.

Novel polymer blend nanofiber-based solid dispersion formulations with Tuneable drug release

Pratchaya Tipduangta\textsuperscript{1}, Peter Belton\textsuperscript{2}, Sheng Qi\textsuperscript{1}

\textsuperscript{1}School of Pharmacy, University of East Anglia, Norwich, UK, P.Tipduangta@uea.ac.uk
\textsuperscript{2}School of Chemistry, University of East Anglia Norwich, UK

Electrospinning has been widely used to fabricate polymer fibres with micron to nanometer diameters from either polymer solutions or melts. The applications of such fibrous formulations can range from filtration membranes, nano-sensors, tissue engineering scaffolds to drug delivery systems [1,2]. In this study, electrospun polymer blend nanofibers containing hydrophilic polymer, polyvinyl pyrrolidone (PVP), and pH dependent soluble polymer, hypomellose acetate succinate (HPMCAS), were used as the carrier system for delivering model drugs with tuneable drug release behaviour. Paracetamol (PCM) was used as a model drug and a blend of PVP and HPMCAS in a range of proportions (3:1, 1:1 and 1:2) were used as the carrier matrices. The morphology of electrospun nanofibres was observed by scanning electron microscopy (SEM). The micron and nano-scale phase separation and drug distribution of the drug loaded PVP/HPMCAS blended fibres were performed by differential scanning caloremetry (DSC), ATR-FTIR spectroscopy, confocal Raman microscopy, powder X-ray diffractometry (PXRD) and solid state NMR. The release kinetics of PCM from different polymer blend matrices in stimulated gastric fluid was studied by mathematical model fitting. The electrospun fibres have smooth morphology, as seen in Figure 1. The diameters of the electrospun fibres are range between 500 nm to 2 \( \mu \)m depending on the ratios between PVP and HPMCAS used in the polymer blend matrices. Confocal Raman imaging results confirmed the homogenous drug distribution at micron scale. This result was confirmed by DSC, ATR-FTIR spectroscopy and PXRD data of the formulations. However, the solid state NMR \( T_{1\rho} \) results indicated nano-scale phase separations in the drug loaded electrospun solid dispersions. The bi-phasic drug release from the polymer blend electrospin fibres also indicated the possible phase separation of PVP-drug rich and HPMCAS-drug rich phases. It is high likely that the PVP-drug rich phase is responsible for the initial burst release and later sustained-released could be attributed to HPMCAS-drug rich domain. The tuneable release rate and kinetics can be obtained by altering the ratio between PVP and HPMCAS in the blend.

Fig.1 Representative SEM image of the PVP-HPMCAS ratio
1:1 blend fibers loaded with 25% paracetamol w/w

Novel Nutritional Iodine Delivery Using Electrospun Fast Dissolving Oral Mat

Cholpon Rustem Kyzy, Peter Belton, Sheng Qi

School of Pharmacy, University of East Anglia, Norwich, C.Rustem-Kyzy@uea.ac.uk

Introduction

Iodine deficiency is still a significant health problem affecting the population in many developing counties. For these regions, the development of cost-effective and highly patient compliant delivery system for such micronutrients becomes increasingly important for improving the wellbeing of the general population. In this study, a novel electrospun nanofiber based oral mat was developed for the enhanced delivery efficiency and patient compliance of the delivery of iodine. Each nanofiber based oral mat contains a daily dose of iodine and dissolves rapidly on the tongue. The administration of the fast-dissolving iodine oral mat does not require swallowing or the use of water which is expected to improve the patient adherence in comparison to traditional oral tablets formulations.

Materials and methods

Potassium iodate, is the more stable form of iodine source under stressed conditions, was used as the active ingredient in this study. Polyethylene oxide (PEO) was selected as the carrier polymer based on good processability by electrospinning and high solubility in water. The stock solution was prepared by dissolving PEO and KIO3 in water, with different concentration of an active ingredient and carrier material. The optimisation of the electrospinning parameters and the maximum loading capacity of the active ingredient in the nanofibers were also investigated. The nanofiber characterization was performed using scanning electron microscope (SEM) in conjunction of elemental analysis, powder X-Ray diffraction, ATR-FTIR spectroscopy, and differential scanning calorimetry (DSC).

Results and discussion

The SEM images of potassium iodate loaded nanofibers showed that the nanofibers are uniform and smooth with diameters in the range of 120 nm and 400 nm. ElementaL analysis of the nanofibers confirmed that presence of iodate located in the fibers. ATR-FTIR spectroscopic results indicated the homogeneous distribution of potassium iodate in the nanofiber mat. According to the PXRD results, after electrospinning potassium iodate is encapsulated in the PEO fibers as its amorphous form. DSC and the detailed analysis of the PXRD results revealed the reduced crystallinity of PEO after electrospinning and the incorporation of potassium iodate. This reduction in crystallinity is proportional to the potassium iodate load in the fibers. The dissolution of the nanofiber based mat was completed within 5 minutes. This is attributed to the water-soluble nature of the polymer and the high surface area of the nanofibers.
Conclusion

Potassium iodate was successfully loaded into PEO nanofibers in its amorphous form. The fast dissolution of the nanofiber was achieved via high exposure surface area to volume ratio. Further investigation into the physical stability of potassium iodate in the solid dispersion based nanofibers will provide new insights into the understanding of behaviour of electrospun of inorganic material.
How dexamethasone release can be adjusted from silicone matrices

M. Gehrke, C. Vincent, J. Siepmann, F. Siepmann

1 University of Lille, College of Pharmacy, 3, rue du Prof. Laguesse, 59006 Lille, France
maria.gehrke@univ-lille2.fr
2 INSERM U1008, Controlled Drug Delivery Systems and Biomaterials, 3, rue du Prof. Laguesse, 59006 Lille, France
3 University of Lille, School of Medicine, 1, Place de Verdun, 59000 Lille, France

Introduction: The administration of drugs to treat diseases of the inner ear is very challenging because of the blood-cochlear-barrier, which is anatomically and functionally similar to the blood-brain-barrier [1]. To overcome this fundamental hurdle, local drug delivery from miniaturized cochlear implants, which are directly placed into the scala tympani, offer an interesting potential. For instance, implants based on silicone with the geometry of tiny cylinders can be inserted directly into the cochlea and offer a great potential for the treatment of postsurgical inflammation [2]. However, surprisingly little is yet known on how to effectively adjust desired drug release kinetics from silicone-based matrices.

Purpose: The aim of this study was to better understand how to easily adjust desired drug release kinetics from silicone-based matrices.

Materials and methods: Dexamethasone-loaded, silicone-based thin films (1x1x0.1 cm) were prepared as surrogates for tiny cochlear implants using silicone kits (NuSil Technology, Carpinteria, CA, USA) [3]. Several types of silicones were studied, differing in the substitution patterns. Part A and B of the silicone kits were blended in a two roll mill with 10 % of dexamethasone, and optionally 5 or 10 % PEG 400 or PEG 1000. The blends were passed through the two roll mill to obtain thin films, which were cured in an oven at 60 °C for 24 h. The systems were thoroughly characterized in vitro: Dexamethasone release was studied in 10 mL artificial perilymph at 37 °C in a horizontal shaker at 80 rpm. Dexamethasone was detected by HPLC.

Results: The release of dexamethasone is mainly controlled by drug diffusion through the polymeric systems. Using Fick’s second law, the apparent diffusion coefficient of dexamethasone could be determined, e.g. the coefficient of dexamethasone in films with 10 % PEG 1000 is seven times higher than without PEG.

The degree of substitution with phenyl-groups significantly affected drug mobility and the resulting drug release kinetics, as well as the apparent drug diffusion coefficient. A higher phenyl-group content resulted in an increased release rate and quadruples the apparent diffusion coefficient. Also the amount of added PEG played a major role.

Conclusions: Using the obtained new knowledge and appropriate mathematical models, it can be expected that desired dexamethasone release kinetics can be easily adjusted from miniaturized cochlear implants.

REFERENCES
Polymorphism of griseofulvin

Aurélien Mahieu¹, Jean-François Willart¹, Emeline Dudognon¹, Mark D. Eddleston², William Jones², Florence Danède¹, Marc Descamps¹

¹Univ Lille Nord de France, UMET, UMR CNRS 8207 F-59650 Villeneuve d’Ascq, France (au.mahieu@gmail.com)
²Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK

Most of the molecular materials have the possibility to form several crystalline states with structural differences which is called polymorphism [1, 2]. In the case of therapeutic materials, these structural differences have a strong and direct influence on the therapeutic properties [3]. The properties which are mainly concerned are the physical and chemical stability [4], the dissolution rate [5], the bioavailability [5] and the manufacturability [6]. The exhaustive determination of drug polymorphs is thus an essential step of the pharmaceutical development. However, although many methods of polymorphs “screening” have been developed, the research of polymorphic forms remains a highly empirical activity and undiscovered polymorphs can never be excluded.

We present here the discovery and identification of two new crystalline forms of griseofulvin (called Form II and Form III) even though this active pharmaceutical ingredient is deemed to have only one crystalline form (Form I) [7]. These two new forms appear during the crystallization of the quenched liquid. Kinetic investigations performed by DSC and X-ray diffraction allowed us to clarify the different mechanisms of transformation and the relative stabilities of the different polymorphs. It appears that the Forms I and II constitute an enantiotropic system and each of them is inherently metastable in comparison with the usual Form I. Also, the influence of cracks -which occur during the quench of the liquid- on the conversion mechanism has been studied in detail.

REFERENCES

Comparative study of ibuprofen, ketoprofen and flurbiprofen in the liquid state by molecular modeling

M. T. Ottou Abe1,2, F. Affouard1, N. T. Correia1, L.-C. Valdes1 and J.M.B Ndjaka2

1Unité Matériaux et Transformation (UMET), UMR CNRS 8207, UFR de Physique, BAT PS, Université Lille 1, 59655 Villeneuve d'Ascq, France; mt.ottou-abe@ed.univ-lille1.fr
2Département de Physique, Faculté des Sciences, Université de Yaoundé I. B.P. 812, Yaoundé, Cameroun

In the framework of the glass transition phenomena, there has been recently revived interest for hydrogen-bonded (HB) liquids composed of molecules of low molecular weight. Due to the strong directional hydrogen bonding, these liquids tend to be locally more organized than ordinary van der Waals liquids and exhibit original structural, dynamical and thermodynamical peculiarities. From broadband dielectric spectroscopy experiments, it was recently shown that the well-known ibuprofen drug exhibits a surprising relaxation corresponding to a purely exponential or Debye-type decay similarly to monohydroxy alcohols [1,2]. In order to shed some light on its origin, properties of three propionic compounds of pharmaceutical interest: (s)-ibuprofen, (s)-flurbiprofen and (s)-ketoprofen have been investigated in the liquid state by means of molecular dynamics computer simulations. Dielectric properties such as single and collective dipole time correlation function, static permittivity and Kirkwood factor have been computed using OPLS all-atom interaction force field: the peculiar Debye process has been found in the three studied compounds. On the basis of these molecular dynamics results, the influence of internal cis-trans motion of the carboxylic acid O=C=O-H group in these intermolecular HB structures have been demonstrated.

REFERENCES


The relationship between crystal structure and physical/chemical properties in pharmaceutical materials

Mark D. Eddleston¹ and William Jones¹

¹Department of Chemistry, University of Cambridge, Cambridge, UK: mde32@cam.ac.uk

Pharmaceutical compounds (APIs) can exist in a variety of different crystal forms such as polymorphs, salts and cocrystals. These forms have different solid state properties and will be absorbed at different rates in the body. Crystal forms selected for use in drug products must be sufficiently bioavailable to be effective, but also be stable (i.e. won’t change form before being taken by a patient).

Analytical tools such as X-ray diffraction (XRD) and differential scanning calorimetry are widely used to distinguish and structurally characterise the different crystal forms of an API, allowing the physical stability of these forms to be studied, but have limitations. We have investigated the use of transmission electron microscopy (TEM) for pharmaceutical analysis, developing strategies for overcoming difficulties with sample preparation and beam damage, allowing the high resolution imaging and diffraction analysis possible with TEM to be utilised [1]. TEM has been applied to the identification of the crystal form of individual crystallites, to mapping crystal habit to crystal structure and to the analysis of crystal defects. Moreover, a new approach to crystal structure determination combining TEM analysis and crystal structure prediction (CSP) was developed and used to study sub-micron sized crystals and mixtures of phases, situations where X-ray diffraction would not be applicable [2,3].

Cocrystals are crystal forms comprised of two or more neutral molecules (coformers), and have different physical properties to the separate molecules. Cocrystals are particularly useful as the bioavailability of an API can be increased through cocrystallisation with a soluble coformer. We have investigated the stability of such cocrystals in the presence of atmospheric humidity, however, and found that they are prone to dissociation [4,5]. Cocrystal dissociation on heating has also been studied [6]. Furthermore, we have developed two alternative approaches to cocrystal preparation, freeze-drying and interfacial cocrystallisation, which offer advantages over other methods and have yielded novel polymorphic forms of cocrystals [7,8].

Pharmaceutical compounds chemically degrade over time resulting in a reduced dose to patients and generation of potentially toxic bi-products. Batch-to-batch variability in solid state API degradation rates is common, and the shelf lives used to protect patients are often shorter than would be desired. There is, therefore, a need to better understand physical degradation processes. Aspirin undergoes hydrolysis to salicylic acid in the presence of water. We have investigated this degradation process in various aspirin crystal forms by HPLC, XRD and atomic force microscopy, leading to new insights.

REFERENCES
Phase transformations of a pharmaceutical drug incorporated in a thermoresponsive biopolymer by using supercritical CO₂

Teresa Cordeiro,¹ Andrea Santos,¹ Catarina Santos,² José P. Farinha,² Alexandre Paiva,¹ Susana Barreiros,¹ Madalena Dionisio,¹ Natália T. Correia³ and M. Teresa Vicioso²

¹REQUIMTE/CQFB, Departamento de Química, Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa, 2829-516 Caparica, Portugal.
²CQFM – Centro de Química-Física Molecular and IN – Institute of Nanoscience and Nanotechnology, Instituto Superior Técnico, Universidade Técnica de Lisboa, Avenida Rovisco Pais, 1049-001 Lisboa, Portugal
³Unité Matériaux et Transformation (UMET), UMR CNRS 8207, UFR de Physique, BAT P5, Université Lille 1, 59655 Villeneuve d’Ascq, France

The low water solubility of most drugs leads to the search for new drug formulations that can stabilize it in a potentially more bioavailable state. The incorporation in a biocompatible matrix is an alternative strategy, since it can preserve the drug in a more disordered state at a molecular level, either amorphous or metastable crystalline, promoting its dissolution and bioavailability relative to the more stable crystalline state [1]. However, these forms are unstable being able to change over time. Physical processes such as aging or recrystallization or conversion between polymorphs may occur under certain conditions which may result in a change in the drug's bioavailability. It is therefore of interest to characterize the phase transformations and molecular mobility of the thus produced composite to evaluate its behavior under different thermal treatments aiming to predict its stability during storage.

In the present work a pharmaceutical drug of the stasin family is characterized by both dielectric relaxation spectroscopy and differential scanning calorimetry in its bulk state and after incorporation in a thermoresponsive biopolymer; the biopolymer it is also characterized in its bulk state. The impregnation was carried out using supercritical fluid (SCF) technology (supercritical carbon dioxide). The SCF technology is an attractive environmentally friendly alternative to conventional methods to prepare novel drug products, avoiding the use of organic solvents and high temperature processing, allowing controlling crystal polymorphism among others [2,3].

In the SCF prepared drug/biopolymer composite contrarily to the polymorphism observed for the bulk drug, only a metastable crystalline form is detected with melting temperature significantly depressed relatively to the stable crystalline form. A amorphous fraction is also observed with a glass transition temperature close to the bulk pharmaceutical drug.

REFERENCES

The Role of Glycerol as Biopreserver in Protein-Trehalose-Water Systems

G. Bellavia, L. Paccou, Y. Guinet, A. Hédoux

Unité Matériaux Et Transformations (UMET), UMR CNRS 8207 - UFR de Physique - BAT P5, Université Lille 1, 59655 Villeneuve d’Ascq, France

giuseppe.bellavia@univ-lille1.fr

We present Raman investigations on lysozyme/trehalose/glycerol solutions at low-water content from room temperature up to the protein thermal denaturation. We studied the Amide I band and the low-frequency spectrum as a function of the glycerol content. The former allows monitoring the protein unfolding, the latter probes the protein and solvent dynamics in anharmonic and quasi-harmonic regimes. The analysis of the Amide I band reveals that glycerol enhances the stabilization effect of trehalose on proteins. Data show that the protein unfolding temperature has a maximum value around 5% Glyc/TRE g/g. The overlapping low-frequency contributions, corresponding to fast anharmonic and quasi-harmonic motions, respectively related to \(<u^2>\) and VDOS usually determined by neutron scattering experiments, have been carefully analyzed to understand the effect of glycerol. It was shown that adding a small amount of glycerol to trehalose enhances the anti-plasticizing effect of trehalose, and stiffens the trehalose-water matrix in which proteins are embedded, thus improving their stability. Glycerol acts then like a promoter of the protein/cosolvent coupling, whose the peculiar 5% glyc/TRE content gives the more rigid matrix along with the higher protein stability. Glycerol/trehalose mixtures are expected to have great efficacy for long-term storage of freeze-dried proteins.
Mathematical modeling of drug release from Kollicoat SR coated pellets


1 University of Lille, INSERM U 1008, College of Pharmacy, 3 Rue du Prof. Laguesse, 59006 Lille, France, juergen.siepmann@univ-lille2.fr
2 Development Laboratories, MSD, Hertford Road, Hoddesdon, EN11 9BU, United Kingdom

Introduction

Polymeric film coatings offer a great potential to accurately control drug release from pharmaceutical dosage forms (1). However, major challenges still need to be addressed, such as potential changes in the systems' structure during long term storage (2) or a better understanding of the underlying drug release mechanisms (3). The aim of this study was to prepare and thoroughly characterize different types of propranolol HCl loaded pellets coated with Kollicoat SR 30D (an aqueous dispersion of polyvinyl acetate, containing also polyvinyl pyrrolidone and sodium lauryl sulfate). Triethyl citrate (TEC) was added as a plasticizer. Thin, free films of identical composition as the film coatings were also prepared and used for side-by-side diffusion cell measurements. Mathematical models were used to determine system specific parameters from these experiments; and then to predict the drug release from coated pellets. The predictions were compared with experimental results.

Materials and methods

Thin, free films were prepared by spraying blends of Kollicoat SR 30D, TEC and propranolol HCl onto Teflon plates and subsequent controlled drying. Drug-layered starter cores (sugar or microcrystalline cellulose) were coated with the same formulations in a fluidized bed, followed by 24 h curing at 60 °C. Drug release was measured using the USP II paddle apparatus in phosphate buffer pH 7.4 (UV drug detection). The mechanical properties of thin films were measured using a puncture test with a texture analyzer from films in contact with the dissolution medium. The water uptake and dry mass loss kinetics of thin, free films upon exposure to the release medium was monitored gravimetrically. Side-by-side diffusion cells were used to determine the permeability of the film coatings with saturated aqueous solutions of the drug.

Results and discussion

The film coatings very rapidly took up significant amounts of release medium at early time points, but the water content subsequently remained constant (Fig. 1). The dry mass loss was very limited within the observation period (Fig. 2). Furthermore, the films were very flexible (Fig. 3).

Using side-by-side diffusion cells with a large excess of drug in the donor compartment and perfect sink conditions in the acceptor compartment, the product of the apparent diffusion coefficient of propranolol in these films and the partition coefficient “film/release medium” (D * K) could be determined to be equal to 1.7 * 10^-8 cm²/s (Fig. 4). Knowing this value and assuming that diffusion through the intact polymeric film coatings is the release rate controlling step from coated pellets, the analytical solution of Fick’s second law of diffusion shown in Fig. 5 could be used to theoretically predict the resulting drug release kinetics for any given coating level, drug loading and pellet size. Here, M_t and M_∞ denote the cumulative amounts of drug released at time t and infinity, respectively; R_i and R_o are the inner and outer radii of the coated pellets. The curves in Fig. 6 show examples for such theoretical predictions; the symbols illustrating the respective independent experimental results. As it can be seen, the theory systematically and significantly overestimates drug release.
from the coated pellets, suggesting that the mechanism of drug transport differs between these pellets and the corresponding diffusion cell measurements with cast films.

**CONCLUSION**

Kollicoat SR coated pellets offer an interesting potential to accurately control drug release, but the underlying drug release mechanisms may be more complex than "simple" drug diffusion through the intact polymeric film coatings. Future studies will aim at a better understanding of these phenomena and their quantitative mathematical modeling.

**REFERENCES**


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T : +33 (0) 3 20 21 84 80 - F : +33 (0) 3 20 21 84 98
contact@interreg4a-2mers.eu

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