ABSTRACT

The skin is the first line of defence against the invasion of diseases and external objects and is the most significant organ in the human body. A cutaneous wound is an injury to the skin that affects even the soft tissues around. These can either be excisional or incisional where the incisional wounds are more prevalent and frequently include complex metabolic alterations. Many underlying factors contribute to the failure of treatment of such complicated wounds to move through a systematic and planned healing stage. Therefore, it is difficult and unavoidable to restore anatomical structure and function in the injured area. However, healing of these wounds is necessary in order to lessen the severe socio-economic burden created on the society.

Such complex wounds occur in the feet due to pressure (Pressure ulcers), accidental trauma to the feet, prolonged and unmanaged hyperglycemic conditions (Diabetic Foot Ulcer). High exudate discharge, necrotic tissues, a lack of gaseous exchange, impaired wound healing due to a lack of angiogenesis, abnormal toe brachial index, higher infection on site, poor inflammatory response, anatomical changes in the feet, variations in pH, and temperature are just a few of the difficulties complex wounds present. Currently employed conventional treatment would not treat the complexities in such wounds. Hence addressing these issues with novel strategies and adjunct therapy is essential to provide a wholesome treatment

Through this study, the property of natural and synthetic polymers in the preparation of hydrogel to treat complex wounds was extensively studied. Natural polymers that are biocompatible, biodegradable, and anti-microbial and those that mimick the extracellular matrix such as collagen, cellulose,

chitosan were considered for the formulation. L-glutamic acid, a precursor in the synthesis of l-proline was included. L-proline, an imino acid is one of the major constituents of type I collagen. Carboxymethyl cellulose served as a cross-linker and rendered stability to the hydrogel. Collagen, having extracted from a freshwater piscine source, *Pygocentrus brachypomus,* was subjected to extensive characterization. The extraction conditions were optimized to be pH-1.9, temperature-22°C, time-37hrs and solid-liquid ratio- 1:30 to obtain the maximum yield of 23.15% using Central Composite Design (CCD) in Design expert software. Extensive characterization was performed on the extracted collagen. Chitosan, Cellulose and L-glutamic acid were subjected to UV and FTIR characterization.

The heteropolymeric hydrogels (Hyd-1 and Hyd-2) with polymers and cross-linking agent were then formulated and the physico-chemical properties of the hydrogels were studied. The biocompatibility, biodegradability, and biomedical potential of the prepared heteropolymeric hydrogel were analyzed for wound healing and were affirmed for its potential. The formulated Hyd-2 possessed 475% swelling ability, 96% *in vitro* degradation property and exhibited release pattern till 480 minutes. Upon incorporation off the L-GA in Hyd-2, an increased healing rate of 80% was observed in the wound scratch assay.

Layers of the skin were modeled as a three-dimensional rectangular block to mimick the feet such as stratum corneum, epidermis, dermis, subcutis using COMSOL Multiphysics modelling and simulation tools. Thickness and electrical conductivity for each of these tissue layers were assigned. A cylindrical wound with definite dimension (incisional type) was modeled extending to the depth of the dermis region. The wound bed was assumed to be filled with the formulated hydrogel assigning the density and dynamic viscosity to be 1200kg/m^3 and 4.5e^{-2}Pa.s. A dermal patch was also

modeled to provide electrical potential which a circular electrode. When simulated, the EF generated were parallel to the endogenous EF and the TEP. This offers the advantage of providing the TEP to be activated and migration of inflammatory cells can be initiated. Prognostic stages of each wound vary depending on the cause, treatment mechanism and environmental factors and is therefore generalised during simulation.

During the simulation, potential difference in the wound carried over by the ions at the wound site was measured for every variation in the applied minimum voltage (30mV). The applied voltage was lower than the trans-epithelial potential (60mV) of the normal skin surface. Electroanalysis through stationary interface and diffusion pattern of the cells from the walls of the intact skin to the wounded area was studied by employing Multiphysics modules of fluid mechanics and transport of chemical species. The velocity, pressure and concentration profile in the stationary interface was studied and that it followed a projectile parabolic flow pattern and the pressure points being concentrated at all the edges of the geometry considered. Concentration profile from the time dependent analysis exhibited a projectile diffusion behavior.

Through this study, an ideal wound dressing with electrical stimulation and the characteristics of the formulated hydrogel to treat a complex wound was conceptualized. The work can further be extended to fabricate the electrical patch that would deliver the desired electrical potential to constrict the wound size from the ulcer bed and to validate the electroactive wound dressing in full thickness skin defect animal models.