The development of an oral single dose emulgel formulation for Pheroid® technology

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"Limitations live only in our minds. But if we use our imagination and will-power, our possibilities and potential become limitless."

∞**Jamie Paolinetti** ∞

Dedicated to my brother

Dirk Uys

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ABSTRACT

Dosage forms have been developed over the years for various applications. The dosage form consists of the active drug in combination with pharmaceutical excipients. The pharmaceutical excipients solubilise, suspend, thicken, dilute, emulsify, stabilise, preserve, colour and flavour medicinal agents into efficacious and appealing dosage forms.

The dosage form under investigation in this study is of the oral type. The Pheroid® is a unique drug delivery system which consists of an oil-in-water emulsion system. Emulsion based drug systems provide a suitable medium for the delivery of both hydrophobic and hydrophilic drugs which can be incorporated into its oil or water phase for delivery to the site of action. These advantages make them more efficient as dosage form.

Emulgels are either emulsion of oil-in-water or water-in-oil type, which is gelled by mixing with gelling agents. Incorporation of emulsion into gel increases its stability and makes it a dual control release system. The presence of the gel phase makes it a non-greasy formulation which favours good patient compliance. A strategy followed to improve the stability of the emulgel system is the packaging of the formula into single dose sachets to protect the product against physical and chemical breakdown during patient usage. All factors such as selection of gelling agent, preservatives and formulation methods influencing the stability and efficacy of Pheroid® emulgel are discussed.

In this study, three different emulsifiers were added to the formula and the analysis of visual appearance, pH measurements, rheological studies, light microscopy and confocol laser scanning microscopy (CLSM) will provide an insight to the potential usage of emulgel as drug delivery system. A range of para-hydroxybenzoate esters was tested in the Pheroid® emulgel and the most suitable candidate chosen for further accelerated stability testing. It was thus possible to prepare a single dose emulgel with Carbopol® 934P (0.2% w/v) as an emulsifier, with Nipastat® (0.175% w/v) and PG (10% v/v) as preservatives into a stable dosage form suitable for further product development.

Keywords: Development; oral; dosage form; emulgel; Pheroid®; stability; Carbopol® 934P; Nipastat®.

UITTREKSEL

Doseervorme word al vir baie jare ontwikkel vir verskeie aanwendings. Die doseervorm bevat ′n kombinasie van die aktiewe bestandeel tesame met farmaseutiese hulpstowwe. Die farmaseutiese hulpstowwe solubiliseer, suspendeer, verdik, verdun, emulsifiseer, stabiliseer, preserveer, kleur en geur medisinale produkte in aantreklike en aanvaarbare doseervorme.

′n Orale doseervorm word ondersoek. Die Pheroid® is ′n doseervorm wat bestaan uit ′n olie-in-water emulsie sisteem. Emulsie gebaseerde doseervorme voorsien ′n medium vir die aflewering van beide hidrofobe en hidrofiele geneesmiddels wat onderskeidelik in die olie of water fase afgelewer kan word by die teikenplek. Hierdie voordele maak dit ′n meer doeltreffende doseervorm.

Emulgels is emulsies van olie-in-water of water-in-olie tipe, wat vermeng word met ′n gel agent. Die inlywing van emulsie in gel verhoog die stabiliteit en maak dit ′n Ïtweeledige aflewerings beheer sisteem. Die teenwoordigheid van ′n gel fase maak dit ′n nie vetterige formulering wat ten gunste van ′n goeie pasiënt samewerking is. ′n Strategie gevolg om die stabiliteit van die emulgel stelsel te verbeter, is die verpakking van die formule in ′n enkele dosis sakkie wat die produk teen fisiese en chemiese afbraak tydens pasiënt gebruik sal beskerm. Alle faktore, soos die keuse van gel agent, preserveermiddels en formulering metodes wat die stabiliteit en doeltreffendheid van die Pheroid® emulgel beïnvloed word bespreek.

′n Verskeidenheid para-hidroksiebensoaat esters is in die Pheroid® emulgel en die mees geskikte kandidaat gekies vir verder versnelde stabiliteit studies. Dit was dus moontlik om ′n enkel doseervorm emulgel met Carbopol® 934P (0.2% m/v) as verdikkingsmiddel en Nipastat® (0.175% m/v) en propileenglikool (10% v/v) as preserveermiddels te berei in ′n stabiele doseervorm geskik vir verdere produk ontwikkeling.

Sleutelwoorde: Ontwikkeling, orale doseervorm, emulgel, Pheroid®, stabiliteit, Carbopol® 934P, Nipastat®.

INTRODUCTION AND AIM OF STUDY

With the proper design and formulation of a dosage form all the physical, chemical and biological characteristics of the drug substance and pharmaceutical ingredients have to be considered. The research pharmacist has to examine the effects of all formulative ingredients on one another to ensure each agent can fulfill is purpose (Allen *et al*., 2005:140). Compatibility between the drug and pharmaceutical materials produce a drug product which is stable, efficacious, attractive, easy to administer and safe (Allen *et al*., 2000:93). The age of the patient determines the choice of the type of dosage form. For infants and children younger than five years of age, pharmaceutical liquids are preferred for oral administration (Allen *et al*., 2005:95).

For a drug to have the most beneficial effect, the product must be taken correctly by the patient. The odour, taste and colour of a pharmaceutical preparation can play a part. The correct combination between flavour, fragrance and colour contributes to a pharmaceutical product that is easily accepted by patients (Allen *et al*., 2005:126). For instance, children prefer flavours that are sweet, candy-like preparations, whilst adults seem to prefer less sweet preparations with a tart rather than fruit flavor (Allen *et al*., 2005:132).

Preservation against microbial contamination in certain liquid and semisolid preparations, in addition to the stabilisation of pharmaceutical preparations against chemical and physical degradation, is important (Allen *et al*., 2005:138). Microorganisms include moulds, yeasts and bacteria, with yeast and moulds generally favouring an acidic medium and bacteria an alkaline medium. Aqueous pharmaceutical preparations are mostly within pH 3 and pH 9 and must be protected against microbial growth (Allen *et al*., 2005:139). All aqueous systems containing polymers of natural origin require a preservative. Cellulose derivatives are degraded by cellulases, enzymes that may be produced by microbial organisms. Even if the polymer chosen is totally resistant to bacteria and moulds, the aqueous medium may allow growth and a preservative is still necessary (Zatz *et al*., 1996:288).

Before approval for marketing, a product‘s stability must be assessed. With regard to its manufacturing, the type of pharmaceutical ingredients used are important; the type of container used for packaging and the conditions of storage (e.g. temperature, light, humidity); the anticipated conditions of the pharmacy shelf-life on the product and the patient usage of the product (Allen *et al*., 2005:122). A change in the

physical properties, colour, odour, taste and texture may in some instances indicate drug instability of pharmaceutical formulations (Allen *et al*., 2005:123). Accelerated stability testing makes use of exaggerated conditions of temperature, humidity and light to test the stability of drug formulations (Allen *et al*., 2005:123). Emulsions may cream and crack; suspensions can agglomerate and cake, whilst ointments and gels may bleed as their matrices contract to squeeze out mobile constituents (Soute, 2005). The shelf life of a dispersion, depends on the chemical as well as the physical stability of the system as a whole. Major changes in viscosity over a short time period are cause for concern in stability of the product (Zatz *et al*., 1996:290).

In classical terms, emulsions are colloidal dispersions comprising two immiscible liquids (e.g., oil and water), one of which (the internal or discontinuous phase) is dispersed as droplets within the other (the external or continuous phase) (Block, 1996:47). Pheroid® technology is based on the formulation of oil-in-water (o/w) emulsions. Emulsions are thermodynamically unstable systems since the contact between oil and water molecules is energetically unfavourable. Emulsifiers and/or thickening agents overcome the activation energy of the system to help form kinetically stable emulsions. Thickening agents are mainly polysaccharides which enhance the emulsion stability by retarding droplet movement by increasing the viscosity of the continuous phase. The combination of protein and polysaccharide delivers a range of properties to emulsions: physicochemical stability, storage stability, texture and mouth feel (Sun *et al*., 2007:555).

An emulgel is defined as a two-phase system consisting of large organic molecules interpenetrated by water and a small fraction of emulsified lipids (Dermis, 2008). The nature of the solvent is used to classify gels into hydrogels and organogels (Zatz & Kushla, 1996:400). Hydrogels include ingredients that are dispersible as colloids or soluble in water; they include organic hydrogels, natural and synthetic gums and inorganic hydrogels. Organogels include the hydrocarbons, animal and vegetable fats, soap based greases and the hydrophilic organogels (Allen *et al*., 2005:418). Among the gelling agents used for hydrogels are synthetic macromolecules, such as Carbomer 934, cellulose derivatives such as carboxymethylcellulose or hydroxypropyl methylcellulose and natural gums such as anthan gum (XG) (Allen *et al*., 2005:282 and Zatz & Kushla, 1996:400). Gelling agents for organogels include tile silicon dioxide and ethylcellulose (Gallardo *et al*., 2005:189 and Zatz & Kushla, 1996:400 and Nash, 1998:491).

The aim of this study was to investigate the influence of formulation variables on the stability and characteristics of an oral emulgel formulated with Pheroid® technology.

To accomplish the aim of this study the following objectives were set:

- Conduct a literature study on the effect of pharmaceutical excipients and different concentrations thereof on the physical stability of the emulgel.
- Conduct a literature study on the effectiveness of a preservative system in the emulgel formulation.
- Determine the effect of the co-solvent propylene glycol (PG) on preservative efficacy.
- Use various concentrations of the appropriate gelling and preservative agents in a pre-formulation study to determine the most suitable formulation and to subject it into an accelerated stability test.
- Determine the physical and chemical properties of the formulations using visual assessment of creaming, pH-measurements, viscosity measurements and confocal laser scanning microscopy.
- Formulate an efficacious and appealing dosage form.
- Determine suitable storage materials and conditions for the final product.

Chapter 1 gives a background of the Pheroid® formulation. The uses, disadvantages and possible areas of improvement are discussed. A classification is given of the various types of gels which can be manufactured and the applications of a gel are outlined.

In Chapter 2, a series of formulations will be designed with qualitative and quantitive differences in some of their components. Various gelling agents will be introduced in different concentration ranges and suitable preparation methods will be developed for each gelling agent incorporated into the emulsion system. The physical and chemical properties of the formulation will be evaluated using visual assessment of creaming, pH-measurements, viscosity measurements, light microscopy and confocal laser scanning microscopy.

Chapter 3 outlines the preservative efficacy in the Pheroid® system. A range of preservatives will be exposed to preservative efficacy tests in the emulgel formulations. The effect of the co-solvent PG on preservative efficacy will be examined. The final product will be packaged in single dose sachets for convenient single dose therapy.

Chapter 4 will outline the results obtained during the accelerated stability test conducted to evaluate the success of the dosage form in the final storage material.