D-Lin-MC3-DMA

Cat. No.: HY-112251

CAS No.: 1224606-06-7

Molecular Formula: $C_{43}H_{79}NO_2$

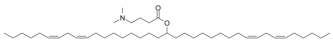
Molecular Weight: 642.09

Target: Liposome

Pathway: Metabolic Enzyme/Protease

Storage:

Pure form	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

Ethanol : 125 mg/mL (194.68 mM; Need ultrasonic)

DMSO : 100 mg/mL (155.74 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.5574 mL	7.7871 mL	15.5741 mL
5 mM	0.3115 mL	1.5574 mL	3.1148 mL
10 mM	0.1557 mL	0.7787 mL	1.5574 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% saline
   Solubility: 6.25 mg/mL (9.73 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: 5 mg/mL (7.79 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
   Solubility: 5 mg/mL (7.79 mM); Suspended solution; Need ultrasonic
4. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (3.89 mM); Clear solution
5. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (3.89 mM); Suspended solution; Need ultrasonic
6. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (3.89 mM); Clear solution
7. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (3.89 mM); Clear solution

BIOLOGICAL ACTIVITY

Description	D-Lin-MC3-DMA, an ionizable cationic lipid, is a potent siRNA delivery vehicle.

In Vitro

Preparation of MC3 Lipid Nanoparticles

Here we provide lipid molar ratios for LNPs in FDA-approved Patisiran (a siRNA targets the transthyretin (TTR) mRNA). The molar ratio of lipids in this formulation is D-Lin-MC3-DMA : DSPC : Cholesterol : PEG2000-C-DMG = 50 : 10 : 38.5 : 1.5[1], and RNA to lipid weight ratio is 0.05 (wt/wt).

A. Lipid Mixture Preparation

1. Dissolve lipids in ethanol and prepare 10 mg/m stock solutions. The lipid stock solutions can be stored at −20°C for later use.

Note 1: The ionizable lipid is usually a liquid. Due to the viscosity, it should always be weighed rather than relying on the autopipette volume.

Note 2: Cholesterol in solution should be kept warm (>37□) to maintain fluidity. Transfer the cholesterol solution promptly to avoid cooling.

2. Prepare the lipid mixture solution as described. For each mL of lipid mixture add the following: 548 µL of 10mg/mL D-Lin-MC3-DMA (HY-112251), 254 µL of 10mg/mL Cholesterol (HY-N0322), 134 µL of 10mg/mL DSPC (HY-W040193), and 64 µL of PEG2000-C-DMG (HY-145411) [2]. Mix the solutions thoroµghly to achieve a clear solution. This mixture contains 10 mg of total lipid.

Note 3: The choice of lipids and ratios may be changed as desired and this will affect the LNP properties (size, polydispersity, and efficacy) and the amount of mRNA required.

B. siRNA Preparation

1. Prepare a 166.7 µg/mL siRNA solution with 100 mM pH 5 sodium acetate buffer.

Note 4: The lipid:siRNA weight ratio influences the encapsulation efficiency. Other weight ratios may be prepared as alternative formulations and should be adjusted accordingly by user.

C. Mixing

There are three commonly used methods to achieve rapid mixing of the solutions: the pipette mixing method, the vortex mixing method, and the microfluidic mixing method. All these mixing methods can be used for various applications.

It is important to note that pipette mixing method and vortex mixing method may yield more heterogeneous LNPs with lower encapsulation efficiencies and is prone to variability. Microfluidic devices enable rapid mixing in a highly controllable, reproducible manner that achieves homogeneous LNPs and high encapsulation efficiency. Within these devices, the ethanolic lipid mixture and aqueous solution are rapidly combined in individual streams. LNPs are formed as the two streams mix and are then collected into a single collection tube.

1. Pipette Mixing Method:

1.1. Pipette 3 mL of the siRNA solution and quickly add it into 1 mL of the lipid mixture solution (A 1:3 ratio of ethanolic lipid mixture to aqueous buffer is generally used.) Pipette up and down rapidly for 20–30 seconds.

1.2. Incubate the resulting solution at room temperature for up to 15 minutes.

1.3. After mixing, the LNPs were dialyzed against PBS (pH 7.4) for 2 h, sterile filtered using 0.2 µm filters, and stored at 4°C.

2. Vortex Mixing Method:

1.1. Vortex 3 mL of siRNA solution at a moderate speed on the vortex mixer. Then, Quickly add 1 mL of the lipid mixture solution into the vortexing solution (A 1:3 ratio of ethanolic lipid mixture to aqueous buffer is generally used.). Continue

	vortexing the resulting dispersion for another 20–30 seconds. 1.2. Incubate the resulting solution at room temperature for up to 15 minutes. 1.3. After mixing, the LNPs were dialyzed against PBS (pH 7.4) for 2 h, sterile filtered using 0.2 μm filters, and stored at 4°C. 3. Microfluidic Mixing Method: 1.1 The 3 mL of siRNA buffer solution and 1 mL of the lipid mixture solution were mixed at a total flow rate of 12 mL/min (A 1:3 ratio of ethanolic lipid mixture to aqueous buffer is generally used.) in a microfluidic device. Note 5: Parameters such as the flow rate ratio and total flow rate can be altered to fine-tune LNPs. 1.2. After mixing, the LNPs were dialyzed against PBS (pH 7.4) for 2 h, sterile filtered using 0.2 μm filters, and stored at 4°C. Reference 1. Curr Issues Mol Biol. 2022 Oct 19;44(10):5013-5027. 2. Curr Protoc. 2023;3(9):e898. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Lipid nanoparticles (LNPs) containing distearoylphosphatidlycholine (DSPC), and ionizableamino-lipids such as dilinoleylmethyl-4-dimethylaminobutyrate (DLin-MC3-DMA) are potent siRNA delivery vehicles in vivo. LNP-siRNA systems optimize to achieve maximum gene silencing potency in hepatocytesfollowing IV administration in mice contain DLin-MC3-DMA (MC3), DSPC, cholesterol and a polyethyleneglycol (PEG)-lipid at mole ratios of 50/10/38.5/1.5. DLin-MC3-DMA exhibits an optimized pK_a value that leads to dramatically enhanced potency[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Nanotechnol. 2023 Jun 26.
- Bioact Mater. 2024 Apr, 34, Pages 125-137.
- ACS Nano. 2023 Jul 17.
- ACS Nano. 2023 Jun 6.
- Nat Commun. 2023 Jan 17;14(1):75.

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REFERENCES

[1]. Ferraresso F, Strilchuk AW, Juang LJ, Poole LG, Luyendyk JP, Kastrup CJ. Comparison of DLin-MC3-DMA and ALC-0315 for siRNA Delivery to Hepatocytes and Hepatic Stellate Cells. Mol Pharm. 2022;19(7):2175-2182.

[2]. Kulkarni JA, et al. Design of lipid nanoparticles for in vitro and in vivo delivery of plasmid DNA. Nanomedicine. 2017 May;13(4):1377-1387.

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