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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.



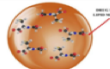
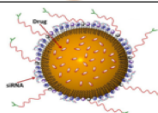

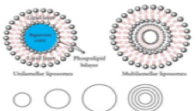




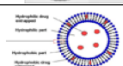



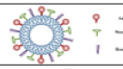

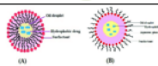
Type of Lipid Nanoparticles		Schema	Size	Structure			Composition	
Solid Lipid Nanoparticle (SLN)	Classical SLN		10 to 1000nm	Spherical, lipid layer			hydrophobic solid matrix core with a phospholipid coating.	
	Polymeric-lipid nanoparticle (PLN)		10 to 1000nm	Spherical, lipid layer			biodegradable polymeric 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		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			amorphous		
	Large unilamellar vesicle (LUV)		100-1000nm			multiple		
	Giant unilamellar vesicles (GUV)		>1μm					
	Multilamellar vesicle (MLV)		>1μm					
	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 (ISCs)			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.

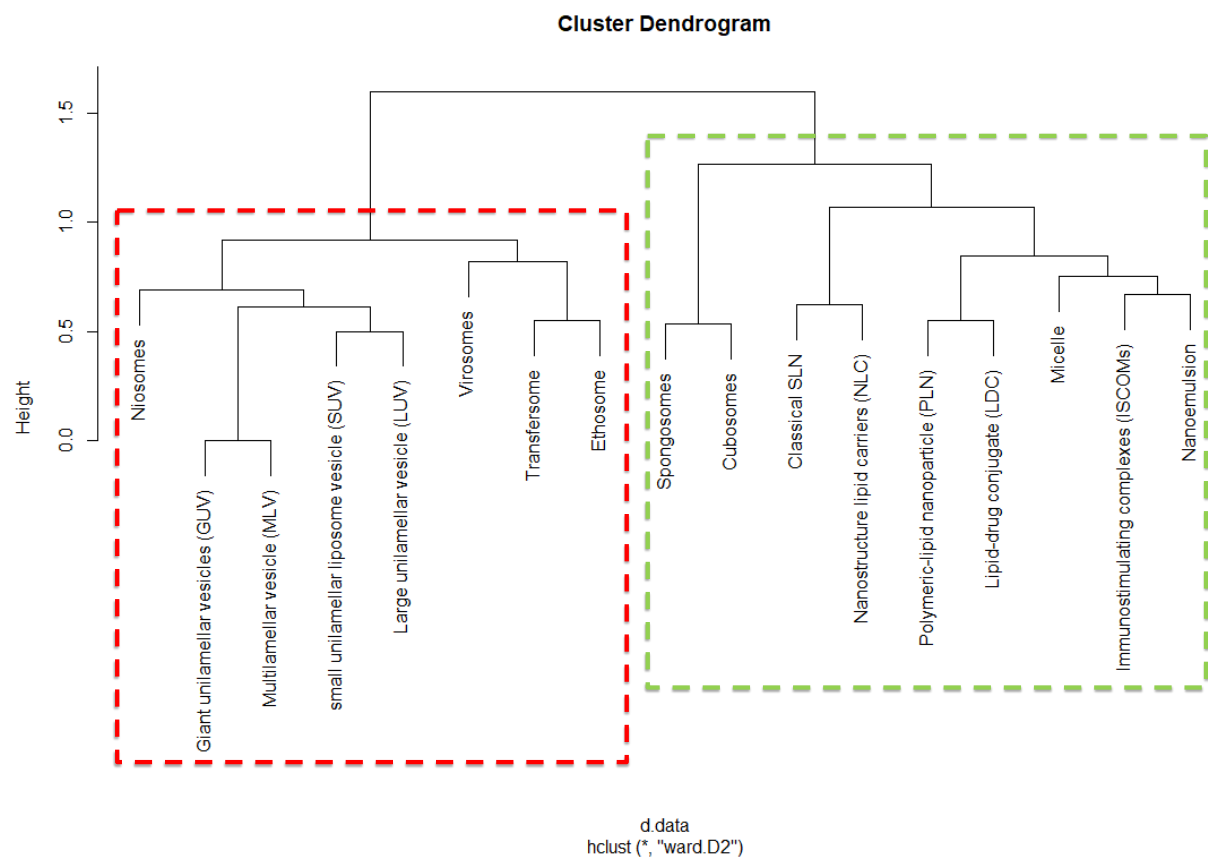


Figure 2: Dendrogram obtained after the analysis of the data obtained from the review of various articles.