Integrating molecular dynamic(MD) simulation in the design and preparation of ibrutinib(IBR)-loaded liposomes for enhanced drug delivery

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NEXT-GENERATION DELIVERY INNOVATIONS

Outlines

- Introduction
  - Ibrutinib physicochemical properties
  - Ibrutinib marketed products and limitations
  - Objective: IBR-loaded liposome
- Methods
  - MD simulation for miscibility study
  - IBR-loaded liposome preparation and characterization methods
  - MD study through martini coarse-grained(CG) simulation
- Results
  - MD simulation results for miscibility study
  - IBR-loaded liposome formulation and characterization
  - Martini CG simulation results of IBR-loaded liposomes
- Conclusion

Introduction– Ibrutinib Properties

Table 1. Basic profile of ibrutinib[1]

Name	Ibrutinib
Description	White to off white powder
Molecular formula	$C_{25}H_{24}N_6O_2$
Molecular weight	440.50
Solubility	Insoluble in water and freely soluble in methanol and dimethyl sulfoxide
pKa	3.74
Melting point	149-158°C
Half life	4-6 hours
Mechanism	Bruton tyrosine kinase(BTK) inhibitor
Indications	Chronic lymphocytic leukemia (CLL) Small lymphocytic lymphoma (SLL) Waldenström macroglobulinemia (WM)

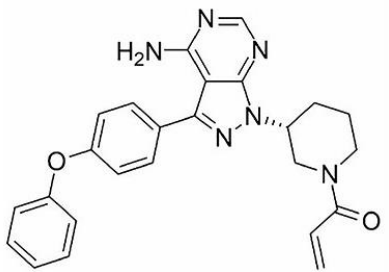


Figure 1: Chemical structure of ibrutinib[1]

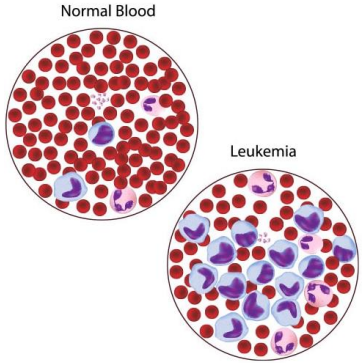


Figure 2: Chronic lymphocytic leukemia (CLL) /Small lymphocytic lymphoma (SLL)

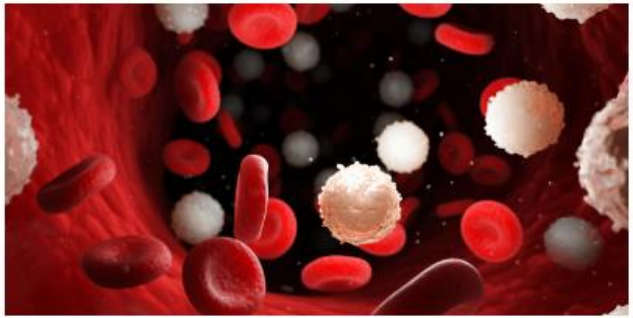


Figure 3: Waldenström macroglobulinemia (WM)

Reference: *FDA & CDER. HIGHLIGHTS OF PRESCRIBING INFORMATION. www.fda.gov/medwatch*
Reference: https://salishcancercenter.com/resources-support/cancer-types/leukemia/
https://docwirenews.com/post/emerging-treatment-options-and-considerations-in-waldenstrom-macroglobulinemia
https://www.differencebetween.com/what-is-the-difference-between-cll-and-sll/?__cf_chl_tk=eZ0U0h83CrmbruyvqpTZf0wqS9Y5RFLbUi0OrlBUgns-1726507808-0.0.1.1-6932

➢ Introduction– IBR marketed product and limitations

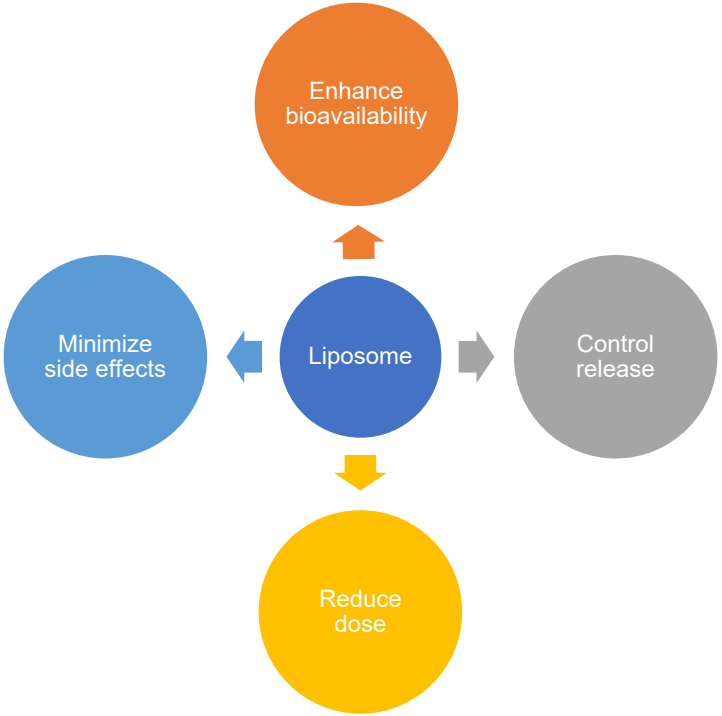
Table 2. **IMBRUVICA®** ibrutinib products

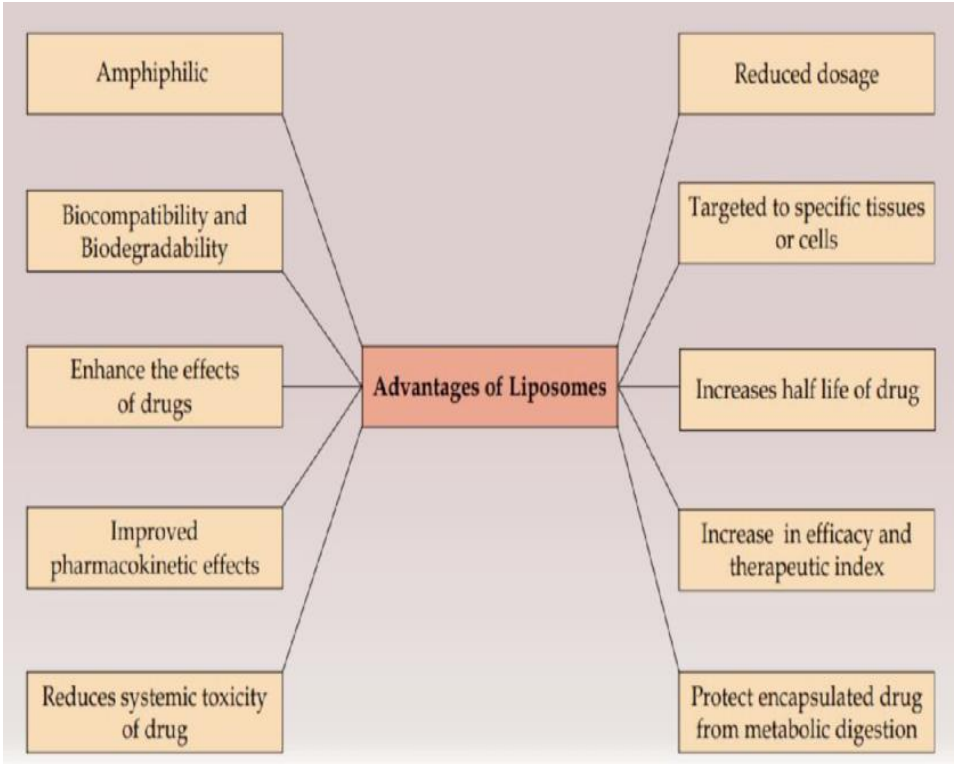
Dosage form	Strength (mg/tab, mag/capsule, mg/ml)	Dosing	Route
Tablets	140,280,420, 560	Once daily	Oral
Capsules	70, 140	Once daily	Oral
Suspension	70	Once daily	Oral

Limitations

Low bioavailability	High dose	Immediate release	Side effects	Adverse reactions
• 2.9% in fasting condition	• up to 560mg/tab	• Daily administration	• left atrial enlargement and atrial fibrillation	•(≥30%) in patients, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, bruising and nausea

➢ Introduction– IBR-loaded liposomes





Methods - Molecular Dynamics (MD) Simulation for miscibility study

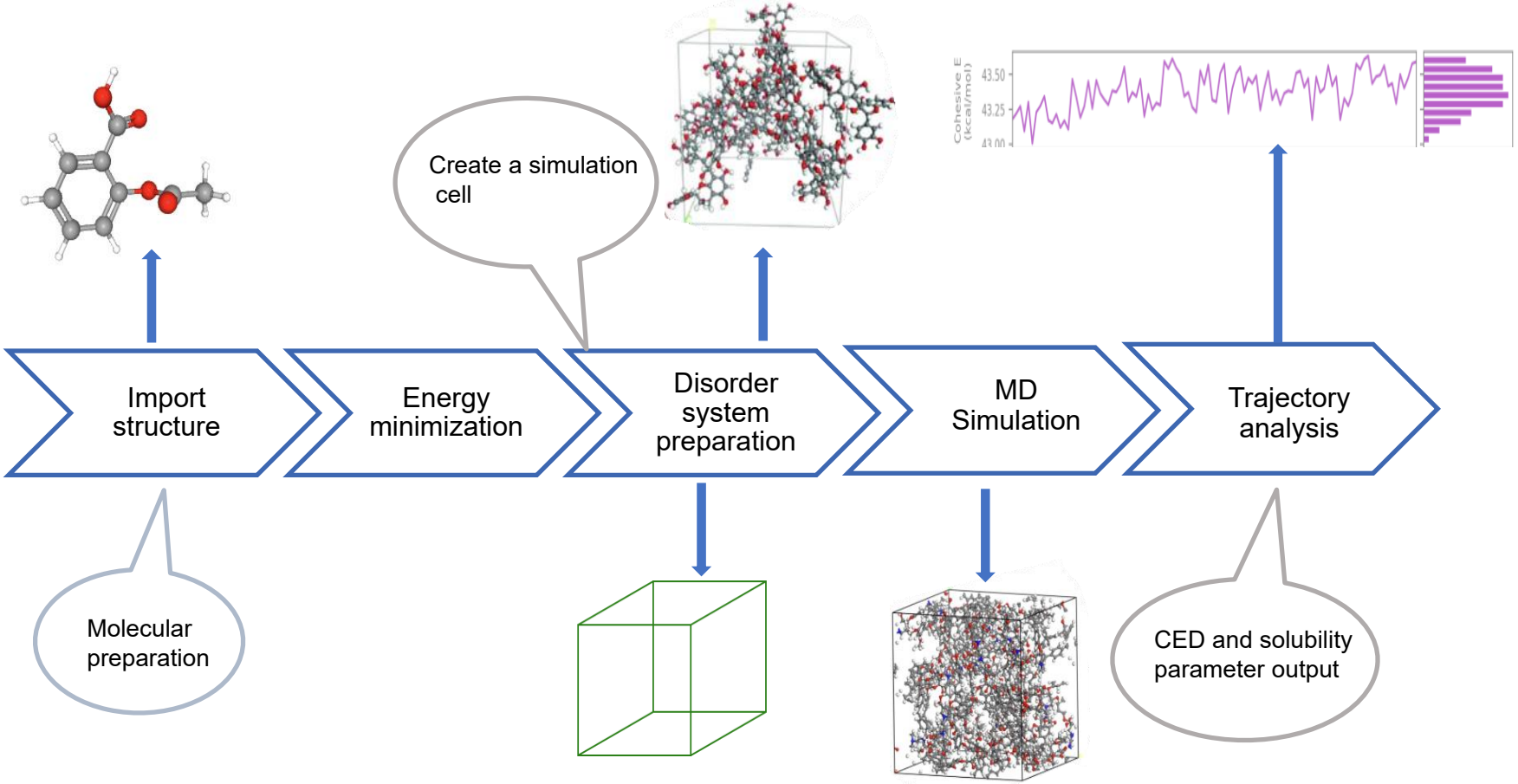


Figure 4: Steps in MD simulation

➢ Methods – Liposome preparation

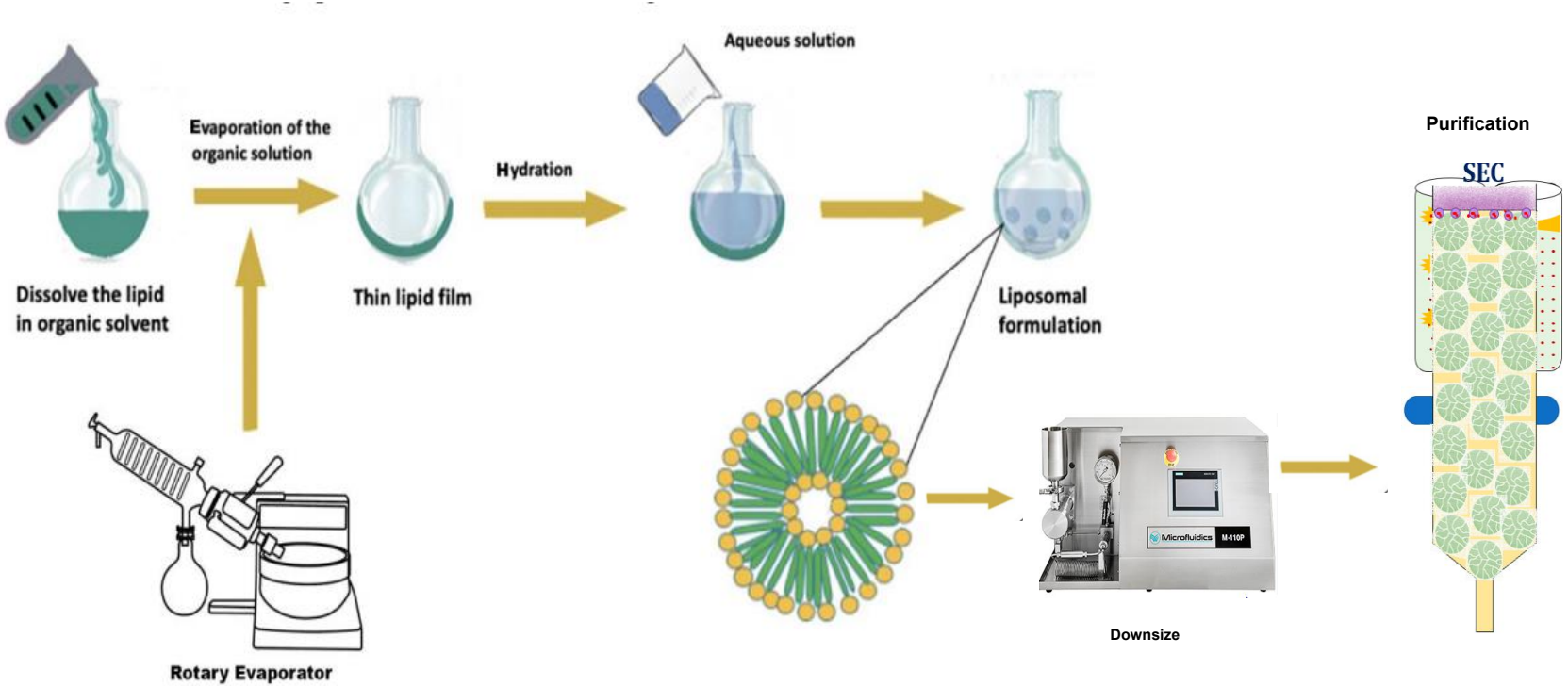


Figure 5: Schematic diagram of ibrutinib liposome preparation

➢ Methods – Liposome Characterization

Table 3. Characterization studies and analytical techniques

Characterization studies	Analytical Techniques	Notes
Morphology	TEM or Cyro-TEM	
Particle size, PDI, Zeta-potential	DLS	
Encapsulation Efficiency	RP-HPLC	
In-vitro drug release	RP-HPLC	USP Apparatus 4

TEM: Transmission electron microscopy DLS: Dynamic light scattering RP-HPLC: Reversed Phase -HPLC

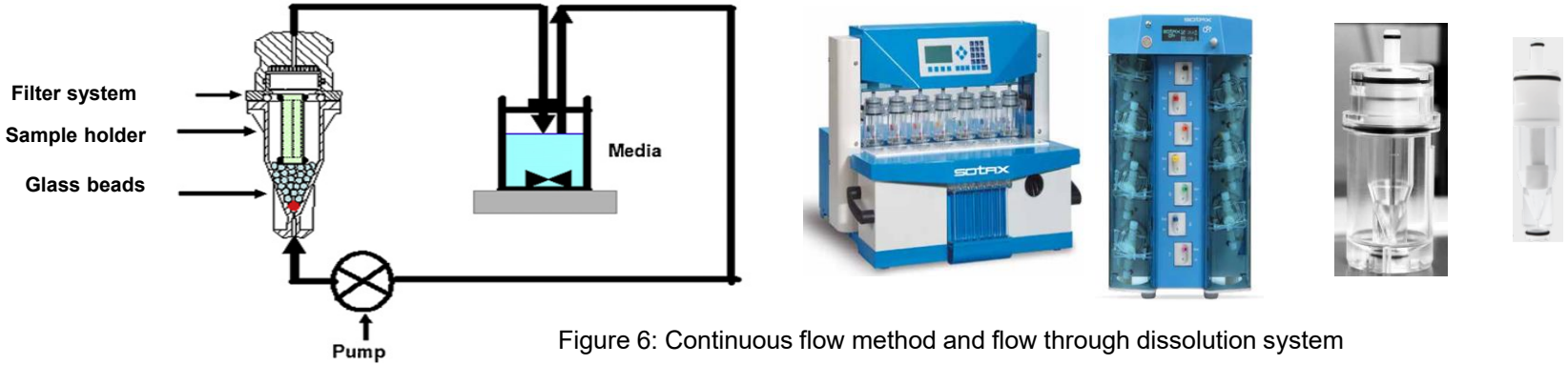


Figure 6: Continuous flow method and flow through dissolution system

➢ Methods – Coarse-grained(CG) Simulation

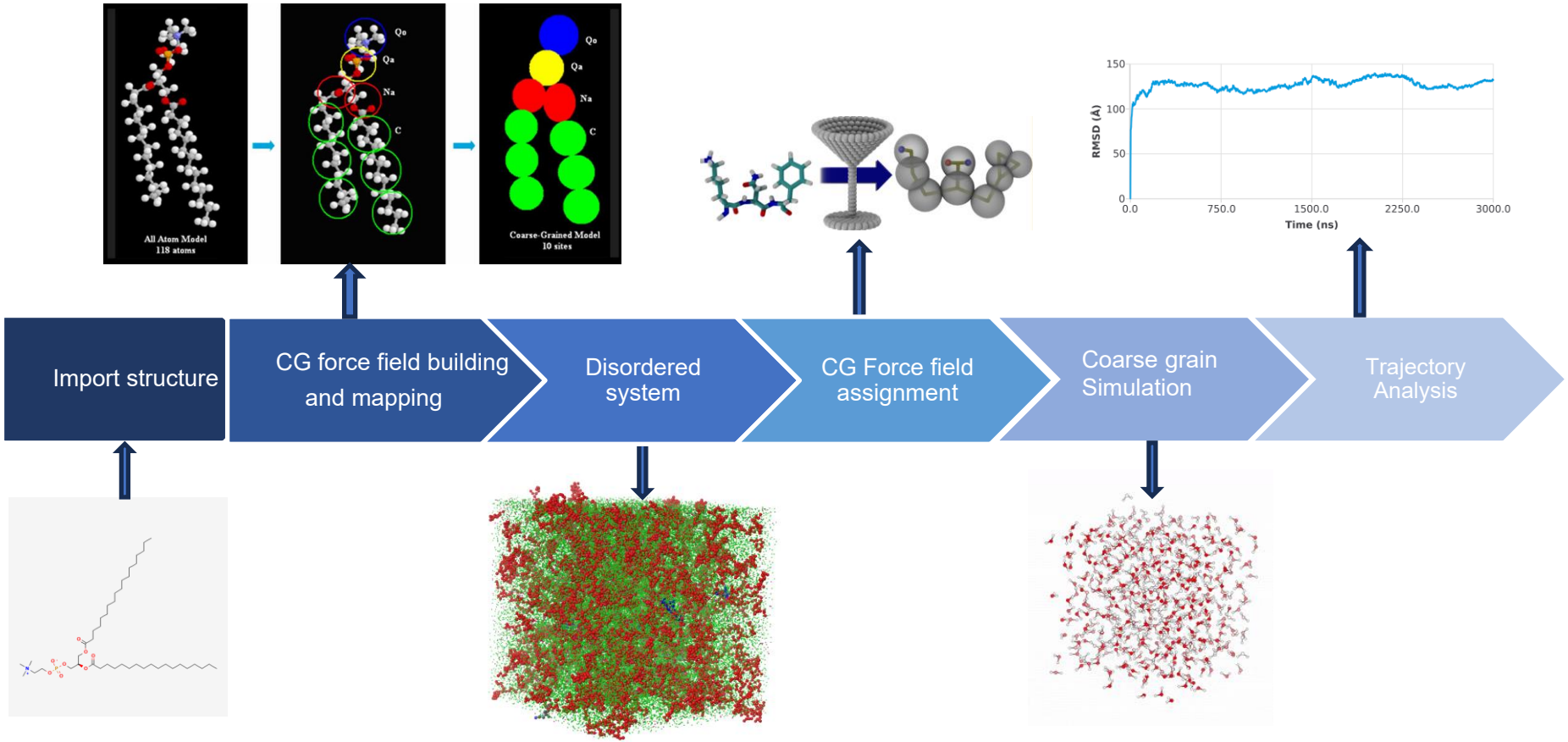


Figure 7: Steps in CG simulation

https://www.researchgate.net/publication/228528333_Exploring_gas_permeability_of_lipid_membranes_using_coarse-grained_molecular_dynamics#pf3

Results – MD simulation miscibility study results

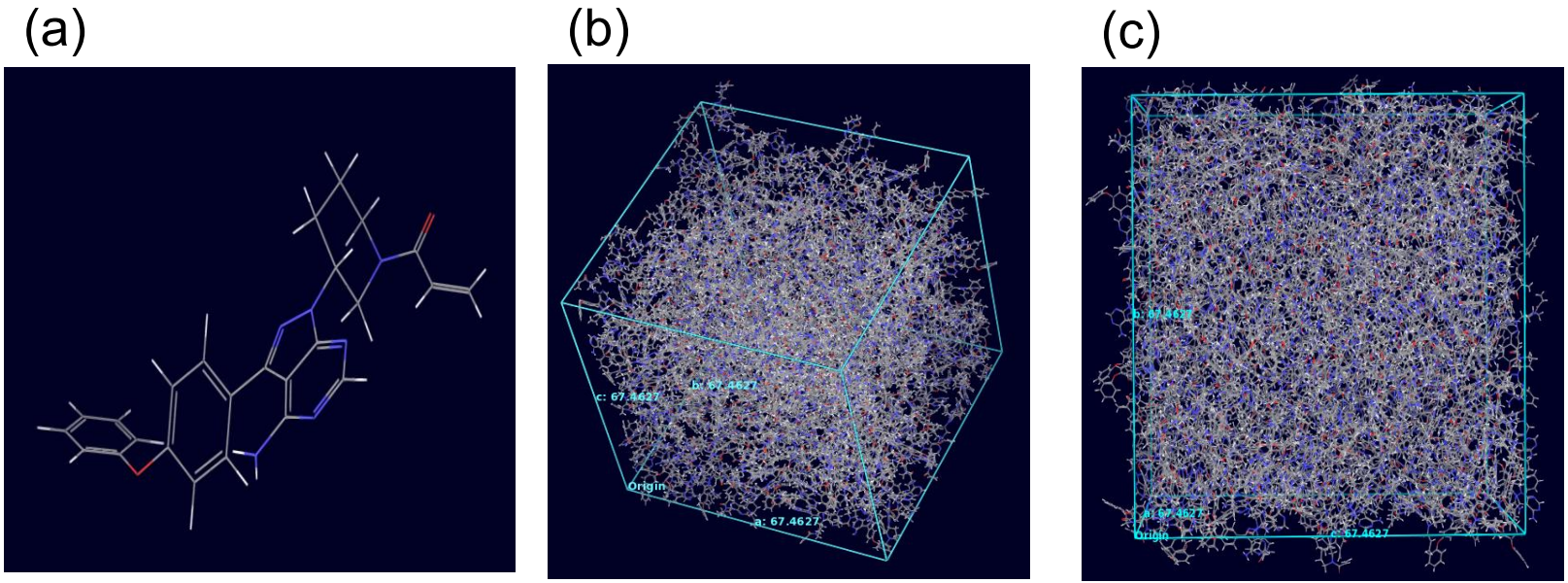


Figure 8: Ibrutinib MD simulation (a) Ibrutinib structure (b) Ibrutinib disordered system (c) Ibrutinib MD simulation final stage

➢ Results – MD simulation miscibility study results

	Volume Angstrom^3	Density g/cm^3	Cohesive E kcal/mol	Solubility Parameter MPa^(1/2)	Solubility Parameter Vdw MPa^(1/2)	Solubility Parameter Ele MPa^(1/2)	Heat of Vap. kcal/mol	Specific Heat Capacity (Cp) J / (g * K)
Average:	307128.28	1.22	43.46	22.44	20.10	9.97	44.05	3.10
Stdev:	563.356	0.002	0.117	0.048	0.044	0.037	0.117	N/A

Note: *Statistics reported are for the final 20% of the simulation.*

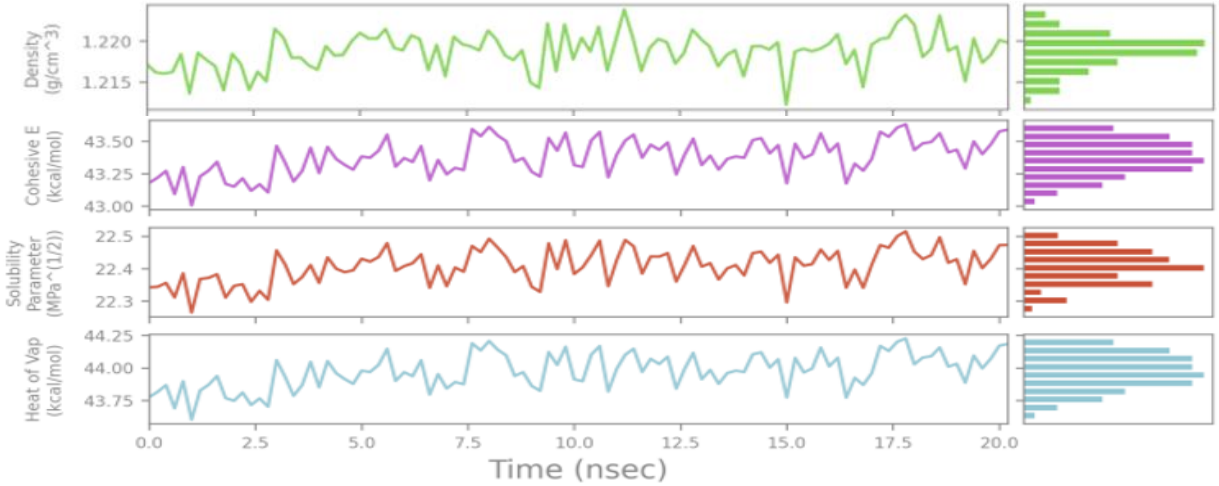


Figure 9: Ibrutinib trajectory analysis output

➢ Results – MD simulation miscibility study results

Table 4. Solubility / miscibility study results by MD simulation

No.	Compounds	$\delta_{\text{MD simulations}}$ $(MPa)^{1/2}$	$\Delta\delta_{\text{MD simulations}}$ $(MPa)^{1/2}$ $(\lvert \delta_{drug} - \delta_{lipid} \rvert)$	Miscibility (Y/N)
1	Ibrutinib	22.24	N/A	Y
2	SPC 3	22.20	0.01	Y
3	POPC	22.25	0.01	Y
4	EPC S	22.20	0.04	Y
5	DOPC	22.15	0.09	Y
6	DSPC	22.07	0.17	Y
7	DPPC	22.57	0.33	Y
8	DMPC	23.06	0.82	Y
9	DEPC	21.36	0.88	Y
10	E80	23.25	1.01	Y
11	Cholesterol	17.08	5.16	Y
12	DOTAP-Cl	29.39	7.15	N
13	MPEG_2000_DMPE	33.06	10.82	N
14	MPEG_2000_DSPE	33.07	10.83	N
15	DSPG_Na	34.02	11.78	N
16	DPPG_Na	35.27	13.03	N

Typically, the components are miscible if the difference is $\Delta\delta < 7 MPa^{1/2}$. If the difference is $\Delta\delta > 10 MPa^{1/2}$, the components are immiscible.

➢ Results – IBR-loaded liposome formulation

Table 5: Liposome formulation

Materials (molar)	F1	F2	F3	F4
	Blank liposome	IBR-liposome (Passive loading)	IBR-liposome (Charged-assisted loading)	IBR-liposome PEGylated
Ibrutinib (IBR)	×	✓	✓	✓
Cholesterol	✓	✓	✓	✓
SPC 3	✓	✓	✓	✓
DSPG-Na	×	×	✓	✓
MPEG-2000-DSPE	×	×	×	✓

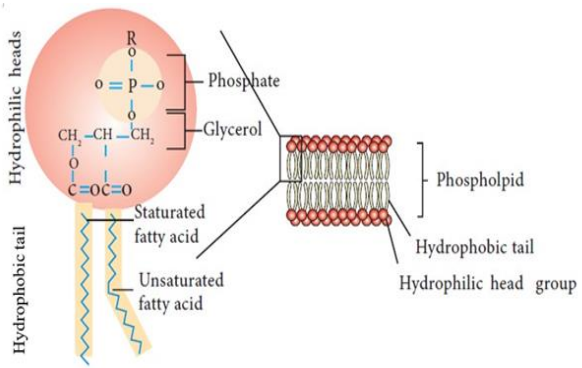


Figure 10: Structure of phospholipid
Source: https://www.brainkart.com/article/Phospholipids_34097/

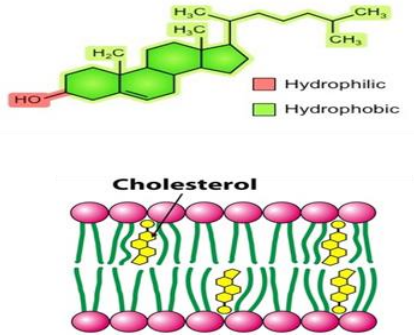


Figure 11: Structure of cholesterol
https://ib.bioninja.com.au/standard-level/topic-1-cell-biology/13-membrane-structure/cholesterol.html

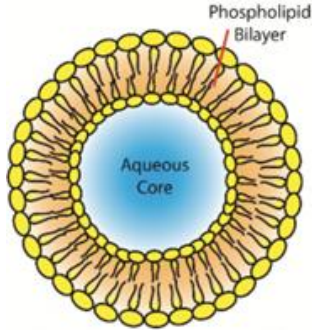


Figure 12: Structure of a liposome
Source: https://www.researchgate.net/figure/Structure-of-a-liposome-A-liposome-consists-of-a-phospholipid-bilayer-with-an-aqueous_fig2_331856444

➢ Results – IBR-loaded liposome characterization

Table 6. Liposome characterization results

Formulation		Encapsulation Efficiency (EE%)	Ave. particle size (d. nm)	Polydispersity index (PDI)	Zeta potential
F1	Blank liposome	N/A	50.2	0.168	0.156
F2	IBR-liposome (Passive loading)	20.3	192.8	0.544	-5.82
F3	IBR-liposome (Charged-assisted loading)	90.73	115.7	0.131	-39.9
F4	IBR- liposome (PEGylated)	95.80	148.7	0.459	-8.88

➢ Results – IBR-loaded liposome characterization

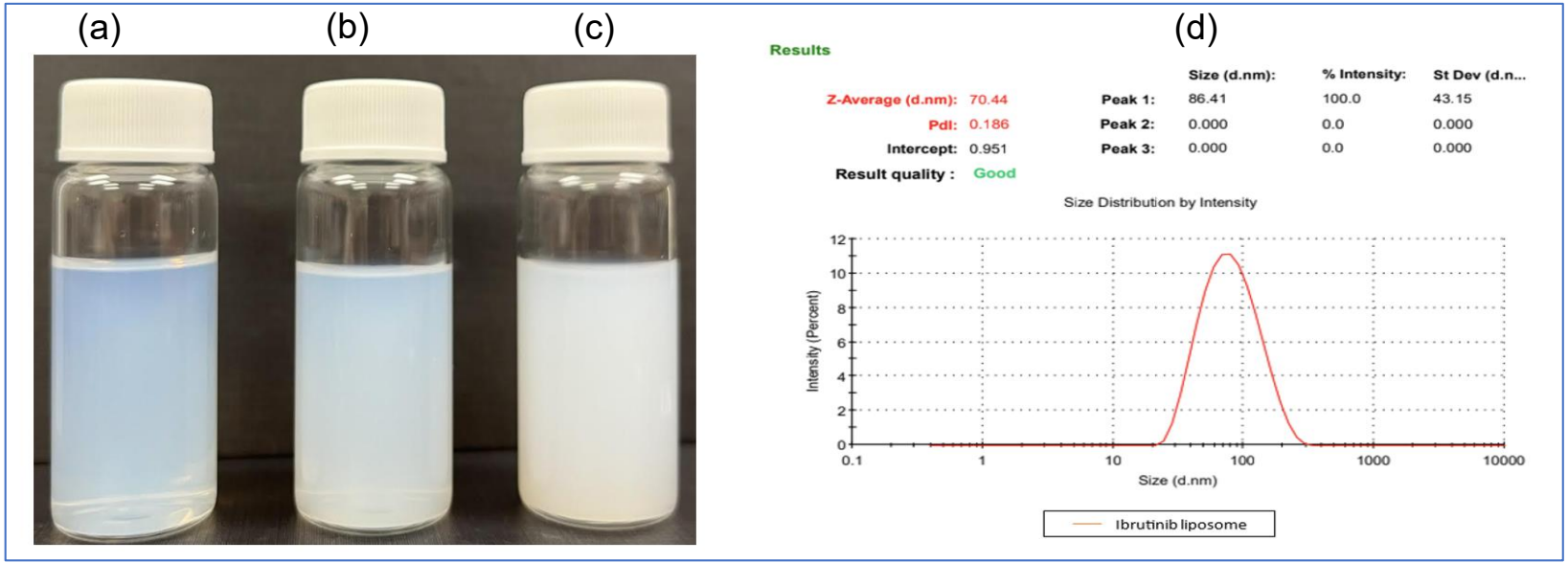


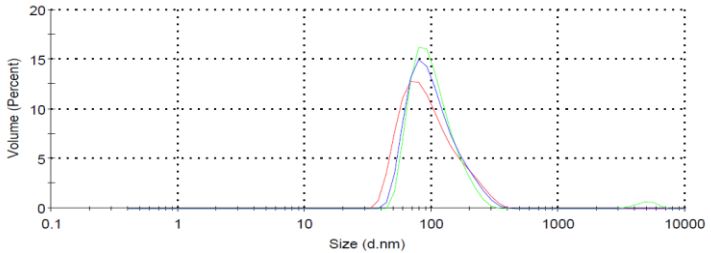
Figure 13: Liposome and particle size distribution
(a) Blank liposome (b) IBR-loaded liposome (1:10) (c) IBR-loaded Liposome (1:40) (d) Particle size distribution

➢ Results – IBR-loaded liposome characterization

Results

		Size (d.nm):	% Volume:	St Dev (d.nm):
Z-Average (d.nm): 115.7	Peak 1:	107.9	100.0	50.50
PdI: 0.131	Peak 2:	0.000	0.0	0.000
Intercept: 0.970	Peak 3:	0.000	0.0	0.000

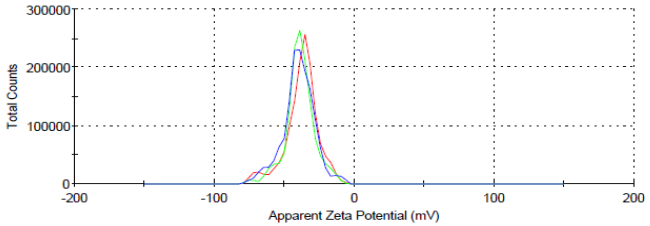
Size Distribution by Volume



Results

		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV): -39.9	Peak 1:	-40.6	96.7	10.9
Zeta Deviation (mV): 11.7	Peak 2:	-12.3	3.3	3.79
Conductivity (mS/cm): 1.23	Peak 3:	0.00	0.0	0.00

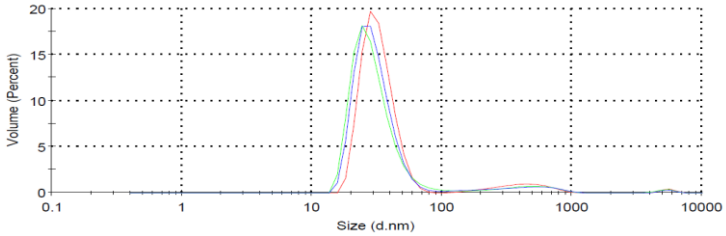
Zeta Potential Distribution



Results

		Size (d.nm):	% Volume:	St Dev (d.nm):
Z-Average (d.nm): 148.7	Peak 1:	422.1	7.0	234.7
PdI: 0.459	Peak 2:	30.31	92.3	10.15
Intercept: 0.912	Peak 3:	5401	0.7	650.7

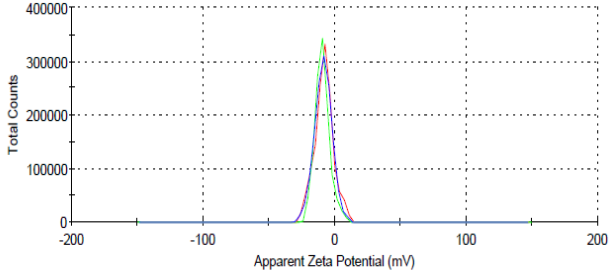
Size Distribution by Volume



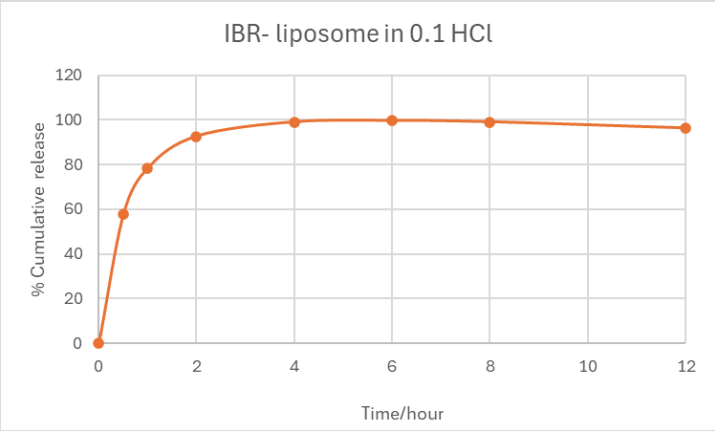
Results

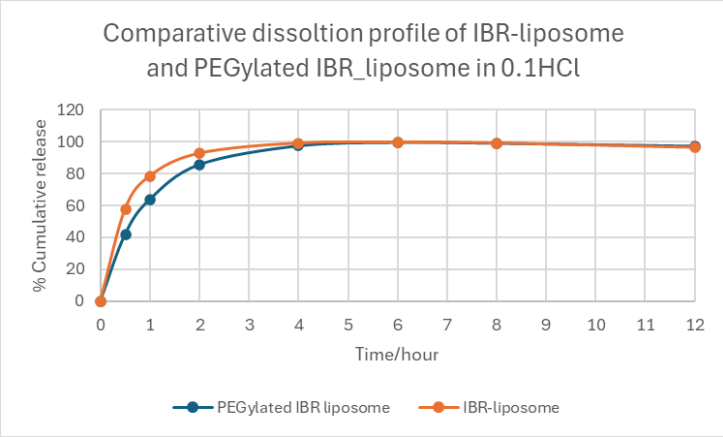
		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV): -8.86	Peak 1:	-8.86	100.0	6.68
Zeta Deviation (mV): 6.68	Peak 2:	0.00	0.0	0.00
Conductivity (mS/cm): 2.01	Peak 3:	0.00	0.0	0.00

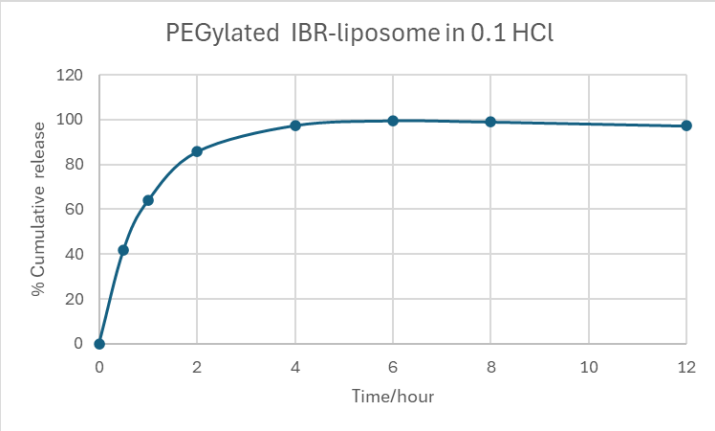
Zeta Potential Distribution

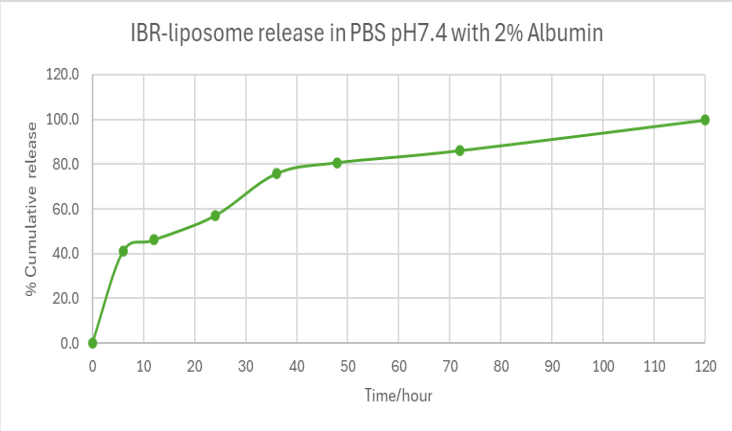


➢ Results – IBR-loaded liposome release profile



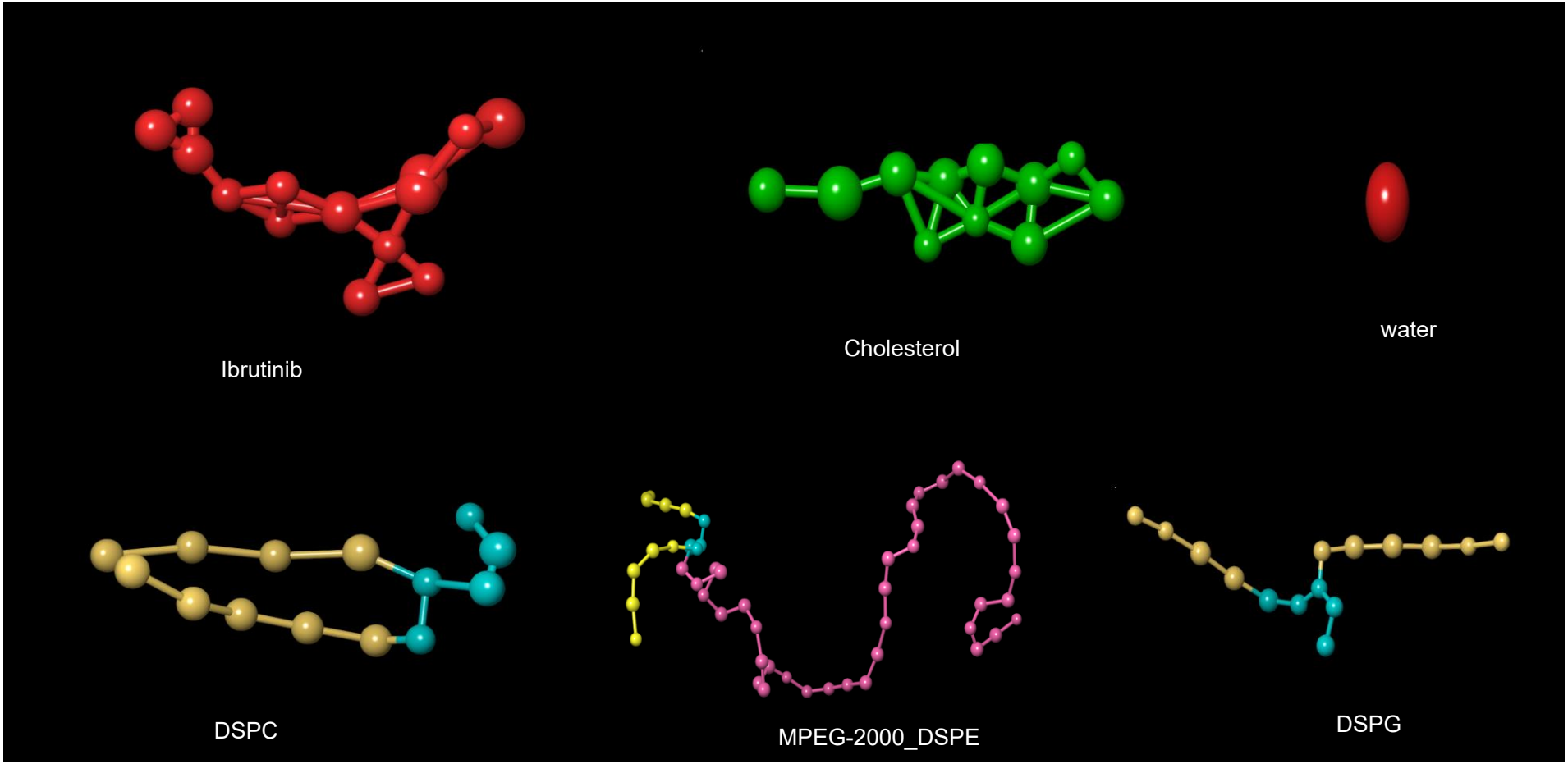






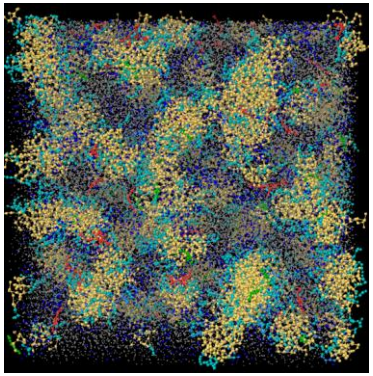
Liposomes are a **promising drug delivery platform** that can: **reduce dosing frequency** (improving patient compliance), **minimize side effects** (through controlled release), **enhance bioavailability** (optimizing drug delivery).

➢ Results – CG simulation ingredients image



➢ Results – Coarse grain simulation

IBR-liposome simulation images



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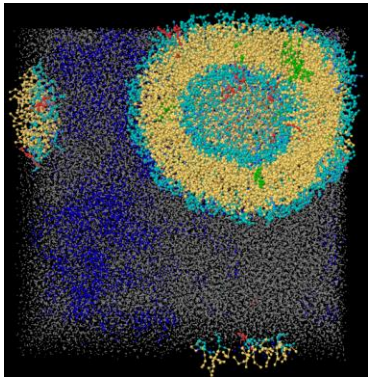

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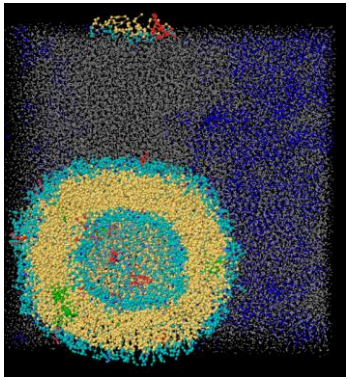

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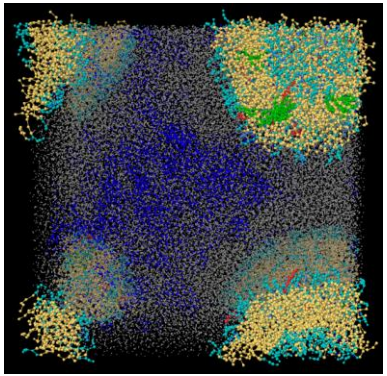
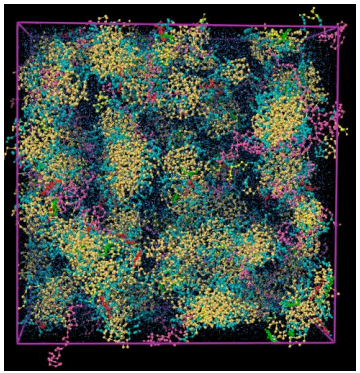


1000 ns

PEGylated IBR-liposome simulation images



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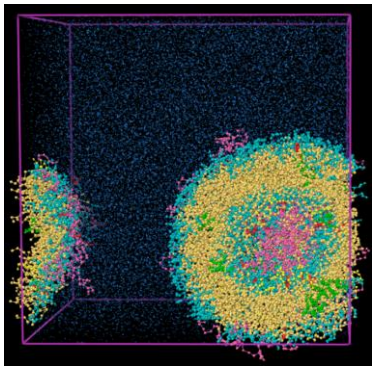

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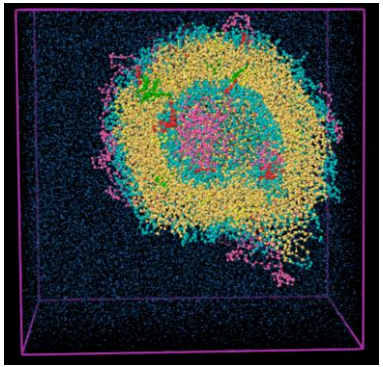

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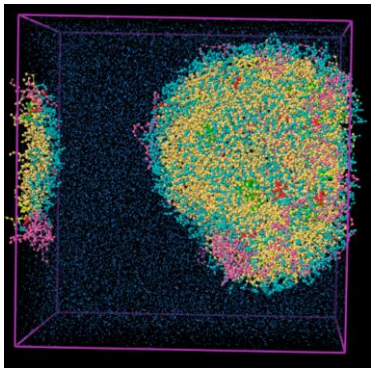

1000 ns

➢ Conclusion

- The physical characteristics, nanoscale size, and controlled release profile of the IBR-loaded liposomes suggest that they represent a promising drug delivery system with the potential to enhance bioavailability, reduce dosing frequency, and minimize side effects.

- The molecular dynamics simulation results provide insights into the interactions between the lipids and the drug, as well as the drug's encapsulation behavior.

- The simulation results play a vital role in the design of drug delivery systems, offering valuable guidance and reference for experimental studies. They help reduce both time and cost associated with experiments and contribute to a more accurate interpretation of experimental findings.

References

- (1) FDA & CDER. *HIGHLIGHTS OF PRESCRIBING INFORMATION*. www.fda.gov/medwatch

- (2) Paydas, S. Management of adverse effects/toxicity of Ibrutinib. *Critical Reviews in Oncology/Hematology* vol. 136 56–63 Preprint at https://doi.org/10.1016/j.critrevonc.2019.02.001 (2019).

- (3) Xiao, L. *et al.* Ibrutinib-Mediated Atrial Fibrillation Attributable to Inhibition of C-Terminal Src Kinase. *Circulation* **142**, 2443–2455 (2020).

Acknowledgements

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