

# **CHAPTER ONE**

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## **1 DOSAGE FORM DESIGN OF EMULGELS: PHARMACEUTICAL AND FORMULATION CONSIDERATIONS**

### **1.1 INTRODUCTION**

Drug substances are seldom administered alone. Non-medicinal agents are given as part of a formulation where they serve a range of varied and specialised pharmaceutical functions. Different dosage forms are manufactured with selective combinations of these non-medicinal agents, referred to as pharmaceutical excipients. The pharmaceutical ingredients solubilise, suspend, thicken, dilute, emulsify, preserve, colour, flavour, stabilise and fashion medicinal agents into appealing and efficacious dosage forms. Each type of dosage form has unique physical and pharmaceutical characteristics. These varied preparations provide advantages to the prescribing physician with the broad choices of drugs and delivery systems to prescribe. Conversely, challenges arise for the manufacturing and compounding pharmacist in the formulation of this vast range of preparations (Allen *et al.*, 2005:92).

### **1.2 ORAL DOSAGE FORMS**

Medicinal agents are categorised for the convenient and efficacious treatment of diseases. Factors considered for formulation are therapeutic considerations such as: the nature of the illness, the general method in which it is treated, the age and the anticipated ability of the patient who needs the treatment. Tablets and capsules are the general dosage forms used for oral administration. These dosage forms are most convenient in the self-administration of medication. In emergency situations, in which patients are unable to take oral medication or are comatose, an injectable form of the medication may be prepared (Allen *et al.*, 2005:94).

For infants and children, pharmaceutical liquids rather than solid dosage forms are preferred. These flavoured aqueous solutions, syrups or suspensions are administered into the infant's or child's mouth by oral dispenser, spoon or dropper.

Infant size rectal suppositories may also be employed. For patients who struggle to swallow tablets, chewable tablets are formulated. Medication for the elderly is commonly formulated into oral liquids. These formulations are homogeneous preparations containing active ingredients in a suitable vehicle intended to be swallowed, diluted or undiluted. There are three main types of oral liquids: solutions, suspensions and emulsions (Lund, 1994:32).

- *Solutions* are mixtures of one substance dissolved in another so the properties are the same throughout. A solution is composed of a solute and the solvent. The solute is the substance being dissolved and the solvent is the part of the solution that does the dissolving. The solute is of molecular size.
- *Suspensions* contain one or more active ingredients suspended in a suitable vehicle. A suspension formulation may be used to mask the unpleasant taste of certain drugs. Sedimentation of suspended solids in suspensions may occur gradually on standing, but redispersion should occur easily when shaken.
- *Emulsions* are stabilised oil-in water dispersions, either or both phases of which may contain dissolved solids. They contain one or more active ingredients. Solids may also be suspended in oral emulsions. Emulsions are used for oils and fats or oily solutions of water-insoluble or unpalatable drugs.

Drugs as liquid dosage forms have some advantages over solid dosage forms:

- Stable emulsions represent an effective formulation approach for the resolution of problems in drug and cosmetic agent delivery. Patient acceptance is seen as the most important reason for the popularity of emulsions for oral and topical formulations. Disagreeable taste or mouth feel of a drug can be dealt with by placing the drug in the internal phase of an emulsion surrounded by an inert, external phase. Increased peroral bioavailability of a compound, administered in an emulsion formulation, may stem from an increase in the concentration or amount of the absorbable (molecularly dispersed) species relative to the total, due to a formulation component (e.g., fatty acid) induced decrease in gastrointestinal motility, or from increased endocytotic uptake(Block, 1996:48).
- Microemulsion systems have emerged as novel vehicles for drug delivery which allow sustained or controlled release for transdermal, topical, oral, nasal, intravenous, ocular, parenteral and other administration routes of drugs. Microemulsion drug delivery is a practical delivery platform for improving target specificity, therapeutic activity and reducing toxicity of drugs. Owing to the existence of different domains of variable polarity in microemulsion systems, they

show a potential to be used as delivery vehicles for a diversity of drugs (Fanun, 2012:306).

- For many patients, the liquid form is preferred over the solid form of the same drug because of the ease of swallowing liquids and the flexibility in the administration of a range of doses (Ansel & Popovich, 1990:226).
- The cost of oral therapy is generally much lower in comparison to parenteral and other routes of delivery (Lee & Young, 2001:164).

However liquid oral dosage forms also have disadvantages:

- The drug may be less stable in a liquid formulation than in tablets or capsules, especially in solutions (Lund,1994:31).
- Liquids, especially aqueous preparations, are susceptible to microbial contamination, which may be unavoidably present from the time of manufacture, however, the proliferation of microorganisms can be controlled by adding a preservative (Lund,1994:31).
- Masking the unpleasant taste of a drug in solution is more difficult than when the drug is in a solid dosage form (Lund,1994:31).
- Liquid preparations tend to be bulky and therefore inconvenient to store and transport (Lund,1994:31).
- Administration of the correct dose is less precise since it involves the use of a 5 ml spoon, an oral syringe, or sometimes a volumetric dropper (Lund,1994:31).
- Suspensions and emulsions have the added drawback that they must be thoroughly shaken to allow accurate dosing (Lund, 1994:31).
- There are limitations on choice and concentration of excipients for pediatric patients (Nunn & Williams, 2005:675).

### **1.3 HISTORICAL PERSPECTIVE OF PHEROID®-BASED DRUG DEVELOPMENT**

Pheroid® technology has its origin in Emzaloid™ technology. Emzaloid™ technology was first unknowingly used in a quick and dirty product formulated by Piet Meyer and Steven Zall in an effort to treat or cure psoriasis. The psoriasis product proved to be more effective with fewer side effects than any comparable product on the market. The company MeyerZall Laboratories was established with the aim of commercialising the psoriasis product. A hypothesis was formulated that the vesicles

constituted a delivery system with wider application than the single topical product and the system may be optimised to entrap and deliver a number of active ingredients (Grobler, 2009:117).

The North-West University (NWU) obtained all intellectual property with regards to the Emzaloid™ technology in 2003. Pheroid® technology is based on Emzaloid™ technology, but the two technologies are not quite equal. The word Pheroid® is a conjugation of the word colloid and the Greek words apo and phero which quite literally mean to deliver. Several differences exist in the manufacturing protocols of Emzaloid™ and Pheroid® systems, the main difference being Emzaloid™-containing products are manufactured using low pressure gas exposure (80kPa) for four hours only, resulting in under-saturation of the formulation with nitrous oxide, whereas Pheroid® formulations are saturated with nitrous oxide at higher than 150kPa for three to four days. Furthermore, all Pheroid®-based formulations contain D/L- $\alpha$ -tocopherol, whereas the same is not true for all Emzaloid™-based products (Grobler, 2009:118).

Pheroid® technology, seen within the context of drug delivery and therapy is a complex polydisperse technology, based on colloidal emulsion system used for the delivery of pharmaceutical and other compounds. Studies on the Pheroid® have shown it has several unique advantages, including (Grobler, 2009:102):

- Pheroid® can be used to transfer molecules by a number of administration routes, such as oral, nasal or transdermal without the need for sophisticated procedures.
- It is a highly effective gene transfer vector and much more efficient than conventional products currently on the market.
- One of the most interesting and exciting properties is that it may be used to package ligands so that vesicles can be targeted to specific cell surface receptors for uptake by these cells.

According to the method of manufacturing and the main components in the formulation of the Pheroid®, the system can be classified as a disperse system and more specifically an oil in water (o/w) emulsion with nano sized particles (Uys, 2006:17). A newer and broader approach is to compare the Pheroid® to its lipid bilayer companion the liposome. Various differences between the two entities proved that Pheroid® can more easily be related to emulsions. Still, this is not the true classification as Grobler explains that Pheroid® is dispersed within a dispersion medium, containing not only two liquid phases, but also a dispersed gas phase which is associated with the fatty acid dispersed phase (Grobler, 2009:152).

In this study, a more detailed classification system will be compiled since an extra few components are added to the basic Pheroid® preparation in an attempt to optimise this oral delivery system to an oral emulgel formulation.

## 1.4 DISPERSED SYSTEMS

A *colloidal dispersion* is a system in which particles of colloidal size of any nature (e.g. solid, liquid or gas) are dispersed in a *continuous phase* of a different composition (or state). The term *colloidal* refers to a state of subdivision, implying that the molecules or polymolecular particles dispersed in a medium have, at least in one direction, a dimension roughly between 1 nm and 1µm, or that in a system discontinuity are found at distances of that order (Koopal, 2001).

Colloidal systems are typically classified as:

- Simple colloids where a clear distinction between the dispersed phase and dispersion medium is found, as in oil-in-water (o/w) or water-in-oil (w/o) emulsions.
- Multiple colloids in which three phases co-exist as two finely divided dispersed phases such as in multiple emulsions of the w/o/w or o/w/o type.
- Network colloids that have two phases forming an inter-penetrating network as found in polymer matrices.

According to Banker and Rhodes (2002:238) disperse systems can be classified in various ways:

1. Classification based on the physical state of the two constituent phases (see Table 1.1). A suspension is a solid in liquid dispersion, for example a solid drug dispersed within a liquid that is a poor solvent for the drug. An emulsion is a liquid in liquid dispersion in which the two phases are either completely immiscible or saturated with each other. In the case of aerosols, either a liquid or a solid is dispersed within a gaseous phase. There is no disperse system in which both phases are gases.

**Table 1.1:** Classification of disperse systems, based on the physical state of the dispersed phase and the dispersion medium (Banker & Rhodes, 2002:238).

<i>Dispersed phase</i>	<i>Dispersion medium</i>		
	<b>Solid</b>	<b>Liquid</b>	<b>Gas</b>
<b>Solid</b>	Solid suspension	Suspension	Solid aerosol
<b>Liquid</b>	Solid emulsion	Emulsion	Liquid aerosol
<b>Gas</b>	Solid foam	Foam	None

2. Another classification is based on the size of the dispersed particles within the dispersion medium (see Table 1.2). The particles of the dispersed phase may vary considerably in size, from large particles visible to the naked eye, down to particles in the colloidal size range and particles of atomic and molecular dimensions. Generally, three classes are distinguished: molecular, colloidal and coarse dispersions. Molecular dispersions are homogeneous in character and form true solutions. Colloidal dispersions are intermediate in size, (1.0nm – 1.0µm), between true solutions and coarse dispersions. Dispersions containing larger dispersed phases, usually 10 – 50 µm in size, are referred to as coarse dispersions which include most pharmaceutical suspensions and emulsions.

**Table 1.2:** Classification of disperse systems, based on the particle size of the dispersed phase (Banker & Rhodes, 2002:238).

<i>Category</i>	<i>Range of particle size</i>	<i>Characteristics of systems</i>
<b>Molecular dispersion</b>	< 1.0nm	Particles invisible by electron microscopy. Pass through semipermeable membranes.
<b>Colloidal dispersion</b>	1.0nm – 1.0µm	Particles not resolved by ordinary microscope but by electron microscopy. Pass through filter paper but not semipermeable membranes.
<b>Coarse dispersion</b>	> 1.0µm	Particles visible by ordinary microscopy. Do not pass through normal filters or semipermeable membranes.

Disperse systems have found a wide variety of applications in pharmacy for example:

- Liquid dispersions, such as emulsions and suspensions, compared to solid dosage forms has the advantage of being easily swallowed and gives flexibility in dosing (Banker & Rhodes, 2002:239).
- The small particle size of the drug present in disperse systems results in a large specific surface area. This leads to a higher rate of drug dissolution and possibly a superior bioavailability compared to solid dosage forms containing larger drug particles. This can be of major importance in the case of poorly soluble drugs (Banker & Rhodes, 2002:239).
- Drugs insoluble in aqueous vehicles at a required dosage are often formulated as a suspension. In cases where the use of co-solvents, surfactants and/or other solubilising agents would compromise the product stability or influence the organoleptic properties, suspensions are often used (Banker & Rhodes, 2002:239).
- Colloidal systems are extensively used in pharmacy with various applications such as colloidal gold, employed in nuclear medicine as diagnostic and therapeutic aids (Banker & Rhodes, 2002:239).
- Disperse systems are often involved in various steps of pharmaceutical manufacturing. Colloid science is used in industrial pharmacy in operations such as particle size reduction, coating of pharmaceutical solid dosage forms, microencapsulation, solubilisation and complexation of drugs (Banker & Rhodes, 2002:240).

Grobler (2009:148) defines the Pheroid<sup>®</sup> delivery system as a colloidal system containing unique and stable lipid-based submicron- and micron-sized structures, called Pheroid<sup>®</sup>, uniformly distributed in a dispersion medium that may be adapted to the indication. The dispersed structures (dispersed phase) can be manipulated in terms of morphology, structure, size and function. Although the ultra-fine particles which remain suspended in the dispersion medium (continuous phase) in a typical colloidal system are usually between 1 – 100 nm in diameter, various types of Pheroid<sup>®</sup> are typically formulated to have a diameter of between 200 nm and 2 µm. Parameters such as the required capacity (i.e., the amount and size of the active compound to be entrapped) and the administration route are taken into account when deciding on the type and diameter of the Pheroid<sup>®</sup>.

### **1.4.1 INGREDIENTS OF PHEROID® AND MOLECULAR ORGANISATION OF THE PHEROID®**

The Pheroid® basically consists of an oil phase, a water phase and a gas phase. A precursor of the Pheroid®, the pro-Pheroid®, contains no water phase and has no particles; macroscopically it looks like an oil phase. Pheroid® micro- and nano-particles form spontaneously upon addition of a water phase to the pro-Pheroid®. While the spontaneous reaction occurs, the Active Pharmaceutical Ingredients (APIs) present are packaged into the particles. When the water phase is added externally, it can contain electrolytes and may be buffered. The water phase can be added externally by the formulator or manufacturer or can consist of body fluid, such as fluid present in stomach/intestinal content. The pro-Pheroid® system unlocks the potential of this technology for administration routes other than the topical route. Pro-Pheroid® is especially important in the case of drugs that are unstable in the presence of moisture, such as rifampicin (Grobler, 2009:119).

Pheroid® consists primarily of ethylated and pegylated polyunsaturated fatty acids, including omega-3 and omega-6 fatty acids, but excluding arachidonic acid. The fatty acids are in the *cis*-formation and therefore compatible with the orientation of the fatty acids in man. The main problem with fatty acids is oxidation and therefore certain precautions have to be taken to help maintain the stability of the delivery system. The various other components of the Pheroid® will be discussed throughout this study and the effect of each component on the physical stability and chemical properties of the delivery system will be evaluated. These fatty acids can be formulated with various compounds for novel and innovative dosage forms. Colloidal dosage forms commonly used include liposomes, emulsions and micro-emulsions, polymeric microspheres and macromolecular microspheres. In the design of the Pheroid®, one or more features of each of these dosage forms have been incorporated and it is therefore important to discuss some of the features of these dosage forms (Grobler, 2009:150).

#### **1.4.1.1 Liposomes**

Liposomes are crystalline spherules typically formed when phospholipids are allowed to swell in aqueous media. They generally consist of concentric lipid bilayers alternating with aqueous compartments; they may be multi-lamellar and therefore quite large (>1 µm). Liposomes can encapsulate water-soluble ingredients in their inner aqueous space and oil-soluble ingredients in the phospholipid membranes without the use of surfactant(s) or other emulsifiers. Water-soluble materials are



dissolved in the water in which the phospholipids are hydrated and when the liposomes form, these materials are trapped in the aqueous centre (Grobler, 2009:151).

#### **1.4.1.2 Emulsions, Microemulsions and Nanoemulsions**

An emulsion is a system consisting of two immiscible liquid phases, one of which is dispersed through the other. The particles of the dispersed phase are usually between 0.1–10 µm in diameter. Nanoemulsions, also referred to as submicron emulsions with droplet diameters in the size range of 0.02– 0.2 µm and with a narrow size distribution, can solubilise water-insoluble drugs within the hydrocarbon core. Whether microemulsions should be regarded as true emulsions or as swollen micelles, is a matter of controversy (Grobler, 2009:151). Emulsion-based delivery systems are well studied. They are advantageous in the incorporation of polar, nonpolar and amphiphilic agents into the formulation. It is also possible to control the rheological properties of the structure and the chemical stability of the encapsulated components. The emulsion-based delivery systems are prepared using simple processing operations and specific for each application. These systems serve the purpose to protect the bioactive lipid compounds against chemical degradation such as oxidation and hydrolysis (Sato *et al.*, 2012:1). Microemulsions (MEs) are thermodynamically stable, transparent, isotropic dispersions composed of oil and water stabilised by an interfacial film of surfactant molecules, suitably combined with a co-surfactant. Recently, MEs have attracted a great interest as a potential drug delivery vehicle, mainly due to their ability to incorporate a wide range of drugs with different lipophilic properties (Furlanetto *et al.*, 2011:610).

#### **1.4.1.3 Pheroid®**

As in the case with liposomes, Pheroid® generally contains a lipid bilayer, but it contains no phospholipids or cholesterol. In contrast to liposomes, Pheroid® is formed by a self-assembly process similar to that of low-energy emulsions and microemulsions and no lyophilisation or hydration of the lipid components is necessary. As in emulsions, Pheroid® is dispersed within a dispersion medium, but it contains not only two liquids, but also a dispersed gas phase which is associated with the fatty acid dispersed phase. The specific ratio of pegylated to ethylated fatty acids used in the assembly of the Pheroid® adds some of the reservoir characteristics of the polymeric microspheres, while the formulation of natural depots is reminiscent of the structure of macromolecular microspheres. The Pheroid® contains one unique component, namely nitrous oxide (N<sub>2</sub>O), which is found distributed in association with

the dispersed phase throughout the continuous phase. The addition of a dispersed gas phase to the respective oil and water phases thus adds another dimension to the basic Pheroid<sup>®</sup> (Grobler, 2009:152).

## **1.5 GELS**

### **1.5.1 DEFINITIONS**

*Gels* are transparent or translucent semi-solid or solid preparations, consisting of solutions or dispersions of one or more active ingredients in suitable hydrophilic or hydrophobic bases. They are made with the aid of a suitable gelling agent (Lund, 1994:134).

*Inorganic hydrogels* are usually two-phase systems such as aluminum hydroxide gel and bentonite magma.

*Organic hydrogels* are generally single-phase systems and include gelling agents such as carbomer and tragacanth (Allen, 1998:202).

*Hydrogels* contain ingredients which are either dispersible as colloids or soluble in water; they include organic hydrogels, natural and synthetic gums, and inorganic hydrogels. Some of these agents are also referred to as "jellies", a subclass of the hydrogels. Methylcellulose, hydroxymethylcellulose and sodium carboxymethylcellulose are among the commercially available cellulose products which may be used to produce gels. These are available in several viscosity types: usually high, medium and low (Allen, 1998:202).

*Organogels* include the hydrocarbons, animal/vegetable fats, soap-based greases and the hydrophilic organogels. Organogels contain a non-aqueous solvent as the continuous phase. Examples of organogels are Plastibase<sup>®</sup> (low molecular weight polyethylene dissolved in mineral oil and shock cooled) (Allen, 1998:202).

*Jellies* are a class of gels in which the structural coherent matrix contains a high proportion of liquid, usually water. They are commonly formed by adding a thickening agent such as tragacanth or carboxymethyl cellulose to an aqueous solution of a drug substance. The resultant product is usually clear and has a uniform semisolid consistency. Jellies are subject to bacterial contamination and growth, therefore most are preserved with antimicrobials (see Chapter 3). Jellies should be stored tightly closed since water may evaporate, drying out the product (Allen, 1998:203).

An interesting product, a *xerogel*, can be formed when the liquid is removed from a gel, leaving only the framework. Examples include gelatin sheets and acacia tears (Allen, 1998:203).

If a hydrogel additionally contains a dispersed lipid phase, it is called an emulsion gel (*cream gel*; *emulgel*) although in pharmaceutical terms it is frequently a quasi-emulsion because the lipid phase is immobilised primarily by the high viscosity of the aqueous phase (Dermis, 2008).

The ideal classification system for the Pheroid<sup>®</sup> is found in the above term called “emulgel”. Chapter 2 will describe the pre-formulation steps taken to determine the most suitable gelling agent to form a stable, elegant and economical gel product adequately suited for its intended use.

The idea to add thickeners to the basic Pheroid<sup>®</sup> formula brought about added advantages and challenges. First a suitable classification had to be found for an o/w emulsion with added thickeners. Second a list of suitable thickeners had to be drawn up with various amounts to be added for specific indication. Thirdly, the effect of each of the new components had to be investigated and a suitable preparation with added advantages over and above the basic Pheroid<sup>®</sup> formula had to be identified. In some cases, the formation of a gel-like structure within the emulsions greatly improves their stability against creaming. The mechanism of the gel-like structure formation is due to colloidal destabilisation, especially droplet aggregation through strong attractive interactions between emulsion droplets. If the rate of droplet aggregation is much higher than the creaming rate in the system, the formation of a space-filling network of droplets (gel formation) may occur (Tang & Liu, 2012:62). Table 1.3 provides examples of two classification systems for gels. One divides gels into inorganic and organic, the other distinguishes them by the classification hydrogels and organogels.

**Table 1.3:** General classification and description of gels (Allen, 1998:202).

<i>Class</i>	<i>Description</i>	<i>Examples</i>
<b>Inorganic</b>	Usually two-phase system	Aluminium hydroxide gel, bentonite magma
<b>Organic</b>	Usually single phase system	Carbomer, tragacanth
<b>Hydrogels</b>	Contain water	Silica, bentonite, methylcellulose, alumina
<b>Organogels</b>	Hydrocarbon type	Petrolatum, mineral oil
	Animal/vegetable fats	Cocoa butter
	Soap base greases	Aluminium stearate with heavy mineral oil gel
	Hydrophillic organogels	Carbowax bases
<b>Hydrogels</b>	Organic hydrogels	Pectin paste, tragacanth jelly
	Natural and synthetic gums	Methylcellulose, sodium carboxymethyl cellulose

### 1.5.2 PHYSICOCHEMICAL CONSIDERATIONS OF GELS

Gels and jellies exhibit a number of different characteristics, including imbibition, swelling, syneresis and thixotropy (Allen, 1998:206).

*Imbibition* is the taking up of a certain amount of liquid by a gel without a measurable increase in volume (Allen, 1998:206).

*Swelling*, is the taking up of a liquid by a gel with an increase in volume. Only those liquids that solvate a gel can cause swelling. The swelling of protein gels is influenced by pH and the presence of electrolytes (Allen, 1998:206).

*Syneresis* is the contraction of a gel caused by the interaction between particles of the dispersed phase. This interaction becomes so great that, on standing, the dispersing medium is squeezed out in droplets, causing the gel to shrink. Syneresis is a form of instability in aqueous and non-aqueous gels. The solvent phase is thought to separate because of the elastic contraction of the polymeric molecules, as swelling increases during gel formation, the macromolecules become stretched and the elastic forces expand. At equilibrium the restoring forces of the macromolecules are balanced by the swelling forces, determined by the osmotic pressure. If the osmotic pressure decreases, on cooling down, water may be squeezed out of the gel. The pH has a significant effect on the separation of water from the gel. At low pH, marked syneresis occurs, possibly because of suppression of ionisation of the carboxylic acid groups, loss of hydrating water and the formation of intramolecular

hydrogen bonds. These conditions would reduce the attraction of the solvent for the macromolecule (Allen, 1998:206).

*Thixotropy* is a reversible gel-sol formation with no change in volume or temperature. It is considered a type of non-Newtonian flow.

These characteristics play a role in how some agents form a gel or once formed remains as a gel (Allen, 1998:206).

### **1.5.3 USES OF GELS**

Gels and gelling agents have various uses for the delivery of oral products, for topical drugs to be applied to the skin, to mucous membranes or the eye. Fragrance products, shampoos, dentrifices and skin-and hair-care preparations often consist of gels (Zats & Kushla, 1996:400).

Gelling agents are used as binders in tablet granulations, as thickeners in oral liquids, as suppository bases and as protective colloids in suspensions. Gelling agents should be safe, inert and non-reactive with other formulation components. A potential incompatibility is illustrated by the combination of a cationic drug, preservative, or surfactant with an anionic gel former. Inactivation or precipitation of the cationic substance is possible (Zats & Kushla, 1996:400).

The term “gel” has also been applied in pharmacy to some viscous suspensions for oral use, for example, aluminium hydroxide gel. As well as being used as delivery vehicles for local anesthetics, spermicides and dermatological agents, gels are also used for lubrication of gloves and instruments, as film-formers in patch testing and for conductivity enhancement on the terminals of an electrocardiograph (Lund, 1994:134).

Gels can be used as vehicles for the delivery of water-soluble medicaments because they have a high water content. Products tend to be smooth, elegant and produce cooling effects because of evaporation of water; they may also dry out to form films. Non-aqueous liquids may also be formed into gels (Lund, 1994:134).

A gelling agent incorporated into a liquid formulation should produce a stable, elegant gel which is economical and adequately suited for its intended use. The gelling agents should provide a liquid formulation with a reasonable solid like matrix that can be easily broken when shaken in a bottle, or squeezed in a tube. Temperature changes should not cause variations to the gel under normal use and storage. Some gels, particularly those of a polysaccharide nature are susceptible to microbial

degradation. Suitable preservatives should prevent contamination and subsequent loss of gel characteristics due to microbial attack. A topical gel should not be tacky and ophthalmic gels should be sterile. Consumers tend to prefer gel products with high optical clarity (Zats & Kushla, 1996:400).

#### **1.5.4 PREPARATION OF GELS**

Many gels are prepared by freshly precipitating the dispersed phase in order to achieve a fine degree of subdivision of the particles and a gelatinous character to those particles. The desired gelatinous precipitate results when solutions of inorganic agents react to form an insoluble chemical having a high attraction for water. As the microcrystalline particles of the precipitate develop, they strongly attract water to yield a gelatinous precipitate (Ansel & Popovich, 1990:251).

Other gels may be prepared by the direct hydration in water of the inorganic chemical, the hydrated form constituting the dispersed phase of the dispersion. In addition to the water vehicle, other agents for example PG and hydroxypropylcellulose may be used to enhance gel formation. Because of the high degree of attraction between the dispersed phase and the aqueous medium in gels, these preparations remain fairly uniform on standing, with little settling of the dispersed phase (Ansel & Popovich, 1990:251).

##### **1.5.4.1 Viscosity enhancers**

A number of polymers are used to provide the structural network which is the essence of gel systems. These include natural gums, cellulose derivatives and carbomers. Although most of these function in aqueous media, several polymers that can gel non-polar liquids are also available. Certain colloidal solids behave as gellants as a result of asymmetric flocculation of the particles. High concentrations of some non-ionic surfactants can be used to produce clear gels in systems containing up to about 15% w/v mineral oil. These are employed mostly as hair dressings (Zats & Kushla, 1996:405).

##### ***Natural polymers***

Natural gums have been used in commerce since the beginning of recorded history. Typically, most are branched-chain polysaccharides, which are anionic (negatively charged in aqueous solution or dispersion) although guar gum is a neutral molecule (Zats & Kushla, 1996:405).

Natural gums are susceptible to microbial degradation and support microbial growth. All aqueous systems containing these gums should be preserved. Keep in mind

cationic antimicrobials are not generally compatible with anionic gums. XG is produced microbiologically. Many derivatives of natural materials, such as cellulose, starch and algin have been prepared. The gums are used widely in food and various industrial products as well as pharmaceuticals. Not all of these applications depend on gelation. Acacia (gum arabic) is an effective emulsifier, gum karaya has remarkable adhesive properties and XG is an excellent retardant of sedimentation in suspensions and emulsions in which water is the external phase. Gums employed as gel formers may produce the desired effect as a result of simple dispersion in water (e.g., tracacanth) or through chemical interaction (e.g., sodium alginate and calcium). The gel is formed because of cross-linking which ties sections of polysaccharide molecules together while the remainder are solvated (Zats & Kushla, 1996:405).

#### Xanthan gum

Xanthan gum (XG), at concentrations below 0.5%, acts as a stabiliser in suspensions and emulsions. Higher concentrations in aqueous media (1% and above) yield viscous solutions, that act jelly-like. XG is produced by bacterial fermentation. Availability and quality of these products are not subject to uncertainties, such as other natural products extracted from plants whose habitats are within politically unsettled parts of the world (Zats & Kushla, 1996:407).

The effect of temperature on the pH of the XG is better understood if the structure of the XG is explained. The xanthan polymer backbone is identical to that of cellulose, but the unique character of XG is derived from the trisaccharide side chain or alternate sugar units. This chain is composed of glucuronic acid salts between a mannose acetate and a terminal mannose unit. A pyruvate is attached to about 60% of these terminal units. The glucuronic acid and pyruvic acid groups on the side chains give XG its anionic charge. The interaction of these anionic side chains with the polymer backbone and with each other determines the beneficial properties of XG solutions (Vanderbilt Company Inc., 2003).

In solutions of low ionic strength or at high temperature, the XG chains adopt a random coil configuration, since the anionic side chains repel each other. The addition of even small amounts of electrolyte, however, reduces the electrostatic repulsion amongst the side chains, allowing them to wrap around and hydrogen bond to the backbone. The polymer chain straightens into a relatively rigid helical rod. This shape tends to revert to the random coil if the gum solution is highly diluted or heated. With increasing electrolyte concentrations, however, the rod shape is

maintained at higher temperature and greater dilutions. At ionic strengths above approximately 0.15 M, it is retained up to 100°C (Vanderbilt Company Inc., 2003).

Aqueous solutions of XG exhibit a very high viscosity, even at low concentrations, and very strong pseudoplasticity with no evidence of thixotropy. These properties result from the unique, rod-like conformation of XG in solution and from its high molecular weight. XG forms reversible entanglements at very low concentration. The flow curves of solutions of XG at different concentrations are presented via a very strong pseudoplastic character where all solutes show a very high viscosity at low shear rates. This behaviour can have various advantages: as the viscosity decreases with the increasing shear rate, the product becomes easy to pour, mix or pump. The thickening properties of XG compared to other food hydrocolloids show the shear-rate viscosity values are always greater, especially at low concentrations. The shear-thinning character of solutions of XG is more pronounced than that of other gums. This behaviour results from the semi-rigid conformation of the xanthan polymer, which is more sensitive to shear than a random-coil conformation. Another feature of solutions of XG is its viscoplasticity, which gives a high yield value even at low concentrations. The yield value is the minimum shear stress required for a solution to flow and results from the formation of a weak network in the solution. This is the result of interactions between xanthan macromolecules, but the network is not a true gel because these interactions are not permanent and are totally shear-reversible. The yield value is difficult to measure because it is necessary to work at very low shear rates and frequently this value is extrapolated with different rheological models, such as those of Bingham and Herschel-Buckley. XG is the only hydrocolloid to exhibit a significant yield value at low concentrations, which explains the ability of solutions of XG to stabilise dispersions such as emulsions and suspensions (Urlacher & Noble, 1997:289).

Solutions are stable at relatively low pH and exhibit a unique temperature-viscosity relationship. Rather than thinning with heat, xanthan solutions exhibit relatively constant viscosity. This polymer is resistant to shear depolymerisation (Zatz *et al.*, 1996:303).

XG is very hydrophilic by nature and problems may arise during hydration if some basic rules are not respected. Before discussing the preparation of solutions of XG, a distinction needs to be made between hydration and dispersibility (Imeson, 1997:296):



- *Dispersibility* is the ease of separation of the individual gum particles when XG is introduced into the liquid.
- *Hydration* is the ease with which these individual particles swell and develop viscosity.

It is necessary to find a compromise between dispersibility and hydration: an easily dispersible product will hydrate very slowly and *vice versa*. For example, a very fine powder is difficult to disperse, but once dispersed it is quick to hydrate. The hydration time depends on several factors, such as:

- The effectiveness of the dispersion method,
- The size of the gum particles,
- The other compounds of the formulation.

Variables which influence the above mentioned factors include:

- Stirring speed: a higher stirring speed improves dispersion and shortens hydration time.
- Variation of the particle size: a finely ground material hydrates quicker when properly dispersed.
- Salt and sugar content: results in a reduction of hydration speed (Imeson, 1997:296).

Suggested procedure for the preparation of solutions of XG without any lumping problems is as follow: make use of a high-speed mixer (1500 rpm) if possible and slowly sprinkle XG onto the upper surface of the vortex. If possible disperse XG with another component of the formulation such as a non-aqueous liquid, such as vegetable oil or ethyl alcohol, in which XG does not hydrate, or other dry ingredients such as sugar and flour (Imeson, 1997:299).

### ***Acrylic polymers***

Carbopol® 934P is the official name given to one member of a group of acrylic polymers cross-linked with a polyalkenyl ether. Manufactured under the trade name Carbopol® 934P, it is used as a thickening agent in a variety of pharmaceutical and cosmetic products. The suffix *-P* identifies a highly purified polymer, suitable for use in orally administered dosage forms, although Carbopol® 934P is also widely used in topical preparations (Zats & Kushla, 1996:409).

Carbomer resins are primarily used in aqueous systems, although other liquids can be used as well. In water, a single particle of carbomer will wet rapidly, but like many other powders, carbomer polymers tend to form lumps of particles when dispersed haphazardly in polar solvents. As the surfaces of these solvate, a layer is formed which prevents rapid wetting of the interior of the lumps. When this occurs, the slow diffusion of solvent through this solvated layer determines the mixing or hydration time. To achieve the fastest dispersion of the carbomer, one should take advantage of the very small particle size of carbomer powder by adding it very slowly into the vortex of the liquid, which is being stirred rapidly. Generally, the higher the agitation rate of the liquid, the better, however extremely high shear mixers should not be used, as they can break down the polymers and reduce gel viscosity. Propeller or turbine-type mixers running at about 800 to 1200 rpm work well. Variable speed mixers are especially desired to reduce vortexing when the mixture begins to thicken and will incorporate less air into the gel. The propeller should be located close to the bottom of the mixing vessel to minimise the incorporation of air into the product. To prevent lumping, the small particle size powder should be slowly sprinkled over the rapidly agitated water. Once the powder is incorporated, continued stirring for 10 to 15 minutes at reduced speed is recommended to avoid excess air entrapment (Allen, 1998:204).

Carbomer forms gels at concentrations as low as 0.5% w/v. The first step in preparing the gel in aqueous media is the dispersion of the polymer in water. After entrapped air has been allowed to escape, the gel is produced by neutralisation with a suitable base (see Annexure A). The introduction of negative charges along the polymer chain causes it to uncoil and expand. In aqueous systems, a simple inorganic base such as sodium-, ammonium- or potassium hydroxide, or a basic salt such as sodium carbonate may be employed. The pH should be adjusted to a neutral value. The gel character will be adversely affected by either insufficient neutralisation or an excessively high pH. The viscosity of carbomer dispersions is lowered in the presence of ions, for example, the addition of 1% w/v sodium chloride causes more than a 50% drop in Brookfield viscosity of neutralised carbomer 941 (Zats & Kushla, 1996:409). The carbomer at low concentration (0.5 – 1.0%) can form high viscosity formulations with characteristic flow behaviour. It shows compatibility with many active ingredients, good thermal stability, bioadhesive properties and excellent organoleptic characteristics with good patient acceptance (Souto, 2005).

The structure of the carbomer characterises its flow property and thixotropy. The carbopol solutions are thixotropic due to the ability to form entanglements and cross-

linkages. The cross-linkages are formed between individual polymer particles (on molecular scale) which are gelled together to form concentrated dispersions at low concentrations. The exterior of the particles is covered with free ends of the gel strands which interact with adjacent microgel particles to produce high viscosity at low shear stresses (Gomez *et al.*, 2009:1289).

### **Cellulose derivatives**

Many useful derivatives are fashioned from cellulose, a natural structural polymer found in plants. Rheological properties are influenced by the nature of the substituent(s), the degree of substitution and the average molecular weight of the resultant polymer. The cellulose derivatives are subject to enzymatic degradation. The influence of microorganisms is prevented by sterilisation of aqueous system or the addition of suitable preservatives to prevent depolymerisation and viscosity reduction caused by the enzyme production by microorganisms (Zats & Kushla, 1996:409).

All of the cellulose esters are generally quite stable in aqueous solution. They are relatively unaffected by pH within the range of 3 – 11. The viscosity stability of solutions exposed to long-term elevated temperature is very good (Zatz *et al.*, 1996:304).

#### Methylcellulose

Methylcellulose (MC) is a polymer whose solubility in water decreases as the temperature is raised. If an aqueous solution is heated the formation of a gel structure (at a certain point) will increase the viscosity. This property, known as thermal gelation, is a function of polymer chemistry. Gelation temperatures are lowered by salts and sugars with a high affinity for water whereas alcohol and PG have the opposite effect.

#### Carboxymethylcellulose

Carboxymethylcellulose (CMC), also known as sodium carboxymethylcellulose and cellulose gum, is an anionic polymer available in a variety of grades which differ in molecular weight and degree of substitution. Gelation requires addition of an electrolyte with a polyvalent cation to a solution of the polymer (aluminum salts are preferred). Gel characteristics, such as firmness and elasticity, depend on polymer concentration and molecular weight (Zats and Kushla, 1996:409).

### Hydroxypropylmethylcellulose

Hydroxypropylmethylcellulose (HPMC) is classified as a thickener, stabiliser, emulsifier or excipient and has the advantage that it forms gels in both water and alcohol (Great vista chemicals, 2004).

The dissolving method followed involves heating of the water to above 85°C and slowly adding HPMC under slow agitation to gradually form a uniform pulp. This pulp is left to cool under agitation to become transparent. A second method is followed when one to two thirds of the needed water is warmed to above 85°C, after which the HPMC is added to form a heat pulp, the residual of the water is added under agitation and stirred until 20°C is reached. The solubility varies with the viscosity; the lower the viscosity, the higher the solubility. HPMC varies in grades of viscosity. For example low, medium and high viscosity HPMC powder can be bought depending on the intended purpose (Great vista chemicals, 2004).

HPMC is a surface-active agent and reduces surface tension and interfacial tension. Solutions of HPMC exhibit pseudoplastic rheology and there is no yield point (Zatz *et al.*, 1996:307). This pseudoplasticity results from a colloidal network structure that aligns itself in the direction of shear, thereby decreasing the viscosity as the shear rate increases (FU berlin, 2007).

### **1.5.5 GENERAL PHARMACEUTICAL FORMULATION CONSIDERATIONS IN PHARMACEUTICS**

In pharmaceuticals it is important to understand the influence of different formulation parameters on the functional properties of the emulgel. Properties for example, particle size and shape, pH values and viscosity measurements give a comparison between different formulations. Stability of each formula can be compared to decide on the most efficient formulation for further product development.

#### **1.5.5.1 Particle properties**

Both physical and chemical properties of drug substances, including dissolution rate, bioavailability, taste, texture, color and stability are affected by particle size distribution. Particle size also influences properties such as flow characteristics and sedimentation rates. It is essential to know how the effect of particle size of a drug substance may effect formulation and efficacy (Allen *et al.*, 2005:97).

The most significant characteristic of dispersions are the size and shape of the dispersed particles. These properties depend on the chemical and physical nature of the dispersed phase and the method used to prepare the dispersion. When

formulating pharmaceutical products, with good physical stability and reproducible bioavailability, the effect of the particle size on the properties of the dosage form must be taken into account. The mean particle diameter and the particle size distribution have an effect on product appearance, settling rate, drug solubility, resuspendability and stability. Clinically, the drug releases from the dosage form, which can be administered via various routes, are also affected by the particle size (Banker & Rhodes, 2002:240).

### **Particle size and shape**

Particle size analysis may often detect a potentially unstable formulation long before any other parameter changes markedly. Lipid nanoparticles may grow or suffer aggregation as a gel network breaks down on storage, thus allowing Brownian motion to bring particles into contact so that they aggregate (FU berlin, 2007).

Emulsification processes produce spherical droplets of the internal phase to maximise the interfacial area between the two phases. Characterisation of the particle shape is generally described by the deviation from sphericity. The viscosity of colloidal dispersions is affected by the shape of the dispersed phase. Sphero-colloids form dispersions of relatively low viscosity, while systems containing linear particles are generally more viscous. The relationship of particle shape and viscosity reflects the degree of solvation of the particles. In an effective solvent, a colloidal particle unrolls and exposes its maximum surface area due to an extensive interaction between the dispersed phase and the dispersion medium. In contrast, in a poor solvent, the particle tends to coil up to assume a spherical shape and the viscosity drops accordingly. Properties such as flow, sedimentation and osmotic pressure are also affected by the changes in the particle shape of colloids (Banker & Rhodes, 2002:242).

### **1.5.5.2 pH**

pH is a critical variable in pharmaceuticals and a basic understanding of its principles and measurement are important. A suitable place to start is with the definition of the term pH, the “p” comes from the word power and the “H” is the symbol for hydrogen; together, the term pH means the hydrogen ion exponent (Allen *et al.*, 2005:102).

The pH of a solution is a measure of its acidity, just as degree Celsius is a measure of temperature. A specific pH value tells the exact acidity. Rather than stating general ideas, such as cherry syrup is acidic or that water is hot, a specific pH value gives the same relative point of reference, thus providing more exact communication (Allen *et al.*, 2005:102).

pH is defined in terms of the hydrogen ion activity (equation 1.1):

$$\text{pH} = -\log_{10} a_{\text{H}^+} \text{ or } 10^{-\text{pH}} = a_{\text{H}^+} \quad (\text{Equation 1.1})$$

pH equals the negative logarithm of the hydrogen ion activity, or the activity of the hydrogen ion is 10 raised to the exponent  $-\text{pH}$ . The latter expression renders the use of the  $-\text{p}$  exponent more obviously. The activity is the effective concentration of the hydrogen ion in solution (Allen *et al.*, 2005:102).

In pure water, hydrogen and hydroxyl ion concentrations are equal at  $10^{-7}$  M at  $25^\circ\text{C}$ . This is a neutral solution. Since most samples encountered have less than 1 M  $\text{H}^+$  or  $\text{OH}^-$ , the extremes of pH are 0 for acids and pH 14 for bases (Allen *et al.*, 2005:102).

#### 1.5.5.3 Viscosity

During each step of the pharmaceutical development process, such as filling, mixing, packing and removal from the container before application on the action site, the flow properties are involved and influence their *in vivo* behaviour. Pharmaceutical scientist must outline the flow properties and influencing factors and their effects on the pharmacological efficacy of thixotropic formulations such as emulsions, ointments, colloids and gels (Lee *et al.*, 2009:89).

As reported previously, hydrogels are transparent to opaque semi-solid containing a high ratio of water to jelling agent. When dispersed in water, the jelling agent merges or entangles to form a three-dimensional colloidal network structure. This network limits the fluid flow by entrapment and immobilisation of the water molecules. The network structure is also responsible for the resistance of the gel to deformation and therefore for its viscoelastic properties. The hydrogel network is prepared through successive increases in the jelling agent concentration. This results in a reduction of the interparticle distances, which subsequently leads to chain entanglement and the establishment of cross-links. As the number of cross-links increases, the chains lock, the water mobility is reduced, and a gel network is formed. The integrity of the gel will be determined by the nature of the polymer-water molecules affinity (FU berlin, 2007:170). The choice of solvent is important because solvents like glycerine and PG can modify hydrogen bonding characteristics between water, solvent and

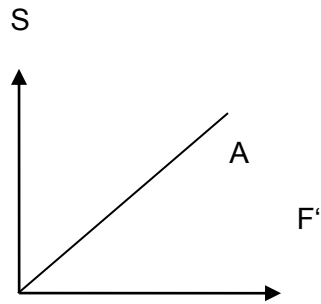
polymer, thereby affecting the swelling and viscoelastic properties of the polymers (FU berlin, 2007:171).

The shelf life of a dispersion depends on the chemical stability of its ingredients, as well as the physical stability of the system as a whole. Because of the importance of viscosity in terms of stability and certain use characteristics, major changes in viscosity over a time period are cause for concern (Zatz *et al.*, 1996:290). Small drifts in apparent viscosity are often encountered and are usually considered acceptable. However, substantial changes are cause for concern because of changes in the resistance to sedimentation and also because they suggest chemical or physical changes of some kind are taking place. In other words, they are a sign that chemical or physical stability might be compromised. Elevated storage temperatures can have an adverse effect on polymer stability which will result in a viscosity change over time (Zatz & Kushla, 1996:291).

Viscosity is a principal parameter when any flow measurements of materials, such as liquids, semi-solids, gases and even solids are made (Brookfield engineering, 2005). Using these simplified terms, viscosity may be defined mathematically by the following formula (equation 1.2):

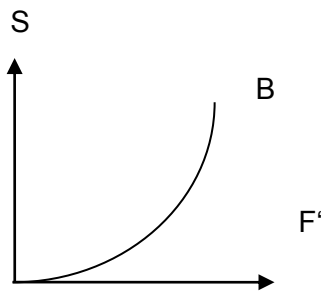
$$\eta = \text{viscosity} = F'/S = \text{shear stress} / \text{shear rate} \quad (\text{Equation 1.2})$$

The fundamental unit of viscosity ( $\eta$ ) measurement is the poise.  $F'$  is referred to as shear stress. It is the the force per unit area required to produce the shearing action and its unit of measurement is dynes per square centimeter (dynes/cm<sup>2</sup>). The symbol  $S$  describes the shearing the liquid experiences and is thus called shear rate and its unit of measure is called the reciprocal second (1/sec). The type of flow behaviour can be defined as Newtonian or Non-Newtonion. In Figure 1.1 the relationship between shear stress and shear rate for a Newtonian fluid is illustrated.

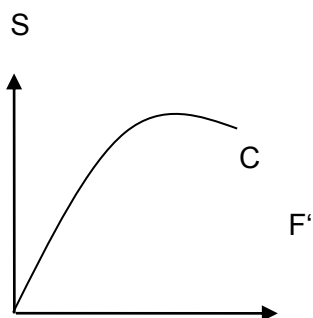


**Figure 1.1:** Graph A shows the relationship between shear stress ( $F'$ ) and shear rate (S) follows a straight line relationship. What this means in practice is that at a given temperature the viscosity of a Newtonian fluid will remain constant (Brookfield engineering, 2005).

In Figures 1.2 – 1.5 the relationship between shear stress and shear rate for Non-Newtonian fluids is illustrated.

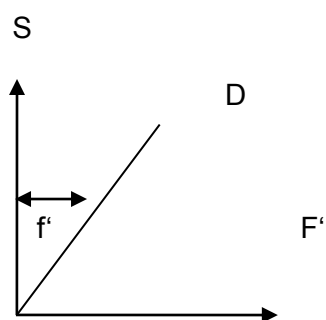


**Figure 1.2:** Graph B represents a rheogram illustrating pseudoplastic flow. This fluid will display a decreasing viscosity with an increasing shear rate (Brookfield engineering, 2005).

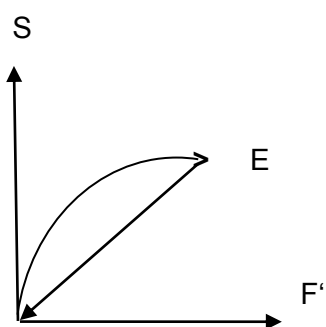


**Figure 1.3:** Graph C represents a rheogram illustrating dilatant flow. Increasing viscosity with an increase in shear rate characterises a dilatant fluid (Brookfield engineering, 2005).





**Figure 1.4:** Graph D represents a rheogram illustrating plastic flow. A certain amount of force must be applied to the fluid before any flow is induced; this force is called the yield value. Approximate yield stress measurements can be gained by plotting the shear stress values for a range of shear rates, fitting a curve to the data. The intercept on the stress axis renders the yield stress ( $f'$ ) measured in the unit pascal (Pa) (Brookfield engineering, 2005).



**Figure 1.5:** Graph E represents a rheogram illustrating thixotropy. When subjected to varying rates of shear a thixotropic fluid will react as illustrated in the figure. A plot of shear stress versus shear rate was made as the shear was increased to a certain value, then immediately decreased to the starting point. This hysteresis loop is caused by the decrease in the fluid's viscosity after slowing of the shear rate. Note the up and down curves do not coincide (Brookfield engineering, 2005).

Thixotropy is the phenomenon of the fluid which shows a gel-sol-gel conversion (a reversible structural transition) due to time-dependant changes in the viscosity caused by temperature, pH or other factors. Thixotropy is also described as an isothermal system where apparent viscosity decreases under shear stress, followed by a gradual recovery when the stress is removed (Lee *et al.*, 2009:89).

#### 1.5.5.4 Pharmaceutical excipients

The International Pharmaceutical Excipients Council defines an excipient as any substance other than the active drug or prodrug that is included in the manufacturing

process or is contained in a finished pharmaceutical dosage form (Chang& Chang, 2007:1).

Under ideal circumstances, excipients should be chemically stable, non-reactive with other excipients or the drug, inert to the human body, have pleasing organoleptic properties, well characterised and well accepted by the industry and regulatory agencies (Chang& Chang, 2007:1).

A good formulation design contains the basic components required. Formulators choose to integrate components when applicable or eliminate redundant elements. Excipients are only incorporated to the formulation if the API (Active Pharmaceutical Ingredient) lacks certain properties. In reality, APIs under development always lack certain properties and excipients facilitate manufacturing processes and enhance product performance. Nonetheless, fewer ingredients in the formulation are better because excipients are not completely inert. Even commonly used excipients deemed to be pharmaceutically inactive and non-toxic may cause adverse reactions. There is less ingredient variability to influence process and product consistency. There is better economic efficiency in product manufacturing. There are fewer excipients for release testing. There is less probability of chemical or physical interactions between the API and excipients and between excipients (Chang & Chang, 2007:3):

Table 1.4 gives a list of excipients with their classification and examples. Various excipients are added to the basic Pheroid<sup>®</sup> preparation. The reason for adding these excipients along with the percentages used will be discussed in further chapters. Special attention will be paid to the effect the excipients have on the stability of the Pheroid<sup>®</sup> preparation. Some of the major challenges that arise with the formulation of a colloidal dispersion include protection against oxidation, preservation from microbial contamination, physical stability problems such as breaking, creaming, flocculation or phase inversion.

**Table 1.4:** Examples of basic pharmaceutical ingredients used in liquid and semi-solids (Ansel & Popovich, 1990:96).

<i>Ingredient Type</i>	<i>Definition</i>	<i>Examples</i>
<b>Acidifying agent</b>	Used in liquid preparations to provide an acidic medium for product stability	Acetic acid, nitric acid, hydrochloric acid
<b>Alkalising agent</b>	Used in liquid preparations to provide an alkaline medium for product stability	Potassium hydroxide, ammonium carbonate
<b>Inert gas</b>	An agent which is employed to displace air in a hermetically sealed container to enhance product stability	Nitrogen
<b>Antifungal preservative</b>	Used in liquid and semi-solid preparations to prevent the growth of fungi	Benzoic acid, parabens, sodium benzoate
<b>Antimicrobial preservative</b>	Used in liquid and semi-solid preparations to prevent the growth of microorganisms	Benzyl alcohol, chlorobutanol, thimerosal
<b>Antioxidant</b>	An agent which exhibits oxidation and thus used to prevent the deterioration of preparations by the oxidative process	Butylated hydroxyanisole, butylated hydroxytoluene
<b>Buffering agent</b>	Used to resist change in pH upon dilution or addition of acid or alkali	Potassium phosphate
<b>Colourant</b>	Used to impart colour to pharmaceutical preparations	FD&C Red No 3, caramel
<b>Emulsifying agent</b>	Used to promote and maintain the dispersion of finely subdivided particles of a liquid in a vehicle in which it is immiscible	Acacia, sorbitan monooleate
<b>Flavourant</b>	Used to impart a pleasant flavour and often odour to a pharmaceutical preparation	Anise oil, menthol, vanillin
<b>Humectant</b>	Used to prevent the drying out of preparations, particularly ointments and creams	Glycerin, PG, sorbitol
<b>Solvent</b>	An agent used to dissolve another pharmaceutical substance or a drug in the preparation of a solution	Alcohol, mineral oil, sterile water for irrigation
<b>Surfactant</b>	Substance which adsorb to surfaces or interfaces to reduce surface or interfacial tension	Polysorbate 80, benzalkonium chloride
<b>Suspending agent</b>	A viscosity increasing agent used to reduce the rate of sedimentation of dispersed particles	Carboxymethylcellulose sodium, tragacanth, agar
<b>Sweetening agent</b>	Used to impart sweetness to a preparation	Aspartame, sucrose

#### 1.5.5.5 Compliance issues

Liquids and chewable tablets are the dosage forms most commonly employed for paediatric formulations. An unpleasant taste is much more evident with liquid or chewable dosage forms than conventional solid oral dosage forms (Banker & Rhodes, 2002:674).

Children younger than six years of age have more acute taste perception than older children and adults. Olfactory receptors and taste buds are fully developed in early infancy. Ageing causes a loss of taste perception (Banker & Rhodes, 2002:674)

#### 1.5.5.6 Product stability

Stability is the extent to which a product retains, within specified limits and throughout its period of storage and use (i.e. its shelf life), the same properties and characteristics it possessed at the time of its manufacture. Allen *et al.*, (2005:113) describes five types of stability concerns:

- *Chemical*: Each active ingredient retains its chemical integrity and labelled potency within the specified limits.
- *Physical*: The original physical properties, including appearance, palatability, uniformity in dissolution and suspendability are retained.
- *Microbiologic*: Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents retain effectiveness within specified limits.
- *Therapeutic*: The therapeutic effect remains unchanged.
- *Toxicologic*: No significant increase in toxicity occurs.

Chemical stability takes into consideration storage conditions (temperature, light and humidity), selecting the proper container for dispensing (glass vs. plastic, clear vs. amber or opaque cap liners) and the anticipated interactions when mixing API's and excipients. Reaction kinetics influence stability and expiration dating of formulas. Reaction kinetics is the study of the rate of chemical change and the way this rate is influenced by concentration of reagents, products and other chemical species and by factors such as solvent, pressure and temperature (Allen *et al.*, 2005:113).

Pharmaceutical excipients can be used to prepare a desired dosage form of an API. Some of these agents help achieve the desired physical and chemical characteristics of the product or help to enhance its organoleptic properties. Certain substances increase the stability of the API, particularly against hydrolysis and oxidation. The

added pharmaceutical excipient must be compatible with and must not influence the stability of the API (Allen *et al.*, 2005:114).

## **1.6 SUMMARY AND CONCLUSION**

The design of a dosage form that is stable for an estimated shelf life, safe and easy to administer to a patient, efficacious for the purpose of design as well as aesthetically favourable to the patient in taste, colour and sweetness can be a daunting task for any formulator.

A list of excipients with its intended use and examples are given in Chapter 1. Several of these excipients will be added to the basic formula of the Pheroid®. A basic knowledge of the chemical and pharmaceutical properties of the various agents added to the basic formula namely the Pheroid® is needed to understand the effect which the various components will have on one another as well as on the physical and chemical stability of the preparation.