Iodinated Liposomes as Contrast Agents

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Abstract: The use of liposomal contrast agents for computed tomography (CT) imaging applications is considered. The properties of the various liposome types as well as methods for their preparation are discussed. Specific challenges for the preparation and use of CT contrast-carrying liposomes are outlined. Available experience on the use of CT liposomes for liver and spleen imaging in preclinical animal models and humans is reviewed. The use of surface-modified and conventional liposomes for CT blood-pool imaging is discussed in light of the published animal data. Finally, new trends in the use of CT liposomes are considered based on the limited data available to date.

Keywords: Liposomes, preparation methods, computed tomography (CT), iodinated contrast agents, surface modification, liver imaging, blood-pool imaging, animal experience, human experience, liver tumors.

18.1. Introduction

The potential usefulness of liposomal contrast agents for liver and spleen imaging has already been demonstrated in the early 1980s (e.g., Havron et al., 1981). Based on the encouraging liver and spleen imaging results in animals, clinical studies (phase II) were contemplated as early as 1984 (Ryan et al., 1984). However, due to technological hurdles associated with the reproducible large-scale production of pharmaceutically acceptable liposomes with high encapsulation (Tilcock, 1999), it took until the second half of the 1990s to finally study the computed tomography (CT) imaging properties of such liposomes in humans (Leander et al., 1998).

Initial development centered on passive targeting of liposomes to the Kupffer cells in the liver and macrophages in the spleen (= reticuloendothelial system (RES)). Since phagocytic activity is not displayed by tumor tissue, the contrast agent can selectively be concentrated in the healthy tissue resulting in an increased tissue to tumor density difference (expressed in Hounsfield Units (HU)).
By the middle of the 1990s, new methods for liposome production (e.g., extrusion) were available which allowed reproducible large-scale production of stable liposomes with encapsulation efficiencies up to 50% and corresponding iodine/lipid ratios (mg/mg) well above 1. The resulting formulations showed acceptable tolerability, elimination, and imaging properties in various animal models (i.e., rat, rabbit, and non-human primates) so that eventually clinical testing (phase I) in humans could be performed by various groups.

Due to the introduction of methods for modification of liposome surfaces, it became possible to produce liposomes which could avoid the RES for prolonged timeperiods (Allen, 1994). Since CT liposomes with extended circulation times may be useful as blood-pool (vascular) imaging agent, various groups evaluated the imaging properties of unmodified as well as PEG-liposomes, in rabbits and non-human primates (e.g., Sachse et al., 1997; Schmiedl et al., 1999).

Recently, CT contrast agent-carrying immunoliposomes which carry an antibody (or their fragments) to a specific cell-surface protein to target the vesicles to the tissue of interest have been contemplated. In the present chapter, the available data on CT liposomes is reviewed and discussed.

18.2. Liposome Types

Liposomes are self-closed spherical or elliptical lipid vesicles composed of one or more lipid bilayers, which entrap an aqueous phase (Figure 18.1). Depending on their size, one can differentiate small unilamellar vesicles (SUVs) with mean diameters up to 100 nm and large unilamellar vesicles (LUVs) with diameters above 100 nm up to the micrometer range. Vesicles with several bilayers (lamellae) are called multilamellar vesicles (MLVs).

For the production of liposomes, mainly phospholipids like phosphatidylcholine (PC) or phosphatidylethanolamine (PE), which are main constituents of biological membranes, are employed. Additionally cholesterol (CH) is often used for membrane stabilization. The physico-chemical properties of the liposomes are dependent on the lipid composition (qualitative and quantitative), size, temperature, pH, and type and strength of the employed buffer.

Liposomes can be loaded with various polar (hydrophilic) or non-polar substances which can be entrapped in the aqueous liposome interior, dissolved in the hydrophobic bilayer, or adsorbed on the liposome surface. For encapsulation of hydrophilic compounds like X-ray (CT) contrast agents, unilamellar liposomes are most effective since the volume of the aqueous compartment in relation to a given lipid concentration is larger compared to multilamellar vesicles (MLVs). Most preferable are large unilamellar vesicles which have the highest captured volume, i.e. liter aqueous phase per mole of lipid compared to the other liposome types. In Table 18.1, the properties of the various liposome types are listed including encapsulation efficiencies (i.e., percent of total employed drug encapsulated) which were obtained with various hydrophilic drugs.