

Critical Parameters Concerning the Design of a Pharmaceutical Dosage Form for Potential Use Against Bioterrorism and Chemical Weapons: AN OVERVIEW ON CURRENT CONCETS AND FUTURE PROSPEVTS

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INTRODUCTION

- As a consequence of increasing risk of war and terrorism with chemical or biological warfare agents, it is a challenging issue to develop optimum Protective pharmaceutical dosage forms against various forms of war and terrorism.
- For efficient protection, development of pharmaceutical systems providing optimal efficacy, worldwide usage and large-scale production is required

KEY POINT TO BE CONSIDERED

In order to achieve the development of a proper dosage form with;

- Optimal efficacy
- Efficiency
- Availability.

some key points, other than scientific and technical challenges and considerations, should be considered carefully during the formulation phase:

- Locally-abundant and inexpensive material should be used for cost effectiveness and readily-availability
- Dosage form should be prepared and applied easily
- Simple and non-problematic administration is necessary, because in most cases, it will be difficult to reach health care centers after an attack while most warfare agents' effects start immediately upon exposure
- One should be able to self-administer the dosage form without professional assistance
- A long shelf-life and high stability in various extreme conditions are of great importance for a safe, economic and practical dosage form
- Chemical compatibility within the system is required
- Packaging and transportation of large-scale produced dosage forms should be possible to reach all regions under threat, rapidly

Recent study and advances in defence technology

- Chemical agents for prophylaxis
- Medical countermeasures for vesicant agents
- Advanced anticonvulsants
- Low-cost adsorbents in order to decontaminate water and natural Resources
- Personal decontamination products

Personal Decontamination Products:

- Passive and active topical protectants
- Alcohol based sanitizers
- Longerlasting formulas that kill infectious germs on contact as well as work to prevent further infections

Passive Skin Protectants

Ointments and creams are preferred pharmaceutical dosage forms as a pre-attack measure against chemical agents (such as extremely lethal vesicants and nerve agents)

- "Barrier Cream" approach
- Goal: To prevent chemical agents' contact with the skin

RSDL (Reactive Skin Decontamination Lotion)

- Developed and licensed in Canada
- Approved by FDA recently
- For use in military
- To remove or neutralise chemical warfare agents and T-2 fungal toxin from the skin
- Used by applying to exposed skin as soon as possible after exposure to a chemical agent
- The lotion is impregnated in a sponge pad packaged a single-unit in a heat-sealed-foil pouch

SERPACWA

(Skin Exposure Reduction Paste Against Chemical Warfare Agents)

- Goal: To prevent exposure to both chemical and biological agents
- The proposed Skin Protectant Technology has been currently approved by the FDA for military use only
- When used in conjunction with appropriate protective clothing, protects soldiers from skin exposure to chemical warfare agents
- Topical Skin Protectant (TSP) cream/paste contains polytetrafluoroethylene resin compounds that are similar to the substances that coat non-stick cooking utensils (50:50 mixture of two high molecular weight fluorine containing polymers: polytetrafluoroethylene, PTPE, and perfluoroalkyl-polyether, PFPE)
- TSP cream/pastes function as a physical barrier between the skin and any potential leakage from chemical protective gear, the so-called MOPP suit
- TSP is not a replacement for use of any level of protective gear, but intended to compliment and provides a secondary barrier

Advantage

- Good occlusive property
- Easy self-application
- Large-scale production possible
- Covering of skin for long duration possible

Disadvantages

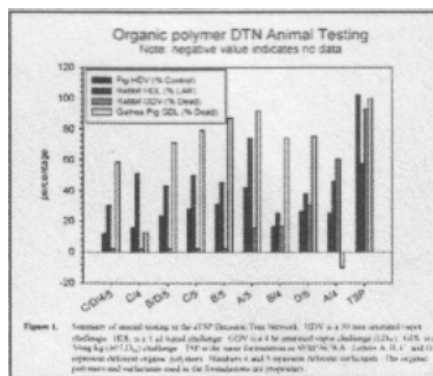
- Must be applied very shortly after exposure
- Efficacy limited, does not destroy or adsorb the chemical agent but only prevent from reaching skin layers
- Repeated application is necessary for efficient protection

Povidone - Jodine (PJ)

- Widely used product as an antiseptic agent and for the treatment of thermal burns its protective use has been suggested against chemical warfare agents such as potent vesicants and powerful alkylators (Wormseretal. 1997,2000)
- Post-exposure treatment with PJ ointment protected against skin ulceration of vesicant agents depending on the interval between exposure and the type of irritant
- The fact that proteolytic activity is involved in inflammatory processes, and lead to skin lesion and necrosis mainly through the separation on the dermo-epidermal Junction
- Therefore, the protective effect of iodine may stem, in part, from the reduced skin collagenase activity. In fact, Wormsar et al (2002) recently reported the strong inhibitory activity of PI, or its active ingredient iodine, on three types of collagenases

Active Topical Skin Protectants

- New active formulations consisting of a base cream and active moiety that act both as protective barrier and an active destructive matrix against chemical warfare agents
- Base cream: Perfluorinated-polyether oil and polytetrafluoroethylene solids (the same as SERPACWA)
- Active moieties (150 different components have been tested by USAMRICD), including organic polymers (leading active moities), enzymes, hybrid organic inorganic materials, polyoxymetalates, inorganic composites, inorganic oxides, metal alloys and small organic molecules
- Active against chemical weapons In pig, rabbit and guinea pig models



Braue et al. "Activa Topical Skin Protectant Nearing Transition to Advanced Development" 23rd Army Science Conference. 2-5 December 2002. Orlando, USA

Active Nanoparticles

- Koper et al (1999)
- Demonstrated the potential for highly "Reactive Nano Particles" (RNP) to absorb destructively highly toxic warfare agents such as GA, GB, HD and VX
- Described RNP as representing a new class of nanoscale particles of metals and metal oxides that differ from other nanoparticles in reactivity and crystalline morphology

Reactive Metal Oxide Nanoparticles

- The potential for incorporating RNP into a protective barrier skin cream has also been demonstrated
- Chemical compatibility of nanoparticles in cream and suspension form ensured
- Nanoparticle oxides synthesized include
 - Aerogel-prepared MgO (AP-MgO)
 - Aerogel-prepared CaO (AP-CaO)
 - Conventionally-prepared MgO (CP-MgO)
 - Conventionally-prepared CaO (CP-CaO)
 - Aerogel-prepared TiO₂ (AP-TiO₂)

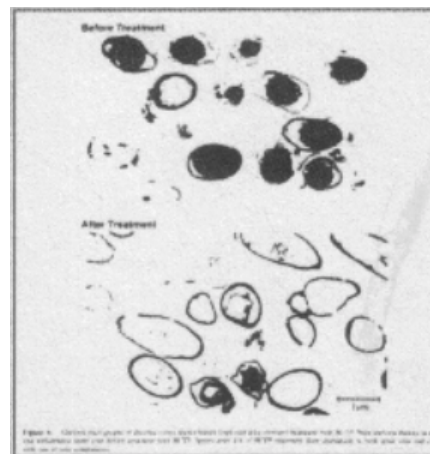
Koper et al (2002) also reported formulations of nanoscale powders possessing antimicrobial properties made of simple, nontoxic metal oxides MgO and CaO in nanocrystalline form, carrying active forms of halogens (MgOCl₂, MgOBr) when contact with vegetative cells of E.coli, B.cereus, B. globigii, >90% were killed within a few minutes spore forms of the Bacillus species were decontaminated within several hours

Disadvantages

- Sophisticated material- difficult to obtain
- Expensive chemicals and solvents involved
- Large-scale production not yet achieved
- Time-dependent physical stability of nanoparticles still unknown
- Lack of animal testing

Protection From Biological Treats-Nanoemulsions

- Nanoemulsions with broad-spectrum sporicidal activity against
- Badlius species
- Oil droplet of 400-800 nm size
- Able to fuse with and subsequently disrupt the membrane of a variety of different pathogens
- Electron micrographs of Bacillus cereus spores before and after treatment
- Spores after 4h BCTP treatment show disruption in both spore coat and cortex, with loss of core components



Hamouda et al. "A novel surfactant nanoemulsion with broad-spectrum sporicidal activity against Bacillus species" Journal of Infectious Disease. 180, 1939-49, 1999

Dacontamination of Resources

- Pollution of natural resources, like water, is another cause for mass casualties after chemical or biological attacks
- Low-cost adsorbents are necessary to decontaminate natural resources after attacks
- Chitosan, was reported to have excellent properties of adsorption of heavy metals from water

CONCLUSION

- It is wed accepted that all nations around the world are threatened by biological and chemical attacks
- It is a challenging issue and growing need, therefore, to develop protective and efficient pharmaceutical dosage forms
- Effective measures should be taken by local regulatory authorities and governments in order to facilitate the development of such delivery systems
- Worldwide cooperation in sharing scientific and clinical data is also necessary
- Otherwise, particularly in case of biological warfare or bioterrorism, a high cost will be paid, more or less by everybody in the world
- Countries should provide effective and conscious project supports to universities and academic and industrial research institutions in order to develop more efficient, less expensive and easier-to-ad minister dosage forms that can be used against chemical and biological warfare.

REFERENCES

- <http://www.mmt.kmi.com>
- <http://medchembio.detrack.army.mil/MedChem/MedChemResearch.html>
- <http://www.fda.gov/bbs/topics/NEWS/2003/NEW00888.html>
- http://www.medscape.com/viewarticle/406719_25
- Wormser U, Brodsky B, Green BS, Arad-Yellin R, Nyska A (1997) Protective effect of povidone-iodine ointment against skin lesions induced by sulphur and nitrogen mustards and by non-mustard vesicants- Arch Toxicol 71:165-170.
- Wormser U, Sintov A, Brodsky B, Nyska A (2000) Topical Iodine preparation as therapy against sulphur mustard- induced skin lesions. Tox App Pharmacol 169, 33-39.
- Wormser U, Brodsky B, Reich R (2002) Topical treatment with povidone-iodine reduces nitrogen mustard- induced skin collagenolytic activity. Arch Toxicol 76, 119-21.
- Braue EH, Graham JS, Snider TH, Doxzon BF, Boecker JD, Miller EC, None TL, Lumpkin HL, Hall RL, Hobson ST (2002) Proceedings of the 23rd Army Science Conference, Orlando, USA
- Braue EH (1999) Development of a reactive topical skin protectant. J Appl Toxicol 19, Suppt 1 S47-53.
- Koper O, Lucas E, Klabunde K (1999) Development of reactive topical skin protectants against sulfur mustard and nerve agents. J Appl Toxicol 19, Suppt 1 S59-70.
- Koper OB, Klabunde JS, Marchin GL, Klabunde KJ, Stoimenov P, Bohra L (2002) Nanoscale powders and formulations with biocidal activity toward spores and vegetative cells of bacillus species, viruses, and toxins- Curr Microbiol 44,49-55.
- Hamouda T, Hayes MM, Cao Z, Tonda R, Johnson K, Wright DC, Brisker J, Baker JR, (1999) A novel surfactant nanoemulsion with broad-spectrum sporicidal activity against Bacillus species. Infect Dis 180, 1939-1949.
- Babel S, Kumiawan TA, (2003) Low-cost adsorbents for heavy metals uptake from contaminated water, a review J Hazard Mater B97,219-243.