CHAPTER 9: SUMMARY AND FUTURE PROSPECTS

The identification of industrially acceptable drugs that can repeatedly achieve therapeutic efficacy is a universal aim. Identifying, testing and formulating a new entity molecule or drug may take years of research and is only the first step in creating a commercially viable pharmaceutical product. Development of a new drug also involves determining a safe, reliable, stable and effective method of administration. This is a complex multi-disciplinary field involving physical and analytical chemistry, pharmacology, toxicology, crystallography, formulation, and chemical engineering. While the next generation of drugs are being tested, the use of alternative formulation strategies such as delivery systems may be applied to classic principles of drug development and testing. The optimization of the efficacy of drugs led to renewed interest in delivering available drug molecules in more innovative and cost-effective delivery systems.

Oral and parenteral medications lose much of their active compounds through metabolism. The drugs and their metabolites may cause considerable damage to body organs such as the intestine and the liver. Pheroid™ vesicles and/or sponges seem to have the ability to pass relatively unscathed through the metabolic process to reach the target organs, thereby enhancing bioavailability and safety. In a healthy human volunteer (phase I) study highly superior bioavailability was demonstrated for anti-tuberculosis drugs. The study also showed evidence of a targeted concentration of the drugs in white blood cells; precisely where the infectious agent, the TB bacilli congregate and multiply. It requires little imagination to appreciate that these results, e.g. better bacterial killing ability (proven *in vitro*) and superior bioavailability will lead to the production of a superior generic medication.

Further investigation into Pheroid™ technology has shown that in terms of infectious diseases and vaccines against these diseases, the technology has:

- The potential of decreased dosages of the API without reducing efficacy;
- The potential to enhance the body's immune responses;
- The potential to decrease side effects;
- The potential to improve patient compliance thereby reducing drug resistance, relapses and re-infections;
- The ability to stimulate the immune system and contribute to the treatment of these diseases.

Since the treatment of a number of infectious diseases, such as tuberculosis treatment, presents with two major challenges - the development of drug resistance and compliance, these findings are good news.

Pheroid™ technology has not been demonstrated by empirical work to be applicable to all drug classes or even to all antimicrobials. However in respect of such APIs that have already been formulated and evaluated by different methods for the anticipated enhancement of action, no negative result has as yet been seen despite the chemical diversity of the anti-infective agents that has been investigated. Pheroid™ technology is therefore expected to have applications in respect of products representing a range of classes of APIs.

High loading and delivery efficiency of Pheroid™ vesicles and sponges have been demonstrated by achieving a high degree of entrapment of a wide range of active compounds. It has further been shown that the Pheroid™ vesicles and sponges have very high delivery efficiencies. The high delivery efficiency relates to tissue penetration, cell adsorption, internalisation of vesicles and sponges by cells, parasites and bacteria, intra-cellular stability, and subsequent subcellular organelle delivery.

Furthermore, the formulated delivery system contains components that have been recognized as pharmaceutically safe. The public health authority of South Africa in concert with many other health authorities, regard the ingredients used in the Pheroid™ as excipients.

The safety of the Pheroid™ allows its use in the agriculture sector to enhance food production and therefore food security. The precise mechanism of enhancement of the action of APIs and agricultural compounds by the Pheroid™ has not yet been elucidated. To allow expansion of the technology to more compounds, mechanistic studies are needed. The Pheroid™ vesicles and sponges seem to have dynamic characteristics in respect of the entrapment and subsequent delivery of compounds at predicted areas in cells and organisms that can be tempered to obtain optimal impact of the compounds through various modes of actions.

Future prospects

Despite an increased knowledge of the human genome and disease causing mutations and great technical improvements in biological activity assays, the number of new medicines being discovered, developed and successfully brought to market has decreased. The problem does not seem to relate to the types of chemicals or molecules used but rather to the conversion of hits obtained by high throughput screening to therapeutic drugs.

This thesis describes the initial stages of product patenting and development, i.e. of the possible pipeline for future pharmaceutical products based on Pheroid™ technology. Although the results suggest that the next stages should be entered into, a number of 'end-users' interact to determine market needs. They include:

- Regulatory authorities such as the MCC and the FDA: Each country's regulatory authority requires stringent tests to ensure efficacy and safety to protect the population. The research and developmental costs are largely to satisfy these requirements
- Medical practitioners, pharmacists and scientists in private and in academic practice: A plethora of drugs exist and these opinion formers will only recommend and/or prescribe a product that has been rigorously tested for safety and efficacy. Thus studies to elucidate efficacy and safety need to be performed.
- Governments: The primary driving force that determines whether a product is accepted on government tender is price. Safety and efficacy are required as the norm. The government may contribute to product development through grants.
- Patients: The patient is the final consumer who requires his/her problem to be fixed in the shortest possible time, at a reasonable price and with the least number of side effects. In the past a greater number of patients simply accepted the medication issued by the doctor or pharmacist, but an increasing number now query the choice of the doctor or pharmacist. Thus cost-effectiveness and lack of side effects are important from the patient's point of view.
- Pharmaceutical industry, both locally and internationally: No new therapies can be effective unless they reach those whose lives depend on them and the industry finally determines whether a product is commercialized or not. Projections indicate that the size of the 'drug delivery' industry is between $12 and 20 billion annually. Intelligent R&D partnerships will ensure that products are priced affordably, embraced by public health-care workers and accessible to patients through adequate infrastructure. It is now crucial to involve a commercialization partner from the pharmaceutical industry for further development of a number of products suggested by the research described.

Both specialized small companies and the major pharmaceutical industries alike realize the fundamental contribution that drug delivery must make (during both the research and development phases) if quality candidates are to emerge with a significant chance of progressing to market. The optimization of properties of biomaterials for a specific drug delivery application is one of the key future factors to be considered. The development of macromolecular, target-specific drug-carrier delivery systems has not yet been broadly successful at the clinical level. It may be argued that drugs generated using the conventional means of drug development [i.e. relying on facile biodistribution and activity after (preferably) oral administration] are not suitable for target-specific delivery and would not benefit from such delivery. The research described here disproves such an argument as the *in vitro* efficacy observed in targeted macrophages, the enhanced *in vivo* efficacy of Pheroid^{TM} vaccines and the improved absorption of such conventional drugs and antigens show.

The ability to tailor the macromolecular chemistry and material morphology to satisfy a given set of physicochemical and biological criteria determines the ultimate success of a biomaterial. Future needs include optimization of engineering and design processes, which should permit biomaterials with precise bulk and surface architectures to show precise biological recognition and specific bio-reactions *in vivo.* These include the so-called 'SMART' or biological stimulus-responsive materials, specific cell binding and site targeting. In this context, various approaches and techniques (from chemistry, molecular biology, material science, etc.) will be applied for the successful synthesis and analysis of a new generation of the Pheroid™ delivery system.

It is suggested that future efforts be directed towards the following fundamental issues:

- The drug-carrier system must preferably avoid nonspecific interactions in the vascular compartment.
- The system should retain its ability to accumulate at the target site(s) and be in an available form for action on its pharmacological activity target, the target being defined in terms of anatomical, physiological or disease conditions.
- Appropriate APIs compatible with the pharmacokinetic properties of the Pheroid™ need to be selected.
- The Pheroid™ need to be compatible with the demands of target-selective drug delivery (especially drug retention at the site of delivery and its ability to access its site of molecular action).
- Antibodies or other targeting ligands would fit ideally in these sub-compartments in the Pheroid™ sponges. Optimal use of such molecules may result in binding to specific epitopes or receptors at the target cell surface.
- The Pheroid™ delivery system has been shown to be highly effective in its transmembrane carrying abilities. Manipulation of the rate of release of compounds at the target site should be attempted. Different types and amounts of PEG may be conjugated to the unsaturated fatty acid fraction of the Pheroid™ delivery system. Regulation of both the lateral and rotational motion of individual fatty acid molecules in their membranes may be used to manipulate delivery.
- As results indicate, the dedicated use of Pheroid™ could prove effective in combating multidrug resistance. The greater absorption and penetration of the formulation could prove effective where multidrug resistance is related to membrane permeability and efflux pump mechanisms within the organism and cells.
- Delivery of drugs and agricultural compounds may be expanded to tissues not genereally reachable by current therapeutic regimes. Pheroid™ may in future be adapted for pulmonary administration. In the case of respiratory diseases, still the ban of paediatric health, this dosage form will bring the formulation into contact with the pathogen at a primary locus thereof and without invasive procedures. The advent of insulin inhalers in

the treatment of diabetes has proven that the aerosol lung administration route can administer very specific dosages of peptide drugs, such as hormones, drugs such as B-blockers and stimulants for treatment of asthma, emphysema and antibiotics. The pulmonary administration route has a number of advantages, such as the absence of gastric side effects and no interference by the pH of the digestive system by ingested food molecules and toxins. There is also no evidence that inhaling autologous (self) proteins presents any immune issues. The lung is a logical target for non-invasive drug delivery, as the delivery targets a very large surface of alveolar epithelium - approximately 100 square meters in adults. This large surface contains approximately a half billion air sacs or alveoli, which are enveloped by an equally large capillary network. The alveoli has a thin single cellular layer enabling absorption into the bloodstream.

- Stereo-chemical and polymorphic integrity of both the ingredients of the Pheroid™ and the active compounds must be assured. Since some modifications of Pheroid™ ingredients may lead to site-specific targeting, suppliers of raw materials may be involved in an attempt to formulate dedicated batches of modified raw materials for Pheroid™ manufacturing.
- Despite its safety and wide applicability, the preclinical efficacy, safety and pharmacokinetic profile will have to be established for every Pheroid™-based formulation.
- The Pheroid™ structures are stable and vesicles and sponges appear to remain structurally intact after 24 months at room temperature. Any entrapped active compound should theoretically remain encapsulated during this time but as for safety, stability has to be confirmed for every product.
- Diseases responsive to central and peripheral agents may benefit from Pheroid™ technology since the long chain fatty acids may contribute to the maintenance of the myelin sheath of the nervous system, being precursors of the sphingomeilin molecules. The cells in this application most probably concern neurons.

The nature of formulations and the type of product development used flow from basic delivery system characteristics, dosage form characteristics and pharmacological active ingredient combination. The Pheroid™-based delivery system provides a system for single or combination drug treatment with a significantly increased therapeutic index, using existing drugs, with a resultant decrease in the development of drug resistance. Although it contains the same therapeutic moieties, it differs in chemical form from the original therapeutic molecule, and dosage of those moieties and can therefore regarded as a pharmaceutical alternative. Furthermore, the higher therapeutic index of the drug facilitates lower dosage, which limits the side effects, which may in turn be expected to improve compliance. Within the larger industrial

arena, the potential application and impact of this research can finally be summarized as follows:

- Improved therapeutic outcomes for vaccines, peptide drugs and anti-microbials.
- Development of cost effective novel and generic drug delivery systems for national priority medicines and new generation drugs.
- Development of novel research technologies in drug and agricultural delivery.
- Topical administration of vaccines and peptides represents an opportunity for the Pheroid™ to be involved in what could potentially become a revolutionary industry trend.
- Generation of patents.
- Generation of new knowledge on drug and cell membrane transport.
- Improved yields of agricultural crops, contributing to food security.
- Enhancement of international competitiveness by innovative research.
- Promotion of multi-disciplinary research.

In summary, a delivery system can decrease the potential toxicity of a compound, can enhance the delivery of a drug, can change the modality of administration of such a drug, can enhance the efficacy of a drug and can thus change a potentially unusable compound or molecule into a viable therapeutic agent. In addition, there is a growing interest in specific delivery systems for use as environmentally responsive materials. The challenge of creating 'intelligent' delivery systems combines sophisticated synthetic methods, physical characterization of surfaces and interfaces, and biology with potentially great impact on functional membrane protein biophysics, biology and biotechnology, pharmaceutics and agriculture. If functional membrane proteins such as ion channels and hormone receptors could be properly aligned on vesicles, this synthetic membrane mimicking cellular characteristics would be of widespread interest to the pharmaceutical industry.