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A Dendrogram Clustering of Lipid Nanoparticles

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In the last two decades, nanomedicine has grown into interest especially for cancer therapy or diagnostics for instance. Scientifics have been particularly attracted by the use of lipid-based nanoparticles as a new pharmaceutical delivery system to overcome biological barriers [1]. Indeed, thanks to their size, components, shape or even their lipid structure, they were shown to be more efficient and effective than pre-existing delivery systems. For instance, due to the fact that their main components are lipids, mostly well tolerated components, this allows them to optimize their pharmacokinetics as well as their bioproduction when introduced into human organism.

Our goal is to propose a new approach to classify the different types of lipid nanoparticles according to their formulation and manufacturing features.

We have analyzed 30 articles devoted to the characterization of lipid nanoparticles as well as the methods employed to produce them. The articles were selected according to the following requirements: published within the last two decades. A total of 39 features were used to characterize each LNP: size (3), shape (3), lipid structure (4), components (11), and preparation method (18) [3] and were gathered in a binary matrix. The latter was then used to produce the dendrogram done by Jaccard index. A dendrogram is a diagram frequently used to illustrate the arrangement of groups or clusters generated by hierarchical grouping where the height reflects the distance between the clusters and the vertical axis indicates a distance or dissimilarity measure [2]. Therefore, the smaller the link height, the more similar the two connected groups are.

Through the statistical dendrogram (Figure 2), we are able to split up the different types of LNP into two main groups, which are in concordance with what is commonly depicted in the scientific committee [1] [4]. Indeed, we can notice that the four types of solid lipid nanoparticles, e.g. SLN, NLC, PLN and LDC, are in the same cluster and that the four sorts of liposomes, e.g. GUV, MLV, SUV and LUV, are also linked together. This dendrogram also allowed us to position specific types of LNP such as niosomes, spongosomes, virosomes, transfersomes or ethosomes, *wrt* commonly used families.

A statistical analysis based on 30 published articles and 39 formulation and preparation features has produced a dendrogram, which allowed to position new LNP with respect to the most studied structures in the scientific committee.

[1] M. Rajabi and S. A. Mousa, *Current pharmaceutical biotechnology*, 2016, vol. 17, No 8, p. 662-672.

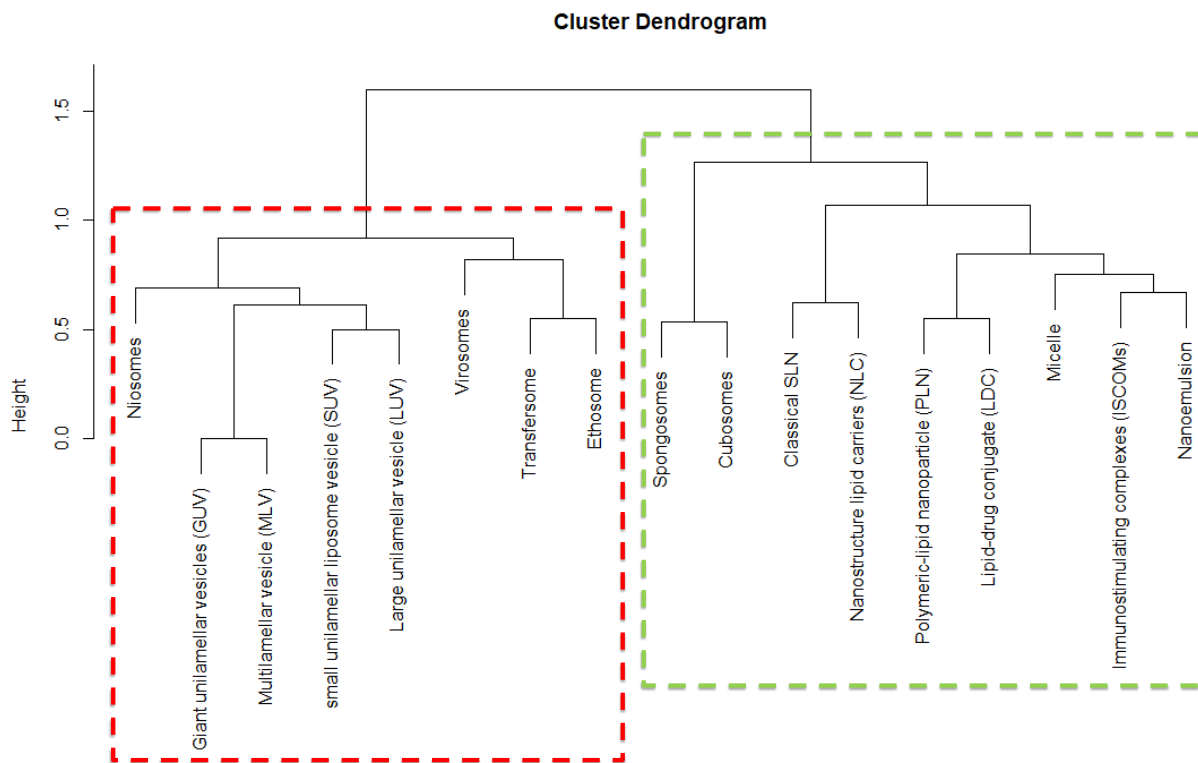
[2] M. Schonlau, *The Stata Journal*, 2002, vol. 2, no 4, p. 391-402.

[3] L. Battaglia and M. Gallarate, *Expert opinion on drug delivery*, 2012, vol. 9, no 5, p. 497-508

[4] N. Naseri, H. Valizadeh and P. Zakeri-Milani. *Advanced pharmaceutical bulletin*, 2015, vol. 5, no 3, p. 305.

Type of Lipid Nanoparticles	Schema	Size	Structure	Composition
Solid Lipid Nanoparticle (SLN)	Classical SLN	10 to 1000nm	Spherical, lipid layer	hydrophobic solid matrix core with a phospholipid coating.
	Polymeric-lipid nanoparticle (PLN)	10 to 1000nm	Spherical, lipid layer	biodegradable polymeric material core containing drugs or any substances which are to be encapsulated then this core is further
	Lipid-drug conjugate (LDC)	10 to 1000nm	Spherical, lipid layer	
	Nanostructure lipid carriers (NLC)	10 to 1000nm	Spherical, lipid layer	3 types: Imperfect, amorphous, multiple. Solid lipid (long chain) forming a solid lipid core matrix that can solubilize lipophilic molecules and liquid lipid (short chain) forming a lipid core which is stabilized by surfactants.
Liposome	small unilamellar liposome vesicle (SUV)	<100nm	one lipid bilayer	Mainly composed of phospholipids but may contain also other lipid compatible with the lipid bilayer.
	Large unilamellar vesicle (LUV)	100-1000nm	one lipid bilayer	Mainly composed of phospholipids but may contain also other lipid compatible with the lipid bilayer.
	Giant unilamellar vesicles (GUV)	>1µm	one lipid bilayer	Mainly composed of phospholipids but may contain also other lipid compatible with the lipid bilayer.
	Multilamellar vesicle (MLV)	>1µm	several lipid bilayers	Mainly composed of phospholipids but may contain also other lipid compatible with the lipid bilayer.
	Transfersome	10 to 100nm	vesicular drug carriersystem	phospholipid, surfactant, and water.
	Ethosome	10nm to 1µm	soft malleable vesicles, lipid bilayer	alcohols, phospholipids and water.
	Niosomes		one lipid bilayer	Single alkyl chain non-ionic surfactants in addition to cholesterol derivatives.
Micelle		droplet size 10–100 nm	Approximately spherical, lipid layer	aggregate (or supramolecular assembly) of surfactant molecules dispersed in a liquid colloid.
Spongosomes			random 3D membrane organization.	Phospholipid, monoglycerides, water
Cubosomes			periodically ordered cubic lattice membrane structures with different symmetries such as double diamond (D), gyroid (G), or primitive (P) cubic types.	Phospholipid, monoglycerides, water
Virosomes			unilamellar phospholipid membrane (either a mono- or bi-layer) vesicle incorporating virus derived proteins (glycoproteins).	Phospholipid, Glycoproteins
Immunostimulating complexes (ISCOMs)		40nm	pentagonal dodecahedron arrangement of micelles containing saponin and lipid held together by hydrophobic interactions and stabilized through its negative surface charge.	cholesterol, phospholipids, saponin adjuvant Quil A, and protein antigen.
Nanoemulsion		droplet size 10–100 nm	Approximately spherical, lipid layer	nanosized dispersions of oil in water (o/w) or water in oil (w/o) stabilized by an interfacial film of surfactant and cosurfactant molecule.

Figure 1: Schematic representation of the different types of lipid nanoparticles within their main properties.



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Figure 2: Dendrogram obtained after the analysis of the data obtained from the review of various articles.