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GEL-BASED SOLID DOSAGE FORM FOR PESTICIDE DELIVERY

By

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DEGREE: MAGISTER SCIENTIAE

SYNOPSIS

The aim of this research was to develop a solid dosage form containing 1.5 g of the pesticide cypermethrin. The dosage should be stable in a tropical climate. In addition, it is to disintegrate and disperse in 10 L of tap water within 3 minutes. Such dissolution should yield a 150 ppm dispersion of cypermethrin, stable for at least one week. This provides for a dip dispersion to treat ticks and fly infestation on livestock.

A new solid dosage was formulated as the scope of this research. It is a gel-based solid dosage form. Polymer electrolyte ASP4 - a copolymer of methacrylic acid, ethyl acrylate and diethyl maleate, was used to produce the gel. Preliminary tests revealed that ASP4-based gel, on its own, failed to meet the required dissolution time of 3 minutes. Strong entanglements of ASP4 chains impeded rapid dissolution. These strong entanglements occurred owing to the use of a high concentration of ASP4. Reducing the concentration of ASP4 yielded a solution of high viscosity instead of a gel. It was therefore decided to

use a superabsorbent (Product Z1069) in conjunction with ASP4 to produce the gel. Product Z1069 is a cross-linked sodium polyacrylate.

Before producing the gel, a 1:1.5 by mass oil/water (O/W) emulsion was prepared using the phase-inversion route. The water (W) phase comprised 85.9% distilled water, 3.9% ASP4 at 20% dispersion, 8.6% sodium carbonate (0.5 M) and 1.6% Emulsogen EL. All concentrations are indicated in mass %. The oil (O) phase consisted of 76.9% cypermethrin, 19.3% Solvesso S200 and 3.8% Phenyl Sulphonate CA, also by mass. This emulsion was gelled by adding the superabsorbent Product Z1069 (ca. 37.5% by mass relative to the W phase of the emulsion).

The superabsorbent strongly absorbed water, depleting it from the emulsion. This resulted in an increase of the effective concentration of ASP4 in the water phase of the emulsion. This increase of the polymer electrolyte concentration brought about a gel-like state corresponding to the desired solid dosage form. Rheometry confirmed that the dosage form maintained a solid gel-like consistency at 50 ^{o}C.

The dosage contained 24.6% m/m cypermethrin. Thus, the required dosage of 1.5 g was achieved in pellets weighing ca. 6.1 g. Such pellets rapidly disintegrated with mild stirring in 10 L of tap water. Complete pellet disintegration and active dispersion occurred within 2.5 minutes at ambient temperature (25 $\pm$ 2 ^{o}C).

Keywords: Cypermethrin; Solid dosage form; Gel; Emulsion.

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DECLARATION

I, the undersigned, declare that the dissertation that I hereby submit for the degree MSc at the University of Pretoria is my own work, and has not previously been submitted by me for degree purposes or examination at this or any other university.

Pretoria, March 2008

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LIST OF SYMBOLS AND ABBREVIATIONS

A_1	surface area of disperse phase before emulsification
A_2	surface area of disperse phase after emulsification
c	propagation of the speed of light ($3.00*10^8$ ms^{-2})
cps	centipoises
CC-MS	conical cylinder measuring system
CMC	critical micelle concentration
CP-MS	cone and plate measuring system
d	diameter of particles/droplets
DL	diffuse layer
E	energy of radiationEC emulsifiable concentrate
EDL	electrical double layer
EO	ethylene oxide
g	gravitational constant (9.81 m/s^2)
G	elastic modulus
G'	storage modulus
G"	loss modulus
G_1	Gibbs free energy before emulsification
G_2	Gibbs free energy after emulsification
h	Planck's constant ($6.63*10^{-34}$ Js)
LVE	linear viscoelastic
m/m	mass by mass (concentration by mass)
m_1	mass of tablet before friability test
m_2	mass of tablet after friability test
MAA	methacrylic acid
mPa.s	millipascal seconds
O/W	oil-in-water

PIT	phase inversion temperature
PP-MS	parallel plate measuring system
ppm	parts per million
rpm	revolutions per minute
S_1	entropy of the system before emulsification
S_2	entropy of the system after emulsification
SL	Stern layer
W/O	water-in-oil
WP	wettable powder

GREEK SYMBOLS

Δ	variation
$\dot{\gamma}$	shear rate
γ	strain or "deformation"
γ_1	interfacial tension between oil and water before emulsification
γ_2	interfacial tension between oil and water after emulsification
γ_{cr}	critical strain
γ_o	surface tension of oil
γ_{ow}	interfacial tension between oil and water
γ_w	surface tension of water
γ_x	interfacial tension between oil and water at a given moment X
δ	phase angle shift
η	viscosity of liquid
η	viscosity of the dispersion medium
η^*	complex viscosity
η'	dynamic viscosity
η''	imaginary part of the complex viscosity
λ	radiation wavelength

μm	micrometer
σ	surface tension or interfacial tension
ρ_1	density of disperse liquid
ρ_2	density of the dispersion medium
τ	shear stress
υ	settling velocity
ν	frequency (Hz)
ω	angular frequency (rad.s^{-1} or s^{-1})

1 INTRODUCTION

1.1 Problem Statement

Cypermethrin is a synthetic pyrethroid pesticide. It is usually supplied as a mixture of cis- and trans-isomers. The chemical structure of the cis-form of cypermethrin is presented in Figure 1. The IUPAC name of this isomer is 3–(2,2–dichloroethenyl)–2,2–dimethylcyclopropanecarboxylic acid cyano–(3–henoxyphenyl) methyl ester.

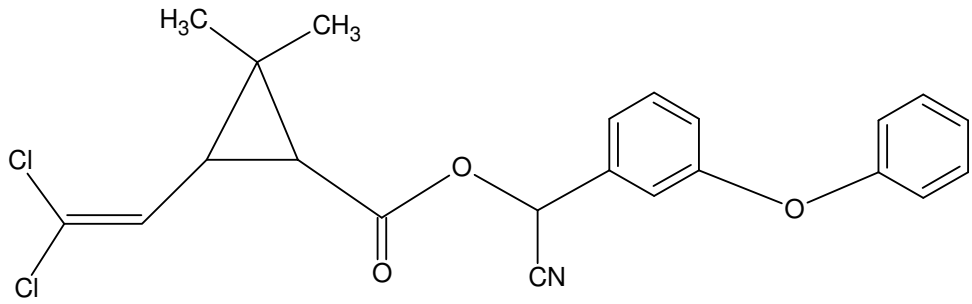

Figure 1: Structural formula for the cis-isomer of cypermethrin

Cypermethrin is used in veterinary applications to treat ticks and fly infestations on livestock. The livestock is immersed in a bath containing a prescribed concentration of cypermethrin.

Emulsifiable concentrate (EC) and wettable powder (WP) are the dosage forms of cypermethrin currently available in the market. Both are supplied in pre-measured water-soluble packets and bulk jars. EC is further diluted with water, yielding an emulsion. WP is diluted in water, yielding a suspension.

The dilution of EC and WP is frequently associated with errors in administering the prescribed dose. Therefore, it is necessary to develop a dosage form that delivers an accurate pesticide dose. Tablets, the most common solid dosage form, may be a potential solution to this problem.

A solid dosage form is a drug-delivery system that includes tablets, capsules, sachets and pills. It also includes bulk or unit-dose powders and granules (Banker & Rhodes, 1990). Tablets account for the highest proportion of all dosage forms (Ansel & Popovich, 1990). They are preferred because of accurate dosage, long shelf life, simple and comfortable packaging, ease of transportation and administration, and relatively low cost (Hess, 1985; Rawlins, 1988; Lieberman *et al.,* 1989; Collett & Aulton, 1990).

Tablets are manufactured by compression of powdered ingredients. However, the cypermethrin supplied for this research project is not a powder but a viscous liquid. Thus, the challenge was to develop a tablet or similar solid dosage form using liquid cypermethrin. Such a solid dosage form should disperse rapidly when placed in water.

The cypermethrin supplied for this project is of technical grade – Cypermethrin Tech. It is preferred because it consists of a mixture of eight different isomers. The advantage is that each isomer possesses its own chemical and biological properties, which gives the dosage a wide application range. The disadvantage is that cypermethrin is water-insoluble. Owing to this hydrophobicity, cypermethrin is expected to coat the solid particles comprising the dosage form. This would impede water penetration into the solid dosage form and so rapid dissolution of the dosage would be unlikely.

For this reason the approach schematised in Figure 2 was hypothesised for this research project. The water (W) phase is first thickened with sodium polymethacrylate. Then, the oil (O) phase, containing cypermethrin, is pre-dispersed in the W phase. Next, the pre-dispersed droplets of cypermethrin are trapped inside a gel matrix. This results in a gel-based solid dosage form. On dissolution in water, the dosage form releases the droplets of cypermethrin previously encapsulated, yielding a stable dispersion of cypermethrin.

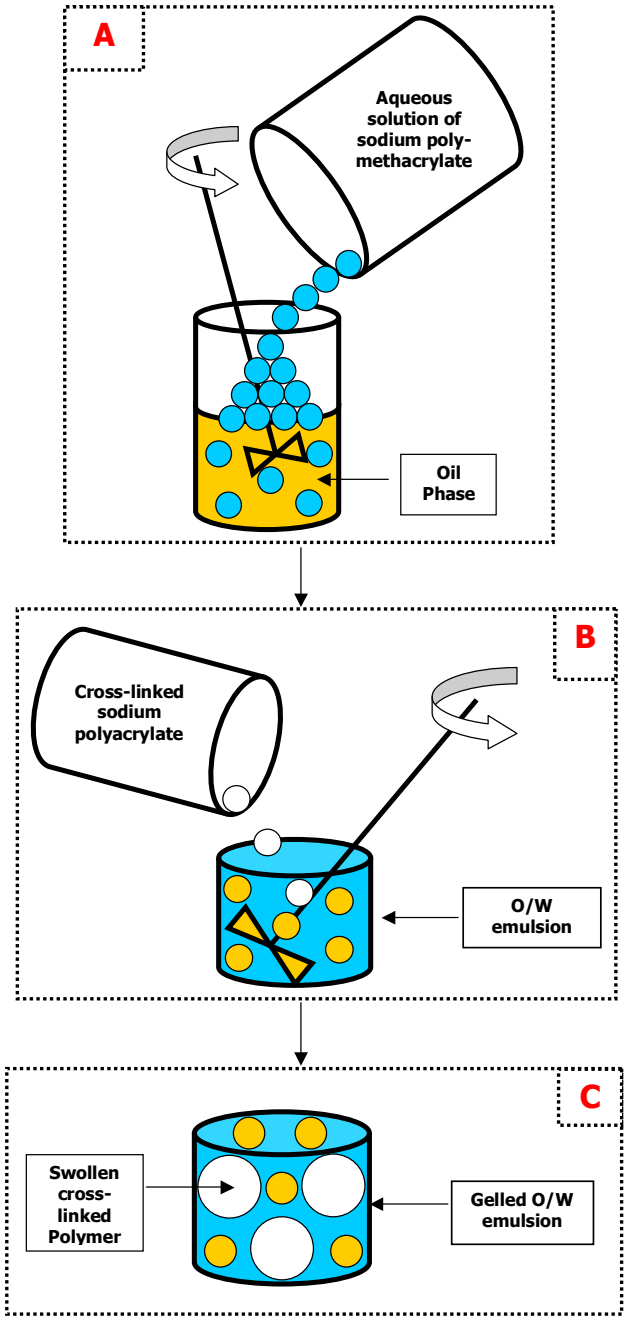

Figure 2: Schematic illustration of the steps for formulation of the desired solid dosage form

A: An emulsion of the active component is prepared in an aqueous solution of sodium polymethacrylate using the phase-inversion route; B: A cross-linked sodium polyacrylate superabsorbent is added to gel the oil-in-water emulsion; C: The superabsorbent extracts water from the emulsion, causing physical cross-linking of the W phase in the emulsion – a gel-like structure results.

1.2 Aim of this Research

The aim of this research was to develop a gel-based solid dosage form for cypermethrin delivery. It was required that such a dosage should:

- Contain 1.5 g of cypermethrin;
- Retain its shape for longer than 6 months at temperatures up to 50 ^{o}C;
- Disperse in a 10 L drum of tap water within 3 minutes, yielding a stable dispersion.

A dose of 1.5 g of cypermethrin in the solid dosage form yields a concentration of 150 ppm of cypermethrin in 10 L of water. This concentration is below the oral LD_{50} of cypermethrin. LD_{50} is the dose that kills 50% of a tested population of animals (usually rats or mice). For cypermethrin, the oral LD_{50} is 250 ppm (Walker, 2000).

The dosage should be stable up to 50 ^{o}C because it is intended to be marketed in tropical countries. The climate in tropical countries is warm to hot and humid. These conditions prevail with little variation throughout the year and provide ideal growing conditions for ticks and fly infestations of livestock.

A gel-based dosage form was considered because it will:

- Maintain its shape when not subjected to an outside force;
- Be easy to prepare; there are numerous polymers that can be used for the purpose;
- Allow rapid penetration of water into its matrix, dissolving rapidly.

1.3 Outline of Dissertation

Chapter 1 is the introduction to the study. Here, the research problem is posed, the aim of the work presented, and the structure of the dissertation outlined. Chapter 2 reviews the literature with the focus on three topics: tablets, emulsions and gels. An overall introduction to the tablets is provided. The methods of tablet manufacture and

characterisation, the mechanisms and factors involved in tablet instability, and the packaging of tablets are described. A background to emulsions and gels is also presented. It includes a classification of emulsions, the emulsion properties, the kinetic stability of emulsions, the interfacial phenomenon, the surfactants, the theory of emulsification, and methods and principles of preparing oil-in water (O/W) emulsions. Also included are the materials and principles used to prepare gels, as well as a background to gel rheology.

Chapter 3 outlines the experimental design. The raw materials and the instruments available for laboratory work are presented. The methods and procedures followed in the laboratory are described. Chapter 4 analyses the experimental results. Eventual modifications to the experimental design are explained. Chapter 5 presents the conclusion and gives recommendations for possible further study. All references used are listed in Chapter 6. Additional supporting information is given in the Appendix.

2 LITERATURE REVIEW

2.1 Tablets

Tablets are solid pharmaceutical formulations containing a single dose of at least one active component, together with excipients. They are produced by compression of uniform volumes of solid particles (Aulton, 2002; Winfield & Richards, 2004).

Only a few tablets dissolve in water prior to administration. Effervescent tablets are the best known of these. These tablets disintegrate in water with evolution of gas bubbles. The gas most commonly released is carbon dioxide. This gas is usually created by a chemical reaction in water between citric acid and sodium bicarbonate (Lieberman *et al.*, 1989).

Effervescent tablets are unsuitable for the usage researched here: they demand the use of ingredients in the anhydrous state. Water, even in small amounts, may cause effervescence and destabilize the tablet during preparation and storage. Effervescent tablets may use ingredients with water molecules bound in a stable hydrate (Lieberman *et al.*, 1989). However, the majority of raw materials supplied for this research are liquids. Thus, it was decided to concentrate on a formulation of gel-based solid dosage.

2.2 Formulation of Tablets and Related Solid Dosage Forms

Tablets constitute the majority of the pharmaceutical dosage forms used. They consist of one active substance, at least, together with excipients. The role of excipients is to assist in the formulation process.

2.2.1 Excipients

Excipients are additives that assist in the formulation process. They promote the effectiveness, stability and identification of the dosage form during its use and storage (Moreton, 1995).

Excipients must be used only when they are explicitly needed. For example, in the preparation of emulsion tablets, *emulsifiers* are indispensable to promote and sustain the dispersion of small drops of one liquid in the second liquid with which it is immiscible. *Thickeners* may be necessary to increase the viscosity of the emulsion medium, which in turn contributes to stabilisation of the emulsion. *Superabsorbents* may be used to absorb huge amounts of water and thus convert aqueous formulations into solids or semi-solids. *Disintegrants* may be used to facilitate break-up of the solid dosage form.

There are many other categories of excipients. However, only these four categories are briefly reviewed below. This is to emphasise the idea of using only those excipients that are explicitly needed for the formulation.

Emulsifiers

Emulsifiers are substances that stabilise a dispersion of droplets of one liquid phase in another intrinsically immiscible liquid phase. An emulsifier can be a polyelectrolyte, a biopolymer, a surfactant, etc (Tadros, 2005). In this study, only the surfactants are further considered. They contribute to the formation and stabilisation of emulsions. Surfactants lower substantially the interfacial tension between the immiscible liquid comprising emulsions. They also enhance emulsion stability. Surfactants are dealt with in more detail in Section 2.12.

Thickeners

A thickener may be a natural or synthetic polymer. It is a polymer with a high molecular mass and a long linear chain. When put into aqueous solution, its linear chains may coil

randomly. Beyond its critical concentration, the chains entangle. At equilibrium, the chains swell and increase solution viscosity (Gupta *et al.*, 2002). The viscosity of the solution increases due to the cooperative motion of the entangled chains. This is how a polymer thickens by the associative mechanism (Tadros, 2005). Further details are given in Section 2.18, which deals with polymers in aqueous solution.

Superabsorbents

Superabsorbents are materials that can absorb and retain huge amounts of liquid (over 100 times their own mass). They are cross-linked polymers and thus are insoluble in water. The degree of cross-linking determines the absorbency and the swelling capacity. Highly cross-linked polymers have a tighter structure. Therefore, they swell less compared with the same polymeric networks with lower cross-linking density (Pepas *et al.*, 2000). Further details about superabsorbents are given in Section 2.18, which deals with polymers in aqueous solution.

Disintegrants

A disintegrant is a material incorporated into a solid dosage to aid disintegration. It expands when wet and rapidly breaks into small fragments. There are three mechanisms by which disintegrants overcome the cohesive strength of a solid dosage form: water uptake, swelling and effervescence. Swelling is the most extensively accepted mechanism of tablet disintegration (Banker & Rhodes, 1990). Cross-linked polymers may act as disintegrants. Further details are given in Section 2.18, which deals with polymers in aqueous solution.

To estimate how the total ingredients affect the properties of one another and the properties of the total formulation, a pre-formulation study should be performed (Lieberman *et al.,* 1989). This is the first step in a meticulous development of pharmaceutical dosage forms.

2.2.2 Pre-formulation

Pre-formulation is the investigation of the physical and chemical properties of the active substance alone and together with excipients (Lieberman *et al.*, 1989). The purpose is to determine whether there is an incompatibility between the potential ingredients of the formulation. Incompatibilities occur when the ingredients interact either physically or chemically, generating an unsuitable product. Incompatibility adversely affects the active substance and the performance of the total formulation (Collett & Aulton, 1990).

Very often, compatibility testing between liquids is skipped until the provisional formulation is finished. Then the stability of the formulation is tested directly (Grimm, 1987). When testing compatibilities between liquids, the major and most important concern is the pH profile.

By the end of the pre-formulation stage, the most suitable manufacturing process for the formulation should have been defined (Lieberman *et al.*, 1989).

2.3 Methods of Manufacture of Tablets and Related Dosage Forms

Tablets and related dosage forms are manufactured by compression of powdered ingredients. Before compression, the ingredients should be homogeneously mixed. When the ingredients cannot be mixed well by simple blending and mixing, they may be granulated before compression. Therefore, three methods are used for tabletting: direct compression, wet granulation, and dry granulation.

2.3.1 Direct compression

Direct compression is a process by which a dry powder blend of active(s) and excipients is compacted (Lieberman *et al.*, 1989). This process is used when the dose of the active

ingredient is less than 50 mg (Wells, 1988: 211). The amount of excipients required is small.

2.3.2 Wet granulation

Granulation is the process by which a powder blend of active(s) and excipients is made to adhere and form granules. In wet granulation, particle adhesion is achieved by addition of a liquid such as water or ethanol (Banker & Rhodes, 1990; Aulton, 2002). Wet granulation is the most popular method of tabletting. It is used most when the dose of the active ingredient exceeds 50 mg (Wells, 1988).

2.3.3 Dry granulation

Dry granulation is the process by which the natural cohesive properties of the ingredients are exploited. It consists in the compaction of large masses of powdered ingredients. These masses are crushed and sized to form suitable granules. Dry granulation is used when the ingredients are sensitive to moisture and heat. It requires that the ingredients have inherent cohesive properties (Ansel, 1985).

2.4 Characterisation of Tablets and Related Dosage Forms

A tablet or similar dosage form should continue to possess the same attributes from the immediate time of manufacture up to the time of use. These attributes characterise the tablet and can even determine whether the solid dosage form is satisfactory. The most important of these attributes are mechanical strength, content uniformity and bioavailability.

2.4.1 Mechanical strength

Mechanical strength refers to the resistance of a solid dosage form to fracture. It indicates whether the dosage form can withstand handling without being damaged

(Lieberman *et al.*, 1989). Mechanical strength depends on the pressure applied during the manufacture of the solid dosage form. Usually, high pressure produces a hard and strong solid dosage form. Preparation of satisfactory tablet or related solid dosage form requires pressure in the range of 13 – 178 MPa (Ansel, 1985).

Mechanical strength is assessed by the test for hardness and friability (Lieberman *et al.,* 1989). The test assesses the mass lost by a tablet subjected to a specified number of rotations in a friabilator. The friabilator simulates the tablet's resistance to fracture when handled, packaged and transported. The friability is calculated as a residual mass percentage, according to the following equation (Ansel, 1985).

$$Friability(\%) = 100\frac{m_1 - m_2}{m_1} \quad (1)$$

where m_1 is the tablet mass before the test, and m_2 is the tablet mass after testing.

2.4.2 Content uniformity

Content uniformity refers to similar composition of individual tablets of the same batch. It is required that all tablets contain the same composition and identical mass (Lieberman *et al.,* 1989: 132). Variations of the total tablet mass constitute a possible warning of variations in the overall tablet dosage (Rawlins, 1988).

There are two tests used to characterise tablets in this regard: one is the mass uniformity measurement and the other is the content uniformity test (Lieberman *et al.,* 1989). The mass uniformity measurement yields meaningful results only for tablets containing at least 50 mg of the active ingredient. This active content should constitute at least 50% of the total tablet mass (Banker & Rhodes, 1990).

The content uniformity test consists in assessing the amount of active substance in 10 tablets of the same batch. The average amount of the active substance in these 10 samples is calculated. Next, it is verified whether the content of the active substance in the individual tablets falls within the limits of the percentage deviation from the calculated mean (Aulton, 2002).

2.4.3 Bioavailability

Bioavailability expresses the rate at which the total dose of the active substance is released at the appropriate target location. It may be measured by tests of disintegration and dissolution (Lieberman *et al.,* 1989). Unless it has been verified that the tablet disintegration is the rate-determining step in dissolution, a disintegration test is not performed. This is because the dissolution test results eliminate the need for a disintegration test (Grimm, 1987).

The dissolution test measures the time that a tablet takes to dissolve completely in the *in vitro* and *in vivo* systems (Ansel, 1985; Grimm, 1987). It is required that the results at the *in vitro* and *in vivo* systems show some correlation (Grimm, 1987: 61).

2.5 Stability of Tablets and Related Dosage Forms

Long-term stability is required for a dosage form to have a long shelf-life. Proper understanding of the instability mechanisms of tablets and related dosages is essential for the formulation of a stable dosage form. There are three degradation mechanisms operative for tablets and similar dosages: chemical, physical and microbiological.

The physical and microbiological mechanisms of degradation may be incorporated into the chemical mechanism. Physical instability is caused by factors such as humidity, temperature and light radiation. Microbiological instability is affected by humidity and oxygen. These factors may affect the appearance, odour and texture, as well the dose

uniformity and the bioavailability of the solid dosage form (Grimm, 1987). *Humidity* may cause hydrolysis of the active substance (Grimm, 1987). This in turn may soften the solid dosage forms, or make them runny or sticky (Hess, 1985: 75). *High temperatures* and exposure to *light* may activate chemical reactions or increase the reaction rates. This in turn can lead to discoloration of the solid dosage surface, or even soften the dosage form (Waterman & Adami, 2005). *Oxygen* is involved in oxidation processes that can cause tablets to degrade or discolour.

Chemical degradation of tablets reduces the dose of the active substance or alters completely its chemical properties. It may change the physical properties of the tablet as well. Chemical instability is caused by degradation reactions such as hydrolysis, oxidation and photolysis (Wells, 1988).

2.5.1 Hydrolysis

Hydrolysis is the most common cause of degradation of the active substance (Wells, 1988). It is more likely to occur when the active substance possesses ester or amide bonds (Grimm, 1987). Although water is indispensable for hydrolysis, its presence does not necessarily lead to hydrolysis of the active. Hydrolysis is catalysed by factors within the solid dosage form. These factors may be acidic or basic functional groups present in the excipients. Temperature and light radiation may also affect hydrolysis of the active substance (Wells, 1988).

2.5.2 Oxidation

Unlike hydrolysis, oxidation of a solid dosage form is controlled only by external factors such as oxygen and other atmospheric oxidising agents. It can also be exacerbated by temperature and exposure to light. Oxidation of organic substances such as the phenol derivates, unsaturated fats and oils comprising the dosage is likely to occur due to photolytic cleavage of covalent bonds. This generates free radicals. Oxidation occurs

when atmospheric oxygen reacts with the unpaired electrons of the free radicals (Well, 1988).

2.5.3 Photolysis

Photolysis is simply a precursor of hydrolysis and oxidation reactions. Light radiation induces chemical degradation only in photosensitive molecules. Therefore, photolysis is dependent only on radiation energy (Well, 1988). The energy of radiation depends, in turn, on the radiation wavelength as indicated in Equation 2.

$$E = \frac{hc}{\lambda} \tag{2}$$

where:
E = the energy of radiation
h = the Planck's constant
c = the speed of light propagation in a vacuum
λ = the radiation wavelength

Since the energy is inversely proportional to the radiation wavelength, shorter wavelength radiations have higher energy. Degradation of photosensitive drug molecules occurs at wavelengths below the visible light radiation, that is, from the UV range (290 – 320 nm) to lower wavelengths (Wells, 1988).

Common sources of ambient radiation are: sunlight and the light of incandescent and fluorescent lamps. Sunlight at the surface of the earth contains radiation in the wavelength of 290 nm. Incandescent lamps emit radiation above 390 nm, whereas fluorescent lamps emit radiation between 320 and 380 nm (Wells, 1988).

Thus, exposure of the solid dosage form to incandescent lamps is safer than exposure to fluorescent lamps and sunlight. The effect of temperature is avoided by adequate control of storage conditions. Suitable packaging controls the adverse effects of light radiation and humidity (Hess, 1985).

2.6 Packaging of Tablets and Related Dosage Forms

Packaging provides safety and stability to the dosage form. Thus, it maintains the quality of the dosage form during transport, storage, display and use (Collett & Aulton, 1990; Winfield & Richards, 2004). Packaging also provides convenience, information and elegance for the product it contains. Therefore, it is useful from the immediate time of manufacture until the moment of dosage administration (Collett & Aulton, 1990).

Some packaging has direct contact with the dosage form and some does not. The packaging that has direct contact with the dosage form is defined as primary packaging. Secondary packaging is the additional covering material that provides mechanical protection for the primary packaging (Hess, 1985).

2.6.1 Requisites for packaging

Selection of the packaging material depends basically on the type of dosage form and its nature (e.g. sensitivity to humidity, temperature and light). An ideal packaging should satisfy the following requirements (Collett & Aulton, 1990).

- Chemically inert. Incompatibility between packaging and formulation ingredients or products may destroy both the packaging and the solid dosage form.
- Ability to withstand exposure to light – UV radiation catalyses chemical reactions in photosensitive materials.
- Imperviousness to humidity. Gain of moisture from the atmosphere may soften a tablet, cause chemical reactions and promote microbial growth, whereas moisture loss can cause a contraction and cracking of tablets.

- Impermeability to atmospheric gases, such as oxygen. Oxygen supports microbial growth and is involved in oxidation processes as well.
- Convenience of handling. It should be easy to remove the product before use.
- Allow identification of product. For the purpose of product identification, it is required that the packaging be either distinctive or able to be labelled.
- Cheap and economical. Generally, light packaging costs less than heavy containers, especially during transport.

This list is generic. Not all the requirements have to be satisfied simultaneously. It depends on the type and nature of the dosage form. For instance, some dosage forms may not be sensitive to humidity. Therefore, their packaging will not be required to be impervious to moisture.

2.6.2 Unit dose packaging

Some packages are intended to be used only once. They are disposable packaging known as unit dose packages. This name typically indicates that a single tablet, for instance, is enclosed in its individual, non-reusable pack. The unit dose packages most widely used and marketed are strip packs and blister packs (Hess, 1985; Winfield & Richards, 2004).

Strip packs

Strip packs are two laminated aluminium foils sealed in the marginal zone surrounding each individual solid dosage form (Figure 3) (Hess, 1985; Winfield & Richards, 2004). They are completely closed pockets that form an excellent barrier against moisture penetration. For this reason, they have been well employed to pack tablets in tropical countries (Hess, 1985).

Figure 3: Illustration of both sides of the same strip pack. Each side consists of an aluminium foil. The two foils are laminated and sealed in the marginal zone surrounding the solid dosage form

Depending on the requirements for the product, a supplementary web can be used to add strength to the thinner aluminium foil. This supplementary web may also block little holes that may occur in the foil (Winfield & Richards, 2004). This additional layer may be applied as an inner layer, that is, within the strip pack.

Blister packs

Commonly, blister packs are transparent thermoformed plastic sheets laminated and sealed with an aluminium covering foil (Figure 4) (Hess, 1985; Winfield & Richards, 2004). The plastic sheet is a rigid base material that contains cavities for each unit dose. Thus, blister packs are more rigid than strip packs (Winfield & Richards, 2004). The individual cavities of blister packs may be broken up and detached. This occurs with a perforated plastic base (Hess, 1985; Winfield & Richards, 2004).

Blister packs are also employed to pack tablets in tropical countries. In this case they have an additional aluminium foil layer to enhance the barrier against high humidity. They are known as tropicalised blister packs (Winfield & Richards, 2004).

Figure 4: Illustration of both sides of the same blister pack. The transparent thermoformed plastic sheet containing cavities for each unit dose (placed on the right) is the base material. An aluminium covering foil is laminated and sealed with the rigid plastic sheet, as showed on the left.

2.7 Emulsions

An emulsion is a mixture of intrinsically immiscible liquid phases. It consists of droplets of at least one liquid dispersed in another liquid. The disperse phase, also known as the internal phase or discontinuous phase, is the liquid broken up into droplets. The liquid surrounding the disperse phase is known as the dispersion medium; it is also called the external phase or continuous phase.

The surface tension of mutually immiscible liquid phases is positive. Therefore, emulsions are thermodynamically unstable. Nevertheless, they are widely used because:

- Maximise the solubility and effectiveness of a substance of interest;
- Allow simultaneous exploitation of the properties of the immiscible phases;
- Kinetically stable for up to several years.

The process of preparing an emulsion is known as *emulsification*. It consists in the fragmentation of one liquid phase into the other. This is achieved by shearing the immiscible liquids in the presence of surfactants. Water is one of the two most common immiscible liquid phases. The other phase is characterised by a lower dielectric constant and is frequently designated as oil (Baglione *et al.,* 2000).

2.8 Classification of Emulsions

There are several types of emulsion. The simplest are oil-in-water (O/W) emulsions and water-in-oil (W/O) emulsions. The former consists of droplets of lipophilic liquid in water. W/O emulsions are the opposite: droplets of water dispersed in a non-polar medium.

Whether the emulsion is O/W or W/O can be assessed by using one of the following techniques (Martens, 1964; Bennett *et al.,* 1968):

- Electrical conductivity – Emulsion conductivity depends on the conductivity of the external phase. Therefore, an O/W emulsion will conduct electricity since water is the continuous phase. A W/O emulsion will not conduct electricity.
- Direction of creaming/sedimentation – If the O phase is denser than the W phase, creaming of oil droplets indicates the presence of W/O emulsions. Conversely, sedimentation of oil droplets indicates the presence of O/W emulsions. If water is denser than the oil, the opposite is true.
- Emulsion dispersibility – The medium in which an emulsion disperses is analogous to the external phase of that emulsion. Therefore, an O/W emulsion will disperse in water. Conversely, a W/O emulsion will disperse in oil.

When assessing the emulsion type, a single method can yield incorrect results. Therefore, measurements made by one method should be confirmed by another method. It should not be used a single method to determine the nature of an emulsion.

A W/O emulsion is more softening to the skin than an O/W emulsion. This is because W/O resists drying out and also resists removal by contact with water (Ansel & Popovich, 1990). However, an O/W emulsion is preferred to a W/O emulsion for environmental reasons: an O/W emulsion exposes water to the atmosphere rather than oil (Israelachvili, 1994).

2.9 Emulsion Properties

The most important properties of emulsions in practical formulations are viscosity and particle size.

2.9.1 Viscosity

Viscosity is a measure of a fluid's resistance to flow. Emulsion viscosity is affected by the (Lieberman *et al.,* 1988):

- Viscosity of the external phase
- Size distribution of dispersed globules
- Volume fraction of the dispersed phase
- Method of emulsification and other factors.

The volume fraction of the dispersed phase is the ratio of the dispersed phase volume to the total volume. The viscosity of an emulsion affects its stability: highly viscous emulsions tend to be stable against phase separation. Enhancement of emulsion viscosity may be achieved by increasing the viscosity of the external phase, changing the proportion of the phases, etc. (Bennett *et al.,* 1968).

2.9.2 Particle size

Emulsion particle size may be considered as the diameter of the droplets of the internal phase. It is usually determined by observing the emulsion under a microscope. When the droplets are not uniform, the size occurring most frequently is considered as the emulsion particle size. However, in this case, the values of the smallest and largest particles should be mentioned as the range of particle size (Lieberman *et al.,* 1988). Particle size affects the viscosity and appearance of emulsions. Thus, it has a great effect on the emulsion's stability.

2.10 Stability of Emulsions

Emulsions are not thermodynamically stable. However, most of them are kinetically stable, i.e. the rate of physical separation of the immiscible phases is sufficiently slow not to affect product performance over the desired product life time. Thus, the control of emulsion stability is limited to the kinetic control of oil and water phase separation.

There are five mechanisms of physical separation of emulsions: creaming/sedimentation, flocculation, coalescence, phase inversion and Ostwald ripening.

2.10.1 Creaming/sedimentation

Creaming refers to the formation of an upper phase made up of emulsion droplets. Sedimentation is the opposite, i.e. the formation of a lower phase made up of emulsion droplets (Figure 5). Creaming takes place in systems where the density of the disperse phase is lower than that of the dispersion medium. Conversely, sedimentation occurs in systems where the density of the dispersion medium is lower than that of the disperse phase (Baglione *et al.*, 2000).

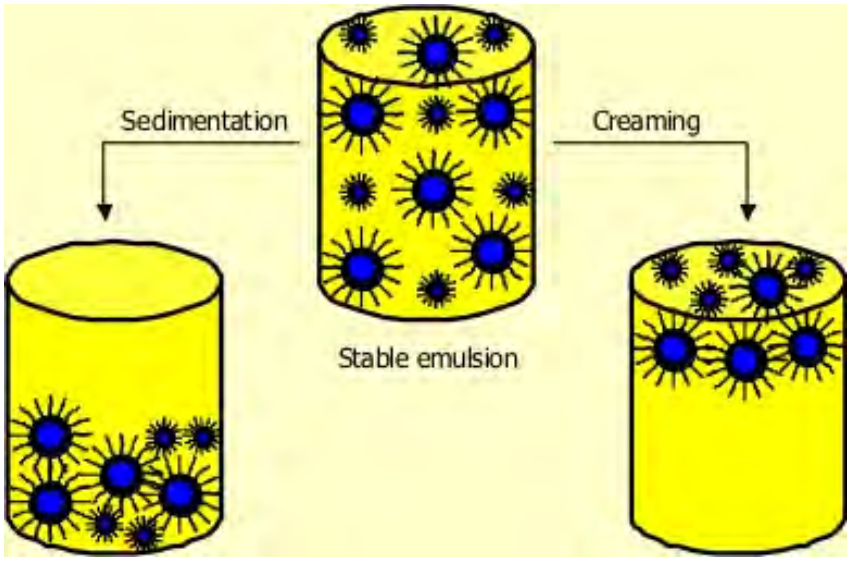

Figure 5: Schematic representation of sedimentation and creaming of an emulsion. In creaming, an upper phase made up of emulsion droplets is observed. In sedimentation it is observed the opposite: a lower phase made up of emulsion droplets.

Creaming and sedimentation are caused by gravitational or centrifugal forces. In the absence of other phenomena, the droplets retain their identity. Therefore, the emulsion can be restored to its original state by simple shaking (Tadros, 2005).

Creaming/sedimentation is only an aesthetic disturbance. It is irrelevant to the performance required in many applications. However, it is undesirable for emulsions stored in transparent packaging. In addition, it may turn into flocculation and coalescence.

The rate of separation between the disperse phase and the dispersion medium may be estimated using Stokes' law for dilute emulsions (Collett & Aulton, 1990; Aulton, 2002; Roland *et al.,* 2003; Winfield & Richards, 2004):

$$\upsilon = \frac{d^2(\rho_1 - \rho_2)g}{18\eta} \qquad (3)$$

where:

υ = settling velocity

d = size of the droplets (droplet diameter)

ρ_1 = density of the disperse phase

ρ_2 = density of the dispersion medium

g = gravitational constant

η = viscosity of the dispersion medium

Equation 3 shows that the rate of phase separation will be lower if the:

- Viscosity of the dispersion medium is higher;
- Difference between the density of the disperse phase and the dispersion medium is smaller;
- Size of the droplets is smaller.

Therefore, matching the densities or the viscosities of the disperse phase and the dispersion medium may impede creaming and sedimentation. This tends to annul the separation velocity of particles. The most common way of increasing the viscosity of an aqueous medium is to use thickeners (Tadros, 2005). The common manner of adjusting oil density is to mix a light and a heavy oil (Rawlins, 1988). When the oil's viscosity is high, it takes time to deform and disperse an oil droplet (Tadros, 2005).

2.10.2 Flocculation

Flocculation is an aggregation of droplets. It occurs following the collision of droplets, when they are no longer able to split themselves (Baglione *et al.*, 2000). Flocculation can occur before, during or after creaming/sedimentation, but it is likely to follow creaming/sedimentation (Lieberman *et al.,* 1988).

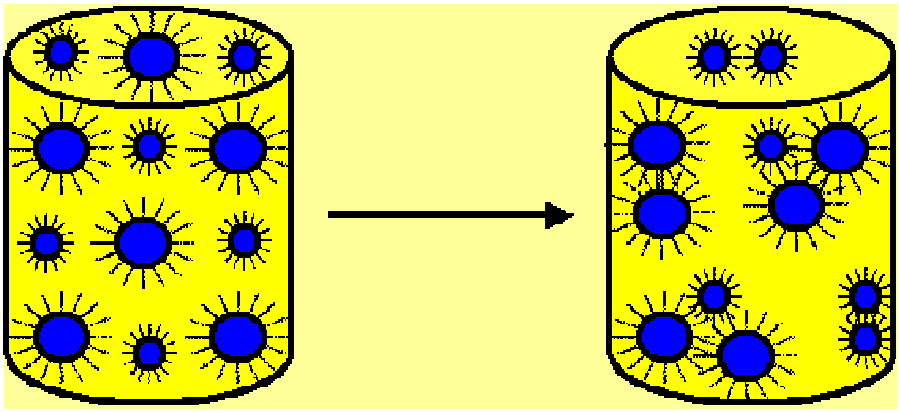

Figure 6: Schematic illustration of emulsion flocculation. Different droplets become attached to each other. However, the droplets retain their identity.

Flocculation results from van der Waals forces. It occurs when the distance between the particles is a small (Tadros, 2005). In flocculation (Figure 6), different droplets become attached to each other. However, they are still separated by a thin film of the continuous phase. Flocculation can be strong and irreversible (even despite shaking) or

weak and reversible. This depends on the magnitude of the van der Waals forces (Tadros, 2004).

Prevention of flocculation requires counterbalance of the attractive van der Waals forces. This may require repulsive forces such as electrostatic or steric forces. Electrostatic forces can be achieved using ionic surfactants. Steric forces can be created by non-ionic surfactants (Baglione *et al.*, 2000; Tadros, 2005).

The mechanism of electrostatic stabilisation is explained on the basis of mutual repulsion of like charged particles. Ionic surfactants introduce into the O/W emulsion charges that produce an electrical double layer (EDL) around the dispersed droplets. Anionic surfactants, for example, adsorb onto the interface of the oil and water and create a negative charge on the surface of the oil droplets. This surface charge is responsible for the droplets' separation. However, the repulsion does not occur directly between the surfaces of two droplets – there is an electric surface potential around the droplets owing to their surface charge. This potential influences the adsorption of counter-ions. Some counter-ions adsorb in a so-called Stern layer (SL), near the droplets' surface. The remaining counter-ions locate in a so-called diffuse layer (DL). The EDL comprises the SL and the DL. Each emulsion droplet has its own EDL and this maintains the droplet's electro-neutrality. Simultaneously, it maintains the separation between droplets. Droplet repulsion occurs when two particles possessing EDLs of the same sign approach each other. For repulsion to occur, the distance between two approaching EDLs should be less than twice the EDL thickness. The valency of the counter-ions strongly affects the thickness of the EDL (Tadros, 2005).

The mechanism of steric stabilisation in O/W emulsions may be explained in the following manner: the hydrophobic portion of a non-ionic surfactant fixes to the surface of the oil particles; the hydrophilic portion projects into the aqueous medium. If the hydrophilic portions are fully hydrated, they will have freedom to extend. When two oil particles approach each other, as the distance between them becomes smaller,

interpenetration of the hydrophilic portions of the surfactant may occur. Since these hydrophilic portions are hydrated, their overlaps cause some dehydration. Therefore, an imbalance in water concentration between the dispersion medium and the region in between the hydrophilic portions of the surfactant occurs. Owing to this water imbalance, the osmotic pressure will tend to force the water molecules back in between the hydrophilic portions of the surfactant. As a result, the oil particle will maintain some separation, i.e. they exhibit repulsion (Aulton, 2002; Tadros, 2005; Gregory, 2006).

2.10.3 Coalescence

When droplets of an emulsion contact each other, the liquid layer between the two separated droplets contracts (Figure 7). The closer the droplets become, the higher the risk of the colliding particles coalescing (Tadros, 2005). Similar to flocculation, coalescence is also an aggregation of droplets. However, unlike in flocculation, the droplets' aggregation results in larger droplets. Coalescence occurs due to collisions owing to Brownian motion of droplets. It is subsequent to creaming and flocculation (Baglione *et al.*, 2000).

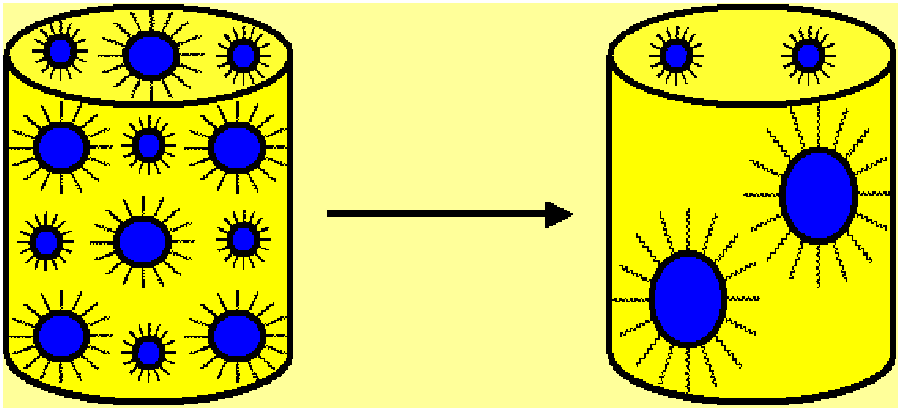

Figure 7: Schematic illustration of emulsion coalescence. Some droplets aggregate yielding larger droplets.

Coalescence is an irreversible emulsion breakdown process. It is prevented by repulsive electrostatic or steric forces (Tadros, 2005). Limiting the volume fraction of the dispersed phase below 60% also tends to prevent coalescence as it prevents close contact between droplets (Bennett, 1968).

2.10.4 Phase inversion

Phase inversion is the phenomenon whereby the internal phase and external phase exchange: the internal phase becomes the continuous phase and the external phase forms the droplets. It is illustrated in Figure 8.

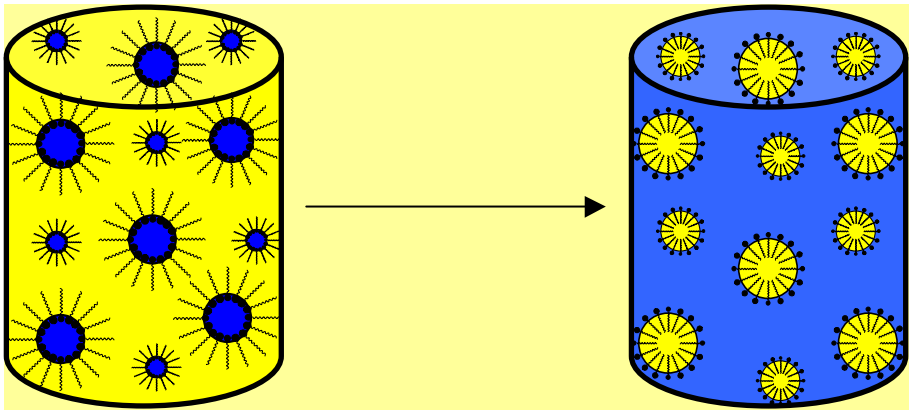

Figure 8: Schematic representation of phase inversion from W/O emulsion to O/W emulsion.

Phase inversion occurs when the volume fraction of the disperse phase exceeds a theoretical limit of about 75% (Bennett, 1968; Lieberman *et al.,* 1988; Collett & Aulton, 1990). Phase inversion may also occur due to changes in the properties of the surfactant. These changes are likely to happen beyond the cloud point or under addition of an electrolyte (Tadros, 2004; Tadros 2005). Beyond the cloud point, some surfactants do not dissolve.

2.10.5 Ostwald ripening

Ostwald ripening is the diffusion of molecules from small to large droplets. The small droplets end up disappearing, while the large droplets grow (Figure 9). This occurs because small droplets are less energetically favoured than larger droplets. Baglione *et al.* (2000) and Tadros (2005) explained the occurrence of Ostwald ripening as follows: the surface tension in small droplets is much higher than in large droplets. This is due to the lower volume and higher surface curvature of the small droplets. A higher internal pressure, the so-called Laplace pressure, balances the higher surface tension. Thus, the molecules inside the small droplets have higher free energy than those in large droplets. Since the systems tend to minimise their surface energy, the molecules with a higher free energy diffuse to the surface of the energetically favourable system.

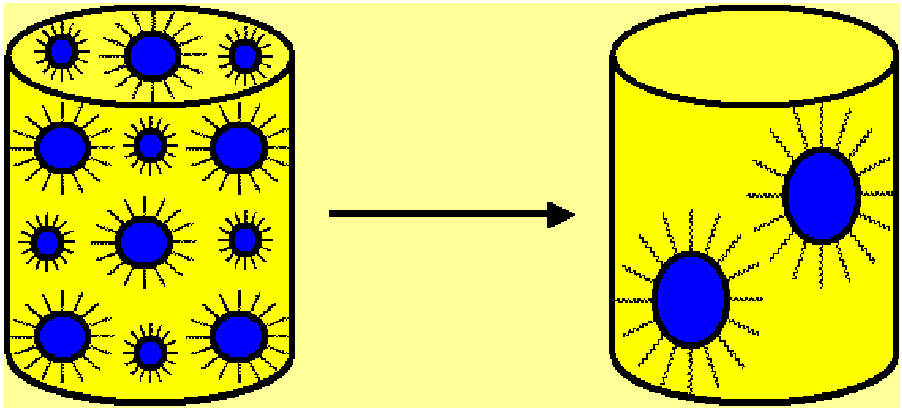

Figure 9: Schematic illustration of Ostwald ripening. The small droplets end up disappearing, while the large droplets grow

To avoid or, at least reduce, Ostwald ripening it may be necessary to (Tadros, 2004; Tadros 2005):

- Reduce interfacial tension - using surfactants
- Incorporate a small fraction of highly insoluble oil to reduce the diffusion of the more soluble oil molecules

- Increase the ionic strength of the aqueous phase to slow down the transport rate of the non-polar phase. Care must be taken because surfactants may be sensitive to external ions.

The highest stability of practical emulsions is observed at 40 – 60% volume fraction of the disperse phase (Bennett *et al.*, 1968). Beyond this volume fraction, the number of droplets and their proximity to each other may result in coalescence (Rawlins, 1988; Kerihuel *et al.,* 2006).

An emulsion's stability depends on the forces acting upon and between its droplets. However, because the droplets are separated by molecular layers of the external phase, emulsion behaviour is dominated by what happens in its interface (Craig, 1997).

2.11 Interface

The interface of immiscible liquid phases is the boundary between them. It is not a simple geometrical plane but a layer of certain thickness. It consists, essentially, of adjacent monolayers of the two liquids (Davies & Rideal, 1963; Ziles, 2005).

The molecules in the interface possess properties different from those in the interior of each phase (Davies & Rideal, 1963). Inside the phases, each molecule has analogous molecules as nearest neighbours. Conversely, the molecules in the interface have dissimilar molecules on the boundary side. Figure 10 illustrates that inside the phases each molecule is equally attracted by analogous molecules. This results in a symmetric attraction between adjacent molecules. However, at the interface the molecules are subjected to inward unsymmetrical attractive forces. Therefore, molecules in the interface tend to move towards the interior of their analogous phase.

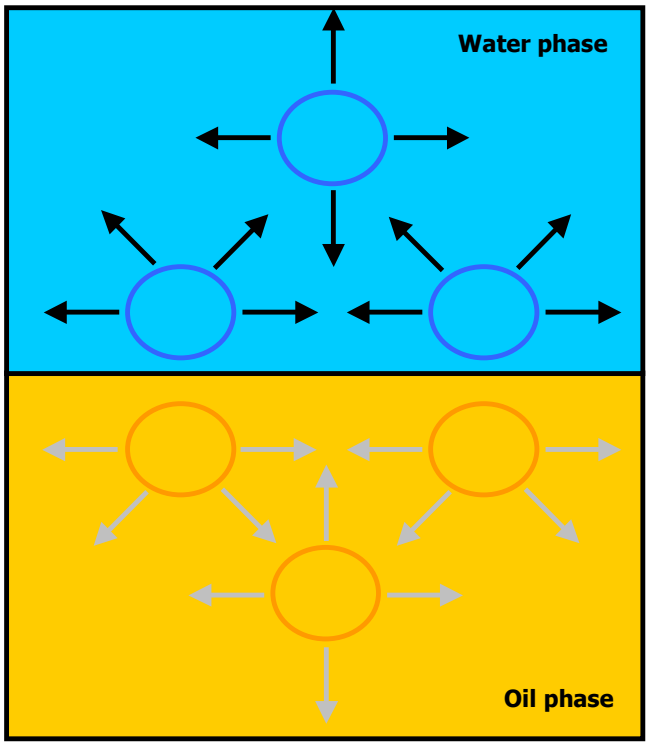

Figure 10: Schematic representation of the attractive forces between molecules at the interface of two immiscible liquids and in the interior of the two phases. Inside the phases a molecule is equally attracted by analogous molecules. At the interface the molecules are subjected to inward unsymmetrical attractive forces. The molecules in the interface tend to move towards the interior of their analogous phase.

The departure of molecules from the interface to the interior of their phase contracts the surface of the phase and increases the distance between the adjacent monolayers of the immiscible liquids. Simultaneously, the surface energy of each phase decreases. This creates the interfacial tension (Davies & Rideal, 1963; Rawlins, 1988; Aulton, 2002).

Interfacial tension is a form of work or potential energy that attempts to minimise the energy of a phase by lessening its surface area (Ziles, 2005). The interfacial tension is responsible for the tendency of liquids to form a perfect sphere – geometry of the

minimal 3D area – when placed into an immiscible liquid bulk. All liquids tend to adopt a spherical shape to minimise the exposed surface area.

The mechanism through which the contraction of a liquid's surface area occurs has been explained by Davies & Rideal (1963): each drop of liquid has in its interior forces that promote association of molecules of the same substance. These forces oppose the deformation of one drop into several small drops. If these forces bring into contact drops of the same liquid, these drops tend to coalesce. Coalescence makes one large drop, which has a smaller surface area than the total surface area of the constituent individual drops. The force that causes drops of liquids to resist breaking up into droplets is called the interfacial tension.

Martens (1964) stated that the stronger the attractive forces between molecules of one liquid the greater is the surface tension of that liquid phase. Water has an extremely high surface tension compared with other solvents due to the strong associative tendency of its molecules.

The interfacial tension σ_{OW} between two immiscible phases O and W in contact may be estimated using the following equation:

$$\sigma_{OW} = \sigma_O + \sigma_W - 2\sqrt{\sigma_O \sigma_W} \tag{4}$$

This postulation is based on the values of the surface tensions of the corresponding pure fluids. If $\sigma_{OW} < 0$, then the implication would be that the attraction between the O phase O and the W phase is greater than the attraction between two analogous O phases, or between two analogous W phases. Therefore, $\sigma_{OW} < 0$ would imply complete miscibility between The O phase and the W phase. However, since the arithmetic mean is always higher than the geometric mean, $\sigma_{OW} > 0$. This implies

immiscibility between the O phase and the W phase. However, σ_{OW} can be annulled or, at least, reduced by adding a surfactant to the system OW.

2.12 Surfactants

The word *surfactant* stands for surface-active agent. A surfactant has a hydrophilic (polar) head, which mixes thermodynamically with water. It has a lipophilic (non-polar) tail, which mixes thermodynamically with oil (Figure 11). The hydrophilic group may be a carboxylate, sulphate, sulphonate, phosphate, alcohol or alcohol-ethoxylate. The lipophilic group may be a long hydrocarbon chain as in fatty acids (Tadros, 2005).

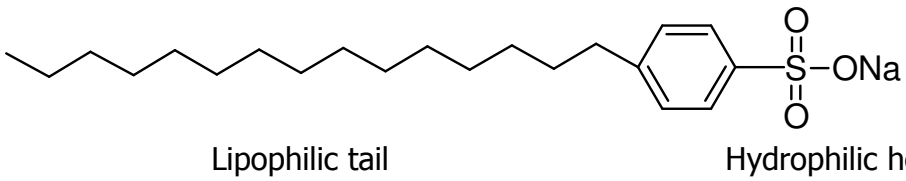

Figure 11: Schematic of a typical surfactant molecule showing a hydrophilic head and a lipophilic tail.

Since the hydrophilic group locates in water and the lipophilic group locates in oil, surfactant molecules accumulate at the interface. The accumulation of surfactant molecules in the interface is known as *adsorption*. Adsorption of surfactant creates an orientated monolayer (Figure 12). This lowers the tension between oil and water. The monolayer adsorption is complete when the solubility limit of a surfactant is reached. Then, the lowering of the interfacial tension stops (Tadros, 2005).

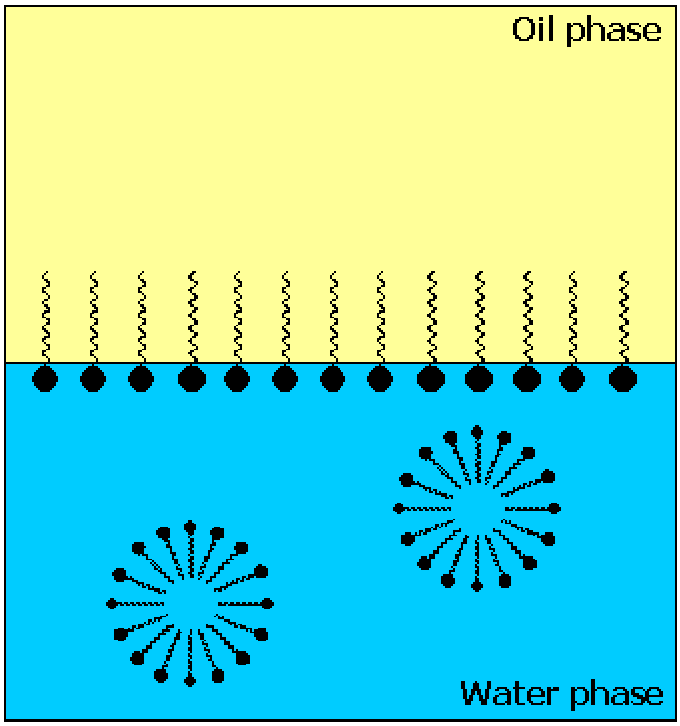

Figure 12: Schematic representation of a surfactant monolayer and concentration of surfactant in the interior of the water phase. The surfactant monolayer is adsorbed in the interface. The hydrophilic portion locates in water and the lipophilic portion locates in oil. When the solubility limit of a surfactant is reached micelles are formed in the interior of the continuous phase.

Continued addition of surfactant above its solubility limit leads to the formation of dispersed surfactant aggregates called micelles. The maximum solubility value of the surfactant required to complete the monolayer adsorption is known as the critical micelle concentration (CMC). Figure 12 illustrates that beyond the CMC, the surfactant concentrates in the interior of the continuous phase in the form of micelles.

2.13 Types of Surfactant

Surfactants are commonly classified as anionic, cationic, non-ionic and amphoteric, depending on the nature of the polar group.

2.13.1 Anionic surfactants

An anionic surfactant is one in which the polar group carries a negative charge when it is dissolved or dispersed in water (Figure 13). In aqueous solution, the negative charge of the surfactant's head attracts the positive charge of water molecules. Anionic surfactants are manufactured at relatively low cost compared to the other surfactant types. Phosphoric acid salts are one good example of anionic surfactants.

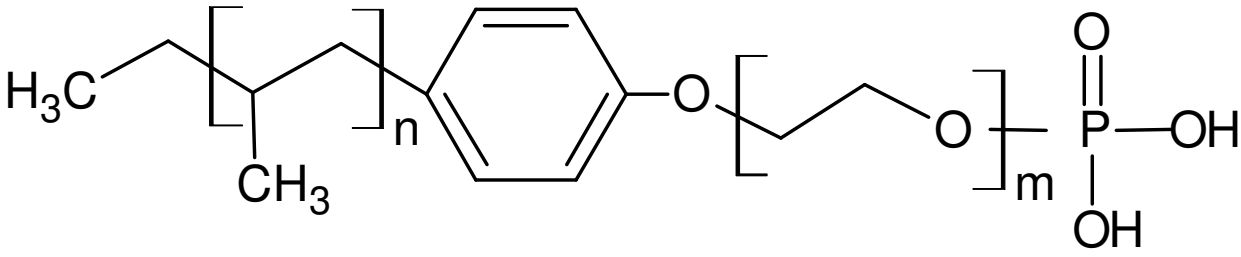

Figure 13: Schematic illustration of the acid form of a typical anionic surfactant.

2.13.2 Cationic surfactants

When a surfactant ionises in water yielding a positive ion, it is classified as a cationic surfactant. This kind of surfactants is incompatible with most anionic surfactants. Cationic surfactants are insoluble in hydrocarbon oil, but generally soluble in water. They tend to be stable to pH variations (Tadros, 2005). Quaternary ammonium salts are one good example of cationic surfactants (Figure 14).

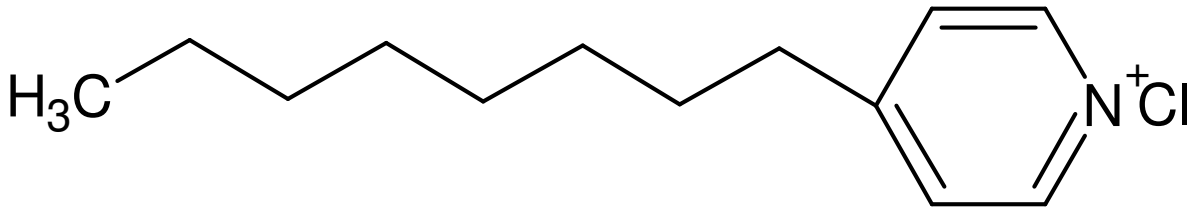

Figure 14: Schematic representation of a typical cationic surfactant.

2.13.3 Non-ionic surfactants

A non-ionic surfactant is one that does not ionise since it is characterised by the absence of an electrical charge in its head (Figure 15). The most common non-ionic heads are the ethylene oxide (EO) group and hydroxyl (OH) group. Non-ionic surfactants are compatible with all other types of surfactant. Alcohol ethoxylates are one good example of non-ionic surfactants.

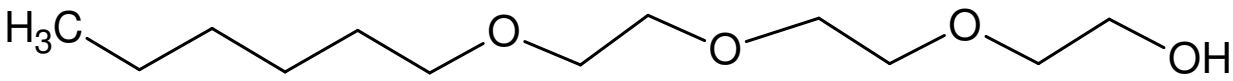

Figure 15: Schematic illustration of typical non-ionic surfactant comprising ethylene oxide (EO) and hydroxyl (OH) groups as its hydrophilic portion.

A particular temperature limits the performance of non-ionic surfactants. Unlike most other organic compounds, which dissolve continuously when the temperature increases, non-ionic surfactants dissolve only up to a certain temperature limit – the so-called *cloud point*. After the cloud point, the surfactant drops out of the solution, making it turbid. Therefore, a non-ionic surfactant performs best just below its cloud point (Tadros, 2005).

The CMC of non-ionic surfactants tends to be lower than that of anionic surfactants. Anionic surfactants have CMCs about two orders of magnitude higher than the CMCs of corresponding non-ionic surfactants with same alkyl chain length (Tadros, 2005).

2.13.4 Amphoteric surfactants

An amphoteric surfactant is one that possesses both cationic and anionic groups in its head. Thus, in an acidic medium its head carries a positive charge, whereas the same head carries a negative charge in a basic medium (Figure 16). These surfactants are compatible with all other types of surfactant. At the iso-electric point, amphoteric surfactants are known as *zwiterionic* surfactants. They ionise the positive and negative groups to the same extent. These opposite charges neutralise each other (Pilemand, 2002). Betaines are very good examples of zwiterionic surfactants. They are neutral chemical substances with a positively charged functional group (e.g. ammonium ions), and a negatively charged functional group (e.g. carboxylic acid ions).

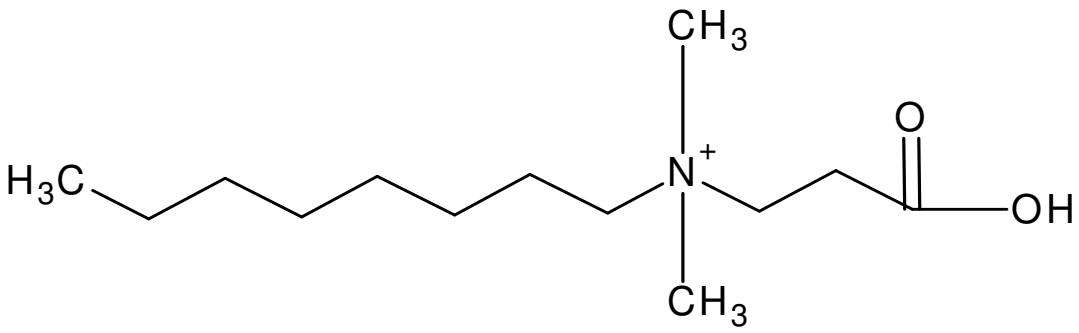

Figure 16: Representation of a typical amphoteric surfactant showing the simultaneous presence in its head of an ammonium ion as a cationic group and a carboxylic acid as an anionic group.

2.14 Choice of Surfactant

To select the proper surfactant it is necessary to define as accurately as possible the properties required in the emulsion. These might be: (i) type of emulsion; (ii) degree of stability; (iii) equipment available; etc (Martens, 1964). It may be important to consider properties like CMC, cloud point, phase inversion temperature (PIT), Krafft point, and the hydrophilic-lipophilic balance (HLB) value (Pilemand, 2002).

PIT is the temperature at which the hidrophile-lipophile properties of the emulsifier just balance. Above the PIT, the emulsion undergoes phase inversion. In turn, Krafft point is the temperature at which the aqueous solubility of a surfactant becomes equal to the CMC. Below the Kraft point, the micelles cannot be formed due to the low solubility of the surfactant in an aqueous medium. HLB is a number calculated and assigned to emulsifiers to indicate their polarity. The range of HLB values has been arbitrarily defined. Hydrophilic emulsifiers have been assigned higher HLB numbers than lipophilic emulsifiers. The HLB number affects the role of emulsifiers, as shown in Table 1 (Ansel & Popovich, 1990).

Table 1: HLB values of emulsifiers and their role (Ansel & Popovich, 1990)

HLB	Activity
1 – 3	Antifoaming
3 – 6	W/O emulsifier
7 – 9	Wetting agent
8 – 18	O/W emulsifier
13 – 15	Detergent
15 – 20	Solubiliser

Two or more emulsifiers may be blended to perform a simultaneous combined activity. Each emulsifier has its own water-loving portion and oil-loving portion. The water-loving

portion consists of the ethylene oxide (EO) chain. The longer the EO chain, the more water-loving is the emulsifier. The functions to be expected from emulsifiers according their EO content are presented in Table 2.

Table 2: Moles of EO in emulsifiers and their applications

Moles of EO	**Function**
1 – 3	Emulsify small amounts of water in bigger amounts of oil
4 – 6	Emulsify small amounts of oil in bigger amounts of water
7 – 12	Cleaning activity, dirt removal
> 12	Solubilising, suspending and other special properties

Surfactants tend to stabilise emulsions according to the Bancroft rule. This rule is purely empirical and states that 'the liquid in which the solubility of the emulsifier is higher becomes the continuous phase of the emulsion' (Baglione *et al.,* 2000). Therefore, hydrosoluble surfactants are expected to stabilise O/W emulsions. Liposoluble surfactants may stabilise W/O emulsions.

2.15 Emulsification Theory

The emulsification process may be represented as in Figure 17. The starting point is when two immiscible phases, such as oil and water, are in contact. At this point, a Gibbs free energy given by Equation 5 characterises the system (Tadros, 2005):

$$\mathbf{G}_1 = \mathbf{A}_1\boldsymbol{\sigma}_1 - \mathbf{TS}_1 \qquad (5)$$

where:

The subscript **1** denotes the starting point of the emulsification process

G = Gibbs free energy

A = the surface area (or rather interfacial area)

σ = interfacial tension between the immiscible phases

T = the temperature

S = the entropy

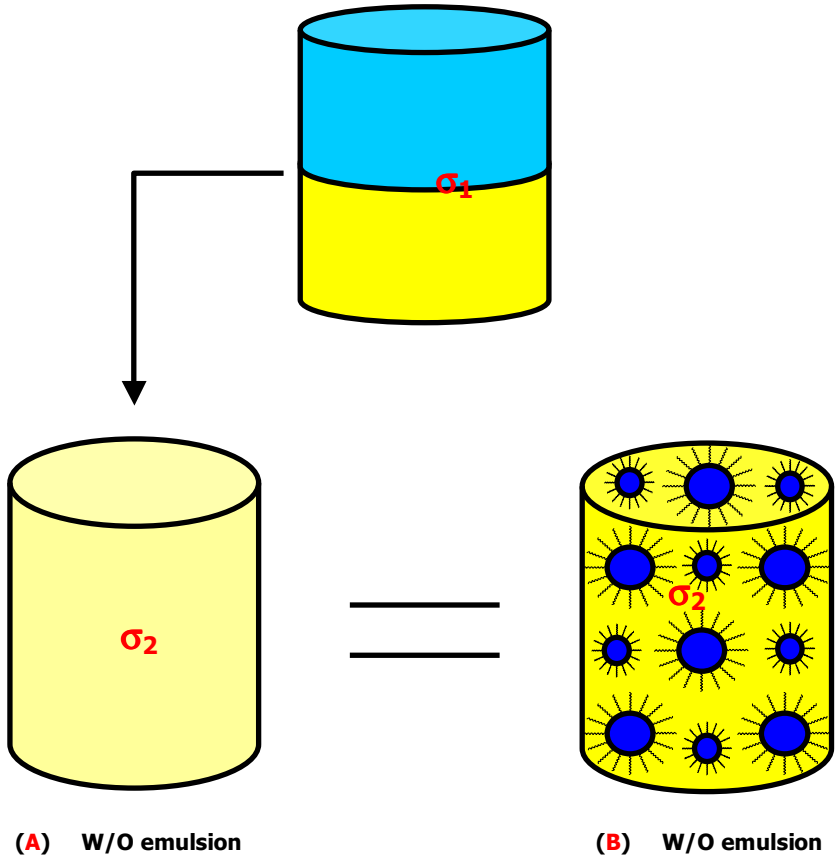

Figure 17: Schematic model of the emulsification process. A represents the resultant W/O emulsion observed through naked oil. B represents the same W/O emulsion observed through microscope.

According to Tadros (2005), usually $\mathbf{A}_1 \boldsymbol{\sigma}_1 >> \mathbf{TS}_1$ and hence $\mathbf{G}_1$ is often positive. This is also true for $\mathbf{G}_2$, the Gibbs energy, in Equation 6. The subscript **2** denotes the stage when a surfactant has been added to the system and some energy has been applied (Figure 17).

$$\mathbf{G}_2 = \mathbf{A}_2 \boldsymbol{\sigma}_2 - \mathbf{TS}_2 \quad (6)$$

The difference between the ending point **2** and the initial stage **1** gives the total variation of Gibbs free energy, $\Delta\mathbf{G}$:

$$\Delta\mathbf{G} = \mathbf{G}_2 - \mathbf{G}_1 = (\mathbf{A}_2 \boldsymbol{\sigma}_2 - \mathbf{A}_1 \boldsymbol{\sigma}_1) - \mathbf{T}(\mathbf{S}_2 - \mathbf{S}_1) \quad (7)$$

In Equation 7, the first brackets contain the total enthalpic term and the last brackets contain the total entropic term. The subdivision of a large drop into small droplets makes $\mathbf{A}_2$ much bigger than $\mathbf{A}_1$. A large number of droplets increases the entropy. Therefore, $\mathbf{S}_2$ is much bigger than $\mathbf{S}_1$. Since it is generally assumed that $\mathbf{A}_X\boldsymbol{\sigma}_X >> \mathbf{TS}_X$, Equation 7 shows that $\Delta\mathbf{G}$ will be positive. Emulsification is therefore thermodynamically disadvantaged: it is non-spontaneous and the emulsion is unstable. However, if $\boldsymbol{\sigma}_2$ is lowered below $\boldsymbol{\sigma}_1$, the total enthalpic term in Equation 7 will decrease lowering $\Delta\mathbf{G}$ (Tadros, 2005).

The lowering of $\boldsymbol{\sigma}_2$ requires usage of a suitable surfactant at its best concentration. However, on its own, a surfactant is not sufficient to cause the spontaneous formation of an ordinary emulsion. The surfactant (i) reduces interfacial tension favouring droplets formation. It also (ii) maintains the separation of the droplets by forming barrier at the interface with the medium. Unfortunately, it also (iii) increases the Laplace pressure. This stimulates droplets growing and opposes its deformation and subsequent break-up into smaller drops (Tadros, 2005).

Equation 8 shows that small drops have high Laplace pressure (ΔP). A high stress is required to deform these drops. Intensive mixing, using high-speed mixers, provides enough energy to overcome ΔP and thus deform the drops sufficiently to cause its break-up (Tadros, 2005).

$$\Delta P = \frac{\sigma}{d} \tag{8}$$

Where **σ** is the interfacial tension between the two immiscible phases, and **d** is the droplet diameter.

2.16 Preparation of O/W Emulsions

The formulation of emulsions may be carried out by a direct route or by the phase inversion route. It is best to start by examining the effects of the W and O phases, as well the concentration of surfactant and co-surfactant (if used) in the emulsion before its formulation.

To study the effects of surfactants, a dispersion of 40 – 60% volume fraction as a starting point may be prepared. This dispersion is used to determine the optimum concentration of surfactants. It requires the construction of curves of viscosity of dispersion vs. concentration of surfactant. These curves tend to be U-shaped. The region of the minimum value of viscosity is the optimum range of the concentration of surfactants. This is because, according to Tadros (1982a and 1982b), the increase in the viscosity after the minimum is an indication of emulsion instability (droplets aggregation and subsequent increasing in the diameter).

Emulsions should be prepared using the optimum concentration of surfactant. Several methods can be used to prepare emulsions. The finest emulsions may be obtained if (Sajjadi, 2006):

- A blend of surfactants is used
- Each surfactant is dissolved in the phase with the inherently highest solubility
- The phase inversion route is followed.

When O/W emulsions are being prepared, the phase inversion method consists in adding the W phase to the O phase. The addition is made gradually under continuous low-shear stirring. The main advantages of the phase inversion method are:

- Smaller droplets of the disperse phase are produced than would be possible by the direct route (Rawlins, 1988)
- An emulsion can be obtained without mechanical work: simple shaking or stirring can disrupt the disperse phase (Baglione *et al.*, 2000).

In the phase inversion route, high-shear stirring is used only for better homogenisation of the emulsion. However, such stirring should not be so vigorous as to cause air-trapping. The viscosity of the emulsion decreases when many air bubbles are present (Kerihuel *et al.,* 2006).

The common practice in formulating emulsions is to regard all oil-soluble components as the O phase. This phase is prepared by heating to about 5 to 10 ^{o}C above the melting point of the ingredient with the highest melting point. This results in a more efficient mixture. Care should be taken not to heat the phases excessively. Heat may degrade the more sensitive components. The water-soluble components are dissolved in water and the resulting solution is regarded as the aqueous phase. This phase is heated to the same temperature as the O phase. Then, the O phase is added dropwise to the W phase, with high-shear mixing (Lieberman *et al.,* 1988).

However, when the phase inversion route is used to prepare an O/W emulsion, the W phase is added dropwise to the O phase until phase inversion occurs. Non-ionic emulsifiers are the most preferred for preparing an O/W emulsion (Chappat, 1994).

2.17 Gels

Martin (1993) and Aulton (2002) defined gel as a semi-solid system comprising a substantial amount of liquid enclosed in a condensed solid mass. This definition conceptualises gel as a three-dimensional (3D) system in which a large amount of liquid is dispersed in a solid, still the system has a more solid-like than liquid-like character.

Gels may contract spontaneously when left for extended periods of time. Thus, some of the liquid inside is pressed out. This phenomenon is known as *syneresis*. It is attributed to the persistent coarsening of the gel matrix with the subsequent squeezing-out effect. The opposite of syneresis, i.e. the absorption of liquid by a gel with a considerable increase in volume, is called *swelling*. However, if a gel absorbs a certain amount of liquid without a considerable volume increase, the phenomenon is no longer swelling, but *imbibition*. The release of fluid (oil or water) from ointment bases usually results from a deficient gel structure rather than from the contraction involved in syneresis. This phenomenon is known as *bleeding* (Martin, 1993).

Gels may be prepared from natural, synthetic or semi-synthetic hydrogels. A hydrogel is a cross-linked network of hydrophilic polymer. It has the ability to absorb large amounts of water and swell, while maintaining its 3D structure. From this definition one can differentiate hydrogels from gels. Gels are polymeric networks already swollen to equilibrium. Further addition of liquid results in dilution of the gel, in contrast to hydrogels (Gupta *et al.*, 2002).

Hydrogels may be polymers containing pendant hydroxyl, amine, amide, ether, carboxylate and sulphonate as functional groups in their side chains. These polymers may form a gel in an aqueous medium (Gupta *et al.,* 2002).

2.18 Polymers in Aqueous Medium

Polymers are long-chain molecules. They contain at least one repeating structural unit – a monomer. The repeating units are inter-linked by covalent bonds. If the polymer contains only one kind of monomer, it is defined as a *homopolymer*. However, if different kinds of monomers comprise the polymer, it is defined as *copolymer* (Wikipedia, 2007).

Polymer chains may be linear or branched. The structure of a polymer with a linear chain is quite simple and flexible. A polymer structure consisting of a chain with at least one side chain is defined as a *branched polymer*. A branched polymer may be grafted or cross-linked. A *grafted polymer* is one comprising a side chain different from the main chain. The difference may be in the composition or in the configuration. A *cross-linked polymer* is one containing more than three chains emanating from the same branch point. High cross-link density yields a polymer network (Wikipedia, 2007).

A polymer may be either a non-electrolyte, if does not possess ionisable groups on its chains, or it may be a polyelectrolyte, if it contains a large number of ionisable groups (Qiu & Park, 2001). Polymer molecules may be either soluble or insoluble in water – this depends on whether the polymer is composed of polar or non-polar monomers (Wikipedia, 2007).

A linear polymeric molecule placed in solution tends to assume a random coil conformation (Figure 18). This chain conformation changes continuously owing its constant coiling and uncoiling. The volume occupied by the coil is least when the chain is in the unperturbed state (Wikipedia, 2007).

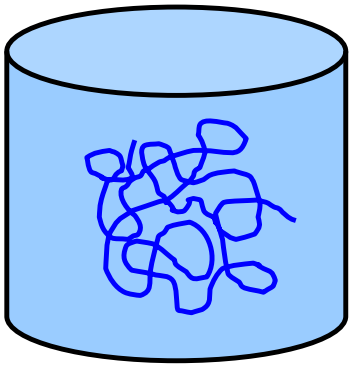

Figure 18: Representation of a coil conformation of linear polymer in solution. The volume occupied by the coil is least in this unperturbed state.

A polymer may exhibit swelling abilities in an aqueous environment. This requires expansion of the chains. All polymers with pendant acidic (e.g. carboxylic acids) or basic (e.g. ammonium salts) groups either accept or release protons in response to pH changes. The pendant groups ionise in aqueous media of appropriate pH and ionic strength. Thus, charges develop on the polymer chains. These charges generate electrostatic repulsive forces that cause polymer chains to expand and hydrate (Figure 19).

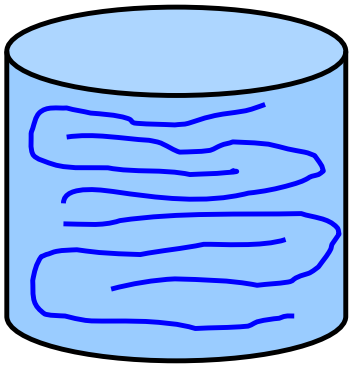

Figure 19: Illustration of uncoiled and hydrated polymer in aqueous medium. Uncoiling owed to electrostatic repulsive forces between like-charges resultant from ionisation of pendant acidic or basic groups in the chains. Hydration owed to presence of pendant polar groups.

Depending on the polymer chain length and concentration, chain entanglements may occur (Figure 20). A higher chain concentration in the overlap region increases the osmotic pressure. Therefore, water molecules diffuse to entangled chains. This explains water swelling by water-soluble polyelectrolyte. Polyelectrolytes swell much more than non-electrolyte polymers. This is due to the presence of ionisable groups in polyelectrolytes (Pepas *et al.,* 2000; Gupta *et al.,* 2002).

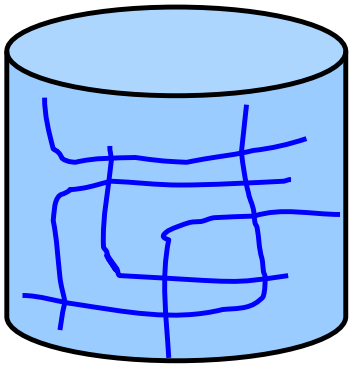

Figure 20: Schematic representation of polymer chain entanglement

Polyelectrolyte swelling is affected by the properties of the swelling medium: pH, ionic strength and the type of counter-ion and its valency. It is also affected by the properties of the polyelectrolyte itself: charge, concentration and p*K*a of the ionisable group, degree of ionisation, cross-link density and hydrophilicity or hydrophobicity (Qiu & Park, 2001; Gupta *et al.,* 2002).

A polyelectrolyte with pendant carboxylic groups does not swell at a pH below the p*K*a of carboxylic acid. This is because the pendant groups are still un-ionised. Only at pH values above the carboxylic acid pKa do the pendant groups ionise (Pepas *et al.,* 2000; Gupta *et al.,* 2002).

Ionisation of the pendant acidic or basic groups on polyelectrolytes is more difficult than ionisation of the acidic or basic groups of monoacids or monobases. The apparent dissociation constant, K_a or K_b, of the pendant groups on polyelectrolytes tends to be smaller than the K_a or K_b of the equivalent monoacid or monobase. This is due to the influences exerted by other adjacent ionised groups in polyelectrolytes (Qiu & Park, 2001).

Polymer swelling contributes to a gain in solution viscosity and may form aqueous gels. For polymers with a high molecular mass, swelling and a subsequent increase in solution viscosity can be explained in terms of cooperative motion. A high-molecular-mass polymer does not swell below its critical concentration. At this concentration, chain entanglements are unlikely to happen. Beyond the critical concentration, polymer chains begin to overlap (Figure 20). Thus, individual chains are no longer able to move, but have to drag along their neighbours in a cooperative motion. Therefore, the viscosity of solution increases rapidly.

The thickening effect of acrylic-based polymers depends on polymer chain entanglements and consequent cooperative motion. Extensive swelling requires high molecular mass and strong interaction with water molecules. However, the swelling behaviour of cross-linked sodium polyacrylate in aqueous medium is explained by a different mechanism: when placed in water, the polyacrylate ions hydrate immediately. Owing the absorbed water, the tightly coiled chain molecules expand, taking up more space.

To monitor viscosity changes and to verify whether the semi-solid aqueous polyelectrolyte structure corresponds to a gel or not, rheological measurements have to be performed.

2.19 Rheology of Gels

Rheology is the study of the flow and deformation properties of materials under applied stress (Aulton, 2002; Shenoy, 1999). Under a constant stress, most of the materials dissipate some of their energy in the form of heat, in viscous flow. The remaining energy is stored and recovered when the stress is removed. These are known as *viscoelastic* materials (Aulton, 2002). They exhibit both solid and liquid properties simultaneously. Their responses to an applied stress lie between the properties of a viscous liquid and the properties of an elastic solid (Shenoy, 1999; Mezger, 2006).

An ideal liquid can be characterised by its flow, or rather by its viscosity, according to Newton's law (Equation 9). An ideal solid is characterised by its elasticity, according to Hooke's law (Equation 10):

$$\eta = \frac{\tau}{\dot{\gamma}} \tag{9}$$

$$G = \frac{\tau}{\gamma} \tag{10}$$

where

η = viscosity

τ = shear stress – the force per unit of area (F/A) required to shear the material

$\dot{\gamma}$ = shear rate – the speed at which the flow occurs

G = elastic modulus

γ = strain or "deformation"

The rheological properties of viscoelastic materials are evaluated by means of creep tests, relaxation tests and oscillatory tests. The last is the test most commonly used to

analyse viscoelastic materials. It is suitable for all materials, from low viscous liquids to rigid solids. This test is also referred as the dynamic test (Mezger, 2006).

Oscillatory measurements give information on the following viscoelastic functions: η^*, G′ and G″. These parameters are respectively referred to as the complex viscosity, the storage modulus and the loss modulus. The storage modulus G′ is a measure of the energy storage of a viscoelastic material. It indicates how well structured a material is and corresponds to the elastic contribution of the viscoelastic material. The loss modulus G″ is a measure of energy dissipation. It corresponds to the viscous contribution of the viscoelastic material (Shenoy, 1999). A G″ larger than G′ implies that the material is predominantly viscous, i.e. the material is a fluid, while a G′ larger than G″ implies that the material tends towards a solid or semi-solid (Bonacucina *et al.*, 2004).

The complex viscosity may be regarded as the flow resistance of a viscoelastic material measured by an oscillatory test. It is defined according to the following equation (Shenoy, 1999):

$$\eta^*(i\omega) = \eta'(\omega) - i\eta''(\omega) \tag{11}$$

In Equation 11, ω is the angular frequency and η' is the dynamic viscosity. The latter is mathematically defined as:

$$\eta'(\omega) = \frac{G''(\omega)}{\omega} \tag{12}$$

The parameter η'' in Equation 11 corresponds to the imaginary part of the complex viscosity. It is defined as:

$$\eta''(\omega) = \frac{G'(\omega)}{\omega} \tag{13}$$

According to Mezger (2006), G' and G" are the parameters most frequently used to examine the rheological properties of materials in industry. They are used to assess whether the viscoelasticity of a given material corresponds to that of a gel structure. The parameters η' and η'' are rarely used in industrial practice.

To perform oscillatory measurements for a viscoelastic fluid, a rheometer with a cone and plate measuring system (CP-MS) is preferred. A CP-MS maintains the shear rate at a constant throughout the whole sample. A parallel plate measuring system (PP-MS) is preferred for viscoelastic solids (Martin, 1993).

The principle of oscillatory measurements is that the viscoelastic material is exposed to a sinusoidal varying strain, and a transmitted stress is measured as a function of time. However, one can do the opposite, i.e. preset the shear stress and measure the subsequent deformation. The common feature is that within the linear viscoelastic (LVE) region, both the stress and the strain will vary sinusoidally. Owing to the viscous nature of the material, energy is dissipated. Depending on the viscosity, the amplitude of the stress wave may be smaller or higher than the amplitude of the strain wave. Therefore, the stress wave and the strain wave will vary with the same frequency, but shifted out of phase. This is exemplified in Figure 21 (Shenoy, 1999; Aulton, 2002; Tadros, 2005). The time shift between the strain and the stress amplitudes (Δt) gives the phase angle shift (δ):

$$\delta = \Delta t \omega \qquad (14)$$

The angular frequency $\boldsymbol{\omega}$ in rad.s^{-1} or s^{-1} is related to the frequency $\boldsymbol{\nu}$ in Hz according to Equation 15:

$$\omega = 2\pi\nu \qquad (15)$$

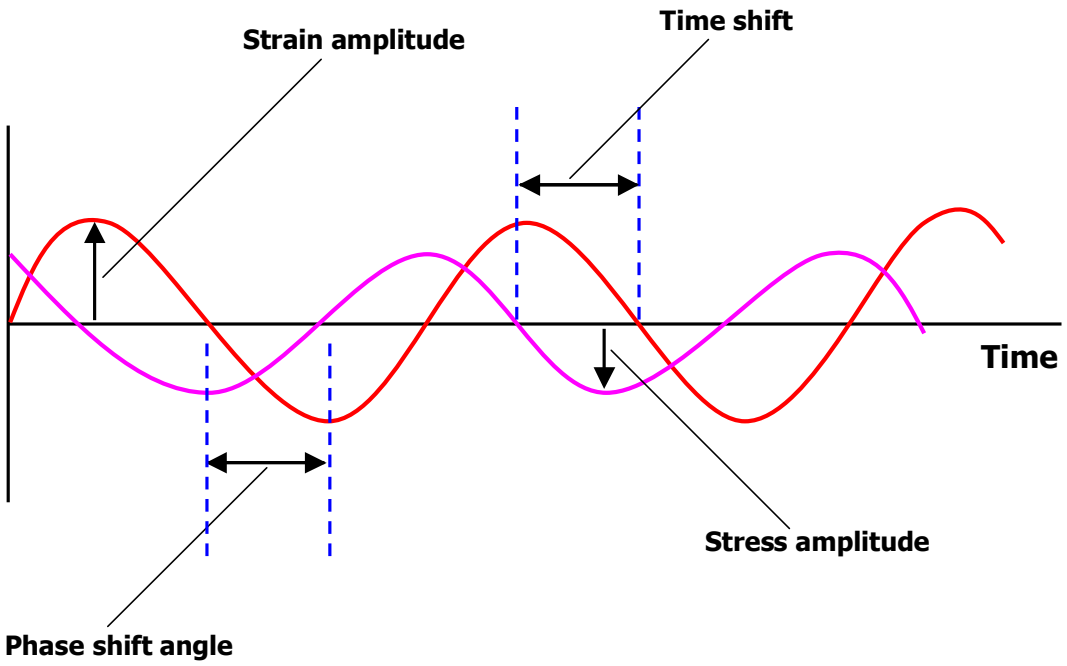

Figure 21: Amplitudes of shear strain wave and shear stress wave as a function of time. The stress amplitude τ and the strain amplitude γ vary with the same frequency, but shifted out of phase. The time shift between the strain and the stress amplitudes gives the phase angle shift.

In a perfectly elastic material, there is no phase angle shift between the stress wave and the strain wave. The phase angle shift $\delta = 0^{o}$ because no energy is dissipated. Conversely, in a perfect fluid, $\delta = 90^{o}$. This is because all the energy of the material is dissipated.

The tangent of δ is known as the *damping factor*. It is also called the *loss tangent* or the *loss factor* and is defined as the quotient of the loss to the storage modulus:

$$\tan\delta = \frac{G''}{G'} \qquad (16)$$

The damping factor is used to compare the magnitudes of the viscous and elastic components of the material. For dilute liquid solutions, tan $\delta > 1$ because G″ is larger than G′. For gels, tan $\delta < 1$ because G″ is smaller than G′. At the gel point, G″ and G′ balance, therefore tan $\delta = 1$ (Bonacucina *et al.*, 2006; Mezger, 2006).

Oscillatory experiments should be performed in the LVE (linear viscoelastic) region. In this region, the structure of the viscoelastic material remains unbroken throughout the measurements. Thus, Hooke's law and Newton's law may be applied successfully to assess the properties of a given material.

The LVE range is frequently determined by one of the following two amplitude sweep tests (Mezger, 2006):

- The shear stress amplitude sweep test, simply called the *stress sweep test*. It consists in exposing a viscoelastic sample to increasing stress amplitude at constant frequency and temperature (Bonacucina *et al.*, 2004 and 2006; Mezger, 2006);
- The shear strain amplitude sweep test, simply called the *strain sweep test* (Figure 22). It consists in exposing a viscoelastic sample to increasing strain amplitude at constant frequency and temperature (Mezger, 2006).

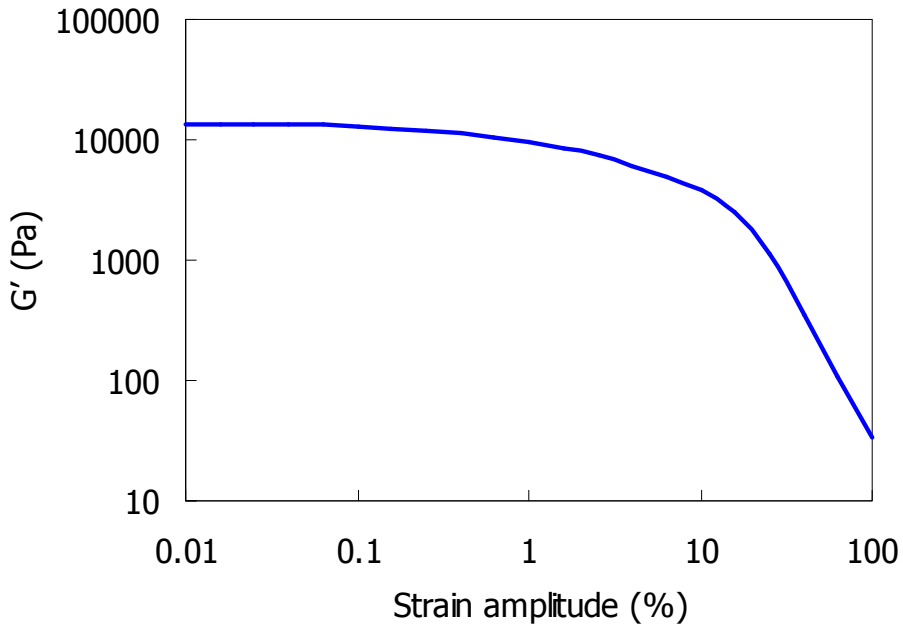

Figure 22: Schematic representation of strain sweep test

In the LVE range, G' and G" are independent of the amplitude of the applied strain and stress. Therefore, the curve of G' shows a constant plateau value (Figure 22). This plateau corresponds to an ideal linear elastic behaviour – Hooke's law. The curve of G" also shows a constant plateau value. This value corresponds to an ideal linear viscous behaviour – Newton's law.

Amplitude sweep tests are only used to determine the LVE range. They are carried out as the first oscillatory test with every unknown sample (Mezger, 2006). For further characterisation of the viscoelastic structure, a frequency sweep test is carried out to assess whether the structure formed is a strong gel-like or weak gel-like structure.

The frequency sweep test consists in exposing a sample to a stepwise increase in frequency at constant strain amplitude and temperature. In the low-frequency regime, the material response is more viscous than elastic. Thus, G" is larger than G'. With

increasing frequency, both moduli increase up to a certain frequency where G' becomes equal to G". This is the cross-over point, often referred as the *gel point*. Beyond this point, the material response to an increase in frequency becomes more elastic than viscous. Thus, G' is larger than G".

It is recommended that the value of the strain amplitude to be used in the frequency sweep test should be the mid-point of the LVE (linear viscoelastic) range, as determined by the amplitude sweep test. The ideal value of the strain should be taken far from γ_{cr} – the critical strain. The γ_{cr} is the point at which the material structure starts to be irreversibly perturbed (Tadros, 2005).

For oscillatory tests, it is recommended that the data be presented on a logarithmic scale limited to the four main parameters: η^*, G', G" and tan δ. The logarithmic scale is recommended to avoid problems caused by analysis showing very small values/results (Mezger, 2006).

3 EXPERIMENTAL

3.1 Raw Materials

3.1.1 Cypermethrin

Technical grade cypermethrin (Cypermethrin Tech) was supplied by Volcano Agrosciences. It is a yellowish viscous liquid, a mixture of eight different isomers. Each isomer has its own chemical and biological properties. Cypermethrin isomers have the molecular formula $C_{22}H_{19}Cl_2NO_3$. The molar mass is 416 g/mol. The melting point of pure isomers ranges from 60 to 80 ^oC.

Cypermethrin is insoluble in water (0.01 mg/L at 20 ^oC), but it is very soluble in methanol, acetone, xylene and methyl dichloride. In neutral or acid aqueous solution, cypermethrin hydrolyses slowly. This is due to the presence of the ester bond in its structure (Figure 1 in Chapter 1). Cypermethrin hydrolysis is more rapid in basic solution, at pH 9.

3.1.2 Solvesso S200

Solvesso S200 is a mixture of aromatic hydrocarbons: alkyl (C_3 – C_6) benzenes. It is a heavy aromatic solvent, i.e. petroleum naphtha. The flash point is 95 ^oC. It was supplied by Exxon Chemical. It is a good solvent for cypermethrin and was selected for this research on the basis of its low cost.

3.1.3 Phenyl Sulphonate CA

Phenyl Sulphonate CA is an anionic calcium salt of an alkylaryl sulphonic acid. It is a brownish viscous liquid, soluble in Solvesso 200. The flash point is 33 ^oC and the density at 20 ^oC is ca. 1.015 g/cm^3.

Phenyl Sulphonate CA is practically insoluble in water. However, it is able to develop interface-active emulsifying properties, especially in conjunction with a second component which should be hydrophilic and non-ionic. Phenyl Sulphonate CA was supplied by Clariant.

3.1.4 Emulsogen EL

Emulsogen EL is a non-ionic hydrosoluble surfactant. It is a yellowish viscous liquid. The pH ranges from 7.0 to 8.5. The flash point is 340 ^{o}C and the density is ca. 0.99 g/cm^{3} at 20 ^{o}C. Emulsogen EL may contain an average of 36 moles of EO. It was supplied by Clariant.

3.1.5 ASP4

ASP4 is a copolymer of methacrylic acid (MAA), ethyl acrylate and diethyl maleate in a molar ratio 7:91:2. It is a synthetic thickener used in emulsion-based paints. It is supplied as an aqueous suspension with solid contents of 20 ± 0.5%. The pH varies between 2 and 3.

ASP4 owes its thickening power to the presence of carboxylic acid groups in its structure. This polymer electrolyte is readily ionisable in an aqueous alkaline medium. The thickening power of ASP4 depends on the concentration of polymer present in the solution, as well as on the pH of the solution. ASP4 was supplied by Makeen Polymers.

3.1.6 Sodium carbonate (anhydrous)

Sodium carbonate is a water-soluble salt. It reacts violently with strong acids. It may be supplied in form of a white powder or granules. The molar mass is 105.99 g/mol. The melting point is approximately 851 ^{o}C. The solubility in water is 45.5 g/100 mL at 100 ^{o}C. Sodium carbonate anhydrous was supplied by Associated Chemical Enterprises.

3.1.7 Product Z 1069

Product Z 1069 is a cross-linked sodium polyacrylate superabsorbent. It is a white powder with a particle size of less than 220 µm. It is insoluble in water despite the fact that sodium polyacrylate is a polyelectrolyte with the repeating unit $–CH_2\text{-}CH(COONa)–$. When placed in water, it ionises immediately into cations Na^+ and anions COO^-. Cross-linking impedes its dissolution. Product Z1069 decomposes above 200 ^oC. It was supplied by Degussa.

3.1.8 Distilled water

Distilled water was prepared in the University of Pretoria's Department of Chemical Engineering. Unless otherwise stated, this is the type of water used in all the experiments.

3.2 Instruments

3.2.1 Rheometer

An Anton Paar Physica MCR 301 rheometer (Figure 23) was used. It is suitable for studying the rheology of all materials, from low viscous liquids up to solids. Its measuring system consists essentially of three geometries: cone and plate (CP-MS), parallel plate (PP-MS) and conical cylinder (CC-MS).

CP-MS and CC-MS are suitable for investigating the rheology of low viscous materials. PP-MS is used mostly for viscoelastic solids. The Physica MCR 301 rheometer performs automated analysis. Figure 23 shows that the rheometer is coupled to a computer and a compressor. Physica RheoPlus software was used for data reduction.

Figure 23: Anton Paar Physica MCR 301 rheometer

Temperature greatly influences the rheological properties of materials. Some fluids may double their viscosity when the temperature is reduced by only 5 ^{o}C. Therefore, for accurate measurements, good control of the sample temperature is required. The Physica MCR 301 rheometer incorporates a temperature controller which covers a range from -150 ^{o}C to 1 000 ^{o}C.

3.2.2 Brookfield digital viscometer

A Brookfield digital viscometer LVT DV – II (Figure 24) was used for viscosity measurements before the rheometer was available. It is a rotational viscometer that measures the torque (shear stress) on a spindle rotating at a constant shear rate. Enough sample is required so that the spindle may be immersed until its groove is covered. A set of four spindles was provided with the instrument. Each spindle has a singular geometry and a single code. The largest spindle is used for fluids with a lower viscosity. A higher shear rate is recommended for this kind of fluid and the converse is also true.

Figure 24: Brookfield digital viscometer, Model LVT DV – II

The viscometer readout may be in %, cps or dynes/cm^2. The readout of interest for this research is that in cps (centipoises). This reading is multiplied by a conversion factor to render a full-scale viscosity in cps. Conversion factors are based on the spindle code and the shear rate. The results correspond to apparent viscosity. Units are converted from cps to mPa.s (millipascal seconds) as follows:

$$1 \text{ cPs} = 1 \text{ mPa.s}$$

In contrast to the rheometer, the viscometer does not control the sample temperature automatically. Therefore, a water bath was prepared and used at 30 ^{o}C.

3.2.3 Conductivity meter

Electric conductivity was measured with a TetraCon 96 WTF – LF 92 conductivity meter (Figure 25).

Figure 25: Tetracon 96 conductivity meter, Model LF 92

3.2.4 Anvil mixer

An Anvil high-speed mixer was used (Figure 26). It is equipped with a stirrer and a mixing cup. The cup has a capacity of 400 mL of liquid. The stirrer possesses two blades, each with a diameter of 2 cm. This mixer can be used at two shear speeds.

Figure 26: Anvil high-speed mixer with its mixing cup

3.2.5 pH meter

A Russell RL060P pH meter was used (Figure 27). It measures the whole range of pHs, from 0 to 14. It is claimed to be accurate to 0.01 pH.

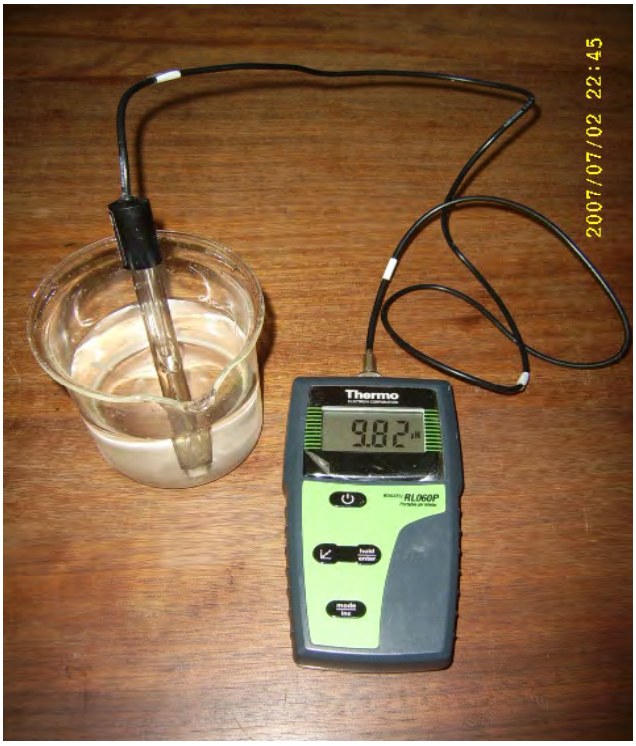

Figure 27: Russell RL060P pH meter

3.2.6 Magnetic stirrer and hot plate

A magnetic stirrer was used for the dissolution tests. The hot-plate function was used to heat both the O phase and the W phase when emulsions had to be prepared. The magnetic stirrer and hot plate may be seen in Figure 42 in Chapter 4.

3.3 Experimental Methods

3.3.1 Preparation of initial dispersion of cypermethrin

The very high viscosity of cypermethrin (7 080 mPa.s at 30 ^{o}C) made it difficult to prepare emulsions directly. Tadros (2005) states that when the oil viscosity is high, deformation and dispersion of its droplet takes a long time. Therefore, the solvent Solvesso S200 was added to reduce the viscosity of the cypermethrin. Preliminary experiments showed good fluidity for a mixture of 80% Cypermethrin Tech and 20% Solvesso S200 (mass concentrations). This mixture was used in all further experiments involving the O phase.

Next, a cypermethrin dispersion was prepared to investigate the effect of different levels of surfactants. The dispersion contained 40% m/m cypermethrin. This concentration was taken as a starting point. The goal was to determine the optimum concentration of surfactant and co-surfactant necessary to prepare a 1:1 by mass O/W emulsion. A blend of surfactants was used here in order to yield a finest emulsion, in accordance with Sajjadi (2006). A non-ionic surfactant was chosen because it helps to stabilize emulsions via a steric mechanism. An anionic surfactant was also used because it tends to stabilize emulsions via the electrostatic mechanism (Baglione *et al.*, 2000; Tadros, 2005). Combined they provide for denser packing of surfactant molecules at the interface owing to charge shielding, i.e. nonionic molecules alternate with the ionic ones.

The 40% cypermethrin dispersion was prepared by mixing 100 g of the O phase with 100 g of the water phase. The W phase consisted exclusively of distilled water. The O phase comprised 80% Cypermethrin Tech and 20% Solvesso S200. Its viscosity was measured at 30 ^{o}C using the rheometer. Owing to the Newtonian character of the O phase, the rheometer was used in flow mode. Next, the O phase was mixed together with the W phase.

3.3.2 Determination of the optimum concentration of surfactant

The optimum concentrations of surfactant and co-surfactant required to prepare the O/W emulsion were determined. The 40% m/m cypermethrin dispersion previously prepared was used. Emulsogen EL and Phenylsulphonate CA are surfactants already used as a blend in the emulsifiable concentrate currently in the market. Hydrosoluble and non-ionic surfactant Emulsogen EL was the first optimised. This was based on two reasons: (i) non-ionic emulsifiers are the most preferred for preparing an O/W emulsion (Chappat, 1994), and (ii) hydrosoluble surfactant may be the ideal to stabilize O/W emulsion, according to the Bancroft rule. The surfactant optimization procedure used was as follows: Emulsogen EL was added gradually to the dispersion in increments of 0.8% m/m. The percentage of increments was relative to the total amount of the O phase. After each addition of surfactant, the dispersion was stirred for 1.5 minutes. The viscosity of the dispersion was measured at 30 ^{o}C using the viscometer. A plot of viscosity vs. concentration of Emulsogen EL is shown in Figure 28 in Chapter 4. The curve is U-shaped. The minimum in the curve is considered to be the optimum surfactant concentration.

For the determination of the optimum concentration of Phenyl Sulphonate CA, the same procedure was followed: Phenyl Sulphonate CA was added gradually to an emulsion of cypermethrin 40% m/m in increments of 0.8% m/m. The emulsion was prepared using the optimum concentration of Emulsogen EL previously determined. After each addition of Phenyl Sulphonate CA, the dispersion was stirred for 1.5 minutes. Emulsion viscosity was measured at 30 ^{o}C using the viscometer. A plot of viscosity vs. Phenyl Sulphonate CA concentration is presented in Figure 29 in Chapter 4. The minimum in this curve was considered the optimum Phenyl Sulphonate CA concentration. The percentages of Phenyl Sulphonate CA were based on the total amount of the O phase.

3.3.3 Determination of emulsion type

The nature of the emulsion prepared using the optimum concentration of Emulsogen EL was determined, as was the nature of the emulsion prepared with the blend of Emulsogen EL and Phenyl Sulphonate CA at the optimum concentration. These determinations were done using electrical conductivity measurements. The conductivity meter showed in Figure 25 was used. Both emulsions contained cypermethrin 40% m/m and were prepared at ambient temperature.

Visual analysis was used as a complementary method to assess the emulsion types (see Figure 31 in Chapter 4). The aim was to confirm the results yielded by the electrical conductivity measurements since incorrect results could be obtained by relying on a single method of determination. The visual analysis consisted in observing the direction of creaming/sedimentation.

3.3.4 Matching the viscosities of the oil phase and aqueous phase

The emulsions previously prepared using the optimum concentrations of surfactants were unlikely to stabilise against creaming/sedimentation. This was due to substantial differences in the densities/viscosities of the O phase and the W phase. Matching the densities/viscosities of the O phase and the W phase reduces the tendency towards creaming/sedimentation of an emulsion. The previous dissolution of Cypermethrin Tech by Solvesso S200 lowered the cypermethrin's viscosity. However, the viscosity remained higher than that of distilled water at ambient temperature. Therefore, ASP4 was used to increase the viscosity of distilled water.

Since acrylic-based thickeners, such as ASP4, are effective in aqueous media of appropriate pH, a solution of Na_2CO_3 was used to yield different values of pH. Thus, it was considered useful to investigate the following effects on the thickening power of ASP4:

- Concentration of Na_2CO_3

- pH of ASP4 solution (after neutralisation by a solution of Na_2CO_3)
- Concentration of ASP4.

Influence of Na_2CO_3 concentration on the thickening power of ASP4

Three different concentrations (0.2 M, 0.5 M and 0.8 M) of the Na_2CO_3 solution were used. The procedure was: constant amounts of each solution of Na_2CO_3 were added to preset amounts of ASP4 dispersion diluted with distilled water (see Tables A.1, A.2 and A.3 in the Appendix). Additions were made whilst stirring. The viscosities of the resultant solutions were measured at 30 ^{o}C using the rheometer. Curves of viscosity vs. shear rate were plotted for the three solutions of Na_2CO_3 (see Figure 32 in Chapter 4). The concentration of Na_2CO_3 that provided a value of viscosity matching the viscosity of the O phase was chosen for all further experiments. 'Optimised stock solution of Na_2CO_3' was the designation given to this solution.

Effect of pH on the thickening power of ASP4

To examine the effect of pH on the thickening power of ASP4, the concentration of ASP4 was kept constant. The total amounts of distilled water and optimised stock solution of Na_2CO_3 used were also kept constant. The procedure followed was: about 2.5 g of dispersion ASP4 was diluted with variable amounts of distilled water. Next, the diluted dispersions were neutralised with different amounts of optimised stock solution of Na_2CO_3 at the ideal concentration. The amounts of distilled water and optimised stock solution of Na_2CO_3 were varied as shown in Table A.4 in the Appendix. Altogether, the amount of distilled water and the amount of optimised solution of Na_2CO_3 corresponded to about 47 g. The pHs of the solutions of ASP4 therefore varied. The rheometer was used to measure the viscosities of these solutions at 30 ^{o}C. The results are presented in Figure 33 in Chapter 4 as curves of viscosity vs. shear rate.

Effect of ASP4 concentration on its thickening power

The thickening power of ASP4 depends on the concentration of polymer present in the system. Five different concentrations (0.39, 0.52, 0.61, 0.79 and 1.01% m/m) of ASP4

were used. All were neutralised up to a constant pH. The optimised stock solution of Na_2CO_3 was used for such neutralisations. The procedure used was: variable amounts of distilled water were added to ca. 2.5 g of ASP4 dispersion (see Table A.5 in the Appendix). The resultant diluted dispersions were then neutralised with ca. 5.5 g of the optimised stock solution of Na_2CO_3. The rheometer was used to measure the viscosities of the resultant solutions at 30 ^oC. The dependence of viscosity on the concentration of ASP4 is plotted in Figure 35 in Chapter 4. The curves were used to determine the critical concentration of ASP4 for its effective thickening.

3.3.5 Preparation of water phase

The W phase used in further experiments was required to match the viscosity of the O phase. Therefore, the critical concentration of ASP4 dispersion determined previously was used. This was neutralised to the appropriate pH. Neutralisation was done by using the optimised stock solution of Na_2CO_3. The viscosity of the W phase was then measured at 30 ^oC. The rheometer was used in its oscillatory mode in anticipation of eventual pseudoplastic behaviour of the W phase.

3.3.6 Preparation of O/W emulsion

The phase inversion method was used to prepare the O/W emulsion. The O phase contained all oil-soluble ingredients (Cypermethrin Tech, Solvesso S200 and Phenyl Sulphonate CA). It was heated to about 50 ^oC and stirred to homogenise. The hot plate shown in Figure 42 in Chapter 4 was used for heating. The W phase comprised distilled water, ASP4, sodium carbonate and Emulsogen EL. It was heated to the same temperature as the O phase in order to avoid chilling and solidification on mixing. The O phase was initially poured into the mixing cup of the Anvil mixer. The W phase was added to the O phase at a rate of ca. 4 g/min. Addition of the W phase was done whilst the emulsion was manually stirred with a glass rod.

Electrical conductivity measurements were performed after addition of each portion of the W phase in order to determine emulsion type. The conductivity meter was used for this purpose. When the composition of the emulsion started to turn from W/O to O/W, it was subjected to high-shear stirring. The Anvil mixer was used for this purpose. The primary emulsion was then prepared. The Anvil mixer was set to low-speed stirring to aid the release of entrained air.

3.3.7 Determination of the critical amount of superabsorbent

Superabsorbent Product Z1069 was used to convert the O/W emulsion into a semi-solid formulation. High amounts of superabsorbent were likely to cause faster disintegration of the semi-solid dosage but too much superabsorbent would reduce the cohesion of the solid dosage form. Therefore, it was necessary to determine the critical amount of superabsorbent, i.e. the minimum amount of superabsorbent required to produce a semi-solid dosage capable of maintaining its shape.

The emulsion contained O phase and W phase. However, Product Z1069 is a water-absorber. For this reason, the W phase was the most relevant in determining the critical amount of superabsorbent. The presence of O phase in the emulsion might not influence water uptake by the superbsorbent Product Z1069, though it might affect the stability of the semi-solid dosage. To make it easier to determine the critical amount of superabsorbent, the W phase was used and the O phase was left out.

Three different amounts of the superabsorbent were added to the W phase, which was maintained constant at 20 g. The amounts of superabsorbent were 7.5, 10 and 12.5% relative to the W phase. A glass stirring rod was used to homogenise the mixture. The viscoelastic properties of each resultant semi-solid were determined using the oscillatory mode of the rheometer.

The oscillatory tests performed were: amplitude sweep test and frequency sweep test. The shear strain amplitude sweep test was used. It consisted in exposing samples to increasing strain amplitudes, from 0.01 to 100%. A constant angular frequency of 10 rad.s^{-1} was preset. The temperature was preset constant to 50 ^{o}C. Plot of the storage modulus G' against the strain amplitude is presented in Figure 38 in Chapter 4. The curve was used to determine the LVE (linear viscoelastic) range. The ideal value of strain amplitude for further use in frequency sweep tests was calculated automatically by the rheometer.

Next, frequency sweep tests were performed at a constant temperature of 50 ^{o}C. The samples were exposed to a stepwise increase of the angular frequency, from 0.1 to 100 1/s. The strain amplitude was kept constant. The value used was previously determined in amplitude sweep tests. The frequency sweep test results are presented in Figure 39 in Chapter 4 and in Figures A.3 to A.5 in the Appendix.

3.3.8 Preparation of boluses and discs of the formulation

Boluses and discs of the formulation were prepared using the critical amount of superabsorbent. This was taken to be the minimum amount of superabsorbent necessary to convert the primary emulsion into a semi-solid dosage. The procedure followed was: the critical amount of superabsorbent Product Z1069 was added to a certain amount of the primary emulsion. A glass rod was used to stir to homogenise the mixture. From the resultant mix, semi-solid boluses and discs containing 1.5 g of cypermethrin were prepared. The boluses were used for dissolution testing and the discs for measurements of the rheological properties of the dosage form.

3.3.9 Dissolution testing

Dissolution testing was performed to measure the time that a bolus requires to disperse completely in water. The test was performed at ambient temperature (25 ± 2 ^{o}C). It consisted of placing a bolus in 10 L of tap water. The magnetic stirrer shown in Figure

42 in Chapter 4 was used with the speed set to 100 rpm. Disintegration and dissolution of the bolus was monitored visually. A stopwatch was used to record the dissolution time.

3.3.10 Rheological measurements of the formulation

The viscoelastic properties of the semi-solid dosage were examined in order to confirm whether the formulation possessed a solid-like consistency. Amplitude sweep tests and frequency sweep tests were carried out at 50 ^{o}C. The procedures followed were identical to those described previously.

The amplitude sweep tests used were the shear strain amplitude sweep tests. The samples were exposed to increasing strain amplitudes, from 0.01 to 100%. A constant angular frequency of 10 rad.s^{-1} was used. The ideal values of strain amplitude for further use in frequency sweep tests were calculated automatically by the rheometer.

Frequency sweep tests were performed by exposing the samples to a stepwise increase in angular frequency, from 0.1 to 100 1/s. The strain amplitude was kept constant. The value used was that previously determined in amplitude sweep tests. The frequency sweep test results are presented in Figure 43 in Chapter 4 and in Figures A.6 and A.7 in the Appendix.

4 RESULTS AND DISCUSSION

4.1 Determination of the Optimum Concentrations of Surfactants

The minimum value of viscosity in Figure 28 was observed for a concentration of approximately 1.6% m/m of Emulsogen EL. This value may be considered the optimum concentration of Emulsogen EL required to emulsify 40% m/m of cypermethrin in water at ambient temperature. The optimum concentration was chosen at the minimum in the curve viscosity vs. surfactant concentration because Tadros (1982a and 1982b) considered the increase in the viscosity after the minimum as an indication of emulsion instability (droplets aggregation and subsequent increasing in the diameter).

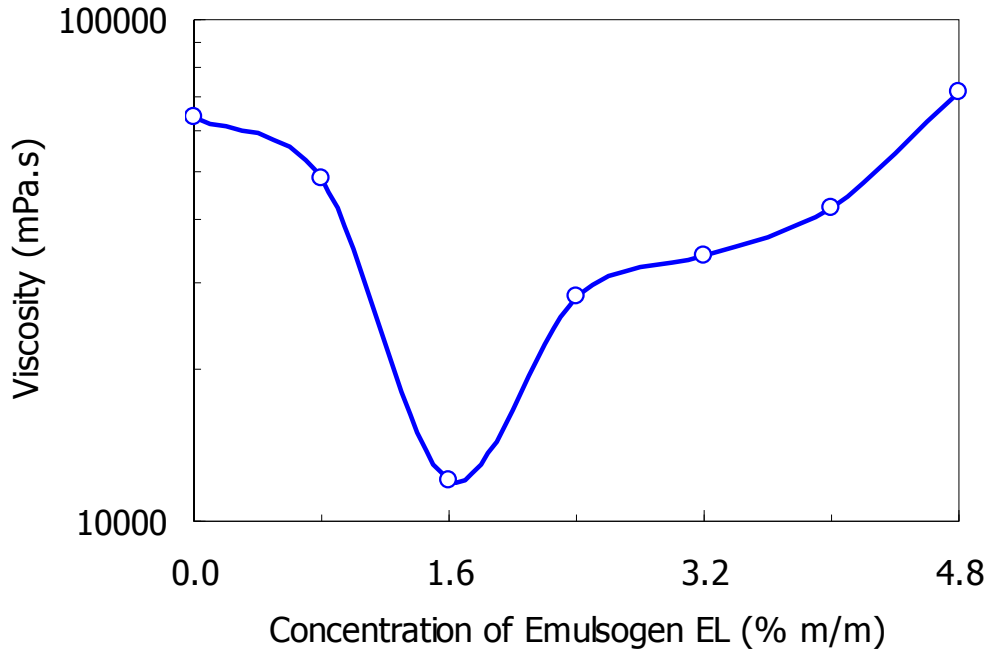

Figure 28: Effect of hydrosoluble surfactant in dispersion of 40 % m/m cypermethrin

Figure 29 shows that, the optimal concentration of Phenyl Sulphonate CA necessary to be used in conjunction with 1.6% m/m Emulsogen EL for better emulsification of 40% m/m of cypermethrin is approximately 4% m/m.

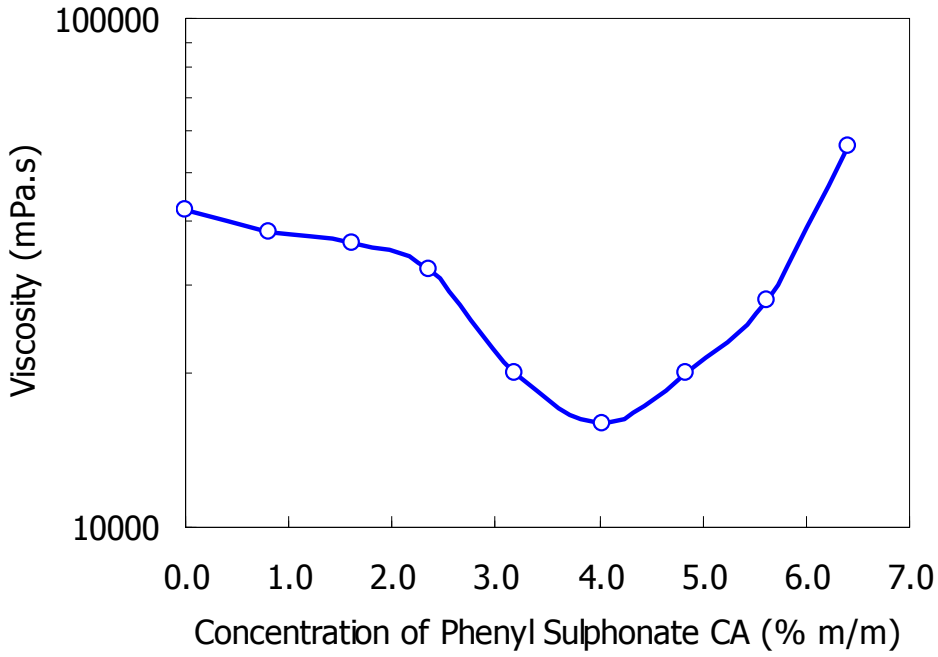

Figure 29: Influence of liposoluble surfactant in dispersion of 40% m/m of cypermethrin and Emulsogen EL 1.6%

Figure 30 shows droplet sizes and distribution of the emulsion with only Emulsogen EL and with a blend of Emulsogen EL and Phenyl Sulphonate CA. Light microscopy was used to determine droplet sizes. The concentrations of both surfactants were used at their optimum levels.

Figure 30 shows reduction of the emulsion's droplet size in the process of optimisation of the surfactant. Using Emulsogen EL alone yielded an emulsion with a large droplet size. However, when Emulsogen EL was blended with Phenyl Sulphonate CA, the

emulsion's droplet size decreased substantially. Relatively fine emulsion was prepared by blending the surfactants.

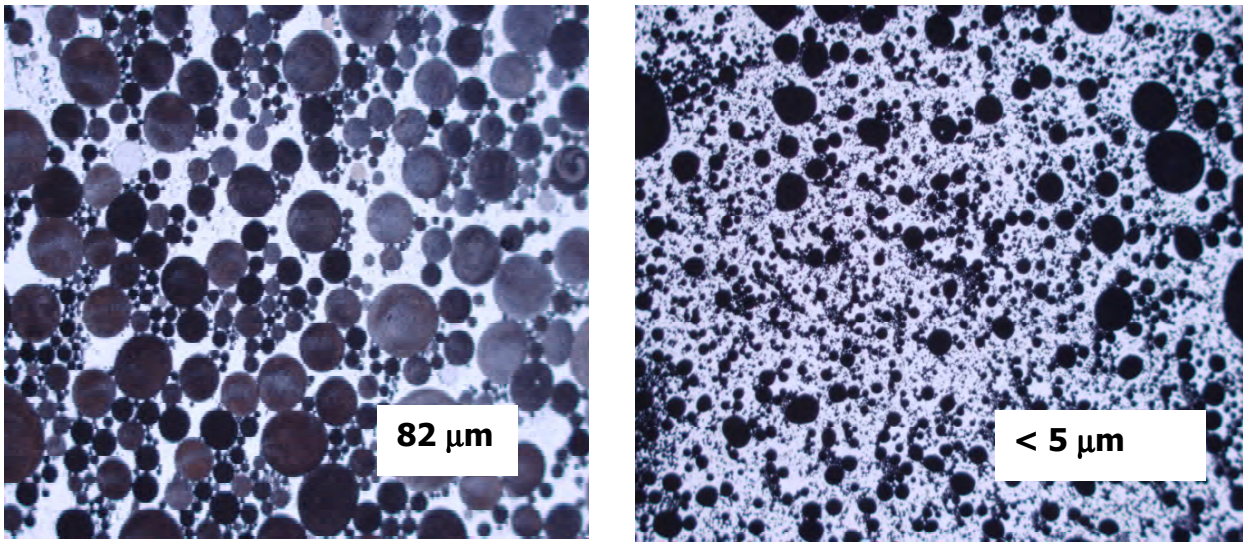

Figure 30: Optical micrographs (light microscopy) of: cypermethrin dispersion with Emulsogen EL only (on the left); and cypermethrin dispersion with a blend of Emulsogen EL and Phenyl Sulphonate CA (on the right). These pictures were taken at the same magnification.

4.2 Determination of the Emulsion Type

The electrical conductivity measurements showed high conductivities for all emulsions. This means that they are O/W emulsions. The emulsion of cypermethrin 40% m/m with only Emulsogen EL showed a conductivity of 87 μS/cm. Addition of Phenyl Sulphonate CA increased the conductivity remarkably to 188 μS/cm. This may be explained by the ionic nature of Phenyl Sulphonate CA, which introduced ions into the emulsion, thus enhancing its electrical conductivity.

Visual assessment of the direction of creaming/sedimentation was also used to determine emulsion type. Both emulsions, either with only Emulsogen EL or with a blend

of Emulsogen EL and Phenyl Sulphonate CA, showed an upper phase consisting of water (Figure 31). This was expected since the densities/viscosities of the O phase and the W phase were not yet matched. Although the optimum amounts of the surfactants were used, up to this stage the O phase was still denser than distilled water. It was therefore not possible to stabilise the emulsion against droplet sedimentation. Since the O phase was denser than W phase, sedimentation of emulsion droplets indicates the presence of O/W emulsions.

Figure 31: Cypermethrin dispersion with Emulsogen EL only (on the left); and cypermethrin dispersion with a blend of Emulsogen EL and Phenyl Sulphonate CA (on the right). A better emulsion was obtained by blending the surfactants.

The two methods, namely electrical conductivity measurements and visual assessment of the direction of creaming/sedimentation, led to the same conclusion about the type of

emulsion. Figure 31 shows that 40% m/m cypermethrin yielded a better emulsion in the presence of the surfactant blend than when Emulsogen EL alone was used. This is in agreement with the optical micrographs presented in Figure 30.

4.3 Matching the Viscosities of the Oil phase and the Aqueous Phase

At 30 ^{o}C, the viscosity of the O phase measured using the Anton Paar rheometer was 206 mPa.s. This value is very much higher than the viscosity of distilled water at the same temperature (0.82 mPa.s). Therefore, and for the sake of emulsion stability, it was necessary to match the viscosity of the W phase with that of the O phase. It was preferred to increase the viscosity of W phase instead of decreasing the viscosity of the O phase too much. Two reasons justified this approach:

- Decreasing the oil viscosity would require dilution of the cypermethrin. This would decrease the concentration of cypermethrin even before it was mixed with the W phase. The target concentration may not be reached.
- Increasing the viscosity of the external phase tends to increase the viscosity of the emulsion. In turn, this enhances emulsion stability against creaming/ sedimentation.

4.3.1 Influence of Na_2CO_3 Concentration on the Thickening Power of ASP4

The influence of the concentration of the neutraliser Na_2CO_3 on the thickening power of ASP4 was investigated. Six per cent was used as a constant by mass concentration of the 0.2 M, 0.5 M and 0.8 M solutions of Na_2CO_3. The procedures followed with each of the three solutions of Na_2CO_3 were the same. All amounts and concentrations used are presented in Tables A.1, A.2 and A.3 in the Appendix. The effects of solutions of Na_2CO_3 with different molar concentrations are compared in Figure 32.

Figure 32 shows decreasing viscosity as the shear rate increases. This is a shear-thinning behaviour and is typical of solutions/dispersions of polymers with high molar mass. This behaviour may be explained in the following manner: in an aqueous medium of appropriate ionic strength, polymer chains of pseudoplastic materials entangle

together. This is due to the high molecular mass and the inherent long chain. It happens when the concentration of polymer rises above its critical concentration. The chain entanglements create regions of high osmotic pressure. Then, water molecules diffuse to the region inside entangled chains. Cooperative motion of entangled chains enhances resistance to flow. Therefore, the viscosity of the solution/dispersion increases. However, under the influence of high shear, the chains have a tendency to disentangle and align in the direction of flow, diminishing the resistance to flow. Thus, the viscosity decreases with increasing shear rate (Aulton, 2002; Mezger, 2006).

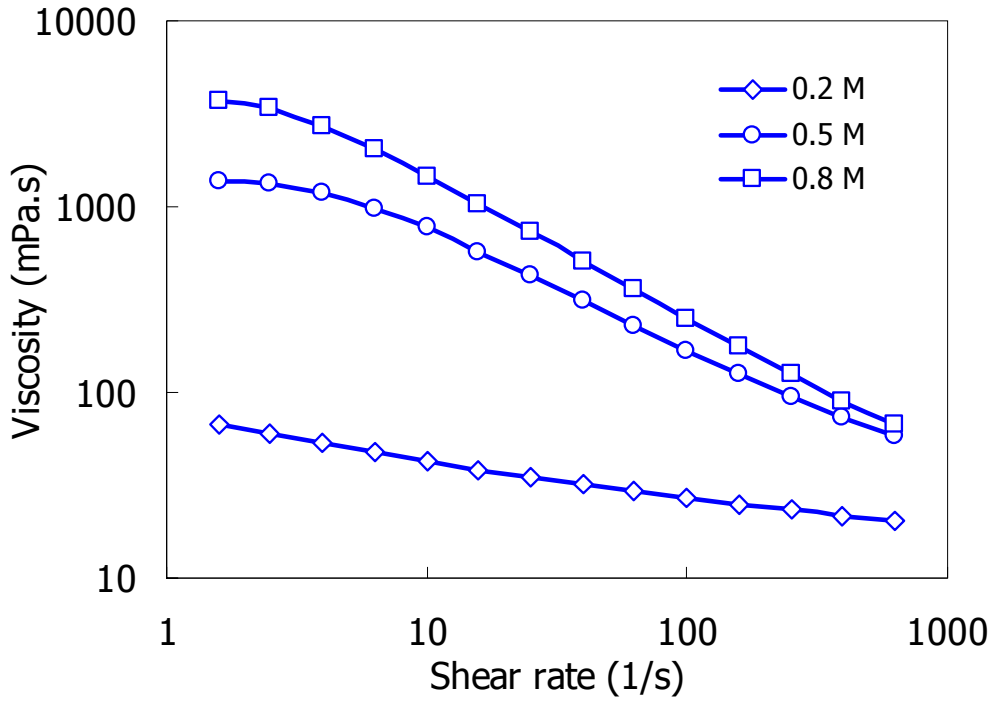

Figure 32: Influence of Na_2CO_3 on the thickening power of ASP4 in water. The concentration of ASP4 was constant (1% m/m) for all experiments.

The thickening power of ASP4 increased as the concentration of Na_2CO_3 increased (Figure 32). There are shear rates (50 – 100 1/s) at which the viscosity results of the 0.5 M and 0.8 M Na_2CO_3 solutions equalled the 206 mPa.s of the O phase used in this research. The viscosity results of the solution 0.2 M Na_2CO_3 do not match at all the

viscosity of the O phase. Therefore, the 0.5 M solution of Na_2CO_3 may be considered the optimum for neutralising dispersions of ASP4.

4.3.2 Effect of pH on the Thickening Power of ASP4

Figure 33 presents the entire flow curves of dispersions of ASP4 neutralised with different amounts of 0.5 M Na_2CO_3 solution. This is the most reasonable way to represent the viscosity of pseudoplastic materials (Aulton, 2002). An entire flow curve is recommended rather than one single value. This is because a single value represents only one point of the viscosity function (Aulton, 2002).

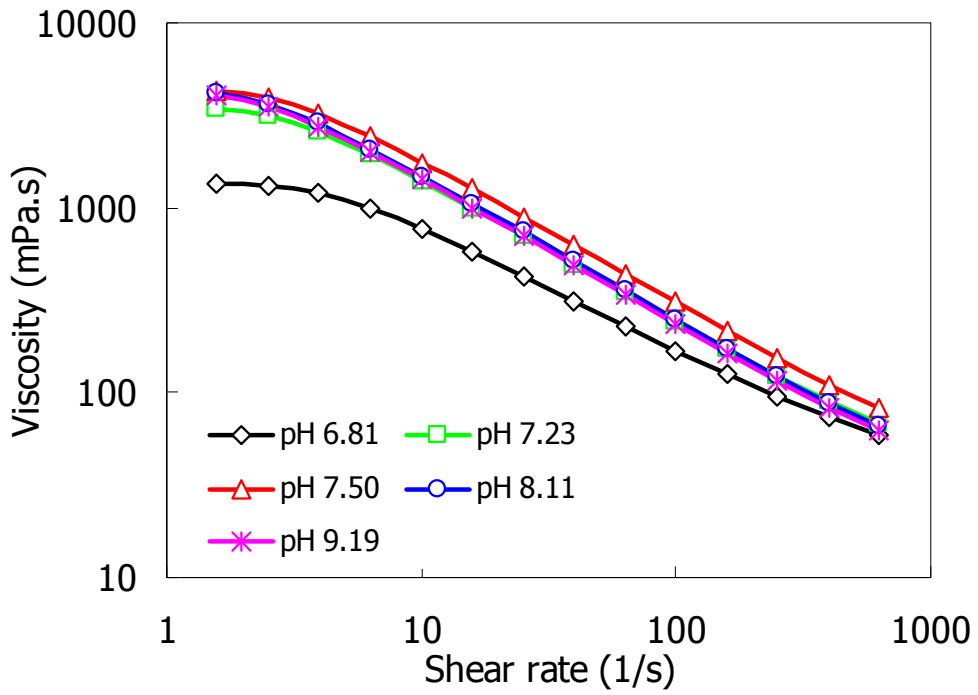

Figure 33: Dependence of viscosity on pH variations using 0.5 M Na_2CO_3. The concentration of ASP4 was constant (1% m/m) for all experiments.

The flow curves in Figure 33 show that the viscosity increases as the pH of the ASP4 dispersions is increased. The viscosity increases up to a certain value, after which it

starts to decrease. Although this decrease in viscosity at high pH is not well illustrated in Figure 33, it is quite clear that the highest viscosity is attained at a pH value of around 7.5.

Curves of viscosity vs. pH changes are plotted in Figure 34 from which it is evident that as the pH of the dispersions of ASP4 increased, the viscosity also increased up to a certain value, after which it started to decrease. To plot this curve, the fact that none of the single values of viscosity showed in Figure 33 can be chosen as characteristic of ASP4 had to be ignored. From the data in Figure 33 the shear rate of 62.9 1/s was chosen. This shear rate was preferred than 1.58 1/s (the shear rate with the value of the zero-shear viscosity). Matching the viscosities of the pseudoplastic W phase with that of the O phase at shear rate other than that yielding a zero-shear viscosity was not seen as problematic since the emulsion to be prepared may not be allowed to rest. It is an intermediary product that may be used immediately to prepare the solid dosage form. The shear rate 62.1 1/s was chosen arbitrarily in the range 50 – 100 1/s, which in Figure 32 yields viscosities of W phase that matched the viscosity of the O phase.

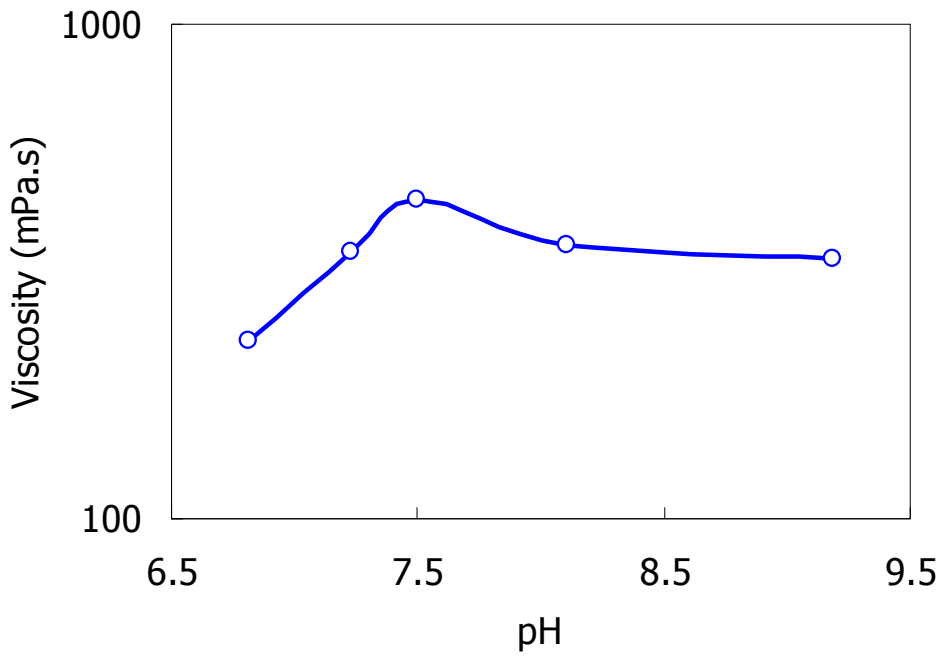

Figure 34: Dependence of viscosity on pH variations at the shear rate of 62.9 1/s. The concentration of ASP4 was constant (1% m/m) for all experiments.

Figure 34 shows relatively very low viscosities at below the pH of 7. This was expected since ASP4 is an anionic polymer. It only starts swelling at pH values above its p*K*a, which is 4.75 for MAA (methacrylic acid). At pH values below the p*K*a of MMA, the carboxylic groups in ASP4 chains were still un-ionised. This was due to their neutral character in an acidic medium. The ASP4 chains were then in the form of compacted coils. The carboxylic groups started to ionise only at pH values above the p*K*a of MAA (Pepas *et al.,* 2000; Gupta *et al.,* 2002). The presence of repeated units of MAA monomers caused more difficulty in ionising the carboxylic groups in ASP4 than would do the single-monomer MAA. This may explain the completion of a fully expanded and entangled structure of ASP4 only at a pH of about 7.5. This was considered the effective pH for thickening of ASP4 in the context of this research.

4.3.3 Effect of ASP 4 Concentration on its Thickening Power

The influence of ASP4 concentration on its thickening power is exhibited in Figure 35. The concentration of ASP4 was measured by mass %. The pH was maintained around 7.5. Figure 35 shows that the viscosity increases as the concentration of ASP4 is increased. However, the figure does not facilitate the determination of the concentration of ASP4 dispersion that gives a viscosity value matching the 206 mPa.s of the O phase.

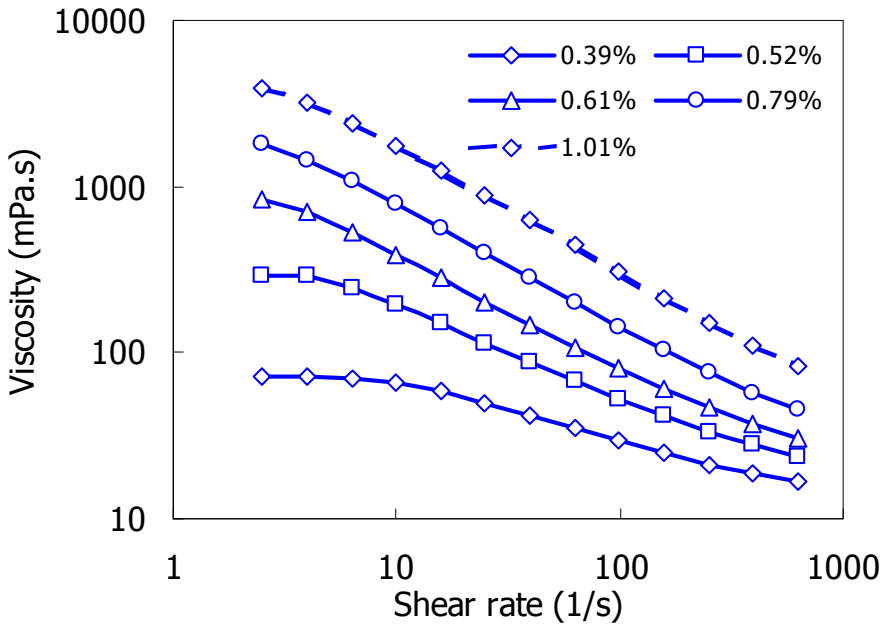

Figure 35: Dependence of thickening power of ASP4 on its concentration

Again, for a better investigation of the optimum concentration of ASP4, the fact that none of the single values of viscosity shown in Figure 35 can be chosen as characteristic of ASP4 had to be ignored. Thus, from the results in Figure 35, a curve of viscosity vs. concentration of ASP4 at a constant pH of 7.5 was plotted. The viscosity values were taken at the shear rate of 62.9 1/s. It has been assumed that this shear rate gives characteristic values of viscosity for ASP4 dispersions.

Figure 36 indicates a value of about 0.80% m/m ASP4 as the critical concentration of ASP4. This concentration gives a viscosity value that matches the 206 mPa.s viscosity of the O phase at 30 ^{o}C.

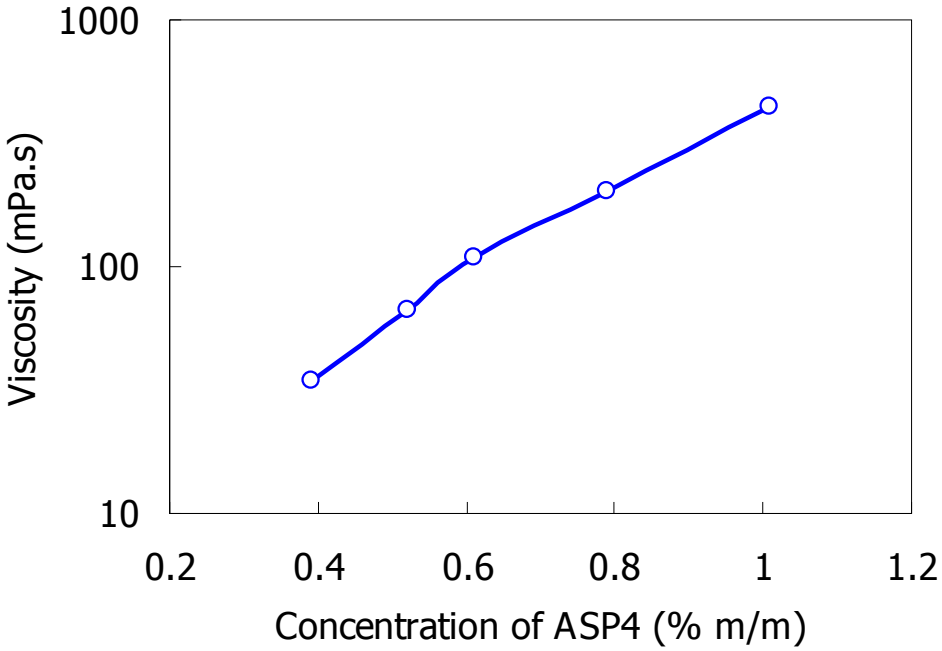

Figure 36: Dependence of the thickening power of ASP4 on its concentration at the shear rate of 62.9 1/s.

4.4 Preparation of the Water Phase

The W phase was prepared using the best combination of the three parameters previously investigated. These parameters were: concentration of Na_2CO_3, pH and concentration of ASP4. The procedure followed was: ca. 4.0 g of ASP4 at 20% m/m dispersion was diluted in 87.3 g of distilled water. A mass of 8.7 g of Na_2CO_3 solution (0.5 M) was used to neutralise the diluted dispersion of ASP4. The resultant solution contained 0.8% m/m ASP4. The viscosity of the W phase was determined at 30 ^{o}C. The

oscillatory mode of the rheometer was used owing to the pseudoplastic behaviour previously observed for aqueous solutions of sodium polymethacrylate. The viscosity of the W phase varied from 360 mPa.s at a low shear rate to 44.3 mPa.s at a higher shear rate. Thus, at rest, the viscosity of the W phase matches the viscosity of the O phase.

4.5 Preparation of O/W Emulsion

An O/W emulsion was prepared using the phase inversion method. It contained a 1:1 by mass O/W. The O phase comprised mass concentrations of 76.9% cypermethrin, 19.3% Solvesso S200 and 3.8% Phenyl Sulphonate CA. It was heated to 50 ^{o}C and stirred to homogenise. The W phase consisted of 85.9% distilled water, 3.9% ASP4 at 20% dispersion, 8.6% solution sodium carbonate (0.5 M) and 1.6% Emulsogen EL. All concentrations are indicated in mass %. This phase was also heated to 50 ^{o}C and stirred to homogenise.

The O phase was initially poured into the stirring cup and the W phase was added at a rate of 4 g/min. Addition of the W phase was done whilst stirring the emulsion manually. Electrical conductivity measurements were performed after each addition of W phase portions. The results are shown in Figure 37.

Figure 37 shows that the phase inversion process occurred when the primary emulsion consisted of 50% O phase and 50% W phase. An abrupt increase in electrical conductivity was observed when the amount of W phase reached 50% of the emulsion. This indicated that the external phase had changed from the electrical non-conductive O phase to the highly conductive W phase at the 1:1 by mass composition.

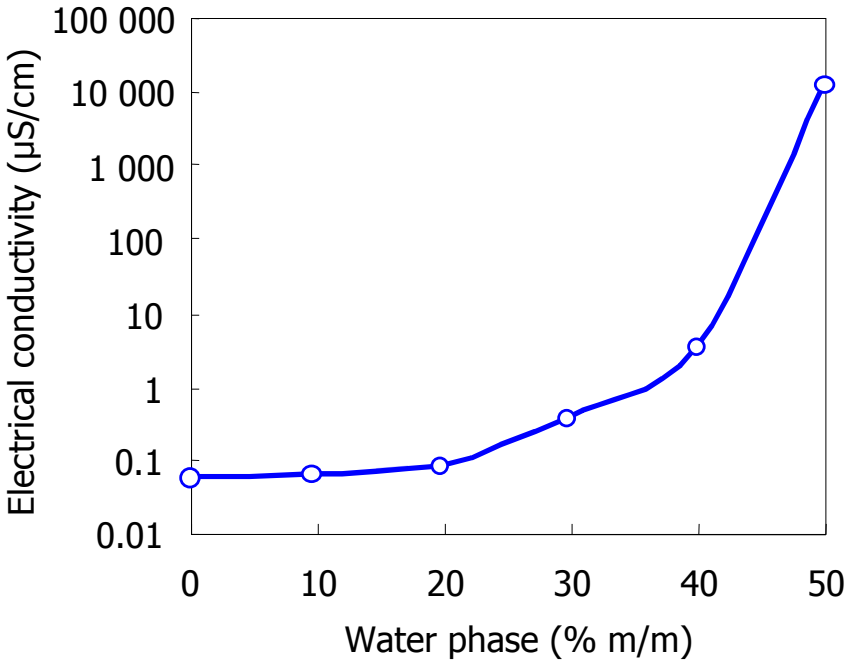

Figure 37: Electrical conductivity results for 1:1 by mass O/W emulsion. An abrupt increase in the conductivity is observed at 50% W phase, indicating occurrence of phase inversion from W/O to O/W emulsion

4.6 Determination of the Critical Amount of Superabsorbent

The critical amount of superabsorbent was determined using ca. 20 g of the W phase. To three identical samples of 100% m/m of the W phase were added 7.5, 10 and 12.5% m/m of superabsorbent Product Z1069. A fourth sample consisted of pure W phase, i.e. the W phase without addition of superabsorbent. Figure 38 presents the amplitude sweep test results of the sample with 12.5% of superabsorbent Product Z1069.

Amplitude sweep tests were used to determine the LVE (linear viscoelastic) range for each sample. The tests were performed using PP25 geometry operating in the oscillation mode. A gap of 10 mm was set for the three samples containing superabsorbent. The

pure sample of the W phase was measured using CP50 geometry owing to its fluid nature. CP50 had a gap of 0.51 mm pre-set by default.

Figure 38 shows quasi-constant plateau values of G' at the strain amplitude values below 10%. This is the range of amplitude strain corresponding to the LVE range. The value of strain amplitude used in the subsequent frequency sweep tests was 0.1%. This was determined automatically by the rheometer. The critical strain was found to be at about 10%. This was the point at which the sample's structure started to be irreversibly perturbed.

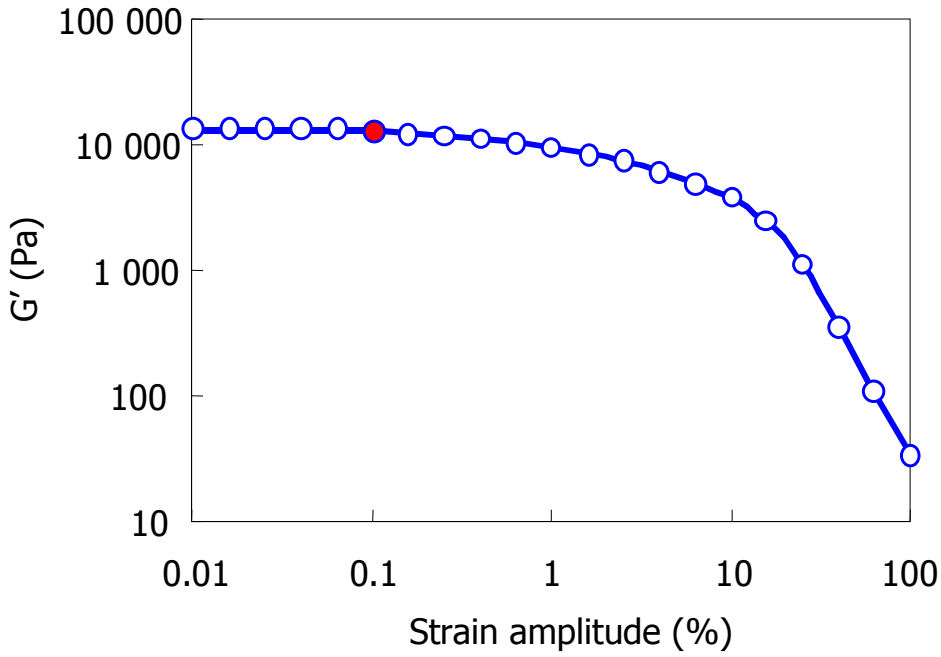

Figure 38: Amplitude sweep curve of the sample with 12.5% superabsorbent. The point filled shows the value of strain amplitude used in the subsequent frequency sweep tests

Figure 39 presents the viscoelastic properties of the W phase sample with 12.5% of superabsorbent Product Z1069. The viscoelastic properties of the samples with 0, 7.5

and 10% of superabsorbent are presented in Figures A.3 – A.5 in the Appendix. All frequency sweep tests were performed in the LVE range.

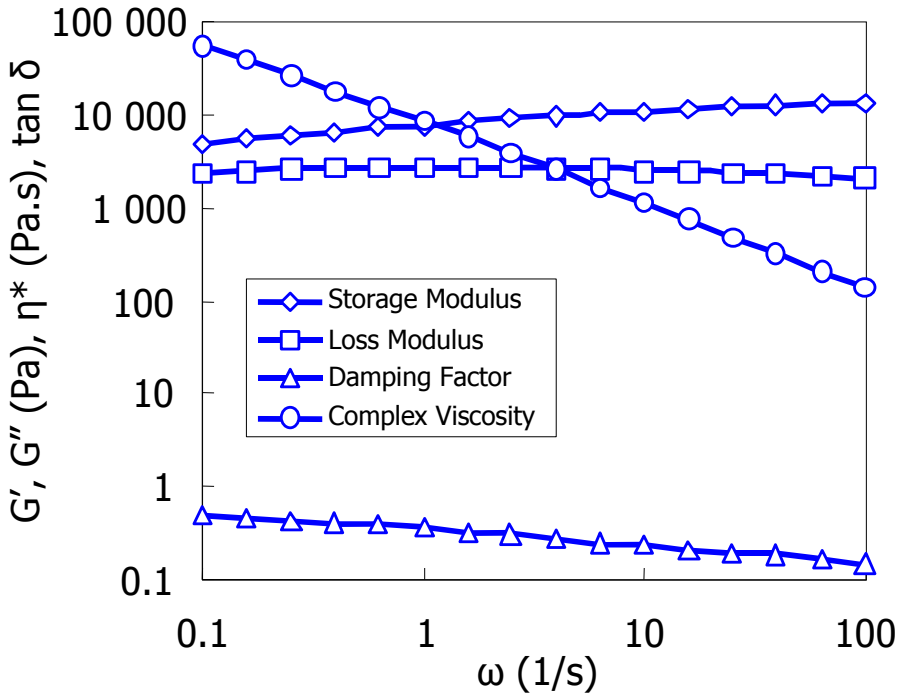

Figure 39: Viscoelastic properties of the sample with 12.5 % of superabsorbent

Figure 39 shows that even at low frequencies, the rheological properties of the sample with 12.5% of superabsorbent were more elastic than viscous. The storage modulus was higher than the loss modulus. This indicated that the gel point had been reached at very low frequencies. The sample was a viscoelastic solid throughout the whole frequency range presented in Figure 39. Of the four samples analysed, only the W phase without supersabsorbent was not a true gel. This is demonstrated in Figure 40 and in Figures A.3 – A.5 in the Appendix.

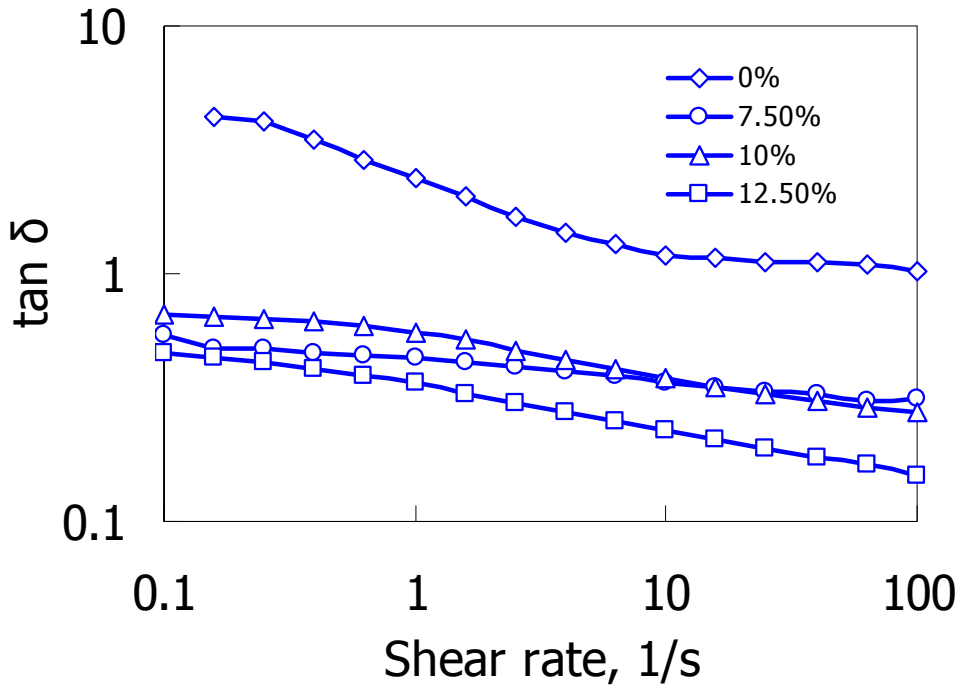

Figure 40: Effect of concentration of superabsorbent on the damping factor (tan δ) of aqueous dispersion of ASP4

Figure 40 shows, for the W phase sample without supersabsorbent, a damping factor above one, i.e. tan δ > 1. This confirmed that its G' was smaller than its G". Thus, the sample was more viscous than elastic – it was in fact a viscoelastic liquid. It was observed that the samples with 7.5 and 10% of superabsorbent were not capable of maintaining a consistent shape. Only the sample with 12.5% superabsorbent possessed this ability. Therefore, 12.5% was considered to be the critical mass concentration of superabsorbent. This amount was used to induce gelation of ASP4 dispersion and was considered to be the minimum amount required to convert the primary emulsion into semi-solid dosage.

4.7 Preparation of boluses and discs of the Formulation

The critical concentration of superabsorbent was used to convert the primary emulsion into a solid dosage form. To a 1:1 by mass O/W primary emulsion was added 12.5% m/m of superabsorbent. The concentration of superabsorbent was measured on the basis of the W phase, i.e. pretending that the concentration of W phase was 100% m/m. A glass rod was used to stir the mixture until complete homogenisation had been achieved. From the resultant semi-solid a bolus containing 1.5 g of cypermethrin was prepared. However, the bolus was observed to be *bleeding*, i.e. it was releasing fluid. It is speculated that the amount of the O phase in the 1:1 by mass O/W emulsion was unsuitably high.

A 1:1.5 m/m O/W emulsion was therefore prepared. It contained 60.6% W phase and 39.4% O phase by mass concentrations. To a certain amount of this emulsion was added 12.5% m/m of superabsorbent Product Z1069. This concentration of superabsorbent was again measured on the basis of the W phase. A new bolus containing 1.5 g cypermethrin was prepared and used to perform dissolution testing. A disc of the new formulation was used to determine its rheological properties.

4.8 Dissolution Testing

The bolus containing 1.5 g cypermethrin failed to meet the required dissolution time of 3 minutes. It was therefore decided to double the amount of superabsorbent used. Although this increased the dissolution rate, the required dissolution time was still not achieved. The amount of superabsorbent was then increased to 37.5% m/m, measured on the basis of the W phase. With this concentration a dissolution time of about 2.5 min was achieved (Figure 41).

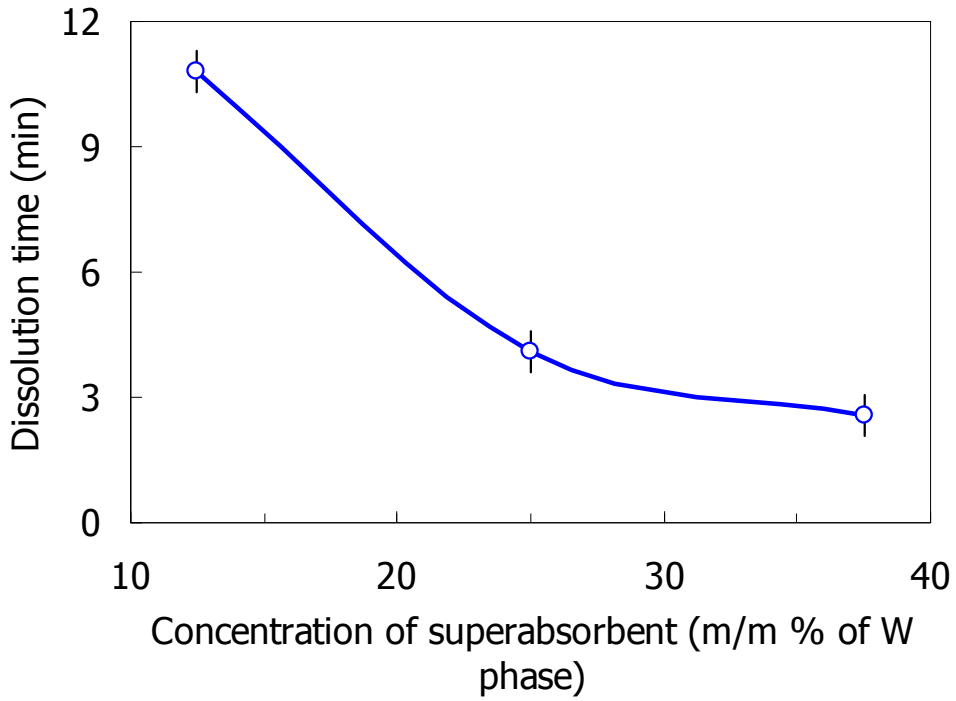

Figure 41: Dissolution time of boluses comprising 1.5 g cypermethrin and different mass concentrations of cross-linked sodium polyacrylate superabsorbent. The concentration of superabsorbent was measured relative to the W phase of the emulsion converted to semi-solid form.

The reason for rapid dissolution of the dosage form as the concentration of superabsorbent increased may be that optimum cohesion of the dosage form had been achieved. It may be speculated that as the amount of superabsorbent increased, dehydration of the W phase of the emulsion also increased and a cooperative motion of the polymer electrolyte ASP4 within the W phase was induced. The viscosity of the W phase increased and a gel-like state with optimum solid cohesion was achieved. On dissolution of the solid dosage form, due to the presence of large amounts of water, the W phase of the emulsion rapidly became rehydrated. The polymer electrolyte disentangled and the viscosity of the W phase dropped to low values. Thus, a rapid dissolution of the dosage form was achieved.

Figure 42 shows a dispersion of cypermethrin resulting from the dissolution of cypermethrin pellets. This dispersion proved stable against creaming/sedimentation for more than a month, as indicated by the absence of phase separation during this period.

Figure 42: A month-old dispersion of cypermethrin pellets in 10 L of tap water showing stability (absence of phase separation)

4.9 Rheological Measurements of the Final Formulation

Figure 43 shows the viscoelastic properties of a disc prepared from the best formulation identified during dissolution testing. The damping factor below one ($\tan \delta < 1$) indicated that the disc possessed a gel structure.

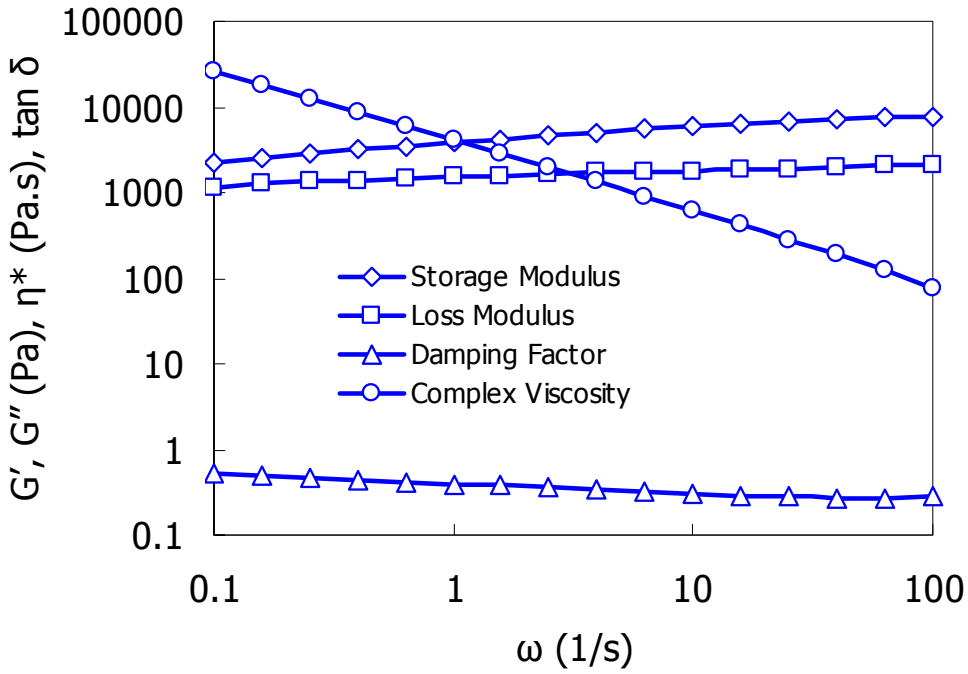

Figure 43: Viscoelastic properties of the formulation with required dissolution time

It was observed that discs and pellets of the formulation containing 60.6% m/m W phase, 39.4% m/m O phase and 37.5% m/m superabsorbent Product Z1069 maintained their shape without assistance. Therefore, this composition was considered to be the best for the gel-based solid dosage form for cypermethrin delivery prepared in the context of this research.

5 CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

A new solid dosage form was formulated. It contains 1.5 g of the pesticide cypermethrin. It may be used in veterinary applications to treat ticks and fly infestations on livestock. The dosage is likely to maintain stability in the warm to hot tropical climate. Rheological studies indicated that the dosage possesses a solid gel-like consistency up to 50 ^{o}C. The solid dosage form disperses in 10 L of tap water within 2.5 minutes. Such dissolution yields a dispersion of cypermethrin stable for more than a month. This was indicated by the absence of phase separation during dispersion storage.

Formulation of this new solid dosage form required pre-dispersing first cypermethrin in water and then trapping the pre-dispersed droplets in a gel matrix. Emulsification was explored to pre-disperse cypermethrin in the form of an oil-in-water (O/W) emulsion. Initially, the aqueous phase of the O/W emulsion comprised only distilled water with the viscosity of 0.82 mPa.s at 30 ^{o}C. Direct emulsification of cypermethrin in distilled water was difficult due to its higher viscosity (7 080 mPa.s). Addition of 20% m/m of the solvent Solvesso S200 to 80% m/m cypermethrin was found crucial to facilitate the emulsification process. Solvesso S200 reduced the viscosity of cypermethrin to 206 mPa.s.

A blend of the surfactants Emulsogen EL and Phenyl Sulphonate CA was successful in producing and stabilising the O/W emulsion. Aqueous 40% m/m cypermethrin dispersion was found suitable for the optimisation of the surfactants. Measurements of viscosity vs. surfactant concentration optimised the concentration of surfactants. The surfactants were added gradually to the 40% m/m cypermethrin dispersion in small increments of 0.8% m/m relative to the O phase. The optimum concentration of the blend was found to be approximately 1.6% m/m Emulsogen EL and 4% m/m Phenyl

Sulphonate CA. These were the concentrations that yielded the minimum viscosity of the respective emulsions.

The nature of the emulsion was proved to be oil-in-water through electrical conductivity measurements. The conductivity of the emulsion containing only Emulsogen EL was 87 μS/cm and that of the emulsion containing the blend of Emulsogen EL and Phenyl Sulphonate CA was 188 μS/cm. These higher conductivities indicated the presence of water as the external phase of the emulsions. The remarkable difference in the conductivities of the two emulsions was attributed to the ionisation of the anionic surfactant Phenyl Sulphonate CA. Emulsogen EL is a non-ionic surfactant.

Sedimentation of the emulsion droplets validated the results of the conductivity measurements. Since the O phase was denser than W phase, sedimentation confirmed the O/W nature of the emulsion. The unmatched densities/viscosities of the O phase and the W phase may have accelerated sedimentation of the emulsion. Thickening the W phase was considered the most practicable way of matching the viscosities of the two immiscible phases. It increases the viscosity of the W phase and ultimately increases the viscosity of the whole emulsion. Simultaneously, it may match the densities of the W phase and the O phase, which would tend to reduce sedimentation of the emulsion droplets.

Polymer electrolyte ASP4 was used as the aqueous thickener. A solution of Na_2CO_3 was used to neutralise the ASP4, creating the necessary conditions for effective thickening of ASP4 in water. Three parameters proved to promote the thickening of distilled water by ASP4: the concentration of Na_2CO_3; the pH of the ASP4 solution after neutralisation by solution Na_2CO_3; and the concentration of ASP4. Increasing these three parameters separately or together had the same effect: the viscosity of the W phase increased.

This may be explained as follows: ASP4 is a linear copolymer of methacrylic acid (MAA), ethyl acrylate and diethyl maleate. In aqueous solution it tends to assume a random coil

conformation. The volume occupied by the coil is least in the unperturbed state. The presence of carboxylic acid groups in MAA causes the ASP4 to release protons in response to changes in the pH. The –COOH groups ionise in aqueous media of appropriate pH and ionic strength. The charges that develop on the MAA chains generate electrostatic repulsive forces between them. These forces make the ASP4 chains uncoil, hydrate and expand. Depending on the polymer concentration, the hydrated and expanded chains may entangle. Entanglements increase the osmotic pressure in the overlap region and therefore, water molecules diffuse to entangled chains. This increases the viscosity of the solution due to the cooperative motion of the entangled chains.

A concentration of Na_2CO_3 higher than 0.2 M was required because the ionic strength created by solution 0.2 M Na_2CO_3 was insufficient to yield a viscosity of the W phase matching that of the O phase. A solution of 0.5 M Na_2CO_3 was then used. The highest viscosity of the W phase was achieved at a pH of approximately 7.5. This pH was above 4.75, the p*K*a of MAA. A final concentration of ASP4 of about 0.80% m/m was found to be suitable for yielding a W phase with a viscosity value that matches the viscosity 206 mPa.s of the O phase at 30 ^{o}C.

The best combination of the three parameters – 0.5 M solution of Na_2CO_3, a pH of 7.5 and 0.8% m/m final concentration of ASP4 – yielded a pseudoplastic W phase. The viscosity at 30 ^{o}C ranged from 360 mPa.s at low shear rates to 44.3 mPa.s at high shear rates. This W phase, together with the O phase, having the viscosities matched at low shear rate, was considered suitable for preparing a stable primary emulsion.

The O/W emulsion was prepared by phase inversion method. The O phase comprised 76.9% cypermethrin, 19.3% Solvesso S200 and 3.8% Phenyl Sulphonate CA. The W phase consisted of 85.9% distilled water, 3.9% ASP4 at 20% dispersion, 8.6% solution 0.5 M Na_2CO_3 and 1.6% Emulsogen EL. All concentrations are indicated in mass %. A phase inversion occurred during the preparation of the emulsion at the composition

50% m/m O phase and 50% m/m W phase. This was indicated by an abrupt increase in electrical conductivity at this composition.

Gelling a 1:1 by mass O/W emulsion failed to produce a stable solid dosage form. The gel was 'bleeding', allowing the O phase to leak out of the dosage form. It was speculated that the possible presence of an unsuitably high concentration of the O phase in the emulsion might be the reason for this bleeding. A 1:1.5 by mass O/W emulsion proved able to produce a stable gel-based dosage form. Rheological measurements optimised the concentration of superabsorbent. About 37.5% m/m superabsorbent Product Z1069 was adequate to gel the 1:1.5 by mass primary O/W emulsion. This concentration was measured relative to the W phase of the emulsion. That is, considering the mass concentration of the W phase as if it was 100%.

Product Z1069 added to the emulsion strongly absorbed water, depleting it from the emulsion. This resulted in an increase of the effective concentration of ASP4 in the W phase of the emulsion. This increase of the polymer electrolyte concentration brought about a gel-like state, corresponding to the desired solid dosage form. Rheological studies performed at 50 ^{o}C indicated that the dosage form possessed a solid gel-like consistency. The loss tangent was located below one ($\tan \delta < 1$) in the rheology spectra. Thus, this solid dosage form is likely to maintain its stability in the warm to hot tropical climate.

The solid dosage contained 24.6% m/m cypermethrin. Therefore, boluses weighing ca. 6.1 g provided the required dosage of 1.5 g cypermethrin. These boluses rapidly disintegrated with mild stirring in 10 L of tap water. Complete pellet disintegration and active dispersion occurred within 2.5 minutes at ambient temperature (25 $\pm$ 2 ^{o}C). The dispersion is stable against creaming/sedimentation for more than a month, as indicated by the absence of phase separation during this period.

It is speculated that the process whereby rapid dissolution of this solid dosage form occurred is as follows: the O/W emulsion was encapsulated in a gel matrix. The W phase of the emulsion was dehydrated. A cooperative motion of the polymer electrolyte ASP4 within the W phase developed, leading to the achievement of a gel-like state. In the presence of large amounts of water, the dosage form swelled. The W phase of the emulsion was then rapidly rehydrated. The polymer electrolyte ASP4 disentangled, and the viscosity of the W phase dropped to low values. Thus, a rapid dissolution of the dosage form was possible.

5.2 Recommendations

Content uniformity tests should be performed to assess whether the concentration of the active ingredient in the boluses weighing ca. 6.1 g is within the limits of acceptable deviation. This test may be simultaneously used to confirm the compatibility between the dosage ingredients.

The maximum pressure that can be used to compress this dosage form and yet maintain its rapid disintegration rate should be investigated before possible industrialisation of the methods and procedures developed in this research work.

The boluses/discs of this solid dosage form should be packed in unit dose packaging because direct contact between two boluses is likely to cause their aggregation due to their slightly moist surfaces. A tropicalised blister pack, owing its rigidity, seems to be the best packaging material for this solid dosage form since the dosage deforms easily when subjected to an external force.

The solid consistency of the dosage form was tested and confirmed at 50 ^{o}C. Therefore, the dosage form should be stored up to this temperature to avoid possible deformation of the solid gel-like structure.

Exposure of this solid dosage form to fluorescent lamps and sunlight is not recommended. This is to prevent adverse effects of light radiations. Only incandescent lamps may be used.

6 REFERENCES

Ansel, H. (1985). *Introduction to Pharmaceutical Dosage Forms.* 4th edition, Lea & Febiger, Philadelphia, USA.

Ansel, H. & Popovich, J. (1990). *Pharmaceutical Dosage Forms and Drug Delivery Systems*. Lea & Febiger, Philadelphia, USA.

Aulton, M.E. (2002). *Pharmaceutics: The Science of Dosage Form Design*. 2nd edition, Churchill Livingstone, Edinburgh.

Baglione, P., Berti, D. and Bonini, M. (2000). Preparation and stability of emulsions. *Chimica & Industria.* September.

Banker, G. and Rhodes, C. (1990). Modern pharmaceutics. 2nd edition, In: *Drugs and the Pharmaceutical Sciences*, Volume 40, Marcel Dekker Inc., New York.

Bennett, H., Bishop, J. and Wulfinghoff, M. (1968). *Practical Emulsions,* Volume I. Chemical Publishing Company Inc., New York.

Bonacucina, G., Martelli, S. and Palmieri, G. (2004). Rheological, mucoadhesive and release properties of carbopol gels in hydrophilic cosolvents. *Int. J. Pharm.,* 282: 115 – 130.

Bonacucina, G., Cespi, M., Misici-Falzi, M. and Palmieri, G. (2006). Rheological, adhesive and release characterization of semisolid carbopol/tetraglycol systems. *Int. J. Pharm., 307*: 129 – 140.

Chappat, M (1994). Some applications of emulsions. *Colloids Surfaces A: Physicochemical Eng. Aspects, 129 – 130: 75 - 94.*

Collett, D. and Aulton, M. (1990). *Pharmaceutical Practice*. Churchill Livingstone, New York.

Craig, V. (1997). An historical review of surface force measurement techniques. *Colloids Surfaces A: Physicochemical Eng. Aspects, 129 – 130: 75 - 94.*

Davies, J. and Rideal, E. (1963). *Interfacial Phenomena*. Academic Press Inc, London.

Gregory, J. (2006). *Particles in Water: Properties and Processes*. IWA Publishers, London.

Grimm, W. (1987). *Stability Testing of Drug Products: Scientific Critiques, Guidelines and Official State Requirements in Europe, Japan and the USA.* Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart.

Gupta, P., Vermani, K. and Garg, S. (2002). Hydrogels: From controlled release to pH-responsive drug delivery. *DDT*, 7: 569-579.

Hess, H. (1985). *Pharmaceutical Dosage Forms and their Use.* Hans Huber Publishers, Bern, Switzerland.

Israelachvili, J. (1994). The science and application of emulsions – An overview. *Colloids Surfaces A: Physicochemical Eng. Aspects,* 91: 1 – 8.

Kerihuel, A., Kumar, S., Bellettre, J. and Tazerout, M. (2006). Ethanol animal fat emulsions as a diesel engine fuel – Part 1: Formulations and influential parameters. *Fuel,* 85: 2640 – 2645.

Lieberman, H.A., Lachman, L. and Schwartz, J.B. (1988). *Pharmaceutical Dosage Forms: Disperse Systems*, 1st edition, Volume 1. Marcel Dekker Inc., New York.

Lieberman, H.A., Lachman, L. and Schwartz, J.B. (1989). *Pharmaceutical Dosage Forms: Tablets*, 2nd edition, Volume 1. Marcel Dekker Inc., New York.

Martens, C. (1964). *Emulsions and Water-soluble Paints and Coatings.* Reinhold Publishing Corporation, New York.

Martin, A. (1993). *Physical Pharmacy*, 4th edition. Lea & Febiger, Philadelphia, USA.

Mezger, T. (2006). *Rheology Handbook: For Users of Rotational and Oscillatory Rheometers*, 2nd revised edition. Vicentz Network GmbH & Co. KG, Hanover, Germany.

Moreton, R. (1995). Excipients to the year 2000. In: *Excipients and Delivery Systems for Pharmaceutical Formulations*, The Royal Society of Chemistry, Cambridge, UK.

Peppas, N., Bures, P., Leobandung, W. and Ichikawa, H. (2000). Hydrogels in pharmaceutical formulations. *Eur. J. Pharm. Biopharm.* 50, 27-46.

Pilemand, C. (2002). Surfactants: *Their abilities and important physico-chemical properties*. Report by the Centre for Miljø og Luftveje, Copenhagen, Denmark.

Qiu, Y. and Park, K. (2001). Environmentally sensitive hydrogels for drug delivery. *Adv. Drug Deliv. Rev.* 53: 321-339.

Rawlins, E. (1988). *Bentley's Textbook of Pharmaceutics*, 8th edition. Baillière Tindall, London, UK.

Roland, I., Piel, G., Delattre, L. and Evrard, B. (2003). Systematic characterization of oil-in-water emulsions for formulation design. *Int. J. Pharm.,* 263: 85 – 94.

Sajjadi, S. (2006). Effect of mixing protocol on formation of fine emulsions. *Chem. Eng. Sci.,* 61: 3009 – 3017.

Shenoy, A. (1999). *Rheology of Filled Polymer Systems*. Kluwer Academic Publishers, London, UK.

Tadros, T. (1982a). Formation and stability of emulsions produced by dilution of emulsifiable concentrates. Part I. An investigation of the dispersion on dilution of emulsifiable concentrate containing cationic and no-ionic surfactants. *Colloids and Surfaces, 5: 105 – 115.*

Tadros, T. (1982b). Formation and stability of emulsions produced by dilution of emulsifiable concentrates. Part II. The influence of surfactant concentration on the stability of oil-in-water emulsions. *Colloids and Surfaces, 5: 117 – 127.*

Tadros, T. (2004). Application of rheology for assessment and prediction of the long-term physical stability of emulsions. *Adv. Colloid Interface Sci.,* 108-109: 227 – 258.

Tadros, T. (2005). *Applied Surfactants: Principles and Applications*. Wiley – VCH Verlag GmbH & Co. KgaA, Weinheim, Germany.

Walker, K. (2000). Cost-comparison of DDT and alternative insecticides for malaria control. *Medical and Veterinary Entomology, 14: 345 – 354.*

Waterman, K. and Adami, R. (2005). Accelerated aging: Prediction of chemical stability of pharmaceuticals. *Int. J. Pharm.,* 293: 101 – 125.

Wells, J. (1988). *Pharmaceutical Preformulation: The Physicochemical Properties of Drug Substances*. Ellis Horwood Ltd, Chichester, UK.

Wikipedia (2007), http://www.en.wikipedia.org/wiki/main_page [2007, August 12].

Winfield, A. and Richards, R. (2004). *Pharmaceutical Practice*, 3rd edition. Churchill Livingstone, New York.

Ziles, J. (2005). The phenomenon of surface tension. *Course in Methods of Measurement of Interfacial Tension, Advanced Laboratory Solutions, Johannesburg.*

APPENDIX

Table A.1: Amounts of 0.8 M Na_2CO_3 used to thicken aqueous dispersion of ASP4

Mass of 20 % ASP4 (g)	Mass of 0.2 M Na_2CO_3 (g)	Mass of distilled water (g)	Final concentration of ASP4 (%)
2.500	0.000	47.136	1.010
2.510	3.001	44.030	1.010
2.500	7.007	40.035	1.010
2.500	9.999	37.047	1.010
2.500	13.012	34.015	1.010
2.500	15.026	32.025	1.010
2.500	16.005	31.032	1.010
2.500	17.021	30.032	1.010

Table A.2: Amounts of 0.5 M Na_2CO_3 used to thicken aqueous dispersion of ASP4

Mass of 20 % ASP4 (g)	Mass of 0.5 M Na_2CO_3 (g)	Mass of distilled water (g)	Final concentration of ASP4 (%)
2.500	0.000	47.000	1.010
2.502	5.002	42.028	1.010
2.511	7.008	40.000	1.010
2.513	3.030	44.012	1.010
2.515	5.542	41.509	1.010
2.532	6.021	41.018	1.010

Table A.3: Amounts of 0.8 M Na_2CO_3 used to thicken aqueous dispersion of ASP4

Mass of 20 % ASP4 (g)	**Mass of 0.8 M Na_2CO_3 (g)**	**Mass of distilled water (g)**	**Final concentration of ASP4 (%)**
2.500	0.000	47.000	1.010
2.502	4.002	43.026	1.010
2.504	3.025	44.044	1.010
2.516	3.431	43.637	1.010
2.517	2.011	45.028	1.020
2.523	5.007	42.002	1.020

Table A.4: Parameters and amounts used to maintain a constant pH

Mass of 20 % ASP4 (g)	**Mass of 0.5 M Na_2CO_3 (g)**	**Mass of distilled water (g)**	**pH**
2.500	0.000	47.000	3.66
2.513	3.030	44.012	6.81
2.502	5.002	42.028	7.23
2.515	5.542	41.509	7.50
2.532	6.021	41.018	8.11
2.511	7.008	40.000	9.19

Table A.5: Parameters and amounts used to study the effect of ASP4 on its thickening power at a pH of about 7.5

Mass of 20 % ASP4 (g)	**Mass of 0.5 M Na_2CO_3 (g)**	**Mass of distilled water (g)**	**Final concentration of ASP4 (%)**
2.514	5.535	120.100	0.39
2.530	5.527	90.012	0.52
2.524	5.527	75.000	0.61
2.518	5.506	55.075	0.80
2.515	5.542	41.509	1.01

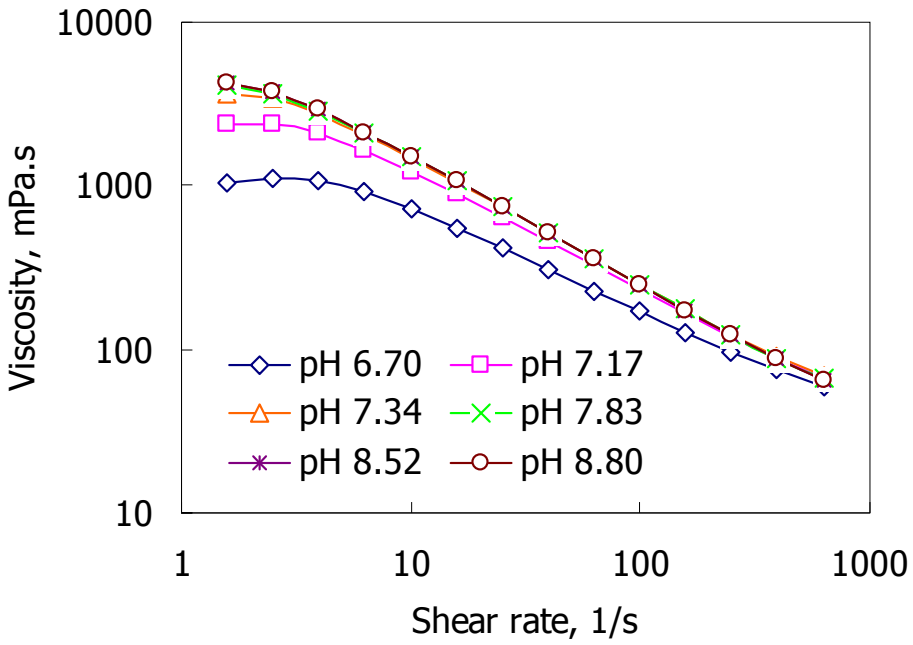

Figure A.1: dependence of viscosity on pH variations using 0.2 M Na_2CO_3

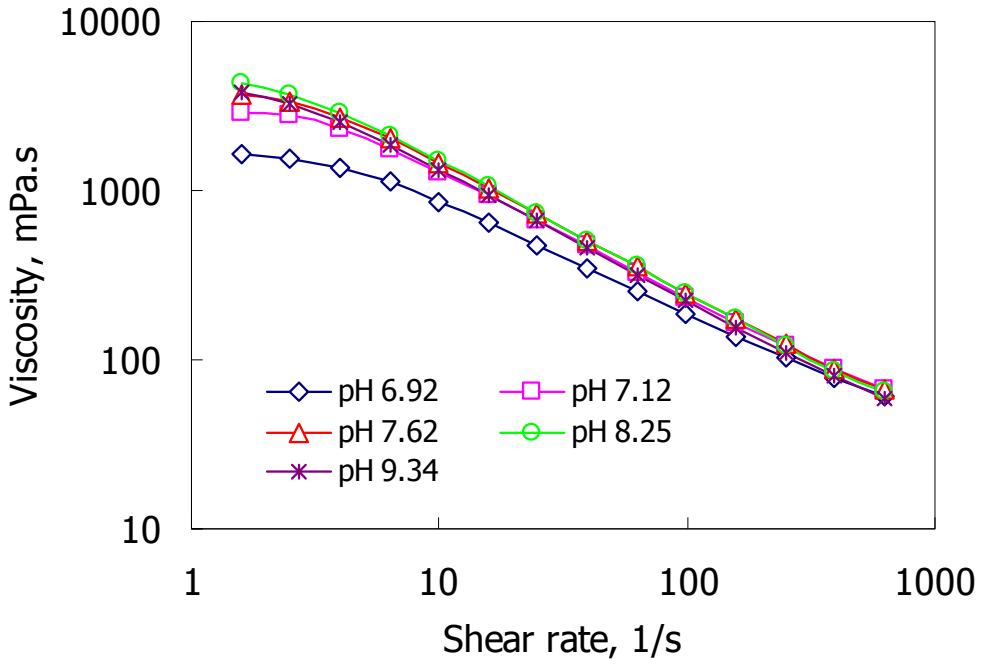

Figure A.2: Dependence of viscosity on pH variations using 0.8 M Na_2CO_3

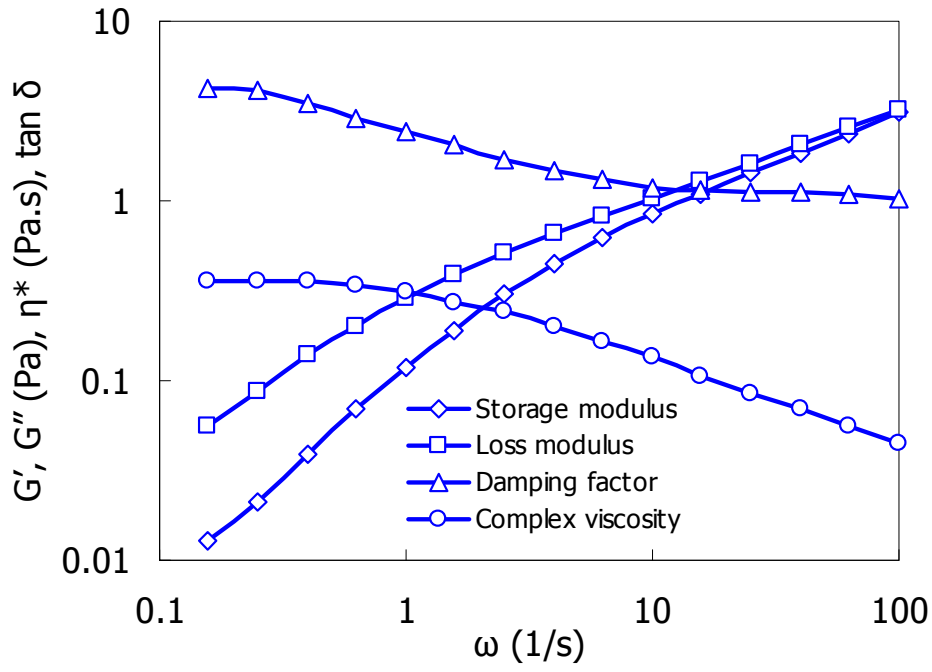

Figure A.3: Viscoelasticity of the W phase sample with 0 % of superabsorbent

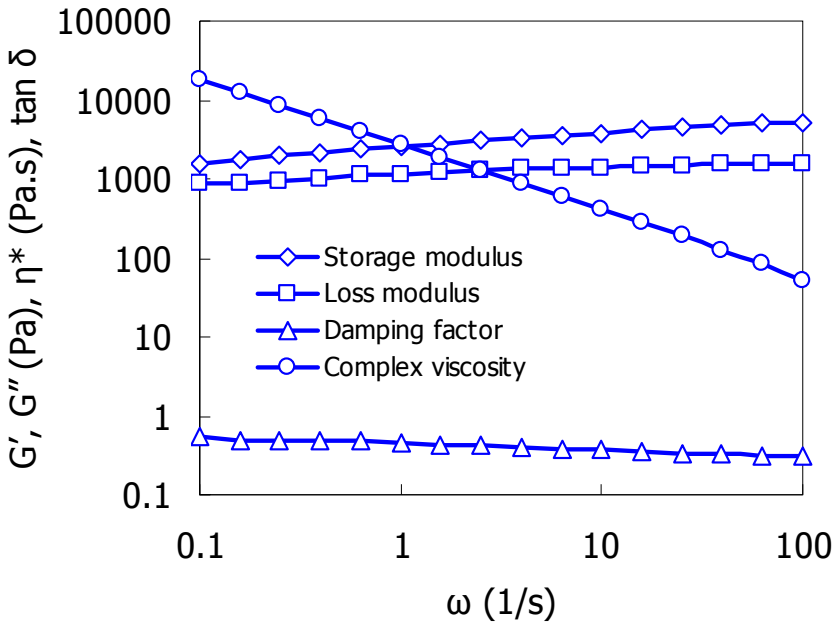

Figure A.4: Viscoelasticity of the W phase sample with 7.5 % of superabsorbent

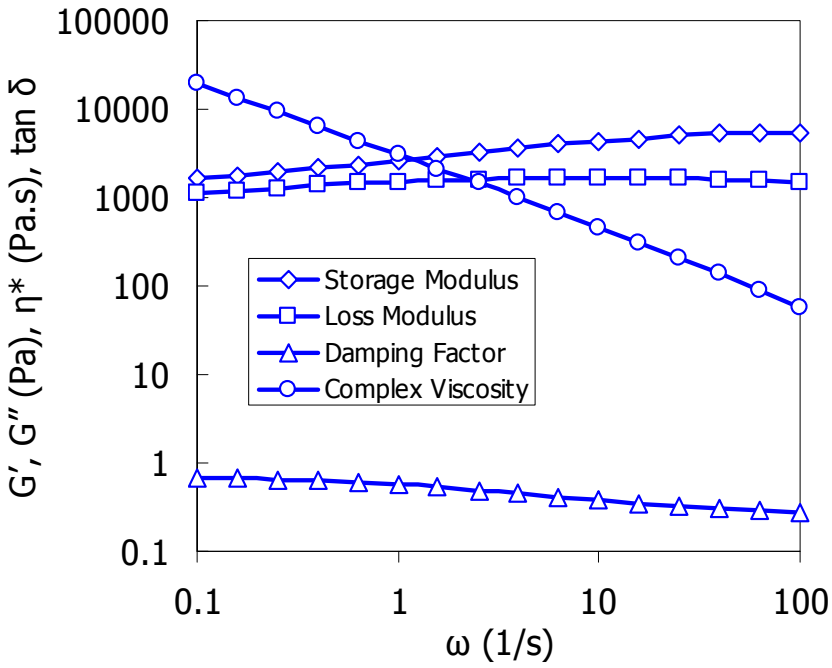

Figure A.5: Viscoelasticity of the W phase sample with 10 % of superabsorbent

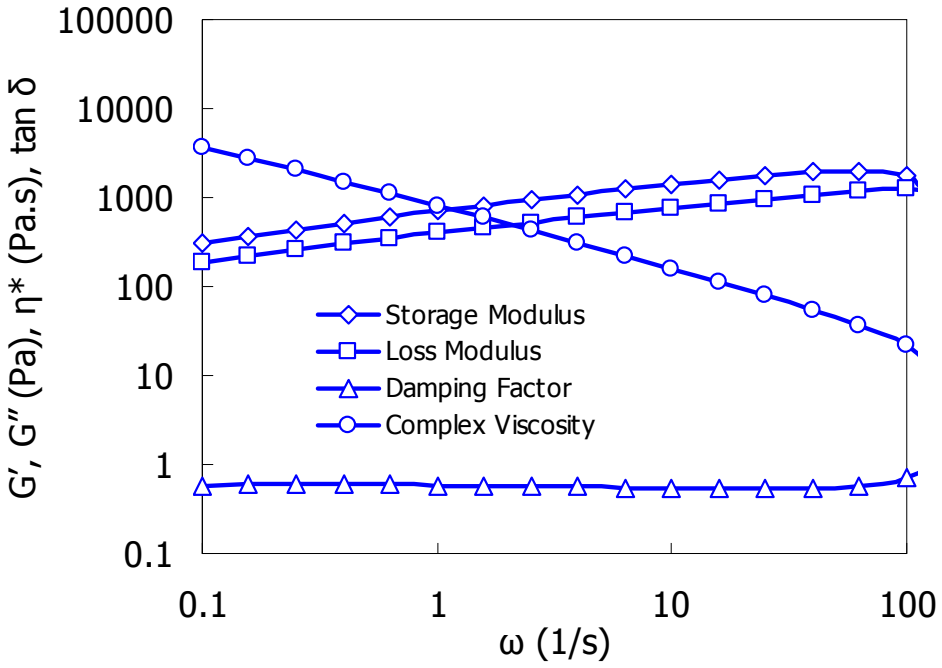

Figure A.6: Viscoelasticity of the formulation with 2.5 g of superabsorbent

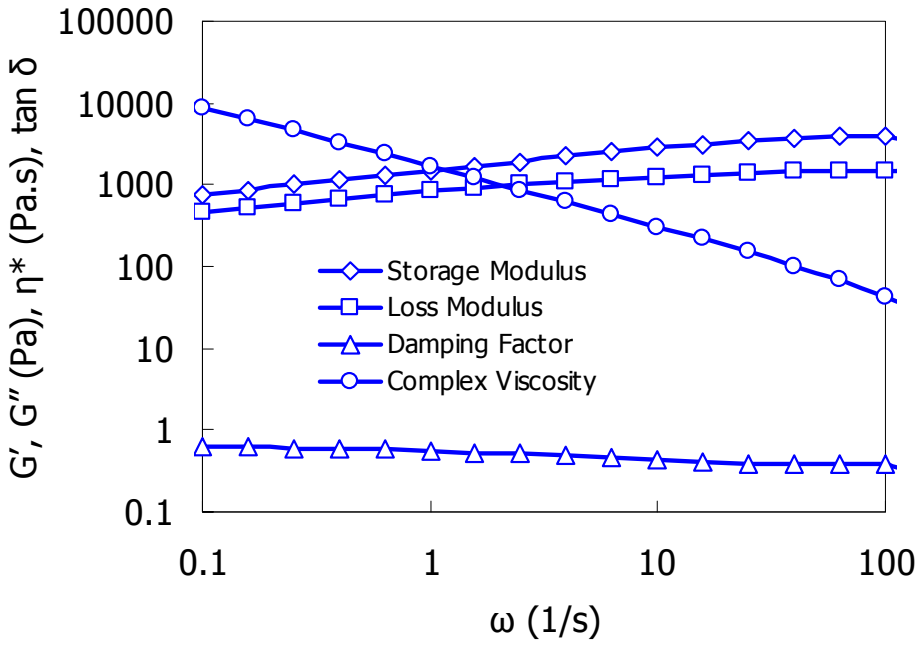

Figure A.7: Viscoelasticity of the formulation with 5 g of superabsorbent