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REVIEW ARTICLE

Pharmaceutics for the anaesthetist

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Summary

Pharmaceutics is that branch of science concerned with the manufacture and formulation of pharmaceutical products, and is a subject almost exclusively in the domain of pharmacists and those concerned with pharmaceutical manufacture. However, there are some aspects of pharmaceutics that are of particular importance to the anaesthetist, such as the pharmacology of the various preservatives, antimicrobials and other additives found in anaesthetic products, and an understanding of basic processes such as emulsification and lyophylisation. This review aims to survey those areas.

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There is little information in the anaesthetic literature on drug additives, and, indeed, it appears that only one previous significant summary has been published [1].

Anaesthetic products can contain a wide range of pharmaceutical additives that are included for a number of reasons. Principal among these is the need to prevent contamination of the product and to maintain potency by reducing its rate of breakdown, although they are also used to modify tonicity or pH, or to stabilise the product. The most common additives used in pharmaceutical products, which are discussed in this paper, are listed in Table 1.

Solvents

Water

Water is the most common and appropriate solvent used in drug preparation. It is tasteless, free from irritating qualities and is pharmacologically inert [2]. Despite these attributes, its use is not without a number of attendant problems. For example, drugs in solution are liable to breakdown, especially by hydrolysis, and the solutions are easily contaminated by micro-organisms.

Most drugs are water-soluble to some degree, depending on the relative polarities of solvent and solute, and this can be determined numerically by calculation of the dielectric constant, which is measured by placing a sample of the substance to be studied between two plates attached to a voltage source and measuring the capacitance between the plates (C_x), which is then compared to the capacitance when a vacuum (C_0) occupies the space. The dielectric constant (ε) is determined by calculating C_x/C_0. Substances with dielectric constants >50 are generally classified as polar; those with constants within the range of 1–20 are non-polar; those with intermediate dielectric constants are referred to as semipolar (Table 2).

The high dielectric constant of water ($\varepsilon = 78$) confirms it as a polar solvent, and it is this feature that facilitates the dissolution of many molecules, especially polar or charged species.

Non-aqueous solvents

Vehicles other than water are used for drug formulation for two reasons. The first is to solubilise drugs, which by virtue of the presence of non-polar or hydrophobic characteristics are relatively insoluble in aqueous vehicles. The second relates to product stability, since, generally, the use of non-aqueous vehicles with lower dielectric constants will reduce the rate of hydrolytic decomposition (see below). Most non-aqueous vehicles, such as glycerol, ethanol and members of the glycol family, are usually used in combination with water.

Propylene glycol

Glycols are dihydric alcohols derived from natural gas and are widely used in foodstuffs and in industrial products

Table 1 Principal pharmaceutical vehicles and additives.

Vehicles	Water
	Propylene glycol
	Benzyl alcohol
Emulsions	
Surfactants	Polyoxyethylated castor oils
	Lecithin
Cyclodextrins	
Anti-oxidants	Alkyl-substituted phenols
	Sulphurous acid salts
	Edetic acid
	Lecithin
Preservatives	Benzalkonium and benzethonium chlorides
	Chlorbutol
	Parabens

such as antifreeze and brake fluid. As might be expected from their chemical structure (Fig. 1a), glycols are miscible with water in all concentrations. Ethylene glycol is too toxic for human use, being metabolised by ethanol dehydrogenase, eventually to form the toxic oxalic acid. However, propylene glycol (more correctly called propylene glycol monomethyl ether) is an agent of generally low toxicity [3, 4] that is used a solubilising agent and for its mild preservative action. After administration, it is metabolised to lactic and pyruvic acids, and although uncommon, acidosis and serum hyperosmolality have occasionally been reported after high doses [5, 6]. Rapid intravenous administration of products containing propylene glycol has been associated with the development of hypotension and arrhythmias – a further reason why intravenous preparations of propylene glycol-containing agents, especially phenytoin and digoxin, should be administered slowly. Products using propylene glycol as a vehicle are also liable to cause significant thrombophlebitis, which in some studies has had an incidence as high as 60% [7], often with serious consequences [8]. Such findings have led manufacturers to reformulate propylene glycol-containing products such as diazepam into injections containing less irritant additives.

Preparations of the intravenous induction agent etomidate can contain up to 35% propylene glycol, and

Table 2 Dielectric constants (ε) of various solvents measured at 20 °C.

Compound	Dielectric constant
N-methylformamide	190
Water	78
Glycerine	46
Methanol	33
Propylene glycol	32
Castor oil	4.6
Olive oil	3.1

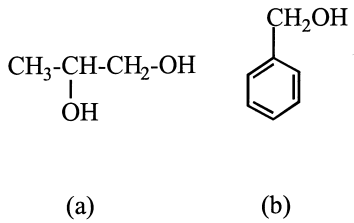

Figure 1 Chemical structure of non-aqueous solvents: (a) propylene glycol, (b) benzyl alcohol.

it has been suggested that the solvent in some formulations may be responsible for pain on injection. Although the mechanism is unclear, it has been suggested that propylene glycol has a direct effect on the vasculature, resulting in local tissue and endothelial cell damage [9, 10], an effect that has been noted previously with other drugs [11].

Benzyl alcohol

In common with other drug additives having multiple actions, benzyl alcohol (Fig. 1b) has two applications in pharmaceutical formulation. In low concentrations of up to 2% it is used as a preservative and antimicrobial, and is employed in preparations of phenobarbitone, d-tubocurarine and some formulations of midazolam and diazepam. In concentrations of greater than 5%, it is used as a non-aqueous solvent.

Its toxicity is dose-related and was responsible for a number of deaths some years ago when benzyl alcohol-preserved saline was given to neonates [12–15]. Benzyl alcohol, which is metabolised to benzoic acid and thence conjugated with glycine to form hippuric acid, also has a number of cardiovascular effects. Animal experiments have confirmed that in sufficient doses its use will result in hypotension by both peripheral vasodilatation and myocardial depression [16–18].

Furthermore, it also possesses local anaesthetic properties – a fact that has been recognised for some time [19]. There has recently been a resurgence of interest in its use for this indication, with some promoting its use intradermally before intravenous cannulation, as it has been suggested that it has an efficacy similar to that of lidocaine but with less pain on injection [20, 21]. However, it use in this role could be limited because of its capacity to cause contact dermatitis and sensitisation [22–24], a response seen with a higher incidence in the population who also demonstrate aspirin allergy [25, 26].

Emulsions

An emulsion is a two-phase system, consisting usually of a pair of immiscible liquids, one of which is dispersed in the

form of small droplets throughout the other. As anybody who has made oil and vinegar salad dressing or mayonnaise will know, such systems are inherently unstable. The reason for this is not poor culinary skill but the laws of thermodynamics. When a dispersed phase is broken down to very small droplets, the result is an increase in total surface area of enormous proportions. For example, 1 ml of oil broken down to fine globules and then dispersed in water results in an interfacial surface in the order of some 500 m^2, which in turn creates a significant increase in the interfacial energy of the system [27].

In order to increase the stability of such an emulsion system, additives called 'emulsifying agents' are employed. This is a general term embracing a range of heterogeneous substances that stabilise emulsion systems by maintaining droplets in the dispersed phase, so preventing their coalescence. They include the surfactants and the hydrocolloids, and achieve their effects through a number of processes. Some form physical or chemical barriers around the dispersed droplets, or impart an electric charge to the external surface of the droplets so that they tend to repel one another. Others reduce the interfacial tension between the two phases, which in turn lowers the interfacial energy within the emulsion.

Emulsions are defined as being of the oil-in-water (o/w) type, where the oil is the droplet, also known as the internal or discontinuous phase, and is dispersed through an aqueous phase. The water-in-oil (w/o) type is where the water is in droplet form in an oily dispersion medium, also called the external or continuous phase. Which of these two forms of emulsion will be formed is primarily dependent on the relative mass of the phases and the nature of the emulsifying agent added. Of the commercial fat emulsions available, soya bean oil is the most common and is used in the emulsions of both propofol and diazepam, with purified egg yolk phospholipids as the emulsifier.

Despite the use of stabilising agents, emulsions remain unstable preparations, and are particularly sensitive to storage conditions, changes in temperature and added molecules. The aqueous phase is prone to contamination and usually contains a water-soluble preservative, while the oil phase is prone to rancidity, which necessitates the addition of a lipophilic anti-oxidant such as tocopherol.

Propofol

Propofol (Diprivan, AstraZeneca) is one of the most widely used emulsions in anaesthetic practise. It was originally marketed as an o/w emulsion using soya bean oil as the oil phase and egg lecithin as the emulsifying agent. While this has remained the standard formulation, there have recently been some changes in other aspects of its manufacture which will be discussed elsewhere.

Propofol causes pain on intravenous injection, a phenomenon that has been extensively reviewed and investigated [28, 29]. The mechanism for this is clearly complex and may be multifactorial. While no firm consensus has been reached, some studies have suggested that the lipid solvent is responsible through activation of the plasma kallikrein system, which results in the production of bradykinin [30]. However, this has not been a consistent finding.

As a general rule, the addition of any other drug to an emulsion is contraindicated. There is a real risk that the admixture of other substances, especially charged species, can interact with either the lipid phase or the emulsifying agents, resulting in emulsion destabilisation [31]. Anaesthetists have taken to adding a wide range of drugs to propofol. These have included the local anaesthetics lidocaine, procaine and prilocaine, in an effort to decrease pain on injection [32–34], as well as thiopental [35]. While the addition of local anaesthetics has not been associated with any untoward effects to date, the stability of thiopental/propofol mixtures appears limited by emulsion stability [36].

Surfactants

Certain molecules possess structural features making them liable to accumulate at the boundaries between heterogeneous or immiscible phases and so reduce the interfacial tension between them. They are called surface-active agents, or surfactants, and permit the solubilisation of substances that would otherwise be impossible by acting as stabilising agents in emulsions.

Chemically they are amphiphiles, possessing both hydrophilic and lipophilic regions. The lipophilic portion is almost universally a long chain hydrocarbon, which may or may not contain an aromatic group, while the hydrophilic portion is more variable and may be anionic, cationic or non-ionic in nature. Surfactants tend to surround individual molecules of the internal phase and so form 'monomolecular' emulsions. Although there is a wide range of surfactants available, most are used in topical or oral products. However, there are some surfactants of anaesthetic interest. The cationic agents benzalkonium and benzethonium chlorides, which are better known as preservatives, and lecithin, an anti-oxidant with surfactant properties, are discussed elsewhere.

Polyoxylated castor oils

The reaction between rinoleic acid (castor oil), or its derivatives, with ethylene oxide results in the formation

of a range of chemicals with surfactant properties. These are called polyoxylated castor oils.

Cremophor EL (also known as Polyoxyl 35 Castor Oil) is the proprietary name of one of these products, and is composed of a number of different molecules that contain both lipophilic and hydrophilic components. The isolated lipophilic extract was once also used as a pharmaceutical solvent under the trade name Tensid, Micellophor or ORPE (oleum ricini polyethoxylate), and was used in the formulation of propanidid injection [1].

The lipophilic portion of Cremophor EL comprises a triglyceride stem to which are attached approximately 40 oxyethylene units. It has been used as a surfactant in pharmaceutical preparations since the 1970s and was incorporated into preparations such as propofol, phytomenadione (vitamin K) and alphaxalone/alphadolone. However, serious anaphylactoid reactions associated with its use eventually led to the withdrawal of many compounds in which it was found, although propofol was later successfully reformulated in a soya bean oil emulsion.

A number of mechanisms have been proposed to account for these reactions [37], including Type I hypersensitivity reactions, complement activation [38] and direct histamine release from mast cells. Although no longer used in anaesthetic products, its efficacy in solubilising highly lipophilic compounds has led to its use in parenteral preparations of a range of substances including cyclosporin, doxorubicin, teniposide and paclitaxel.

Anaphylactic and hypersensitivity reactions continue to be reported after the administration of these Cremophor EL-containing products [38–40], as well a range of other adverse effects including pancreatitis [41] and central neurotoxicity [42], many of which seem to be dose-related [43, 44]. Experiments in which either rat aortic rings or rabbit artery segments were exposed to Cremophor EL resulted in persistent contractions through a direct action on vascular smooth muscle [45, 46]. The significance of this is unknown, but could imply that intra-arterial injection of Cremophor-containing products could be harmful. Further investigations have shown that a similar vasoconstrictor effect of the vehicle on the pulmonary vein can be demonstrated [47]. Some researchers have proposed that these toxic reactions may be due not so much to the Cremophor itself but rather to the residual ethylene oxide or polymeric by-products produced as a result of the manufacturing process [48]. Additionally, there have been other interesting effects observed after the administration of Cremophor-containing drugs. The first was an observation that Cremophor EL favourably modifies the pharmacokinetics of a number of antineoplastic agents, with a resulting increase in antitumour efficacy of the drugs [49]. Another unusual effect of Cremophor is its capacity to modulate multidrug resistance (MDR). Certain cells have the capacity to produce high concentrations of proline-glycoprotein, a membrane protein that acts as a pump to extrude a range of antineoplastic drugs from within the cell [37]. Importantly, some antineoplastic agents have been shown to induce this effect, thus reducing their own efficacy. However, several surface-active agents, including Cremophor EL, used in preparations of, for example, daunorubicin and paclitaxel, have been shown to reverse MDR [50], acting more as a synergist than an inactive surfactant [51].

Lastly, in studies where the ratio of blood and plasma paclitaxel concentrations were measured, the ratio was lower in Cremophor-treated patients, which was thought to be due to an interaction between the two products, resulting in paclitaxel becoming trapped in the Cremophor EL matrices, reducing its capacity to be transported to other sites [52]. Other researchers have suggested that this phenomenon of molecular trapping could be exploited as a means to reduce the haemolytic properties of some drugs.

Cyclodextrins

Another novel approach to solubilising lipophilic drugs is the use of cyclodextrins. These are cyclic oligosaccharides derived from starch, containing 6–8 glucopyranose units. The three-dimensional structure of the resulting molecule has been likened to a segment of a hollow cone, with a hydrophilic exterior surface and lipophilic interior surface into which individual molecules can become incorporated. Such a configuration is particularly useful for the encapsulation of highly hydrophobic molecules, which can then be rendered soluble in aqueous solution. A number of studies of the administration of propofol complexed with 2-hydroxypropyl-β-cyclodextrin have been completed, and these have shown similar pharmacological and anaesthetic properties to the commercial products currently available [53]. Some of these propofol–cyclodextrin products have already been patented, and may be destined for clinical trials in the near future [54].

Drug decomposition and contamination

In compounding drug products, and especially parenteral products, the challenge is to make a stable and appropriate formulation of a drug in which, amongst other things, the active drug will be soluble and resistant to the two main problems likely to occur with time: decomposition and contamination.

Decomposition

The most common consequence of decomposition or degradation is the diminution of product potency because

of a reduction in the concentration of the active ingredient [55]. A more serious, but less frequent, outcome is the formation of decomposition products, which may themselves be harmful. Prevention of decomposition is important since, with rare exceptions such as the formation of the coloured adrenochrome as a decomposition product of epinephrine, there is generally no physical evidence that a product may have undergone considerable reduction in potency, and the user is therefore unaware that such a process has occurred. Drugs in solution may decompose by many pathways, but chief among these are hydrolysis, oxidation, isomerisation and photochemical decomposition [56].

Hydrolysis and its prevention

Hydrolysis is the chemical reaction of a compound with water and is the most common method of drug degradation. Hydrolytic cleavage is promoted by the presence of hydroxyl and hydrogen ions found in aqueous solutions, although other basic and acidic species can also be involved, and essentially any drug in aqueous solution will be liable to hydrolysis to some degree. Compounds containing lactam groups, or ester and amide bonds, are particularly liable to hydrolytic breakdown, and so drugs such as atropine, procaine, cocaine and physostigmine, as well as penicillin and cephalosporin antibiotics, are primary candidates for hydrolytic degradation.

There are a number of approaches to reduce the rate of hydrolysis, most of which rely on reducing the amount of drug in the aqueous phase [56]. Such strategies include:

- Determining by laboratory experiments at what pH the product is most stable and adjusting the pH of the product accordingly by the use of buffers.
- Alteration of the dielectric constant by the addition of non-aqueous solvents such as glycerine or propylene glycol.
- Addition of agents to form complexes to increase stability.
- Solubilisation by surfactants.
- Modification of side chain substituents.
- Lyophilisation.

Some of these processes deserve further comment. Modifying the pH of the formulation to enhance drug stability relies upon determining the ion having the greatest effect on the hydrolytic reaction [57]. In general, the hydroxyl ions have the stronger effect, and so the pH range of minimum decomposition is often found to be 3–4. Reducing the rate of hydrolysis by modification of molecular structure is clearly a process fraught with problems, as it could result in reduction of pharmacological activity. However, through careful alteration of non-critical areas of the molecule, it is possible to produce modifications that retain the required activity, but with enhanced stability.

A further means to reduce hydrolysis is by lyophilisation or freeze-drying. This is employed in both the food and the pharmaceutical industries and is said to have been first used, at least in principle, by the Incas several centuries ago. They preserved food by storage atop high mountains, where a combination of very low temperature and low pressure existed. Modern freeze-drying of pharmaceutical products such as vecuronium relies on the removal of water from solution by sublimation and desorption. It is a complicated process requiring several steps that take place within a chamber, wherein the temperature is first reduced so that the solution of the drug is frozen. Then the pressure is lowered to a point at which it is less than the vapour pressure of ice at that temperature. When these conditions coexist, the ice is converted directly to water vapour by sublimation, leaving behind the lyophilised powder. Naturally, such products require reconstitution before use.

Oxidation and its prevention

The term oxidation was formerly used to describe the reaction of a substance with oxygen, although it is more properly defined as a reaction involving the loss of electrons. It is a common means of chemical breakdown, and compounds prone to degradation by this method include vitamins, phenolic compounds such as propofol, and catecholamines. Reduction in the rate of oxidation of drugs can be accomplished either by removing (to as greater extent as possible) available oxygen in the pharmaceutical preparation, or by the addition of anti-oxidants.

Removal of oxygen

Removing oxygen from drug products and replacing it with less reactive gases such as nitrogen would seem an attractive strategy to reduce the rate of oxidation, and indeed propofol injection uses nitrogen to fill ampoule headspace. However, it is a process that sounds deceptively simple. As one author succinctly said: 'it is easy to remove most of the oxygen from a container, but very difficult to remove it all!' [57]. This is an important consideration, since even trace amounts of oxygen can be enough to cause the initiation of the oxidation process, since many such reactions proceed by 'auto-oxidation'. This is a process initiated by the interaction of ultraviolet radiation with trace amounts of oxygen resulting in the formation of free radicals, charged molecules containing an unpaired valence electron in the outer shell that makes them both reactive and unstable. The reaction is then propagated by the reaction of these free radicals with other parts of the drug molecule, which in so doing

creates further free radicals, and so on. The process is catalysed by trace amounts of heavy metal ions and is promoted by increased temperatures.

Anti-oxidants

Anti-oxidants are generally classified into three groups [58]. The true anti-oxidants (also once appropriately called 'anti-oxygens') include alkyl-substituted phenols such as thymol, tocopherol, alkyl gallates and hydroxy anisole. They exert their anti-oxidant effect by interacting with free radicals, which makes them effective against auto-oxidation (above), but not against reversible oxidation–redox reactions. All of the substances are found in a range of parenteral products. Thymol, for example (Fig. 2a), is added to halothane to attenuate its rate of oxidation. Interestingly, propofol itself has been shown to have significant anti-oxidant properties [59], not an unexpected finding, as it shares the basic structure of a substituted phenol with other members of this group.

Reducing agents act as molecular sacrifices. Having a low redox potential, they are preferentially oxidised, thus leaving the active drug free from attack. They are also active against free radicals. Examples include ascorbic acid and the sulphurous acid salts, also known as sulphites.

Sulphurous acid salts

Sulphurous acid salts or 'sulphites' comprise a range of agents including sulphur dioxide and sodium sulphite, bisulphite and metabisulphite, all of which release sulphur dioxide, the active moiety. Aminoglycosides and catecholamines are particularly liable to oxidation and often contain sulphiting agents, as do epinephrine-containing local anaesthetic solutions. In the last case, control of acidity is important, since at pH $>$ 4 the two products react, forming the inactive epinephrine sulphonate [60].

Sulphites are well known as mediators of hypersensitivity reactions [61], and the incidence of these reactions is dependent upon the route of administration [62]. Reactions are most likely after inhalation of sulphite-containing products [63–65], followed by oral ingestion. Such a reaction is usually characterised by wheeze, bronchospasm, pruritus and chest pain, and occurs almost exclusively in patients with pre-existing reactive airways disease and who are almost 10 times as likely to be steroid-dependent [66, 67]. The incidence of such reactions increases with age [68]. In the past, sulphites were common additives in inhaled bronchodilators and are now thought responsible for so-called 'paradoxical bronchospasm' sometimes seen after the use of inhaled sympathomimetics [63]. Reactions to parenteral injection of sulphites are rare but not unknown [69], and this response does not show the same predilection for steroid-dependent asthmatics [70]. In particular, total parenteral

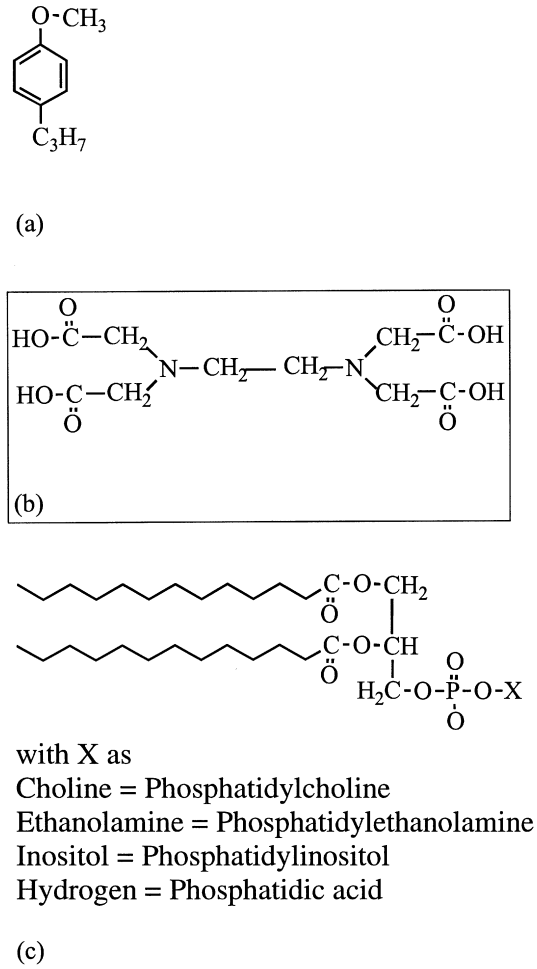

Figure 2 Chemical structure of the anti-oxidants (a) thymol, (b) edetic acid and (c) lecithin.

nutrition (TPN) solutions can contain large amounts of sulphites, with one report suggesting up to 950 mg of bisulphites per day could be administered [62], and that this should be a source of concern. Another suggested that the inadvertent administration of sulphite-containing TPN solutions over a number of days was responsible for the development of headache, vomiting, tachypnoea and coma in one patient [71]. Large doses in animal studies have also implicated sulphites in the development of renal cellular damage [72]. There has been a report of the development of generalised seizures in a patient given high doses of sodium bisulphate contained in intravenous morphine solution [73]. Dose-related toxicity is also theoretically possible with peritoneal dialysis fluids, some of which contain sodium metabisulphite in concentrations of 0.005–0.012% [74]. There has been a general desire by regulatory authorities to reduce the use of sulphites in pharmaceutical preparations [75, 76], and

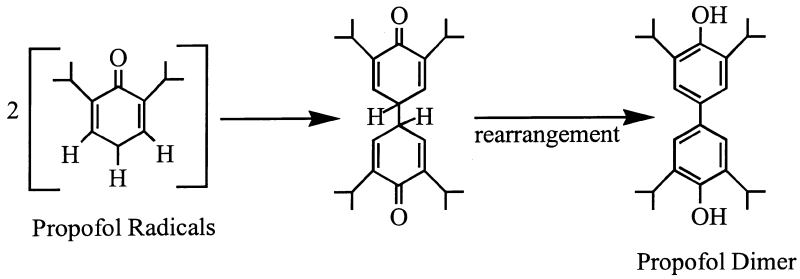

Figure 3 Proposed chemical transformation of propofol to its dimer, a process facilitated by the presence of metabisulphite (after [90]).

debate continues as to whether the sulphite concentration of some formulations of propofol could be potentially toxic [77, 78].

Anti-oxidant synergists enhance the activity of the 'true anti-oxidants', and are used in combination with them. This effect is mainly thought to come about through their interaction with heavy metal ions, which would otherwise catalyse the oxidation process. Examples of anti-oxidant synergists include lecithin, and citric, tartaric, and ethylenediaminetetra-acetic acid (EDTA, Edetic acid). Ethylenediaminetetra-acetic acid is a chelating agent used therapeutically in the treatment of heavy metal poisoning (Fig. 2b). It is used as an additive in some nebuliser solutions to chelate metal ions and to prevent discolouration of the solution [79]. It has also been used as an anti-oxidant synergist, but has insignificant antimicrobial activity. Ethylenediaminetetra-acetic acid has also been shown to have bronchoconstrictor properties [80, 81], and although the precise mechanism is unclear, it seems that the drug's calcium chelating properties may be responsible [82]. However, these effects have been seen only in concentrations far in excess of those used in human preparations and are unlikely to be clinically significant.

Lecithin (from the Greek lekithos, meaning 'egg yolk') is a phospholipid compound comprising a range of phosphatidyl esters such as phosphatidyl choline, ethanolamine and serine (Fig. 2c) together with varying amounts of other substances such as triglycerides and fatty acids [83]. It was originally obtained from eggs, although nowadays soya beans and other vegetables with a high lecithin content are also useful sources. Apart from its use as an anti-oxidant synergist, lecithin has important surfactant properties and is used as an emulsifying agent. It has also been proposed as an oral source of choline in the treatment of Alzheimer's disease and as an agent to reduce serum cholesterol, although in this case the promoters seem oblivious to the fact that lecithin is degraded in the gastrointestinal tract before having a chance to be absorbed.

The question of whether propofol injection, because of its lecithin content, should be avoided in patients with egg allergy is problematic. There have been no reports of adverse effects in the literature to date and although hypersensitivity reactions to both soya bean extract and lecithin have been demonstrated, they have only been reported when the allergens have been inhaled or ingested. Furthermore, patients who are designated as having a so-called 'egg allergy' generally demonstrate an IgE-mediated hypersensitivity to allergenic proteins found in egg whites. The derivation and chemical structure of egg lecithin would suggest that the risk of its administration to such individuals is very low.

Recent re-formulations of propofol

Propofol was initially manufactured as a preservative-free product, and in some countries, such as Australia, this is still the case. However, as usage of the drug increased, reports of bacterial contamination of propofol emulsion also started to appear, with the suggestion that some cases of postoperative infection might have been due to the injection of contaminated product [84–86]. The concern that the preservative-free product could easily be contaminated through handling [87, 88] led the original patent holders, AstraZeneca, to reformulate the preparation. Antimicrobial studies demonstrated that EDTA at a concentration of 0.005% successfully retards microbial growth and has no adverse effects on the physicochemical stability of the product [89].

At about the same time that the EDTA preparation of propofol was being formulated, another manufacturer was marketing a sulphite-containing product. This product (propofol injectable emulsion 1%, Baxter Pharmaceutical Products) contains sodium metabisulphite 0.25 $mg.ml^{-1}$ and is formulated in a slightly more acidic medium (pH 4.5–6.4) than the AstraZeneca product (pH 7.0–8.5). The release of these products has initiated a number of studies examining whether the new additives might have any effect on the stability of the emulsion product. A study by Baker [90] determined that both EDTA and sulphite-containing propofol products promoted the formation of a propofol dimer, formed after the propofol molecule had donated a hydrogen and resulting in the formation of a phenol-derived free radical species

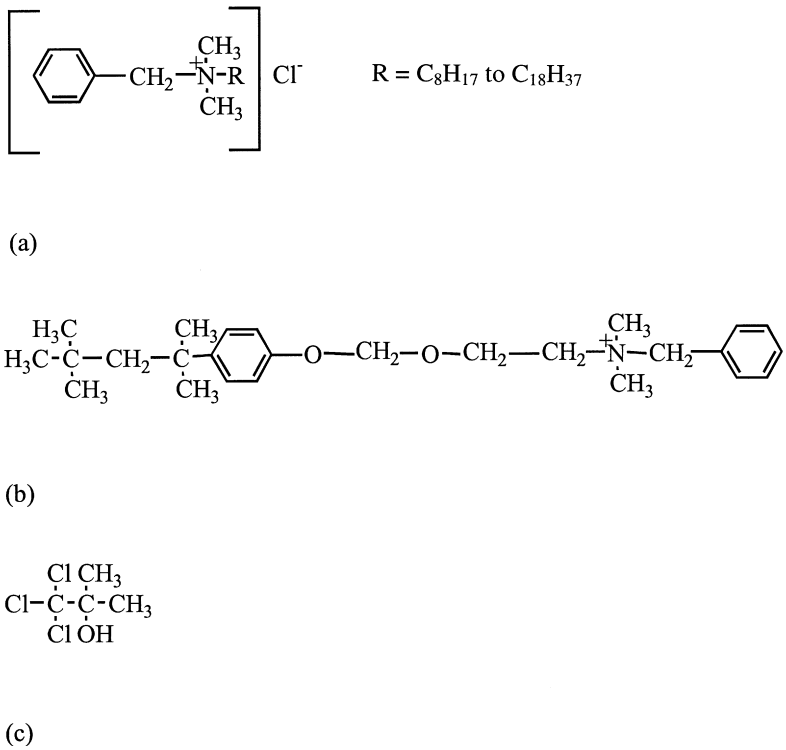

Figure 4 Chemical structure of the preservatives (a) benzalkonium chloride, (b) benzethonium chloride and (c) chlorbutol.

(Fig. 3). While the propofol dimer was found in only trace amounts in the propofol–EDTA product (< 0.015%), its concentration in the sulphite–propofol product was significantly higher (0.18%). In addition, there have been reports of yellow discolouration in sulphite–propofol products, which the author suggests could be due to increased dimer production, which then undergoes further chemical transformation to coloured quinone species. Interestingly, both products are promoted by their respective manufacturers as being 'preservative free', since the concentration of both EDTA and sodium metabisulphite are below the United States Pharmacopoeia minimum standard that would otherwise require appropriate labelling.

Isomerisation

Isomerisation (or racemisation) refers to the process of conversion of a drug into its optical or geometric isomers [56]. Numerous studies on this topic have confirmed that potencies of drugs may differ substantially between isomers. As products begin being formulated as single isomers (such as ropivacaine), loss of potency through isomerisation must be considered. The rate at which racemic degradation occurs usually follows first-order kinetics and is dependent on temperature, solvent, catalyst and the presence of light [57].

Photochemical decomposition

Many compounds, especially those in solution, are light sensitive and will undergo complex multistep degradation after exposure to ultraviolet light. Fortunately, adequate protection can be afforded by storing products away from direct sunlight and by manufacturing them in dark amber glass. This effectively excludes ultraviolet radiation with wavelengths of less than 470 nm.

Preservatives

Preservatives are substances added to pharmaceutical products that prevent or inhibit the growth of micro-organisms that may have been introduced during the manufacturing process. They are widely used in pharmaceutical products [91]. Almost all preservatives are weak acids with pKa's in the order of 4–5. They will therefore

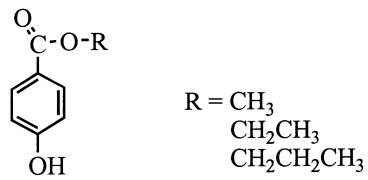

Figure 5 General chemical structure of the parabens.

be most effective in environments of an acid pH where, following the tenets of the Hendersen–Hasselbach equation, a greater proportion of the drug will exist in the un-ionised form and so be able to pass through microbial cell walls and membranes to exert an antibacterial effect. To achieve this end, acidifying agents are usually added to adjust the product pH accordingly.

Benzalkonium chloride (BAC)

Benzalkonium chloride, actually a mixture of quaternary benzyl-dimethylalkylammonium chlorides (Fig. 4a), is a common preservative found in eye and nose installations and in bronchodilator solutions [79]. Benzalkonium chloride causes reproducible bronchoconstriction that has a more rapid onset and prolonged duration compared with that caused by sulphites [92]. The mechanism may be direct histamine release, which occurs at concentrations > 30 $\mu g.ml^{-1}$, almost the same as that suggested as the minimum effective dose as an antimicrobial [93]. In addition to BAC-induced bronchoconstriction, long-term sensitisation to BAC has also been reported. A chemically related preservative, benzethonium chloride (Fig. 4b), is used as a preservative in a number of formulations of ketamine injection. A recent study [94] has suggested that the its inhibitory effect on muscarinic receptors could significantly contribute to the analgesic effect of ketamine.

Chlorbutol

Chlorbutol (chlorbutanol, Fig. 4c) has weak antibacterial and antifungal properties and has been used as a preservative, especially in ophthalmic preparations, and was formerly used in preparations of ketamine. A number of reports of hypersensitivity reactions have been received [95]. Chlorbutol also has weak sedative properties and there has been a case in which the chlorbutol added to morphine was though to have contributed to the drug's sedative effects [96]. Other studies [97] have suggested that in doses of 10–100 $\mu g.ml^{-1}$, chlorbutol could activate the sodium–potassium pump in muscle preparations.

Parabens

The parabens are aliphatic esters of parahydroxybenzoic acid, from whence their name derives, and comprise methyl, propyl and butyl parabens (Fig. 5). Sodium benzoate and benzoic acid, although not parabens by strict chemical definition, are closely related structurally and possess a degree of cross-reactivity with members of the paraben class [98]. The parabens are preservatives that prevent the growth of fungi and yeasts, having less activity against bacteria. Some studies [99, 100] have suggested that parabens in general are weakly oestrogenic, although the authors suggest that significant clinical problems are only likely to occur after long-term use of topically applied paraben-containing cosmetic products, and are unlikely to be of any concern after the systemic administration of the small amounts found in pharmaceutical products. Chronic use can also result in a reduction of cyclic adenosine monophosphate (cyclic AMP) through phosphodiesterase stimulation [101]. Reports of allergic reactions to parabens are uncommon, with one study estimating an incidence of approximately 0.3% [102]. However, another report [103] demonstrated that the incidence of intradermal reaction to prilocaine was reduced from 17% to 4% when paraben-free prilocaine was used, suggesting a slightly higher incidence of reaction.

Whether parabens have any direct vascular effects is unclear. Early studies suggested that parabens might have direct vasodilator activity on isolated human pial arteries and might be responsible for vasoactive effects of preparations of suxamethonium or naloxone [104, 105]. However, further studies failed to demonstrate any particular vasodilator properties of the group [106, 107].

Preservatives are biologically reactive substances, and their allergenic potential has been recognised for some time. One study that examined data from over 28 000 patch tests [108] concluded that the incidence of reactions to preservatives was: benzalkonium chloride 2%; benzyl alcohol 0.4%; sodium benzoate 0.4%; chlorbutol 0.1%; parabens 1.6%. In any case, their low allergenic potential and relatively high efficacy have made parabens the most popular preservatives in use today [109].

Adjustment of tonicity and pH

Adjustment of the osmolality of parenteral products to achieve isotonicity is important to decrease pain on injection, the incidence of thrombophlebitis and possible haemolysis. Many of the additives already discussed make a considerable contribution to the osmolality of pharmaceutical preparations, thus rendering them hypertonic. This is not usually of any clinical significance unless the osmolality exceeds 550 $mosm.l^{-1}$. Where solutions are hypotonic, solutions of sodium chloride of varying strengths are added to adjust tonicity, although other agents such as glycerol are sometimes used. The amount required is either calculated using appropriate tables or is determined directly by measurement of freezing point depression. Glycerol is a common additive used to increase osmolality in hypotonic products and is used in propofol injection for that purpose.

As outlined in previous sections, adjustment of the pH of a drug product is performed for a wide range of reasons. It might be done for the purpose of promoting

drug solubility or stability, or to maintain the pH of a product in the acidic range where other additives, such as preservatives, are maximally active. Where pH adjustment is desired it is usual to use buffer pairs.

Adverse effects due to drug additives

The vast majority of additives used in pharmaceutical preparations are also widely used in the food industry. It is therefore far more likely that patients will be exposed to a wider variety, and to greater amounts, of these products as a result of ingestion of foodstuffs compared to the small amounts contained in pharmaceutical products [110, 111].

Adverse reactions can be dose-related or of an allergic or hypersensitive nature, in which case only a small amount will be needed to elicit a response in a susceptible individual. Although dose-related adverse responses to pharmaceutical additives are uncommon, there are at least four subgroups of patients who are at risk. These are: children, especially neonates; patients receiving TPN solutions; patients who for any reason are receiving long-term parenteral drug treatment, such as patients in intensive therapy units; those with chronic pain states who are using indwelling pump systems.

Intrathecal and epidural toxicity

Advances in the fields of chemotherapy and chronic pain management have resulted in an increase in the number of drugs introduced into the intrathecal space. Despite the fact that early work by Sjoberg [112] suggested the use of long-term intrathecal infusions containing preservatives was not associated with any histopathological damage, there have been continuing concerns about the relative safety of using non-preservative-free products [113, 114]. While there is evidence to suggest that the use of chlorbutol [115] or sodium bisulphite [116] under certain conditions can be linked to neurotoxic sequelae after intrathecal administration, such conclusions cannot be extrapolated to include all preservatives. For example, there have been a number of studies of the safety of paraben-containing solutions of neostigmine [20, 113, 117], the conclusions of which suggest that their administration is not associated with any obvious sequelae [117, 121].

Sulphites received attention in the 1980s when their accidental intrathecal administration in combination with the local anaesthetic 2-chlorprocaine resulted in a number of cases of permanent neurological impairment [116]. Investigations by a number of workers [122, 123] determined that it was the sodium bisulphite preservative which was responsible for the observed nerve damage, perhaps enhanced by the acidic pH of the solution [124].

There is also conflicting evidence concerning the safety of solutions containing benzyl alcohol given by the intrathecal route [125, 126], since under certain conditions their administration has been associated with neurotoxic sequelae [127, 128]. There have been insufficient studies performed to completely clear the drug for intrathecal use, and at least one group has suggested that more controlled studies should be conducted on aspects of its use near the spinal cord [114].

Similarly, it has also been advocated that any drug administered into the epidural space should also be preservative-free [129, 130]. Despite the general feeling that all drugs administered intrathecally or epidurally should be preservative-free [114], this is not always practically possible, as manufacturers are sometimes unable or reluctant to produce preservative-free products. Furthermore, the costs involved in the preparation of these products are often prohibitive, costing more than 10 times the cost of its preservative-containing counterpart [131]. Practitioners are therefore often faced with a choice between using preservative-containing products originally produced for systemic use, or not giving the drug at all. However, to complicate the picture further, reports of epidural inflammation following the implantation of long-term epidural catheters continue to occur despite the use of preservative-free solutions [132, 133], causing some to question the relative importance of demanding the use of preservative-free solutions when they are introduced into the epidural space [131].

Propylene glycol is a common additive in depot steroid injections such as methylprednisolone and triamcinalone, in concentrations of up to 3%. These products were never intended for spinal use [134] but have been introduced into the epidural space for decades for the treatment of a variety of conditions [135, 136]. A number of writers have suggested that pharmaceutical additives such as propylene glycol or benzyl alcohol might be responsible for cases of arachnoiditis occasionally seen after epidural steroid injection [137–139], although, as pointed out by Spaccarelli in an extensive review [140], most of these cases had complicating factors, making it difficult to draw any clear conclusions. Furthermore, a wide range of animal studies failed to demonstrate that either propylene glycol or benzyl alcohol had any direct neurotoxic effects [141–144].

Conclusions

The various additives used in pharmaceutical manufacturing represent a diverse range of chemical compounds with varied actions. Indeed, many drug additives exhibit more than one action. Importantly, information detailing the exact pharmaceutical excipients that are included in any

particular product can be difficult to obtain [145]. Such data are often omitted on drug labels, and may only be found by a careful examination of either the package insert or the manufacturer's prescribing information [146].

As long as 10 years ago, those involved in pharmaceutical manufacturing made the point that many drug additives were less than ideal and had a number of deficiencies which should be addressed, such as a high degree of sensitisation or dose-related toxicities [147, 148]. They concluded that new classes of preservatives were urgently needed. Unfortunately, there have been few advances in the development of new preservative agents in particular, or drug additives in general, in recent years, although the cyclodextrins offer an improved method of enhancing the solubility of highly lipophilic compounds which are found so often in anaesthesia.

Commercial pharmaceutical preparations usually contain at least one of the so-called 'additives' in combination with the active drug. Under normal circumstances, these additives have little pharmacological activity. Nevertheless, the anaesthetist should be aware of the rationale behind their inclusion, and of the circumstances under which they may exhibit toxicities.

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