APV FOCUS GROUP DRUG DELIVERY

COMBINING SCIENCE & TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER **ISSUE 1/2012**

TABLE OF CONTENTS

DRUG DELIVERY EVENTS

BACK TO TABLE OF CONTENTS

Provided by Christoph Blümer

◇ **8th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology**
March 19 - 22, 2012, Istanbul, Turkey — Details

CRS German Chapter Annual Meeting: Controlled Release Systems for Proteins & Small Molecules
March 17 - 18, 2012, Wuerzburg, Germany — Details

◇ **CLINAM 2012 - The European Summit for Clinical Nanomedicine**
May 07 - 09, 2012, Basel, Switzerland — Details

Nanoformulation 2012
May 28 - June 01, 2012, Barcelona, Spain — Details

The 39th Annual Meeting & Exposition of the Controlled Release Society
July 15 - 18, 2012, Quebec, Canada — Details

Suggest a meeting to be announced!

APV COURSE SUMMARIES

BACK TO TABLE OF CONTENTS

NANOCARRIERS FOR DRUG DELIVERY

November, 17th - 18th 2011, Berlin, Germany

Provided by Verena Weiss

The two-day course "*Nanocarriers for Drug Delivery*" took place in November 2011 in Berlin, Germany. About 30 participants and speakers from several European countries, including those from academia, industry and agencies, met to discuss the progress, current research and the market for nanocarriers for drug delivery.

The course was opened by the chairs, Prof. Dr. Karsten Mäder (University of Halle/Saale) and Dr. Carsten Olbrich (Bayer Pharma, Berlin) who emphasized the importance of the dialogue between academia and industry. In the opening lecture, Dr. Karsten Cremer (Pharma Concepts, Basel) compared expectations with the current market situation and discussed future business opportunities. He was followed by several speakers from academia who gave an overview of what is done in research: from liposomes (Prof. Dr. R. Schubert, Freiburg) and lipid carriers (Dr. J. Kuntsche, Odense/Denmark) to the *in vivo* fate of nanocarriers (Prof. Dr. S. Klein, Greifswald) and a critical view of their postulated structures, advantages and release mechanisms (Prof. Dr. K. Mäder, Halle).

Dr. B. Obermeier from Evonik Röhm (Darmstadt) presented some of their polymers which can be used for biodegradable nanocarriers. Dr. C. Olbrich from Bayer Pharma highlighted the complex process from an idea to the market product with

particular regard to technical challenges in large-scale production. Every lecture was followed by a discussion. In the evening all course participants were invited to take part in a guided city tour.

On the second day, Prof. Dr. H. Bunjes (Braunschweig) and Prof. Dr. R. Haag (Berlin) gave insights into research on other drug delivery systems like liquid crystals and dendrimers. The complexity of nanoformulations in industry was discussed by Dr. B. Riebesehl (Novartis Pharma, Basel) who again emphasized that academic researchers should not lose sight of industrial requirements. The last lecture was given by Prof. Dr. A. Briel from nanoPET Pharma (Berlin) who vividly presented their concept of nanocarriers for diagnostic imaging. After a short final statement by the chairs, a roundtable discussion highlighted the successful organization of the course with an inspiring combination of talks from speakers with different backgrounds.

DESIGN AND DEVELOPMENT OF NOVEL OTC PRODUCTS

November 7th - 8th 2011, Neuss, Germany
Provided by Johannes Bartholomäus

The course "*Design and Development of Novel OTC Products*" was jointly organized by two APV Focus Groups "Liquid Formulations" and "Drug Delivery" and was co-chaired by Johannes Bartholomäus and Joachim Herrmann. Around 40 attendees and speakers took part.

The first day started with general aspects of OTC development and innovation. Joachim Herrmann's introduction gave a first insight into the specifics of the OTC market and general trends for improvement and optimization of product. "Innovation – or just a new product" was the leading theme of Felix Ecker's talk on "Innovation in Self-Medication". Innovation needs management processes and mind-sets that do not kill projects too early because they are seen to be too risky under the management rules typically applied to late stage projects. Since a lot of OTC products are developed in co-operations between marketing companies and technology providers, Johannes Bartholomäus gave an insight into managing such co-operations and their key success factors. A clear definition of the target product profile, milestones and work packages, the choice of a really complimentary partner and a fair contract, as well as excellent project and risk management, are the basis, and to achieve real success it's then all about communication and trust between the partners. "IP Strategies for OTC Products" should be an integral part of OTC development and need to be aligned to the business strategy as Karsten Cremer pointed out. Not only patents but also trademarks and registered designs add a great deal of value to OTC products. Besides efforts to get patent protection for a new product – which may not always be possible – freedom to operate is a must for a product to be marketed. It should be checked during development in a continuous process, preferably in a cross disciplinary approach by patents departments, R&D and marketing.

Annemarie Dengler emphasized in her presentation on "Regulatory Implications of OTC product development" that choosing the right product category for new OTC products is a critical first step in the regulatory strategy. Using a lot of examples she demonstrated that placement of new products as medical devices, foodstuff/dietary supplements or cosmetics, if feasible, allow for faster access to the market than the classical medicinal product approach. Particular classes of OTC products with very specific requirements in the European regulatory environment are herbal medicinal products (HMPs) and botanicals as Joachim Hermann elaborated in the last talk of the general aspects session. The pharmaceutical definition of the drug substance is different for herbal actives, due to the fact that they are complex mixtures and the total extract is considered as the API in most cases. The evidence for safety and efficacy follows the same directions as chemically defined products, except for herbals falling into the "Traditional Herbal Medicinal Product" (THMP) category, where no clinical studies are formally required for registration. New plant extracts and a broader variety of formulations are on their way to or have already reached the market. Markets for HMPs vary in different countries. Some countries, like Germany and France, have a longer tradition of HMPs and might be considered "herbal countries" with a large number of registered HMPs, while in other countries, like the Netherlands or Belgium, fewer HMPs are registered.

Taste plays an extraordinary role in the acceptance and success of OTC products. Although taste is a very individual perception and flavouring often seems to be more of an art than science, there is an increasing need to find standardizable and objective parameters for taste. Thus, the technological session was opened by Jörg Breitkreutz's presentation on "Taste-masking Strategies for Oral Dosage Forms" in which he first discussed the basic qualities of taste followed by the physiology of taste and human test panels. Electronic tongues are entering the arena and need qualification as well as multivariate data analysis. His talk included examples of how to design a taste for a product and how to demonstrate taste differences between different liquid formulations of the same drug substance. The first day was closed by Felix Ecker's view on "New Packaging Concepts for OTC-Products" and how they drive innovation. This could be achieved by new dosing and application devices, new packaging systems like stickpacks or powders in bottle caps that can be released into a liquid by pushing. Senior friendly packaging is another aspect that may have even bigger effect on success in the future.

The second day focused on specific technologies and compounds that are often used in OTC products and are either on their way to market or of increasing importance. Gabriele Reich opened the morning session by sharing her experience and knowledge on "Alternative Materials for Hard and Soft Capsules." A variety of polymers originating from vegetable sources and semisynthetic approaches has been already introduced into marketed products. The particular properties of products made by different technologies as well as upcoming products were highlighted. The recommendation was first to select the formulation approach and then the appropriate capsule technology. Coating materials and trends for "clean labels" were the focus of Felix Specht's talk on "Functional and Clean Label Coatings for OTC and Dietary Supplements." He showed how in clean labels "E-numbers" and chemical names of compounds, which often look ugly to the customer, are replaced by well

sounded and legally approved names for the compounds. Franz Häusler in "Effervescent Dosage Forms – an Overview" discussed the greater commercial success of this dosage form in Europe and compared with e.g. the US. His talk also covered successful products to particulars of formulation, manufacturing technologies, packaging trends, stability issues and pitfalls. "Oral Dispersible Granules," a growing technology over the last few years, was the subject of Stefanie Bold's presentation. She covered formulation aspects and taste masking requirements, specific manufacturing technologies and the particulars of stick pack filling followed by examples of successfully implemented products and their bioavailability. The specific technologies session was concluded by Rick Chan who introduced "Oral Thin Films – A Realm of Possibilities." Starting from marketed products he gave an overview of formulation and manufacturing technologies and different packaging options for films. He also discussed the advantages and disadvantages of this dosage form and the future opportunities for multilayer, mucoadhesive and extended release films. The final presentation of the course was an outlook on future possibilities given by Johannes Bartholomäus who asked "What else?" His talk compared the similarities between already marketed medicinal and food formulations and forced the audience to think about from which food products, future new medicinal formulations may be derived while balancing attractivity and seriousness of the product.

The varied audience included those with science, technology, formulation, regulatory and marketing backgrounds, whose affiliations ranged from pharmaceutical companies, marketing organisations, technology providers and universities. All enjoyed the lively interdisciplinary discussions and networking opportunities as well as the as always perfect organization by the APV staff.

INTENSIVE PATENT WORKSHOP: HOW TO DRAFT, ANALYSE AND CIRCUMVENT A FORMULATION PATENT

November 14th - 15th and December 1st - 2nd 2011, Berlin, Germany
Provided by Katrin Steiner

The course was organized by the APV Focus Group Drug Delivery in partnership with Pharma Concepts GmbH and was chaired by Dr. Karsten Cremer (Pharma Concepts GmbH). It was first held in November 2011 with 20 participants from various fields of industrial drug product development. Due to the very high demand, a second workshop was scheduled just a few weeks later and was equally booked out with another 22 attendees; highlighting the widespread interest in intellectual property (IP) related knowledge.

The two-day course was divided into 8 sessions in which Dr. Cremer explained the different steps of the patenting process, the strategies involved and the numerous ways to read and evaluate patents. Starting from the role of patents in life cycle management, Dr. Cremer elucidated how to identify the subject and scope of inventions and how to strengthen them by well-designed experiments in cooperation with the R&D department. Sessions focussing on the actual patenting process followed; i.e. from idea to patent grant. The attendees learned e.g. who should be involved in the writing and filing of a patent application, the way it should be drafted and how to react to the patent office's communications such as the examination report.

On the second day, patents were looked at from a different angle. Dr. Cremer first explained the essential knowledge on freedom to operate (FTO) and highlighted common pitfalls. He also offered guidances for the decision on suitable time-points and extents of FTO searches during different stages of drug product development. In order to map the FTO-range, techniques for performing meaningful yet time-saving patent searches and for the deconstruction of patents were provided. A last session was then aimed at viable options for the circumvention of competitor's patents.

The majority of sessions were followed by short workshop exercises in which the attendees, working in small teams, could apply their new insights to exemplified, realistic problems. On one hand, the summaries of the audience's various solution approaches – as well as the lively discussions involved - helped a deeper understanding of the subject matter. On the other hand, it raised everybody's awareness of the different viewpoints of scientists from different fields. This reflected Dr. Cremer's heartfelt wish for the course: to improve the interaction and cooperation between management, R&D and the "IP-people". Hence, at the end of the course, all attendees took home not only a folder of well-structured materials but also a renewed sense of their own function in the interdisciplinary patenting process.

The entire course was deemed a success, and may thus be re-run on a regular basis.

DRUG DELIVERY PRODUCTS

BACK TO TABLE OF CONTENTS

Provided by Dr. Louise Rosenmayr-Templeton

Opana® ER (Oxymorphone hydrochloride) Extended-Release tablets, CII
Endo Pharmaceuticals

On 12th December 2011 the FDA approved Endo Pharmaceuticals' new crush-resistant controlled release formulation of oxymorphone , Opana® ER [1]. The new product is designed to increase obstacles to the abuse and misuse of the opioid agonist, as the tablets cannot be easily broken up or powdered to produce a material suitable for snorting or rapid extraction of the oxymorphone. In addition, the potential for the sustained release matrix to be destroyed is diminished, thus, reducing both the chance of a "high" being obtained on oral administration of pulverized tablets and accidental overdose through dose dumping.

It is based on Gruenenthal's INTAC™ technology. This technology involves the production of sustained release monolith tablets thermoformed by extrusion of a formulation containing of a high molecular weight polyalkylene oxide. The tablets have a crushing strength of at least 500 N [2].

A US patent, which covers the technology, was granted to Gruenenthal by the U.S. Patent and Trademark Office (USPTO) on 13 Dec 2011[2]. It is expected to provide protection for the technology in the USA until November 2023. One of the inventors named on the patent, Johannes Bartholomäus, is a founding member of the APV Drug Delivery Focus Group. The new formulation will replace the existing Opana ER product but will retain the same name. It is available in the same dosage strengths, colour and packaging and is of a similar tablet size and shape as the currently marketed product [1].

Bydureon™ (Exenatide extended-release for injectable suspension)
Amylin Pharmaceuticals/Alkermes

On 27th January 2012 after a long, uphill struggle, Amylin Pharmaceuticals finally received approval from the FDA for Bydureon, its sustained release exenatide formulation for subcutaneous injection [3, 4]. Exenatide is a glucagon-like (GLP-1) agonist which is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings.

The company had previously received two complete response letters from the regulatory agency with respect to this product. The first letter concerned issues involving product labeling, the Risk Evaluation and Mitigation Strategy (REMS) and existing manufacturing processes, while the second included a request for a detailed QT (tQT) study with exposures of exenatide higher than typical therapeutic levels [5].

Bydureon is based on Alkermes Medisorb® technology in which the peptide is entrapped in biodegradable microparticles formed from 50:50 poly(D,L-lactide-co-glycolide) polymer. By formulating the peptide in this way administration frequency is reduced from twice daily with the currently marketed exenatide product (Byetta®) to once weekly. Exenatide's main competitor, Victoza®, (liraglutide injection) (Novo Nordisk) is injected once daily [6].

Annual sales of Bydureon are predicted to exceed $1 billion eventually [6]. The product has been approved in Europe since April 2011 [7].

References and Further Information

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DRUG DELIVERY COMPANIES

BACK TO TABLE OF CONTENTS

Provided by Jeffry Grunkemeyer

FORMAC PHARMACEUTICALS NV (Heverlee, Belgium)

Founded:	2007
Location:	Bio-incubator 1, Leuven, Heverlee, Belgium
Ownership:	Privately funded
Employees:	6
Key technology:	**Silica-based drug delivery: stable, amorphous formulations that boost the bioavailability of poorly soluble drugs** FORMAC Pharmaceuticals has developed a mesoporous silica-based technology that increases the bioavailability of poorly water soluble drugs. The technology consists of loading a drug on inert silica materials and offers a novel approach to the solubilisation of BSC 2 & 4 compounds.

	The active molecules are deposited in silica pores tuned to the size of the active molecule, thus, preventing crystallization occurring during storage. On contact with aqueous media the active molecules are displaced through competitive binding of water molecules, releasing the active molecules out of the pores and making them available for absorption. The molecules leave the silica pores gradually and are absorbed through the gastro-intestinal membrane. Using this approach, several active compounds showed a multiple-fold increase in bioavailability when compared with current bioavailability enhancing technology platforms. FORMAC has developed a high-throughput system (the "silica research engine") that assesses different silica materials originating from FORMAC's collaboration with W.R. GRACE & Co., a global leader in material science and worldwide producer of silica products, to select the best performing silica-API combinations. Given the simplicity of FORMAC's technology, it can be easily introduced into preclinical development, while the same silica-based formulation can proceed into Phase 1, 2 and 3 and into the market without complex changes, thereby eliminating the need for different formulations during development. The silica materials can be formulated with active drugs using standard pharmaceutical equipment and filled into capsules or developed into tablets.
Products:	All medicinal drug products are under development and/or in co-development with large and small pharmaceutical R&D companies and with biotech firms. The most advanced FORMAC silica-based drug delivery program is entering the clinical phase.
Development status:	The technology is readily available for application and introduction into a new drug development program. Phase 1 and 2 production is available. Development of a Phase 3 & market supply chain is under development.
Partnerships:	FORMAC has entered a partnership with W.R. GRACE & Co., to co-develop and supply different types of silica for a wide variety of drug delivery applications.
Website:	http://www.formacpharma.com
Contact:	Jan Rosier, Ph.D. (CEO) Laurent Schueller, Ph.D., MBA (CSO/COO) Bioincubator I, Gaston Geenslaan 1 BE-3001 Heverlee, Belgium Phone: +32 (0) 16 751 370 Fax: +32 (0) 16 751 371 E-Mail: jan.rosier@formacpharma.com or: laurent.schueller@formacpharma.com

DRUG DELIVERY PEOPLE

BACK TO TABLE OF CONTENTS

Provided by Prof. Dr. Karsten Mäder

GERRIT BORCHARD is a pharmacist and obtained his Ph.D. in pharmaceutical technology from the University of Frankfurt (Germany). After holding several academic posts, including a lecturer position at Saarland University (Germany) and an Associate Professorship at Leiden University (The Netherlands), he joined Enzon Pharmaceuticals, Inc. (USA) as Vice President of Research. In 2005, he was appointed Full Professor of Biopharmaceutics at the University of Geneva (Switzerland), and Scientific Director of the Centre Pharmapeptides in Archamps (France), an international center for biopharmaceutical research and training.

His main areas of interest are macromolecular drug formulation and delivery, molecular biopharmaceutics and mucosal vaccination. He has published more than 90 papers and book chapters, 6 patents and 1 patent application. He has also served as Scientific Advisor to the Controlled Release Society (CRS), as head of the academic section of the International Association of Pharmaceutical Technology (APV), and as Scientific Secretary for the European Association for Pharmaceutical Biotechnology (EAPB). Prof. Borchard was editor of the European Journal of Pharmaceutics and Biopharmaceutics from 2005 to 2010, and currently serves on the editorial boards of three international scientific journals.

In 2008, Prof. Borchard was appointed Vice President of the Section of Pharmaceutical Sciences at the University of Geneva. In 2010, he was nominated as Fellow of the Swiss Academy of Pharmaceutical Sciences, and in 2011 elected president of the Swiss Society of Pharmaceutical Sciences. In addition, to his scientific achievements, Professor Borchard is fluent in four languages.

PHARMACEUTICAL EXTRUSION TECHNOLOGY – STATUS QUO

By Markus Thommes, Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Duesseldorf, Germany

1. Introduction

Pharmaceutical extrusion technology has become an important processing technology within the last few decades. As a result of this, academia as well as industry is focusing research efforts on this area. It is likely that extrusion will become one of the most important technologies for many pharmaceutical applications, based on its many assets as compared to other technologies.

The term extrusion originates from the Latin word "extrudo", meaning "to force or to push out". This refers to the process by which a plastic material is shaped by squeezing it through a die of a particular geometry. Today, the term extrusion usually implies a multistep process, in which various unit operations are combined in one machine (named the extruder). This process frequently terminates with the extrusion itself, when the material is forced through a die. Two dimensions of the final extrudate are usually defined by the die geometry, while the third dimension is variable. In the past, several die geometries have been employed like cylinders [1] and more complex shapes [2]. It is also possible to inject the material from the extruder into a mould, to produce complex structures [3]. The most common extrudate shape is a cylinder, the diameter of which can vary from 0.2 to 13 mm [4, 5] depending on the application.

2. Extruder Types

A variety of machines have been used in industry and research which qualify as extruders, based on the definition of extrusion. An overview of the various types is given by Erkoboni [6]. The ram, radial and screw extruder are quite common these days (see Figures 1 and 2). The flat die is a novel extrusion setup recently introduced in the pharmaceutical field, which allows a high throughput coupled with cost efficiency [7] (Figure 1). Ram extruders are simple and useful for performing rheological measurements [8-10]. They usually operate discontinuously, which is often a disadvantage in large scale production, but ram extruders have outstanding properties for early development using small quantities of material. Some radial extruders are frequently used for wet extrusion in pharmaceutical production like the Nica System. These extruders apply less mechanical energy and heat to the material due to less pressure at the die caused by the high number of holes in a thin extrusion screen [11].

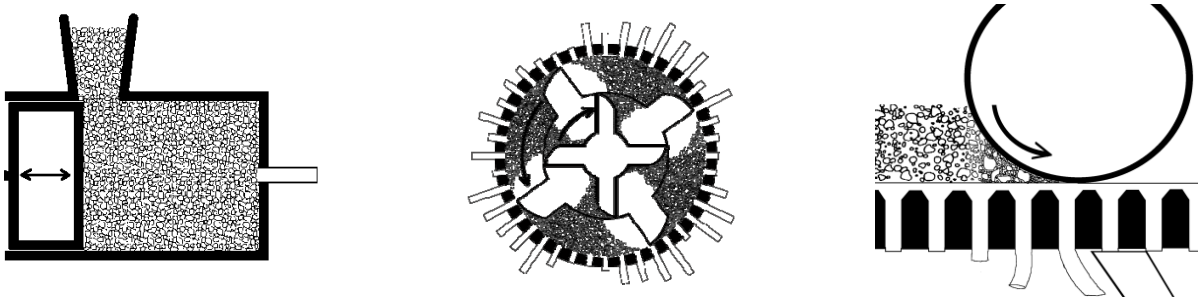

Figure 1: Extruder types - ram extruder (left), radial extruder (middle), flat die extruder (right)

At this time the screw extruders are most commonly used. They can be separated into two groups consisting of single and twin screw extruders. There are also multi screw extruders but they are not relevant for pharmaceutical applications [12].

The single screw extruders are comparatively unimportant when compared to the twin screw extruders, because they have a lower mixing capacity and the throughput depends on the screw speed [13]. As a result of this they are frequently used to feed highly viscous materials, or run discontinuously as in injection moulding. Twin screw extruders are more complex and versatile. The counter-rotating twin screw extruders are characterized by a forced transportation of material though the extruder, causing high pressures and air entrapment. The mixing capacity of a counter-rotating twin screw extruder is much lower than that of a co-rotating extruder [14]. Intermeshing screws in the co-rotating extruder are self-wiping, allowing them to transport material through the extruder with a gentle force. This is the major difference between a co-rotating and counter-rotating extruder. Co-rotating extruders can be run with partly-loaded barrels, which is impossible using single screw extruders. This makes the process much more flexible. In the pharmaceutical field, the co-rotating twin screw extruder is often considered to be "the extruder", while other extrusion technologies are neglected. In addition to the large variety of extruders, there are also several differences within the group of co-rotating twin screw extruders. Modular extruder systems can accommodate the requirements of various applications with easy adjustments such as changing the barrel length or sequence of the screw elements. Each co-rotating twin screw extruder has a feeding, transportation and a discharging zone. This basic configuration can be extended by multiple feeding (solids, liquids or gases), melting, dispersing, homogenizing, degassing and an extrusion zone.

Independent from the extruder configuration, process variables can be adjusted to achieve the desired product properties. These variables include feed rate, screw speed, and temperature, to name but a few.

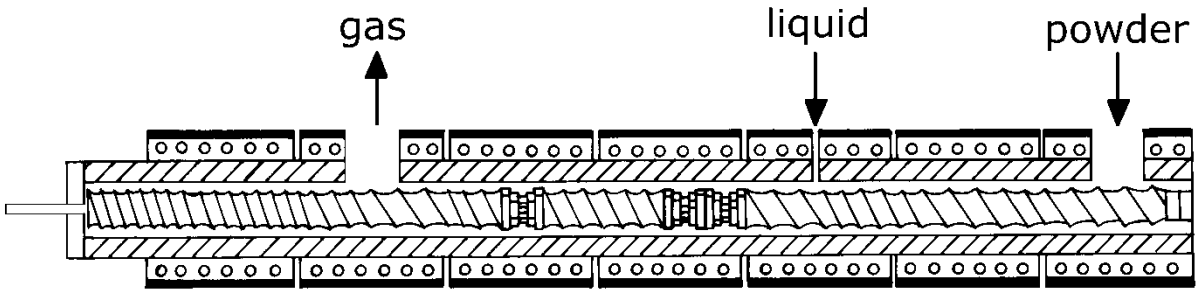

Figure 2: Co-rotating twin screw extruder – modular setup (barrel, screw, die)

3. Extrusion Types

3.1 General

Extrusion requires particular material behaviour, including deformation, self-lubrication, and rigidity following the process. Based on the definition of extrusion—forcing a material through a die—the process always involves material flow. The prerequisite for this flow is that the material displays viscous or plastic deformation behaviour. In contrast to the need for deformation during extrusion, rigidity after extrusion is essential in order to maintain the geometry of the extrudate. This issue can be addressed in three different ways, depending on whether the process involves wet, melt or cold extrusion. Each of these will be discussed in the following paragraphs. Self-lubrication is another essential property, requiring low adhesion forces between the die and the material. Especially when using low die diameters or long dies, high adhesion could cause blocking of the die that would terminate the extrusion process.

3.2 Wet Extrusion

One strategy for achieving the desired material properties is the addition of a liquid phase, like water or alcohol, to the powder formulation. This results in wet extrusion. After extrusion the liquid is removed by drying in order to increase the rigidity of the product. Wet extrusion is usually done far below the melting or the glass transition temperature of the solid materials involved in the extrusion process. As a result of this, wet extrusion is also frequently termed "paste extrusion" [15]. However, this terminology is not discriminative because pastes are also used in hot melt extrusion, where a high fraction of material usually remains in the solid state.

The hurdle to be overcome in wet extrusion is phase separation between solid and liquid, because it changes the rheological behaviour of the material and often leads to a blocking of the die [16, 17]. Liquid migration can be observed especially when high pressures are applied, there are large dead volumes in front of the die [18], or when there is poor interaction between the materials forming the solid and liquid phases [19]. Therefore low-pressure extruders, like the radial extruder or the flat die press, are particularly suitable for wet extrusion. Hydraulic pressure can be minimized by reducing dead volumes between the screw and die, making screw extruders also suitable for wet extrusion [20].

In the last 30 years a great deal of pharmaceutical research has been focused on the interaction of solid and liquid phases in a given formulation. Several investigations in this field have been done in relation to extrusion/ spheronisation, which is one of the main applications of wet extrusion. In 1970 Reynolds and Conine [21, 22] proposed a new concept of bead manufacturing using a process known as extrusion/spheronisation. Based on the outstanding properties of spherical agglomerates (pellets) for many pharmaceutical applications, as well as the advantages of extrusion/spheronisation compared to other pelletization techniques, extrusion became an active area of research in the pharmaceutical community for the first time. The extrusion/ spheronisation technique has a short process time and gives high yield. The pellets have a high sphericity and narrow size distribution [23]. Therefore these pellets have a more uniform surface area and are suitable for functional coating.

The spheronisation process requires particular material properties, usually achieved by using a pelletization aid in the formulation. Several substances have been investigated and summarized by Dukic-Ott et al. [24]. However, microcrystalline cellulose (MCC) is the gold standard and can therefore be found in most commercial products. Typically, water is used as the granulation liquid. Recently, microcrystalline cellulose II (MCC II), a polymorph of MCC, has been introduced as a pelletization aid [25]. Using this substance, fast-disintegrating pellets were obtained. These pellets were found to be particularly suitable for drugs with low aqueous solubility, as release was faster that from pellets formulated with regular MCC [26, 27]. More recent studies have focused on crospovidone, which also results in fast disintegrating pellets, when used as a pelletization aid [28, 29].

There are two different models proposed to describe the rheological behavior of MCC/water combinations in wet extrusion. The "sponge-model" considers the MCC-particles as a sponge that is able to incorporate water [30, 31]. On application of mechanical stress the water is squeezed out, leading to an increase in the mobility of solid particles as well as lubrication. If afterwards the mechanical stress is lower, the liquid is reincorporated into the MCC-particle, leading to a rigid extrudate. When using the sponge-model some properties cannot be explained, such as shrinkage on drying,

as well as the effect of the shear rate on the extrudate properties [32, 33]. Therefore the sponge model was extended to the "crystallite-gel-model" [34]. According to this model the MCC-particles, named crystallites, consist of a crystalline core and an amorphous shell. Since there is no void space in the crystal lattice, the water is bound in the amorphous regions of the crystallite. This causes a swelling or gelling of the shell region, allowing an interaction of multiple crystallites. It is claimed that a molecular interaction of sugar chains allows multiple crystallites to couple, forming a framework which may be considered as a molecular "sponge". This second model is consistent with the work of Battista [35].

3.3 Hot Melt Extrusion (HME)

The second approach of achieving mechanical deformation of a material or mixture is to heat it above the melting point or the glass transition temperature (TG) of one or more of its components. For many pharmaceutical polymers, a much higher process temperature than the glass transition temperature is required, because the viscosity of the melt just slightly above the TG is often too high. A further temperature increase usually leads to much lower viscosities [36, 37]. After extrusion, the material is usually solidified by cooling. The term HME is rather confusing because comparatively low temperatures of 40 to 60°C can be used too, especially when plasticizers are included in the formulation [38, 39]. HME is widely carried out in co-rotating twin screw extruders, developed by Erdmenger [40, 41]. For many formulations, the heat is generated in the material by a transformation of mechanical to thermal energy. Therefore parameters such as barrel temperature don't necessarily correlate with the temperature of the material [42].

Most products produced by hot melt extrusion are, at least, partly amorphous. Therefore these products have inherent physical instability that could result in a change in the product properties on storage by either relaxation or crystallization [43, 44]. In order to achieve kinetic stabilization and enable the product to have a commercially relevant shelf-life, formulations with a high glass transition temperature are preferred, due to their lower molecular mobility [45]. On the other hand, high glass transition temperatures lead to high process temperatures in manufacturing that could cause polymorphic changes or thermal degradation [46].

Hot Melt Extrusion is used to produce films [47, 48], sustained release formulations [49, 50], and implants [44]. Based on the fast solidification of the material and the missing drying step, there are a lot of opportunities for downstream processing. These include calandering [51], injection moulding (section 3.4), and hot compression [52]. However, a hot topic currently is the use of HME for the preparation of solid dispersions.

Most new chemical entities exhibit low aqueous solubility and low oral bioavailability. This phenomenon was noticed some time ago, and has been discussed intensively [53, 54]. Several approaches have been suggested [55, 56]. In particular, the preparation of solid dispersions seems to be quite promising. Generally, solid dispersions can be produced by a solvent method such as spray drying, or by the fusion method [57]. As a fusion method, HME is a suitable technique because it is reliable, cheap, and capable of handling high viscosity melts. Frequently, highly viscous polymers are used as carriers in solid dispersions to reduce the molecular mobility of the amorphous drug and to extend the shelf life of the product. Solid dispersions can be differentiated based on their number of phases and solid state properties (Table 1). Generally, all types of solid dispersions can be produced by HME [51, 58].

Table 1: Overview of solid dispersions (modified to [51, 59, 60])

Term	Solid Solution	Glassy Solid Solution	Compound Complex Formation	Solid Crystal Suspension	Eutectic Mixture	Amorphous Precipitation	Glassy Suspension
Phases	1	1	1	2	2	2	2
API	molecularly dispersed	molecularly dispersed	molecularly dispersed	crystalline	crystalline	amorphous	amorphous crystalline
Carrier	crystalline	amorphous	crystalline amorphous	crystalline	crystalline	crystalline	amorphous

Ideally, the drug is molecularly dispersed in the carrier as it would be in a glass solution or in a solid solution, because when dissolving the carrier, the drug is already molecularly dispersed in the medium. However in reality, the solubility of the drug in the carrier is too low to make the administration of reasonable doses to the patient possible. As a result of this, multi-phase systems must frequently be considered, such as glass suspensions and amorphous precipitations. The manufacturing conditions and physical stability of these systems are related to the drug solubility in the carrier during the manufacturing process, and at storage temperature. Unfortunately, these solubilities cannot be determined experimentally. For this reason, calculations of solubility parameters are frequently utilized to optimize the formulations [61, 62]. So far these calculations tend to fail when working with complex structures, particularly large molecules, or when there are specific interactions between the components, such as complexes. Eutectic mixtures and co-crystals [63, 64] usually require specific interactions between the drug and the carrier, which means these solid dispersions require screening for these specific interactions. Recently, solid crystal suspensions were proposed in which the crystalline drug is dispersed in a crystalline carrier. This approach makes use of an increase in the specific surface area of the drug particles,

and should be applicable to many dissolution rate controlled drugs [65]. HME can also be used to produce micro- and nano-particles by a controlled crystallization in the carrier [66].

Several substances have been considered as carriers for hot melt extrusion. These include sugars, sugar alcohols, and natural and synthetic polymers. Since the carrier must be adjusted to the specifics of each drug, it is not meaningful to compare the carrier systems at this point [13, 51, 58, 67]. It is also worthy to note that there is a large number of patents that cover hot melt extrusion making the patent landscape in this area very busy.

3.4 Cold Extrusion

The final approach to achieving deformation is to choose materials that yield under mechanical stress. For such materials, the extrusion temperature does not exceed the melting or glass transition point of any component of the formulation, which is often crystalline. This technique was established specifically for triglycerides, and is therefore also known as solid-lipid-extrusion. In the last few years, this concept has been extended to polyethylene glycols, and polyethylene-polypropylene-copolymers, making the term solid-lipid-extrusion misleading.

In 2003 Breitkreutz reported the development of a pediatric formulation that enabled the administration of high doses of a drug to treat an orphan disease [68, 69]. In this particular case, most pharmaceutical excipients and technologies were considered to be inappropriate for toxicological reasons, based on the high drug dose. Therefore Breitkreutz decided to use triglycerides in a solvent free HME process, which he ran at surprisingly low temperatures. For this reason, it was named cold extrusion. Further investigation found that these triglycerides had a taste-masking effect [70], which might be related to a thin triglyceride layer at the surface of the extrudate. Further investigations dealt with the downstream processing. It was possible to spheronise triglyceride extrudates by using a combination of different triglycerides [71]. By adjusting the formulation, a tailor-made drug release could be obtained [72-74]. The crucial aspect of solid-lipid-extrusion is the polymorphic changes that can occur during the extrusion process, as well as on storage. This is a challenge in formulation and process development.

4. Actual Trends

4.1 Quality by Design (QbD)

Based on an initiative by the American Food and Drug Administration, pharmaceutical scientists have been forced to develop a fundamental understanding of the manufacturing process, rather than act on empirical data alone. The aim is to improve the product quality and safety. Several of these efforts have been combined under the term "Quality by Design" [75], and have been applied to various pharmaceutical technologies. Continuous twin screw extrusion has the outstanding advantage that the different sub processes, such as feeding, mixing, and extrusion, run simultaneously in the same machine, although spatially separated. This gives the opportunity to apply specific sensors to the different compartments of the machine, in order to monitor and understand each sub-process. In a batch process, such as conventional high-shear-granulation, the sub-processes frequently occur in the same place and time. As a result of this it is much harder to isolate a sub-process for systematic investigation.

An important tool of QbD is process monitoring, using analytical methods called Process Analytical Technologies (PATs) [76]. Twin screw extruders have been equipped with temperature and pressure sensors for a very long time [20]. Gravimetric powder and liquid feeders are now standard for monitoring the feed rates [77]. Measurements of the specific mechanical energy can be used to recognize process fluctuations and trends, as well as to predict the behaviour of the material in downstream processing [78, 79]. Spectroscopic measurements are used to determine the drug load and content uniformity, and to monitor chemical reactions [80, 81].

4.2 Continuous Granulation

Continuous granulation is identical to twin screw extrusion, but without forcing the material through a die at the end. Therefore, it is technically not an extrusion process. However, the process is related to wet-extrusion, which is why several concepts from wet-extrusion can be directly transferred to continuous granulation. When using a die the granules are highly densified, which is frequently problematic for further processing such as tabletting. For this reason the die was removed resulting in the continuous granulation process [82, 83]. Numerous studies have been recently performed to evaluate the effect of material and process parameters [84-87]. Continuous melt granulation was also investigated [88]. Based on the results, commercial continuous granulation lines from Bohle and GEA Pharma Systems are now available [89, 90].

4.3 Downstream Processing

A significant amount of research currently deals with the processing of the material after extrusion, the so-called "downstream processing". The simplest processing method is to extrude a strand and cut it before or after solidification [5, 91]. In some cases, the cooling rate of the material affects the product properties because of crystallization or relaxation. This problem is addressed by a chill roll in which the extrudate is squeezed between temperature controlled rolls [92]. Injection moulding is another popular topic, because it can be used to shape the material based on the requirements of the dosage form [3, 93, 94]. It should be mentioned that for this purpose, two extrusion steps are usually required because the requirements of the injection moulding are not the same as the requirements of the compounding. Twin screw extruders are known for their comparatively inhomogeneous material flow, which may be compensated by a gear pump at the die [95]. Recent studies deal with co-extrusion in order to achieve particular properties such as sustained release [96, 97].

4.4 Down sizing

Another currently popular topic is the downsizing of extrusion equipment. This is because, especially in early development, high drug quantities are expensive or not available. Since twin screw extrusion is a continuous process, the material consumption in standard equipment is particularly high. Therefore most machine suppliers have focused their research on small size twin screw extruders for about the last 10 years (Table 2).

Table 2. Different types of miniature extruder (up dated from [77])

Machine type	Screw Diameter [mm]	Screw Length [mm]	Throughput
Brabender KETSE 12	12	432	100 – 5000 g/h
DSM Xplore 15 ml	< 22	170	10 g/batch
Leistritz Nano-16	16	400	20 – 100 g/batch
MP&R ME7.5 Mini-Extruder	7.5	112.5	50 – 200 g/h
Rondol Microlab 10	10	400	25 – 400 g/h
Steer Omicron 12P	12	744	200 - 2000 g/h
ThermoScientific HAAKE MiniLab	5.3 – 14	109	10 g/batch
ThermoScientific Pharma 11 HME	11	440	20-2500g/h
ThermoScientific Pharma TSG 16	16	400	< 5000 g/h
Three-Tec ZE 5	5	100	0.5 – 5 g/batch
Three-Tec ZE 16	16	512	1 – 250 l/h

Besides scalability issues, which are related to the surface to volume ratio, constant feeding becomes both very important, as well as more challenging, in small scale extrusion [77]. Small scale extruders are also of interest for the production of implants because low quantities of dosage form are required to treat the patient for several days [98, 99].

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ABOUT THE FOCUS GROUP

BACK TO TABLE OF CONTENTS

The APV Drug Delivery Focus Group (APV DD) is a section of the APV (Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e.V. / International Association for Pharmaceutical Technology), a major European society for those sharing a professional interest in pharmaceutical sciences. The Focus Group was established in 2003 in response to the increasing importance of drug delivery within modern pharmaceutics.

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COMBINING SCIENCE AND TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

OUR MISSION STATEMENT:

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

All disciplines relevant to the above mentioned areas of drug delivery R&D are invited to contribute to the APV Drug Delivery Group:

Pharmaceutics, Biopharmaceutics, Analytics, Biology, Physical Chemistry, Biochemistry, Physics, Engineering Sciences, Nano Technology, Material Sciences, Polymer Science, Toxicology, Drug Safety, Clinical Research, Drug Regulatory Affairs, etc.

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