Cool Approaches to Delivery of Medicines

Bozena Michniak-Kohn, Ph.D.,
M.R.Pharm.S.

Ernest Mario School of Pharmacy/ NJ Center for Biomaterials, Rutgers-The State University of New Jersey, Piscataway, NJ
Materials and Drugs have been used before ........
2000 BC to 1600 AD: Natural materials/actives used without major refinement.

1600 to 1860: Natural materials/actives used with minor refinement and processing.

1860 to 1900: Initial breakthroughs in metallurgy, initial use of synthetic polymers.

1900 to 1980: Materials sciences create a wealth of new materials with optimized performance characteristics. The current biomaterials are created.

1980 to 2015: Materials with biologically active interfaces revolutionize the treatment of aging and trauma related diseases. Tissue engineering approaches are developed into clinically useful therapies. Actives are incorporated.

2015 and after: Science unravels the biological mechanisms of tissue self-assembly and regeneration. Body parts can now be reconstructed using biological mechanisms with only minimal assistance from exogenous materials. Actives in small multicomponent MEMS/Nanopharmaceutical devices- more specificity to disease target(s).
History of Drugs

- 1817: Article about morphine effects published
- 1884: Rabies vaccine for dogs
- 1915: First aspirin tablets made
- 1924: Barbiturates used
- 1928: Penicillin discovered
- 1940: Vitamin B synthesized
- 1946: Penicillin synthesized
- 1955: Polio vaccine licensed
Progression of Stent Development

• Metal stents
  – ’93 Palmaz-Schatz stent FDA approved for coronary use

• Antiplatelet or anticoagulant coated metal stents
  – ’00 Phosphorylcholine coated and heparin coated stents FDA approved

• Resorbable polymeric stents
  – ’00 Tamai et al. first to implant resorbable PLLA coronary stents in humans using a heated balloon technique

• Anti-restenosis drug-eluting, coated stents
  – ’03 CYPHER™ Sirolimus-eluting coronary stent FDA approved

• Resorbable, radio-opaque, drug eluting stent
  – A natural progression to an optimal stent therapy
Resorbable stents - Examples

Stack et al. ‘88 Poly(L-lactic acid) stent

Yoklavich et al. ‘96 PLA/TMC stent by J&J Cordis molded by Tesco Assoc.

Tamai et al. ‘00 Zigzag helical coil Poly(L-lactic acid)
Deployed in humans

Biosensors and Guidant Prototype Self-Expanding Stent
The process started with the identification of desirable polymer properties by the customer, a stent company. Searching within a library space of over 10,000 possible compositions, a polymer with optimized properties was found, synthesized and tested within 9 months.

The combinatorially designed material performed as predicted. A fully deployable stent could be fabricated upon first trial.

Visibility by fluoroscopy of the polymer stent (top) and a market leading steel stent (bottom).

Hemocompatibility in the pig coronary model: 3 weeks post implantation, there was no evidence for necrosis, inflammation, thrombosis or restenosis.
Nondeforming Slide and Lock Stent
TyRx Pharma Surgical Mesh
Hernia Device- TyRx Pharma, Inc.

• Bioresorbable polymer coated surgical mesh product for hernia repair & other abdominal fascial or muscular deficiencies requiring addition of a reinforcing/bridging material.

• Polymer coating-tyrosine polyarylates
Incorporation of drugs into device

- Jan 9th, 2006: Anesthetic Coated Surgical Mesh received designation as “Combination Product with Device Primary Mode of Action (PMOA). Faster regulatory timeline for the product. Clinical trials Spring 2006*
- Jan 17, 2006: Antibiotic eluting surgical mesh is second in series of combination products which TyRx hopes to launch in 2006*

*According to TyRx Pharma press releases
Human Skin & Drug Delivery Devices
Newest approaches to overcome skin barrier

• Stratum corneum, thinnest uppermost layer of skin responsible for majority of barrier property of skin

• Decrease or eliminate barrier by making holes in skin or applying electric current to skin—next slides will provide examples of approaches.
Cool Click™-Bioject

Cool.click™ (June 2000) works by the same principle as all of Bioject's needle-free injection systems: by forcing liquid medication through a tiny orifice that is held against the skin. This creates a very fine, high-pressure stream of medication that penetrates the skin, depositing medication in the tissue beneath.
Cool.Click™

• Bioject developed needle free injection for delivery of Saizen® recombinant human growth hormone
• Injector can deliver over 3000 doses
• Less discomfort than traditional injectors
Radio-frequency (RF) Ablation

- Electric current at 100-500 kHz
- Microelectrodes placed on skin causes local heating, liquid evaporation, cell ablation
- Small microchannels form across stratum corneum and epidermis
- Useful for hydrophilic drug delivery
- Examples include Human Growth Hormone
- MEMS (Micro Electro Mechanical Systems): Small droplets of hGH “printed” onto 1.4 cm² transdermal backing liner and then dried
Cell Ablation Technology-\textsuperscript{RF}
Microchannels (less than 100 microns)

www.transpharma-medical.com
ViaDerm System-Transpharma Medical

• The microelectrode array is snapped onto the control unit
• Light pressure creates RF-Microchannels within a few seconds
• Beep tone and light indicate RF-Microchannels present

www.transpharma-medical.com
ViaDerm System

- Release button ejects disposable microelectrode array from treatment site
- Release liner removed from patch and drug patch is applied to skin
How about needles????

BUT….these are different needles that do not hurt…..
Microneedle Approach

• Minimally invasive, painless
• Consist of small arrays of needles
• Needles made of: silicon, metal, biodegradable polymers
• Uses MEMS (Micro Electro Mechanical Systems): microfabrication, micromachining, microelectronic circuitry
Biodegradable Polymer Microneedles

• Advantage is that if they break in the skin-biodegradable & biocompatible
• Poly(lactic acid) (PLA), poly(glycolic acid) (PGA) or PLGA used
• Beveled- tip needles, length 600µm, 10 µm tip.
• 120 needle arrays made of PGA
• Images on next slides
Microneedles for transdermal delivery

Needles 300 and 600 microns in length are used to deliver drug solutions through the stratum corneum. The skin is pierced with the needles with a force of 5-10 lbs in 20 sec. This painless delivery method is being investigated for delivery of macromolecules and vaccines.
Examples

- Macroflux® skin patch technology (Alza)
- Array of solid titanium microneedles which can either be coated with drug to give bolus effect or with reservoir to give passive delivery or with iontophoresis to enhance delivery
- Length 200μm, width 170μm and thickness 35 μm.
- 321 microneedles/cm² on a 2cm² patch
- Useful for delivery of large molecular weight drugs ex. Desmopressin 1100Da (intranasal & oral gives low bioavailability) for diabetes
Macroflux® Patch

J. Controll. Rel. (2004), 97, 503
How about applying current????

BUT….this current application does not hurt or burn…..
**FIGURE 1**

Vyteris Electrophoresis Device
Iontophoretic device

Cathode

Skin

Anode

Systemic circulation
Based on reverse iontophoresis:

- Glucose pulled through the skin by charged molecules
- The ions migrate to the anode (+) and cathode (-)
- Glucose reacts with glucose oxidase to form hydrogen peroxide
- The reaction produces an electrochemical measured by the AutoSensor
- Reverse iontophoresis: insulin delivery method in response to glucose

GlucoWatch G2 Biographer

www.glucowatch.com
Combination of insulin delivery & sensor

- Medtronic MiniMed Paradigm insulin pump combined with Becton Dickinson glucose monitor
- Device cleared by FDA in July 2003
- Integrated system reduces errors & enhances convenience for patients
What’s next???

- Devices applied in or on the body - replace tissue, release drugs
- Drugs will be more specific to disease state (siRNA)
- Drug release in controlled manner - pumps, release devices
- MEMS, tissue engineering and nanotechnology will provide novel approaches & concepts
- Future will be a device, drug(s), delivery system with or without a (bio)sensor i.e. a multicomponent combination device
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