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Co-entrapment of sorafenib and cisplatin in poly[ε-caprolactone-co-(12-hydroxystearate)] copolymer for dual drug delivery application

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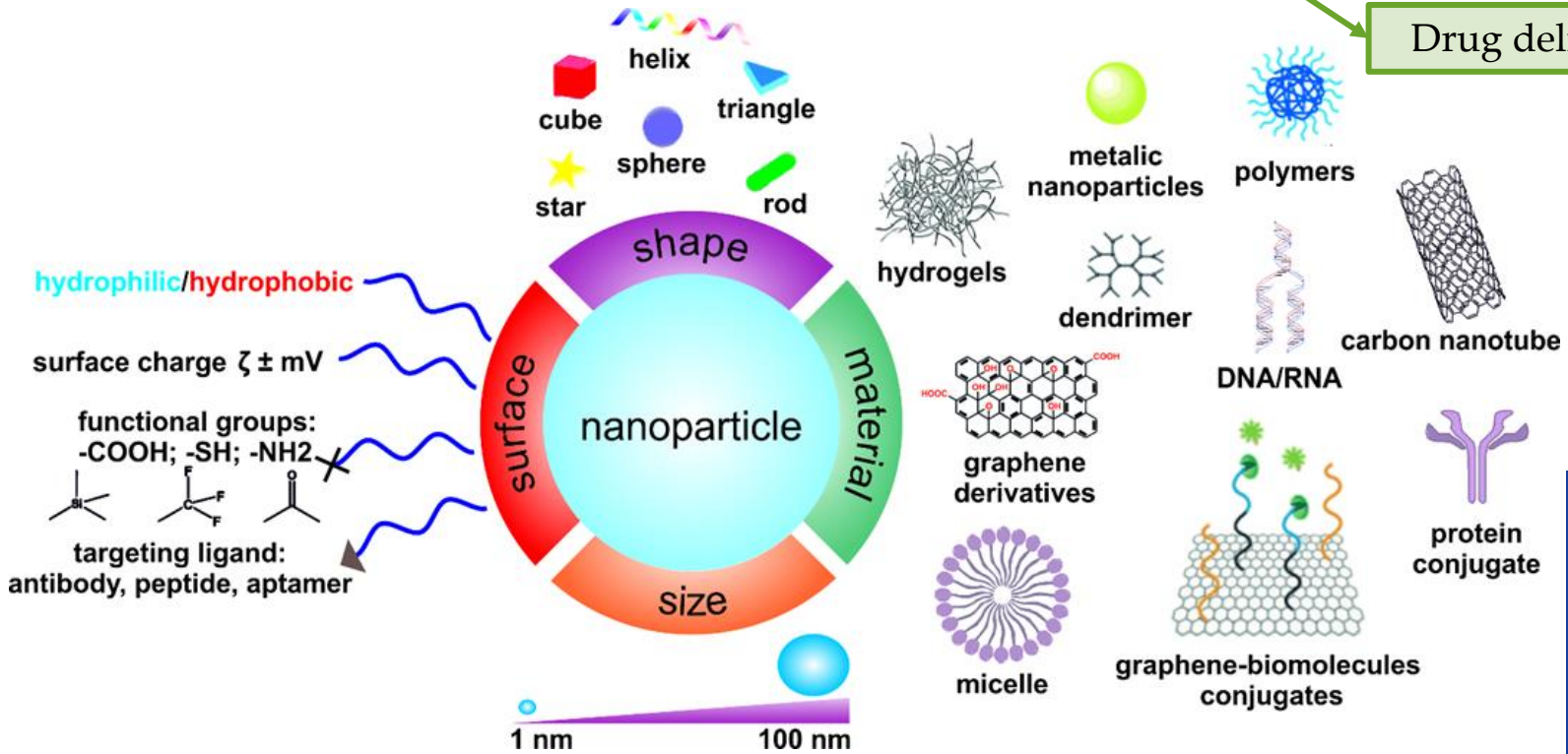
Abstract: sciforum-044771
Drug-loaded nanocarriers have overcome various challenges compared with the bare chemo-drug, such as limited bioavailability, multiple drug resistance, poor patient compliance, adverse drug reactions, particularly side effects of chemotherapy and offer advantages such as protection from degradation in the blood stream, better drug solubility and improved drug stability. One promising group of controlled and targeted drug delivery systems is the polymer-based nanoparticles which can sustain release of active agent by diffusion and their degradation.
Sorafenib is the only drug which is capable to prolong the life of patients suffered from hepatocellular carcinoma. Cisplatin remains one of the most widely used broad spectrum anticancer drug for the treatment of a variety of solid tumors. Nanoformulations can exert synergistic effect by entrapping two drugs with different mode of action, such as sorafenib and cisplatin.
In our study, we prepared polymeric nanoparticles by optimised double emulsion solvent evaporation method with a good production yield by a novel biocatalytically synthetized 12-hydroxystearic acid ε-caprolactone copolymer (12CL) which is biocompatible and biodegradable carrier for the co-entrapment of sorafenib and cisplatin in nanotherapeutics in order to investigate the synergistic effect of sorafenib in combination with cisplatin. The active agents were encapsulated and also cross-linked with carbodiimide to increase the encapsulation efficiency. To improve the drug encapsulation efficiency, bovine serum albumin (BSA) was also incorporated as a protein capable of complexation with the cisplatin.

Keywords: polymeric nanoparticles; drug encapsulation; drug delivery; sorafenib; cisplatin

Introduction

- Nanomedicine
  - One of the most growing fields of pharmaceutics.
  - Nanomaterials in medical applications.
  - Integration of nanomaterials with biology.

- Diagnostic devices.
- Contrast agents.
- Analytical tools.
- Drug delivery vehicles.



Source: http://cnbm.amu.edu.pl/en/nanomaterials

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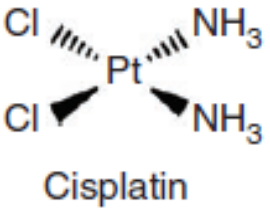
Introduction



Cisplatin

- Cisplatin (CIS)
  - Is administrated intravenously, interferes with DNA replication.
  - 1978 – FDA approval: testicular and ovarian cancer.
  - The most widely used and effective anticancer agent.
  - Side effects: nephrotoxicity, neurotoxicity, auditory toxicity.

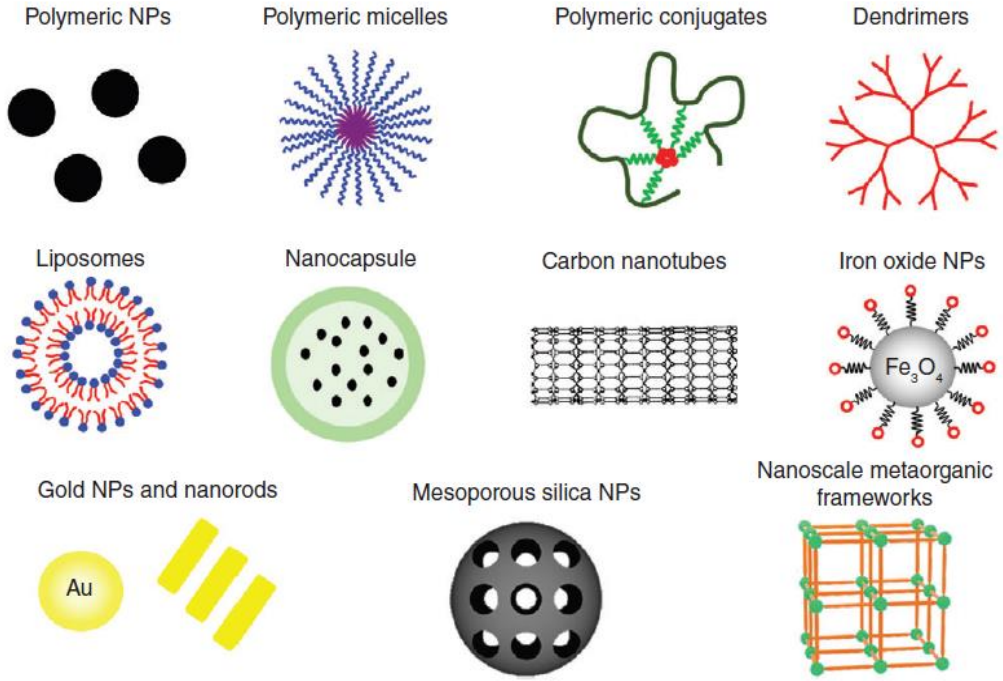


FIGURE 1 | Nanoparticle formulations used for cisplatin delivery.

Source: Duan et al., 2016.

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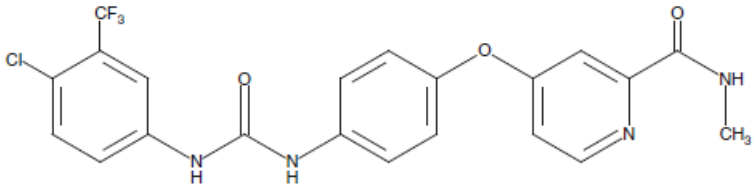
Introduction



- Sorafenib (SOR)
  - Orally active multikinase inhibitor drug.
  - Is used against:
    - Hepatocellular carcinoma,
    - Kidney cancer,
    - Thyroid cancer.
  - Side effects:
    - Diarrhoea, rash, vomiting,
    - Hand-foot skin reaction,
    - Weight loss.
  - Hepatocellular carcinoma (HCC)
    - LIVER CANCER – 5th most common cancer.
    - Its mortality rate ranks third among all cancers.
    - The most common type – HCC.
    - Causes: Hepatitis B or C, cirrhosis.

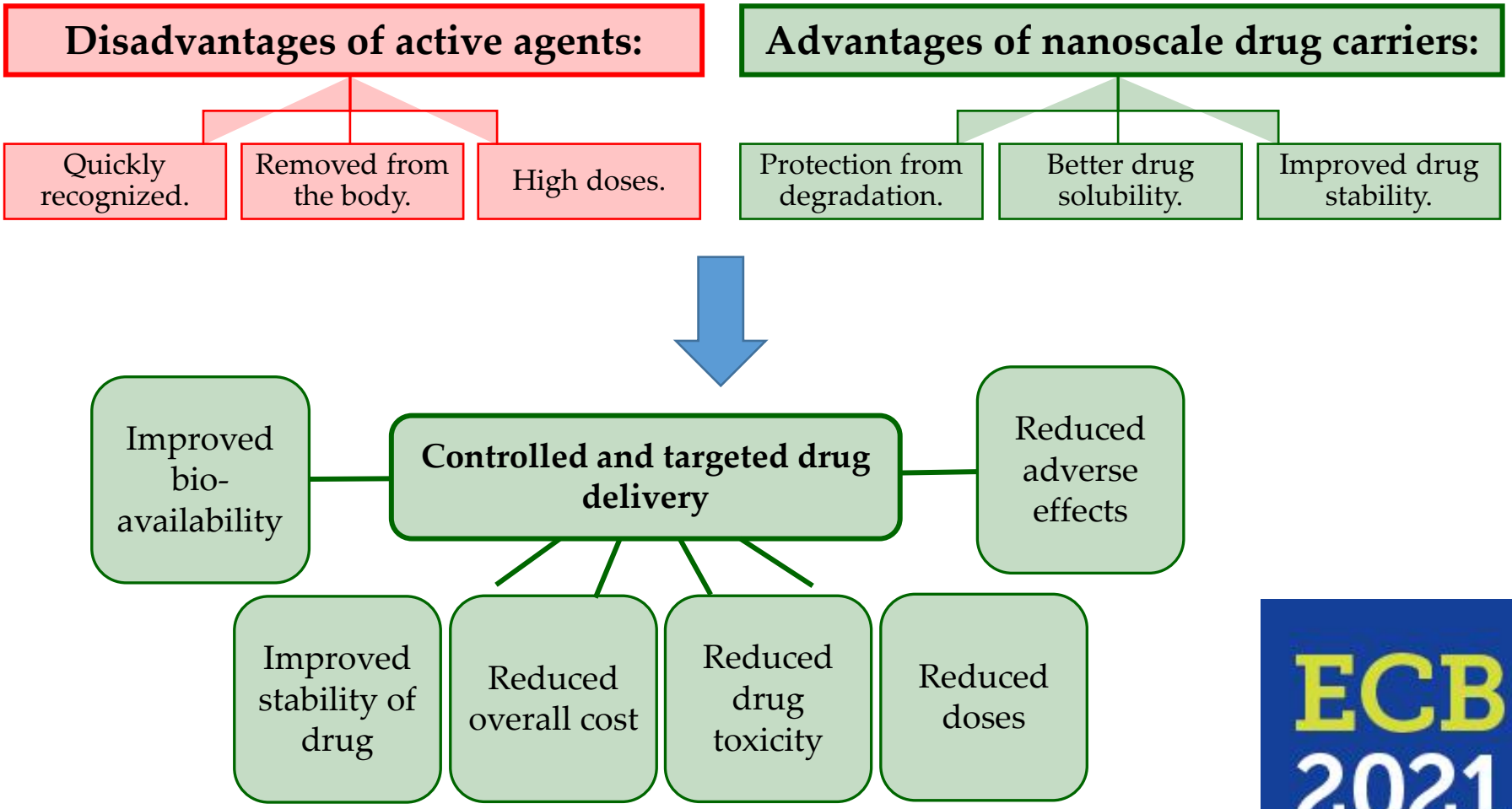
	Llovet (2008)[72]		Cheng (2009)[73]	
	Sorafenib 800 mg per day (n=303)	Placebo (n=299)	Sorafenib 800 mg per day (n=150)	Placebo (n=76)
Response rate	..	..	..	..
Complete response	0	0	0	0
Partial response	7	2	5	1
Stable disease	211	204	81	21
Progressive disease	..	..	46	41
Time to progression (months)	5·5	2·8	2·8	1·4
Hazard ratio (95% CI)	0·58 (0·45–0·74)	..	0·57 (0·42–0·79)	..
Median survival (months)	10·7	7·9	6·5	4·2
Hazard ratio (95% CI)	0·69 (0·55–0·87)	..	0·68 (0·50–0·93)	..

Data are number of patients, unless otherwise stated.

Source: Forner et al., 2012.

Introduction

- Nanoscale drug delivery



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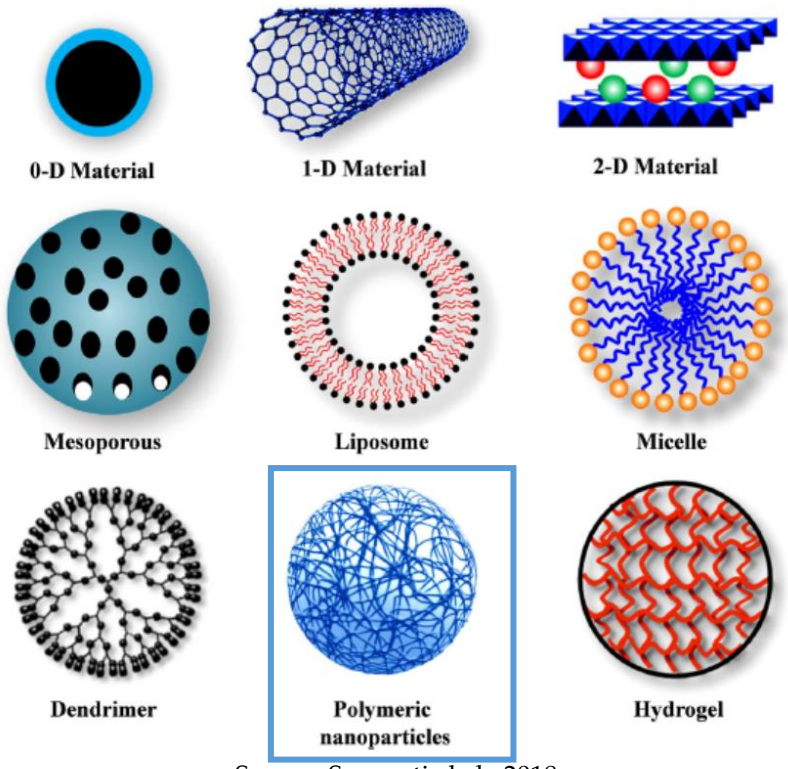
Aims

- Preparation of anticancer drug-loaded nanocomposites that can become effective sustained and targeted drug delivery devices.
- Finding of the proper biodegradable and biocompatible polymer.
- Investigation of the encapsulation possibility of the active agent.



Source: Senepati el al., 2018.

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Encapsulating polymer

- Preparation of sorafenib-loaded PCL nanocomposites by emulsion method with a very good production yield.
- Selection of most suitable polymer in which the active agent was encapsulated with a satisfying encapsulation efficiency.

Sample 12CL	Z-avg [nm] (before washing)	PDI (before washing)	Z-avg [nm] (after washing)	PDI (after washing)	ζ-potencial [mV]	Yield (%)	EE SOR (%)	Loading capacity (%)
SOR7	257.1 ± 14.6	0.160 ± 0.01	222.7 ± 27.4	0.142 ± 0.02	-9.2 ± 1.8	74 ± 5	72 ± 6.6	4,8 ± 1,0

Kántor I., Aparaschivei D., Todea A., Biró E., Babos Gy., Szerényi D., Kakasi B., Péter F., Șișu E, Feczkó T. 2021. Biocatalytic synthesis of poly[ε-caprolactone-co-(12-hydroxystearate)] copolymer for sorafenib nanoformulation useful in drug delivery, *Catalysis Today*, 366, p. 195 – 201.

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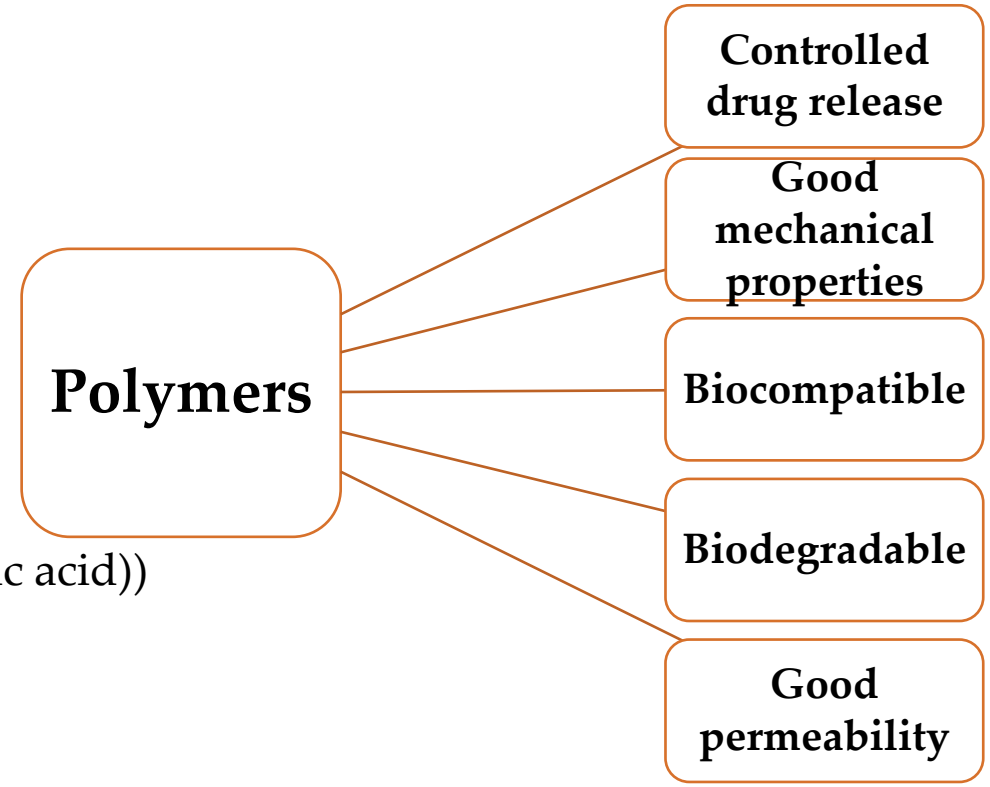
Encapsulating polymer

- New active agent: **Cisplatin**.
- Encapsulation possibility.
  - PLGA (poly(lactic-co-glycolic acid))
  - PCL (polycaprolactone)
  - 12CL, 16CL (hydroxy-stearic-acid epsilon-caprolatone copolymers)
- Co-encapsulation: **Sorafenib**.



Encapsulating polymer

- 12HSA_ECL (12CL)

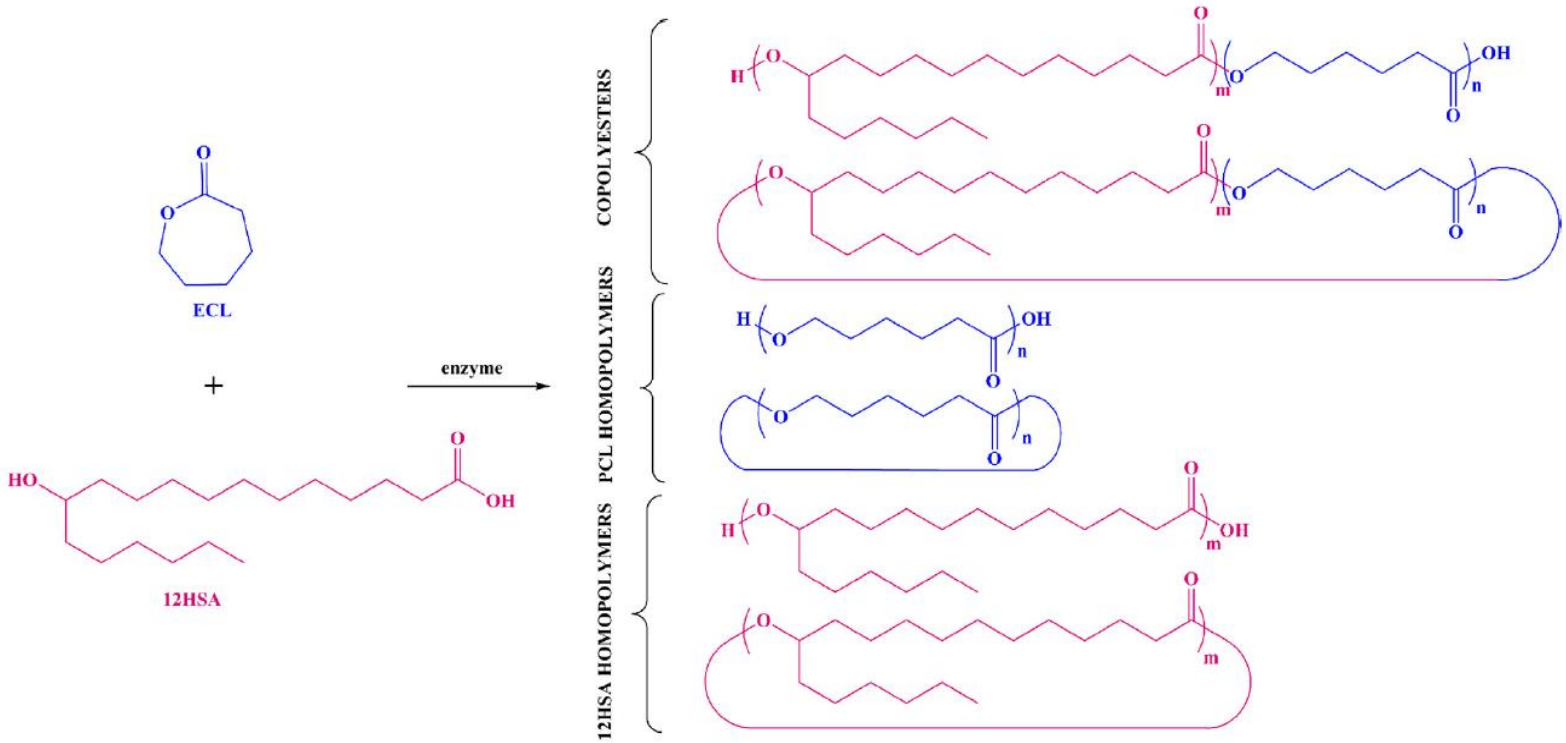


Fig. 1. Reaction scheme of the synthesis of copolyesters and homopolyesters from ε-caprolactone and 12-hydroxystearic acid.

Kántor I., Aparaschivei D., Todea A., Biró E., Babos Gy., Szerényi D., Kakasi B., Péter F., Șișu E, Feczkó T. 2021. Biocatalytic synthesis of poly[ε-caprolactone-co-(12-hydroxystearate)] copolymer for sorafenib nanoformulation useful in drug delivery, *Catalysis Today*, 366, p. 195 – 201.

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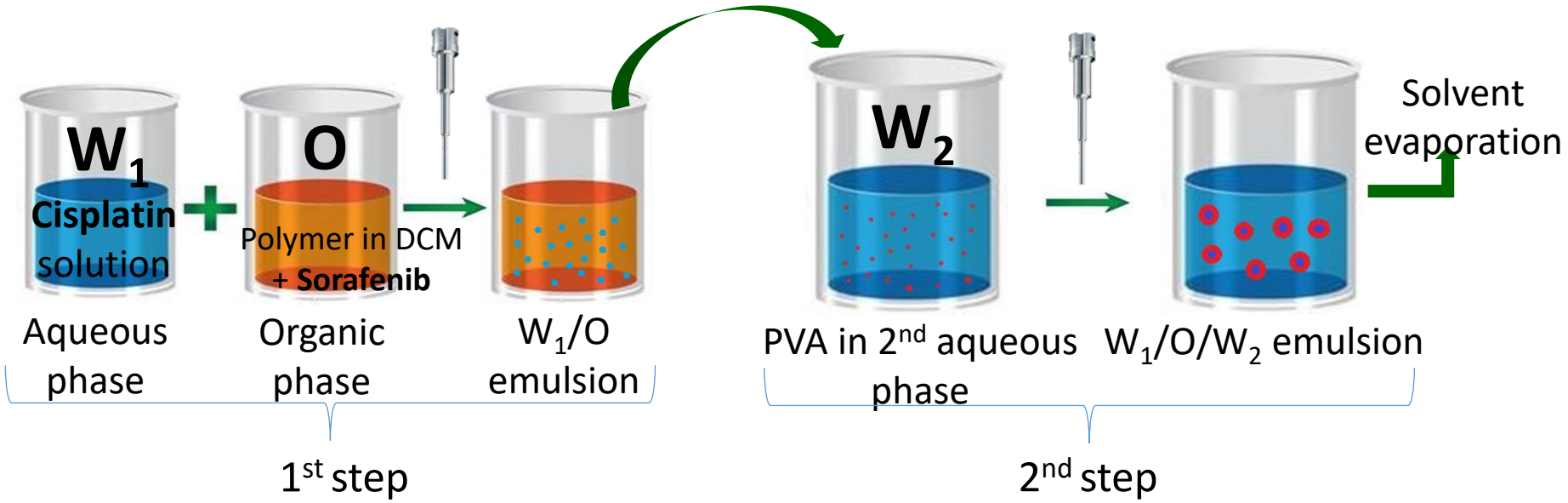
Preparation method



Analytical methods and instruments

- Zetasizer Nano ZS (Malvern Instruments, Malvern, UK)
  - Particle size measurement - Before and after washing with MilliQ water
  - Zeta potential measurement - After removing the PVA by washing with MilliQ water
- UV-VIS Spectrophotometer
  - Encapsulation efficiency
  - Concentration of SOR
- ICP-OES
  - Encapsulation efficiency
  - Concentration of CIS
- Production yield

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Results

Sample	Z-avg [nm] (before washing)	PDI (before washing)	Z-avg [nm] (after washing)	PDI (after washing)	ζ-potencial [mV]	Yield (%)	EE SOR (%)	Loading capacity SOR (%)	SOR (mg)	CIS (mg)	o/w ratio	Polymer %	PVA %
12CLCIS2	224,6	0,182	272,9	0,260	-14,00	66	47	5,9	1	1	1/5	1	2
16CLCIS2	210,7	0,102	279,1	0,252	-8,28	40	49	10	1	1	1/5	1	2
PCLgCIS2	216,2	0,122	299,2	0,329	-20,60	33	52	13,2	1	1	1/5	1	2
PCLsCIS1	210,6	0,082	262,7	0,176	-15,30	41	59	12	1	1	1/5	1	2

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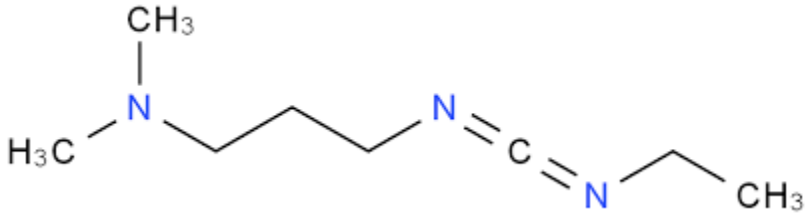
Results

- Improvement of encapsulation efficiency.
- Conjugation of cisplatin.
- EDC cross-linker (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide).



Sample	Z-avg [nm] (before washing)	PDI (before washing)	Z-avg [nm] (after washing)	PDI (after washing)	ζ-potencial [mV]	Yield (%)	EE SOR (%)	Loading capacity SOR (%)	SOR (mg)	CIS (mg)	o/w ratio	Polymer %	PVA %
12CLCIS3	175,4	0,230	175,7	0,150	30,5	24	24	3,1	1	1	1/2	1	1
16CLCIS3	192,9	0,168	237,7	0,197	31,3	22	17	2,4	1	1	1/2	1	1
PCLsCIS2	227,6	0,060	242,8	0,131	33,7	50	70	4,4	1	1	1/2	1	1

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Results

- Human serum albumin (HSA)
  - It is the most abundant protein in human blood plasma
  - Encapsulation of proteins is widely used:
    - Controlled release kinetics
    - Preservation of secondary structure
    - High loading efficiency
- BSA – Model protein

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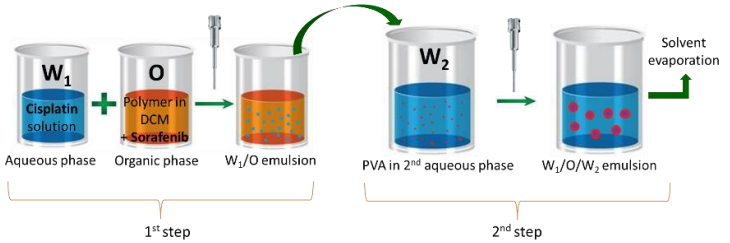
Results

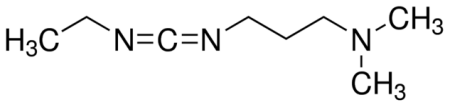


Encapsulation

Cross-linking with EDC

Sample 12CL	Z-avg [nm] (before washing)	PDI (before washing)	o/w ratio	Polymer %	PVA %	BSA (mg)
12CLBSA1	476,6	0,450	1/2	1	0,5	1
12CLBSA2	241,3	0,341	1/3	1	1	1
12CLBSA3	481,9	0,692	1/3	2	1	1
12CLBSA4	232,3	0,360	1/3	1	1	0,5
12CLBSA5	269,9	0,355	1/5	1	1	1
12CLBSA6	245,5	0,275	1/5	1	1	0,5
12CLBSA7	301,2	0,461	1/4	1	1	1
12CLBSA8	338,8	0,568	1/4	1	1	0,5
12CLBSA9	438,5	0,810	1/5	1	1	1
12CLBSA10	250,7	0,353	1/5	1	1	0,5
12CLBSA10*	271,6	0,414	1/5	1	1	1

EDC = 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide



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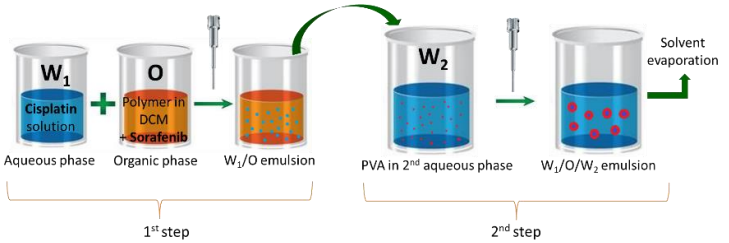
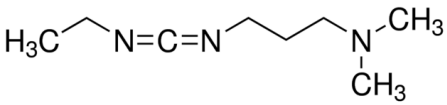
Results



- Encapsulation of BSA in presence of active agents SOR and CIS.

Sample 12CL	Z-avg [nm] (before washing)	PDI (before washing)	BSA (mg)	SOR (mg)	CIS (mg)	EDC (mg)
12CLBSASOR1	223.4 ± 2.69	0.243 ± 0.01	0.5	1	-	-
12CLBSASOR2	274.4 ± 9.62	0.582 ± 0.02	0.5	1	-	1
12CLBSASOR3	212.3 ± 0.90	0.258 ± 0.03	0.5	1	-	1
12CLBSASORCIS1	239.6 ± 4.13	0.378 ± 0.02	0.5	0.5	0.5	-
12CLBSASORCIS2	196.1 ± 1.86	0.081 0.02	0.5	0.5	0.5	1
12CLBSASORCIS3	249.3 ± 9.07	0.362 ± 0.02	0.5	0.5	0.5	1
12CLBSACIS1	252.2 ± 15.02	0.413 ± 0.02	0.5	-	1	-
12CLBSACIS2	246.3 ± 30.37	0.397 ± 0.08	0.5	-	1	1
12CLBSACIS3	188.9 ± 2.27	0.091 ± 0.01	0.5	-	1	1

EDC = 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide



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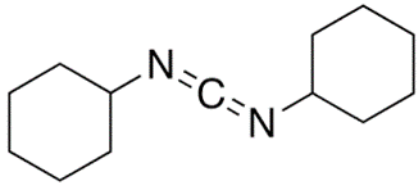
Results

- Encapsulation of BSA using DCC.

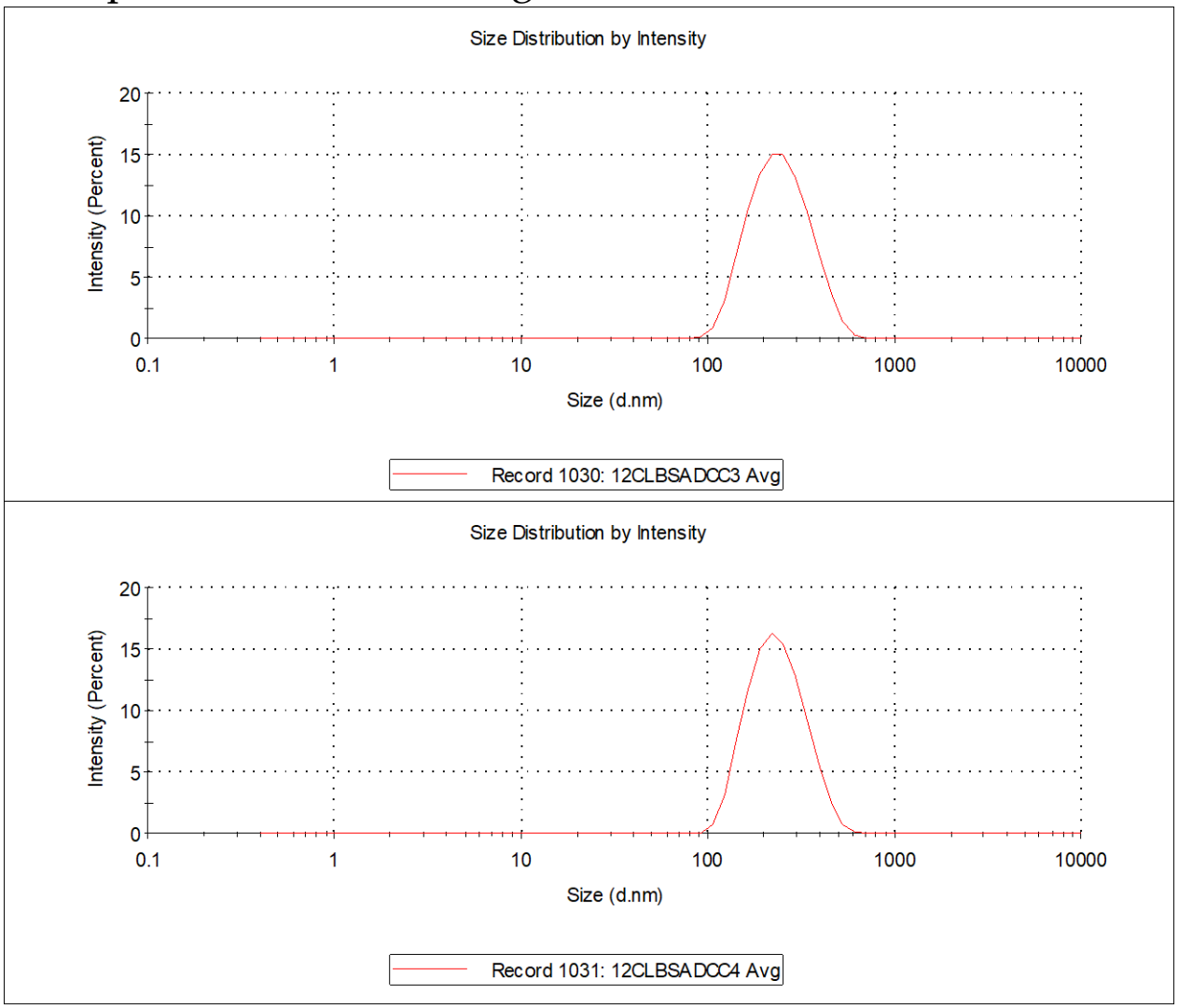
Sample 12CL	Z-avg [nm] (before washing)	PDI (before washing)	EE (%)	Yield (%)	BSA (mg)	EDC (mg)
12CLBSADCC1	217.6 ± 2.27	0.129 ± 0.02	71	-	0.5	1
12CLBSADCC2	229.9 ± 5.88	0.332 ± 0.01	-	-	0.5	1
12CLBSADCC3	225.9 ± 2.47	0.115 ± 0.02	73	46	0.5	2
12CLBSADCC4	219.7 ± 1.87	0.121 ± 0.01	82	46	1	2
12CLBSADCC Blank	233.4 ± 1.51	0.136 ± 0.02	-	47	-	2

DCC = N,N'-Dicyclohexylcarbodiimide



Results

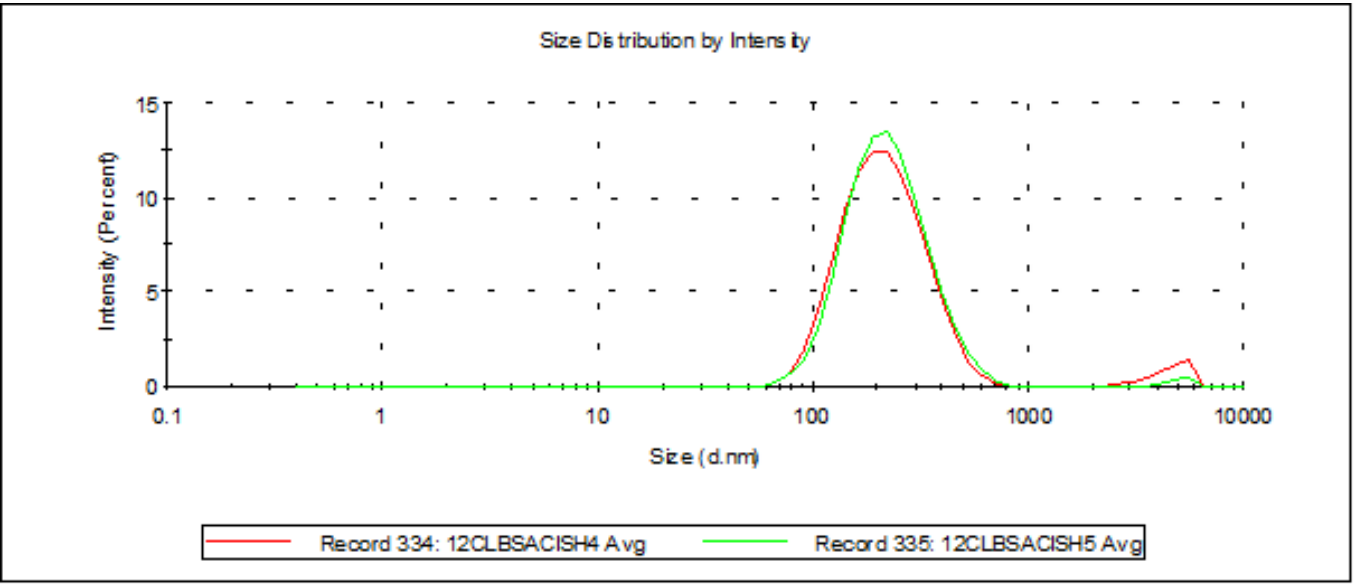
- Encapsulation of BSA using DCC.



Results

- Encapsulation of BSA and CIS using DCC.

Sample	Z-avg [nm] (before washing)	PDI (before washing)	Yield (%)	EE CIS (%)	Loading capacity SOR (%)	CIS (mg)	DCC (mg)	o/w ratio	Polymer %	PVA %
12CLBSACISH4	204,6	0,250	40	24	2,0	0,5	-	1/5	1	1
12CLBSACISH5Blank	212,9	0,171	39	-	-	-	2	1/5	1	1
12CLBSACISH5	209,8	0,209	61	28	0,7	0,5	2	1/5	1	1



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Conclusions

- The double emulsion-solvent evaporation method for the preparation of nanoparticles was optimized.
- The BSA was encapsulated and cross-linked successfully by using DCC.
- The cisplatin and sorafenib was co-encapsulated successfully by double emulsion method.
- The presence of active agents decreases the particle size and using DCC with active agents improves the encapsulation efficiency and the system stability.

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Thank you for the attention!