DEAR READER,

Asking for feedback at the beginning of a newsletter may seem like putting the cart before the horse. However, it is now five years since the first edition of the APV Drug Delivery Focus Group Newsletter was published. Since then some changes have occurred, e.g., the inclusion of course summaries for the workshops organised by Focus Group members, but overall the format remains the same. Each edition contains a featured article on a specific area of drug delivery plus sections on drug delivery products, companies, people, events, terminology and literature.

However, the key question is, is this what our readers really want? If you are one of our around 500 subscribers, please let us know what you think. We are particularly interested in your opinion on the following:

- Newsletter length and layout
- Which sections you find most interesting/useful
- Which sections you find less interesting/useful
- Suggestions for new or alternative sections
- Topics of interest for future featured articles

Feedback on the questions above should be sent either to drug_delivery@apv-mainz.de or direct to the editor-in-chief at louise.templeton@towerpharmacon.com.

Since we value your time and effort all replies received before August 20th 2010 will be automatically entered into a raffle for an APV book prize. The winner will be informed by email.

Yours sincerely
Louise Rosenmayr-Templeton
Editor-in-chief
NanoDDS'10
3rd-5th Oct. 2010, Omaha, Nebraska, USA

2nd Conference on Innovation in Drug Delivery: from Preformulation to Development through Innovative Evaluation Process
3rd-6th Oct. 2010, Aix-en-Provence, France

Poorly Soluble Drugs (APV Course No. 6336 - in cooperation with BASF)
28th-29th Oct. 2010, Ludwigshafen, Germany
Chairs: Dr. Carsten Timpe, Novartis Pharma AG, Basel, Switzerland
      Dr. Oskar Kalb, F. Hoffmann-La Roche AG, Basel, 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.

Transdermal Drug Delivery Systems - The Essentials of Industrial Development (APV Course No. 6315)
28th-29th Oct. 2010, Miesbach, Germany
Chairs: Dr. Stefan Bracht, Bayer Schering Pharma AG, Berlin, Germany
       Prof. Dr. Johannes Bartholomaeus, Pharmakreativ Consulting, Aachen, Germany
The objective of this seminar is to provide participants from industry, regulatory bodies and academia with an insider perspective of the challenges involved in the industrial development of transdermal drug delivery systems. Typical issues and specific problems will be addressed in order to facilitate a deeper understanding of this dosage form and the related manufacturing processes. The course will also specifically address the needs of those participants who are in charge of managing, regulating or in-licensing development projects in this field.

Patent Workshop for Scientists and Managers in Drug Product Development
Berlin, 25th-26th February 2010
By Isabella Treser, APV, Kurfürstenstrasse 59, 55118 Mainz , Germany.

Patents and Patentability took centre stage at the first APV "Patent Workshop for Scientists & Managers in Drug Development" which was held on 25th-26th February 2010 in Berlin. This course was organized by the APV focus group Drug Delivery for scientists working in different fields of drug product development such as formulation, drug delivery and preformulation. It was chaired by Karsten Cremer, Pharma Concepts GmbH, Switzerland, who is the current chairman of the APV Drug Delivery Focus Group, and more than 50 people attended. The two-day schedule was divided into 5 sessions in which 16 experts including ones from Big Pharma passed on their knowledge to the audience.
**Day 1**

After some short introductory remarks by Karsten Cremer, the first session started with a keynote speech by Philippe Ducor from B.M.G. Avocats. He addressed the role of patents and other forms of exclusivity and their business impact for pharmaceutical, generic, biotech and drug delivery companies. The following speaker, Peter England from Pfizer UK, challenged the audience by quizzing their basic patent knowledge in a "Who wants to be a Millionaire" game. Anne-Marie Lademann from LifeCycle Denmark then completed the picture of patent fundamentals with a talk on "The Interface of IP and Drug Regulation".

In Session 2 on patent searching and reading Bart van Wezenbeek from Vereenigde, the Netherlands and Louise Aagaard of Hoiberg S/A, Denmark respectively provided advice on how best to carry out these activities and the pitfalls to avoid, while Karsten Cremer focused on the formulation expert’s role in successful search strategies and patent review. All course participants then took part in Patentopolis, a business game on patent strategies in a simulated economy. This gave them the chance to learn in small groups about the effects of patent strategy including licensing, joint ownership and enforcement of patent rights on company success. Day 1 ended with a bus tour of historic Berlin accompanied by a very informative and amusing guide, followed by a networking dinner at a traditional city restaurant.

"I was impressed by the enormous interest of the delegates whose questions and comments evoked lively discussions throughout the first day of the workshop. This showed me that the speakers had addressed those patent issues that really matter to professionals working in drug product development", Karsten Cremer commented after the first day.

**Day 2**

Martin Gosmann and Björn Timmerbeil from Solvay Pharmaceuticals in Hannover opened up the third session "Obtaining Patent Protection for Novel Formulations & Processes" at the start of the second day. They discussed the challenge of innovation in pharmaceutical technology. The speakers showed with pertinent case studies that innovation is always more than just life cycle management. Innovative companies should be rewarded for their investments and risk-taking in R&D was one of their take-home messages. Karsten Cremer then spoke on the subject of identifying patentable inventions from R&D outcomes. This was followed by a talk from Bettina Hermann from Vereenigde in Munich which dealt with the main characteristics of an inventive step especially with regard to formulations. The session then continued with Lars Sparre Conrad from Lundbeck in Denmark with his talk on "Drafting Patents Applications". In his lecture he focussed on global prosecution and the required data to support claims. Following this Michael Bech Sommer from Zacco, Denmark, gave a talk about decision points in the drug life cycle relating to process development and intellectual property (IP) protection. Among other topics he discussed what kind of IP may emerge from process development and could be considered patentable. Luc Vandamme from Patentopolis, The Netherlands rounded up the morning session with a presentation on understanding and supporting viable patent strategies.

In the afternoon Session 3 continued with the talks by Hajo Kraak and Harrie Marsman who both are from Vereenigde in The Netherlands. Hajo Kraak spoke about the chance to optimize life cycle management by aligning your pharmaceutical and patent strategy. Harrie Marsman made the audience aware of the possibilities for publishing without damaging or precluding the filing of patent applications in his talk about publication strategies. Jens Viktor Norgaard in Session 4 talked about the challenge of establishing freedom to operate and developing a proprietary patent strategy including the crucial role of the R&D expert. The workshop ended with a round table discussion involving almost all speakers where the audience had the opportunity to ask questions and discuss open points. Written feedback from the delegates showed that they were highly satisfied with the workshop and that the course had reached its objective of conveying a solid understanding of patents and their role in the pharmaceutical industry.
Oravig® Buccal Tablets (Bioalliance Pharma)

In April 2010 the FDA approved Oravig® Buccal Tablets containing 50 mg of miconazole for the treatment of oropharyngeal candidiasis in adults. This product is already on the market in Europe under the brand name Loramyc®. The formulation is based on Bioalliance Pharma’s Lauriad® technology and enables the rapid and continuous release of the active from a tablet applied once daily to the upper gum area. Its mucoadhesive properties are due to the inclusion in the formula of a protein concentrate which is widely used in food. Release of miconazole from the tablet matrix is prolonged with a study in 18 healthy individuals showing that a single dose results in a mean maximum saliva concentration of 15 mcg/ml at 7 hours (AUC0-24h 55.2±35.1 mcg.h/ml).

Bioalliance licensed Oravig to Strativa Pharmaceuticals, a subsidiary of Par Pharmaceutical Companies Inc, in July 2007. Approval by the FDA triggers a $27 million milestone payment for the French company with the launch of the product expected in the second half of 2010. The NDA submission was based on the European filing plus a Phase III study comparing Oravig to Mycelex® Troche ( clotrimazole, the reference product in the USA). It is predicted that peak US sales of this product will reach €100 million in 5 years.

References and Further Information:
- Bioalliance Pharma Website: http://www.bioalliancepharma.com/
- Product entry in Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

Exalgo® Extended-Release Tablets (Mallinckrodt)

Exalgo® is an extended release formulation of the μ-opioid receptor agonist, hydromorphone HCl. It was licensed in March by the FDA for the treatment of moderate to severe pain in opioid tolerant patients requiring continuous 24 hr pain relief over a prolonged period of time. It employs Alza’s Oros® Push-Pull™ technology to enable the once-daily delivery of 8 mg, 12 mg or 16 mg hydromorphone and removes the need to dose the drug every 6 hours.

The formula employed was first launched by Janssen-Cilag on to the German market in 2006 as Jurnista® and the product is now licensed using this brand name in a number of countries. In the US the marketing rights were acquired from the ALZA Corporation first by Neuromed Pharmaceuticals in 2007 and then by Mallinckrodt Inc., a Covidien company, in June, 2009. Regulatory approval of Exalgo triggers a $40 million milestone payment from Covidien to CombinatoRx, which merged with Neuromed in Dec 2009. Under the agreement CombinatoRx is also entitled to tiered royalties on Exalgo net sales.

References and Further Information:
- CombinatoRx Website: http://www.combinatorx.com
- Product entry in Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

Ozurdex™ Intravitreal Implant (Allergan)

In May the EMA’s Committee for Medicinal Products for Human Use (CHMP) gave the green light for the approval of Allergan’s Ozurdex™ intravitreal implant for the treatment of macular edema following branch or central retinal vein occlusion. This product contains 0.7 mg of dexamethasone in Allergan’s solid polymer drug delivery system, Novadur™. The poly(lactide-co-glycolide) polymer implant is preloaded into a specially designed applicator to facilitate its direct injection into the vitreous humor. The CHMP’s recommendation is based on the results of two multi-center, double-masked, sham-controlled studies which showed that 20% to 30% of patients gained 3 or more lines of vision on the eye chart within 1 to 2 months compared with 7% to 12% of those who received sham injections. This improvement lasted around 1-3 months. The implant is already approved in the US, and the company hopes to launch the product in Europe in Q3 pending final approval.

References and Further Information:
- EMA’s website: http://www.ema.europa.eu
- Ozurdex website: http://www.ozurdex.com
- Kate Kelland (Reporter), Will Waterman (Editor), UPDATE 2-Allergan hopes to launch Ozurdex in Europe in Q3 - Reuters News Report May 21st 2010 http://www.reuters.com/article/idUSLDE64K0W820100521
PANTEC BIOSOLUTIONS AG - INTRAEPIDERMAL DRUG DELIVERY (Ruggell, Liechtenstein)

Pantec Biosolutions AG is a drug-delivery company focused on the transdermal delivery of high molecular weight drugs.

Its novel transdermal delivery technology is based on the creation of controlled aqueous microspores in the epidermis, without reaching the dermis, using a hand-held laser device. Its lead product is entering phase II clinical trials.

Fact sheet:

| Founded: | 2005 |
| Location: | Ruggell, Liechtenstein |
| Ownership: | Private - lead investor: Gamma Capital Partners; total raised nearly CHF 12 million to date |
| Employees: | 6 |
| Key technology: | Pantec Biosolutions proprietary technology is P.L.E.A.S.E.® (Painless Laser Epidermal System), a novel transdermal delivery method for high molecular weight drugs. A handheld laser device creates controlled aqueous microspores in the epidermis, without reaching the dermis, where nerves and blood vessels reside. The actual poration process can take from 1 to 5 seconds depending on the drug dose to be applied. Immediately after the poration process is finished the poration area is covered with the drug patch system. The drug then diffuses easily through the dermis where it can be absorbed by the blood system. Pores have a diameter of about 200 um and a pore depth of 20 - 150 µm. Up to 5000 pores are created per dosing, with a treatment area of up to 5 cm². Safety of the system was tested in a Phase I clinical trial in 12 healthy volunteers. |
| Products: | Phase I study completed on transdermal delivery of FSH (Follicle Stimulating hormone). Phase I study completed on triptorelin - release over 24 hour was demonstrated |
| Development status: | Phase I clinical trials completed |
| Partnerships: | Undisclosed |
| Website: | http://www.pantec-biosolutions.com |
| Contact: | Pantec Biosolutions AG
Industriering 21
9491 Ruggell
Liechtenstein, Europe
Tel: +423 377 78 00
Fax: +423 377 78 99
E-Mail: info@pantec-biosolutions.com |
THIOMATRIX GmbH (Innsbruck, Austria)

Founded in 2003, ThioMatrix is already a leading European drug delivery company that is globally renowned for its professionalism and expertise. ThioMatrix is in partnership with over 100 small and large pharma and biotech companies throughout the world. Business activities include drug delivery technologies such as the thiomer-technology, formulation development services and product co-development.

**Fact sheet:**

<table>
<thead>
<tr>
<th>Founded:</th>
<th>2003</th>
</tr>
</thead>
</table>
| Locations:     | Research Center Innsbruck: Innsbruck, Austria  
Business center St. Veit: St. Veit/Glan, Austria |
| Ownership:     | Private company |
| Employees:     | 12 |
| Key technology:| **Thiomer Technology** |

Due to the immobilization of thiol groups on well-established polymers such as polyacrylates or chitosans their mucoadhesive, permeation enhancing and efflux pump inhibitory properties are strongly improved.

- Utilizing thiolated polymers (=thiomers) the potential of numerous drugs can be tremendously improved.
- The thiomer-technology can be easily combined with other drug delivery technologies.
- The great potential of thiomers was shown in a clinical Proof of Principle study in healthy volunteers.
- For various thiomers GMP material and up-scaled manufacturing processes are available.
- ThioMatrix offers the thiomer-technology for licensing to third parties on a product-by-product basis.

<table>
<thead>
<tr>
<th>Products:</th>
<th>Several products in pre-clinical development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development status:</td>
<td>Lead products in pre-clinical development</td>
</tr>
<tr>
<td>Partnerships:</td>
<td>Partnership with Croma Pharma Holding</td>
</tr>
<tr>
<td>Website:</td>
<td><a href="http://www.thiomatrix.com/">http://www.thiomatrix.com/</a></td>
</tr>
</tbody>
</table>
| Contact:      | Prof. Dr. Andreas Bernkop-Schnürch (CSO)  
Trientigasse 65  
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Phone: +43 (0) 650 7536270  
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E-Mail: a.bernkop@thiomatrix.com |

**DRUG DELIVERY TERMINOLOGY**  
Provided by Dr. Karsten Cremer

**DRUG TARGETING – ACTIVE AND PASSIVE**

*The use of any means to direct a drug substance, after its administration, to a particular target site within the body.*  
[Write a comment on this definition](#)

The target site may be an organ, a tissue, or a cell type, and is usually the site where the desired pharmacological interaction between the drug substance and its molecular target takes place. Without drug targeting, a drug substance, after its administration and absorption into the systemic circulation, will be distributed throughout the various tissues of the body according to its own physicochemical and pharmacokinetic properties. In drug targeting, the distribution pattern of the compound is modified so as to increase the exposure of the target site while decreasing the exposure of other tissues and organs. In **active drug targeting**, the targeting effect is reached by a **targeting ligand**, such as an antibody or another molecule which specifically interacts with a molecular structure of the target site. In **passive drug delivery**, no targeting ligands are used. Instead, the distribution pattern of the drug substance is altered by means of e.g. colloidal drug carriers or local hyperthermia. **Targeted drug delivery** is another expression for drug targeting.
TARGETED THERAPY

The use of an anticancer compound which specifically interacts with a molecular target which is unique for, or overexpressed by, a cancer cell. Write a comment on this definition

Frequently, the molecular target is a particular receptor (or subtype thereof) which is significantly overexpressed by certain cancer cells. In contrast, "non-targeted" antineoplastic compounds interfere with molecular structures involved in cell division, and thus affect all rapidly dividing cells such as cancer cells or epithelial cells to a higher degree than slowly dividing cells. Targeted therapy, which is related to pharmacodynamics, should not be confused with targeted drug delivery or drug targeting, which is related to the delivery of a compound rather than its mechanism of action.

Suggest a term to be defined
Suggest a definition

THOMAS RADES is the Chair in Pharmaceutical Sciences at the National School of Pharmacy, University of Otago, New Zealand.

He received a PhD from the University of Braunschweig, Germany for his work on thermotropic and lyotropic liquid crystalline drugs in 1994. He worked for one year as a Scientific Assistant at the Technical University of Braunschweig/Germany.

Thomas became a Lecturer (1996-98) in Pharmaceutical Sciences, School of Pharmacy, University of Otago, Dunedin, New Zealand. From 1998-1999, he returned to Europe to work as a Research Scientist in the Preclinical Development and Formulation at F. Hoffmann-La Roche in Basle, Switzerland. He moved back to Otago in 1999 to hold a position as a Senior Lecturer (1999-2003) and finally (since 2003) as a Chair in Pharmaceutical Sciences.

His main research interests are in formulation and drug delivery and physical characterization of the solid and liquid crystalline state of matter. The research in both areas aims to improve drug therapy through appropriate formulation of medicines and to increase our understanding of the physico-chemical properties of drugs and medicines. It combines physical, chemical, and biological sciences and technology to optimally formulate drugs for human and veterinary uses. Specific research interests are:

1. Colloidal delivery systems for bioactives.
2. The solid state of drugs and dosage forms.

Professor Rades has developed an international outstanding reputation for his research in drug delivery and physical characterization of drugs. He is well known for his expertise and initiative to implement the link between formulation and analytics. A key example is his contribution to establish terahertz-spectroscopy and imaging as a pharmaceutical analytical tool. Thomas Rades was also one of the key persons to initiate the "Pharmaceutical Solid State Research Cluster" (PSSRC). It links eight highly acknowledged research centers in the pharmaceutical sciences from the Universities of Cambridge (United Kingdom), Copenhagen (Denmark), Düsseldorf (Germany), Ghent (Belgium), Helsinki (Finland), Lille (France), Lisbon (Portugal) and Otago (New Zealand). The cluster was formed to catalyze research activities in the solid state by sharing facilities, collaborating on specific projects and giving research students the possibility to engage with other researchers in the area.

Thomas Rades has published more than 190 papers in international peer review journals as well as several book chapters and nine patents. In the book Fasttrack: Pharmaceutics - Drug Delivery and Targeting (2009) he acted as a co-author (with Prof. Yvonne Perrie). He is active as an Associate Editor of the Journal of Pharmaceutical Sciences and the Journal of Pharmacy and Pharmacology. He is a member of many societies and a former President of the New Zealand Chapter of the Controlled Release Society (2004-2009).

He holds a visiting professorship at the Department of Medicine at the University of Adelaide, Australia, The School of Life and Health at Aston University, Birmingham, UK and the Faculty of Pharmacy, University of Copenhagen, Denmark.

In addition he supervised successfully more than 30 PhD students. For his undergraduate and postgraduate teaching he received the University of Otago Teaching Excellence Award and the New Zealand Tertiary Teaching Excellence Award for Sustained Excellence (2005).
MUCOADHESIVE POLYMERS

By Andreas Bernkop-Schnürch
Department of Pharmaceutical Technology, Institute of Pharmacy, University of Innsbruck, Innrain 52, 6020 Innsbruck, Austria

1. Advantages of mucoadhesive polymers

In the early 80s, academic research groups pioneered the concept of mucoadhesion as a new strategy to prolong the residence time of various drugs on the ocular surface. Encouraging first results led to applications also on other mucosal membranes such as the intraoral, vaginal and nasal mucosa. Generally, mucoadhesion is defined as the phenomenon by which natural and synthetic polymers adhere to a mucus gel layer. This property renders such polymers very useful excipients in drug delivery for the following reasons:

i. Through the use of mucoadhesive polymers the residence time of dosage forms on mucosal membranes can be greatly prolonged, which allows a sustained drug release at a given target site in order to maximize the therapeutic effect. The mucoadhesive polymer polycarbophil, for instance, is capable of remaining on vaginal tissue for 3 to 4 days providing an excellent vehicle for the delivery of drugs such as progesterone and nonoxynol-9 [1]. Whereas drugs formulated in simple solutions disappear from the ocular surface within a few minutes, their residence time can be extended up to several hours by utilizing mucoadhesive polymers.

ii. Drug delivery systems can be localized on a certain surface area for the purpose of local therapy or of drug liberation at the ‘absorption window’. The absorption of riboflavin, for example, having its ‘absorption window’ in the proximal segments of the GI-tract, could be greatly improved by its oral administration in mucoadhesive microspheres versus non-adhesive microspheres as illustrated in Fig. 1 [2].

iii. Mucoadhesive polymers can guarantee an intimate contact with the absorption membrane providing the basis for a comparatively steeper concentration gradient as the driving force for passive drug uptake, excluding presystemic metabolism of orally administered drugs which would be otherwise degraded, for instance, by gastrointestinal enzymes (Fig. 2) [e.g. 3], and enabling interactions of the polymer with the epithelium such as a permeation enhancing [e.g. 4] and efflux pump inhibiting effects [e.g. 5].

Because of these advantages, research and development in the field of mucoadhesive polymers has been considerably intensified within the last two decades resulting in numerous promising ideas, strategies, systems and techniques based on a more and more profound basic knowledge base.

2. Types of mucoadhesive polymers

Non-covalent binding polymers

Anionic polymers

Within this group of polymers mainly -COOH groups are responsible for adhesion to the mucus gel layer. These moieties are capable of forming hydrogen bonds with hydroxyl groups of the oligosaccharide side chains on mucus proteins. Alternatively, the anionic groups are sulfate as well as sulfonate moieties, which seem to be more of theoretical than of practical relevance. Important representatives of this group of mucoadhesive polymers are polyacrylates, polymethacrylates, hyaluronic acid, sodium carboxymethylcellulose and alginate [e.g. 6, 7].

Because of their high charge density poly(meth)acrylates, in particular, display a high buffer capacity. They are able to maintain the pH inside the polymeric network over a considerable time period. Matrix tablets based on neutralized carbomer, for instance, can buffer the pH inside a swollen carrier system even for several hours in the gastric milieu of pH 2 [8]. This high buffer capacity seems to be advantageous for various reasons. On the one hand drug release from
anionic mucoadhesive polymers is in many cases controlled by ionic interactions between the drug e.g. therapeutic peptides and the polymer. As controlled drug release based on ionic interactions is strongly pH-dependent, pH adjustment and maintenance inside the polymeric network is substantial. On the other hand a protective effect towards luminaly secreted enzymes in the GI tract can be achieved by adjusting the pH inside the polymeric network to a pH at which these enzymes are inactive.

A drawback of anionic mucoadhesive polymers, however, is their incompatibility with multivalent cations like Ca$^{2+}$, Mg$^{2+}$ and Fe$^{3+}$. In the presence of such cations, most of these polymers precipitate and/or coagulate [9] leading to a huge reduction in their adhesive properties.

**Cationic polymers**

The strong mucoadhesion of cationic polymers can be explained by ionic interactions between these polymers and anionic substructures such as the sialic and sulfonic acid moieties of the mucus gel layer. In particular chitosan (poly(ß1→4 D-glucosamine), which can be produced in high amounts for a reasonable price, seems to be a promising mucoadhesive excipient. It is obtained by the deacetylation of chitin, which can be isolated from insects, crustacea such as crab and shrimp as well as from fungi such as aspergillus niger. Because of its superior characteristics together with a very safe toxicity profile, chitosan is widely used as a pharmaceutical excipient. Apart from its mucoadhesive properties, chitosan is also reported to display permeation enhancing properties [10]. Due to the primary amino group at the 2-position of each polymer-subunit further chemical modifications are easily feasible. A drawback of chitosan, however, is that it precipitates at pH > 6.5.

**Non-ionic polymers**

The formation of secondary chemical bonds due to ionic interactions can be completely excluded for this group of polymers. In contrast, some of them such as poly(ethylene oxide) are able to form hydrogen bonds. Apart from these interactions, their adhesion to the mucosa seems to be based on interpenetration followed by polymer chain entanglements. These theoretical considerations are in accordance with mucoadhesion studies, demonstrating no adhesion or comparatively weak adhesion of non-ionic polymers, if they are applied to the mucosa in the completely hydrated form, whereas they are adhesive if applied in the dry form. Consequently, non-ionic polymers are generally less adhesive than anionic as well as cationic mucoadhesive polymers. Representatives of this type of polymer, in addition to poly(ethylene oxide), are mainly cellulose derivatives such as hydroxyethylcellulose, methylcellulose and hydroxypropylmethylcellulose and polymers such as starch and polyvinylpyrrolidone. In contrast to ionic polymers, non-ionic polymers are not influenced by multivalent metal ions in the surrounding milieu.

**Ambiphilic polymers**

Ambiphilic mucoadhesive polymers display cationic as well as anionic substructures. Their adhesive properties are based on ionic substructures as described above. The combination of positive as well as negative charges on the same polymer, however, seems to cancel out both effects leading to the quite limited adhesive properties of ambiphilic polymers. Mucoadhesion studies of chitosan-EDTA conjugates with increasing amounts of covalently attached EDTA can clearly show this effect. An exclusively anionic chitosan-EDTA conjugate exhibiting no remaining cationic moieties and the exclusively cationic polymer chitosan displayed the highest mucoadhesive properties, whereas the mucoadhesion of chitosan-EDTA conjugates with both cationic moieties of remaining primary amino groups and anionic moieties of covalently attached EDTA was much lower [11]. Lueßen et al., for instance, could show greatly increased intestinal buserelin bioavailability in rats using chitosan as a mucoadhesive excipient. In contrast, a mixture of this cationic polymer with the anionic polymer carbomer, however, led to significantly reduced bioavailability of the therapeutic peptide [4]. Representatives of this type of mucoadhesive polymers are mainly proteins such as gelatin, which is reported to be mucoadhesive in various studies.

**Covalent binding polymers**

In the 1990s a new generation of mucoadhesive polymers was introduced into the pharmaceutical literature [12]. Until then the attachment of mucoadhesive polymers to the mucus layer was achieved by non-covalent bonds, whereas these novel polymers are capable of forming covalent bonds. The bridging structure most commonly encountered in biological systems—the disulfide bond—was thereby discovered for the covalent adhesion of polymers to the mucus layer of the mucosa. Thiomers designated thiomers are mucoadhesive polymers displaying thiol bearing ligands (Fig. 3).

Based on thiol/disulfide exchange reactions and/or a simple oxidation process, disulfide bonds are formed between such polymers and the cysteine-rich subdomains of mucus glycoproteins. Hence, thiomers mimic the natural mechanism of secreted mucus glycoproteins, which are also covalently anchored in the mucus layer by the formation of disulfide bonds. Due to the covalent attachment of thiol groups to chitosan, for instance, the adhesive properties of this polymer are more than 100-fold improved [13]. In 2005 Grabovac et al. screened
all mucoadhesive polymers reported in the literature under standardized conditions establishing a rank order from 1-69. In Table 1 an overview of the ‘top ten’ of this rank order is provided, demonstrating that on positions 1-5 there are exclusively thiomers.

Tab. 1. Overview of the mucoadhesive properties of various polymers. Adapted from Grabovac et al. [14]

<table>
<thead>
<tr>
<th>Polymer</th>
<th>pH</th>
<th>Time in hours; means ± SD (n = 3–5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiolated Chitosan</td>
<td>pH 3 lyophilized</td>
<td>161.2 ± 7.2</td>
</tr>
<tr>
<td>Thiolated Chitosan</td>
<td>pH 6.5 precipitated</td>
<td>40.4 ± 2.1</td>
</tr>
<tr>
<td>Thiolated Polycarbophil</td>
<td>pH 3 lyophilized</td>
<td>26.0 ± 0.9</td>
</tr>
<tr>
<td>Thiolated Chitosan</td>
<td>pH 6.5 lyophilized</td>
<td>20.4 ± 1.5</td>
</tr>
<tr>
<td>Thiolated Poly(acrylic acid)</td>
<td>pH 3 lyophilized</td>
<td>19.4 ± 0.8</td>
</tr>
<tr>
<td>Hydroxypropylcellulose</td>
<td>pH 7 precipitated</td>
<td>15.2 ± 0.4</td>
</tr>
<tr>
<td>Carbopol 980</td>
<td>pH 7 precipitated</td>
<td>12.5 ± 0.9</td>
</tr>
<tr>
<td>Carbopol 974</td>
<td>pH 7 precipitated</td>
<td>10.3 ± 0.9</td>
</tr>
<tr>
<td>Polycarbophil</td>
<td>pH 7 precipitated</td>
<td>10.2 ± 0.8</td>
</tr>
<tr>
<td>Carbopol 980</td>
<td>pH 3 lyophilized</td>
<td>9.8 ± 0.2</td>
</tr>
</tbody>
</table>

Furthermore, thiomers exhibit greatly improved cohesive properties. Tablets consisting of polycarbophil, for instance, disintegrate within two hours, whereas tablets based on the corresponding thiolated polymer remain stable even for days in the disintegration apparatus according to the European Pharmacopoeia [15]. This effect can be explained by the continuous oxidation of thiol moieties on thiomers which takes place in aqueous media at pH >5. Adhesion of many fast swelling polymers is limited by insufficient cohesion of the polymer resulting in a break within the polymer network rather than between the polymer and mucus layer. Although thiolated polymers are rapidly hydrated, they are able to form highly cohesive and viscoelastic gels due to the formation of additional disulfide bonds. The formation of an over-hydrated slippery mucilage can thereby be excluded. Meanwhile, various anionic as well as cationic thiolated polymers have been synthesized. They all display greatly improved mucoadhesive properties compared to the corresponding unmodified polymers. The potential of thiolated polycarboxylates could be demonstrated even in clinical trials. As illustrated in Fig. 4 sustained release of sodium fluorescein over several hours was achieved with thiolated polycarboxylate minitablets adhering to the eye of volunteers [16]. Apart from strong mucoadhesive properties, thiomers also exhibit high permeation enhancing and efflux pump inhibiting properties [17].

3. Marketed products

Within the last decade numerous products comprising mucoadhesive polymers have reached the market. In particular for intraoral and vaginal applications mucoadhesive polymers are utilized to provide a prolonged residence time of various APIs on the mucosal membrane. The following products are therefore just examples.

Striant®️, for instance, is a controlled- and sustained-release buccal testosterone product acting by rapidly adhering to the buccal mucosa. The mucoadhesive polymers used in this formulation are the polyacrylates Polycarbophil and Carbopol 974P. As the formulation is exposed to saliva it softens into a gel-like form remaining comfortably in place over each 12-hour dosing period. The product delivers testosterone through the buccal mucosa, where it is absorbed into the bloodstream bypassing the gastrointestinal system and liver [18].

Advantage®️ 24, for instance, is a gel designed to provide a steady release of nonoxynol-9 after a single vaginal application. Commonly available spermicidal formulations must be used close to the time of intercourse. In contrast, the vaginal contraceptive gel utilizes the mucoadhesive polymer Polycarbophil to achieve its steady release profile. The delivery system has been shown to remain on the vaginal surface for extended periods of time following application. Once attached, the vaginal contraceptive gel allows sustained release of nonoxynol-9 over a period of 24 hours. Available clinical data show that the gel provides effective contraceptive protection for up to 24 hours following initial application prior to a single act of intercourse [19].
4. Future trends

Challenges in the field of mucoadhesive polymers ahead are attempts to develop novel more adhesive polymers and to discover and utilize further functions of mucoadhesive polymers such as efflux pump inhibiting or cytoinvasive properties.

Further challenges are in the field of orally used mucoadhesive polymers, where the adhesive properties are in most cases still insufficient to provide a prolonged residence time in the defined GI area. The localisation of mucoadhesive delivery systems on a certain GI-segment, ideally where the drug has its ‘absorption window’, would lead to a tremendous improvement in the oral bioavailability of numerous drugs. Evidence for the feasibility of such delivery systems has already been provided in human volunteers as illustrated in Fig. 1. Apart from the high motility of this organ in the form of peristaltic waves and the presence of food, the main reason in many cases for insufficient mucoadhesion in the GI-tract seems to be the fact that polymers reach the mucosa in an already prehydrated state. Consequently, the driving force for polymer mucus interpenetration which provides comparatively high mucoadhesive properties is already lost. Accordingly, polymers must reach the adhesion site in the GI-tract in the dry form. The problem, however, cannot be solved by a simple enteric coating, as the coating material does not dissolve quickly enough. In addition, the swollen coating material remains as an isolating layer between the mucoadhesive polymer and the mucus gel layer. Attempts to tackle this problem focus on mucoadhesive polymers, which swell per se like an enteric coating material only at a higher pH.

Further challenges are in the development of novel more efficient mucoadhesive formulations. Liposomes coated with mucoadhesive polymers such as carbopol or chitosan, for instance, significantly improve the bioavailability of orally administered peptides such as illustrated in Fig. 2. Particulate delivery systems exhibit per se a prolonged GI residence time. By diffusing into the mucus gel layer their transit time is often significantly increased even without exhibiting any mucoadhesive properties. Coupe et al. could show in human volunteers that 50% of an orally administered particulate formulation was still present in the small intestine, when single unit dosage forms had already left this gut segment entirely [20]. The potential of micro- and nanoparticles in oral drug delivery could already be demonstrated in numerous in vivo studies. Optimized combinations of both promising strategies—the use of mucoadhesive polymers on the one hand and micro- and nanoparticulate formulations on the other—should additionally improve the potential of these delivery systems.

With the great potential of mucoadhesive polymers in mind and taking all the opportunities ahead into consideration, mucoadhesive polymers will certainly further alter the landscape of drug delivery towards more potent and safer therapeutic systems. This review should encourage scientists in academia and industry to move into or intensively their activities in this promising field.

5. Literature/References


**RECENTLY PUBLISHED LITERATURE REVIEWS IN THE FIELD OF DRUG DELIVERY**


**Delivering the code: polyplex carriers for deoxyribonucleic acid and ribonucleic acid interference therapies.** Christie RJ, Nishiyama N, Kataoka K. Endocrinology. 2010 Feb;151(2):466-73.


Nanofiber micelles from the self-assembly of block copolymers.

Targeted drug-delivery approaches by nanoparticulate carriers in the therapy of inflammatory diseases.

Pulmonary drug delivery systems for antimicrobial agents: facts and myths.

Nanoporous inorganic membranes or coatings for sustained drug delivery in implantable devices.

Design and fabrication of magnetic nanoparticles for targeted drug delivery and imaging.

Better safe than sorry: Understanding the toxicological properties of inorganic nanoparticles manufactured for biomedical applications.

Nanosystem drug targeting: Facing up to complex realities.

Cell penetrating peptides: overview and applications to the delivery of oligonucleotides.

Intranasal delivery to the central nervous system: mechanisms and experimental considerations.

Polymer-based nanocapsules for drug delivery.

Colloidal nanocarriers: a review on formulation technology, types and applications toward targeted drug delivery.
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.

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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