



APV Focus Group Drug Delivery

Combining Science & Technology to Create Advanced Drug Delivery Systems

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

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DRUG DELIVERY EVENTS

Provided by Christoph Blümer

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[SFI Irish Drug Delivery Network \(IDDN\) & UKICIRS: OPTIMISING DRUG DELIVERY](#)

Dublin, August 19th 2009

[Details](#)

[Drug Delivery Summit](#)

London (UK), September 2nd - 4th 2009

[Details](#)

[The British Pharmaceutical Conference 2009](#)

Manchester (UK), September 6th - 9th 2009

[Details](#)

◇ [APV course: Modern Concepts in Pharmaceutical Profiling & Preformulation](#)

Berlin, September 30th - October 1st 2009

[Details](#)

[Suggest a meeting to be announced!](#)

REVIEW OF DRUG DELIVERY EVENTS

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[APV COURSE SUMMARY – IVIVC OF SPECIAL DOSAGE FORMS](#)

November, 12th – 13th 2008, Mainz

By Michael Horstmann, Ph.D., LTS Lohmann Therapie-Systeme AG, R & D, D-Andernach

Summary

Together with Professor Peter Langguth and Dr. K. Kälkert of the APV, we held this course (No. 6208) in an interactive multidisciplinary environment where we could discuss the many possibilities to learn about IVIVC from the different disciplines and forms of application. The agenda of the meeting was based on the selection of most speakers by Johannes Krämer (who unfortunately could not participate).

1. Introduction

P. Langguth and M. Horstmann introduced the topic by bringing participants up to date with the essentials of IVIVC and the dilemma of its application outside oral controlled release formulations, that means special dosage forms. Participants from different fields of application were invited to share the biopharmaceutical peculiarities of their formulations and regulatory applicability. The interactive participation of clinicians and regulatory representatives in the course reminded us once again of the pharmacokinetic / biopharmaceutical roots of the APV.

2. Introductory lecture: Definition of IVIVC / state of the art / limitations and guidelines

M. Holz, as a long-term expert of assessment of in vitro / in vivo correlations, brought us into the details of the "tools boxes" like numerical and model dependent deconvolution, e.g. Wagner-Nelson or Loo-Riegelman models. M. Holz also set the keywords of "significance" but primarily "relevance" for the selection of justifiable in vitro-tests for IVIVC.

3. Pharmacokinetic peculiarities

T. Thomsen continued. As a clinician he modified the title to "Alternative routes of administration" - the role of a clinical Research Institute - a physician's view. His presentation covered a wide range including clinical evaluation of

performance tests like adhesion in transdermal systems, some formal assessments about clinical trials, and IVIVC to the specific experience of clinicians with their in vitro / in vivo correlations. (After the meeting, he confirmed the likewise wish of his clinical organization, the AGAH, to interact further by possibly inviting pharmaceutical / APV-experts to meetings).

4. Value of IVIVC for sustained parenteral dosage forms

Patrick Marroum, FDA, USA, introduced the details of the FDA Guideline and the sequence of applicability of "level A, level B or level C"-correlation. He illustrated his lecture with examples of intrauterine systems like Mirena and the NuvaRing. With these systems reasonable correlations could be established.

5. Biopharmaceutical considerations in drug product design and evaluation

Peter Langguth, University of Mainz, Germany introduced the biopharmaceutical view, starting with the delivery-pharmacokinetics-effect cascade. He covered the biopharmaceutical character of different types of biological membranes and their transport mechanisms. He touched on the possibility for the formulator to influence permeability as well as specifics of transdermal and transmucosal absorption.

6. TTS

In the first of 5 lectures about the application of IVIVC to different dosage forms, there was a presentation on TTS (transdermal drug delivery systems) by M. Horstmann, LTS, Andernach, Germany. Thermodynamic and kinetic factors in the assessment of transdermal systems were discriminated and a special emphasis was given to the influence of the construction of the system (membrane systems, specific release profiles) on delivery. Due to the rare applicability of a true IVIVC to transdermal patches, it was recommended to rely on membrane permeation tests in addition to simple in vitro release. Physicochemical tests were covered as well and the need to address adhesion in clinical trials was explained.

7. Inhalers

Herbert Wachtel of Boehringer Ingelheim, Germany introduced all technical and bio-pharmaceutical details of inhaler construction and formulation. Instead of release tests, in this formulation family the aerodynamic assessment of fine particles is of prominent value as well as assessment of airflow profiles and particle sizing. Also in this working field, performance tests, which are closer to reality, have been at least experimentally applied ("Finlay's" idealized model, or experimental in vitro deposition tests). Nevertheless, in this area major product changes without providing human data appears as difficult to establish as in many other special dosage forms.

8. Long-acting injectables

Stefaan Rossenu from Janssen Pharmaceutica in Beerse showed the applicability of non-linear mixed effects models to establish an IVIVC for long-acting injectables. This excellent clinical / mathematical approach was shown to be able to predict the individual plasma concentration-time profiles here very well.

9. Medicated chewing gums

Jayachandar Gajendran from Phast GmbH in Homburg / Saar introduced special in vitro models for chewing gum, like the Ph. Eur instrument of chapter 2.29. The verification of the in vitro methodology can in this case more simply be confirmed by "spit-out"-tests.

10. Implants

Karsten Mäder, member of the APV focus group drug delivery and professor the University Halle / Wittenberg in Germany gave a well received lecture about implants and illustrated concerns about assuming bioequivalence from in vitro results, specifically in the case of disintegrating systems. Misunderstanding the nature of release from these dosage forms is based on the fact that real release mechanisms may be different from the theoretical ones. Instead of diffusion controlled release by matrix erosion and solubilisation, more complex, multiphase release profiles have often been recorded.

11. Regulatory remarks: FDA respective

P. Marroum, after his introductory lecture on the day before, illustrated the requirement of a finally justified in vitro method. He explained the need to study details of rotation speed, solvent amount, pH and other peculiarities in order to check for the robustness of the method or at least find the best correlatable setting of the test.

12. General regulatory remarks, EU perspective

Both J. Limberg and Jürgen Schomakers, BfArM, Bonn, Germany took a more restrictive view on the applicability of IVIVC applications for special dosage forms and see a value only in cases where it is proven to be justified. On the other hand e.g. for support of changes to products, an unchanged in vitro release curve is likely to be acceptable as a primary basis also in Europe. Specifically for transdermal drug delivery systems, Jürgen Schomakers expressed the need to apply tests beyond the currently applied pharmacopoeial in vitro tests.

Overall the meeting resulted in a lively final discussion. Some concerns for some special products were raised that clinically good and reliably working products may be regarded as unacceptable to authorities just because of the lack of IVIVC correlation methods.

The use of similarity factors to compare in vitro curves appears for some scientists unnecessary, because such differences are already visible by plain observation. Other discussion partners in the auditorium, however, like them as it gives a numerical decision basis. As one of the main fields of applicability for IVIVC, regulators and most speakers in general considered surrogate methods instead of pure in vitro release curves as a possible, at least additional basis to support variations. The influence of consumer-based factors, like in chewing gums and in inhalers, was addressed and taken into consideration including the notion that in the end pharmacists always create products for therapeutic use whose application is in human beings.

Qutenza™ 179 mg cutaneous patch (NeurogesX)

In May the European Commission approved NeurogesX's Qutenza™ 179mg cutaneous patch. This product is for the treatment of peripheral neuropathic pain in non-diabetic adults, either alone or in combination with other pain-killing agents. The patch contains a high concentration (8% w/w, 640 µg/cm²) of synthetic capsaicin solubilised in a permeation enhancer to allow rapid penetration of the active into the skin (1, 2). In clinical trials up to 1000 cm² of skin were treated using multiple patches that could be cut to fit the affected area. Patch application time is limited to 30 minutes on the feet and 60 minutes elsewhere. It is always preceded by pre-treatment of the skin with a topical anesthetic. Following patch removal, the skin is cleansed of capsaicin using a proprietary gel.

Capsaicin is the agent that gives chillis their heat and is a highly selective agonist of the transient receptor potential vanilloid 1 (TRPV1) receptor found on small-diameter afferent neurons. These neurons are involved in the detection of noxious sensations including pain. Initial binding of capsaicin to the TRPV1 receptors results in symptoms such as burning sensations and erythema. However, prolonged stimulation causes their desensitisation and, hence, a reduction in pain transmission.

Chronic neuropathic pain can be caused by a numbers of factors and is the result of damage or injury to nerves. Potential triggers include viral infections (herpes zoster or HIV), diseases such as diabetes or multiple sclerosis or nerve damage induced by drugs used to treat cancer or HIV. Treatment to date has been unsatisfactory and includes the use of anticonvulsants, antidepressants, lidocaine patches and analgesics. In three Phase 3 trials, two in post-herpetic neuralgia and one in painful HIV distal sensory polyneuropathy (HIV-DSP) patients, NeurogesX demonstrated that treatment with high dose capsaicin significantly reduced pain scores over a 12 week period when compared to a low dose (0.04 %w/w, 3.2 µg/cm²) control patch (2). These conditions represent niche markets within the overall demand for neuropathic pain control. It is estimated that there are approximately 200,000 to 500,000 sufferers of post-herpetic neuralgia in the US and 300,000 in the 5 most populous Western European countries taken as a whole. Similarly, the NeurogesX 2008 Annual Report quotes estimated numbers of HIV-DSP patients in the region of 200,000 to 300,000 in the US and 136,000 in the UK, Spain, France, Germany and Italy markets combined. However, by far the largest potential market for the patch is Painful Diabetic Neuropathy, a condition affecting an estimated 3 million US citizens and almost 3 million in the 5 largest countries in Western Europe (2). The patch is not licensed for this condition, but an open label tolerability study has been completed (2).

The company is currently in discussions with a European partner to commercialise Qutenza™ and hopes to launch the product in early 2010.

References and Further Information

1. Simpson D. M. et al, *J. Pain Symptom Manage Vol 111 (3) (2007) pp 360-367.*
2. *The NeurogesX Annual Report 2008 including incorporated references.*
www.NeurogesX.com – accessed 28.5.2009.

Edluar™ Sublingual 5 and 10 mg Tablets (Orexo AB)

In March 2009 the FDA approved Edluar™ Sublingual 5 and 10 mg Tablets from Orexo AB for the treatment of short-term insomnia characterized by difficulties with sleep initiation. The sublingual tablets contain either 5 or 10 mg of the atypical hypnotic, Zolpidem, a blockbuster drug which generated US sales of \$2 billion in 2005 for its originator, Sanofi Aventis. Edluar™ represents the latest novel formulation of this compound (others include Ambien™ CR (Sanofi Aventis) - a controlled release version of the originator's formulation, Tovalt™ ODT (Biovail) - an orally disintegrating tablet and Zolpimist™ (Novadel) - an oral spray).

The tablets are based on Orexo's sublingual mucoadhesive technology which involves the preparation of ordered mixes of carrier particles with much smaller particles of both drug and mucoadhesive agent (1). The tablets, formerly branded as Sublinox™, are administered under the tongue and without water. Clinical data from patients with sleep disturbances show that Edluar™ induced sleep 30% earlier than the original Sanofi Aventis formulation and that patients slept through the night. However, the safety profile for Edluar™ is comparable with that of Ambien™/Stilnoct™ and the products are bioequivalent in terms of C_{max} and AUC (1, 2).

Orexo licensed Edluar™ to the specialty pharmaceutical firm, Meda, in 2008 and approval triggers a \$5 million milestone payment to Orexo AB. Meda is planning to launch the product on the US market during the second half of 2009.

References and Further Information

1. www.orexo.com – assessed 28.5.2009.
2. *Orexo AB Year-End Report 2008.*

ASCENDIS PHARMA A/S (Hellerup, Denmark)

Ascendis Pharma is built upon a novel transient linker technology, TransientLink, which conjugates peptides, proteins and small molecules to carrier molecules in a reversible fashion. The lead product based on this technology is in pre-clinical development.

Fact sheet:

Founded:	2007
Location:	Ascendis' commercial headquarters are based in Copenhagen, Denmark with research and development sites in Heidelberg Germany, and Short Hills, NJ, USA.
Ownership:	Private company; investors include Sofinnova Partners, Gilde Healthcare Partners, TechnoStart.
Employees:	20
Key technology:	<p>The company is built upon a novel transient linker technology, TransientLink. The aim of this approach is to achieve reversible conjugation of polymer carrier to drug compound; carrier molecules such as PEG are linked in a reversible fashion to the drug (either protein, peptide or small molecule) resulting in the release of unmodified active drug. The drug molecules are released (unlinked) in a precise, time-controlled fashion, creating a long-acting effect. The approach is different from the more traditional conjugation technologies, in that they are unable to achieve this type of slow-release mechanism because the polymer cannot de-link from the drug.</p> <p>A key element of Ascendis Pharma's chemically controlled delivery approach is a group of unique and proprietary reversible linker reagents. These linkers are specifically designed to slowly autohydrolyse at a predictable rate. Linkers self-cleave according to high-precision kinetics in the blood or under the skin. Linker cleavage does not depend on the presence of certain enzymes or intracellular conditions such as a reducing or acidic environment.</p> <p>Linker design provides for great flexibility with respect to half-life engineering, polymer and drug compatibility. Through variation of activation chemistry and conjugation sequence, various combinations of polymer carriers and drug compounds are accessible.</p>
Products:	Ascendis' pipeline comprises several products in endocrinology and infectious diseases indications.
Development status:	Lead product currently in pre-clinical development. First clinical trial is expected to start in 2010
Partnerships:	Not disclosed
Website:	http://www.ascendispharma.com/
Contact:	<p>Jan Møller Mikkelsen, President and CEO Ascendis Pharma A/S Tuborg boulevard 12 DK-2990 Hellerup, Denmark Tel: +45 36 94 44 86 Fax: +45 36 94 40 10 Email: info@ascendispharma.com</p>

DRUG TARGETING

An effort, means, or technology for achieving a target site-specific release or accumulation of a drug substance after administration. [Write a comment on this definition](#)

The target site may be a body region, organ, tissue, or cell type, and usually represents the primary site of action of the drug substance in terms of its therapeutically desired activity. Drug targeting may involve a chemical manipulation of the drug substance itself, such as conjugation with a moiety which modifies the physical properties of the compound and thereby alters its biodistribution (e.g. PEGylation), or with a moiety which is capable of selective interaction with a molecular structure of a target cell or tissue (e.g. antibodies or antibody fragments). Alternatively, it may be based on the association of the drug substance with a carrier such as a liposome or nanoparticle which is designed to enable targeted delivery by means of its physical or biochemical properties. Related terms are "targeted drug delivery" and "site-specific drug delivery".

German: [Drug Targeting](#)

PRODRUG

A drug substance which is converted after administration into a pharmacologically more active chemical species. [Write a comment on this definition](#)

The chemical conversion of the prodrug in the body is often catalysed by enzymes; in this case, the conversion product is an active metabolite, and the reaction is referred to as bioactivation. Alternatively, the activation may simply be the result of non-enzymatic hydrolysis. An example of a prodrug is L-dopa or levodopa, which is metabolised in the body into the primary active species, dopamine. To maximise the conversion and availability of levodopa in the central nervous system (CNS), which is the site of its desired activity in Parkinson patients, it is co-administered with a decarboxylase antagonist such as carbidopa or benserazide, which achieves a reduction of the metabolism of levodopa outside the CNS.

German: [Prodrug](#)

[Suggest a term to be defined](#)

[Suggest a definition](#)

DRUG DELIVERY PEOPLE

Provided by Prof. Dr. Karsten Mäder

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JÜRGEN SIEPMANN studied pharmacy and did his Ph.D. at the Freie Universitaet Berlin, Germany, supervised by Prof. R. Bodmeier. Since 2004, he has been Professor of Pharmaceutical Technology at the Université Lille Nord de France, Lille, France.

His awards include the "APV Prize for the outstanding doctoral thesis in Pharmaceutical Sciences from the years 1998/99" and a Marie Curie Individual Fellowship (European Framework Programme). He was visiting scientist/postdoctoral fellow at Purdue University (Prof. N. Peppas), the University of Paris-Sud (Prof. G. Couarraze), the University of Iowa (Prof. P. Veng-Pedersen) and the University of Angers (Prof. J.P. Benoit).

His research focuses on controlled drug delivery systems, in particular, on the elucidation of the underlying mass transport phenomena and the optimization of devices (e.g. coated pellets, matrix tablets, biodegradable microparticles and lipid implants). Prof. Siepmann is head of the research group "Controlled Drug Delivery Systems and Biomaterials: Mechanisms and Optimization", consisting of 4 professors, 5 lecturers and about 15 Ph.D. students/post docs.



So far, he has published his work in more than 80 articles in peer-reviewed, international scientific journals, 170 poster presentations and 75 oral presentations at national and international scientific meetings. He is editor of 2 books, author of 14 book chapters and theme editor of issues of the "International Journal of Pharmaceutics" and "Advanced Drug Delivery Reviews". Prof. Siepmann is Reviews Editor of the "International Journal of Pharmaceutics" and member of the editorial boards of the "European Journal of Pharmaceutics and Biopharmaceutics", "European Journal of Pharmaceutical Sciences", "Drug Development and Industrial Pharmacy", "Journal of Drug Delivery Science and Technology", and the "Journal of Controlled Release". He is member of the EUFEPS (European Federation for Pharmaceutical Sciences) Committee for Training and Education, member of the APV (German Association for Pharmaceutical Technology) Committee for Education and Science, and vice-president of the APGI (French Association for Pharmaceutical Technology).

IMPROVING TRANSUNGUAL DELIVERY

By Dr. Louise Rosenmayr-Templeton, Tower Pharma Consulting, Vienna, Austria

1. Introduction

Transungual delivery is the absorption of drugs across the hard keratinized nail plate to treat diseases of the nail itself. The hardness and impermeability of the nail makes it an unpromising route for drug delivery. However, improvements in the topical delivery of compounds for the treatment of nail fungal disease and psoriasis, would reduce the need for systemic administration of drugs with its associated side-effects. In addition, it may reduce the length of time required for treatment and help prevent relapse. This article sets out to provide an overview of the challenges involved in transungual delivery, and look at some of the current approaches being taken to improve the treatment of diseases of the nail.

2. The Function, Structure and Physiology of the Nail

2.1 Function

Nails have three distinct physiological functions: firstly they protect the part of the digits most in danger of damage; secondly, they can be used as tools or weapons and thirdly, they aid the precision and accuracy with which we can handle objects. They also have social and cultural significance with cared-for, unblemished nails being seen as a sign of beauty, health and well-being.

2.2 Structure

The structure of the nail apparatus is shown in Figure 1. It consists of the following main structures:

- The nail plate
- The nail matrix
- The nail bed
- The nail folds – proximal and lateral

2.2.1 The nail plate

The nail plate is the largest component of the nail apparatus. It is composed of approximately 25 layers of dead, keratinized, flattened cells, and is 0.25-0.6 mm thick on the fingers and up to 1.3 mm on the toes. It can be divided into three layers: a thin, outer dorsal layer, the thicker, highly fibrous intermediate layer (accounts for most of the nail's thickness) and a ventral layer that connects the nail plate to the nail bed. The keratinized cells are tightly bound to each other by numerous intercellular links, granules and desmosomes (involved in cell-to-cell adhesion) (1, 2).

80 % of the nail plate keratins are of the "hard" type found in the hair with the rest "softer" resembling those found in the skin (2). The "hard" type keratins contain more cysteine than the "soft" (3). The former are only found in the middle intermediate layer while the latter are found in both the dorsal and ventral layers. It is thought that this sandwich type structure together with the orientation of the different keratin fibre types are, in part, responsible for the nail's mechanical strength and rigidity. Other important factors in nail plate hardness are the presence of cysteine-rich keratin-associated proteins which stabilize the keratin network through disulphide links, the numerous intercellular links between the keratinized cells, nail shape, curvature and water content (2). The water content of the nail (10 – 30%) influences its elasticity and flexibility and is related to the relative humidity. The nail plate also contains 0.1 % - 1 % lipid in the form of bilayers. This lipid is mainly located in the dorsal and ventral layers (2).

2.2.2 Other structures

The other structures of the nail apparatus provide the growing nail plate either with cells, nutrients, waste removal, mechanical support or protection. One of the most important of these is the nail matrix. This is a fast-dividing epidermal tissue located underneath the proximal nail fold. It is partially visible through the nail plate as the white half-moon, known as the lunula. The cells of the nail matrix constantly divide, mature and keratinize to form the continually growing nail plate (1, 2).

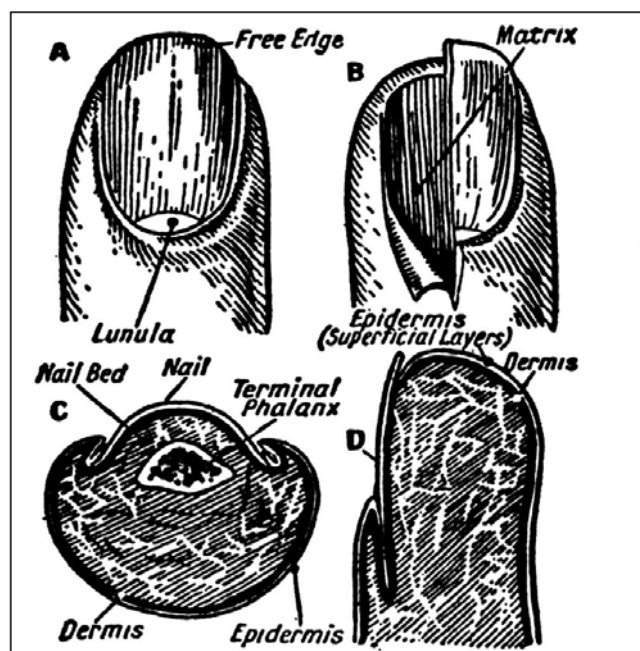


Figure 1: Structure of the Nail

A: Outer view, B: The matrix beneath the proximal fold, C: Cross Section, D Longitudinal view

The activities of the nail matrix are augmented by that of the nail bed. It consists of an epidermal and a dermal layer but, unlike skin, has no subcutaneous fat (1). The epidermis is only 2-3 layers thick. Its cells divide and keratinize to thicken the growing nail plate as progresses from the lunula to the hyponychium where the nail separates from the nail bed. The dermal fibrous tissues of the nail bed are well-supplied with blood vessels and lymphatics and contain elastic fibres and some isolated fat cells. The nail bed also has a structural support role as it acts as a holder for the growing nail plate (1, 2).

The proximal and lateral nail folds, together with the cuticle, provide protection to the nail by screening its most vulnerable points and help anchor it to the digits. The structure of the proximal and lateral folds is very similar to that of the adjacent skin, while the cuticle is composed of a modified stratum corneum (1).

3. Nails – in Sickness and in Health

The appearance and condition of the nails can be an indicator not only of their health, but also that of the individual as a whole (4). Nail linear growth rate is highly variable with average values of 3 mm and 1 mm per month for finger and toenails respectively (1). It is affected by physiological and environmental factors such as the time of day and season (faster growth during daytime and summer), age, pregnancy and minor trauma e.g. nail biting. In addition, nail growth is influenced by disease or poor nutrition. Pathological conditions that speed up nail growth include psoriasis and hyperthyroidism, while fever and hypothyroidism are among those that decrease nail growth (1). In addition, disease, administration of certain drugs, chemical exposure or trauma can result in them becoming discoloured, flaky, brittle or in the case of toenails cause them to grow into the adjacent skin to produce an in-growing toenail. Diseases of the toenails are often related to issues with the foot e.g., ill-fitting shoes can worsen fungal infections (1).

Nail diseases and conditions can be localised to the nail apparatus itself (5-6), appear in combination with those of the skin (7) or be the topical manifestation of a systemic pathology e.g. splinter haemorrhages in multiple nails can indicate bacterial endocarditis (4). Common diseases of the nail apparatus include onychomycosis, a fungal infection of the nail plate and/or nail bed, typically caused by dermatophytes, and psoriasis.

Onychomycosis is thought to affect 2-26 % of the general population and results in nail thickening, discolouration, splitting and disfigurement (5-6). It is more common in the elderly, in diabetic patients and those with poor circulation or compromised immune function. Onychomycosis is normally treated with oral antifungals such as terbinafine and itraconazole (5, 6). The topical treatments currently available have a lower success rate due to poor penetration of drugs through the nail plate. For example, ciclopirox olamine applied daily as a 8 % topical lacquer for 48 weeks has been reported to eradicate the fungus in 28-36 % of cases, but achieved a disease-free nail in only 7% (discussed in 5). This is compared with results showing a complete cure (fungus-free, normal nail) rate of 55 % and 26 % in patients taking oral terbinafine and itraconazole for 16 weeks respectively (5, 7). However, despite the relative greater success rate with oral therapy, it is clear that the treatment of onychomycosis is far from ideal. In order to effect a clinical cure, prolonged therapy is required with drugs that can cause serious side-effects, are associated with drug interactions and whose use necessitates the monitoring of liver function. In addition, 25 -30 % of patients relapse after the initial "cure" (5).

Nail psoriasis can exist on its own or in combination with skin manifestations of the same disease and, in a high percentage of cases, together with psoriatic arthritis (8, 9). Treatment can be topical e.g., with corticosteroids (with or without salicylic acid), urea/propylene glycol, 5-fluorouracil, calcipotriol, anthralin or tazarotene; intralesional with corticosteroids injected into the nail folds; systemic or a combination of these. Systemic treatments include oral photochemotherapy, cyclosporine, retinoids, nimesulide, infliximab and alefacept (8, 9). The success of these treatments have been recently reviewed (8, 9), and shows that further research is required to develop effective treatments for this chronic and sometimes distressing condition.

4. Factors Affecting Permeation Through the Nail Plate.

The issues discussed in the previous sections clearly indicate that better delivery strategies are urgently required. To date, a great deal of work has been carried out to understand the factors that affect partitioning and permeation of drugs into and through the nail plate. These include the following:

- Molecular size of compound
- Degree of ionization
- Level of nail plate hydration
- Presence of an intact dorsal layer
- Binding of the drug to keratin and other nail constituents
- Formulation factors: pH, ionic strength, solvent effects, penetration enhancers, drug suspensions versus solutions, formulation-nail contact time
- Nail thickness and presence of disease

Molecular Size

Molecular size has been shown in numerous studies to play a major role in determining the permeability of compounds (10, 11, 12) through the nail. For example, Kobayashi et al (11) found that the logarithm of the permeability coefficient decreased as the molecular weight increased for a series of non-ionic model drugs that varied in molecular weight from

20 to 236 Da. These researchers established a similar relationship for a series of ionic compounds and demonstrated that molecular weight played a greater role in determining permeability than degree of dissociation.

Degree of Ionisation

In general, the nail plate is less permeable to ionic compounds than to their non-charged equivalents with permeability coefficients for lidocaine and benzoic acid reducing 10-fold when the molecule is ionized (11). These results are somewhat surprising given that the nail plate is essentially a hydrophilic matrix, and may be due to the increase in apparent molecular size due to ion hydration (11) and/or charge repulsion (the Donnan effect) between the diffusing compounds and the ionized keratin (13) (the pI of keratin is said to be around 5 (14)).

Nail Plate Hydration

The level of nail plate hydration is also an important factor in determining drug penetration. For example, Gunt and Kastig (15) studied the permeation of ketoconazole through excised human nails under different relative humidities, and found that increasing the RH from 15 to 100 % resulted in a 3-fold improvement in the delivery of the radiolabeled drug. The fact that nail hydration and increased drug permeability are so clearly linked has prompted some researchers to use water uptake as a marker for screening potential enhancers of transungual delivery (16, 17). As previously mentioned, the water content of the nail can vary between 10 and 30 %. Hydration occurs rapidly if the nails are immersed (18), but the time taken may vary depending on the experimental conditions (18, 19). Water loss also occurs rapidly, although at an apparently slower rate than uptake (18). Since nail hydration is difficult to control in practice due to activities such as hand-washing, topical treatments formulated as varnishes, which have been shown to reduce water loss (18), may improve drug delivery by increasing hydration.

Presence of an Intact Dorsal Layer

It is generally recognized that the very thin dorsal layer with its overlapping cells represents the greatest barrier to drug penetration across the nail plate (2). If this layer is partially or totally removed e.g., by debridement (5) or chemical etching with 30-40 % phosphoric acid (20) or use of keratinolytic enzymes (21), then drug permeability increases.

Binding of the Drug to Keratin and other Nail Constituents

Keratin is thought to have a pI of around 5 (14) and therefore is positively and negatively charged at pHs below and above this respectively. It therefore may bind or repel molecules depending on their charge. This may be part of the reason for the lower nail permeability of ionic compounds (11, 13). In addition, it has been shown that a number of drugs including terbinafine and amorolfine bind strongly to keratin (22), and this is likely to influence their anti-fungal activity

Formulation Effects

pH affects the degree of ionization of weak acids and bases which, as previously described, decreases their permeability through the nail plate (11, 13). It also affects their solubility in formulations, their ability to partition into the nail plate and their interactions with keratin. Higher ionic strength helps screen charges and is likely to reduce potential attractive or repulsive forces between the permeating molecules and the keratin.

The nature of the solvent will affect nail hydration, drug solubility in the formulation and its partitioning into the nail plate. Theoretically, aqueous-based formulations should provide the best delivery although there is also evidence that dimethyl sulphoxide improves permeability (reviewed in 2). However, the positive effects of aqueous-based products on nail hydration have to be counter-balanced with the ease by which they can be removed during everyday activities. The use of lipophilic vehicles or lacquers may therefore have some advantages. Mertin and Lippold (23) found the flux from suspensions of chloramphenicol in octanol and medium chain triglycerides across hoof and nail was comparable to that of a saturated solution of drug in phosphate buffer. In addition, there are marketed treatments for onychomycosis in form of lacquers e.g, Loceryl® (amorolfine) and Penlac® (ciclopirox) (treatment and effectiveness reviewed in 2, 5). Lacquers are thought to facilitate delivery by drying to form a depot of drug on the nail and assist its hydration by reducing transonychia water loss.

Nail Thickness and Presence of Disease

The thicker the nail the more difficult it will be for drugs to reach the nail bed. Studies have shown that the flux of drugs, such as 5-fluorouracil, are reduced by increasing nail thickness (11). Nail conditions, like onychomycosis, can cause nail thickening and this may further reduce the amount of active reaching the nail bed. However, it appears that onychomycosis itself does not alter nail permeability when plate thickness is taken into account (11).

5. Models of Absorption Across the Nail Plate

Studies into the factors affecting permeation across the nail plate indicate that its structure can be likened to a hydrogel under high ionic strength conditions, in that it is a hydrophilic matrix with very small water-filled pores created through thermal movement of the keratin fibres (2, 10, 11, 13). As compounds of medical interest are often of the same size order as these pores, their diffusion through the nail plate can be hindered so that their diffusion coefficients are less than in solution (12). Such a model is backed-up by the fact that molecular weight, geometry and, as previously discussed, ionisation (11, 13) appear to influence permeability. In addition to diffusion through pores, drugs may simply partition into the nail and diffuse along the polymer segments (2).

Evidence has also been found of a lipid pathway for drug diffusion across the nail. For example, in one study assessing the transport of a series of alcohols (C1-C12), the permeability coefficients first decreased as the carbon chain lengthened (C1-C8) and then increased (10). While the permeability decrease supported the concentrated hydrogel pore diffusion model, the increase in the coefficients for the C10 and C12 alcohols suggested that compounds of sufficient hydrophobicity may partition into nail lipid and be transported that way. Other studies, however, have found no evidence of a relationship between nail permeability and molecular hydrophobicity and log P (2, 11, 13). Since lipid accounts for only 0.1 – 1 % of the nail, existence of such a pathway seems unlikely.

6. Strategies for Improving Drug Delivery Across the Nail Plate

A number of strategies have been explored to improve transungual delivery:

Penetration Enhancers Acting on the Keratin Matrix and/or Intercellular Links

One of the most common approaches to improving transungual delivery is the use of penetration enhancers that modify the keratin matrix and/or breakdown intercellular links to enlarge diffusion pathways and increase hydration. These can be broken down into approximately 3 groups: reducing agents, oxidizing agents and substances with keratolytic activity or the ability to break intracellular links. Examples of disulphide bond breakers include thioglycolic acid (shown to improve terbinafine flux approx. 8-fold) (16, 24), and thiol containing amino acids, such as N-(2-mercapto-propionyl) glycine (MPG) and N-acetyl-1-cysteine (AC) (17, 25). In one study MPG and AC, in combination with 20% urea, increased tritiated water flux 3.5 and 8-fold across human nails respectively (17).

In general, penetration enhancers that act through oxidation e.g., hydrogen peroxide, and the commonly used nail softening agents, such as urea and salicylic acid, been found to be less successful in improving drug permeability across the nail when compared to other compounds (2, 16, 24). For example, 17.5 % Urea H₂O₂ only significantly improved terbinafine flux (19-fold) when the nails had been pre-treated with 5 % thioglycolic acid (24) and not vice-versa, showing that disulphide links must be first broken before it can exert its activity. This study is not the only one to demonstrate the long-lasting activity of enhancers, such as thioglycolic acid (16, 17 and 24). This would suggest that it may be possible to pre-treat nails followed by application of the active, thus, avoiding any incompatibilities between drug and enhancer.

Other Types of Penetration Enhancer

Recently, researchers have found that solutions of inorganic salts such as sodium citrate, potassium phosphate and ammonium carbonate can influence drug permeation through nail. The mechanism of enhancement is thought to be a combination of increased nail hydration and changes in the drug's thermodynamic activity. For example, in a novel screening study 5 % salt solutions were shown to improve terbinafine loading and uptake rate into nail (26). These results were confirmed by Franz cell permeation experiments that showed loading and permeability of the drug was increased by 4-7-fold and 3-5-fold respectively in the presence of 0.5 M salts (27).

2-n-nonyl-1, 3-dioxolane is a known transdermal penetration enhancer which does not appear to penetrate the nail plate. However, when added at a concentration of 18 % to EcoNail® nail lacquer (econazole), it improved drug delivery 6.3-fold into the deeper layers of the plate, and increased 200 times the amount absorbed through the complete nail compared with the lacquer on its own (28). 2-n-nonyl-1, 3-dioxolane is thought to exert its effects at the nail/formulation interface by acting as a plasticizer promoting adhesion of the lacquer to the nail.

Iontophoresis

A number of studies have assessed iontophoresis as a method of improving delivery across the nail (12, 17, 29, 30, 31). For example, Transport Pharmaceuticals (www.transportpharma.com) have recently completed a successful Phase 1 study which demonstrated the potential of this technique to deliver anti-fungals to the big toe nail *in vivo*. The clinical data showed that initial nail concentrations from around 200 µg/g terbinafine to almost 1000 µg/g could be achieved, and that significant levels remained in the nail throughout the 12 week post-treatment period. In some studies iontophoresis has been used in combination with certain nail penetration enhancers (31) and keratolytic agents (30) to enhance delivery.

Partial or Complete Removal of the Dorsal Layer

Despite the dorsal layer being only a few cells thick, the overlapping arrangement of its cells makes it the biggest barrier to transungual delivery. Typically, even when loaded, most drug remains in the upper dorsal regions of the nail and fails to penetrate any further (30). Part or total removal of this layer can be achieved by a number of mechanisms including mechanical abrasion and acid etching. For example, in one study using phosphoric acid to etch nails prior to application of a ketoconazole gel, delivery of the anti-fungal was improved by approximately 60 %. The improvements in drug permeability seen in *in vitro* experiments are borne out in clinical practice where regular debridement of infected nails is recommended (5).

Improved and Prolonged Contact between Drug and Nail Surface

A number of currently marketed topical treatments for onychomycosis are in the form of lacquers (2). Close and prolonged apposition of drug against the nail will facilitate treatment and, therefore, good bioadhesion properties of such films are important. Recent work in this area include films containing 20 % ketoconazole produced by hot melt extrusion (20) applied to nails etched with phosphoric acid. The improvement in drug permeation was attributed to a combination of dorsal layer removal, and enhanced bioadhesion between the film and nail due to the formation of microporosities.

Other researchers evaluated different pressure sensitive vehicles and found that ciclopirox showed highest permeability across porcine hoof from an acrylic adhesive with a functional OH group (32).

Other Approaches - Acidified Nitrite (Citric Acid/Na Nitrite)

Acidified nitrite is anti-fungal in itself as it releases nitric oxide and other related species. These, in turn, form S-nitrosothiols throughout the nail due to reaction of the nitrite with cysteine residues in keratin. In a clinical trial treatment with a 13.5% citric acid cream followed by 9% sodium nitrite resulted in all 13 patients becoming culture negative for dermatophytes after 16 weeks treatment (33). ProStrakan Pharmaceuticals (www.prostrakan.com) currently have topical nitric oxide for onychomycosis in Phase II clinical trials.

7. Products and Technologies in Clinical Development

The US market for onychomycosis in 2007 alone was worth in the region of \$750 million and it is estimated that only 20% of those affected with this disease are treated (34). This, taken together with the poor cure rates and issues with current oral and topical therapy, it is no surprise that a number of companies are developing novel topical therapies for fungal nail disease. The products being assessed by Transport Pharmaceuticals and ProStrakan Pharmaceuticals have already been discussed. However, a search of the US National Institutes of Health's clinical trials database listed 29 trials under nail and onychomycosis including Phase 3 trials on a 10 % terbinafine HCl topical therapy from Novartis. Further examples of companies developing topical therapies for onychomycosis include MacroChem (Econail™ with 18 % 2-n-nonyl-1, 3-dioxolane in Phase II), Anacor Pharmaceuticals (AN2690 solution in Phase II) and Dow Pharmaceutical Sciences (DP-108 in Phase II). For further details of these trials and other companies developing products for this disease, please see www.clinicaltrials.gov/. In addition, MediQuest Therapeutics is assessing topical methotrexate treatment for nail psoriasis in humans, and MedPharm UK (www.medpharm.co.uk) has an enhancer technology, MedNail®, specifically to improve transungual delivery.

8. References and Further Information

1. Dawber R. P. R. Science of the nail apparatus in "A Text Atlas of Nail Disorders. Techniques in Investigation and Diagnosis" (3rd Edit), (2003) Taylor & Francis: 1-7.
2. Murdan S. Drug delivery to the nail following topical application. *Int J Pharm* (2002) 236 (1-2):1-26.
3. Yu J et al. Human hair keratins. *J Invest Dermatol* (1993) 101(1 Suppl):56S-59S.
4. Zaiac M.N., Daniel III C.R. Nails in systemic disease. *Dermatol Ther* (2002) 15 (2):99-106.
5. De Berker D. Fungal nail disease. *N Engl J Med* (2009) 360(20):2108-2116.
6. MacKay-Wiggan J. et al. The diagnosis and treatment of nail disorders: systemic fungal therapy. *Dermatol Ther* (2002) 15(2):78-88.
7. Evans E.G., Sigurgeirsson B. Double blind, randomized study of continuous terbinafine compared with intermittent itraconazole in the treatment of toenail onychomycosis. *BMJ* (1999) 318(7190):1031-1035.
8. Lawry M. Biological therapy and nail psoriasis. *Dermatol Ther* (2007) 20(1):60-67.
9. Cassell S., Kavanaugh A.F. Therapies for psoriatic nail disease. A systematic review. *J Rheumatol* (2006) 33(7):1452-1456.
10. Walters K. A. et al. Physicochemical characterization of the human nail: permeation pattern for water and the homologous alcohols and differences with respect to the stratum corneum. *J Pharm Pharmacol* (1983) 35(1):28-33.
11. Kobayashi Y. et al. In vitro permeation of several drugs through the human nail plate: relationship between the physicochemical properties and nail permeability of drugs. *Eur J Pharm Sci* (2004) 21(4):471-477.
12. Hao J., Li S. K. Transungual iontophoretic transport of polar neutral and positively charged model permeants: effects of electrophoresis and electroosmosis. *J Pharm Sci* (2008) 97(2):893-905.
13. Mertin D., Lippold B. C. In vitro permeability of the human nail and of a keratin membrane from bovine hooves: influence of the partition coefficient octanol/water and the water solubility of drugs on their permeability and maximum flux. *J Pharm Pharmacol* (1997) 49(1):30-34.
14. Marshall R.C. Characterisation of the proteins of human hair and nail by electrophoresis. *J Invest Dermatol* (1983) 80(6):519-524.
15. Gunt H. B., Kasting G. B. Effect of hydration on the permeation of ketoconazole through human nail plate in vitro. *Eur J Pharm Sci* (2007) 32(4-5):254-260.
16. Khengar R.H. et al. Nail swelling as a pre-formulation screen for the selection and optimization of unguinal penetration enhancers. *Pharm Res* (2007) 24(12):2207-12.
17. Malhorta G.G., Zatz J. L. Investigation of nail permeation enhancement by chemical modification using water as a probe. *J Pharm Sci* (2002) 91(2):312-323.
18. Murdan S. et al. A few aspects of transonychia water loss (TOWL): Inter-individual, and intra-individual inter-finger, inter-hand and inter-day variabilities, and the influence of nail plate hydration, filing and varnish. *Eur J Pharm Biopharm* (2008) 70 (2):684-689.
19. Hao J et al. Time-dependent electrical properties of human nail upon hydration in vivo. *J Pharm Sci* Published Online 21.5.2009.

20. Repka M. A. et al. Influence of human nail etching for the assessment of topical onychomycosis therapies. *Int J Pharm* (2004) 282(1-2):95-106.
21. Mohorcic M. et al. An investigation into keratinolytic enzymes to enhance ungual drug delivery. *Int J Pharm* (2007) 332(1-2):196-201.
22. Tatsumi Y. et al. Therapeutic efficacy of topically applied KP-103 against experimental tinea unguium in guinea pigs in comparison with amorolfine and terbinafine. *Antimicrob Agents Chemother* (2002) 46(12): 3797-3801.
23. Mertin D., Lippold B. C. In vitro permeability of the human nail and of a keratin membrane from bovine hooves: penetration of chloramphenicol from lipophilic vehicles and a nail lacquer. *J Pharm Pharmacol* (1997) 49(3):241-245.
24. Brown, M. B. et al. Overcoming the nail barrier: A systematic investigation of ungual chemical penetration enhancement. *Int J Pharm* (2009) 370(1-2):61-67.
25. Sun Y et al. Antifungal treatment of nails. US Patent 5696164. (1997).
26. Murthy S. N. et al. TransScreen-N™: Method for rapid screening of transungual drug delivery enhancers. *J Pharm Sci* Published online 10.04.2009.
27. Nair A. B. et al. A study on the effect of inorganic salts in transungual drug delivery of terbinafine. *J Pharm Pharmacol* (2009) 61(4):431-7.
28. Hui X. et al. Enhanced econazole penetration into human nails by 2-n-nonyl-1,3-dioxolane. *J Pharm Sci* (2003) 92(1):142-148.
29. Nair A. B. et al. Trans-ungual iontophoretic delivery of terbinafine. *J Pharm Sci* (2008) 98(5):1788-1796.
30. Nair A. B. et al. Alteration of the diffusional barrier property of the nail leads to greater terbinafine drug loading and permeation. *Int J Pharm* (2009) 375(1-2):22-27.
31. Hao J. et al. Chemical method to enhance transungual transport and iontophoresis efficiency. *Int J Pharm* (2008) 357(1-2):61-69.
32. Myoung Y, Choi H-K. Permeation of ciclopirox across porcine hoof membrane: effect of pressure sensitive adhesives and vehicles. *Eur J Pharm Sci* (2003) 20(3):319-325.
33. Finnen M. J. et al. Topical application of acidified nitrite to the nail renders it anti-fungal and causes nitrosation of cysteine groups in the nail plate. *Br J Dermatol* (2007) 157(3):494-500.
34. DeLuccia R. J. SEPA®, DermaPass™ and MacroDerm™: Exciting possibilities for topical delivery and Specialty Pharma. *Drug Delivery Technology* 7(7):46-51.

DRUG DELIVERY LITERATURE

Provided by Dr. Karsten Cremer

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RECENTLY PUBLISHED LITERATURE REVIEWS IN THE FIELD OF DRUG DELIVERY

Novel drug delivery systems for retinal diseases. Lee SS, Robinson MR. *Ophthalmic Res.* 2009;41(3):124-35.

Overcoming biological barriers to in vivo efficacy of antisense oligonucleotides. White PJ, Anastasopoulos F, Pouton CW, Boyd BJ. *Expert Rev Mol Med.* 2009 Mar 23;11:e10.

Various non-injectable delivery systems for the treatment of diabetes mellitus. Yadav N, Morris G, Harding SE, Ang S, Adams GG. *Endocr Metab Immune Disord Drug Targets.* 2009 Mar;9(1):1-13.

Development of multifunctional nanoparticles for targeted drug delivery and noninvasive imaging of therapeutic effect. Sajja HK, East MP, Mao H, Wang YA, Nie S, Yang L. *Curr Drug Discov Technol.* 2009 Mar;6(1):43-51.

Ophthalmic drug delivery: development and regulatory considerations. Novack GD. *Clin Pharmacol Ther.* 2009 May;85(5):539-43.

Supramolecular approaches to biological therapy. Ariga K, Ji Q, Hill JP, Kawazoe N, Chen G. *Expert Opin Biol Ther.* 2009 Mar;9(3):307-20.

Impact of nanotechnology on drug delivery. Farokhzad OC, Langer R. *ACS Nano.* 2009 Jan 27;3(1):16-20.

Targeting: the ADEPT story so far. Bagshawe KD. *Curr Drug Targets.* 2009 Feb;10(2):152-7.

Toxicity of therapeutic nanoparticles. Maurer-Jones MA, Bantz KC, Love SA, Marquis BJ, Haynes CL. *Nanomed.* 2009 Feb;4(2):219-41.

Nanodiamonds for nanomedicine. Xing Y, Dai L. *Nanomed.* 2009 Feb;4(2):207-18.

Magnetoliposomes: versatile innovative nanocolloids for use in biotechnology and biomedicine. Soenen SJ, Hostenius M, De Cuyper M. *Nanomed.* 2009 Feb;4(2):177-91.

Knocking down barriers: advances in siRNA delivery. Whitehead KA, Langer R, Anderson DG. *Nat Rev Drug Discov.* 2009 Feb;8(2):129-38.

Lessons from nature: "Pathogen-Mimetic" systems for mucosal nano-medicines. Mrsny RJ. *Adv Drug Deliv Rev.* 2009 Feb 27;61(2):172-92.

Crucial functionalizations of carbon nanotubes for improved drug delivery: a valuable option? Pastorin G. *Pharm Res.* 2009 Apr;26(4):746-69.

Barrier properties of mucus. Cone RA. *Adv Drug Deliv Rev.* 2009 Feb 27;61(2):75-85.

Novel platforms for oral drug delivery. Colombo P, Sonvico F, Colombo G, Bettini R. *Pharm Res.* 2009 Mar;26(3):601-11.

Mucus-penetrating nanoparticles for drug and gene delivery to mucosal tissues. Lai SK, Wang YY, Hanes J. *Adv Drug Deliv Rev.* 2009 Feb 27;61(2):158-71.

Stimuli-responsive polymersomes for programmed drug delivery. Meng F, Zhong Z, Feijen J. *Biomacromolecules.* 2009 Feb 9;10(2):197-209.

Multiparticulate formulation approach to pulsatile drug delivery: current perspectives. Roy P, Shahiwala A. *J Control Release.* 2009 Mar 4;134(2):74-80.

pH-controllable supramolecular systems. Leung KC, Chak CP, Lo CM, Wong WY, Xuan S, Cheng CH. *Chem Asian J.* 2009 Mar 2;4(3):364-81.

Issues to consider in the pharmaceutical development of a cardiovascular polypill. Guglietta A, Guerrero M. *Nat Clin Pract Cardiovasc Med.* 2009 Feb;6(2):112-9.

Polymeric drugs for efficient tumor-targeted drug delivery based on EPR-effect. Maeda H, Bharate GY, Daruwalla J. *Eur J Pharm Biopharm.* 2009 Mar;71(3):409-19.

Multifunctional micellar nanomedicine for cancer therapy. Blanco E, Kessinger CW, Sumer BD, Gao J. *Exp Biol Med (Maywood).* 2009 Feb;234(2):123-31.

Efficient siRNA delivery with non-viral polymeric vehicles. Kim WJ, Kim SW. *Pharm Res.* 2009 Mar;26(3):657-66.

Mucoadhesive polymeric platforms for controlled drug delivery. Andrews GP, Lavery TP, Jones DS. *Eur J Pharm Biopharm.* 2009 Mar;71(3):505-18.

Engineered polymers for advanced drug delivery. Kim S, Kim JH, Jeon O, Kwon IC, Park K. *Eur J Pharm Biopharm.* 2009 Mar;71(3):420-30.

Multifunctional and stimuli-sensitive pharmaceutical nanocarriers. Torchilin V. *Eur J Pharm Biopharm.* 2009 Mar;71(3):431-44.

Polymersome carriers: from self-assembly to siRNA and protein therapeutics. Christian DA, Cai S, Bowen DM, Kim Y, Pajeroski JD, Discher DE. *Eur J Pharm Biopharm.* 2009 Mar;71(3):463-74.

Dendrimers as versatile platform in drug delivery applications. Svenson S. *Eur J Pharm Biopharm.* 2009 Mar;71(3):445-62.

Engineering design and molecular dynamics of mucoadhesive drug delivery systems as targeting agents. Serra L, Doménech J, Peppas NA. *Eur J Pharm Biopharm.* 2009 Mar;71(3):519-28.

Emerging intra-articular drug delivery systems for the temporomandibular joint. Mountziaris PM, Kramer PR, Mikos AG. *Methods.* 2009 Feb;47(2):134-40.

Characterization and potential applications of nanostructured aqueous dispersions. Yaghmur A, Glatter O. *Adv Colloid Interface Sci.* 2009 Mar-Jun;147-148:333-42.

Recent developments in drug delivery to prolong allograft survival in lung transplant patients. Watts AB, Williams RO 3rd, Peters JI. *Drug Dev Ind Pharm.* 2009 Mar;35(3):259-71.

Drug delivery of siRNA therapeutics: potentials and limits of nanosystems. Reischl D, Zimmer A. *Nanomedicine.* 2009 Mar;5(1):8-20.

Ultrasonic-activated micellar drug delivery for cancer treatment. Hussein GA, Pitt WG. *J Pharm Sci.* 2009 Mar;98(3):795-811.

Pharmaceutical aspects of intranasal delivery of vaccines using particulate systems. Sharma S, Mukkur TK, Benson HA, Chen Y. *J Pharm Sci.* 2009 Mar;98(3):812-43.

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