A Formulation-Based Approach to Infection Prevention

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Introduction

Professors of Pharmaceutics mix and make the actual medicines into dosage forms – tablets, caplets, liquids, creams, ointments. They produce the "recipes" for the drugs.

Our job: to make sure that we can get the right amount of drug to the right place in the body at the right dose at the right time so it can do its job.

What is the most effective way to do that?

Targeted drug delivery

Delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body and even some cells relative to others.

Largely founded on nanomedicine, which plans to employ nanoparticle-mediated drug delivery in order to combat the downfalls of conventional drug delivery

We can make nano-sized drug delivery carriers so the drug is trapped within particles that are 100-200 nanometers in dimension.

For wound care, we need lipid-based nanocarriers.

Application: Topical antiseptics

Initially looking at skin antisepsis:

- pre-surgery to prevent SSI
- to reduce wound bioburden

Increased effectiveness of the skin antiseptics should ultimately decrease the use of antibiotics.

Topical antiseptics are preferable to antibiotics because less likely to induce resistance, owing to their unspecific mode of action and the high concentrations in which they can be used.

Topical antiseptics can prevent biofilm build-up as well as antimicrobial action.

Challenge: unknown depth of penetration and unknown effective concentration

Transdermal delivery routes: 3 pathways

Stratum corneum is the outermost layer of skin; it's the major barrier. 3 ways drugs can get though it:

1. The paracellular path: tortuous route through the membrane
2. The transcellular path
3. The transappendageal path: follicular route

Transappendageal pathway is ideal, as hair follicles penetrate deep into the skin. But follicles encompass only 1% of total skin area, and also varies per individual depending on follicle density and size. Other factors that affect transport ability of transappendageal pathway are other fill materials, such as sebum and desquamated cells, in addition to cultural habits and weather conditions (sweat, deodorant, etc.)

Microorganisms reside both on the skin surface as well as in hair follicles and lower skin depths.

Endogenous infections arise from endoflora from skin, mucous membranes and hollow viscera, seeding from another infection. Follicles also present a unique microbial niche for microorganisms within the skin.

When the barrier is breached, commensal microoganisms may therefore persist at the site. Therefore, effective and rapid permeation of the antimicrobial into the deeper layers of the skin may prevent infection.

Our goal: Try and increase how much drugs penetrate into the skin and influence where they go.

Penetration enhancers

Terpenes are the major ingredient in essential oils. They bind in large quantities to SC and act as skin penetration enhancers by

- increasing drug partitioning into the skin (solvent effect)
- enhancing drug diffusion
- reversibly disrupting lipid bilayers

Furthermore, these volatile compounds may alter the thermodynamic activity of the drug due to evaporation of terpenes like alcohol

Skin permeation studies are done by putting the formulation to be tested on top of a skin sample (varying depths) and then measuring below what penetrated at what depth.

> ***Case study: does eucalyptus oil help penetration?*** Tested with above methodology. **Conclusion:** it did. Even after 2 minutes, drugs were found in a deeper layer of the skin. It seemingly did not work as well as crude oil for penetration effectiveness, however. Olive oil, however, did not work as well as eucalyptus oil in permeation studies.

Nanotechnology and targeting

Goal: to target drugs to the hair follicles and have them accumulate and remain there. Sustained release and preferential targeting.

Unique size dependent properties of lipid nanoparticles offer possibilities for delivery of drug for both controlled release and site specific drug delivery.

Control of particle size and surface properties determines how delivery system interacts with target.

Example: Triclosan targeting via nanoparticle

Triclosan is difficult to work with. It doesn't dissolve in water, BUT it does form well into a lipid nanoparticle. We can get more triclosan into the skin by forming it into nanoparticles.

Process: melting of lipids and dissolving drug into the lipid > hot aqueous surfactant solution > high shear homogenization > hot pre-emulsion > ultrasonication > hot nanoemulsion > solid lipid nanoparticles.

When emulsion particle size is decreased to the nano level, it becomes clear (no longer diffuses light) and you can get a nice, even particle size distribution.

Much higher percentage of triclosan retained in skin when delivered by nanoparticles.

Example: Chlorhexidine targeting via nanoparticle

Also increases skin penetration.

We've tried incorporating chlorhexidine into Altrazeal gels in saline – what happens?

- Chlorhexidine solution is crosslinked with gel and not released
- Chlorhexidine in nanoemulsions can be incorporated and released

Where we are now with this work

1. Successful formulation of potentially synergistic combination of ingredients into nano-sized delivery systems (solid and liquid)
2. Preferential increase in delivery of antimicrobial to hair follicles
3. Incorporation of nanoemulsions into porous flexible gel structure, sustaining release of CHG