# APV Focus Group Drug Delivery

**Combining Science & Technology to Create Advanced Drug Delivery Systems**

**INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY**

**NEWSLETTER** **ISSUE 1/2010**




## TABLE OF CONTENTS



## DRUG DELIVERY EVENTS


BACK TO TABLE OF CONTENTS


Provided by Christoph Blümer

◇ **Patent Workshop for Scientists & Managers in Drug Product Development (APV course 6287)**
Feb 25th - 26th 2010, Berlin, Germany
Chair: Dr. Karsten Cremer, Pharma Concepts GmbH, Basle, Switzerland

This course is designed to convey a solid understanding of patents and their role in the pharmaceutical industry, and to provide the attendee with the professional skills required to collaborate successfully with patent experts. Especially recommended for scientists and managers who are involved in evaluating inventions, preparing patent applications, supporting freedom-to-operate analyses, or who are members of due diligence teams.

Details

◇ **7th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology**
March 08th - 11th 2010, Valletta, Malta

Details

**Injectable Drug Delivery - Devices, Technology & Development**
March 22nd - 23rd 2010, London, UK

Details

◇ **2nd European Conference on Medical Devices: IP-Management, Materials and Development of Drug Delivery Devices (APV Course No. 6293)**
April 13th - 14th 2010, Berlin, Germany
Chairs: Peter Wallrabe, item GmbH, Münster, Germany
Dr. Karsten Cremer, Pharma Concepts GmbH, Basle, Switzerland

Details

This conference is of interest to all those who are involved in development, production, quality management und registration of medical devices as well as for those who work in the field of DRA. Additionally, this course will also be of relevance to employees developing and producing pharmaceutical products using medical devices.

◇ **Formulation of Parenteral Protein Products (APV Course No. 6290)**
April 22nd - 23rd 2010, Basle, Switzerland

Details

**7th Controlled Release Conference**
April 28th - 29th 2010, London, UK

Details

***Suggest a meeting to be announced!***

### Clonidine Extended Release (ER) Tablets and Oral Suspension (Tris Pharma)

Two of Tris Pharma's controlled release products were approved by the FDA in Dec 2009. Both contain the central alpha-adrenergic agonist, clonidine, and are licensed for the treatment of hypertension. They represent the first oral once daily presentations of this drug.

The liquid product is a beige to tan viscous suspension containing 0.09mg/ml clonidine base (equivalent to 0.1 mg/ml clonidine HCL), while the sustained release tablet formulation is available in two strengths: 0.17 mg and 0.26 mg (equivalent to 0.2 mg and 0.3 mg of clonidine hydrochloride, respectively). Both are formulated using the company's OralXR™ platform technology which enables both the sustained release and taste-masking of this bitter compound. The technology is based on the coating of regulatory acceptable ion-exchange resins with a flexible, water-insoluble coat.
In addition to the ion-exchange resin (sodium polystyrene sulfonate) and the coating (polyvinyl acetate), the controlled release suspension also contains various preservatives, viscosity modifying agents, sweeteners and citric acid as a pH modifier. Additional inactive ingredients in the tablet formulation include crospovidone, dental-type silica, lactose monohydrate and microcrystalline cellulose. Both tablet strengths are film-coated and are designed with a score so that they can be split if necessary.

In human studies assessing the pharmacokinetics of these formulations, single doses of 0.17 mg Clonidine administered either as a sustained release tablet or as 2ml of the suspension, resulted in a clonidine mean peak plasma concentrations of 0.49 (±0.09) ng/mL after 7.8 (±1.7) hours. In both cases the plasma half-life of clonidine was 13.7 (±3.0) hours and food had no effect on drug pharmacokinetics.

**Further Information:**

- Product Entries in Drugs@FDA, http://www.fda.gov
- http://www.trispharma.com

### Zyprexa® Relprevv™ Extended Release Injectable Suspension (Eli Lilly)

Zyprexa® Relprevv™ is an extended release injection of olanzapine, Eli Lilly's blockbuster atypical antipsychotic, and is intended for deep intramuscular injection into the gluteal region. It was approved in Dec 2009 by the FDA and by the EU in 2008 (tradename in EU - ZypAdheraTM) for the treatment of schizophrenia. However, unlike the existing oral dosage forms and the short-acting intramuscular injection version of this drug (Zyprexa® Intramuscular), it is not licensed for bipolar disorder.

It contains the drug in the form of a poorly soluble pamoate monohydrate salt, and hence, does not use drug delivery technology per se to achieve extended release. Zyprexa® Relprevv™ appears to have a predictable release profile with peak concentrations being achieved with four days and does not require refrigerated storage (a disadvantage of the other marketed atypical antipsychotic, Risperidone long acting injection).

It is available in kits with vials containing either 210mg or 300mg of yellow olazapine pamoate powder (for delivery over two weeks) and in 405 mg vials for delivery over 4 weeks. Each kit also contains excess (3ml) diluent (carboxymethylcellulose sodium, mannitol, polysorbate 80, NaOH and/or HCL - pH adjustment, and water for injection) to facilitate uniform suspension of the compound and achieve a concentration of 150mg/ml. The recommended dose of Zyprexa® Relprevv™ varies based on the oral olanzapine dose required to stabilize the patient and is higher for the first two weeks than for the maintenance phase. There is no requirement to supplement patients with oral therapy in the first few weeks.

In general, the side-effects of Zyprexa® Relprevv™ are similar to those seen for other formulations of olazapine: weight gain, dyslipidaemia and elevated glucose levels. However, following < 0.1 % of injections in clinical trials, patients developed a Post-Injection Delirium/Sedation Syndrome that resembles overdosage of this drug. This post-injection syndrome may appear after any injection, and although its occurrence is not fully understood, it may be related to the higher solubility of olanzapine pamoate in blood compared to muscle. Due to the seriousness of these symptoms, Zyprexa® Relprevv™ can only be prescribed to patients in the US enrolled in a restricted distribution program, and must be administered in registered healthcare facilities with ready access to emergency services. In addition, patients must be continuously monitored for at least 3 hours post-injection and accompanied home. These precautions may, of course, impact on the potential market for this product and it is not clear to what extent Zyprexa® Relprevv™ will contribute to the global sales of the Zyprexa® portfolio. These stood at $4.7 billion in 2006 out of a total global market for antipsychotics of $18.2billion.

**Further Information:**

- Product Entry in Drugs@FDA, http://www.fda.gov
- http://www.lilly.com
- S. Bleakley, *New depot formulation for schizophrenia treatment*, The British Journal of Clinical Pharmacy, Vol.1 July/August 2009 and references contained within.

## ALRISE BIOSYSTEMS GmbH (Berlin, Germany)

ALRISE Biosystems GmbH is a drug-delivery company focused on advanced nano- and micro-encapsulation for drug development. ALRISE's core business includes controlled-release formulations (parenteral delivery) and targeting of gastrointestinal tract (oral delivery).

### Fact sheet:

| | |
|---|---|
| Founded: | 2004 |
| Location: | Berlin, Germany |
| Ownership: | Private |
| Employees: | 11 |
| Key technology: | ALRISE's proprietary *ImSus*® technology is an innovative, economic and high quality platform technology for the manufacture of drug-loaded polymeric nano and micro particles.<br><br>*ImSus*® technology allows an efficient encapsulation of both hydrophilic and hydrophobic drugs independent of the molecule size (from small molecules to peptides and proteins), and is compatible with all kinds of polymers commonly used for drug delivery applications (for both biodegradable and non-biodegradable polymers). The technology can be designed for parenteral (controlled-release) or oral administration. *ImSus*® technology produces homogeneous microparticle morphologies (capsules, sponges or spheres) resulting in highly reproducible drug release performances. All excipients used to date with the technology are either approved by FDA for parenteral applications or generally regarded as safe (GRAS).<br>One of the key characteristics of the Alrise technology is that the micro particles are formed in a One-Pot Process: In the manufacturing process, the polymer is dissolved in non-toxic and halogen-free solvents (generally regarded as safe, GRAS) or solvent mixtures to form organic polymer solutions. The organic solvent is selected on the basis of its polymer solubilization properties and its solubility in the aqueous surfactant phase. A drug solution is dispersed in this polymer solution and an aqueous surfactant solution is added. The aqueous surfactant phase contains approved surfactants such as Poloxamer 188. As an important advantage over its competing technologies, *ImSus*® technology uses small volumes of surfactant efficiently, thus minimizing waste and associated costs. The aqueous surfactant solution acts as both the continuous phase and the organic solvent extraction medium; thereby, an immediate formation of dispersed solid micro particles is facilitated (suspension). This rapid process shortens the time-consuming and costly solvent evaporation / solvent removal step evident in existing encapsulation processes. Moreover, the quasi immediate formation of solid particles (suspension) facilitates achieving a very high core loading and encapsulation efficiency as well as avoiding the initial burst. The micro particles can be removed from the suspension by means of filtration or centrifugation.<br>Finally, the particle suspension is transferred to the solid state by means of a commonly used drying process (e.g., freeze-drying). In addition, these particles are produced with a high degree of morphological homogeneity making them an excellent vehicle for controlled drug release. |
| Products: | Alrise's initial focus is on development of supergenerics; improved formulations of established depot products. Specific products in pipeline are undisclosed. |
| Development status: | Lead product in pre-clinical development currently. First clinical trial is expected to start in 2010 |
| Partnerships: | Undisclosed |
| Website: | http://www.alrise.de |
| Contact: | Dr. Celal Albayrak - CEO<br>ALRISE Biosystems GmbH<br>Robert-Roessle-Straße 10<br>Otto-Warburg-Haus<br>D-13125 Berlin, Germany<br>Phone +49 - (0)30 - 94 89 24 83<br>Fax +49 - (0)30 - 94 89 24 82<br>E-Mail: info@alrise.de |

### INHALER

***A device for delivering an aerosolised medicine to the respiratory system of a patient.***
*Write a comment on this definition*

Inhaler is a generic term for various types of devices which have in common that they are adapted to convert a solid or liquid pharmaceutical formulation into an inhalable aerosol. The aerosol is typically administered through the mouth, but sometimes also through the nose. While in most cases the delivery of the aerosolised medicine to the lung is intended, the actual deposition of the aerosol occurs at various sites of the respiratory system including the throat and the bronchi.

### METERED-DOSE INHALER

***An inhaler for dispensing a pressurised liquid formulation in metered quantities.***
*Write a comment on this definition*

A metered-dose inhaler (MDI) essentially consists of a canister containing a liquid formulation including a propellant; a metering valve for emitting a metered quantity of the formulation with each actuation; and an actuator by which the patient operates the device.

### DRY POWDER INHALER

***An inhaler for dispensing a powder formulation.***
*Write a comment on this definition*

A dry powder inhaler (DPI) typically contains its medication in already metered form, for example within capsules or other segregated reservoirs which are loaded into the device. Powder inhalers usually require a greater degree of skill to operate them correctly than other inhalers.

### NEBULISER

***An inhaler for dispensing a non-pressurised liquid formulation.***
*Write a comment on this definition*

Various types of nebulisers using different aerosolisation methods are available, such as jet nebulisers, ultrasonic nebulisers, and vibrating-mesh nebulisers. Nebulisers are typically used to deliver larger volumes of liquid formulations which cannot be delivered with metered-dose inhalers, or for patients having difficulty using a powder inhaler or metered-dose inhaler.

***Suggest a term to be defined*** ***Suggest a definition***

## DRUG DELIVERY PEOPLE



**VINCENT H.L. LEE** is Professor and Director of the School of Pharmacy, Chinese University of Hong Kong. Prior to that he was Associate Director at the Office of Pharmaceutical Science, US Food and Drug Administration; Vice President of Biological, Formulation and Material Science at ALZA; and, Gavin S. Herbert Professor of Pharmaceutical Sciences, Professor of Ophthalmology, Chairman of the Department of Pharmaceutical Sciences, and Associate Dean for Research and Graduate Affairs at the University of Southern California (USC).

Professor Lee is a world-renowned leader in drug delivery. His research was funded by the National Institutes of Health in the United States for more than 20 years, a record that has placed him among the top 5% of all the NIH grant applicants. He has published more than 270 papers.

Prof. Lee is recognized internationally as an outstanding scientist in, first and foremost, ocular drug delivery. He pioneered new approaches of ophthalmic drug delivery by using the conjunctiva as a new pathway of targeting drugs to the back of the eye. His research increased our knowledge about physiological, biochemical, and molecular properties of this thin, vascularized mucosal issue. This work subsequently paved the way for the development of revolutionary concepts to treat dry eye and to design mucoadhesive delivery platforms for targeting drugs to treat age-related macular degeneration in the elderly.

The second area for which Prof. Lee is highly regarded is peptide and protein drug delivery. Using a very simple experimental design, he convincingly demonstrated the overpowering role of mucosal proteases as a deterrent to peptide and protein drug delivery – perhaps as a gatekeeper to systemic entry. As this research evolved, Prof. Lee ventured into the transporter research community. His main contribution there was the building of a multidisciplinary research team to

undertake the challenging task of modelling the active site of the dipeptide transporter, Pept1 in order to facilitate targeted drug design. This group of talented investigators was among the first to propose a topology for the binding site of this important drug transporter. This breakthrough is instrumental in changing the course of research and accelerating its pace of development of carrier-mediated drug transport as a means to implement personalized medicine.

He encourages and supports young scientists. Over 30 graduate students, postdoctoral fellows, and visiting scientists from North America, Asia, and Europe have been trained by Professor Lee. Some of them are now accomplished professors in the United States, United Kingdom, Germany and Japan.
Several international honors and awards, including the Young Investigator Award of the Controlled Release Society, Research Achievement Award in Pharmaceutics and Drug Delivery of the American Association of Pharmaceutical Scientists, and Pharmaceutical Scientist of the Year award of the FIP Board of Pharmaceutical Sciences, have recognized Professor Lee's research accomplishments. In 2002, he was awarded a Citation of Merit by the University of Wisconsin School of Pharmacy (only an honorary degree constitutes a higher honour than a citation.) In 2003, he was awarded an Honorary Doctor of Science degree from the University of London, United Kingdom.

Prof. Lee's lasting contributions to the research and pharmacy community could well be summed up as building bridges. He has served on the editorial board of over 10 peer-reviewed scientific journals, a total of three editorships, grant review panels, foundations, scientific advisory boards, and FDA advisory committees. Professor Lee is presently editor-in-chief of Advanced Drug Delivery Reviews, the leading journal drug delivery. Professor Lee was elected President of the American Association of Pharmaceutical Scientists in 1996 and of the Controlled Release Society in 1993.

Prof. Lee is a unique, outstanding and truly international scientist. He is not only dedicated to science in his own research field and laboratory, but is also passionately committed to mentoring, networking, and building alliances for the development of the interdisciplinary field of drug delivery. He has discovered innovative ways of working in partnership and building bridges with academia, industry, national and community-based organizations, and professional organizations.

## FEATURED ARTICLE

BACK TO TABLE OF CONTENTS

### ORAL DRUG SOLUBILIZATION STRATEGIES: APPLYING NANOPARTICULATE FORMULATION AND SOLID DISPERSION APPROACHES IN DRUG DEVELOPMENT

*By Carsten Timpe, Novartis Pharma AG, CH-Basle*

**1. Abstract**

Over the last decade, a large number of publications and pharmaceutical conferences have dealt with drug delivery strategies for the increasing number of poorly water soluble and lipophilic drugs. To deliver these appropriately, typically requires application of more advanced formulation technologies than simple salt formation and micronization. Examples of these include lipid/surfactant based SEDDS/SMEDDS (self-emulsifying/self-micro-emulsifying) or solid dispersion formulation approaches. However, many molecules cannot be adequately delivered even when they are formulated with these tools, due to their low solubility in lipidic and polymeric excipients. In such cases it may be possible to apply nanoparticulate formulation approaches.

Despite their potential to solve the problem of poor solubility, advanced drug delivery techniques, like solid dispersions and nanoparticle formulations, have taken many years to penetrate into commercial drug product development. This is due to them being generally rather difficult to develop (e.g. as a result of meta-stability). The article gives an overview of nanoparticulate and solid dispersions formulation technologies, highlighting the often underestimated similarities between them. It also discusses screening options for feasibility studies, technical challenges regarding stabilization, further processing and up-scaling aspects. In addition, a number of case studies have been included to illustrate the landscape. Further details can also be found in the references at the end of this article.

**2. Concepts behind nanoparticulate and solid dispersion approaches**

The enormous interest in solubility-enhancing delivery strategies has been generated due to the increasing number of poorly soluble drug candidates, and is reflected in the number of scientific papers and presentations at drug delivery conferences [1, 2, 3, 4, 5] on this subject. The reasons why solid dispersions and nanoparticulate based formulations have in the past been adopted mainly by academia, but not by major parts of pharmaceutical industry, are manifold:

- The meta-stable nature of the systems e.g. the risk of physical instability/re-crystallization in solid solutions/dispersions with the potential of deteriorating drug release and bioavailability.
- Lack of appropriate manufacturing and analytical characterization tools available in-house (e.g. solvent based technologies for preparing solid dispersions need to have expensive solvent recovery systems [6])
- Lack of experience and trained personnel to apply these systems effectively in drug product development. For example, to prepare these formulations and screen them analytically in-house usually requires additional methodologies such as modulated DSC, particle size and zeta potential analysis for nanoparticles and polymorphic characterization of Nanoparticles.

- Concern about infringing the patents of specialist technology companies with expertise in the field of making nanoparticles or melt extruded solid dispersions.
- Lack of sufficient senior management support to invest in these more risky technologies.

***The Fenofibrate Case – Improvements with Nanoparticles***

A good example is the case of the lipid lowering drug Fenofibrate: Originally, Abbott brought this product onto the market as a capsule containing 100 mg unmicronized drug. This formulation was replaced in the US by a micronized capsule formulation (67, 134, 200, 267 mg) and then finally by a nanocrystalline tablet formulation (48, 145 mg). With the dramatic drop in particle size from the µm ranges down to the nanometer scale, an enhancement in bioavailability was achieved. This, in turn, enabled a significant dose reduction and removed the need to take the medication together with food.

Another example for the benefit of nanoparticulates can be a significant food effect reduction as has been published by J. Jinno et al. [7]: Cilostazol, a BCS class II compound, shows a positive food effect which was dramatically reduced in a beagle dog study when the drug was nanosized using nanomilling technology.

As shown by the Noyes-Whitney equation (see Equation 1): Nanoparticulate formulations improve bioavailability by accelerating the dissolution rate due to the large increase in the surface area A at smaller particle sizes.

**Equation 1:**

$$\frac{dw}{dt} = \frac{D}{h} * A * (Cs - Ct)$$

Dw/dt = Dissolution rate
D= Diffusion coefficient
h = Thickness of diffusion layer
A = Interfacial surface area
Cs = Saturation solubility
Ct = Solubility at t

In addition to a surface area increase, the saturation solubility of the drug compound also improves due to the higher intrinsic dissolution ("vapour") pressure for particles in the lower submicron range. This is due to their much higher particle curvatures (smaller radius of curvature) - the relationship between particle curvature and saturation solubility being mathematically described by the Freundlich-Ostwald equation. It has been estimated that this increase in intrinsic dissolution pressure contributes to approximately 10 – 50 % of the saturation solubility improvements seen with nanoparticulate formulations [8].

In the case of solid dispersion formulations, the dissolution rate can also be dramatically increased (similar to nanoparticulate drugs), if the compound is either in its pure amorphous form - assuming sufficient wettability of the drug surface by the dissolution medium- or amorphously embedded in a suitable carrier matrix which is typically a pharmaceutical polymer or a polymer plus a surfactant or another carrier like urea or a sugar alcohol (e.g. Mannitol): The amorphous nature of such systems means that there is no crystal lattice energy barrier that needs to be thermodynamically overcome which, hence, promotes faster dissolution.

However, it has also been recently reported that nanoparticulate structures were observed and measured when sold dispersion particles started to dissolve: Bikaris et al. found small nanometer particles when Felodipine solid dispersions in Polyvinylpyrrolidone with 10 – 20 % drug load were dissolved in pH 6.5 phosphate buffer solutions (with 2 % Polysorbate 20, 100 rpm paddle) [9]. So it seems as if there are ultrafine nanometer range particles available once the solid dispersion starts to dissolve – resulting in a dramatic increase in surface area, in addition to the much higher intrinsic saturation solubility achieved due to the compound being in the amorphous state.

***Overcoming Drug Precipitation***

Another extremely important aspect of developing the right formulations for a poorly soluble drug from the beginning is the problem that pH-sensitive molecules like weak bases or weak acids can undergo dramatic changes in solubility during their gastrointestinal passage. This can mean that the solubility in the gastric juice might be sufficiently high to dissolve the weak base or a corresponding salt, but with the entrance of the dissolved drug into regions of higher pH, e.g. in the small intestine, solubility might drop dramatically associated with a precipitation of the corresponding free drug base into particles of increasing sizes. These have then a low probability of getting re-dissolved and absorbed in later compartments of the gut. A similar situation could happen with the ingestion of a meal: D. Hörter and J. Dressman reported that postprandial pH increases up to 5 circa 0.5 – 1 hour after a meal. This shift could then be the trigger for converting a soluble salt species into its insoluble corresponding precipitate.

The following Figure 1 depicts the dramatic particle size increase of a poorly soluble weak base given as a salt from the first measurement after 10 min. up to one hour in a pH 6.8 buffer solution and FaSSIF and FeSSIF dissolution media. It shows while size ranges of a few 10 µm dominated after 10 minutes, particle growth up to large 100 µm particles occurred within the first hour.

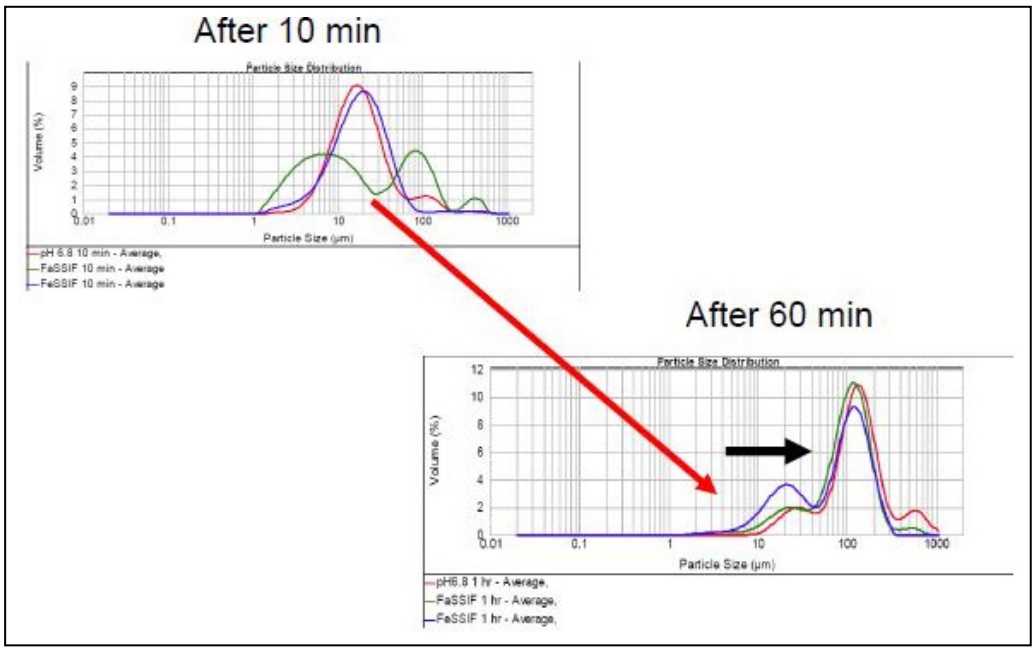



*Figure 1: Precipitation of corresponding weak base from a salt in different intestinal media (buffer solution pH 6.8, FaSSIF, FeSSIF)*

Proper characterization of the precipitates (i.e. particle size ranges, type of polymorph formed) is important to make an assessment about the likelihood of re-dissolution and later absorption. Formation of a precipitated very insoluble hydrate for instance would give a low chance that this might actually occur. In some cases the occurrence of double-peaks in blood plasma levels could hint that the precipitated drug has received a 2nd chance for absorption (if entero-hepatic circulation is not responsible for this phenomenon). Suitable in-vitro dissolution systems to investigate drug precipitation have been described in literature, e.g. [10, 11]. More elaborated models combine a precipitation model with a Caco-2 cell one: The dissolution fluid at pH 6.8 is pumped into the donor compartment where the drug can then penetrate through a Caco-2 cell layer. The drug concentration in the acceptor compartment corresponds to the fractions of absorbed drug [12].

Since the bioavailability enhancing mechanism of nanoparticulate approaches is fast dissolution, there is, per se, no principle integrated into these systems which would efficiently avoid drug precipitation. On the other hand, as in the case of solid dispersions and SEDDS/SMEDDS formulations, the soluble drug exists for a certain time in an oversaturated solution stabilized by the polymeric or surfactant-rich micro-environment. In a 20% (w/w) solid dispersion eighty percent of the polymer is present to potentially stabilize the oversaturated system. This is not the case for nanosuspensions which have typically much lower polymer concentrations. Stabilization of the oversaturated system allows poorly water soluble drugs that are rapidly absorbed to permeate through the intestinal cellular membranes within a certain timeframe which, in many cases, can lead to dramatic increases in bioavailability.

## 3. Nanoparticulate Formulations

The following Table 1 shows currently marketed products based on nanoparticulate formulations:

| Product | Company | Indication | Formulation | FDA approval |
|---|---|---|---|---|
| Sirolimus | Wyeth | Immunosuppressant | Tablet | 1999 |
| Aprepitant | Merck | Nausea, vomiting | Capsule | 2003 |
| Fenofibrate | Abbott | Hypercholesterinemia | Tablet | 2004 |
| Megestrol acetate | PAR | Appetite stimulant | Nanosuspension | 2005 |
| Paliperidone | J&J | Schizophrenia | Nanosuspension | Submitted 2007 (FDA requested additional data August 2008) |

*Table 1: Marketed products with nanoparticulate formulations*

***Manufacturing Technologies***

Nanoparticles can generally be prepared in two different ways, either by

- Top-down technologies: wet-milling/ball-milling or high pressure homogenization. The crystal structure is mechanically affected by mechanical energies which lead to crystal destruction. Partial or total amorphisation or polymorph conversion can occur. The nanoparticles are stabilized by surfactants (electrostatic) and/or polymers (steric).

- Bottom-up technologies: in these cases the drug typically is dissolved in a solvent together with a stabilizer. The drug solution is precipitated e.g. through a nozzle into an anti-solvent. The formed nanoparticles are stabilized by surfactants (electrostatic) and/or polymers (steric).

Typically initial nanoparticulate products are in aqueous solution. Further processing into solid oral dosage forms is possible i.e. by freeze- or spray-drying or spray-granulation together with suitable carrier excipients (Lactose, Mannitol, Microcrystalline Cellulose etc.). Figure 2 shows schematically the manufacturing flow for a bottom-up process:

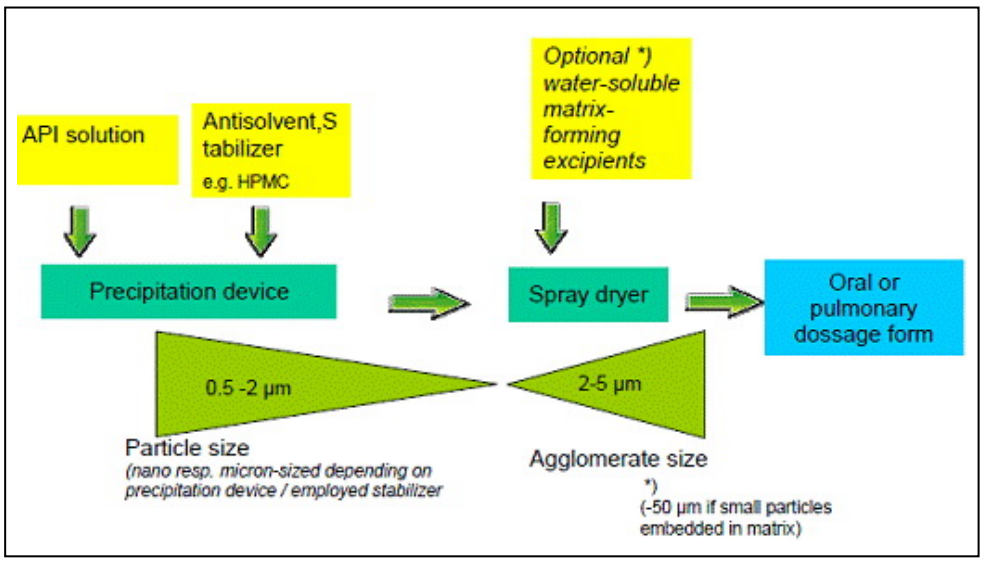



*Figure 2: Schematic scheme of a bottom-up process*

***Wet Ball Milling***

Among the top-down technologies the ball-milling process, in particular, has led to successful launches of the above mentioned marketed products. The proprietary technology is owned by one company which developed it circa 1990. Their applications have been widely described in patents and the literature [e.g. 13-15]. In the ball milling process the drug is typically suspended in its micronized form in an aqueous medium to facilitate the nanomilling process. The milling chamber contains the raw suspension together with a grinding medium, i.e. zirconium oxide, polystyrene or glass beads of less than 1 mm. A motor driven mechanical agitator shaft bears the impeller and provides high-shear agitation up to several thousand rpm. The fluid is pumped through a media separator screen and back again into the milling chamber. The mill and outside re-circulation vessel are jacketed to control the temperature sufficiently (e.g. inlet temperature 5-10°C). Milling chamber sizes from 300 mL up to 60 L allow for up-scaling of the process from lab into production scale.

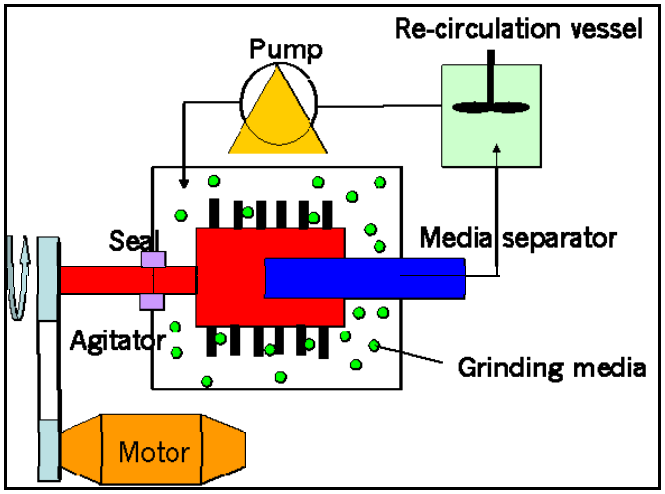



*Figure 3: Simplified scheme of ball milling technology*

***High-pressure Homogenization***

High-pressure homogenization has been evaluated in many publications by R.H. Müller et al (e.g. a good overview is given in [16]). A macro-suspension containing an aqueous surfactant, for instance, is forced through a small gap of 20 – 30 µm with a piston. The streaming velocity of the fluid is dramatically increased by pushing the material through the gap. Since the static pressure drops behind the gap, the water starts to boil. Implosion of the resulting water gas bubbles creates very strong cavitational forces that lead to mechanical destruction of the crystals. The technology has also been used commercially by several companies and led to marketed products (i.e. applied for Fenofibrate).

***Stabilization of Nanoparticles***

One of the very important aspects of nanoparticles is that they typically have the tendency to re-agglomerate due to the increasing importance of attractive inter-particulate forces (van der Waals forces) in the nanometer range. Another important phenomenon that is described as "Ostwald ripening" is based on an imbalance between the higher saturation concentration in the vicinity of very small particles (higher diffusion/"vapour" pressure due to higher curvature!) and lower concentrations close to larger particles. Smaller particle fractions vanish over time due to higher solubility while larger particles fractions start to grow.

To overcome these phenomena nanoparticles can be separated by fostering repulsive forces between them (electrostatic stabilization e.g. by adding ionic surfactants or charged polymers) or keeping them apart via steric hindrance by adsorbing polymeric stabilizers such as hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), povidone (PVK K 30) and copolymers like Pluronic F68 or F127 (see Figure 4). The chain lengths of these molecules should be not too long to slow down dissolution.

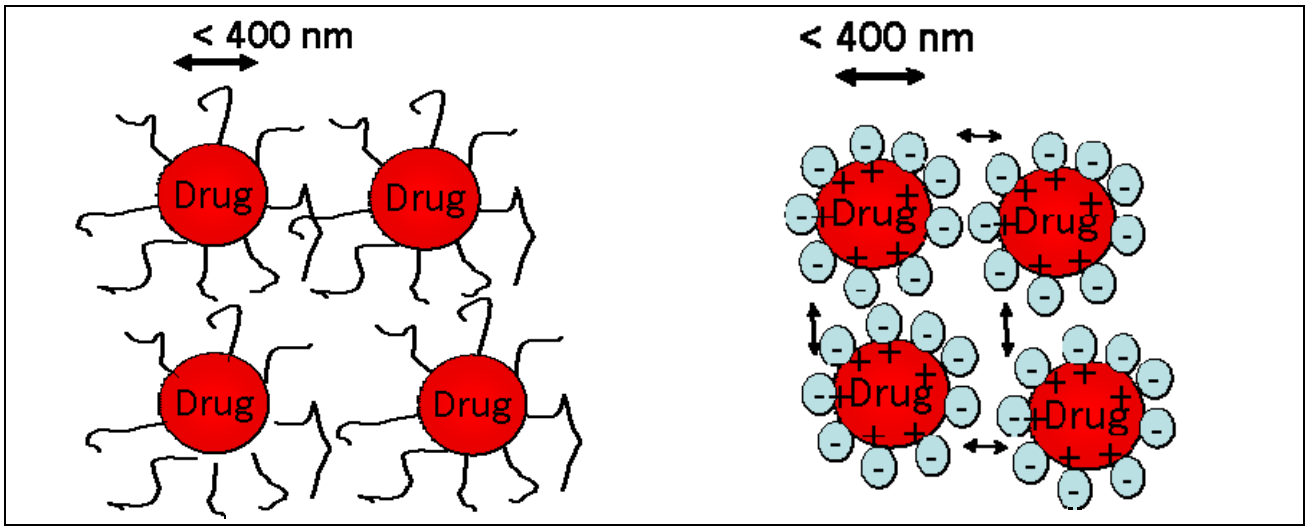



*Figure 4: Stabilization of drug nanoparticles via steric hindrance (left) or repulsive electrostatic forces (right)*

Recently another stability phenomenon has been described as "gel relaxation" by Z. Deng et al. [17]: Shortly after wet-milling particle agglomeration/cluster formation has been observed with dramatic morphology changes seen under the SEM: With particle growth reaching a maximum within 24 hours a significant viscosity increase was measured which dropped dramatically when the nanosuspension was standing for more than a day (gel relaxation). By modifying the milling conditions (extended milling time, increased concentration of surfactants etc.) the extent of this phenomenon could be reduced.

Adsorption of positively or negatively charged molecules at the charged drug surface leads to an electrical double-layer and a specific nanoparticle surface electrical charge which decreases with increasing distance from the nanoparticle surface. The potential at the slipping/boundary plane is expressed as the "zeta potential" which is measured in mV units. The zeta potential should be typically at least 30 mV. pH dependency of the zeta potential is shown in Figure 5: At 0 mV the risk of flocculation becomes very high due to the absence of interparticulate repulsive forces.

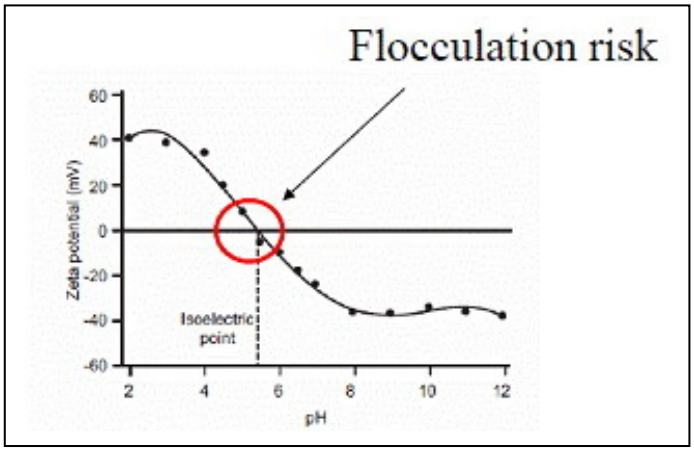



*Figure 5: pH dependence of zeta potential and flocculation risk*

***Screening of Nanoparticulate Formulations***

Designing stable nanoparticulate formulations efficiently, for instance with polymeric or ionic surfactant stabilizers, is currently more a trial and error based screening process than a strict science based approach. L. Lindfors et al. described the rational stabilization of amorphous Felodipine nanoparticles with middle-chain triglycerides (MCT) prepared by a solvent quench method. The Ostwald ripening rate was slower than predicted from the Liftshitz, Slyozow,Wagner model equation when MCT was present. Inhibition of ripening was only effective in the case of other candidates tested when MCT was completely miscible with the drug. The interaction can be calculated by a Bragg-Williams chi parameter $\chi$: particle growth inhibition was efficient when $\chi$ was < 2 [18]. Miscibility of the drug with the inhibitor was also monitored via 1H-NMR spectroscopy.

J. Lee evaluated combinations of five common polymer stabilizers, two low molecular weight surfactants and eleven insoluble drugs while keeping processing and characterization conditions the same [19]: 2 ml vials with 500 ?m polystyrene beads were used and milling was performed on a high-speed shaker. Attempts to correlate the drug substance and polymer surface energies (determined via static contact angle measurements) with the milling results (particle sizes) were not straightforward; nevertheless in several instances, similar surface energies seem to be favorable. The poor stabilization results gained with PEG were interpreted as being due to lack of hydrophobic units.

As a rule of thumb drugs with the following characteristics can be successfully transformed into nanoparticles of unimodal particle size distribution:

- High molecular weight
- Low solubility
- High melting points,
- A surface energy similar to that of the polymers

In addition, it has been found:

- Adding surfactants results in an additional size reduction in certain polymer/drug pairs,
- Both anionic and cationic surfactants produce similar size reductions in a polymer/drug pair.

B. van Eerdenbrugh et al. have recently published a nanosuspension scaling-down production study by milling compounds in glass vials in a ball mill which allows for screening nanosuspension formulations with very low drug substance amounts of circa 10 mg and less (1 mg) per experiment [20]. Analytical characterization of these nanosuspensions (particle size by laser light scattering, SEM, DSC and solid state characterization by XRPD) allowed for efficient formulation screening.

***Transformation into solid products***

Solid oral dosage forms represent from a market and patient convenience standpoint the most-favored of all drug delivery forms. Therefore one very important aspect for nanoparticulate formulations is how to transfer these into a solid oral product: i.e. granules that could be further compressed into a tablet which might be further film-coated etc. Technically this could be achieved by e.g. spray-drying, freeze-drying or spray granulation [21]. The key aspect of such solidified nanosuspensions is the maintenance of their re-dispersibility and the regeneration of a nanoparticulate size distribution once the solid form comes into contact with gastric or intestinal fluids. Different carriers, like Sucrose and Mannitol for freeze-drying and Mannitol, Microcrystalline Cellulose, Anhydrous Calcium Phosphate, colloidal Silicon Dioxide and hydrophobically modified Inuline for spray-drying, were evaluated with a set of nine poorly soluble drugs [22]. It was found that nanosuspensions of drugs with more hydrophobic surfaces displayed a decrease in dissolution rate after spray-drying, which underlines the need to include appropriate carrier excipients in the formulation: i.e. the hydrophobically modified Inuline showed superior performance due to its surface active properties.

Figure 6 shows a Novartis compound that has been spray-dried by embedding the drug nanoparticles (ca. 320 nm) in PVP, Lactose or Mannitol (drug load 47%). The highest dissolution rates under non-sink conditions were achieved with PVP > Lactose > Mannitol.

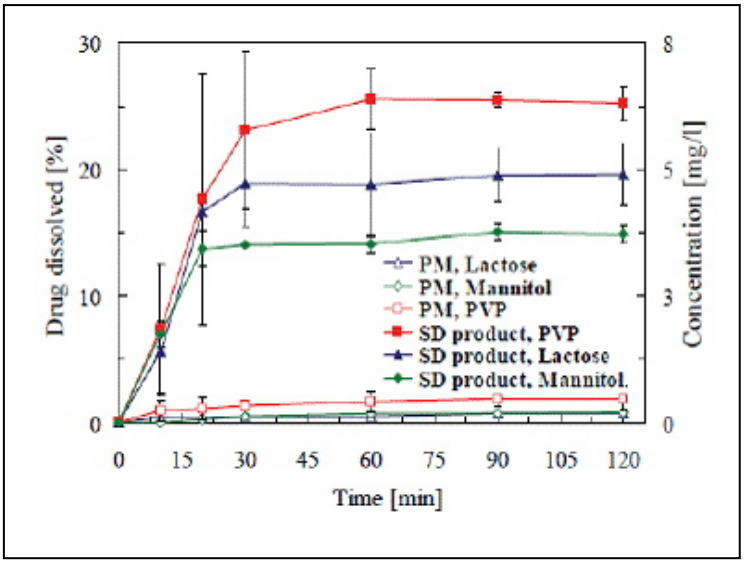



*Figure 6: Carrier dependent differences in dissolution rates of a nanoparticulate formulation*

Significant differences could be observed under the electron microscope: The PVP embedded particles showed the smoothest surfaces of the spray-dried particles.

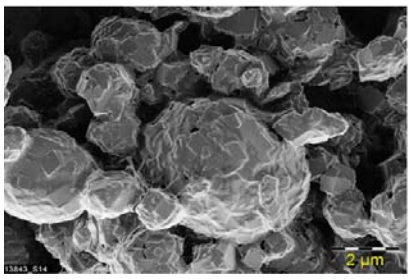
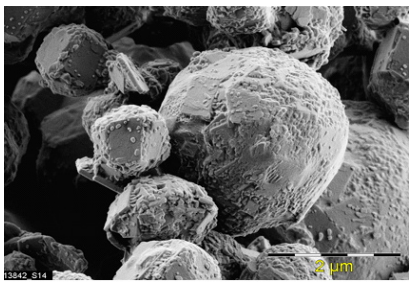
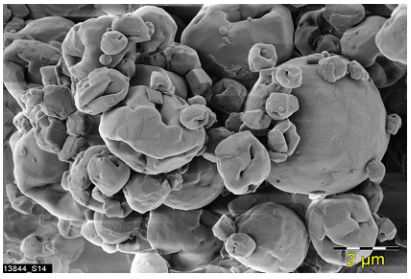
| Lactose | Mannitol | PVP |
|---|---|---|
|  |  |  |



*Figure 7: SEM images of spray-dried nanoparticulate formulations*

## 4. Solid Dispersion Formulations

The drug solubility enhancing principle of solid dispersions is based ideally on an amorphous and molecular dispersion of a poorly soluble drug in a carrier matrix which enables improved drug dissolution in water or in physiological media due to there being no crystal lattice energy barrier to be overcome. Typically an oversaturated solution is generated, bearing the risk of rapid recrystallization/precipitation.

Three different generations of solid dispersions can be differentiated [24]:

- 1st generation solid dispersions (1960s) using crystalline carriers like Fructose, Urea, Mannitol: They lead to an improvement in wettability, but require energy to break up the crystalline structures of the carrier.
- 2nd generation solid dispersions (1970s) using polymeric carriers like PVP, PVA, HPMC, HPC, Ethyl cellulose, PEG: At that time the systems were often heterogeneous mixtures of amorphous drug solutions in the polymer carrier and non-dissolved small microcrystalline particles due to only partial miscibility.
- 3rd generation solid dispersions (1990s until now): In these modern systems typically the drug is kept in an amorphous (or nanocrystalline) state, no crystal structures need to be broken down during dissolution. Inclusion of surface active substances and/or carriers (e.g. a novel non-ionic, polymeric-based surfactant system derived from chicory, Inulin, Lauroyl Macrogolglycerides or Glyceryl Behenate) improve precipitation robustness (see discussion above) and increase bioavailability of these solid dispersions.

Table 2 gives an overview of marketed solid dispersion formulations (see [6]):

| **Product** | **Active** | **Indication** | **Technology** |
|---|---|---|---|
| Pedinol Pharmaceuticals | Griseofulvin dispersed in polyethylene glycol | Antimycoticum | Melting/tabletting process |
| Valeant Pharmaceuticals (formerly from Eli Lilly) | Nabilone dispersed in PVP | Antiemeticum | Organic (ethanolic) wet-granulation |
| Abbott | Ritonavir dissolved in Gelucire *)<br>* was replaced by new soft gelatine capsule formulation | HIV (Proteaseinhibitor) | Melting/capsule filling process |
| Abbott | Ritonavir/Lopinavir | HIV (Proteaseinhibitor) | Melt extrusion process (developed by Soliqs) |
| Fujisawa | Tacrolimus dispersed in HPMC | Immunosuppressant | Solvent process (spray drying, fluid bed granulation) |
| Novartis | Everolimus dispersed in HPMC | Immunosuppressant | Solvent process (vacuum contact dryer technology, see below) |

*Table 2: Marketed solid dispersions and corresponding technologies*

Classical methods of preparing solid dispersion formulations are as follows:

- The melting method (melt extrusion)
- Solvent evaporation techniques [4]

The melting processes require often high temperatures >> 100°C which may lead to thermal degradation of the drug substance. Melt extrusion offers here an attractive, solvent-free solution to extrude thermoplastic materials (polymers) together with dissolved drugs homogeneously at much lower temperatures than the melting point of the drug and the softening temperature of the polymer [5]. A more detailed overview of solvent based manufacturing processes for solid dispersions is given in [6] and a melt extrusion process was compared with a solvent co-precipitation based one in [23].

Typically for melt extrusion processes the drug substance is extruded together with a polymer at temperatures > 100°C in a twin-extruder to dissolve the drug in the molten polymeric carrier matrix. The mechanical shear-forces applied during extrusion represent - apart from the high temperature - another factor that fosters dissolution of the poorly soluble compound in the polymer matrix. Twin-screw extruders comprise both shearing elements and heating and cooling segments and allow for short residence times and reduced heating stress due to the continuous mass flow. Manufacturing processes are typically developed on a drug substance and carrier specific basis. Homogeneity of the extrudates should be carefully checked: application of confocal Raman spectroscopy has for instance been described as a tool for such investigations by J. Breitenbach [25].

***Physical stabilization principles of solid dispersions***

Solid dispersions can principally be stabilized by

- *Thermodynamic stabilization:* In this case the drug concentation is kept below its saturation solubility e.g. in the polymeric carrier matrix. Testing of the drug candidate's solubility in dimers corresponding to the polymer components has been shown to be predictive regarding saturation solubility [25].

- *Kinetic stabilization:* In the case of drugs that are not so soluble in the polymer, the viscosity of the resulting solid dispersion – typically expressed by the glass transition temperature Tg - should be sufficiently high (Reference [26] recommends 40 – 50 K above the intended storage temperature).

Physical stability predication of solid dispersion formulations is not an easy task and normally real time stability data are used to generate relevant information for regulatory purposes. Angell plots, which monitor the characteristic relaxation time $\tau$ (relaxation time of the glass transition signal) via modulated DSC over the ratio Tg/T (glass transition temperature divided by the storage temperature), have been modified to make re-crystallization predictions. Lowering of the storage temperature leads to an increase of the Tg/T ratio and alters the relaxation time $\tau$ - the increased viscosity of the solid dispersion helps avoid drug re-crystallization in the amorphous matrix.

***Screening of solid dispersions***

Solid dispersion formulations can be analyzed by different analytical techniques with respect to

- In-vitro performance in water, physiological media (SGF, FaSSIF, FeSSIF)
- Physical stability: XRPD (absence of crystallinity), DSC/mDSC (monitoring of Tg), SEM, GC and Karl Fischer (residual solvents and/ water acting as destabilizing plasticizers lowering Tg)

With the Tg determination, solubility of the drug compound in the polymer can be monitored: In the case of good solubility only a single Tg signal becomes visible. Each phase separation (i.e. separation of the amorphous drug phase from the polymer phase) can lead to separation of individual Tg signals [6].

***Solid Dispersions – Carrier Embedded Nanoparticles?***

As discussed above it was found by D. Bikirias et al [9], that solid dispersion particles of nanometer size can be formed by dissolving a Felodipin/PVP solid dispersion in a pH 6.5 phosphate buffer solution with 2 % polysorbate. An advantage of solid dispersions over pure dried nanosuspensions might be a more efficient stabilization of the oversaturation of the dissolved particles due to the much higher polymer concentrations present. Typically solid dispersions are formulated as tablets which normally disintegrate more slowly than a conventional immediate release tablet containing a low percentage of polymer as a binder. Many solid dispersions contain high polymer concentrations of up to 80 – 90 %.

In an internal in-vivo beagle dog study a comparison was made between a larger monolithic tablet containing a solid dispersion of a poorly soluble drug (no pH dependent solubility) (drug load 20% w/w) and a multi-particulate solid dispersion mini-tablet formulation, which was in addition coated with a gastric resistant polymer to prevent premature drug precipitation in the stomach. The following figure shows that the monolithic tablet gave slightly higher drug exposure (bioavailability) compared to the small multi-particulates with larger surface area: This would suggest that the slower polymer erosion of the monolithic solid dispersion with reduced free accessible surface could be beneficial with respect to preventing rapid drug precipitation from the oversaturated drug concentration state. Similar observations were made for glassy solid dispersion melt-extrudates which protect against drug precipitation for a certain time.

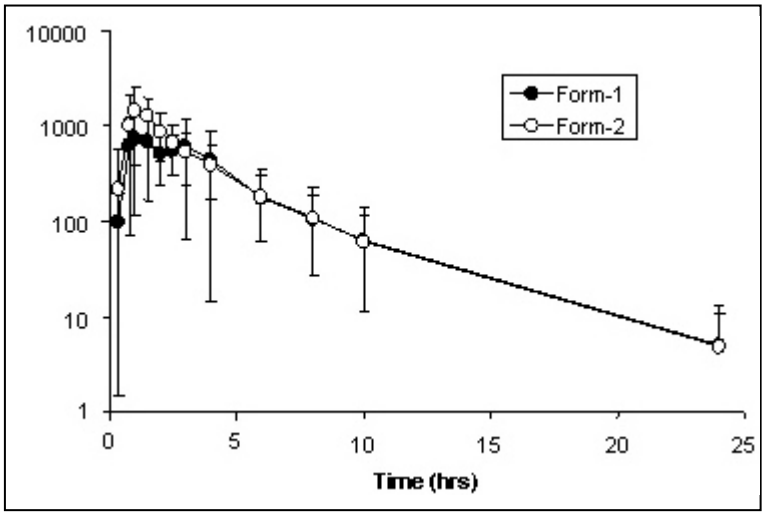



*Figure 8: Higher exposures in a cross-over beagle dog study for a monolithic solid dispersion (Form 2) over a multiparticulate enteric coated formulation (Form 1)*

**5. Summary and Conclusions**

Nanoparticulate and solid dispersion formulations have taken time to gain acceptance in routine commercial pharmaceutical development and it has taken a few decades before the first products appeared on the market. Nowadays these special drug delivery systems are becoming more and more important with the increasing number of poorly soluble drugs in early development stages. In particular, nanosuspension based formulations have gained popularity where drugs display only marginal solubility in lipidic and surfactant excipients and polymers, making development of a SEDDS/SMEDDS or solid dispersion nearly impossible.

Typically many "brick dust" molecules with high melting points > 150 – 200°C could be interesting candidates for this technology, whereas "grease ball" drugs may be better formulated with a lipidic system. Nanoparticulate and solid dispersions seem to have some similarities since drug particles in the nanometer range play a role during dissolution in both cases. Precipitation robustness is another extremely important aspect. However, further research work is required to optimally develop these enhanced formulations with improved performance under real in-vivo conditions.

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BACK TO TABLE OF CONTENTS

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Modern drug delivery research and development is a truly multidisciplinary approach and must combine all relevant scientific, technical, medical and regulatory aspects required for the design, preparation, testing, manufacturing and registration of drug delivery systems and their components. It is the mission of the APV Drug Delivery Working Group to foster and promote all aspects of research and development required to transform drug molecules into safe, applicable and acceptable drug delivery systems, which provide therapeutic benefit, convenience to the patient and improve patient compliance.

**Our mission includes in particular the following tasks:**

- Thoroughly understanding the physical-chemical and biopharmaceutical properties of the drug substance to be delivered and the components of the drug delivery system
- Understanding the biological barriers and the interactions of the drug molecule and its delivery system with the biological environment and the biological target including PK/PD and PK/safety relationships
- Research on excipients, materials and technologies required for the design, preparation and manufacturing of drug delivery systems for a selected route of administration
- Development and understanding of methods for in vitro and in vivo evaluation of drug delivery systems and their components
- Knowledge of regulatory requirements for clinical testing, manufacturing and registration of drug delivery systems

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