

Supplementary Information for:

Liposome production by microfluidics: potential and limiting factors

Dario Carugo^{1,2}, Elisabetta Bottaro³, Joshua Owen¹, Eleanor Stride¹ and Claudio Nastruzzi*³

¹Institute of Biomedical Engineering, Department of Engineering Science, Old Road Campus Research Building, University of Oxford, Oxford, United Kingdom

²Faculty of Engineering and the Environment, University of Southampton, Southampton, UK

³Department of Life Science and Biotechnology, University of Ferrara, Italy

*Correspondence to:
Prof Claudio Nastruzzi, PhD
Department of Life Sciences and Biotechnology
University of Ferrara
via Fossato di Mortara 17, 44121, Ferrara, Italy
Phone: +39-0532-455348
e-mail: nas@unife.it
Web: www.biomaterials.it

Table S1 | Medicinal products containing liposomes (currently on the market)

product name/ drug/ formulation	composition	lipid composition (mg/ml)		diluent	route of injection
Abelcet Amphotericin B Suspension	<i>Lipids</i> DMPC, DMPG <i>Other excipients</i> Sodium Chloride	<i>Starting</i> DMPC 5.01 DMPG 2.14 Tot=7.15	<i>Ending</i> DMPC 3.4 DMPG 1.5 Tot=4.9	After mix withdraw the correctly dose and dilute to 1 mg/ml with dextrose 5%	Intravenous
Ambisome Amphocil Amphotericin B Powder	<i>Lipids</i> HSPC,DSPG, chol, α -Toc, DSH <i>Other excipients</i> Sucrose, disodium succinate hexahydrate	<i>Starting</i> HSPC 23.35 Chol 11.19 DSPG 8.98 α -Toc 0.124 DSH 13.88 Tot=57.52	<i>Ending</i> HSPC 5.83 Chol 2.79 DSPG 2.25 α -Toc 0.031 DSH 3.47 Tot=14.37	Dilute it in dextrose 5 %	Intravenous
Curosurf Phospholipid fraction from porcine lung suspension	<i>Lipids</i> Phospholipid fraction from porcine lung	Phospholipid fraction from porcine lung 80 Tot=80		No dilution needed	Intratracheal or intra bronchial
DaunoXome Daunorubicin Emulsion	<i>Lipids</i> DSPC, chol, <i>Other excipients</i> Sucrose, glycine, calcium chloride	<i>Starting</i> DSPC 28.16 chol 6.72 Tot=34.80	<i>Ending</i> DSPC 14.08 Chol 3.36 Tot=17.44	Diluted 1:1 with 5% dextrose	Intravenous

Depocyt Cytarabine Suspension	<i>Lipids</i> DOPC, triolein, DPPG <i>Other excipients</i> Sodium chloride	DOPC 5.7 Chol 4.4 Triolein 1.2 DPPG 1 Tot=12.30		No dilution needed	Intravenous
DepoDur Morphine sulfate Suspension	<i>Lipids</i> HSPC,DSPG,DOPG, chol, tricaprylin, triolein	Chol 3.3 Triolein 0.1 DOPC 4.2 DPPG 0.9 Tricaprylin 0.3 Tot=8.80		No dilution needed	Epidural
Doxil Lipo-dox Caelyx Doxorubicin Suspension	<i>Lipids</i> HSPC,DSPG, chol, MPEG–DSPE <i>Other excipients</i> Ammonium sulfate, sucrose, histidine	<i>Starting</i> HSPC 9.58 Chol 3.19 MPEG–DSPE 3.19 Tot=15.96	<i>Ending</i> HSPC 1.72 Chol 0.57 MPEG– DSPE 0.57 Tot=2.86	Diluted in 250 ml of 5% dextrose	Intravenous
Epaxal Inactivated hepatitis A virus (strain RG-SB) Suspension	<i>Lipids</i> <i>Lecithin, cephalin</i> <i>Other excipients</i> Sodium chloride	Lecithin 0.08 Cephalin 0.02 Tot=0.10		No dilution needed	Intramuscular
Inflexal V Inactivated hemagglutinine of Influenza virus strains A and B Suspension	<i>Lipids</i> Lecithin <i>Other excipients</i> Sodium chloride, disodium phosphate dehydrate, potassium dihydrogen phosphate	Lecithin 0.234 Tot=0.234		No dilution needed	Intramuscular
Marqibo Vincristine sulfate suspension	<i>Lipids</i> Sphingomyelin, chol <i>Other excipients</i> Mannitol, sodium citrate, sodium phosphate, sodium chloride	Sphingomyelin 73.5 Chol 29.5 Tot=103.0		The final drug product is prepared on site from the components in the Marqibo Kit	Intravenous

Myocet Doxorubicin Powder	<i>Lipids</i> EPC, chol <i>Other excipients</i> Citric acid, sodium hydroxide	EPC Chol (55:45 molar ratio)	Withdraw 20 ml sodium chloride solution for injection (0.9%), and inject into Myocet doxorubicin HCl, intended for preparation	Intravenous
Visudyne Verteporfin Powder	<i>Lipids</i> HSPC,DSPG, chol ascorbyl palmitate <i>Other excipients</i> Butylated hydroxytoluene	EPC DMPC (3:5 molar ratio)	Reconstitute Visudyne with 7.0 ml water for injections to produce 7.5 ml of a 2.0 mg/ml solution	Intravenous

Abbreviation: **HSPC = hydrogenated soy phosphatidylcholine; DSPG = distearoylphosphatidyl glycerol; chol = cholesterol; α-Toc = alpha-tocopherol; DSH = disodium succinate hexahydrate; DMPC = dimyristoylphosphatidylcholine; DMPG = dimyristoylphosphatidylglycerol; DSPC = distearoylphosphatidylcholine ; MPEG-DSPE = N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phospho-ethanolamine sodium salt ;EPC = egg phosphatidylcholine; DOPC= dioleoylphosphatidylcholine; DPPG = dipalmytoilphosphatidylglycerol; DOPG = dioleoylphosphatidylcholine**

Date were obtained from the information leaflets included into the packaging of the reported medicines. Leaflets can be consulted at the following websites.

Abelcet: www.medicines.org.uk/emc/PIL.28850.latest.pdf

Ambisome: www.medicines.org.uk/emc/PIL.8363.latest.pdf

Amphocil: www.infarmed.pt/infomed/download_ficheiro.php?med_id=360&tipo_doc=fi

Curosurf: www.medicines.org.uk/emc/PIL.21480.latest.pdf

DaunoXome: www.medicines.org.uk/emc/PIL.25594.latest.pdf

Depocyt: www.medicines.org.uk/emc/PIL.15024.latest.pdf

DepoDur: www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1428643391518.pdf

Doxil: www.doxil.com/shared/product/doxil/doxil-prescribing-information.pdf

Lipo-dox Caelyx: www.janssen.com/canada/sites/www_janssen_com_canada/files/product/pdf/cae10102013cpm_nc.pdf

Epaxal: www.medicines.org.uk/emc/PIL.26278.latest.pdf

Inflexal V: www.medicines.org.uk/emc/PIL.24908.latest.pdf?isAttachment=true&documentid=24908

Marqibo: www.accessdata.fda.gov/drugsatfda_docs/label/2012/202497s000lbl.pdf

Myocet: www.tevauk.com/mediafile/id/20670.pdf

Visudyne: www.medicines.org.uk/emc/PIL.4647.latest.pdf

Table S2 | Volumetric ratio and relative volumes for water, ethanol and lipid solution in ethanol employed in the bulk, controlled ethanol injection experiments.

Variation	Vr = 10			Vr = 20			Vr = 30			Vr = 40			Vr = 50		
	L	Et	W	L	Et	W	L	Et	W	L	Et	W	L	Et	W
Lipids	455	-	4545	238	217	4545	162	293	4545	122	333	4545	98	357	4545
Et	98	357	4545	98	140	4762	98	64	4838	98	24	4878	98	-	4545
Lipids Et	455	-	4545	238	-	4762	162	-	4838	122	-	4878	98	-	4902

Abbreviation: Vr = volumetric ratio between water and the ethanolic lipid solution; L = lipid solution; Et= ethanol; W = water. Volumes are expressed in microliters.