chapter 3
Pharmaceutical disperse systems 2: emulsions and creams

Overview

In this chapter the following points will be discussed:

- the physical properties of disperse systems in which an insoluble liquid is dispersed in a second liquid phase (generically termed emulsions)
- types of emulsions and creams
- factors affecting the stability and methods that may be used to stabilise pharmaceutical (liquid) disperse systems (emulsions and creams)
- formulation strategies for emulsions and creams
- the advantages and disadvantages and uses of emulsions and creams
- considerations for the manufacture of pharmaceutical emulsions and creams.

General description

Pharmaceutical emulsions/creams are commonly used pharmaceutical products that are primarily prescribed for the treatment of external disorders. In addition to this use emulsions are clinically used for total parenteral nutrition (see Chapter 5), for the oral administration of therapeutic agents and for the rectal administration of antiepileptic agents. The terms emulsions and creams refer to disperse systems in which one insoluble phase is dispersed as droplets within a second liquid phase. The rheological properties (and hence the structure of the network within the formulation) of the two systems differ considerably. Creams are pseudoplastic systems with a greater consistency than, for example, oral or parenteral emulsions.

There are two principal types of emulsion/cream, termed oil in water (o/w) and water in oil (w/o). In the former system the oil (or internal) phase is dispersed as

KeyPoints

- Emulsions and creams are disperse systems in which an insoluble liquid phase is dispersed within a second liquid phase. Creams are emulsions that offer greater consistency (viscosity) and are applied topically.
- Emulsions and creams are termed either oil in water (o/w), in which oil is the disperse phase and water the external phase, or water in oil (w/o), in which water is the disperse phase and oil is the external phase.
- The major use of emulsions is as cream formulations (for external application); however, emulsions may also be administered intravenously (see Chapter 5), rectally or orally.
- Emulsions/creams are physically unstable: the various excipients in the formulation are present primarily to stabilise the physical properties of the system.

droplets through the external aqueous phase. Conversely, in w/o emulsions, the internal phase is composed of water droplets and the external phase is non-aqueous. In addition to the emulsion types described above there are further more structurally complex types, termed *multiple emulsions*. These are termed water in oil in water (w/o/w) and oil in water in oil (o/w/o) emulsions. However, the pharmaceutical uses of these are extremely limited due to their possible reversion to the parent primary emulsion. For example, an o/w/o emulsion may revert to a w/o emulsion. As the reader will observe later in this chapter, the nature of the excipients and the volume ratio of the two phases used in the formulation of these systems determine both the type and consistency of the emulsion.

Emulsions and creams, akin to pharmaceutical suspensions, are fundamentally unstable systems, which, in the absence of *emulsifying agents*, will separate into the two separate phases. The emulsifying agents used are principally surface-active agents. O/w emulsions may be administered topically or orally whereas the use of w/o creams is principally (but not exclusively) limited to formulations designed for topical application.

The characteristics of an acceptable pharmaceutical suspension include the following:

- Physical stability (no phase separation).
- The flow properties of the emulsion/cream should enable the formulation to be easily removed from the container. Furthermore, if the formulation is designed for external application to, for example, the skin, the formulation must be easily spread over the affected area.
- The formulation must be aesthetically and texturally pleasing. If the emulsion is designed for oral application, the flavour must be suitable whereas if emulsions are to be externally applied, they must have the correct 'feel' (termed texture).

Tips

Emulsions are physically unstable systems and indeed are more unstable than suspensions

The type of emulsion dictates the final use of the formulation

Oil in water emulsions (but not water in oil emulsions) may be administered orally

Both oil in water and water in oil creams are administered topically.

Advantages and disadvantages of pharmaceutical emulsions

Advantages

- Pharmaceutical emulsions may be used to deliver drugs that exhibit a low aqueous solubility. For example, in o/w emulsions the therapeutic agent is dissolved in the internal oil phase. Following oral administration the oil droplets (and hence the drug) may then be absorbed using the normal absorption mechanism for oils. Some drugs are more readily

absorbed when administered as an emulsion than as other oral comparator formulations.

- Pharmaceutical emulsions may be used to mask the taste of therapeutic agents, in which the drug is dissolved in the internal phase of an o/w emulsion. The external phase may then be formulated to contain the appropriate sweetening and flavouring agents.
- Emulsions may be commonly used to administer oils that may have a therapeutic effect. For example, the cathartic effect of oils, e.g. liquid paraffin, is enhanced following administration to the patient as droplets within an o/w emulsion. The taste of the oil may be masked using sweetening and flavouring agents.
- If the therapeutic agent is irritant when applied topically, the irritancy may be reduced by formulation of the drug within the internal phase of an o/w emulsion.
- Pharmaceutical emulsions may be employed to administer drugs to patients who have difficulty swallowing solid-dosage forms.
- Emulsions are employed for total parenteral nutrition.

Disadvantages

- Pharmaceutical emulsions are thermodynamically unstable and therefore must be formulated to stabilise the emulsion from separation of the two phases. This is by no means straightforward.
- Pharmaceutical emulsions may be difficult to manufacture.

Emulsion instability and theories of emulsification

Emulsion instability and the role of surface-active agents

Emulsions are termed thermodynamically unstable systems. Following dispersion of an insoluble liquid, e.g. an oil into an aqueous phase, the oil phase will adopt a spherical (droplet) shape as this is the shape associated with the minimum surface area per unit volume. If the droplet contacts a second droplet, coalescence will occur to produce a single droplet of greater diameter and, in so doing, the surface area of the new droplet will be less than the surface areas of the two individual droplets prior to coalescence. This process will continue until there is complete phase separation, i.e. two liquid layers occur. An interfacial tension exists at the interface between the two phases due to the imbalance of forces at the interface. For example, at the interface between the two layers, there will be a net attractive force that is directed towards the bulk of each phase, due to the imbalance between the cohesive forces (oil–oil and water–water) within each

phase and the oil–water attractive forces at the interface. The interfacial tension therefore acts both to stabilise the system into two phases and to resist the dispersion of one phase as droplets within the other phase.

Thermodynamically, this situation may be described in terms of the change in the interfacial Gibb's free energy (ΔG), interfacial tension ($\gamma_{o/w}$) between the two phases and the change in surface area of the disperse phase when this is dispersed, albeit temporarily, as droplets within the external phase (ΔA) as follows:

$$\Delta G = \gamma_{o/w} \Delta A$$

The dispersion of one phase within the other will cause a dramatic increase in the surface area of the interface between the two phases which, in turn, renders the system unstable (due to the increase in the interfacial Gibb's free energy). The system will therefore attempt to correct this instability; the subsequent coalescence of the droplets reduces the surface area of the interface, thereby reducing ΔG. In this fashion the spontaneous coalescence of droplets of the internal phase may be explained. Accepting that a fundamental requirement for the formulation of pharmaceutical emulsions is the dispersal of one internal phase within a second external phase, this relationship provides an insight into one of the mechanisms of stabilisation of emulsions by emulsifying agents. As the reader will be aware, surface-active agents lower the interfacial tension and therefore, when present in emulsion systems, will partially negate the destabilising effects of the increase in surface area of the disperse phase. It is important to note that this is not the only mode of emulsification of these agents.

Classical studies on the stabilisation of emulsions have shown that the stability of the adsorbed layer was of primary importance. In these studies it was shown that whenever sodium cetyl sulphate (a hydrophilic surface-active agent) and cholesterol (a lipophilic surface-active agent) were employed as emulsifying agents, the two agents formed a stable film due to their interaction at the interface. The mechanical properties of this mixed surfactant film were sufficient to prevent disruption even when the shape of the droplets changed. Furthermore, the close-packed nature of the surface-active agents at the interface resulted in a greater lowering of the interfacial tension that could be achieved by either component when employed as a single emulsifying agent. The role of the interaction between surface-active agents (resulting in a mechanically robust interfacial film) was highlighted by replacing cholesterol with oleyl alcohol (a *cis* isomer), which resulted in a poor emulsion; however, the use of the *trans* isomer of oleyl alcohol, elaidyl alcohol, produced a

stable emulsion. Further studies have shown that interfacial surfactant films form three-dimensional liquid crystalline layers of defined mechanical structure.

In addition to the mechanical properties of the adsorbed interfacial (liquid crystal) film, the adsorbed layer may carry a charge which, depending on the magnitude, may offer electrical repulsion between adjacent droplets. This is frequently observed whenever the droplets have been stabilised using ionic surface-active agents. Interestingly, flocculation of droplets of the disperse phase may lead to physical instability (see later) and, therefore, controlled flocculation (see Chapter 2) is not performed.

Emulsion instability and the role of hydrophilic polymers

Hydrophilic polymers are frequently used as emulsion stabilisers in pharmaceutical emulsions. In contrast to surface-active agents, hydrophilic polymers do not exhibit marked effects on the interfacial tension. However, the stabilisation effect of these materials is due to their ability to adsorb at the interface between the disperse phase and the external phase to produce *multilayers* that are highly viscoelastic (gel-like) and can therefore withstand applied stresses without appreciable deformation. In so doing these polymers mechanically prevent coalescence. It should be noted that surface-active agents produce *monomolecular* not multimolecular films.

If the chosen hydrophilic polymer is ionic (e.g. gelatin, sodium alginate, sodium carboxymethylcellulose), then the multimolecular adsorbed film will be charged and therefore will exhibit a zeta potential. This may further protect the emulsion droplets from coalescence by offering an electrical repulsion, as described in the previous section (and in Chapter 2). Furthermore, it would be expected that stearic stabilisation of the droplets would occur due to the presence of the adsorbed polymeric layer. A similar phenomenon was described for suspensions in Chapter 2.

In addition, hydrophilic polymers will increase the viscosity of the external phase in an o/w emulsion and, in a similar fashion to suspensions, will affect the sedimentation rate of the droplets. This point is addressed in subsequent sections.

Emulsion instability and adsorbed particles

Emulsions may also be stabilised by the addition of finely divided solid particles, if the particles are sufficiently wetted by both the oil and water phases (but preferentially wetted by one of the phases). The particles will accumulate at the interface between the phases and, if the particles show high interparticulate adhesion (thereby ensuring mechanical robustness to the adsorbed layer), the stability of the emulsion will be greatly

enhanced. The type of emulsion produced by this method depends on the preference of the particles for each phase. For example, if the particles are wetted preferentially by the aqueous phase (i.e. the contact angle between the particle and water is less than 90°), an o/w emulsion will result. Conversely, if the finely divided solid is preferentially wetted by the oil phase, the resulting emulsion will be a w/o emulsion. Examples of finely divided solids that are employed in the formulation of o/w and w/o pharmaceutical emulsions are:

- o/w emulsions
  - aluminium hydroxide
  - magnesium hydroxide
  - bentonite
  - kaolin
- w/o emulsions
  - talc
  - carbon black.

Type of emulsion

In the preparation of an emulsion, oil, water and the specified emulsifying agents are mixed together, resulting in the formation of droplets of each phase. At this stage theoretically either an o/w or a w/o emulsion may form. The resultant emulsion type is defined by the stability of the droplet phase; the phase of lower stability (i.e. the greater rate of coalescence) coalesces to form the external (or continuous) phase. There are several determinants of the type of emulsion produced, including: (1) phase volume of the internal phase; (2) the chemical properties of the film surrounding the internal phase; and (3) viscosity of the internal and external phases.

Phase volume of the internal phase

Assuming that the internal phase is composed of spheres, it may be calculated that the maximum volume that may be occupied by the internal phase is 74%. This is termed the *critical value* and is dependent on the droplet size range and shape. Moreover, a large particle size range and irregular droplet shape may increase this value. In practice it is customary to use a phase volume ratio of 50% as this results in a stable emulsion (due to the loose packing of the internal phase). It should be remembered that the higher the phase volume of the internal phase, the greater the probability of droplet coalescence.

Interestingly, although the above description holds true for o/w emulsions, the critical value for w/o emulsions is markedly lower (circa 40%). This is due to the greater mechanical properties of hydrophilic polymer or polar surface-active agents (used to form o/w emulsions) than the hydrophobic groups that

stabilise w/o emulsions. This point is extended in the next section.

The chemical properties of the film surrounding the internal phase

As the reader will now appreciate, the adsorption of a mechanically robust film around the droplets of the internal phase is important to prevent droplet coalescence. The chemical composition of the surface-active agents (and hydrophilic polymers) at the droplet/external phase interface will dictate whether an o/w or w/o is formed. Typically oil droplets are stabilised by an adsorbed film composed of non-ionic, and especially ionic, surfactants or alternatively hydrated hydrophilic polymer chains. The surface-active agents and polymers that are responsible for this stabilisation are therefore predominantly (but not exclusively; the reader should recall that surface-active agents also possess hydrophobic groups) aqueous-soluble. Conversely, in w/o emulsions, the droplet is stabilised by the non-polar portion of the surface-active agent, which protrudes into the non-aqueous external phase. Furthermore, the length of this non-polar section plays an important role in the stabilisation of w/o emulsions, enhancing the mechanical integrity and reducing the tendency for the internal phase to coalesce.

The reader will therefore appreciate from this description that the solubility characteristics of the emulsifying agent define the type of emulsion that is formed. Therefore polymers and surface-active agents that are predominantly hydrophilic will form o/w emulsions, whereas predominantly hydrophobic surfactants will form w/o emulsions. Surface-active agents contain both hydrophilic and lipophilic groups and therefore it is the relative contributions of these that determine whether the agent is predominantly hydrophilic or lipophilic (hydrophobic). The contribution of these to the overall solubility is commonly referred to as the *hydrophile–lipophile balance* (HLB), a ratio scale that assigns a number to a surface-active agent, based on the contributions of the individual groupings on the molecule. This number can then be used when selecting surface-active agents for the formulation of either o/w or w/o emulsions.

The main features of the HLB scale are as follows:

- The HLB scale runs from circa 1 to 40; the water solubility of the surface-active agent increases as the HLB increases.
- Surface-active agents exhibiting an HLB between circa 3 and 6 are used to produce w/o emulsions and are therefore termed w/o emulsifying agents. These agents form poor dispersions in water but are soluble in the oil phase. Examples include:
  - sorbitan sesquioleate (e.g. Arlacel 83): HLB 3.7
  - sorbitan monooleate (e.g. Span 80): HLB 4.3

- sorbitan monostearate (e.g. Span 60): HLB 4.7
- glyceryl monostearate: HLB 3.8.

- Surface-active agents that exhibit an HLB between circa 6 and 9 form non-stable milky dispersions in water. Examples include:
  - orbitan monopalmitate (e.g. Span 40): HLB 6.7
  - sorbitan monolaurate (e.g. Span 20): HLB 8.6.
- Surface-active agents exhibiting an HLB between circa 9 and 16 are used to produce o/w emulsions (termed o/w emulsifying agents). These agents form stable milky dispersions in water (HLB 9–10.5), translucent/clear dispersions in water (HLB 10.5–13) or clear solutions (HLB 13–16). Examples include:
  - polyoxyethylene sorbitan tristearate (e.g. Tween 65): HLB 10.5
  - polyoxyethylene sorbitan trioleate (e.g. Tween 85): HLB 11.0
  - polyoxyethylene sorbitan monostearate (e.g. Tween 60): HLB 10.5
  - polyoxyethylene sorbitan monooleate (e.g. Tween 80): HLB 15.0
  - polyoxyethylene sorbitan monopalmitate (e.g. Tween 40): HLB 15.6
  - polyoxyethylene sorbitan monolaurate (e.g. Tween 20): HLB 16.7.
- The HLB value of ionic surface-active agents is frequently greater than 16.

Viscosity of the internal and external phases

The type of emulsion produced is affected by the viscosity of both the internal and external phases. If the viscosity is high the diffusion of the surface-active agent to the droplet surface will be reduced, as viscosity is inversely proportional to the diffusion coefficient of the surface-active agents. Furthermore, the increased viscosity will affect the process of coalescence of the droplets of the external phase. In general, if the viscosity of one phase is preferentially increased, there is a greater chance of that phase being the external phase of the emulsion.

Tests to identify the type of emulsion

There are several tests that may be performed to identify the type of emulsion that has formed:

- *Electrical conductivity*: o/w emulsions conduct electric current whereas w/o emulsions do not.
- *Dilution with water*: o/w emulsions may be diluted with water (as this is the composition of the external phase) whereas w/o emulsions cannot be diluted with water.
- *Use of dyes*: oil-soluble dyes will stain the internal phase if the emulsion is an o/w emulsion whereas water-soluble dyes will dye the internal phase of a w/o emulsion.

Emulsion instability

One of the goals of the pharmaceutical scientist is to formulate an emulsion that is physically stable, i.e. where the droplets of the internal phase remain discrete, retain their diameter and are homogeneously dispersed throughout the formulation. Fundamental to achieving this goal is the presence of the interfacial film (monomolecular or multilayered) at the interface between the droplet and the external phase. Emulsion instability may be either reversible or irreversible and is manifest in the following ways: (1) cracking (irreversible instability); (2) flocculation; (3) creaming; and (4) phase inversion.

Cracking (irreversible instability)

Cracking refers to the complete coalescence of the internal phase, resulting in the separation of the emulsion into two layers, and occurs due to the destruction of the mono/multilayer film at the interface between the droplet and external phase. If an emulsion has cracked it cannot be recovered. This phenomenon may be due to:

- *Incorrect selection of emulsifying agents.* This results in the production of an interfacial film of insufficient mechanical properties. The role of complexation (interaction) between the surfactant molecules at the interface between the two phases has already been described earlier in this chapter.
- *Presence of incompatible excipients.* In the formulation of emulsions it is important that excipients do not interact with and destroy the interfacial film of surface-active agents. This will occur if, for example, a cationic surface-active agent (commonly used as a preservative in creams) is added to an emulsion in which the interfacial film of surface-active agents bears an anionic charge (e.g. due to sodium oleate, potassium oleate or sodium lauryl sulphate). Similarly, if a therapeutic agent or a divalent ion bears an opposite charge to that exhibited by the interfacial film, disruption of the film will occur due to this ionic interaction.
- *Temperature.* Emulsions are generally unstable at high and low storage temperatures.
- *Microbial spoilage.* Microbial growth generally leads to destabilisation of the emulsion and is thought to be due to the microorganisms being able to metabolise the surface-active agents.

Flocculation

The ability of emulsion droplets to flocculate has been introduced earlier in this chapter. In the flocculated state the secondary interactions (van der Waals forces) maintain the droplets at a defined distance of separation (within the secondary minimum). Application of a shearing stress to the formulation (e.g. shaking)

will redisperse these droplets to form a homogeneous formulation. Although flocculation may stabilise the formulation, there is also the possibility that the close location of the droplets (at the secondary minimum) would enable droplet coalescence to occur if the mechanical properties of the interfacial film are compromised.

Creaming

This phenomenon occurs primarily as a result of the density difference between the oil and water phases and involves either the sedimentation or elevation of the droplets of the internal phase, producing a layer of concentrated emulsion either at the top or bottom of the container. Creaming is predominantly an aesthetic problem as the resulting emulsion is rather unsightly; however, upon shaking the emulsion is rendered homogeneous. Patients often believe that an emulsion that shows evidence of creaming has exceeded its shelf-life.

It is therefore important to understand the physicochemical basis of creaming in emulsions and, in so doing, reduce the rate of or inhibit this phenomenon. The rate of creaming $\left(\frac{\delta v}{\delta t}\right)$ in an emulsion (in a similar fashion to suspensions) may be described by Stokes' equation:

$$\frac{\delta v}{\delta t} = \frac{2r^2(\rho_o - \rho_w)g}{9\eta}$$

where: r refers to the average radius of the droplets of the internal phase; $(\rho_o - \rho_w)$ refers to the density difference between the oil phase and the water phase; g refers to gravity (which is negative if upward creaming occurs); and η refers to the viscosity of the emulsion.

As may be observed, creaming may be prevented if the density difference between the two phases is zero. In practice, however, this cannot be easily achieved. Therefore, the most straightforward methods by which the rate of creaming may be reduced are:

- Reduce the average particle size of the disperse phase. This may be achieved by size reduction methods, e.g. the colloid mill.
- Increase the viscosity of the emulsion. This may be achieved by adding hydrophilic polymers to the external phase of o/w emulsions or by incorporating non-aqueous viscosity enhancers (e.g. aluminium stearate salts, Thixin®) into w/o emulsions.

Phase inversion

Phase inversion refers to the switching of an o/w emulsion to a w/o emulsion (or vice versa). This is a phenomenon that

frequently occurs whenever the critical value of the phase volume ratio has been exceeded. In o/w emulsions the frequently cited phase volume ratio (o:w) is 74:26 and for w/o emulsions this value is 40:60.

Formulation of pharmaceutical emulsions

In the formulation of pharmaceutical emulsions there are a number of questions that require to be initially addressed, including the type of emulsion required (o/w or w/o), the route of administration of the emulsion (e.g. oral or topical, the latter as a cream), the volume of the internal phase, the droplet size and the consistency required. These aspects are individually addressed below.

Tips

Emulsion instability may be classified as either reversible or irreversible.

Cracking is irreversible.

Phase inversion will result in the switching of the type of emulsion. Although the preparation may be stable, the nature (and hence the clinical performance) of the emulsion has changed and therefore this phenomenon should be avoided.

Creaming, whilst unsightly, is reversible upon shaking.

Type of emulsion

As the reader is now aware, there are two types of primary emulsions; however the clinical uses of these types differ. Emulsions that are designed for oral or intravenous administration are o/w, whereas emulsions for topical administration (creams) may be either o/w or w/o. O/w creams are generally (but not exclusively) used for the topical administration of water-soluble drugs to the skin to achieve a local effect (e.g. for the treatment of infection or inflammation). They are typically easily applied to the surface, are non-greasy and may be washed from the skin. Conversely, w/o emulsions are greasy in texture and, following application, will hydrate the skin. Most moisturising formulations are w/o emulsions.

Volume of the internal phase

The effect of the volume of the internal phase on emulsion stability has been addressed previously in this chapter. The ratio of the internal-to-external phase of o/w emulsions is typically 1:1; however, large oil-to-water ratios are theoretically possible. Usually the concentration of the internal phase is restricted to circa 60% to ensure stability. The maximum concentration of internal phase of w/o emulsions is 30–40%. Higher concentrations will result in phase inversion.

Droplet size

Previously it was shown that the rate of creaming of an emulsion may be reduced by reducing the average droplet size of the internal phase. In light of this it is customary when industrially

processing emulsions and creams to reduce the droplet size (and reduce the polydispersity of the size distribution) by passage through a colloid mill. The clinical importance of droplet size in parenteral emulsions, e.g. total parenteral nutrition, will be specifically addressed in Chapter 5.

Viscosity of the internal and external phases

One of the major differences between traditional emulsions for oral or parenteral administration and creams is the increased viscosity of the latter. The superior viscosity of these formulations facilitates the location and spreading of the formulation on the skin. In addition, the viscosity of emulsion/cream formulations also affects the stability, controlling the rate of upward/downward sedimentation (as described by Stokes' law).

Selection of type and concentration of emulsifying agents

All emulsion and cream formulations require the inclusion of emulsifying agents (principally surface-active agents) to ensure emulsion stability, the choice of which is determined by the type of emulsion required, clinical use and toxicity. For example, the use of anionic surfactants is restricted to external formulations. To determine the type of emulsifying agents used, reference is made to the HLB requirements of the internal phase of the formulation. If the HLB requirements are not known, it is common practice for the formulation scientist to prepare a series of emulsions using a mixture of surface-active agents that provides a range of HLB values using a weighted-mean approach. For example, an o/w emulsion may be prepared using a mixture of surface-active agents (1% w/w in total) that provides an overall HLB value of 10. A mixture of Span 60 (HLB 4.7) and Tween 80 (15.0) may be chosen for this purpose; the ratio of these two surfactants is calculated using the simple weighted-averages equation:

$$10 = 4.7x + (1-x)15$$

where x refers to the fraction of Span 60 and $(1 - x)$ is the fraction of Tween 80.

In this example the mixture of surface-active agents would be 0.485% w/w Span 60 and 0.515% w/w Tween 80. In practice a series of emulsions would be prepared, each differing in the HLB of the surfactant mixture but constant in terms of the overall concentration of surfactants. From this the most stable emulsion would be selected.

Alternatively, for certain non-aqueous components information is available regarding the required HLB to produce stable o/w or w/o emulsions. For example, to prepare a stable o/w

emulsion using cottonseed oil as the internal phase requires a mixture of surface-active agents that produces an HLB value of 10.0, whereas the formation of a w/o emulsion in which cottonseed oil is the external phase requires a mixture of surface-active agents that produces an HLB value of 5. If the lipophilic component of the formulation is composed of more than one excipient, then the combined HLB value for this phase should be calculated and the ratio of surface-active agents in the mixture selected to provide this HLB requirement. For example, consider an o/w cream in which the internal phase (of total weight 35% w/w) has the composition shown in Table 3.1.

Table 3.1 Calculation of required hydrophile–lipophile balance (HLB) values for an oil in water (o/w) cream

Components (% w/w of final formulation)	HLB requirement to produce an o/w emulsion	Composition (fraction of the oil phase)	Calculated HLB requirement
Cottonseed oil (30%)	10	$\left(\frac{30}{35}\right)=0.86$	$(0.86\times10)=8.6$
Stearyl alcohol (3%)	14	$\left(\frac{3}{35}\right)=0.09$	$(0.09\times14)=1.26$
Beeswax (2%)	12	$\left(\frac{2}{35}\right)=0.05$	$(0.05\times12)=0.6$
			Total: 10.46

The HLB requirement for the formulation of a stable emulsion is 10.46. For this example we will choose a mixture of two non-ionic surface-active agents – polyoxyethylene sorbitan monostearate (Tween 60: HLB 14.9) and sorbitan monostearate (Span 60: HLB 4.7). Allowing x to equal the fraction of sorbitan monostearate in the surfactant mixture and $(1 - x)$ to represent the fraction of the second surfactant, the following calculation may be performed:

$$10.46 = 4.7x + (1 - x)14.9$$

Therefore the ratio of Span 60 to Tween 60 is 0.44:0.56.

Two further points should be noted regarding the use of surface-active agents for the stabilisation of pharmaceutical emulsions: (1) the choice of the mixture of surfactants and (2) the overall concentration of surfactant.

- In choosing the surfactant blend, the formulation scientist should examine the structure of the surfactants to ascertain whether the two components may interact at the interface between the internal and external phases. In addition, it is preferable that the surfactant blend used should not be composed of one surfactant with a low HLB and the second with a high HLB, as in this case emulsion stability may be problematic. However, the addition of a third surface-active agent of intermediate HLB may resolve this issue.
- The concentration of surfactant used should be the lowest concentration required to ensure stability.

Types of surface-active agents used as emulsifying agents

There are four categories of surface-active agents used to stabilise emulsion/cream formulations: (1) anionic; (2) cationic; (3) non-ionic; and (4) amphoteric. Examples of these are provided in the section below. It should be noted that the cited examples are representative of the surface-active agents within each of the four classes. Moreover, the details provided for each example/category of surfactant are designed to provide an insight into the types and uses of the various agents. For a more comprehensive understanding of these agents, the reader should consult the companion text in the FASTtrack series by David Attwood and Alexander T Florence (*FASTtrack: Physical Pharmacy*: London: Pharmaceutical Press, 2008).

Anionic surfactants

- These dissociate to produce negatively charged ions with surface-active activity.
- Whilst examples in this category are inexpensive, they are comparatively more toxic than for other categories of surface-active agent. This limits their use to external formulations, e.g. creams.
- Examples of anionic surfactants include:

– *Sodium/potassium salts of fatty acids*

  - Examples include sodium oleate (Figure 3.1), sodium stearate and ammonium oleate

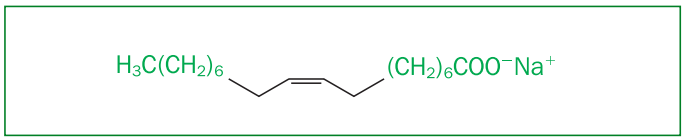


Figure 3.1 Structural formula of sodium oleate.

  - These agents produce o/w emulsions (usually in combination with a second surface-active agent to ensure

the formation of a mechanically robust film at the oil/water interface)
    - Due to the effect of pH on the ionisation (and hence surfactant properties) of these molecules, the emulsifying properties are lost under acidic conditions. Similarly, the emulsifying properties are negated in the presence of di/trivalent cations.
    - These surfactants may be formed in situ in the formulation by the co-addition of the fatty acid and a suitable counterion.
- *Calcium salts of fatty acids*
    - These are generally formed in situ by the interaction of a calcium salt, e.g. calcium hydroxide, with a fatty acid, e.g. calcium oleate. This approach is used in Zinc Cream BP and in certain lotions.
    - Calcium salts of fatty acids form w/o emulsions, due to their limited dissociation (and hence solubility: Figure 3.2).

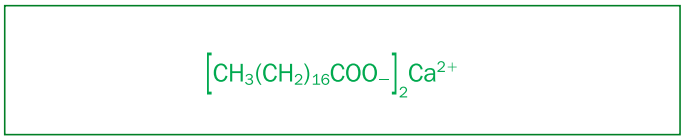


Figure 3.2 Structural formula of calcium stearate.

- *Amine salts of fatty acids*
    - These are typically formed in situ in pharmaceutical emulsions, e.g. triethanolamine stearate.
    - These surface-active agents form o/w emulsions.
    - Akin to sodium/potassium salts of fatty acids, their emulgent properties are pH-dependent and may be negated in the presence of electrolytes.
- *Alkyl sulphates*
    - These are used to produce o/w emulsions (in conjunction with a second non-ionic surfactant of low HLB, i.e. < 6). Fatty alcohols (e.g. cetyl, stearic alcohol) are frequently used for this purpose.
    - Examples of these include sodium lauryl sulphate (Figure 3.3) and triethanolamine lauryl sulphate.

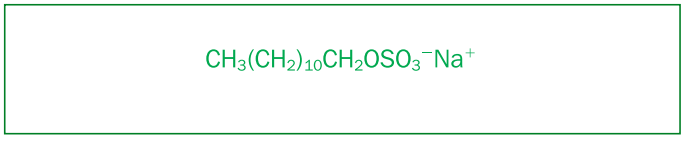


Figure 3.3 Structural formula of sodium lauryl sulphate.

Cationic surfactants

- These dissociate to produce positively charged ions with surface-active activity.

- They are primarily used pharmaceutically as preservatives of topical formulations; however, they may be used to form o/w emulsions (when combined with a second non-ionic surfactant of low HLB, i.e. < 6).
- The main example used in topical formulations is cetrimide, a mixture of trimethylammonium bromide, with smaller amounts of dodecyltrimethylammonium bromide and hexadecyltrimethylammonium bromide (Figure 3.4).

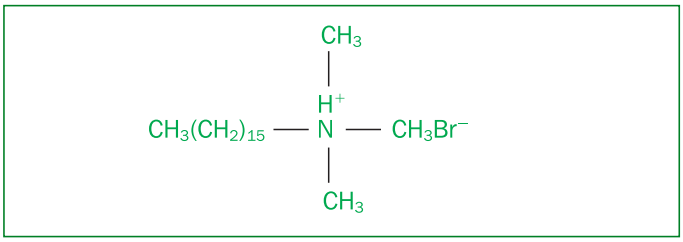


Figure 3.4 Structural formula of hexadecyltrimethylammonium bromide (cetrimide).

- Their emulgent properties are compromised in the presence of anionic agents (e.g. anionic surface-active agents, di/trivalent anions and polyelectrolytes, e.g. anionic polymers).

Non-ionic surfactants

- These are by far the most popular category of surface-active agents used for the formulation of pharmaceutical emulsions.
- They may be used to formulate both o/w and w/o emulsions.
- Generally combinations of two non-ionic surfactants (one water-soluble and the other oil-soluble) are employed to ensure the formation of a stable interfacial film around the surface of the droplets of the disperse phase. In certain circumstances a single non-ionic surfactant may be used that is of intermediate HLB value.
- Non-ionic surface-active agents are more stable than ionic surfactants in the presence of electrolyte and/or changes in pH.
- Generally the hydrophobic portion of the molecule is composed of a fatty acid or fatty alcohol whereas the hydrophilic portion is composed of an alcohol or ethylene glycol moieties.
- Examples of non-ionic surface-active agents include:

– *Sorbitan esters (e.g. Span series)*
  - This is a family of chemically related esters that are produced by esterifying a fatty acid to at least one of the hydroxyl groups of sorbitan.
  - Modification of the length of the fatty acid (denoted by the symbol R in Figure 3.5) will generate a range of surface-active agents with emulsifying properties (and low HLB values).

- By themselves sorbitan esters will form w/o emulsions; however, when combined with the polysorbates (see below), both o/w and w/o emulsions may be formulated.

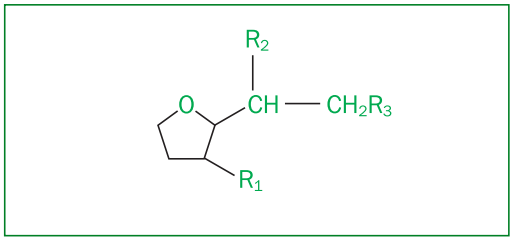


Figure 3.5 Generic structure of the sorbitan fatty acid esters. In sorbitan monoesters R_1 and R_2=OH, R_3 is the specific fatty acid derivative (e.g. lauric, stearate). R_1=OH and R_2 and R_3 refer to the specific fatty acid derivative for sorbitan diesters. In sorbitan trimesters R_1, R_2 and R_3 refer to the specific fatty acid derivative.

– *Polyoxyethylene fatty acid derivatives of the sorbitan esters (e.g. Tween series)*
  - This family of surface-active agents is prepared by forming polyoxyethylene esters of the sorbitan esters.
  - The emulsifying properties of the molecules in this series may be modified by altering the number of oxyethylene (OCH_2CH_2) groups and the type of fatty acid (denoted as R in Figure 3.6).
  - These surfactants are used to form o/w or w/o emulsions in combination with a second surface-active agent, e.g. sorbitan esters, cetyl alcohol, glyceryl monostearate, to ensure emulsion stability.
  - The emulsifying properties of this series are tolerant of changes in electrolyte concentration and pH.
  - Generally they are non-toxic and are used in both parenteral and non-parenteral emulsions.

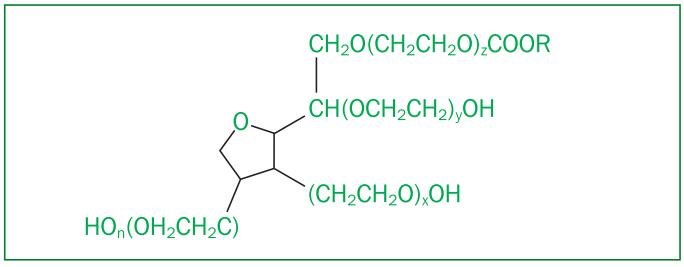
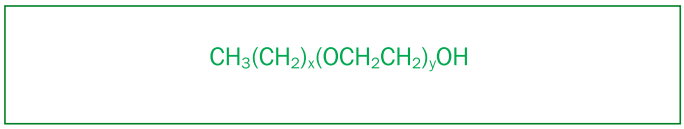


Figure 3.6 Generic structure of the polyoxyethylene sorbitan fatty acid monoesters. Di- and tri-esters may be formed by esterification of the terminal alcohol groups.

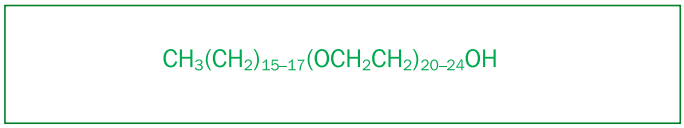
– *Polyoxyethylene alkyl ethers (macrogols)*
  - These are ethers formed between polyethylene glycol and a range of fatty alcohols (lauryl, oleyl, myristyl, cetyl, stearyl). Two commercial series of these compounds are *Cremophor* and *Brij.*
  - The physicochemical properties of these *non-ionic* surface-active agents may be modified by altering the length of the polyoxyethylene group and the length of the aliphatic chain (denoted as *x* and *y* in Figure 3.7).

Figure 3.7 Structural formula of the polyoxyethylene alkyl ethers.



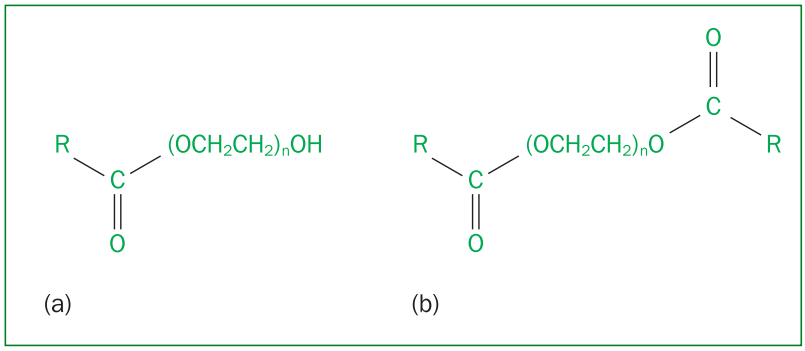
- The macrogols are used as emulsifying agents for both o/w and w/o emulsions. Combinations of the more lipophilic and hydrophilic examples of this series are combined to produce stable emulsions.
- For example, cetomacrogol 1000 (Figure 3.8) is combined with cetostearyl alcohol to produce cream formulations.

Figure 3.8 Structural formula of cetomacrogol 1000.



– *Polyoxyethylene fatty acid esters*
- These are a series of polyoxyethylene derivatives of fatty acids. The most commonly used derivatives are the stearate derivatives (the Myrj series). The surface-active properties of these compounds may be modified by varying the length of the oxyethylene substituent and, in addition, by mono- or diesterification of the acid, as shown in Figure 3.9.

Figure 3.9 Generic structures of polyoxyethylene monoester and poly(oxyethylene) ester. The number of repeating oxyethylene groups is denoted by n, whereas R refers to the chain length of the fatty acid.



- Polyoxyethylene stearates (and related compounds) are non-ionic surfactants, offering a range of HLB values.
- They are frequently combined with stearyl alcohol (or related fatty alcohols) in the formulation of o/w emulsions.
- The emulsifying properties are tolerant of the presence of strong electrolytes.

– *Fatty alcohols*
- Examples include cetyl alcohol and stearyl alcohol (Figure 3.10).

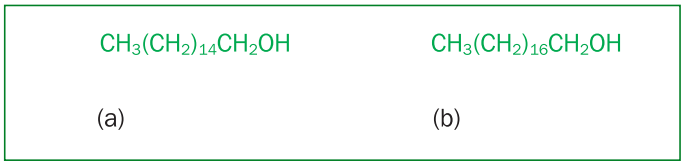


Figure 3.10 Structural formula of (a) cetyl alcohol and (b) stearyl alcohol.

In addition, cetostearyl alcohol (a mixture of cetyl (20–35%) and stearyl (50–70%) alcohols, although other alcohols, e.g. myrisitc alcohol, are present) is available (see later in this chapter).

- Fatty alcohols are generally used in combination with more hydrophilic surfactants to produce stable o/w emulsions.
- When used alone, fatty alcohols act as w/o emulsifiers. Furthermore, the addition of these to a hydrophobic base will increase the water absorption properties of the formulation.
- In cream formulations excess fatty alcohols interact with the hydrophilic emulsifier to produce a viscoelastic external phase. In turn, this increases the viscosity of this phase (thereby decreasing upward/downward sedimentation), producing the consistency expected of cream formulations.
- Fatty alcohols may be used to enhance the viscosity of w/o creams.

– *Amphoteric surfactants*
  - These are compounds that possess both positively and negatively charged groups (cationic at low pH values and anionic at high pH values).
  - The emulsifying properties are reduced as the pH approaches the isoelectric point of the surface-active agent.
  - The most commonly used amphoteric surface-active agent is lecithin (Figure 3.11).

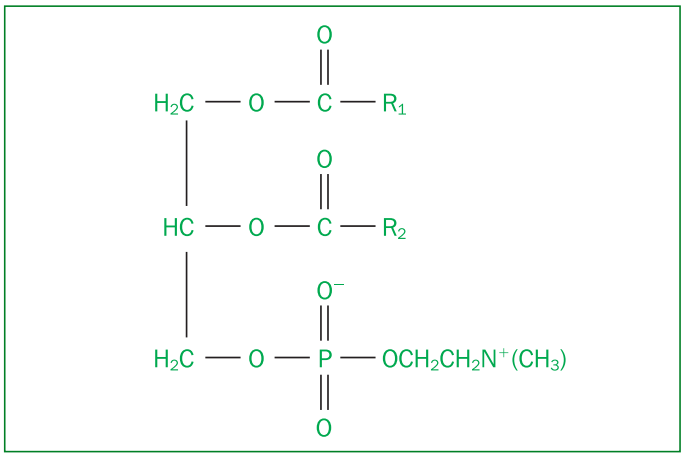


Figure 3.11 Structural formula for lecithin (R_1 and R_2 refer to either identical or different fatty acids).

- Lecithin is used in emulsions (for intravenous and intramuscular administration) and creams, in which it acts as an o/w emulsifying agent.

Miscellaneous surfactants that are used in emulsion and cream formulations

The following emulsifying agents are derived from natural sources and are composed of mixtures of compounds. They are used as emulsifying agents either alone, or, preferably, along with a second emulsifying agent in the production of o/w and w/o creams.

Lanolin (wool fat)

- Lanolin is a wax-like material that is derived from sheep's wool. It is a mixture of fatty alcohols, fatty acid esters of cholesterol and other sterols.
- On its own it may be used to produce w/o creams. Mixtures of this emulsifying agent with oils or soft paraffin produce emollient creams.
- Lanolin can absorb approximately twice its weight of water – this property is advantageous in the formulation of ointments.

Lanolin alcohols (wool alcohols)

- This is a mixture of steroid alcohols and triterpene alcohols (including cholesterol).
- Lanolin alcohol is an excellent emulsifying agent for w/o emulsions.
- It has excellent water-absorptive properties.
- It is prone to oxidation (and therefore requires an antioxidant).

Anionic emulsifying wax

- This is a mixture containing cetostearyl alcohol, water and sodium lauryl sulphate (or a related sulphated alcohol). The specific formula for anionic emulsifying wax in the British Pharmacoepeia (2004) is as follows:
  cetostearyl alcohol (90 g)
  sodium lauryl sulphate (10 g)
  purified water (4 ml).
- This mixture is used to produce o/w emulsions (using 2% w/w wax) or creams, at a higher wax concentration (10% w/w). However, the use of anionic emulsifying wax is predominantly for topical (cream) formulations.
- Due to the anionic nature of one of the ingredients, the emulgent properties of this wax are compromised by the presence of polyvalent metals and cations (e.g. quaternary ammonium compounds).

Non-ionic emulsifying wax

- Non-ionic emulsifying wax (also called cetomacrogol emulsifying wax) is composed of cetostearyl alcohol and cetomacrogol 1000.
- This wax is used as an emulsifier for the preparation of emulsions (at concentrations up to 5% w/w). However at higher concentrations this material additionally enhances the rheological structure of the preparation (15–25% w/w), thereby promoting stability. The primary use of non-ionic emulsifying wax is for the preparation of creams.
- The emulgent properties of non-ionic emulsifying wax are tolerant to the presence of electrolytes (and therapeutic agents).

Beeswax (white and yellow)

- There are two forms of beeswax – white and yellow. White beeswax is a bleached form of yellow beeswax.
- Beeswax is a mixture of esters of monohydric alcohols (C_{24}–C_{36}, in even numbers only) and straight-chain acids (even numbers of carbon atoms up to C_{36}), long-chain hydroxyacids (e.g. C_{18}). The principal component is myricyl palmitate.
- Beeswax is used as a w/o emulsifying agent for creams and is also used to enhance the consistency of creams.

Excipients used in pharmaceutical emulsions

One major category of excipients for pharmaceutical emulsions, namely surface-active agents, has been described above. However, as in other pharmaceutical formulations, other excipients are required to enhance the physical and chemical stability and to render the formulation aesthetically pleasing to the patient. These are described below.

Vehicle

There are two liquid phases in pharmaceutical emulsions: an aqueous phase and an oil phase, each of which is formulated separately. The vehicle in the aqueous phase for pharmaceutical emulsions designed for oral or topical administration is usually *purified water*, the details of which have been provided in Chapter 1. When formulated for intravenous administration, *sterile water for injections* is used as the external aqueous phase,

Tips

The type of surfactants used dictates the stability and type of the emulsion.

In the choice of surfactant type for an emulsion, due attention must be paid to the toxicity of the surfactant. For example, non-ionic, but not anionic, surfactants may be administered orally. Certain surfactants are only used in the formulations for topical administration. Cationic surfactants are principally used as preservatives and not for the stabilisation of emulsions.

Combinations of surfactants are used to stabilise emulsions. The elastic properties of the surfactant layer at the interface are important in the stabilisation of emulsions.

the details of which are provided in Chapter 5. If control of the pH of the aqueous external phase is required, buffers, e.g. citrate, phosphate, may be included in the aqueous vehicle. In light of the ability of electrolytes to compromise the emulsifying properties of surface-active agents (and certain hydrophilic polymers), the concentration and type of buffer should be carefully chosen.

The oil phase of pharmaceutical emulsions is typically composed of vegetable oils, e.g. cottonseed oil, arachis oil, almond oil (mono-, di- and triglycerides of mixtures of unsaturated and saturated fatty acids). However, pharmaceutical emulsions for topical application (creams) may be formulated using a greater range of non-aqueous components. Alternative non-aqueous phases used in the formulation of creams and ointments include: (1) petrolatum and mineral oil; (2) isopropyl myristate; (3) antioxidants; (4) flavours and sweeteners; (5) viscosity modifiers; (6) preservatives for emulsions and creams.

Petrolatum and mineral oil

Petrolatum and mineral oil are hydrophobic excipients that are derived from petrolatum. The former is a complex mixture of hydrocarbons (e.g. aliphatic, cyclic, saturated, unsaturated, branched hydrocarbons) that results in a wide range of chemical and physical specifications in the USP monograph. Mineral oil is a more purified fraction of petrolatum and is a mixture of aliphatic (C_{14}–C_{18}) and cyclic hydrocarbons.

Both materials are employed as the internal phase in o/w emulsions and as the external phase in w/o emulsions (usually in combination with a fatty alcohol as the emulsifying agent).

Isopropyl myristate (Figure 3.12)

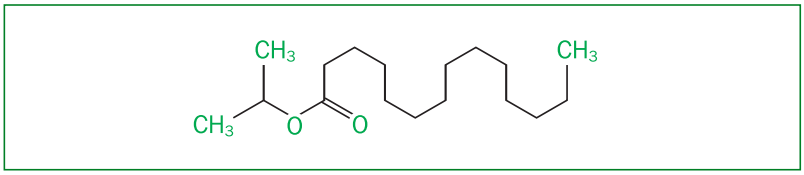


Figure 3.12 Structural formula of isopropyl myristate.

Isopropyl myristate is used as a non-aqueous component of cream formulations, either as the internal phase of o/w creams or as the external phase of w/o creams. More recently isopropyl myristate has been reported to enhance the permeation of drugs through the skin when applied topically.

Antioxidants

As described in Chapter 1, antioxidants are included within pharmaceutical formulations to enhance the stability of

drugs/components to oxidation. In emulsions and creams the two major components that may be liable to oxidise are the therapeutic agent and the oil selected for the oil phase, vegetable oils. Therefore the inclusion of lipophilic antioxidants within the oil phase may be required, e.g. butylated hydroxyanisole (circa 0.02–0.5% w/w), butylated hydroxytoluene (circa 0.02–0.5% w/w) and propyl gallate (< 0.1% w/v) (Figure 3.13).

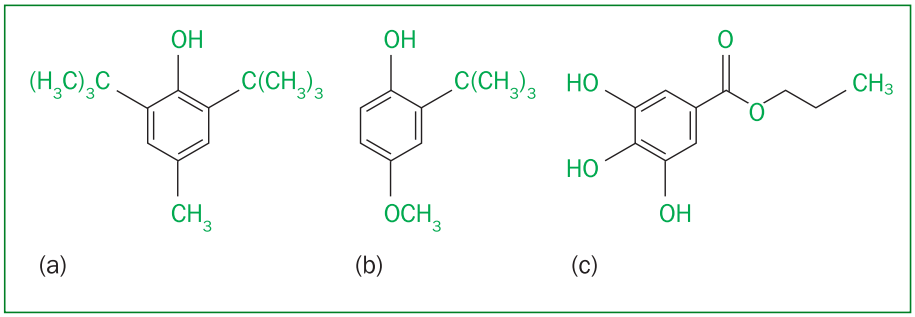


Figure 3.13 Structural formula of (a) butylated hydroxytoluene; (b) butylated hydroxyanisole; and (c) propyl gallate.

If the antioxidant is required in the aqueous phase of an emulsion or cream then a water-soluble example should be used, e.g. sodium metabisulphite (0.01–1.0% w/v) or sodium sulphite (0.1% w/v).

Flavours and sweeteners

Flavours and sweeteners are commonly included in emulsions for oral administration to mask the unpalatable taste of the therapeutic agent or the internal oil phase. Suitable examples of these have been given in Chapter 1.

Viscosity modifiers

The viscosity of emulsions and creams has been previously described to influence the physical stability of emulsions by decreasing the rate of creaming and therefore viscosity control within a formulation is an important attribute. The inclusion of hydrophilic polymers, e.g. methylcellulose, hydroxyethylcellulose, polyacrylic acid and sodium carboxymethylcellulose, to increase the viscosity of aqueous systems has been described in Chapters 1 and 2 and the same principles exist for emulsion formulations. It must be remembered that, as the viscosity of formulations increases, so does the difficulty in administration and, therefore, this must be borne in mind when the final viscosity of the o/w emulsion is selected. Furthermore, the ability of hydrophilic polymers to form a multimolecular layer around the surface of the dispersed-oil droplet is an important function of polymers within emulsion formulations.

Preservatives for emulsions and creams

The concept of preservation of pharmaceutical systems, i.e. solutions and suspensions, has been discussed in previous chapters. In particular the effects of pH and the presence of hydrophilic polymers, dispersed particles and surfactant micelles on the available preservative concentration were highlighted. The preservation of o/w emulsions and creams becomes a challenging task to the pharmaceutical scientist due to the possible co-requirement for pH control of the external phase and the inclusion of hydrophilic polymers. However, the complexity of this issue is enhanced due to the presence of a dispersed-oil phase into which the antimicrobial active form of the preservative may partition and hence be unavailable to exert its antimicrobial effect. An equilibrium is therefore established, as depicted in Figure 3.14.

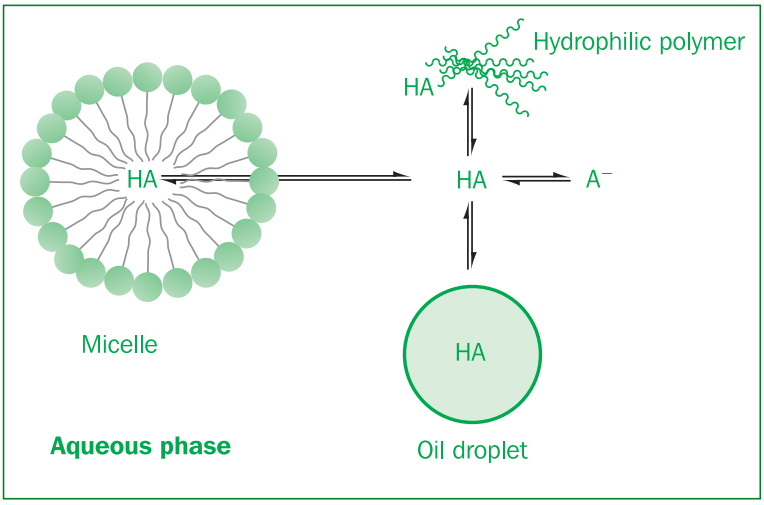


Figure 3.14 Diagrammatic representation of the equilibrium that exists between a dispersed-oil phase, the external aqueous phase, micelles of surface-active agent, a hydrophilic polymer (e.g. methylcellulose, polyvinylpyrrolidone) and the antimicrobially active form of an organic acid preservative (denoted as HA).

Figure 3.14 illustrates the partitioning of the unionised form of a weak acid preservative into micelles and oil droplets. The term HA may be replaced by a non-ionisable (or minimally ionisable) preservative, e.g. chlorocresol. As may be observed in Figure 3.14, the available (active) concentration is decreased by these various partitioning phenomena and therefore the concentration of preservative must be increased to ensure that required concentration of free preservative is obtained. The concentration of preservative required to inhibit microbial growth in emulsions/creams may be estimated using the following formula:

$$C_w = C\left(\frac{\phi+1}{K_w^o\phi+R}\right)$$

where: C_w refers to the concentration of 'free' preservative in the aqueous phase; C refers to total concentration of preservative; ø refers to the ratio of oil (internal phase) to water in the emulsion/cream; K_w^o refers to the partition coefficient of the preservative between the oil and water phases; and R is the ratio of the total preservative to the free preservative.

With knowledge of the above parameters, the free concentration of preservative may be calculated, as illustrated in the example below.

Worked example

Example 3.1

Calculate the free concentration of chlorocresol in an emulsion in which the oil:water partition coefficient of the preservative is 1.5, the phase ratio in the emulsion is 1:1, the ratio of total to free preservative is 4, the pH is 7.2 and the initial concentration of preservative is 0.3% w/v.

According to the above equation the concentration of free preservative is:

$$C_w = 0.3 \left(\frac{1+1}{1.5 \times 1+4} \right) = 0.1\%$$

Therefore, 33.3% of the preservative is available to the formulation to exert its antimicrobial effect within the formulation.

This situation becomes further complicated if the preservative ionises as a function of the pH of the formulation. To accommodate this, the degree of ionisation must be calculated (again using the Henderson–Hasselbalch equation). The pKa for chlorocresol is 9.2.

$$Fraction = \frac{1}{(1+10^{pH-pKa})} = \frac{1}{(1+10^{-2})} = 0.99$$

It can therefore be seen that at pH 7.2 chlorocresol is essentially unionised and no modification of the concentration is required. Conversely, if an organic acid is used (pKa 4.2), the fraction unionised will be 0.001 and therefore this must be considered in the calculation of the required concentration.

From the discussions to date, the role of the oil:water partition coefficient in the calculation of the free concentration of preservative is apparent. Therefore, to optimise preservative efficacy, the oil used as the internal phase should have low oil:water partition coefficient for the selected preservative. For

example, the partition coefficients of methyl parahydroxybenzoic acid in mineral oil and vegetable oil are 0.02 and 7.5. Therefore an obvious method of minimising the concentration of preservative in the formulation (whilst retaining the required antimicrobial activity) would be to select mineral oil as the internal phase. Alternatively, if an internal phase is specified, the total concentration of preservative may be minimised by selecting an alternative preservative with a low oil:water partition coefficient.

Manufacture of emulsions

Generically the manufacture of emulsions involves the following steps:

1. dissolution of the oil-soluble components in the oil vehicle and the (separate) dissolution of the water-soluble components in the aqueous phase
2. mixing of the two phases under turbulent mixing conditions to ensure the dispersion of the two phases into droplets.

At the laboratory the manufacture of emulsions usually involves the use of a mechanical stirrer whereas the manufacture of creams involves mixing the two (heated) phases using a mortar and pestle. The emulsification of production-scale batches is normally performed using mechanical stirrers, homogenisers, ultrasonifers or colloid mills. The use of colloid mills is usually reserved for formulations of higher viscosity, e.g. creams, due to the high running cost and slow production rate of this apparatus.

Tips

The formulation of emulsions requires the incorporation of several excipients to maintain stability and to ensure product performance.

As in other dosage forms, all excipients must be physically and chemically compatible (with each other and with the therapeutic agent).

The choice of preservative for an oil in water emulsion requires consideration of both the pH of the aqueous phase (if the preservative is acidic) and the solubility within the oil phase. Significant solubility of the preservative in the oil phase (and/or excessive ionisation of the preservative) lowers the preservative efficacy.

Multiple choice questions

1. Regarding the stability of pharmaceutical emulsions, which of the following statements are true?

a. Emulsions are inherently pharmaceutically unstable.

b. The stability of pharmaceutical emulsions is affected by the size of the dispersed phase.

c. The stability of pharmaceutical suspensions is affected by the concentration of dispersed phase.

d. Phase volume of the internal phase directly affects the stability of pharmaceutical emulsions.

2. Regarding the rate of creaming of pharmaceutical emulsions, which of the following statements are true?

a. The rate of creaming is increased as the diameter of the internal phase is increased.
b. The rate of creaming is increased as the viscosity of the continuous phase is increased.
c. The rate of creaming is affected by the concentration and type of incorporated surfactants.
d. The rate of creaming is decreased by centrifugation.

3. Regarding emulsions, which of the following statements are true?

a. Multiple emulsions are more stable than primary emulsions.
b. Water in oil emulsions are commonly administered orally.
c. Oil in water emulsions are stable following dilution with water.
d. Dispersed globules of the internal phase do not possess a zeta potential.

4. Regarding the role of surfactants in the formulation of emulsions, which of the following statements are true?

a. Oil in water emulsions are promoted by the presence of surfactants with HLB values > 8.
b. The elastic properties of the surfactant layer at the interface between the internal and external phases are important in the stabilisation of the emulsion.
c. Anionic surfactants may be used for the stabilisation of emulsions designed for oral administration.
d. Surfactants stabilise emulsions by increasing interfacial Gibb's free energy of the emulsion.

5. Regarding the role of adsorbed particles in the stabilisation of pharmaceutical emulsions, which of the following statements are true?

a. Adsorbed particles promote the formation of oil in water emulsions.
b. Examples of adsorbed particles that are employed pharmaceutically include kaolin.
c. The elastic properties of the adsorbed layer are primarily responsible for the stabilisation of emulsions.
d. The particle size of the adsorbed particles directly affects emulsion stability.

6. Regarding the use of hydrophilic polymers for the stabilisation of pharmaceutical emulsions, which of the following statements are true?

a. Hydrophilic polymers stabilise pharmaceutical emulsions by increasing the viscosity of the continuous phase.
b. Hydrophobic polymers may be employed to stabilise oil in water emulsions.
c. Hydrophilic polymers form a stable monomolecular layer at the interface between the internal and external phases.
d. Pharmaceutical emulsions may exhibit thixotropy.

7. Regarding the preservation of pharmaceutical suspensions for oral administration, which of the following statements are true?

a. Hydrophilic polymers that are present in pharmaceutical emulsions may reduce preservative efficacy.
b. Preservative efficacy may be reduced by partitioning of the preservative from the oil phase to the water phase of water in oil emulsions.
c. Parabens are commonly used as preservatives for emulsions.
d. The preservative efficacy of organic acids in oil in water emulsions may be affected by the type of oil used as the internal phase.

8. Concerning the physical properties of emulsions, which of the following statements are true?

a. Water in oil emulsions conduct electrical current.
b. Water in oil emulsions are more stable than oil in water emulsions.
c. High-speed mixing of water in oil emulsions results in dilatant flow.
d. The particle size distribution of the internal phase may be reduced postmanufacture using a colloid mill.

9. Concerning the use of oil in water emulsions, which of the following statements are true?

a. Oil in water emulsions may be used for the oral administration of therapeutic agents.
b. Oil in water emulsions may be formulated for topical administration.
c. Drugs with high aqueous solubility are frequently formulated as oil in water emulsions.
d. Oil in water emulsions designed for oral administration must be coloured.

10. Concerning the formulation of pharmaceutical emulsions, which of the following statements are true?

a. Emulsions for oral administration may require the addition of sweetening agents.

b. Emulsions for oral administration may require the addition of flavours.

c. Emulsions for oral administration may require the addition of antioxidants.

d. The optimum phase–volume ratio for emulsions is 50:50.

chapter 4

Pharmaceutical disperse systems 3: ointments, pastes, lotions, gels and related formulations

Overview

In this chapter the following points will be discussed:

- an overview/description of the physical properties and uses of ointments, pastes, lotions, liniments, collodions and gels
- formulation strategies for ointments, pastes, lotions, liniments, collodions and gels, including consideration of the excipients used
- the advantages and disadvantages and uses of ointments, pastes, lotions, liniments, collodions and gels
- considerations for the manufacture of ointments, pastes, lotions, liniments, collodions and gels.

Introduction

This chapter deals with the formulation of several types of *disperse* systems, namely ointments, pastes, lotions, liniments, collodions and gels. In the vast majority of cases these formulations contain a therapeutic agent and are designed for the localised treatment of a designated area, e.g. haemorrhoids, infection, inflammation. Whilst the above formulation types may be classified as disperse systems, there are distinct differences in their uses and the strategies utilised in their successful formulation. Accordingly, in this chapter, each dosage form is discussed separately.

KeyPoints

- Ointments, pastes, lotions, liniments, collodions and gels are further examples of disperse systems into which a therapeutic agent may be incorporated.
- Ointments, pastes, lotions, liniments, collodions and gels are topical formulations, being applied externally or into accessible body cavities (e.g. mouth, rectum, vagina).
- These formulations exhibit similar concerns as other disperse systems regarding physical stability.

Advantages and disadvantages of pharmaceutical ointments, pastes, lotions, liniments, collodions and gels

Advantages

- Pharmaceutical ointments may be easily spread on skin, being retained at the site of application as an occlusive layer, thereby preventing moisture loss from the skin. This is particularly useful whenever restoration of the physical characteristics of the skin is required (e.g. due to inflammation).
- Pharmaceutical ointments are associated with lubricating/emollient properties, properties that may be employed to reduce trauma of an affected site upon spreading.
- In general, pharmaceutical ointments persist at the site of application, enabling the duration of drug release to be greater than for many other topical dosage forms. The increased viscosity of pharmaceutical pastes ensures that a thick film of the dosage form is applied to the site of action, which shows excellent persistence. This property is particularly useful if protection of an inflamed site is required, e.g. in eczema, psoriasis.
- The hydrophobicity and retention of pharmaceutical ointments are useful attributes whenever applied to mucosa, e.g. inflamed haemorrhoids, eyelids, where fluid flow/inflammation at these sites would normally serve to remove other formulations (e.g. oil in water creams) by dilution. It should be noted, however, that spreading of ointments on to moist surfaces may be difficult due to the hydrophobic properties of most ointments.
- Due to the high solids content, pharmaceutical pastes are often porous, allowing moisture loss from the applied site. Furthermore, pastes may act to absorb moisture and chemicals within the exudates.
- The opaque nature of pastes (due to the high solids content) enables this formulation to be used as a sunblock.
- The chemical stability of therapeutic agents that are prone to hydrolysis will be dramatically enhanced by formulation within pharmaceutical ointments and pastes.
- Pharmaceutical gels may be formulated to provide excellent spreading properties and will provide a cooling effect due to solvent evaporation. Similarly solvent evaporation from liniments will provide a cooling effect.

Disadvantages

- Pharmaceutical ointments are generally greasy and difficult to remove (and are therefore often cosmetically unacceptable). Similarly, liniments and lotions may also be cosmetically unacceptable to the patient and difficult to use.
- Pharmaceutical pastes are generally applied as a thick layer at the required site and are therefore considered to be cosmetically unacceptable.
- Staining of clothes is often associated with the use of pharmaceutical pastes and ointments.
- The viscosity of pharmaceutical ointments, and in particular pastes, may be problematic in ensuring spreading of the dosage form over the affected site. Conversely, the low viscosity of liniments and lotions may result in application difficulties.
- Pharmaceutical ointments may not be applied to exuding sites (however, please note that this does not hold for pastes). Liniments may not be applied to broken skin.
- Problems concerning drug release from pharmaceutical ointments may occur if the drug has limited solubility in the ointment base.
- Pharmaceutical pastes are generally not applied to the hair due to difficulties associated with removal.
- Therapeutic agents that are prone to hydrolysis should not be formulated into aqueous gels.

Pharmaceutical ointments and pastes

General description

Pharmaceutical ointments (termed *unguents*) are semisolid systems that are applied externally, primarily to the skin and also to mucous membranes, e.g. the rectum, the vagina/vulva, the eye. Typically, medicated ointments are used for the treatment of infection, inflammation and pruritus. However, non-medicated ointments are commonly used due to their emollient/lubricating properties. Pharmaceutical pastes are generally composed of ointment bases that contain a high concentration (frequently $> 50\%$ w/w) of dispersed drug. The viscosity of pharmaceutical pastes is greater than that of pharmaceutical ointments.

Introduction

The formulation of ointments and pastes involves the dispersal or dissolution of the selected therapeutic agent into an *ointment base* and, therefore, in addition to the physical properties of the dispersed/dissolved drug, the physicochemical properties of the ointment base are fundamental to the clinical and non-clinical performance of this type of dosage form. The choice of ointment

base is dependent on several factors, including: (1) the site of application; (2) the required rate of drug release; (3) the chemical stability of the drug; and (4) the effect of the therapeutic agent on formulation viscosity.

The site of application

In certain clinical conditions the site to which the ointment will be applied may be dry, e.g. psoriasis, or moist. If the area is dry, ointments are often used to occlude the site, thereby retaining moisture. Indeed, this effect is considered to play an important role in the treatment of certain clinical conditions. Conversely, occlusive ointment bases are not applied to sites in which there is fluid exudate.

The required rate of drug release

Following application, the therapeutic agent must be released to exert its pharmacological effect, either locally or, after absorption, systemically. Drug release from the ointment base requires solubility (albeit partial) of the therapeutic agent within the formulation. This will allow diffusion of the therapeutic agent (a molecular process) through the ointment base until it reaches the biological substrate. Therefore the choice of the ointment base is partially dictated by the physicochemical properties (and in particular the solubility) of the therapeutic agent.

The chemical stability of the drug

If a therapeutic agent is prone to hydrolysis, incorporation into a water-based formulation, e.g. oil in water creams, may lead to drug degradation and hence a shortened shelf-life. This problem may be obviated by incorporating the drug into a hydrophobic ointment base. For example, the shelf-life of hydrocortisone is markedly greater in an ointment formulation than in an oil in water cream formulation.

The effect of the therapeutic agent on formulation viscosity

The effect of the physical incorporation of a therapeutic agent into an ointment base on the rheological properties of the formulated product will be dependent on the required drug concentration, the physical properties of the therapeutic agent (e.g. particle size, shape) and the chemical composition and viscosity of the ointment base. Therefore, it is important that an ointment base is selected that will produce a product that may be readily applied to the required site. In light of the high drug content, this point is particularly important in the formulation of pastes.

Types of base for ointments and pastes

There are four types of base that are used to formulate pharmaceutical ointments and pastes: (1) hydrocarbon; (2) absorption; (3) water-miscible/removable; and (4) water-soluble.

Hydrocarbon bases

Hydrocarbon bases are non-aqueous formulations, based on various paraffins, that have the following properties:

- emollient, thereby restricting water loss from the site of application due to the formation of an occlusive film
- excellent retention on the skin
- predominantly hydrophobic, and therefore difficult to remove from the skin by washing and difficult to apply to (spread over) wet surfaces (e.g. mucous membranes, wet skin)
- only a low concentration (< 5%) of water may be incorporated into hydrocarbon bases (with careful mixing)
- chemically inert.

Hydrocarbon bases frequently contain the following components: (1) hard paraffin; (2) white/yellow soft paraffin; (3) liquid paraffin (mineral oil); and (4) microcrystalline wax.

Hard paraffin

This is a mixture of solid saturated hydrocarbons that are derived from petroleum or shale oil. Hard paraffin is a colourless or white wax-like material that is physically composed of a mixture of microcrystals. The melting temperature of hard paraffin is between 47 and 65°C and, when solid, it is used to enhance the rheological properties of ointment bases.

White/yellow soft paraffin

This is a purified mixture of semisolid hydrocarbons (containing branched, linear and cyclic chains) that are derived from petroleum. White/yellow soft paraffin consists of microcrystals embedded in a gel composed of liquid and amorphous hydrocarbons that are themselves dispersed in a gel phase containing liquid and amorphous hydrocarbons. The melting range of the soft paraffins is between 38 and 60°C. White soft paraffin and yellow soft paraffin (the former being a bleached form of yellow soft paraffin) may be used as an ointment base without the need for additional components, although it may be combined with liquid paraffin (see below)

Liquid paraffin (mineral oil)

This is a mixture of saturated aliphatic (C_{14}–C_{18}) and cyclic hydrocarbons that have been refined from petroleum. It is usually formulated with white/yellow soft paraffin to achieve the required viscosity for application to the required site.

Formulations containing liquid paraffin require the incorporation of an antioxidant due to the ability of this material to undergo oxidation.

Microcrystalline wax

This is a solid mixture of saturated alkanes (both linear and branched) with a defined range of carbon chain lengths (C_{41}–C_{57}). This excipient is used to enhance the viscosity of ointments (and creams). One of the advantages of microcrystalline wax is the greater physical stability provided to formulations containing liquid paraffin (reduced bleeding of the liquid component).

Absorption bases

Unlike hydrocarbon bases, absorption bases may be formulated to contain significant amounts of an aqueous phase. These may be either non-aqueous formulations to which an aqueous phase may be added to produce a water in oil emulsion (termed *non-emulsified bases*) or *water in oil emulsions* that can facilitate the incorporation of an aqueous phase (without phase inversion or cracking). Although absorption bases can accommodate a larger volume of aqueous phase than hydrophobic bases, they are still difficult to remove from the site of application by washing. This is due to the predominantly hydrophobic properties of this formulation class.

The key properties of both non-emulsified bases and water in oil emulsions that are relevant to the formulation of ointments and pastes are detailed below.

Non-emulsified bases

These are hydrophobic formulations to which water may be added. Following application, a film is formed that offers occlusion (and hence emollient properties); however, the extent of occlusion is less than for hydrocarbon bases. The spreading properties of these formulations are more favourable than for hydrocarbon bases.

Typically non-emulsified bases are commonly composed of: (1) one or more paraffins (see previous section) and (2) a sterol-based emulsifying agent. Examples of the types of emulsifying agents used in absorption bases include: (1) lanolin (wool fat); (2) lanolin alcohols (wool alcohols); and (3) beeswax (white or yellow).

Lanolin (wool fat)

Lanolin is a wax-like material that is derived from sheep's wool. It is available in two forms, termed lanolin (wool fat) and hydrous lanolin (wool alcohols). Lanolin is typically mixed with vegetable oils or paraffins to produce an ointment base that can absorb

approximately twice its own weight of water to produce water in oil emulsions. The usual concentrations of lanolin used in ointments (e.g. Simple Ointment BP) range from 5 to 10% w/w.

Lanolin alcohols (wool alcohols)

As detailed in Chapter 3, wool alcohol is a crude mixture of sterols and triterpene alcohols and contains at least 30% cholesterol and 10–13% isocholesterol. This is added to mixtures of paraffins (hard, so white/yellow soft or liquid) to produce the required consistency. The inclusion of wool alcohols (5% w/w) results in a 300% increase in the concentration of water that may be incorporated into paraffin bases.

Beeswax (white or yellow)

Beeswax is a wax that consists of esters of aliphatic alcohols (C_{24}–C_{36} even numbers) and linear aliphatic fatty acids (up to C_{36}, even numbers) that is combined with paraffins to produce non-emulsified bases. White beeswax is the bleached form of yellow beeswax.

Water in oil emulsions

Ointment bases in this category can accommodate a greater concentration of water but yet can still provide similar performance to that provided by non-emulsified bases with respect to, e.g. occlusion, spreading properties. A common excipient that is employed in the formulation of this type of ointment base is *hydrous lanolin*, which is a mixture of lanolin and circa 25–30% water. It is incorporated into paraffins and oils to produce a base that can incorporate the subsequent addition of an aqueous phase. The water content of bases that have been formulated using hydrous lanolin is significant, e.g. Oily Cream BP is a water in oil emulsion ointment base that is composed of wool alcohols (50% w/w) and water (50% w/w).

Water-miscible/removable bases

These are water-miscible bases that are used to form oil in water emulsions for topical applications. The use of these bases offers a number of advantages, including:

- They are able to accommodate large volumes of water, e.g. aqueous solutions of drug, excess moisture at the site of application, e.g. exudate from abrasions and wounds.
- They are not occlusive.
- They may be easily washed from the skin and from clothing. Furthermore, they may be readily applied to (and removed from) hair.
- They are aesthetically pleasing.

The British Pharmacopoeia describes three water-miscible/removable bases:

1. emulsifying ointment
2. cetrimide emulsifying ointment
3. cetomacrogol emulsifying ointment.

Each of these contains:
liquid paraffin 20% w/w
white soft paraffin 50% w/w
anionic, cationic or non-ionic emulsifying wax 30% w/w.
As may be observed, an important component of this ointment base is emulsifying wax, of which there are three types: (1) anionic; (2) non-ionic; and (3) cationic. The important properties of these waxes are as follows:

Anionic emulsifying wax

- This is a waxy solid that, when incorporated into a paraffin base, may be used to produce an oil in water emulsion, e.g. Aqueous Cream BP (which contains 10% w/w anionic emulsifying wax).
- Anionic emulsifying wax is composed of:
  cetostearyl alcohol 90 g
  sodium lauryl sulphate 10 g
  purified water 4 ml.

Non-ionic emulsifying wax

- This is also referred to as *Cetomacrogol Emulsifying Wax BP* and is composed of:
  cetostearyl alcohol 800 g
  cetomacrogol 1000 (macrogol cetostearyl ether 22) 200 g.

Cationic emulsifying wax

- This is also referred to as *Cetrimide Emulsifying Wax BP.*
- Cationic Emulsifying Wax BP is composed of:
  cetostearyl alcohol 900 g
  cetrimide 100 g.

Water-soluble bases

The reader will have observed that the three previous ointment bases are predominantly hydrophobic, are hydrophobic with added surface-active agents or are water-miscible, containing both water-soluble and insoluble components. In contrast, water-soluble bases are composed entirely of water-soluble ingredients.

The advantages of the use of these bases include:

- They are non-greasy and may be easily removed by washing.
- They are miscible with exudates from inflamed sites.
- They are generally compatible with the vast majority of therapeutic agents.

Water-soluble bases are predominantly prepared using mixtures of different molecular weights of polyethylene glycol (Figure 4.1) to produce the required ointment consistency. Lower average molecular weights of this polymer (200, 400 and 600 g/mol) are liquids. As the average molecular weight increases, the consistency of this polymer changes from a liquid to a waxy solid (≥ 1000 g/mol).

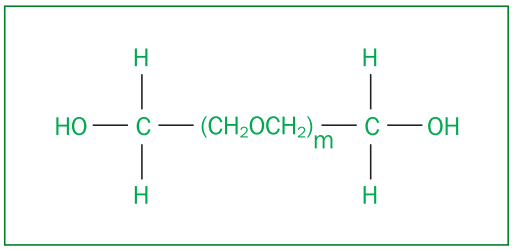


Figure 4.1 Structural formula of polyethylene glycol (m refers to the number of repeating ethylene oxide groups).

Blends of 60% w/w polyethylene glycol 400 (a liquid) and 40% w/w polyethylene glycol 4000 (a solid) have been used as a water-soluble ointment base. If required, the consistency may be increased by lowering the ratio of polyethylene glycol 400 to polyethylene glycol 4000 in the ointment base. Blending the two polyethylene glycol fractions is performed by heating the mixture followed by cooling of the homogeneous liquid at a controlled rate.

The main disadvantage associated with water-soluble bases is their inability to incorporate large volumes of aqueous solutions as these will soften and, if the concentration of water is large enough (> 5% w/w), dissolve the ointment base. Therefore the use of these bases is usually reserved for the incorporation of solid therapeutic agents. However, these bases may incorporate up to 25% of an aqueous solution if a portion of the lower-molecular-weight polyethylene glycol is replaced with stearyl alcohol. This will enhance the mechanical properties of the ointment.

Miscellaneous excipients used in the formulation of ointments and pastes

This chapter has described various strategies for the formulation of bases for ointment and paste formulations. In these the therapeutic agent may be directly incorporated as a solid component or, in the case of the absorption and water-miscible bases, the addition may be in the form of a solution. This solution may be aqueous, alcoholic (e.g. propylene glycol, glycerol) or hydroalcoholic and must not adversely affect the physical stability and/or appearance of the formulated product.

Tips

The choice of ointment base employed in the formulation of ointments is dependent on the proposed use of the dosage form and other formulation factors, e.g. stability of the therapeutic agent and the capacity of the formulation for water.

The properties of ointment bases range from highly hydrophobic (e.g. hydrocarbon bases) to water-miscible systems.

Hydrophobic ointment bases should not be applied to exuding areas due to poor water uptake capacity of these dosage forms. Conversely, ointments prepared using water-miscible bases may be applied to such sites.

Other excipients may be included in ointments and pastes, including: (1) additional/alternative solvents; (2) preservatives; and (3) antioxidants.

Additional/alternative solvents

These are hydrophobic liquid components that may be added to ointment bases (predominantly hydrophobic or absorption bases). Examples of these include: (1) liquid silicone; (2) vegetable oils; and (3) organic esters.

Liquid silicone (polydimethylsiloxane)

This may be used in barrier ointments due to the water-repellent properties of this component.

Vegetable oils

Vegetable oils may be used either to replace mineral oils or, alternatively, may be added to hydrophobic or absorption bases to increase the emollient properties of the formulated product. Examples of oils that are used for this purpose are coconut oil and arachis oil.

Organic esters

These may be used partly to replace a mineral oil to enhance the spreadability and to enhance drug dissolution within the ointment base. One of the most commonly used examples is isopropyl myristate.

Preservatives

Topically applied ointments and pastes are not sterile products; however, they are manufactured under clean conditions to minimise the microbial bioburden within the formulated product. Ointments/pastes that do not contain water do not usually require the addition of a preservative (due to the low water activity in the formulation). However if the product contains water, then a preservative will be required. Preservatives that may be used in formulations designed for external use include:

- phenolics: phenol (0.2–0.5%), chlorocresol (0.075–0.12%)
- benzoic acid and salts (0.1–0.3%)
- methylparabens (methylparahydroxybenzoic acid) (0.02–0.3%)
- propylparabens (methylparahydroxybenzoic acid) (0.02–0.3%) (and their mixtures)
- benzyl alcohol (≤ 3.0%)
- phenoxyethanol (0.5–1.0%) (Figure 4.2).
- bronopol (0.01–0.1%, usually 0.02%) (Figure 4.3).

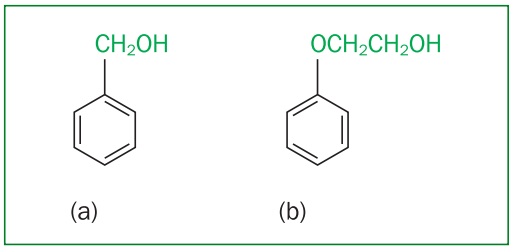


Figure 4.2 Structural formulae of (a) benzyl alcohol and (b) phenoxyethanol.

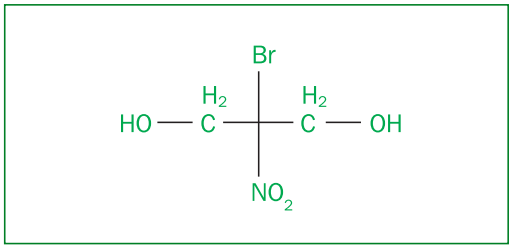


Figure 4.3 Structural formula of bronopol.

In the preservation of ointments, the same physicochemical and microbiological principles exist and therefore partitioning of the preservative from the aqueous to the non-aqueous phase may occur. Under these circumstances it is important to ensure that the required concentration (≥ minimum inhibitory concentration) of the antimicrobial species is present within the aqueous phase.

Antioxidants

The use of antioxidants has been described in previous chapters. In pharmaceutical ointments antioxidants are employed to prevent or reduce oxidation of either the non-aqueous components of the ointment base (e.g. mineral/vegetable oils) and/or the therapeutic agent. The types of preservatives used for this purpose include:

- lipophilic antioxidants (to be dissolved within the non-aqueous vehicle), e.g. butylated hydroxyanisole (0.005–0.02%), butylated hydroxytoluene (0.007–0.1%), propyl gallate (≤ 1%)
- hydrophilic antioxidants (to be dissolved in the aqueous phase), e.g. sodium metabisulphate (0.01–0.1%), sodium sulphite (0.1%).

Tips

Ointments, similar to emulsions and creams, contain a range of excipients that are required to stabilise the formulation.

The formulator must ensure that no interactions occur between the excipients.

The use of pastes is generally reserved for certain topical conditions, e.g. the treatment of warts.

Manufacture of ointments and pastes

The manufacture of ointments and pastes is similar to that described for emulsions and creams. The most straightforward example involves the dispersal of the powdered therapeutic agent into the preheated hydrocarbon base using a mechanical mixer.

Heat is required to lower the viscosity of the base, thereby facilitating the mixing of the solid drug.

If the therapeutic agent is incorporated into the ointment base as a separate liquid phase, the hydrophobic components and hydrophilic components are separately dissolved in the lipophilic and hydrophilic liquid phases, respectively (again with the aid of heating and mechanical mixing). In general (following dissolution of the various components), the two phases are maintained at circa 70°C and then mixed together (with stirring). The mixing of the two phases may be performed by:

- mixing the two phases simultaneously
- adding the aqueous phase to the non-aqueous phase.

Following complete mixing, the temperature of the formulation is gradually reduced to room temperature.

Pharmaceutical lotions, liniments, collodions and paints

General description

Pharmaceutical lotions, liniments, collodions and paints are external, liquid-based formulations that are applied externally for the treatment of local conditions, e.g. inflammation, acne, infection (bacterial, fungal, viral and parasitic). Although the clinical use of these classes of formulation is relatively minor, they still represent a formulation option to the pharmaceutical scientist.

Lotions

Lotions are formulated either as solutions or suspensions and, in addition to the therapeutic agent(s), may contain:

- *alcohol*: this acts as a coolant (due to evaporation following application) and as a co-solvent.
- *humectants*: these act to retain moisture on the skin after application. The most commonly used example is glycerol.
- *vehicle*: lotions are aqueous formulations and therefore will contain *purified water* (with or without the addition of buffer salts).
- *preservatives*: examples of these have been described previously in this chapter.
- *components to stabilise the suspended therapeutic agent*: if the lotion has been formulated as a suspension, agents are required to maintain the physical stability of the formulation (see Chapter 2).

Liniments

Liniments are alcohol- or oil-based solutions that are applied externally to unbroken skin with gentle rubbing. There are two

types of formulation bases that are used in the formulation of liniments: (1) alcohol-based liniments; and (2) oil-based liniments. Alcohol-based liniments act as counterirritants and rubefacients (causing reddening of the skin) and may act to increase the penetration of the drug through the skin. In addition, these formulations will provide a cooling effect due to evaporation of the alcohol base. Conversely, oil-based liniments are employed for conditions in which a massage effect is required. Typical oils used for this purpose are arachis oil and cottonseed oil.

Liniments are normally employed for the treatment of inflammatory conditions, e.g. sciatica, fibrositis and neuralgia. Examples of oil-based liniments include Camphor Liniment BP and Methyl Salicylate Liniment BP. Soap Liniment BPC is an example of an alcohol-based liniment.

In general, no other excipients are used in the formulation of liniments.

Collodions

Collodions are solutions of pyroxylin (a nitrated cellulose, predominantly cellulose tetranitrate, that is obtained following the treatment of defatted cellulose with nitric and sulphuric acids), castor oil and colophony dissolved in an organic solvent (composed of alcohol and ether). These are normally applied to dry skin using a brush applicator and, following the evaporation of the solvent, will form an occlusive film. Collodions may contain therapeutic agents, e.g. colliodion and salicylic acid collodion.

Collodion

This is a solution of pyroxylin in a solvent composed of ether (3 parts) and alcohol (1 part). This forms an inflexible, mechanically strong film on the skin and is normally used to seal abrasions. The film may be rendered more flexible by adding 2% camphor and 3% castor oil to the above formulation (termed flexible collodion). The oil acts as a plasticiser (thereby facilitating the use of the product over flexible areas) whereas the presence of camphor renders the films waterproof.

Salicylic acid collodion

This is a solution of salicylic acid (10%) in flexible collodion that is used for the treatment of warts.

Paints

These are aqueous, hydroalcoholic, alcoholic or organic solutions of a therapeutic agent that are applied topically. The use of paints nowadays is limited due to the emergence of more elegant dosage forms.

Pharmaceutical gels

General description

Pharmaceutical gels are semisolid systems in which there is interaction (either physical or covalent) between colloidal particles within a liquid vehicle. The vehicle is continuous and interacts with the colloidal particles within the three-dimensional network that is formed by the bonds formed between adjacent particles. The vehicle may be aqueous, hydroalcoholic, alcohol-based or non-aqueous. The colloidal particles may be dispersed solids, e.g. kaolin, bentonite or, alternatively, dispersed polymers. *Xerogels* are gels in which the vehicle has been removed, leaving a polymer network, e.g. polymer films.

There are two main categories of pharmaceutical gels, based on the nature of the three-dimensional network of particles: (1) dispersed solids and (2) hydrophilic polymers.

Gels based on dispersed solids

As discussed in Chapter 2, under certain conditions dispersed solids will undergo flocculation. If flocculation extends throughout the system a continuous solid particle network is established, with the liquid vehicle dispersed in the void volume between the particles. The nature of the interaction between the particles in the network may be van der Waals interactions (at the secondary minimum), e.g. *Aluminium Hydroxide Gel USP*. However, for certain dispersed solids the nature of the interaction is electrostatic bonding. Examples of the particles that exhibit this type of interaction include kaolin, bentonite and aluminium magnesium silicate. The particles exhibit a plate-like crystal structure in which there are electronegative regions along the flat face of the crystal (due to O^-) and electropositive regions (due to the ionised aluminium and magnesium ions) at the edges of the plates. The interaction of these two regions facilitates the establishment of a structured 'house of cards'-type particle network. The bond strength between the particles is weak: interparticle bonds are broken by the application of relatively low shearing stresses (such as those that occur whenever the product is shaken), thereby liberating the individual particles. Following removal of the stress the bonds between the particles will reform and hence the rheological structure of these systems is recovered. This time-dependent recovery of the rheological structure (that was lost upon shaking) is termed *thixotropy*.

Gels based on hydrophilic polymers

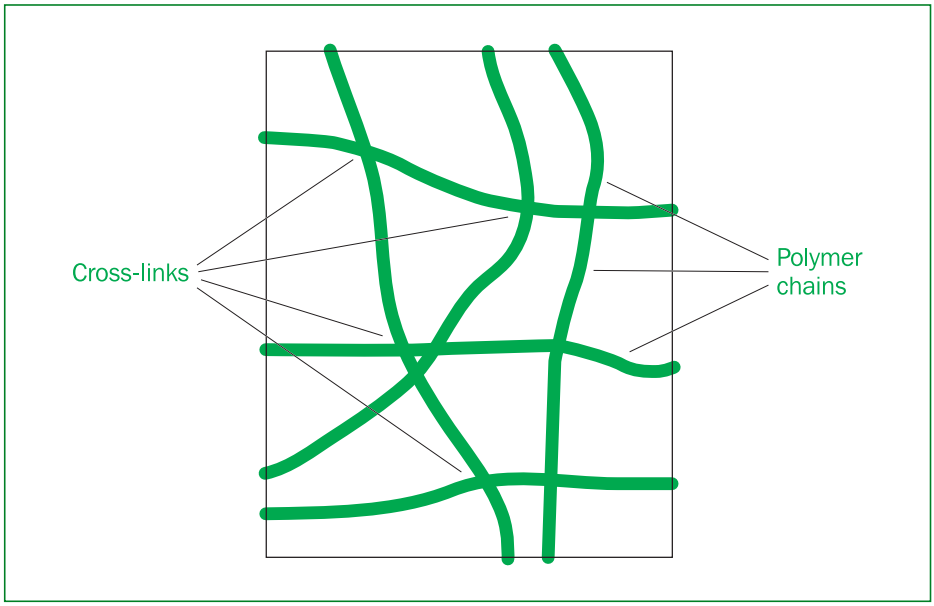
Pharmaceutical gels are most commonly (but not exclusively) manufactured by dispersing hydrophilic polymers within an appropriate aqueous vehicle. When dissolved within an aqueous

phase, hydrophilic polymers behave as lyophilic colloids and their unique physical properties result from the self-association of the dissolved polymer and its interaction with the aqueous medium. There are two types of self-association (termed irreversible and reversible) that may be demonstrated by lyophilic colloids and this allows gels that are manufactured from lyophilic colloids to be classified as either type 1 or type 2 gels.

Type 1 gels

In type 1 gels (often termed *hydrogels*) the interaction between the polymer chains is covalent and is mediated by molecules that cross-link the adjacent chains (termed cross-linkers). A diagrammatic representation of the covalent interactions within a type 1 (chemical) is shown in Figure 4.4.

Figure 4.4 Diagrammatic representation of polymer–polymer interactions within a type 1 (chemical) gel.

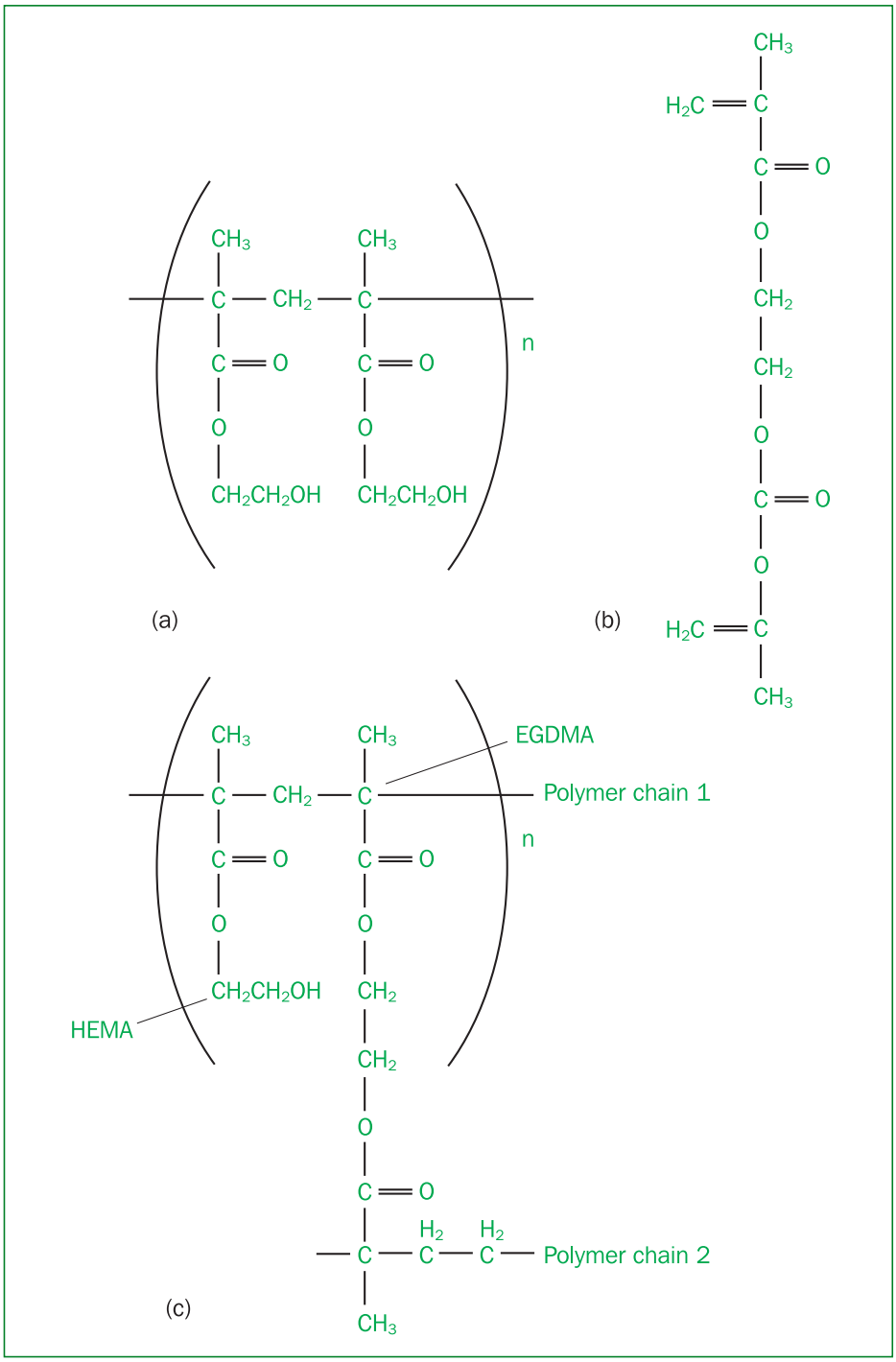


An example of the chemical structures of a cross-linked hydrogel and the monomer (hydroxyethylmethacrylate) and cross-linker (ethyleneglycol dimethacrylate) used in the synthesis of the hydrogel is provided in Figure 4.5 below. In this diagram the points of intersection of the polymer chains are covalent cross-links.

These gels exhibit unique physicochemical properties, including:

- The ability to absorb a considerable mass of aqueous fluid (often 100 times the original mass) whilst still retaining a three-dimensional structure.
- Hydrogels exhibit robust mechanical properties, being resistant to fracture following exposure to stresses frequently up to 1 kPa. Moreover, hydrogels exhibit excellent flexibility.

Figure 4.5 Structural formula of (a) hydroxyethylmethacrylate, (b) ethyleneglycol dimethacrylate and (c) poly(hydroxyethylmethacrylate) that has been cross-linked using ethyleneglycol dimethacrylate.



Conversely, xerogels (hydrogels from which the aqueous phase has been removed by drying) are brittle. In this case the absorbed solvent acts as a plasticiser. Unlike type 2 gels (see below), type 1 gels do not exhibit flow when exposed to an applied stress due to the inability of the stress to overcome

(destroy) the covalent bonds. Under these conditions, the elastic properties of type 1 gels enable the applied energy to be stored and utilised (after the stress is removed) to return the polymer chains to their equilibrium position.

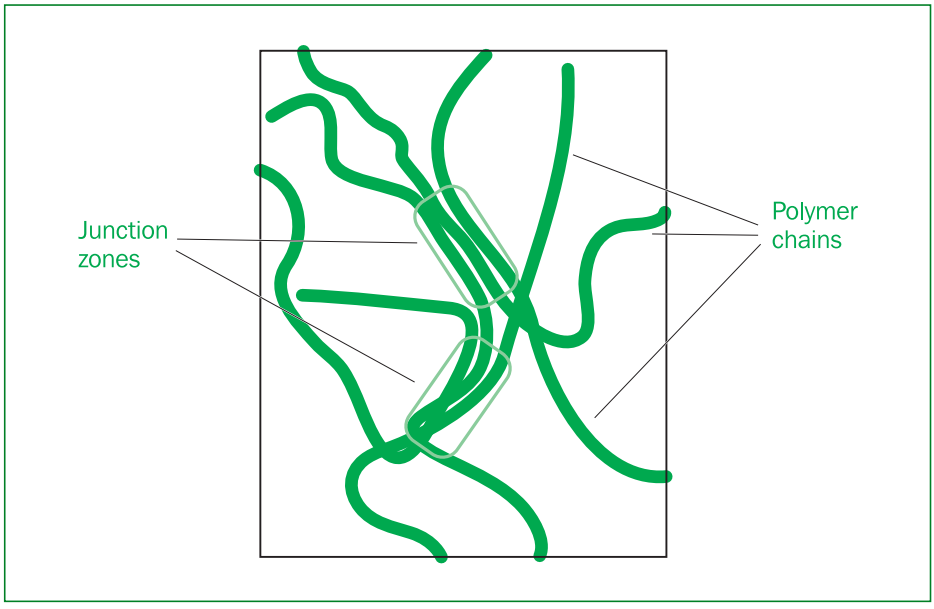
Due to this ability to absorb a large mass of fluid (whilst retaining their mechanical properties), hydrogels are clinically used as wound dressings, as lubricious coatings on urethral catheters and as soft contact lenses. In addition, hydrogels may be used for the controlled delivery of therapeutic agents at the site of implantation.

Type 2 gels

In type 2 gels the interactions between the polymer chains are reversible and are facilitated by weaker bonds, e.g. hydrogen bonding, ionic association or van der Waals interactions. The application of stresses to type 2 gels will end in the temporary destruction of these bonds, thereby enabling the formulation to flow. As a result, type 2 gels are rheologically referred to as *pseudoplastic (shear-thinning)* systems. Following the removal of the stress, the intermacromolecular bonds are reformed and the viscosity of the formulation returns to its equilibrium value.

A diagrammatic representation of the interactions that occur in type 2 (physical) gels is shown in Figure 4.6. As may be observed, the areas where adjacent polymer chains interact are referred to as junction zones and, in practice, a substantial fraction of the polymer is involved in polymer–polymer interactions at these zones.

Figure 4.6 Diagrammatic representation of the interactions between polymer chains in a type 2 gel.



The overwhelming majority of pharmaceutical gels are type 2 gels and typically the following polymers are employed in the formulation of these systems: (1) cellulose derivatives; (2) polysaccharides derived from natural sources; and (3) polyacrylic acid.

Cellulose derivatives

The cellulose derivatives represent a family of chemically related polysaccharides that are structurally derived from cellulose (following the appropriate chemical substitution). The most commonly used examples from this series that are used to formulate pharmaceutical gels include:

- methylcellulose
- hydroxyethylcellulose
- hydroxypropylcellulose
- sodium carboxymethylcellulose.

The structural formulae of these polymers are presented in Figure 4.7.

Polysaccharides derived from natural sources

Polysaccharides that have been derived from natural sources are commonly used as the basis for pharmaceutical gels. Examples of these include: (1) carrageenan; and (2) alginic acid/sodium alginate.

Carrageenan

This is a family of polysaccharides that is derived from red seaweed. There are three chemically related carrageenans, termed lambda, iota and kappa which differ according to the location of sulphate groups and the presence or absence of anhydrogalactose. Kappa carrageenan exhibits excellent gelling properties (due to the presence of a tertiary helical structure); iota carrageenan (but not lambda carrageenan) also displays gelling (albeit weaker) properties. The typical range of concentrations of kappa carrageenan used to form pharmaceutical gels is 0.3–1.0% w/w.

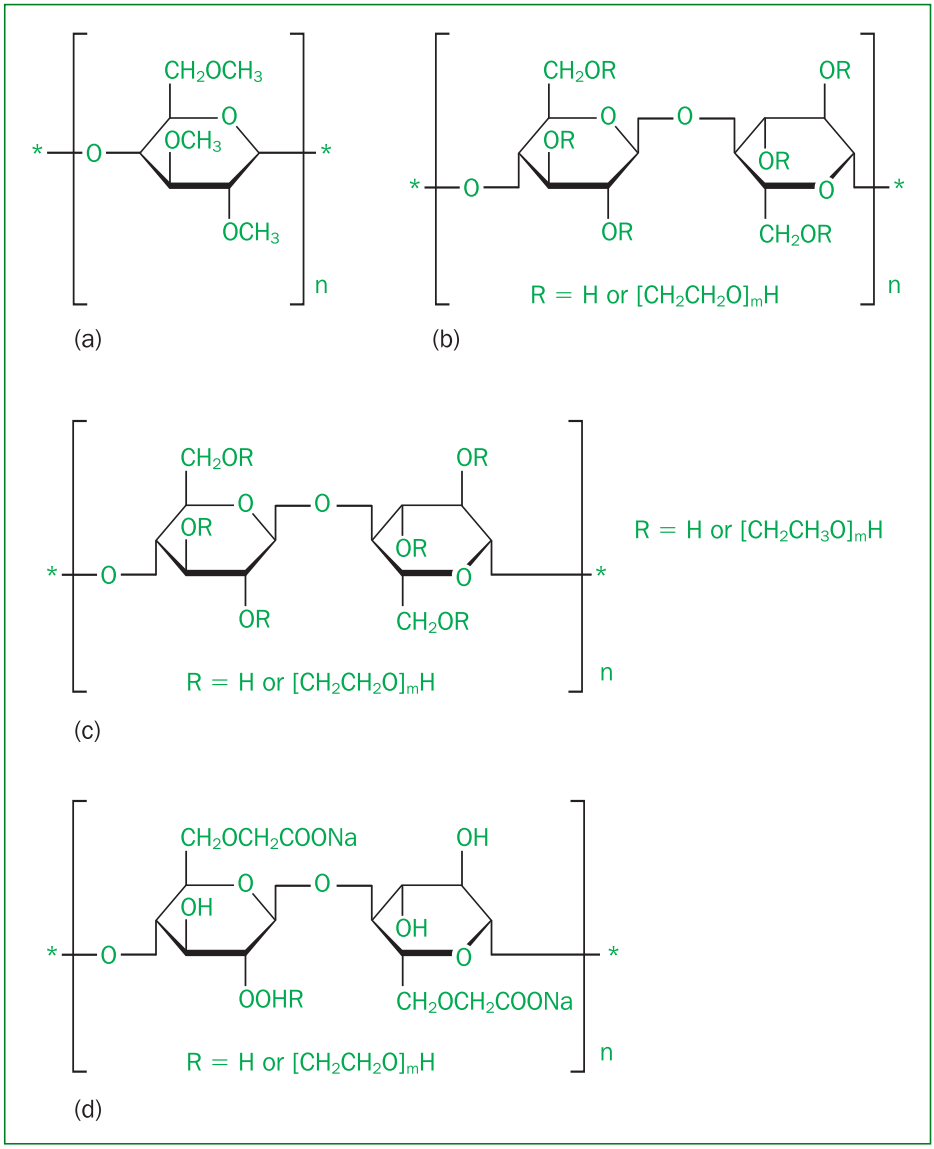
Alginic acid/sodium alginate

Alginic acid is a polysaccharide that is derived from algae (Phaecophyceae family). Addition of calcium ions to a solution of alginic acid will result in an electrostatic interaction, producing a viscous gel at low concentrations of calcium and a cross-linked polymer at higher concentrations. Alginic acid is incompatible with basic drug molecules.

Poly(acrylic acid)

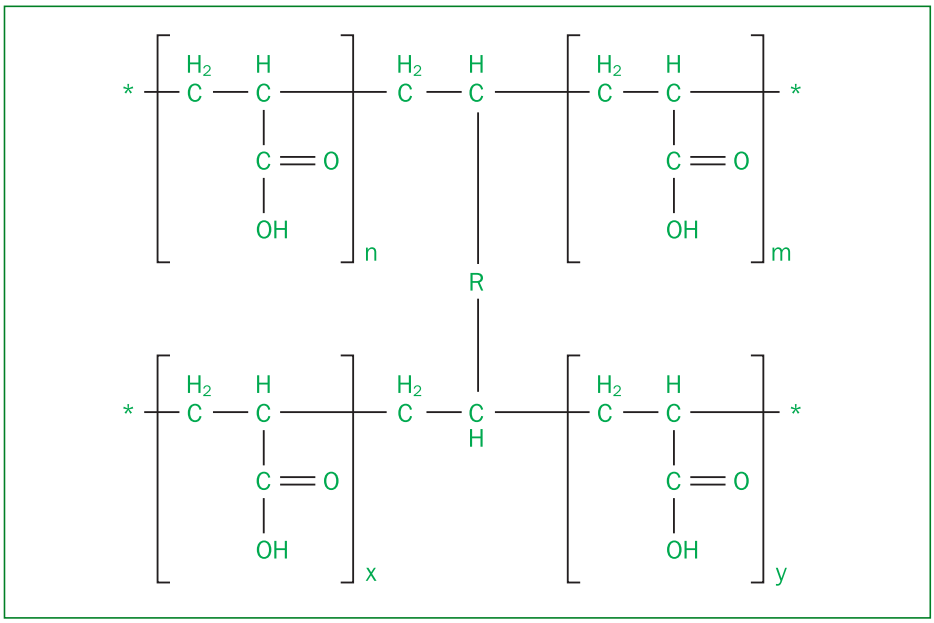
Poly(acrylic acid) (Figure 4.8) is a synthetic polymer that is produced following the polymerisation of acrylic acid and cross-linking with either allyl sucrose or allyl ethers of pentaerythritol.

Figure 4.7 Structural formulae of cellulose derivatives commonly used to formulate pharmaceutical gels. (a) Methylcellulose; (b) hydroxyethylcellulose; (c) hydroxypropylcellulose; (d) sodium carboxymethylcellulose. Typically concentrations within the range of 1–10% w/w are required to produce pharmaceutical gels.



In water polyacrylic acid exists as aggregated (coiled) colloidal particles of minimal viscosity (pH circa 3). However, if the pH of the system is neutralised by the addition of an appropriate base, e.g. triethanolamine, triethylamine or sodium hydroxide, the pendant carboxyl groups will ionise, resulting in expansion of the polymer chains due to repulsion of the adjacent ionised groups. In so doing the viscosity of the formulation is dramatically increased. Typically pharmaceutical gels are produced using 0.5–2.0% w/w poly(acrylic acid) that has been neutralised with an appropriate base. Incompatibilities exist between poly(acrylic acid) and basic therapeutic agents.

Figure 4.8 Structural formula of poly(acrylic acid). R refers to allylsucrose or pentaerythritol. The subscripts refer to a number of repeating units of acrylic acid that reside between the cross-links.



Furthermore, the viscosity of gels prepared using poly(acrylic acid) is adversely affected by medium/high concentrations of electrolytes.

Factors affecting gelation of type 2 gels

Gelation in type 2 gels occurs whenever a sufficient number of polymer–polymer interactions (junction zones) occur. However, both the mechanism of gelation and the number (frequency) of interactions are affected by physicochemical and environmental factors, as outlined below.

Concentration of hydrophilic polymer

At low concentrations, solutions of hydrophilic polymers exhibit Newtonian flow due to the limited number of polymer–polymer interactions. As the concentration of polymer increases, the number of polymer–polymer interactions increases and eventually, at a defined polymer concentration, the flow properties of these systems become non-Newtonian (termed the gel point). Further increases in the concentration of polymer lead to an increase in the number of junction zones and hence the resistance to deformation from an applied stress (the viscosity) increases. Therefore, the physicochemical and rheological properties of a pharmaceutical gel may be readily manipulated by altering the concentration of hydrophilic polymer.

Molecular weight of the polymer

As the molecular weight of the hydrophilic polymer increases (at a defined concentration of polymer), there are a greater number of available sites on the polymer chains that may engage in polymer–polymer interactions. As a result the viscosity of the formulation increases.

Nature of the solvent

In solvents that are described as 'good solvents', the chains of a polymer will exist in the expanded state. Conversely, in the presence of a poor solvent, the polymer chains will exist in a non-expanded (coiled) state. The viscosity of a polymer solution is dependent on the expansion of the polymer chains. Therefore, the concentration of polymer that results in gel formation and the physicochemical (rheological) properties of the gel are dependent on the solvent system into which the hydrophilic polymer is dissolved. In poor solvents gelation will not occur.

pH of the solvent

As previously discussed in this chapter, the pH of the solvent directly affects the ionisation of acidic or basic polymers which, in turn, affects the conformation (expansion) of the polymer chains. In the non-ionised state acidic and basic polymers exist in a coiled (non-expanded) state and gelation does not occur. The rheological properties of ionic polymers are optimal with a range of pH values at which maximum expansion of the polymer chains occurs. The rheological properties of non-ionic polymers are unaffected by the pH of the solvent, usually over a large pH range (circa 4–10).

Ionic strength of the solvent phase

The rheological properties of both non-ionic and (in particular) ionic polymers are affected by the ionic strength of the solvent. At high concentrations of electrolytes (and hence large ionic strength), non-ionic polymers may be 'salted out' of solution due to desolvation of the polymer chains. Conversely, at lower concentrations of electrolyte, shielding of the charge on the pendant groups of the ionic polymer by a counterion will occur. This will therefore reduce the capacity of the polymer to interact with the solvent and hence the rheological properties of the gel will be compromised. If the concentration of electrolyte is sufficiently large, salting out of the ionic polymer will result.

Temperature

Certain hydrophilic polymers may undergo a thermally induced transition that results in an increase in the rheological properties. Two examples of this are solutions of methylcellulose and

hydroxypropylcellulose which have been reported to undergo gelation at elevated temperatures (circa 50–60°C). Whilst this transition has limited biological relevance, one polymer system, poly(oxyethylene)-poly(oxypropylene) block co-polymers (the Pluronic or Synperonic series) undergoes a thermal transition within a biologically useful temperature range (< 37°C). At temperatures below this (sol–gel) transition temperature ($T_{sol/gel}$), solutions of this polymer exhibit Newtonian flow and low viscosity (the sol state). Conversely, above $T_{sol/gel}$ the polymer sol is converted into a gel with pronounced elasticity and viscosity. In solution at temperatures below $T_{sol/gel}$ and above the critical micelle concentration, the polymer exists in the micellar state. Elevation of the temperature (to above the $T_{sol/gel}$) results in the further production of micelles and (close) intermicellar aggregation. This results in a gel of pronounced rheological structure. Lowering the temperature of the system to below the $T_{sol/gel}$ will result in deaggregation of the micelles and the re-emergence of the sol (low-viscosity) state. The ability to modulate the rheological structure of these gels in the manner described has led to an interest in their use as drug delivery systems within the oral cavity and rectum.

Ionic gelation

Certain hydrophilic polymers may undergo gelation in the presence of inorganic metal ions. Examples of these include:

- The gelation of polyhydroxypolymers, e.g. poly(vinyl alcohol) may occur in the presence of suitable anions, e.g. borate, permanganate. Poly(vinyl alcohol) is known to form structured gels in the presence of borate anions. The mechanism of the interaction between the polymer and borate anions is shown in Figure 4.9. The gels formed by this mechanism exhibit excellent mechanical strength, due to the borate anion-mediated cross-links. A non-pharmaceutical application of this interaction is the children's toy Kids Slime.
- As highlighted previously, gelation of alginic acid occurs in the presence of positively charged di/trivalent ions, e.g. Mg^{2+}, Ca^{2+}, Al^{3+}.

Formulation considerations for pharmaceutical gels

There are several formulation considerations open to the pharmaceutical scientist concerning the formulation of pharmaceutical gels. These include: (1) the choice of vehicle; (2) the inclusion of buffers; (3) preservatives; (4) antioxidants; (5) flavours/sweetening agents; and (6) colours.

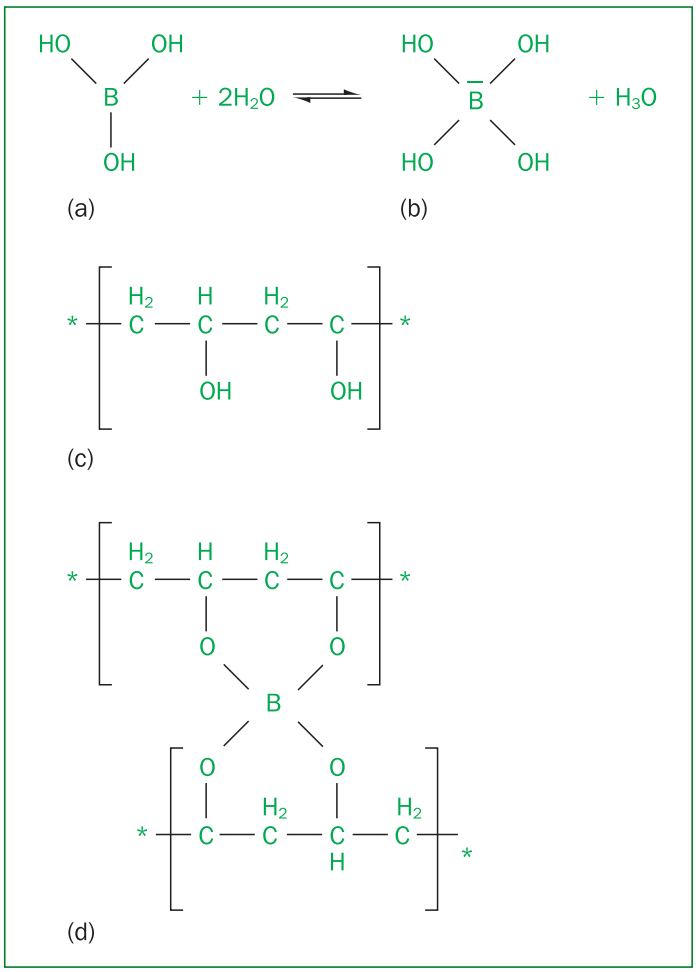


Figure 4.9 Diagrammatic representation of the interaction between borate anions and poly(vinyl alcohol) that leads to gel formation. (a) Boric acid; (b) borate anion; (c) poly(vinyl alcohol); (d) the interaction between poly(vinyl alcohol) and borate anions.

The choice of vehicle

Purified water is the normal solvent/vehicle used in the formulation of pharmaceutical gels. However, co-solvents may be used, e.g. alcohol, propylene glycol, glycerol, polyethylene glycol (usually polyethylene glycol 400) to enhance the solubility of the therapeutic agent in the dosage form and/or (in the case of ethanol) to enhance drug permeation across the skin.

If the drug has poor chemical stability and/or poor solubility in water or water-based vehicles, pharmaceutical gels may be formulated using polyhydroxy solvents, e.g. propylene glycol, glycerol, polyethylene glycol 400 and polyacidic polymers, e.g. poly(acrylic acid). In these systems gelation is facilitated by hydrogen bonding between the hydroxyl and carboxylic acid groups and this results in: (1) expansion of the pendant groups on the polymer chain and (2) non-covalent cross-linking of adjacent polymer chains.

Tips

The main difference between type 1 and type 2 gels is the nature of the cross-links between adjacent polymer chains. In type 1 gels the cross-links are covalent, whereas in type 2 gels the cross-links are non-covalent (secondary).

The vast majority of gels used as dosage forms are type 2. The use of type 1 gels is reserved for wound dressings.

The commonly used polymers for the formulation of type 2 gels are cellulose derivatives, alginates and poly(acrylic acid). Gels are normally formed by increasing polymer concentration and, if the polymer is ionic, by altering the pH.

The inclusion of buffers

As in other pharmaceutical formulations, buffers (e.g. phosphate, citrate) may be included in aqueous and hydroalcoholic-based gels to control the pH of the formulation. It should be noted that the solubility of buffer salts is decreased in hydroalcoholic-based vehicles.

Preservatives

Pharmaceutical gels require the inclusion of preservatives and, in general, the choice of preservatives is similar to that described for ointments and pastes in the early sections of this chapter. It should be remembered that certain preservatives, e.g. parabens, phenolics, interact with the hydrophilic polymers used to prepare gels, thereby reducing the concentration of free (antimicrobially active) preservative in the formulation. Therefore, to compensate for this, the initial concentration of these preservatives should be increased.

Antioxidants

As in other formulations, antioxidants may be included in the formulation to increase the chemical stability of therapeutic agents that are prone to oxidative degradation. The choice of antioxidants is based on the nature of the vehicle used to prepare the pharmaceutical gel. Therefore, as the majority of pharmaceutical gels are aqueous-based, water-soluble antioxidants, e.g. sodium metabisulphite, sodium formaldehyde sulphoxylate, are commonly used.

Flavours/sweetening agents

Flavours and sweetening agents are only included in pharmaceutical gels that are designed for administration into the oral cavity, e.g. for the treatment of infection, inflammation or ulceration. As before, the choice of sweetener/flavouring agents is dependent on the required taste, the type and concentration selected to mask the taste of the drug substance efficiently. Examples of flavours/sweetening agents used for this purpose have been detailed in Chapter 1.

Colours

Colours, e.g. those described in Chapter 1, may be (but are not usually) added into pharmaceutical gels.

Manufacture of pharmaceutical gels

In the manufacture of pharmaceutical gels, generally the water-soluble components/excipients are initially dissolved in the vehicle in a mixing vessel with mechanical stirring. The hydrophilic polymer must be added to the stirred mixture slowly