1 Historical perspective

Emulsions in various guises have been around since the dawn of time (e.g. mammalian milk, opal gemstones). What we describe as an ‘emulsion’ is today a very measured and well-understood entity (Becher, 2001), as a result of a chronology of profound and insightful scientific discoveries (see Table 1.1) and industrial practices (Valtcheva-Sarker et al., 2007; Sarker, 2010). Some very ‘big’ names feature in the list of events behind ‘emulsion’ and associated colloid (nanotechnology) science (Gregoriadis, 1973, 1977; Sarker et al., 1999; Pashley and Karaman, 2004; Sarker, 2009a,b, 2012a).

1.1 Landmarks

These are largely definable by their subsequent impact on the area of colloid science and pharmaceutics (Florence and Attwood, 1998). There have been some noteworthy exceptions to good practice, which have impacted on key considerations in later drug development:

- **1937** Sulphanilamide elixir, containing diethylene glycol, kills 107; established a need for drug safety before marketing.
- **1958** The US Food and Drug Administration (FDA) publishes in the Federal Register the first list of substances ‘generally recognized as safe’ (GRAS). This paved the way to formalisation of the regulation of drugs:
  - **1958** Thalidomide (Kevadon) licensed for use in the UK.
  - **1961** McBride writes about increased frequency of malformations (phocomeliae).
  - **1962** Amendments to FDA-US legislature are made based on findings (Sarker, 2008).
Table 1.1  Historical landmarks in the development of the fundamental and applied sciences relevant to the manufacture and use of ‘pharmaceutical emulsions’

<table>
<thead>
<tr>
<th>Fundamental science</th>
<th>Discovery</th>
<th>Applied (e.g. pharmaceutical science)</th>
<th>Discovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1661, Hooke</td>
<td>Capillarity</td>
<td>1904, Pickering</td>
<td>Solid particle-stabilised emulsions</td>
</tr>
<tr>
<td>1805, Young and Laplace</td>
<td>Curvature equations, wetting</td>
<td>1909, Erhlich</td>
<td>Targeted delivery (magic bullet)</td>
</tr>
<tr>
<td>1827, Brown</td>
<td>Particulate motion</td>
<td>1932, Langmuir</td>
<td>Surface adsorption of amphiphiles</td>
</tr>
<tr>
<td>1860, Graham</td>
<td>Existence of colloids</td>
<td>1961, Bangham</td>
<td>Liposome</td>
</tr>
<tr>
<td>1907, Ostwald</td>
<td>Notion of disperse/continuous phase</td>
<td>1975, L’Oréal</td>
<td>Invention of the niosome</td>
</tr>
<tr>
<td>ca. 1905, Einstein</td>
<td>Viscosity, shape and frictional models</td>
<td>ca. 1993, Gasco-Müller-Lucks et al.</td>
<td>Invention of the solid lipid nanoparticle (SLN)</td>
</tr>
<tr>
<td>ca. 1910, Gouy and Chapman</td>
<td>Description of electrical double layer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1913, McBain</td>
<td>Idea of the micelle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1941–1948, Derjaguin/Landau &amp; Verwey/Overbeek</td>
<td>Theory of colloid stability</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Numerous historical ‘colloid science’ figures have been omitted.

Many products of the type covered here are initially microheterogeneous dispersions, so any means of enhancing or creating ‘better’ uniformity is most welcome to industrialists and clinicians alike (Sarker, 2008; Benson and Watkinson, 2012). Revolutionary improvements in general, fundamental and pharmaceutical understanding are indicated in Table 1.1. The history of colloid and emulsion science is profound and covers more than 5 millennia of invention and design. Current products which employ emulsions and various ‘forms’ of emulsification (e.g. entrapment of drug in the liposome leaflet) have uses which include flavour encapsulation, multiple emulsions for drug encapsulation and microemulsions or multiple emulsions (Florence and Attwood, 1998; Sarker, 2008).

It is a gross simplification to present the list above without recognising the diverse scientific applications that have arisen from additional theories, too numerous to mention in this book, but which include estimation of dispersion forces (London, ca. 1920), double-layer theories (Gouy and Chapman, ca. 1910) and pioneering work on microemulsions (Schulman, ca. 1959).
1.2 Significant discoveries

Pickering emulsions (Ramsden, 1903; Pickering, 1907; Binks, 2002; Aveyard et al., 2003; Arditty et al., 2004; Concannon et al., 2010) are not a new concept but are gaining in interest in pharmacy applications. They are based on solid rather than molecular emulsifier coverage of dispersed droplets, are able to promote far ‘greater product stability’ than dispersed droplets and have been used as drug delivery platforms in a two-tier drug delivery system (DDS) (Concannon et al., 2010). Nanoemulsion products of this type can be used to improve therapeutic efficacy (Sarker, 2005a; Valtcheva-Sarker et al., 2007). Lipinski (Lipinski et al., 1997; Lipinski, 2000) has described a series of rules for and established an understanding of the mechanism by which drug molecules traverse cell membranes and deliver a ‘payload’ of drug to the cell of interest (Valtcheva-Sarker et al., 2007), and these have been pivotal to the understanding of the rigours of preformulation and good product manufacture. Solid lipid nanoparticle (SLN) DDSs and related de novo technologies and products were first discussed by a well-established group of researchers (Eldem et al., 1991; Gasco, 1993; Müller et al., 1995; Müller and Lucks, 1996) in the 1990s. These types of gel-phase lipid delivery system offer huge potential due to their control over drug entrapment, as seen with the novel drug product Qutenza (capsaicin).

The liposome, since its initial conception in 1959, has developed into many forms, some of which are used routinely to produce long circulating nanoparticles of use, for example, in cancer treatment (see Section 2.1.2 and Chapter 7). Liposome technology products and related chemicals such as stealth liposomes (using poly(ethylene glycol), PEG), niosomes, chitosomes, polymersomes, virosomes and so on, which may also be used diagnostically (Maurer et al., 2001; Tiwari et al., 2012), usually act as a form of lipid dispersion for delicate and lipophilic drugs and have revolutionised drug delivery (see Section 2.1.2 and Chapter 7). Liposomes and micelles can ‘emulsify/solubilise’ lipophilic drugs in the aliphatic portion of their superstructure (Sarker, 2010). Thermodynamically stable microemulsions, proposed by Shulman in 1959, provide an alternative means of solubilisation for apolar drugs. These types of dispersed system are often also referred to as ‘swollen micelles’, ‘transparent emulsions’ and ‘solubilised oil’. New forms of emulsion, such as solid (SLN), core and shell lipid nanoparticles (LNCs, SLCs, LNPs), along with polymer micelles (which may or may not include lipid derivatisation) now look very promising in terms of extensions to a multitude of products, such as biomimetic and biocompatible materials and composite materials (Sarker 2006a, 2010, 2012a; Tiwari et al., 2012). Such biomimetic materials are only likely to grow in number and applications to medicine (e.g. state-of-the-art treatments, radioimaging/radiopharmacy, etc.).
1.3 Difficulties

The pharmaceuticist is faced with problems over the route of delivery, possible destabilisation (phase inversion (PIT), Ostwald ripening, creaming, cracking and flocculation) and chemical changes (such as autoxidation and rancidity, and a subsequent modification of efficacy based on form and release profile). These are impacted on greatly by:

- The product’s form (formulation aids, excipients) and its interrelationships (Sarker, 2002; Di Mattia et al., 2010) and intrinsic stability.
- How the product is made.
- How and where in the body the product is intended to be used (Figure 1.1).
- How successfully and categorically the product can be tested and controlled in terms of consistency.

Fluidity of the low-molecular-weight (LMW) emulsifier adsorbed layer is necessary for surface repair (Sarker et al., 1995a,b). This is not so important when solids or polymers are used to stabilise the oil/water interface. Increasing either temperature or oil phase volume and emulsifier (surfactant) concentration can cause phase inversion, which can be devastating for parenteral emulsions, for example (Araujo

![Figure 1.1](image)
et al., 2007; D’Ascenzo et al., 2011). Natural fats are also susceptible to autoxidation (Sarker, 2005a, 2012a), which can result in a modification of phase or form, leading to a reduction in the shelf life and in the chemical stability of the emulsion and any encapsulated drug. Key considerations are:

- Release and control of release.
- Hygienic status and sterility/pasteurisation, and their impact on effective drug delivery.

Effective drug delivery is based upon three notions:

- Efficient encapsulation of the drug.
- Successful ‘targeting’ of the drug to a ‘specific’ region of the body.
- Successful release of the drug in situ.

These difficulties are further compounded by the location to which the drug product is delivered and by variations in pH, ionic strength, temperature and permeability (see Figure 1.1).

Any discrepancy in the compatibility of excipients and formulation and the activity of the encapsulated drug (Sarker, 2004a,b) can lead to poor product performance (see Section 15.1). For any kind of emulsion or emulsifier/lipid dispersion, a key consideration is the temperature changes experienced by the product. Temperature influences solubility and the solubility of a drug in lipid obeys Bancroft’s rule (oil in which the surfactant is more soluble will tend to form the dispersed phase of an emulsion), which can lead to a catastrophic phase inversion. This can be overcome in part by using several emulsifiers and employing hydrophile–lipophile balance (HLB) matching (see Table 1.1) of surfactant mixtures to best formulate the size and type of the emulsion droplets. The product is also defined by its potency, which covers the drug content. We can define entrapment efficiency for any drug thus:

\[
\text{entrapment efficiency} \, (\%) = \left( \frac{\text{amount entrapped}}{\text{total amount}} \right) \times 100 \, \text{(1.1)}
\]

This entrapment can be augmented by using solubilising aids and penetration enhancers, such as PEG. The expression does not indicate where the drug might be located in the particle or its homogeneous dispersion.

Although emulsions (coarse type) are inherently unstable, given that there are different formulation types and different excipients, we are able to discuss ‘relative stability’ or ‘product stability’ by comparing emulsions to a standard or to one another. Thus, product stability is important in accounting for the behaviour of emulsions under the different conditions they encounter (e.g. in the gastrointestinal
(GI) tract (gut pH and absorption efficacy; see Section 12.4.3), and the effect this has on emulsion stability and drug release (see Figure 1.1). The mechanisms for the release of the drug from the oil phase are critical.

Other issues that deserve appropriate consideration include: product syneresis (weeping), Ostwald ripening, crystallisation, recrystallisation, sequestration, coacervation, dose and drug flux estimation, particle sizetexturerheologycoverage and uniformity. Flocculation of the product and subsequent creaming and ‘cracking’ are driven by Derjaguin–Landau–Verwey–Overbeek (DLVO) colloidal stability theory (see Section 3.2.1). It is also important to make sure the manufacturing environment is clean and organised before initiation of the production run. This reduces the chances of making mistakes and of wasteful manufacture. It is mandatory before commencement of any pharmaceutical production that the manufacturing conditions do not compromise the content, form or efficacy of the product.

1.4 Traditional uses

The two most common manifestations of ‘simple’ emulsions (Figure 1.2) are found in topical and injectable medications. These involve:

- Creams (oil and water in approximately equal proportions) and ointments that combine oil and water (composition varies from 80:20 to 20:80) or lotions (mostly water).
- Parenteral and intravenous (IV) preparations.

In more recent times, variation combination products have been routinely seen. These include:

- Gels and pastes (three agents: oil, water and solid).

Lesser products for pharmacy use include:

- Parenteral nutrition products.
- Vitaminised nutraceutical suspensions and vitamin supplements.

These products are usually fabricated by combinatorial mixing of emulsifiers of varying HLB (apolarity), shape and form, as discussed at length in Section 2.3 (see Table 1.2, Figure 1.3). This gives the product designer the scope for greater emulsifier interfacial complexation (Sarker et al., 1995a) and better product stability.
The complexity, scope and variety of dispersions, making use of fats, oils, lipids and emulsifiers, are represented schematically in Figure 1.2. The emulsion, liposome and micelle represent the most widely used nanoparticles in contemporary pharmacy (Sarker, 2005a, 2006a). Traditionally, the vast majority of emulsions have been used for internal application (parenteral drugs) and externally for topical (skin and mucous membrane) use. However, in recent
Table 1.2 Hydrophile-lipophile balance (HLB) or ratio of some notable emulsifiers (surfactants) used in pharmacy

<table>
<thead>
<tr>
<th>Sample</th>
<th>Value (20°C)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium dodecyl sulphate</td>
<td>40</td>
<td>Ionic</td>
</tr>
<tr>
<td>Hexadecyl trimethyl ammonium bromide</td>
<td>18</td>
<td>Ionic (disinfectant <em>ex vivo</em>)</td>
</tr>
<tr>
<td>Tween 20</td>
<td>16.7</td>
<td>Polyoxyethylene-based</td>
</tr>
<tr>
<td>PEG400 monooleate</td>
<td>13.1</td>
<td>Derivatised polymer</td>
</tr>
<tr>
<td>Methylcellulose</td>
<td>11</td>
<td>Polymer</td>
</tr>
<tr>
<td>Gelatin</td>
<td>9.8</td>
<td>Protein</td>
</tr>
<tr>
<td>Span 20</td>
<td>8.6</td>
<td>Sorbitan fatty acid ester</td>
</tr>
<tr>
<td>Span 80</td>
<td>4.3</td>
<td>Sorbitan fatty acid ester</td>
</tr>
<tr>
<td>Lecithin, e.g. soya</td>
<td>4</td>
<td>Amphoteric emulsifier</td>
</tr>
<tr>
<td>Glyceryl monostearate</td>
<td>3.8</td>
<td>Lecithin derivative</td>
</tr>
<tr>
<td>Span 85</td>
<td>1.8</td>
<td>Sorbitan fatty acid ester</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>1</td>
<td>Fatty acid</td>
</tr>
</tbody>
</table>

HG Large means polarity (hydrophilicity) Small means apolarity (lipophilicity) tail

Large means lipophilicity Small means hydrophilicity

Figure 1.3 Hydrophile–lipophile balance (HLB) and surfactant–emulsifier shape, and its impact on use

approaches they have been used more widely as parts of transdermal patch products (Benson and Watkinson, 2012).

HLB mixing is used in creating nanostructured vehicles. Novel emulsifier blends and emulsifiers (e.g. Janus particles), along with fabrication of structured surfaces to withstand process-induced destabilisation, may also be used to compensate for small compositional variances. A new wave of pharmaceutics research (Bivas-Benita et al., 2004; Sarker, 2010, 2012a) is considering the use of emulsions in pulmonary (Bivas-Benita et al., 2004), nasal (Kumar et al., 2008), colonic and
tablet (Corveleyn and Remon, 1998; Pouton, 2000; Hansen et al., 2005) routes to drug administration.

1.5 Product regulation

Regulation of pharmaceutical emulsions follows the same criteria as that of other pharmaceutical products in general (Sarker, 2008). Where it differs is in the inclusion of potent or noxious actives such as radioisotopes, e.g. Indium ($^{111}$In), or cytotoxic (anticancer, etoposide, cisplatin, doxorubicin) or even controlled drugs such as diamorphine. This regulation is centred on the risks of hypo- or hyper-dosing of the drug (Roberts, 1981). Many of the safety concerns are eradicated at the preclinical stage of development, through the validation of a consistently formulated product (Sarker, 2008). During oversight by the relevant drug regulatory bodies (FDA, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), World Health Organization (WHO)), concerns over consistent fabrication should be addressed and aligned with regular quality control intervention to secure product acceptability, known as PCQ (purity, consistency, quality (i.e. safety and efficacy); Sarker, 2008). In pharmacy, excipients are usually restricted to approved GRAS-grade materials. A system of practice can reduce the risk of noncompliance. Such systems are driven by the regulatory bodies themselves and by the industrial manufacturer. They include adherence to specifications and guidelines and adoption of a total quality management system (GMP, QA, QC) in order to ensure the quality of the product (see Figure I.1).