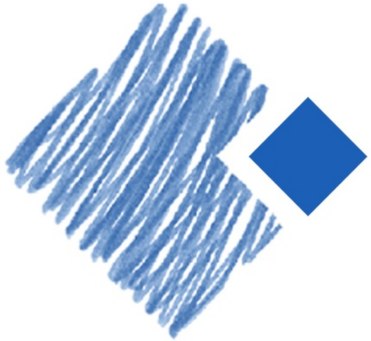

SocraTec R&D
We make it work

Patch development with new drugs versus generic development – principles and methods

Dr. Barbara Schug
SocraTec R&D, Oberursel , Germany
www.socratec-pharma.de

AGAH Workshop, The new European modified Release Guideline- from cook book to interpretation, Bonn, June 15th – 16th, 2015

Some basics

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Physico-chemical properties / conventional patches

- small molecule < 500kDa
- lipophilic
- potent
- therapeutic concept which requires low fluctuation

Skin controls release rate

- drug substance dispersed in adhesive matrix

Patch controls release rate

- rate controlling membrane between drug reservoir and skin

Currently marketed patches

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Year	Generic (Brand) Names	Indication
1979	*Scopolamine (Transderm Scop®)*	Motion sickness
1982	*Nitroglycerine (Nitroderm TTS®)*	Angina pectoris
1984	*Clonidine (Catapress TTS®)*	Hypertension
1986	*Estradiol (Estraderm®)*	Menopausal symptoms
1990	*Fentanyl (Duragesic®)*	Chronic pain
1991	*Nicotine (Nicoderm®, Habitrol®, Prostep®)*	Smoking cessation
1993	*Testosterone (Androderm®)*	Testosterone deficiency
1995	*Lidocaine/epinephrine (Iontocaine®)*	Local dermal analgesia
1998	*Estradiol/norethindrone (Combipatch®)*	Menopausal symptoms
1999	*Lidocaine (Lidoderm®)*	Post-herpetic neuralgia pain
2001	*Ethinyl estradiol/norelgestromin (OrthoEvra®)*	Contraception
2003	*Estradiol/levonorgestrel (Climara Pro®)*	Menopause
2003	*Oxybutynin (Oxytrol®)*	Overactive bladder
2004	*Lidocaine/ultrasound (SonoPrep®)*	Local dermal anesthesia

Source: modified from Wilson EJ, Three Generations: The Past, Present, and Future of Transdermal Drug Delivery Systems, May 2014

Currently marketed patches

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Year	Generic (Brand) Names	Indication
2005	*Lidocaine/tetracaine (Synera®)*	Local dermal analgesia
2006	*Fentanyl/iontophoresis (Ionsys®)***	Acute postoperative pain
2006	*Methylphenidate (Daytrana®)*	Atention deficit hyperactivity disorder
2006	*Selegiline (Emsam®)*	Depression
2007	*Rotigotine (Neupro®)***	Parkinson's disease
2007	*Rivastigmine (Exelon®)*	Dementia
2008	*Granisetron (Sancuso®)*	Chemo-induced emesis
2009	*Oxybutynin (Gelnique®)*	Overactive bladder
2010	*Buprenorphine (Butrans®)*	Chronic pain

To be kept in mind:
Several compounds show a problematic tolerability!

Source: modified from Wilson EJ, Three Generations: The Past, Present, and Future of Transdermal Drug Delivery Systems, May 2014

New patches

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Questions, which had to and still have to be answered

- PK / BA / BE after single dose application
- dose linearity/ proportionality
- risk of end-of-dose failure
- characterisation of how levels decrease after removal
- influence of absorption site
- risk of accumulation
- achievement of steady-state
- patch adhesion
- irritation and sensitisation

Initial development as patch

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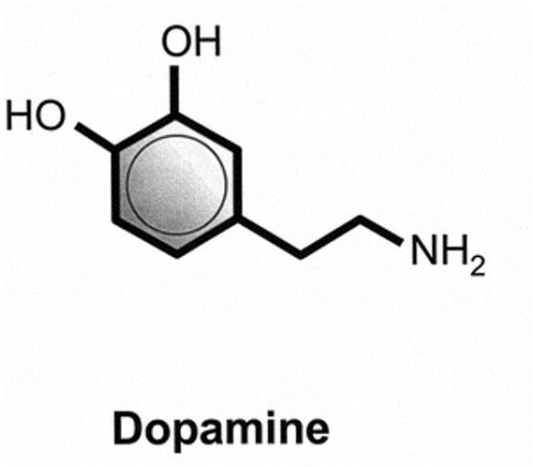
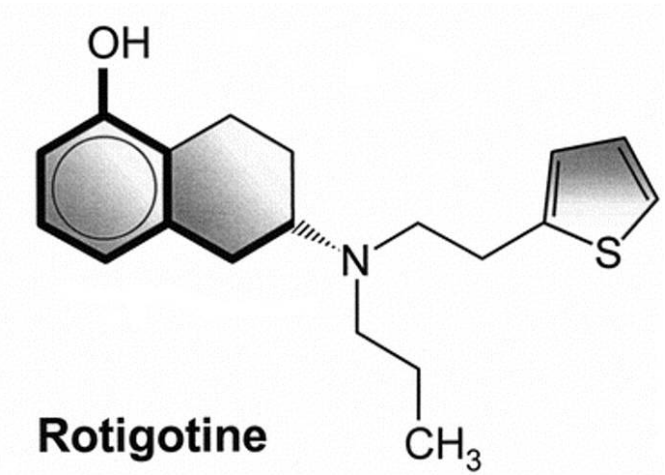
The rare case: rotigotine

- struktural similarity with dopamine
- high first-pass metabolism
- oral administration not meaningful



Dopamine



Rotigotine

Source: Pfeiffer RF, Neurology 2005, 65 6-10

Rotigotine – development program

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Summary of studies performed during early development

- ADME with i.v. administration in healthy subjects
- sequential repeated measurement design with increasing i.v. doses in PK/PD trial (patients)
  - dose finding done with i.v. administration
  - titration against the L-dopa dose needed
- early characterisation of absorption site
  - abdomen
  - flank
  - upper arm
  - shoulder
  - thigh
  - hip

⇨ all absorption sites demonstrate adequate systemic availability

Source: CDER Document: Application; Number: 21-658

PK – characterisation of rotigotine

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"Classical" PK-program due to systemic action after patch administration

- single dose
- multiple dose
- drug-drug interactions
- special populations
- different patches: bioavailability/ bioequivalence

Summary: rotigotine

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Relevant aspects of the clinical development program

- systemic availability is prerequisite for efficacy
- i.v. administration for proof-of-concept study and early dose finding
- transdermal administration to overcome first-pass metabolism
- "classical" PK programme
- "classical" PD programme
- characterisation of route of administration incl. influence of body area used for application

“Old” drug ⇨ “New” as patch

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Reference to the available data possible …

- pharmacokinetics
- efficacy
- safety

… but of limited value due to

- modified route of absorption
- modified extent of systemic availability
- modified metabolic pattern/ ratio
- modified peak-trough-fluctuation

Complicating factor: first-pass-metabolism!

Patch development for "old drugs"

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So-called "corridor" approach is a meaningful tool if

- the metabolic pattern - qualitatively and quantitatively – does not depend on route of administration
- the mechanism of action does not indicate that peak-trough-fluctuation is of relevance

Remaining questions to be answered on a case-by-case basis with additional studies on efficacy (and maybe safety)

Patch development

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New questions to be answered

- AUC_{0-T} > 90%
- influence of patient´s behaviour (e.g. shower, sauna, exercise)
- active substance utilisation (% absorbed) and residual (mass remaining in patch)
- patch area activity (%/cm^2) as a surrogate for thermodynamic activity
- cold flow

A lot of questions – a lot of effort

Population characteristics

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Characteristics of the study population for narrow therapeutic index drugs

- depending on the tolerability of the dose to be tested
- example rotigotine patch: dose of 1mg/d tolerated by healthy subjects, higher doses require patients (maximum dose 8mg/d)

Characteristics of the study population for opioids

- no relevant risk of developing drug addiction
- no respiratory disease
- no history of constipation
- expected good tolerability of antagonist (i.e. no high endorphine levels)

However, still a lot of side effects and high risk of drop-outs especially for long trials

Population characteristics

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Sexual hormones

- baseline levels to be considered in endogenous compounds (i.e. testosterone)
- hormonal effects to be considered especially for long trials
- sex-hormone binding globulin to be considered for subject selection (pre- or postmenopausal)

Reference to guidelines covering the question of endogenous compounds / baseline assessment

FDA – guideline: testosterone patches

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1. Type of study: Fasting
   Design: Single-dose, two-way crossover in vivo
   Strength: 4 mg/24 hr
   Subjects: Testosterone-deficient (hypogonadal) male volunteers.
   Additional comments:
   - Due to the risk of teratogenicity of testosterone, do not conduct the study in women.
   - The transdermal patch should be applied to clean, dry, intact, healthy skin. Avoid areas of skin that are oily, perspire heavily, or are covered with hair.
   - The transdermal patch should be applied to the same skin site (e.g., back, stomach area (abdomen), upper arms, or thighs only), as recommended in the approved reference listed drug (RLD) labeling, and worn for 24 hours.

Analytes to measure (in appropriate biological fluid): Testosterone in plasma (PK study only)

Please measure baseline testosterone levels at -12 and 0 hours before dosing. Use the mean of the pre-dose testosterone levels for the baseline adjustment of the post-dose levels. Baseline concentrations should be determined for each dosing period, and baseline corrections should be period specific. If a negative plasma concentration value results after baseline correction, this should be set to 0 prior to calculating the baseline-corrected AUC. Submit the baseline corrected and uncorrected data and statistical analyses to the Agency. Please refer to the Draft Guidance on Ergocalciferol Capsule for additional information regarding endogenous compounds.

Source: FDA Draft Guideline for Testosterone (Dec. 2014)

Population characteristics

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Applicable for all substances

- avoidance of intensely haired, hirsute body areas due to cross-sections through the skin

- avoidance of tattoos
- avoidance of scans and pathological changes of the skin

BA/ BE trial – typical setting

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Detailed advise to be given in the study protocol

"If possible, within one subject a comparable but not identical body area should be used for the subsequent patch applications in period II; if necessary the application to the contra-lateral site of the body (referring to the original application site) is permitted within one subject. In any case the area where the previous patch (period I) was applied to should not be used again. The body area, where the patch will be applied, should be visible for the subject. Thus, the patch will be applied in the upper chest region.

Any contact with the adhesive when applying the patch to the subject is to be avoided. The skin at the application site should be hairless, non-irritated and non-irradiated (non-sunburned). Hair at the application site should be clipped (not shaved). The application site will be cleansed with clear water before the patch is applied. No soaps, oils, lotions, alcohol or any other agents that might irritate the skin or alter its characteristics are allowed. The skin should be completely dry prior to patch application. Therefore, the skin should not be rubbed but dabbed slightly.

The transdermal system should be pressed firmly in place with the palm of the hand for 30 seconds, making sure that the contact is complete. Care should be taken that the complete patch is properly attached and pressed to the skin (the center of the patch including the drug and the over-tape area), especially around the edges."

Parameters to be determined

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Single dose trial

- C_{max}
- AUC of the dosing interval
- AUC after patch removal
- partial AUCs as representative metrics of the shape of the curve

Parameters to be determined

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AUC_{0-T} : Relevance for steady state

"Bioequivalence of TDDS should generally be assessed after single dose as well as after multiple dose application. A multiple dose study is needed unless a single dose study has been performed with the highest strength which has demonstrated that the mean AUC(0-τ) after the first dose covers more than 90% of mean AUC(0-∞) for both test and reference, and consequently a low extent of accumulation is expected."

Is this meaningful?
Controversial positions!

Relevance of residual drug content

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News collected from NBC

"An 8-month-old Maine boy who overdosed on powerful painkillers after sucking on a grandparent's used medication patch is raising alarms about the dangers of drugs that stick to the skin.

The unconscious, barely breathing child was rushed to a local emergency room, where doctors discovered a missing 50-microgram-per-hour fentanyl patch stuck to the roof of his mouth. He had to be treated with two doses of a quick-acting opiate antidote, said Thomas Clemence, a registered pharmacist at Central Maine Medical Center in Lewiston.

The boy survived the June scare, but the close call is prompting patient safety experts to warn parents, grandparents and other caregivers about potential hazards to kids posed by growing numbers and types of transdermal medications.

Government records show that at least four children have died and six have been hospitalized since 1997 after being exposed to just one type of transdermal drug, the fentanyl patch, which also sickened the Maine boy. Another three were exposed to the drug, but the outcome wasn't recorded, according to information from the federal Food and Drug Administration's adverse events reporting system."

How to determine the residual?

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FDA – Guideline for Industry

- surplus of drug is necessary but should be minimized e.g. using penetration entrances
- acceptance of amount of surplus depends on safety issues

EU – included in Guideline on quality of transdermal patches

- surplus should be minimized due to safety issues …
- … and to avoid misuse
- to be determined for all dosage strengths

In case of generic or hybrid applications the amount of residual should not exceed that of the reference product, unless scientifically justified

Source: FDA Guidance for Industry: Residual drug in transdermal and related drug delivery systems, August 2011
Source : EMA Draft Guideline on quality of transdermal patches, May 2012

How to determine patch area activity?

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Expressed in %/cm^2

- measure of the formulation´s intrinsic capability to release drug substance in vivo
- surrogate for "thermodynamic activity" or "effective concentration"
- example given in guideline
  - overall drug content 4,8 mg
  - 25 mg/h over 72 h ⇨ 1,8 mg absorbed (37,5 %)
  - patch size 15 cm^2
  - patch area activity 37,5 % / 15 cm = 2,5 %/cm^2

Indirect tool to determine appropriateness of a generic formulation development; i.e. patch area and total amount of drug needed to achieve bioequivalence

Generic patches should have either the same or higher patch area activity!

Behavioural effects

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Requirements of the preceding draft guidance published for consultation March 15, 2013

"In addition to conventional phase I studies skin irritation, sensitisation, phototoxicity, patch adhesion and, in general, the effect of sauna and sun cream on the patch adhesion should be investigated."

Final version – requirement for new patches only

"The investigation of in vivo adhesive performance will be usually part of the efficacy studies. The robustness of the product to normal human behaviours (e.g. moisture resistance to washing, showering, saunas, use of moisturisers and risk of removal during exercise and/or sleeping, possible transfer to partners or family) should be evaluated, as appropriate, based on risk analysis and the instructed conditions of use for the individual products."

No such requirement for generics!?

Influence of site of application

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Testing procedure for new drugs

- investigation of different sites to be used by patient, e.g. shoulder, breast, upper arm, abdomen, thigh, hip, etc.
- selection of site depends on pragmatic aspects like risk of detachment due to clothes (e.g. hip - trousers) and whether the patch is visible for the subject for control reasons

Open question: confirmatory or descriptive testing needed?

Influence of site of application

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Testing procedure for generic approval

- there is no reason to assume a product interaction
- no investigation of application site dependency needed
- comparable situation to be ensured for test and reference

Common approach: contralateral site!

Influence of site of application

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Example: low dose EE/ LNG contraceptive patch

- Comparison abdomen, buttock, upper torso

Ethinylestradiol

Parameter	% Geometric mean ratio (90 % CI)	
	Buttock vs. lower abdomen	Upper torso vs. lower abdomen
C_{max}	130 (113-151)	115 (99.2-133)
$C_{ss\ 48\text{-}168h}$	116 (101-132)	122 (107-139)
$AUC_{0\text{-}240h}$	124 (109-141)	121 (107-138)

Levonorgestrel

Parameter	% Geometric mean ratio (90 % CI)	
	Buttock vs. lower abdomen	Upper torso vs. lower abdomen
C_{max}	107 (89.9-127)	117 (98.0-139)
$C_{ss\ 48\text{-}168h}$	101 (86.1-118)	117 (99.5-136)
$AUC_{0\text{-}240}$	107 (91.2-124)	116 (99.6-136)

Source: Stanczyk et al, Contraception 2013

New example abaloparatide

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Similar to parathyroid-hormone related protein PTHrP)

- anabolic agent for treatment of postm
  osteoporosis
- bone mineral density ↑
- molecular weight 3960.6 Da
- no regular transdermal appl ation possible

„Transdermal Drug Delivery Systems"

Galenical solutions

- subcutaneous injection
- transdermal system equipped with 300 microneedles

Microneedles – "the future"

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- "Poke and Patch" microneedles pierce the skin before the drug containing formulation is placed on the skin
- "Coat and Poke" application of drug coated needles
- "Poke and Release": dissoluble microneedles
- "Poke and Flow" injection technique

Guideline applicable?

Source: Michael Wolff, UCB

Many thanks to ...

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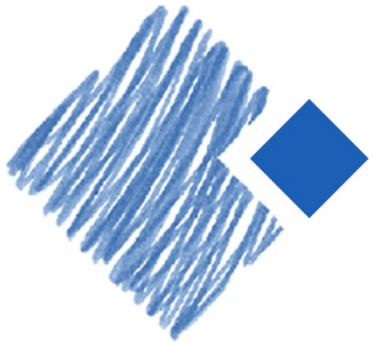
Annika Dax for contributing with a literature search,

Marina Breit for excellent technical assistance

… and to all who contributed to the trials presented !



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Concepts in Drug Research and Development

Contact:

Dr. Barbara Schug

Phone: +49-6171-5857-111
barbara.schug@socratec-pharma.de

André Warnke

Phone: +49-6171-5857-122
andre.warnke@socratec-pharma.de

Fax +49-6171-5857-25; Postal Address: Im Setzling 35, 61440 Oberursel (Taunus), Germany