Intravenous Emulsions

Description

This report covers three different types of emulsions, each of which can be used intravenously. These three emulsions are liposomes, lipid emulsions for parenteral nutrition and perfluorochemical emulsions.

Liposomes

Liposomes are somewhat different than what one normally considers to be an emulsion, but in size and physical characteristics there is some similarity to emulsions. Liposomes are closed, pherical shells composed of one or more lipid bilayers. The interior of the liposome is aqueous. A lipid is any molecule soluble in nonpolar, organic solvents such as chloroform and ether. The type of lipid associated with liposomes is phospholipid. The phospholipid molecule has a water-soluble end and an oil-soluble end. An example of a phospholipid is lecithin in egg yolk. The bilayer (double layer) is composed of two monolayers of phospholipid with the nonpolar (oilsoluble) molecular ends facing inward and with the polar ends of both monolayers facing out. The liposome vesicle can be made up of a single bilayer or multiple bilayers. They are described with respect to size and number of layers (lamella):

a. 20 to 50 nanometers - small unilamellar vesicles

b. 0.10 to 1.00 micrometers - large unilamellar vesicles

c. 0.10 to 5.00 micrometers - multilamellar vesicles

The importance of liposomes lies in the fact that they can be used as carriers for drugs, enzymes and other biologically active molecules. These active ingredients are encapsulated in the liposome and are transported by these vesicles to different organs in the body. Liposomes are also used in cosmetic products for skin-care treatments. The liposomes enhance the penetration of moisturizing and other agents into the skin. The food industry is using liposomes to encapsulate flavors, functional ingredients and vitamins.

Liposome vesicles can be prepared by many different methods:

a. Homogenization

b. French press

c. Sonication by probe or cleaning bath

d. Detergent dilution and dialysis

e. Injection of ethanolic solution into an aqueous solution

Although liposomes are expensive to prepare, usually because of the high cost of ingredients and the small sample size (2mL), their potential importance and usefulness have led researchers into the development of larger batches. The Gaulin and Rannie homogenizers are well suited to the preparation of larger batches of these products and have been successfully used to make liposome vesicles.

In order to prepare liposomes of smaller diameter, the homogenizing pressure should be 6000 psig (41.38 MPa) to 15,000 psig (103.4 MPa), and multiple passes are usually required to obtain a narrow size distribution.

The liposomes are analyzed in a variety of ways such as gel chromatography, NMR, electron microscopy, light scattering and dynamic light scattering such as performed with a NICOMP Submicron Particle Sizer (Particle Sizing Systems, Santa Barbara, CA).

Lipid Emulsions for Parenteral Nutrition

These intravenous emulsions for nutritive therapy are used when a patient is not able to take food or accept vascular administration of nutrition. These emulsions consist of an oil, such as soybean oil or safflower oil; an emulsifier, such as egg lecithin or soybean lecithin; and a balanced blend of amino acids in a continuous phase of distilled water. The composition of the lecithin used is important, because the stability of the emulsion depends on the types and amounts of phospholipids in the lecithin. These emulsions are injected into the vein and provide a means of administering a nutritive fluid to the patient.

To prevent serious side effects and to enhance the physical stability of the emulsion, the droplet size of the oil must be kept small, usually below 0.6 μm with an average size of about 0.3 μm. It is important to minimize the number of droplets greater than one micrometer. Larger droplets can be trapped in the capillaries of the lungs.

The AccuSizer Optical Particle Sizer (Particle Sizing Systems, Santa Barbara, CA) has been used to reveal the presence of these oversized droplets (see reference by Driscoll). As described above, the Gaulin and Rannie homogenizers are used at high pressures and with multiple passes to generate a small particle size and a narrow size distribution. This homogenized product may then be filtered and autoclaved at 110°C for 40 minutes, further reducing particle size.

Another similar application is the use of submicron emulsions to carry an intravenous anesthetic agent such as propofol. The active ingredient is dissolved into soybean oil and the oil is emulsified into water. Phospholipids are the surface-active agent. The mean droplet size is in the range of 160 to 200 nanometers, which is achieved by high-pressure homogenization.

The use of pre-mixers to the homogenizer may be able to eliminate one pass for these multi-pass processes, because they reduce oversized droplets and generate a uniform, medium droplet-size distribution in the premix to the homogenizer. Therefore, the homogenizer is used more efficiently because the energy it imparts to the emulsion is used to reduce these medium droplets to a much smaller size range, and the energy is not dissipated on work to reduce oversized droplets to medium-sized droplets.
These emulsions can be tested for droplet size by using a dynamic light-scattering device such as a NICOMP analyzer (Particle Sizing System, Inc., Santa Barbara, CA).

Perfluorochemical Emulsions

The emulsions of perfluorochemicals have been called artificial blood or blood substitutes because they have been used to replace blood temporarily in animals and humans. A better description is temporary oxygen carrier. These emulsions consist of a perfluorocarbon oil; an emulsifier, Pluronic F68 was used in the original formulations; hydroxyethyl starch and various salts in water. The perfluorocarbon oil is the oxygen carrier; that is, the oil can dissolve oxygen and carry it through the body. Various oils have been studied, and some oils are more effective than others. Some oils make good emulsions but have low excretion rates, while other oils have higher excretion rates (less retention in the body) but make poor emulsions. Work is being carried out to find the best possible perfluorochemical for this application.

These emulsions have a great deal of potential for the following reasons: non-availability of compatible blood, blood transfusion refused for religious reason, bloodless surgery, for the treatment of heart infarction, cerebral circulatory troubles, severe burns, carbon monoxide poisoning, organ perfusion and for avoidance of disease during blood transfusion.

The perfluorochemicals, themselves, are chemically and biologically inert and are generally nontoxic. However, in their pure form they would cause immediate embolism; therefore, they must be emulsified in water. The droplet size of the emulsion must fall in the range of 0.1 μm to 0.6 μm, because acute toxicity was found to increase with the proportion of particles greater than 0.4 μm.

A more recent form of this emulsion is called OxygentTM (Alliance Pharmaceutical Corp., San Diego, CA). This emulsion uses a perfluorochemical called perflubron and egg yolk lecithin as surfactant.

The homogenizer has been extensively used to prepare these emulsions. To obtain the small average droplet size, high-pressure homogenization is used with multiple passing. The average droplet size of these emulsions can be determined using a NICOMP Submicron Particle Sizer (Particle Sizing Systems, Santa Barbara, CA).
Another product being currently investigated as an oxygen carrier is quite different from the perfluorochemical emulsion. This artificial red blood cell product consists of modified hemoglobin dispersed into a carrier liquid. There have been various approaches to producing this type of product. Some of these products are: HEMOLINK (Hemosol Inc.), PolyHeme® (Northfield Laboratories Inc.), and Hemopure (Biopure Corporation).

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