Pharmaceutical applications of Pheroid™ technology

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"kan jy sien hoe ver het ons gekom
in die sirkels van die tyd
met ons medaljes en ons wonde
stap ons saam die drumpel uit
ongeskonde…."

Uit Blou aarde; Johannes Kerkorrel (1985)

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ABSTRACT

For a drug to have a therapeutic effect, it has to reach its site of action in sufficient quantities. The Pheroid™ drug delivery system enhances the absorption of drugs in various pharmacological categories and is the focus of this study. A number of patents are registered in various countries to protect its application. Pheroid™ technology is trademarked, but may for ease of reading, be called Pheroid(s) only. The Pheroid™ itself is composed of an organic carbon backbone composed of unsaturated fatty acids with some side-chain interactions that result in self-emulsifying characteristics. The resulting vesicles and nano-sponges can entrap hydrophilic, hydrophobic or amphiphilic compounds for biomedical and agricultural application and can be manipulated as to loading ability, mechanical resistance, permeability, size and solubility.

Pheroid™ was investigated for its potential use in the areas of vaccines, peptide drugs, topical products and cosmeceuticals, antimicrobial treatments and agriculture. In all of these areas, the Pheroid™ has indeed shown applicability: the results showed improved uptake and/or efficacy of the entrapped chemical or biological compounds after administration by a number of administration routes. For oral administration, a precursor format, the pro-Pheroid™, was used, wherein the vesicles and/or sponges are formed post-administration.

Proof of concept studies on the *in vivo* absorption and bioavailability, as well as studies on *in vitro* efficacy of Pheroid-based formulations were carried out for antimicrobials, such as tuberculosis drugs, antimalarials and antiretrovirals. In all cases, the *in vitro* efficacy of the active compounds was increased, compared to well-known standard drug treatments. In a phase I bio-equivalence study, a Pheroid™-containing combination formulation was compared against the comparative market leader. The results demonstrated that the bioavailability of the active compounds in the Pheroid™ was at least as good but mostly significantly better than that of the comparative medication. In addition, the incidence of side-effects was decreased in the case of the Pheroid™ formulations. Furthermore, *in vitro* results indicate that drug resistance can at least partially be negated. Pheroid™ technology may also be capable of protecting labile drugs such as peptides against degradation and increasing efficacy so that lower dosages can be administered less frequently and with fewer side effects.

Based on *in vitro* and *in vivo* results, a number of products are currently in development. The application of Pheroid ™ technology is potentially limitless and includes such areas as TB, malaria, cancer, AIDS, gene delivery, vaccines, patented medicines and generics and agriculture.

Keywords: delivery system, Pheroid™ technology, cosmetics, anti-infective, vaccines, peptides, plants.

UITTREKSEL

'n Geneesmiddel kan slegs terapeuties effektief wees indien dit sy teiken in genoegsame hoeveelhede bereik. Die Pheroid™ geneesmiddel afleweringsisteem verhoog die absorpsie van verskillende klasse geneesmiddels en is die kern van die studie. 'n Aantal patente wat handel oor die verskillende toepassings van Pheroid™ tegnologie is in verskillende lande ingedien en is reeds in etlike lande geregistreer. 'n Handelsmerk bestaan rondom Pheroid™ tegnologie, maar die ™-simbool word soms weens tegniese of ander redes weggelaat. Pheroid™ bestaan uit 'n organiese koolstof ruggraat wat opgebou is uit onversadigde vetsure. Syketting interaksies van die vetsure is vir self-emulsifiserende gedrag verantwoordelik. Die vesikels en nano-sponsies wat so ontstaan is in staat om hidrofiele, hidrofobe en amfifiliese substanse vas te vang of te verpak vir biomediese an landboukundige toepassings. Die belading, meganiese weerstand, elastisiteit, penetrasie deur biologiese grense soos die vel en selmembrane, grootte en oplosbaarheid van die Pheroid™ kan gemanipuleer word.

Die potensiaal van Pheroid™ tegnologie vir gebruik op die gebied van entstowwe, peptied geneesmiddels, topiese produkte en kosmetiek, antimikrobiese middels en landboukundige middels is ondersoek. Op al die gebiede het die Pheroid™ wel bruikbaar blyk te wees: die resultate dui op verbeterde absorpsie en doeltreffendheid van die chemiese en/of biologiese middels onafhanklik van die toedieningsroete vir die Pheroid™–verpakte substans of middel. Vir mondelinge toediening is 'n voorloper Pheroid™, die pro-Pheroid™, ontwikkel.

Konsep studies oor die *in vivo* absorpsie en biobeskikbaarheid, asook *in vitro* effektiwiteit van Pheroid™-gebaseerde formulasies van tuberkulose middels, anti-malaria middels en antiretrovirale middels is ondersoek. In alle gevalle het die *in vitro* doeltreffendheid van die geneesmiddels verhoog in vergelyking met standaard behandeling. 'n Pheroid™-gebaseerde kombinase formule van tuberkulose middels is met die vergelykbare markleier in 'n fase 1 bio-ekwivalensie proef vergelyk. Die resultate wys dat die Pheroid™ net so goed maar in meeste gevalle beduidend beter as die markleier gevaar het. Daarby het die voorkoms van newe-effekte in die geval van die Pheroid™ behandeling verlaag. *In vitro* resultate dui ook daarop dat geneesmiddel weerstandbiedendheid minstens gedeeltelik opgehef kan word. Die tegnologie mag ook bydra in die beskerming teen degradering van labiele geneesmiddels, soos peptiede.

Gebaseer op *in vitro* en *in vivo* resultate is 'n aantal produkte tans onder ontwikkeling. Die toepassing van Pheroid™ tegnologie is potensieel onbeperk en sluit sodanige gebiede soos tuberkulose, malaria, kanker, VIGS, geen aflewering, entstowwe, generiese medisyne en landbou in.

Sleutelwoorde: aflewering sisteem, Pheroid™ tegnologie, kosmetika, anti-infektief, entstowwe, peptiede, plante.

OUTLINE OF THESIS

This thesis documents the initial development of Pheroid™ technology. The technology started out as a single topical product for the effective relief of psoriasis. The psoriasis product was formulated and commercialized by P.J. Meyer and S. Zall as Exorex or Linotar. An analysis of the product showed that it contained submicron sized stable vesicles. These vesicles were subsequently characterized as a delivery system and trademarked as Pheroid™. It is the potential of this delivery system that is the focus of this study. In the course of the thesis this technology, the particles or vehicles contained within the system and its pro-form, may be referred to as Pheroid™, Pheroid, Pheroids, pro-Pheroid™, pro-Pheroid and pro-Pheroids. In most cases the symbol indicating a trademark, i.e. ™, is used but it is sometimes left out for ease of reading or other technical reasons. All of the work included in this thesis was performed by the applicant, unless specifically stated otherwise.

The use of delivery systems is common in the pharmaceutical industry and as several delivery systems are available, the development of another delivery system may be questioned. In Chapter 1, the problem statement and the motivation for this study are addressed. Some attention is given to the general industrial requirements for the production of pharmaceutical preparations containing delivery systems as inherent ingredient in the preparations. The need for novel customizable drug delivery systems is discussed, in conjunction with the specific objectives of the study.

The need for and type of delivery systems used are closely related to the route of administration of pharmaceutical preparations, the mechanism of absorption and the biological distribution of the absorbed active pharmaceutical ingredients (API's). These aspects and the physical, biological and production factors that influence the characteristics of delivery systems are addressed in Chapter 2.

As background for the development of Pheroid™ technology as a patentable product, Chapter 3 starts out with a discussion of the generation of an idea for a new product or technology and process and the requirements of patenting such an idea or technology. It then addresses the process of product development and identifies the similarities and differences of the various stages of the two processes. The chapter continues with a historical background of Pheroid™ technology. The reasons for and the development of the pro-Pheroid™ are described. An exposition of the ingredients, the parallel processes of manufacturing both Pheroid™ and pro-Pheroid™ and the equipment used in the manufacturing processes are discussed. The analysis required for quality control of the produced formulations is explained, with reference to quality assurance issues and regulatory requirements.

Chapter 4 contains a book chapter that was written on invitation. The chapter was published in the book "Science and Applications of Skin Delivery Systems" in 2008. It concerns the use of Pheroid™ technology in topical and cosmeceutical products and delves into the reasons for the use of specific ingredients of the Pheroid™. A comparison between the Pheroid™ and other systems are made and the unique character of the Pheroid™ system is highlighted. The design and clinical evaluation of a Pheroid™-based and comparative essential oil-based cosmeceutical product are discussed in the book chapter.

An exploration of the potential of Pheroid™ delivery technology in the treatment of infectious diseases is described in Chapter 5. The specific infectious disease chosen as a model for studying this application of the technology is tuberculosis. The causes of the high incidence of an ultimately treatable disease and the need for a new treatment regime for this disease are summarized. A theoretical discussion of the roles of two of the Pheroid™ ingredients, namely α-tocopherol and nitrous oxide, in this specific application is included. An investigation into the formulation, bioavailability and efficacy of the existing anti-tuberculosis drugs rifampicin, isoniazid, ethambutol and pyrazinamide in conjunction with the pro-Pheroid™ is described. Dosage form development and stability analysis are touched upon. The efficacy analyses are based mainly on bacterial efficacy studies and infection studies in an *in vitro* model. The bioavailability evaluation is based on single case volunteer studies and a phase 1 clinical trial, approved by both the South African Medicines Control Council and the South African Medical Association Research Ethical Committee. Studies such as clinical trials of necessity include a number of skilled people working as a team as will be indicated in Chapter 5.

The use of Pheroid™ as an adjuvant able to enhance the efficacy of vaccines is described in Chapter 6 in the following manner: Besides a short chapter summary, the research performed on Pheroid™ as vaccine adjuvant is contained in the complete patent submission to the European Patent Office under the Patent Cooperation Treaty. It is therefore presented as it was published by the World Intellectual Property Organization (WIPO). The vaccine patent has been granted in South Africa. The patent submission includes animal efficacy studies on several vaccine candidates – a rabies vaccine, a hepatitis B vaccine and a diphtheria vaccine. Morbidity and specific immune responses are studied, including systemic and mucosal responses.

In Chapter 7, the use of Pheroid™ technology in the effective administration of peptides is explored. As in Chapter 6, the full patent submission to the European Patent Office under the Patent Cooperation Treaty, and published by WIPO is included after a short summary. While the patent submission focuses on the *per-oral* and nasal administration of insulin, some addition material is included with reference to other model peptides. This patent has been granted in South Africa.

Although not strictly a pharmaceutical application, the use of Pheroid™ technology as a delivery system for plants is investigated in Chapter 8. As in the previous two chapters, the full patent submission to the European Patent Office under the Patent Cooperation Treaty, and published by WIPO is included after a short summary. The patent has been granted in South Africa. Since the arena may be less well known to the reader, a discussion of the applicability of Pheroid™ technology in agriculture is included. The product development, the trials, the design of manufacturing equipment and the legal and regulatory process involved in this chapter were mostly performed outside of the university in my private capacity. It has nevertheless been patented by the NWU as part of its Pheroid™ technology portfolio and forms as much part of unlocking the potential of Pheroid™ technology as any of the other applications described in the preceding chapters. It is therefore included in the thesis. This investigation, and the resultant commercialization of the product, has been one of the most satisfying experiences of my career as a scientist and of my life as a human being.

The last chapter of the thesis, Chapter 9, summarizes the results and proposes future directions and studies. The format of the thesis is not the usual format. The format has been specifically chosen to reflect the exploration of the applications of a unique technology. In the reader's perusal of this thesis, cognizance must be taken that the very nature of patents are conceptual and not analytical: A patent makes the original statement. Furthermore, one of the requirements of a patent is that it should be understandable and repeatable by persons skilled in the art. The granting of a patent is therefore an indirect recognition of the repeatability of the work, while the type of statistical analysis generally used in scientific writings may cloud the original concept of a patent.