Appendix

Analytical method development and method validation

1. Docetaxel (DOC)

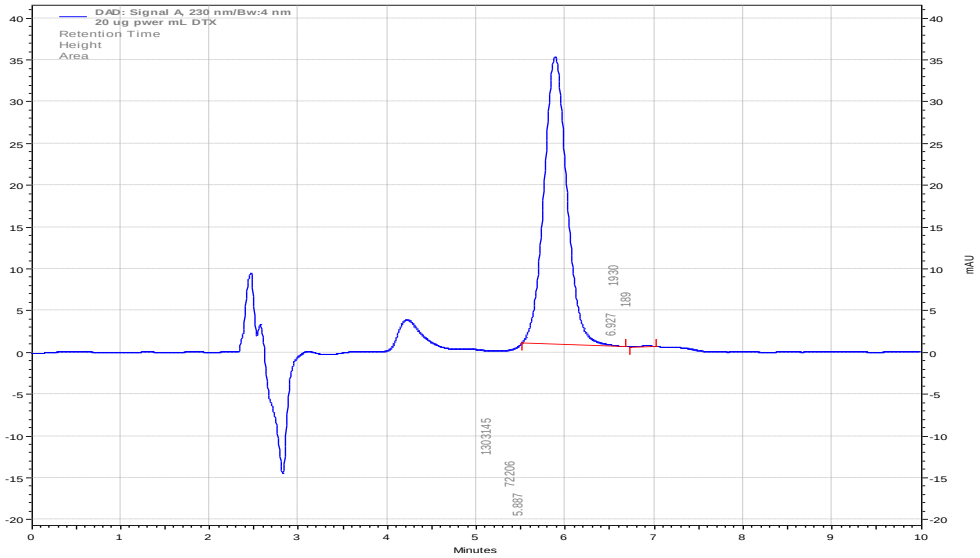

Figure A. 1: HPLC–DAD signal chromatograms of DOC at wavelength 230 nm, mobile phase methanol:0.02% acetic water (80:20), 1ml/min flow rate, with retention time (RT) at 5.8 min

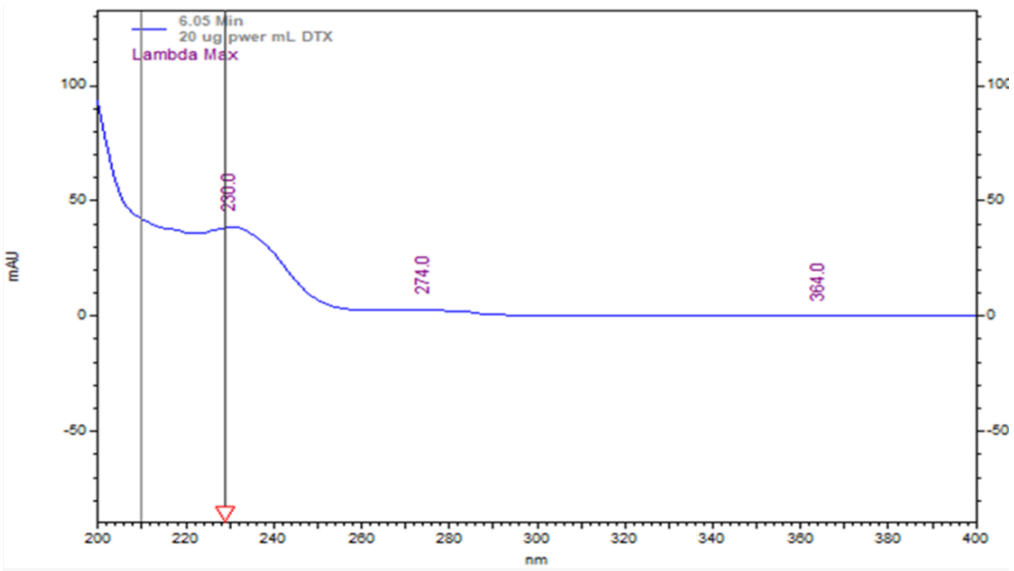

Figure A. 2: HPLC spectra of DOC in mobile phase methanol:0.02% acetic water (80:20), 1ml/min flow rate

Range and Linearity

Table A. 1. Calibration plot of DOC at maximum wavelength (λ_{max})=230 nm

Concentration (µg/ml)	Area±SD (mAu*min)	RT±SD (min)
2	127856±3297	5.88±0.08
4	246714±3573	5.76±0.05
6	350292±2672	5.83±0.06
8	485951±1471	5.86±0.08
10	622362±5091	5.74±0.04
12	781626±5452	5.86±0.03
14	896053±6586	5.73±0.03
16	1016274±2523	5.91±0.07
18	1180560±3526	5.88±0.04
20	1323198±3259	5.87±0.05

Mean±SD (n=3)

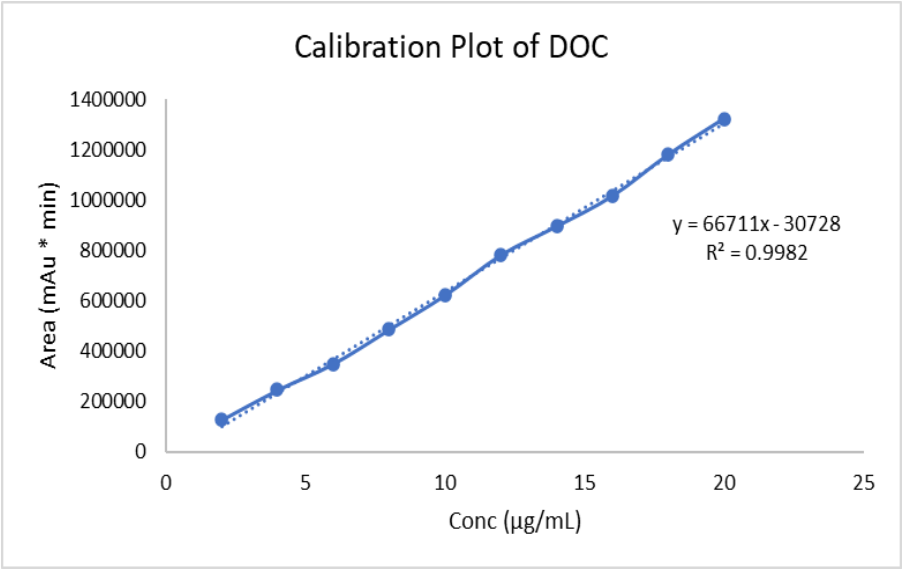

Figure A. 3: Calibration plot of DOC showing linearity at 230 nm at concentration ranging from 2–20 µg/ml

Accuracy

Table A. 2: Recovery study (Accuracy) of DOC at λ_{max}=230 nm

Pre–analysed sample	Amount added (µg/ml)	% Recovery±SD	%RSD
10µg/ml	8	98.18±0.05	0.168
	10	99.02±0.07	0.113
	12	98.93±0.03	0.370

Mean ± SD (n=3)

Precision

Table A. 3: Precision study of DOC for intra–day at λ_{max}=230 nm

Concentration (µg/ml)	**Intra - Day**					
	Shift I (Morning)		Shift II (Afternoon)		Shift III (Evening)	
	Area±SD	%RSD	Area±SD	%RSD	Area±SD	%RSD
2	128477±2243	1.75	125543±2124	1.69	132456±2086	1.57
4	244049±3655	1.50	257358±2876	1.12	254345±2446	0.96
6	347248±2543	0.73	333863±2627	0.79	334546±2548	0.76
8	487118±1633	0.34	498396±1986	0.40	486534±1694	0.35
10	619876±5243	0.85	632673±4375	0.69	619776±3769	0.61
12	783128±4573	0.58	764725±4118	0.54	774326±4216	0.54
14	898878±6243	0.69	894534±6638	0.74	893847±5986	0.67
16	1012754±3733	0.37	1023452±3174	0.31	1025486±3211	0.31
18	1185489±3856	0.33	1163647±3952	0.34	1176523±3848	0.33
20	1324363±3725	0.28	1354182±3455	0.26	1334529±3556	0.27

Mean ± SD (n=3)

Table A. 4: Precision study of DOC for inter–day at λ_{max}=230 nm

Concentration (µg/ml)	**Inter - Day**					
	Day I		Day II		Day III	
	Area±SD	%RSD	Area±SD	%RSD	Area±SD	%RSD
2	128477±2243	1.75	127637±2134	1.63	128637±2023	1.48
4	244049±3655	1.50	254334±3528	1.39	247589±3222	1.30
6	347248±2543	0.73	342674±2245	0.66	336545±2154	0.64
8	487118±1633	0.34	489537±2011	0.41	492674±1989	0.40
10	619876±5243	0.85	621765±5312	0.85	610378±5218	0.85
12	783128±4573	0.58	776298±4427	0.57	776483±4267	0.55
14	898878±6243	0.69	886278±6034	0.68	883758±5876	0.66
16	1012754±3733	0.37	1026574±3588	0.35	1017859±3277	0.32
18	1185489±3865	0.33	1178639±3017	0.26	1165673±2967	0.25
20	1324363±3725	0.28	1347638±3528	0.22	1378765±3427	0.25

Mean±SD (n=3)

Repeatability

Table A. 5: Repeatability studies of DOC at λ_{max}=230 nm

Concentration (µg/ml)	Area±SD (mAu*min)	RT±SD (min)	%RSD
10	625442±4451	5.86±0.07	0.72

Mean±SD (n=6)

Sensitivity

Table A. 6: Limit of Detection (LOD), and limit of quantification (LOQ) of DOC in HPLC

LOD (µg/ml)	LOQ (µg/ml)
0.62	1.88

2. Erlotinib (ERL)

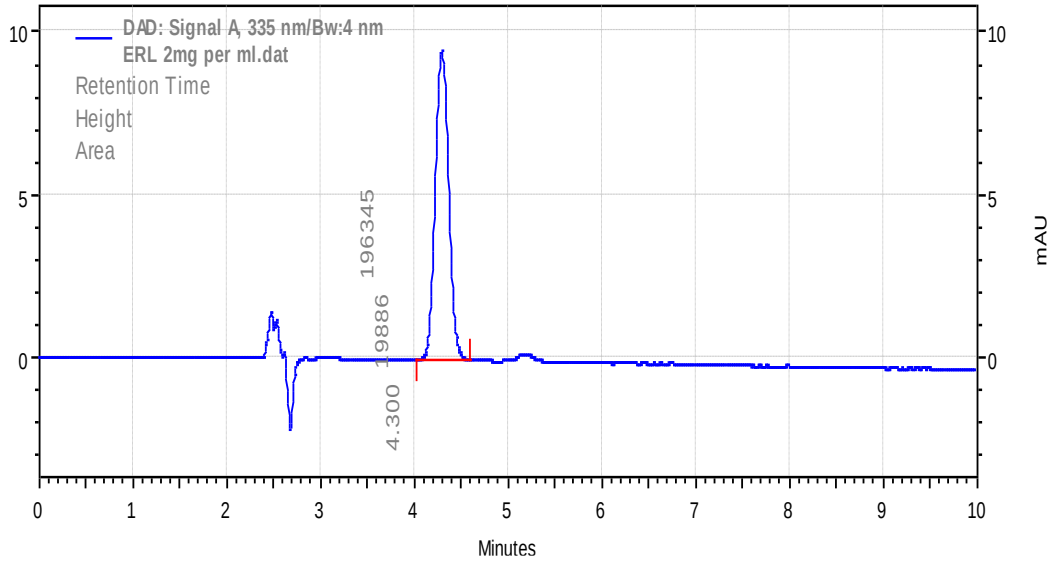

Figure A. 4: HPLC and DAD signal chromatograms of ERL at wavelength 335 nm, mobile phase methanol:0.04% acetic water (80:20), 1ml/min flow rate at retention time of 4.3 min

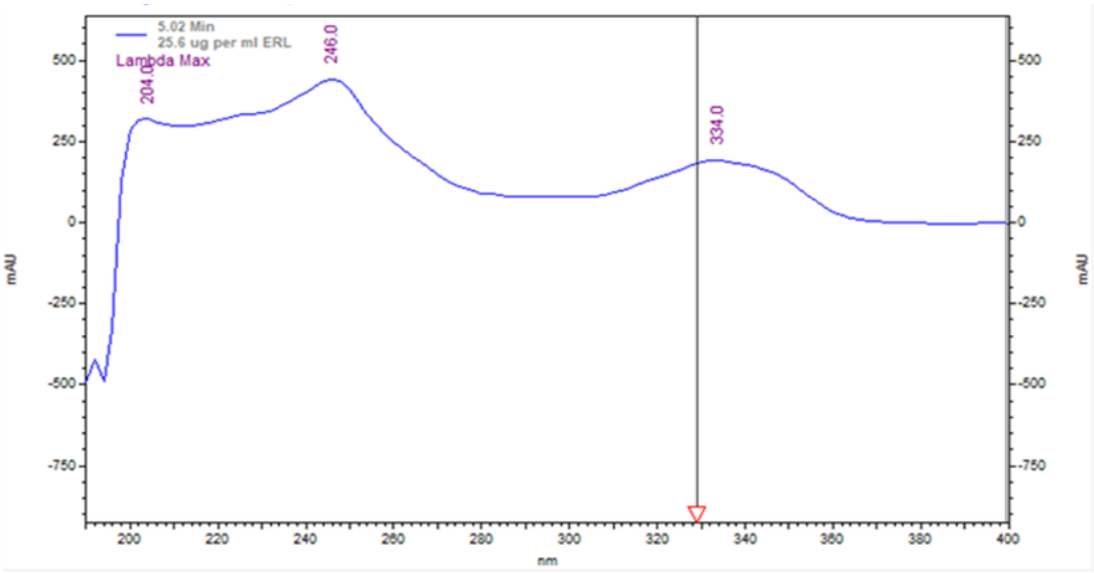

Figure A. 5: HPLC spectra of ERL in mobile phase methanol:0.04% acetic water (80:20), 1ml/min flow rate

Range and Linearity

Table A. 7: Calibration plot of ERL at maximum wavelength (λ_{max})=335 nm

Concentration (µg/ml)	Area±SD (mAu*min)	RT±SD (min)
2	196493±1326	4.36±0.03
4	447056±2164	4.42±0.02
6	667968±3864	4.32±0.05
8	852517±7383	4.39±0.04
10	1080670±5698	4.41±0.03
12	1296829±5611	4.34±0.02
14	1516711±3491	4.43±0.07
16	1750781±3557	4.39±0.06
18	2005258±6807	4.31±0.07
20	2228529±4253	4.32±0.04

Mean±SD (n=3)

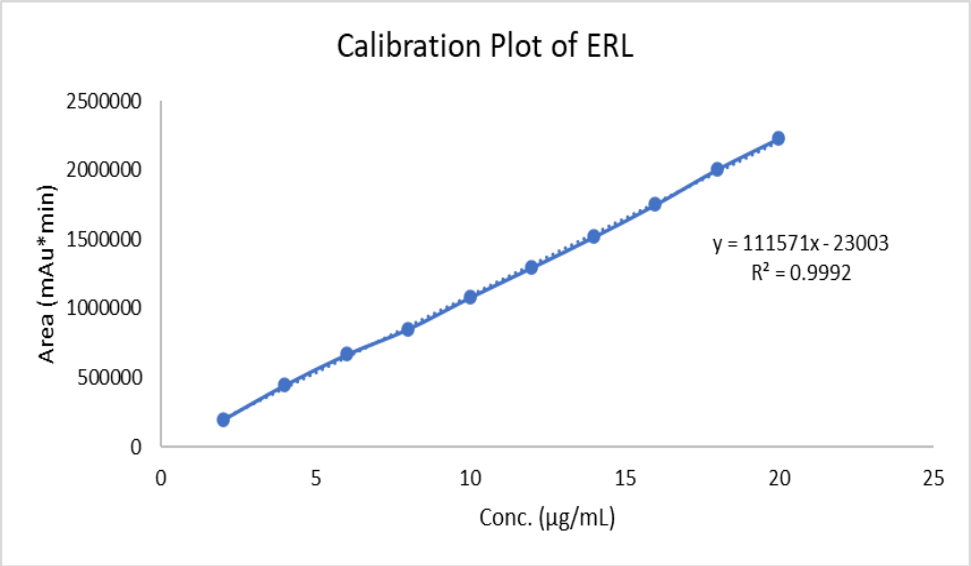

Figure A. 6: Calibration plot of ERL showing linearity at 335 nm at concentration ranging from 2–20 µg/ml

Accuracy

Table A. 8: Recovery study (Accuracy) of ERL at λ_{max}=335 nm

Pre–analysed sample	Amount added (µg/ml)	% Recovery±SD	%RSD
10µg/ml	8	99.72±0.03	0.84
	10	99.56±0.05	1.71
	12	99.37±0.02	0.85

Mean±SD (n=3)

Precision

Table A. 9: Precision study of ERL for intra–day at λ_{max}=335 nm

Concentration (µg/ml)	**Intra - Day**					
	Shift I (Morning)		Shift II (Afternoon)		Shift III (Evening)	
	Area±SD	%RSD	Area±SD	%RSD	Area±SD	%RSD
2	197553±1256	0.64	197786±1479	0.75	195788±1367	0.71
4	457656±2344	0.51	457889±3167	0.69	455891±3745	0.82
6	675669±3644	0.54	675902±3867	0.57	673904±2344	0.35
8	852364±3423	0.40	852579±3298	0.39	853697±2521	0.30
10	1083570±5428	0.51	1087026±5303	0.49	1088144±2744	0.25
12	1287659±4621	0.36	1284403±4496	0.35	1285751±3254	0.26
14	1517531±3621	0.24	1520987±3445	0.23	1522105±4462	0.29
16	1752131±3473	0.20	1749564±3297	0.19	1747579±3184	0.18
18	2012328±6621	0.32	2014896±6445	0.32	1995876±6432	0.32
20	2224569±4352	0.21	2221912±4175	0.19	2219217±5752	0.26

Mean±SD (n=3)

Table A. 10: Precision study of ERL for inter–day at λ_{max}=335 nm

Concentration (µg/ml)	**Inter - Day**					
	Day I		Day II		Day III	
	Area±SD	%RSD	Area±SD	%RSD	Area±SD	%RSD
2	197553±1256	0.64	203268±2142	1.05	195478±2254	1.15
4	457656±2344	0.51	442748±2877	0.65	459463±3213	0.70
6	675669±3644	0.54	684934±3456	0.50	665398±4356	0.65
8	852364±3423	0.40	894637±4632	0.52	879437±2766	0.31
10	1083570±5428	0.51	1124637±2844	0.25	1127483±2987	0.26
12	1287659±4621	0.36	1328789±3741	0.28	1384798±4322	0.31
14	1517531±3621	0.24	1672314±2297	0.14	1539986±4167	0.27
16	1752131±3473	0.20	1893728±3742	0.20	1783748±3855	0.22
18	2012328±6621	0.32	2192361±5593	0.26	2094738±5876	0.28
20	2224569±4352	0.21	2321265±4399	0.19	2287467±4265	0.19

Mean±SD (n=3)

Repeatability

Table A. 11: Repeatability studies of ERL at λ_{max}=335 nm

Concentration (µg/ml)	Area±SD (mAu*min)	RT±SD (min)	%RSD
10	1078811±4224	4.33±0.06	0.40

Mean±SD (n=6)

Sensitivity

Table A. 12: Limit of Detection (LOD), and limit of quantification (LOQ) of ERL in HPLC

LOD (µg/ml)	LOQ (µg/ml)
0.98	1.96

Bioanalytical method development and method validation

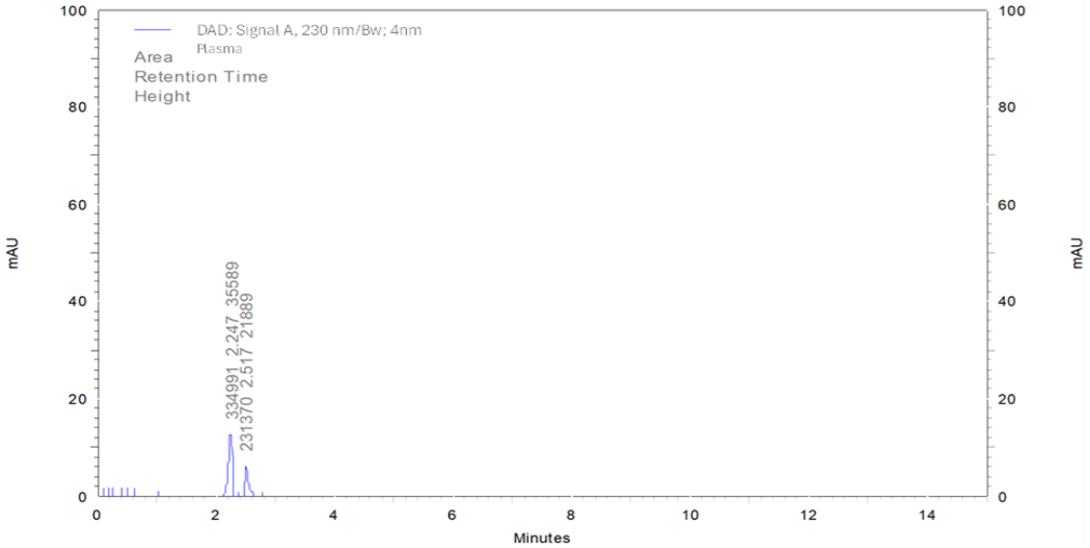

Figure A. 7: Blank Plasma DAD signal chromatogram

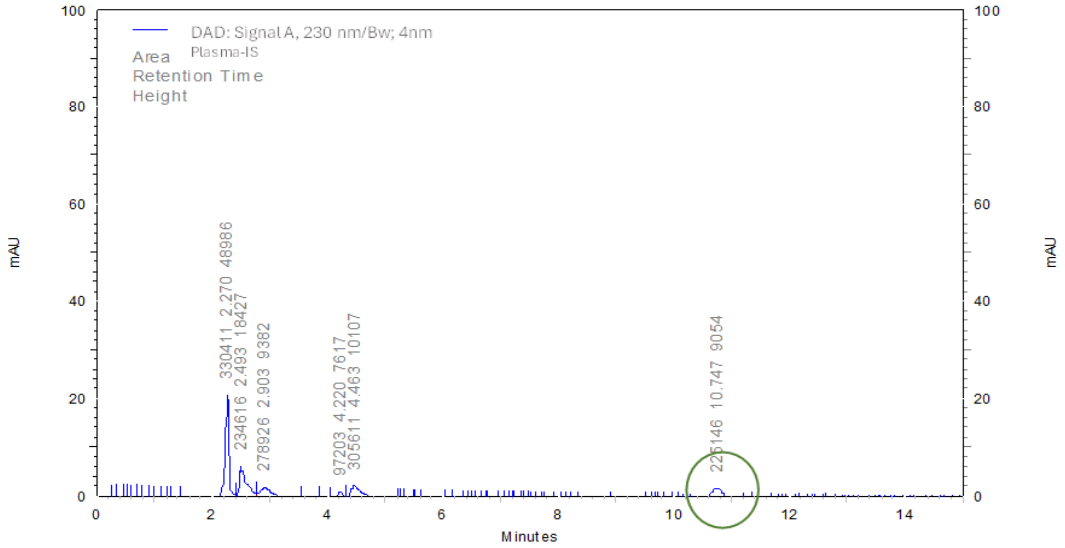

Figure A. 8: HPLC–DAD signal chromatograms of plasma spiked with paclitaxel (IS) at wavelength 230 nm, mobile phase methanol:0.02% acetic water (80:20), 1ml/min flow rate, at retention time (RT) 10.7 min

1. Docetaxel (DOC)

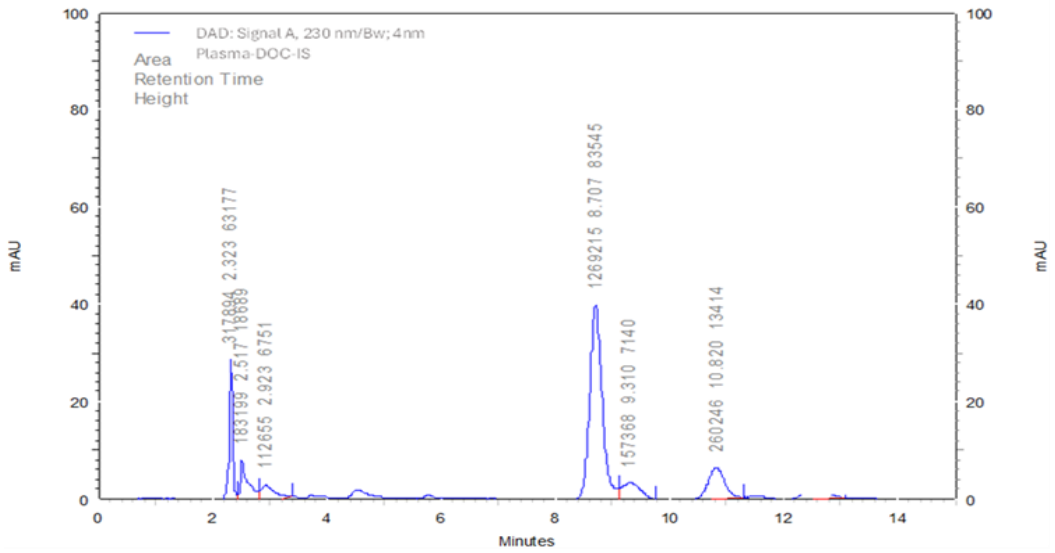

Figure A. 9: HPLC–DAD signal chromatograms of plasma spiked with DOC and paclitaxel in at wavelength 230nm, mobile phase methanol: 0.02% acetic water (80:20), 1ml/min flow rate at a retention time (RT) 8.7 min for DOC

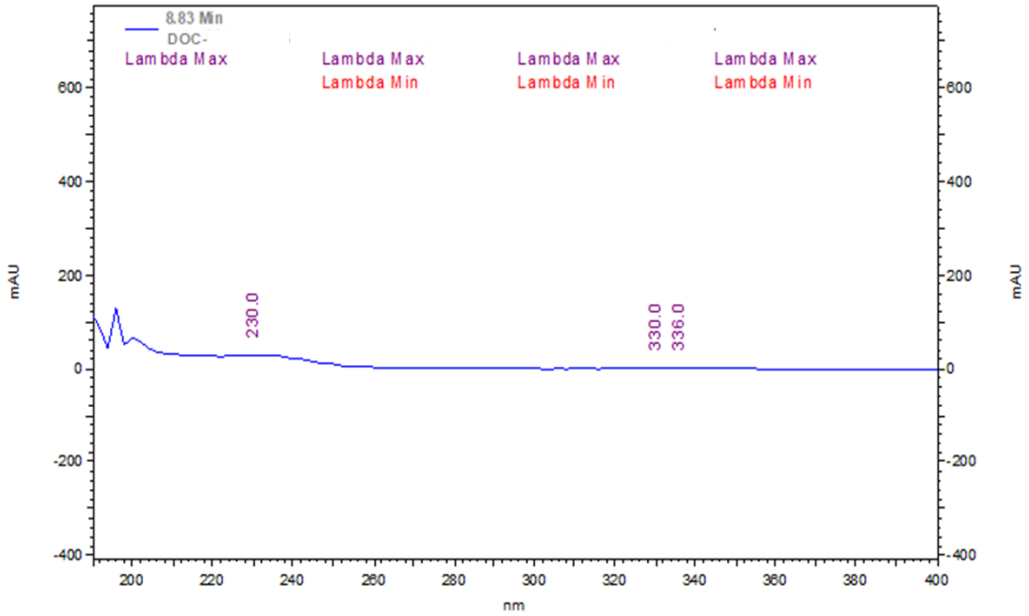

Figure A. 10: HPLC spectra of plasma spiked DOC in mobile phase methanol:0.02% acetic water (80:20) at1ml/min flow rate

Range & Linearity

Table A. 13: Calibration plot of DOC in plasma at maximum wavelength (λ_{max})=230 nm

Concentration (µg/ml)	Area±SD (mAu*min)	RT±SD (min)
0.05	28989±716	8.78±0.05
0.1	44569±809	8.76±0.02
0.2	87197±816	8.75±0.05
0.4	144387±8180	8.80±0.04
0.8	358699±8131	8.77±0.04
1.6	455953±8158	8.72±0.06
3.2	891569±6849	8.70 ±0.02
6.4	1890479±41094	8.79±0.08
12.8	3610930±55592	8.88±0.07

Mean±SD (n=3)

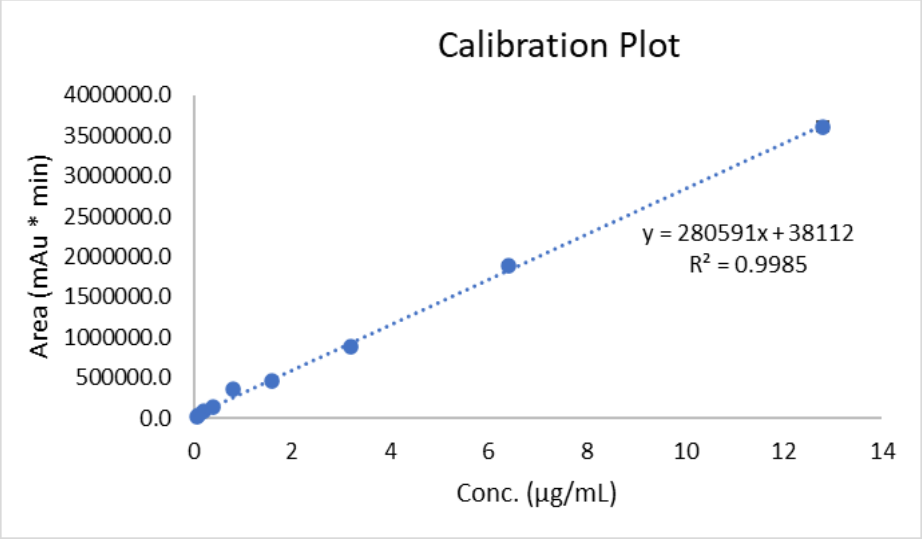

Figure A. 11: Calibration plot of DOC in plasma showing linearity at 230 nm at concentration ranging from 0.05–12.8 µg/ml

Accuracy

Table A. 14: Recovery study (Accuracy) of DOC in plasma at λ_{max}=230 nm

Pre–analysed sample	Amount added (µg/ml)	% Recovery±SD	%RSD
0.8 µg/ml	0.64	98.18±0.07	1.45
	0.80	98.71±0.03	1.19
	0.96	99.41±0.06	1.39

Mean±SD (n=3)

Precision

Table A. 15: Precision study of DOC in plasma for intra –day at λ_{max}=230 nm

Concentration (µg/ml)	**Intra - Day**					
	Shift I (Morning)		Shift II (Afternoon)		Shift III (Evening)	
	Area±SD	%RSD	Area±SD	%RSD	Area±SD	%RSD
0.05	29122 ±520	1.79	29562±344	1.16	29634±486	1.64
0.1	45435 ±813	1.79	46327±866	1.87	45673±746	1.63
0.2	86281±843	0.98	85117±727	0.85	87841±683	0.78
0.4	162320±3157	1.94	173217±2626	1.52	178734±2554	1.43
0.8	356340±6888	1.93	367735±6754	1.84	377452±5663	1.50
1.6	445343±7160	1.61	465832±4118	0.88	475838±4527	0.95
3.2	871923±6664	0.76	889417±5883	0.66	882453±5942	0.67
6.4	1875765±32413	1.73	2073443±33174	1.60	1945165±24243	1.25
12.8	3478838±54229	1.56	3584342±43652	1.22	3753817±47326	1.26

Mean±SD (n=3)

Table A. 16: Precision study of DOC in plasma for inter–day at λ_{max}=230 nm

Concentration (µg/ml)	**Inter - Day**					
	Day I		Day II		Day III	
	Area±SD	%RSD	Area±SD	%RSD	Area±SD	%RSD
0.05	29122±520	1.79	30152±576	1.91	29876±520	1.74
0.1	45435±813	1.79	46723±765	1.64	48645±783	1.61
0.2	86281±843	0.98	85374±855	1.00	85328±828	0.97
0.4	162320±3157	1.94	185318±3049	1.65	174318±2787	1.60
0.8	356340±6888	1.93	374822±6926	1.85	367533±5389	1.47
1.6	445343±7160	1.61	435275±7055	1.62	457466±6599	1.44
3.2	871923±6664	0.76	884577±6266	0.71	876929±6240	0.71
6.4	1875765±32413	1.73	1987528±36233	1.82	1883143±31543	1.68
12.8	3478838±54229	1.56	3684576±52538	1.43	3436173±53529	1.56

Mean ± SD (n=3)

Repeatability

Table A. 17: Repeatability studies of DOC in plasma at λ_{max}=230 nm

Concentration (µg/ml)	Area±SD (mAu*min)	RT±SD (min)	%RSD
0.8	361138±6944	8.75±0.04	1.92

Mean±SD (n=6)

Sensitivity

Table A. 18: Limit of Detection (LOD), and limit of quantification (LOQ) of DOC in plasma

LOD (µg/ml)	LOQ (µg/ml)
0.44	0.91

2. Erlotinib (ERL)

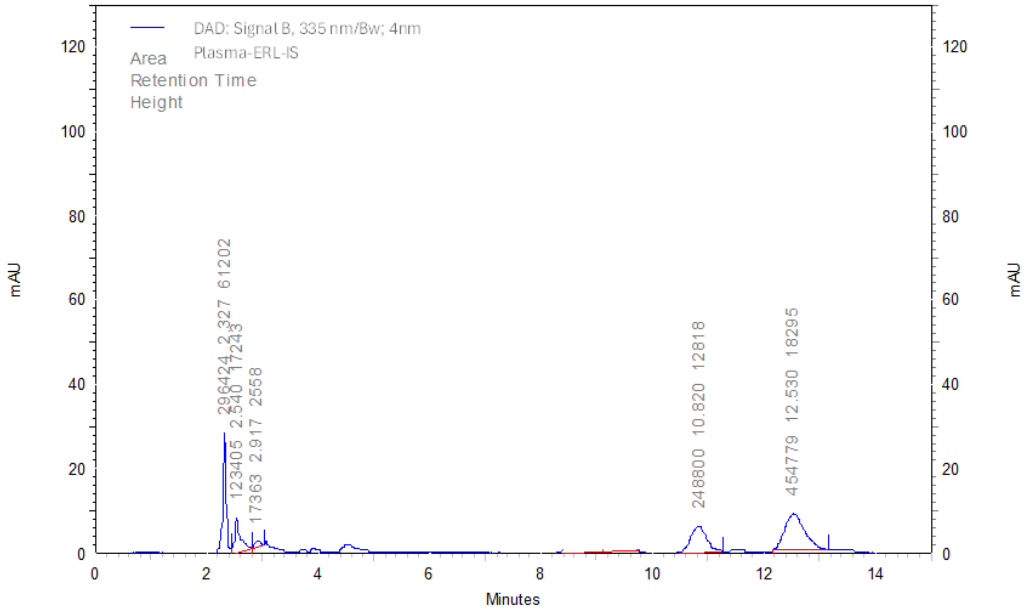

Figure A. 12: HPLC–DAD signal chromatograms of plasma spiked with ERL in at wavelength 335 nm, mobile phase methanol: 0.04% acetic water (80:20), 1ml/min flow rate at retention time (RT) 12.5 min

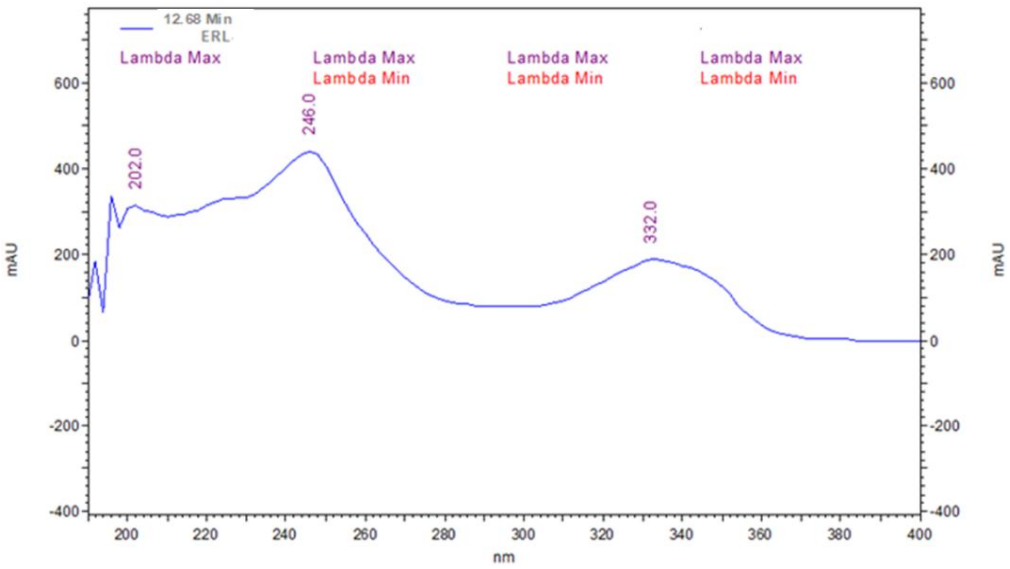

Figure A. 13: HPLC spectra of plasma spiked ERL in mobile phase methanol:0.04% acetic water (80:20) at1ml/min flow rate

Range and Linearity

Table A. 19: Calibration plot of ERL in plasma at maximum wavelength (λ_{max})=335 nm

Concentration (µg/ml)	Area±SD (mAu*min)	RT ± SD (min)
0.1	11238±91	12.58±0.03
0.2	15415±273	12.64±0.05
0.4	21500±369	12.52±0.05
0.8	35667±340	12.28±0.07
1.6	51501±451	12.54±0.05
3.2	108032±1024	12.62±0.06
6.4	192173±257	12.68±0.03
12.8	449461±1718	12.57±0.03
25.6	890655±1547	12.51±0.04

Mean±SD (n=3)

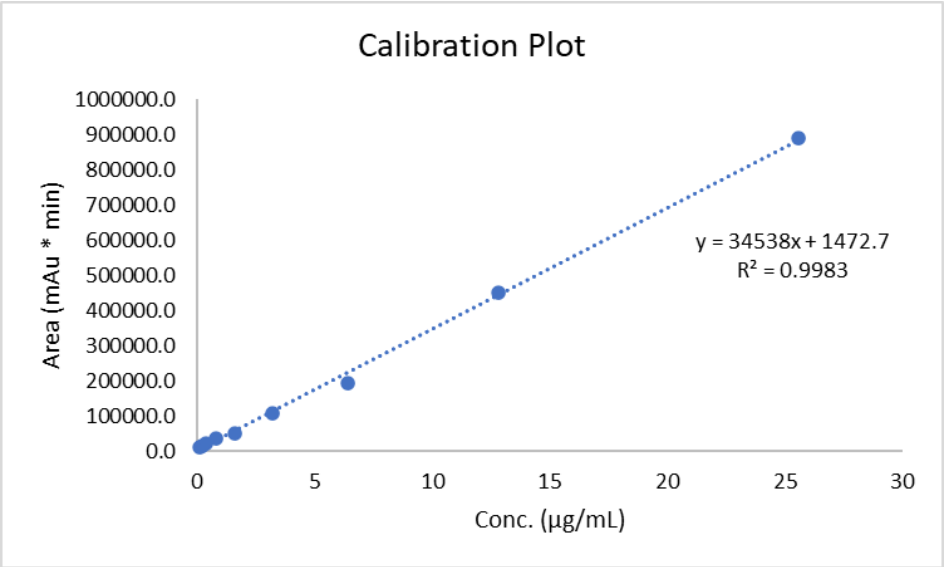

Figure A. 14: Calibration plot of ERL in plasma showing linearity at 335 nm at concentration ranging from 0.1–25.6 µg/ml

Accuracy

Table A. 20: Recovery study (Accuracy) of ERL in plasma at λ_{max}=335 nm

Pre–analysed sample	Amount added (µg/ml)	% Recovery±SD	%RSD
1.6 µg/ml	1.28	99.42±0.05	0.86
	1.60	98.31±0.03	1.25
	1.92	98.13±0.04	1.31

Mean±SD (n=3)

Precision

Table A. 21: Precision study of ERL in plasma for intra–day at λ_{max}=335 nm

Concentration (µg/ml)	**Intra - Day**					
	Shift I (Morning)		Shift II (Afternoon)		Shift III (Evening)	
	Area±SD	%RSD	Area±SD	%RSD	Area±SD	%RSD

0.1	11332±91	0.81	11278±94	0.84	11355±87	0.77
0.2	15385±274	1.78	15453±242	1.57	15276±255	1.67
0.4	21853±369	1.69	22639±415	1.84	22738±387	1.70
0.8	35834±340	0.95	35746±378	1.06	35631±427	1.20
1.6	51775±451	0.87	51884±498	0.96	51742±522	1.01
3.2	106624±1024	0.96	106738±1027	0.96	106824±1121	1.05
6.4	191764±258	0.13	191726±327	0.17	192065±257	0.13
12.8	447627±1719	0.38	447286±1755	0.39	446523±1763	0.40
25.6	891573±1547	0.17	892176±1673	0.19	891834±1426	0.16

Mean±SD (n=3)

Table A. 22: Precision study of ERL in plasma for intra–day at λ_{max}=335 nm

Concentration (µg/ml)	**Inter - Day**					
	Day I		Day II		Day III	
	Area±SD	%RSD	Area±SD	%RSD	Area±SD	%RSD
0.1	11332±91	0.81	11326±96	0.85	11412±88	0.77
0.2	15385±274	1.78	15176±239	1.57	15834±287	1.81
0.4	21853±369	1.69	22824±375	1.64	21528±331	1.54
0.8	35834±340	0.95	35882±287	0.80	34934±452	1.29
1.6	51775±451	0.87	52184±521	1.01	51718±586	1.31
3.2	106624±1024	0.96	107133±1123	1.05	106623±1176	1.10
6.4	191764±258	0.13	192133±441	0.23	192741±366	0.19
12.8	447627±1719	0.38	448093±1872	0.42	451528±1624	0.36
25.6	891573±1547	0.17	892743±1438	0.16	901163± 583	0.18

Mean±SD (n=3)

Repeatability

Table A. 23: Repeatability studies of ERL in plasma at λ_{max}=335 nm

Concentration (µg/ml)	Area±SD (mAu*min)	RT±SD (min)	%RSD
1.6	51707±402	12.52±0.02	0.78

Mean±SD (n=6)

Sensitivity

Table A. 24: Limit of Detection (LOD), and limit of quantification (LOQ) of ERL in plasma

LOD (µg/ml)	LOQ (µg/ml)
0.56	1.54

List of publications from Ph.D. work

Research Articles

1. **Chaudhuri A,** Naveen Kumar D, Kumar D, Kumar Agrawal A. Functionalized solid lipid nanoparticles combining docetaxel and erlotinib synergize the anticancer efficacy against triple-negative breast cancer. Eur J Pharm Biopharm. 2024 Aug; 201:114386. doi: 10.1016/j.ejpb.2024.114386

2. **Chaudhuri A,** Kumar DN, Srivastava SK, Kumar D, Patil UK, Parmar AS, Singh S, Agrawal AK. Combinatorial Delivery of Docetaxel- and Erlotinib-Loaded Functionalized Nanostructured Lipid Carriers for the Treatment of Triple-Negative Breast Cancer Using Quality-by-Design Approach. Pharmaceutics. 2024 Jul 11;16(7):926. doi: 10.3390/pharmaceutics16070926.

3. **Chaudhuri A,** Naveen Kumar D, Kumar D, Kumar Agrawal A. Combining Docetaxel and Erlotinib in folic acid targeted solid lipid nanoparticles for triple negative breast cancer: In vitro and in vivo studies (**Under Communication**)

4. **Chaudhuri A,** Naveen Kumar D, Kumar D, Kumar Agrawal A. Nanostructured lipid carriers – mediated combinatorial delivery of Docetaxel and Erlotinib targeted by Folic acid: An effective approach for triple-negative breast cancer therapy (**Under Communication**)

Review Articles

1. **Chaudhuri A**, Kumar DN, Dehari D, Singh S, Kumar P, Bolla PK, Kumar D, Agrawal AK. Emergence of Nanotechnology as a Powerful Cavalry against Triple-Negative Breast Cancer (TNBC). Pharmaceuticals (Basel). 2022 Apr 27;15(5):542. doi: 10.3390/ph15050542

2. **Chaudhuri A**, Kumar DN, Shaik RA, Eid BG, Abdel-Naim AB, Md S, Ahmad A, Agrawal AK. Lipid-Based Nanoparticles as a Pivotal Delivery Approach in Triple Negative Breast Cancer (TNBC) Therapy. Int J Mol Sci. 2022 Sep 3;23(17):10068. doi: 10.3390/ijms231710068.

3. **Chaudhuri A**, Kumar DN, Dehari D, Patil R, Singh S, Kumar D, Agrawal AK. Endorsement of TNBC Biomarkers in Precision Therapy by Nanotechnology. Cancers (Basel). 2023 May 8;15(9):2661. doi: 10.3390/cancers15092661.

Conferences attended in the Ph.D. tenure

1. Presented poster at **International Conference on Nanotechnology for Better Living NBL–2023** held from 25 to 29 May 2023 at NIT Srinagar, a joint venture with IIT (BHU) Varanasi, and in association with Parul University.
2. Delivered oral presentation at **International Symposium on Advances in Drug Delivery Technologies (ADDT),** held on Feb 16–17, 2024, at BITS Pilani, Pilani Campus, Rajasthan, India
3. Presented poster at **22nd International Conference on Advances in Technology and Business Potential of New Drug Delivery Systems**, **CRS–Indian Local Chapter** on 29th Feb–1st Mar, 2024.

भारतीय प्रौद्योगिकी संस्थान
काशी हिन्दू विश्वविद्यालय
INDIAN INSTITUTE OF TECHNOLOGY
BANARAS HINDU UNIVERSITY

Department of Pharmaceutical Engineering & Technology

Regd. No. 2123/GO/Re/S/21/CPCSEA

Date: 25 Aug, 2023

IAEC Approval Number: **IIT(BHU)/IAEC/2023/II/064**

CERTIFICATE

This is to certify that the project proposal entitled "***Folic acid-functionalized drug cocktail loaded lipid Nano-constructs for ameliorating the triple-negative breast cancer therapy***" submitted by **Dr. Ashish Kumar Agrawal** has been approved/recommended by the IAEC of Indian Institute of Technology, Banaras Hindu University, Varanasi in its meeting dated **25 August, 2023** and has been sanctioned **70 (Female BALB/c Mice) & 45 (Female SD Rats)** under this proposal for a duration of **12 (Twelve) months.**

Prof. Vikash Kumar Dubey	Dr. Vinod Tiwari	Dr. Shesh Narayan Mishra
Name & Signature	**Name & Signature**	**Name & Signature**
Chairman	**Member Secretary**	**Main Nominee of CPCSEA**

Note: The CPCSEA Guideline should be followed strictly while handling the animals.

भारतीय प्रौद्योगिकी संस्थान
काशी हिन्दू विश्वविद्यालय
IIT INDIAN INSTITUTE OF TECHNOLOGY
BANARAS HINDU UNIVERSITY

Department of Pharmaceutical Engineering & Technology

Regd. No. 2123/GO/Re/S/21/CPCSEA

Date: 09 February, 2023

IAEC Approval Number: **IIT(BHU)/IAEC/2023/001**

CERTIFICATE

This is to certify that the project proposal entitled **"Preparation and evaluation of folic acid conjugated Docetaxel-Erlotinib loaded solid–lipid nanoparticles for the effective treatment of Triple Negative Breast Cancer"** submitted by **Miss. Aiswarya** under supervision of **Dr. Ashish Kumar Agrawal** has been approved/recommended by the IAEC of *Indian Institute of Technology, Banaras Hindu University, Varanasi* in its meeting dated **09/02/2023** and has been sanctioned **45 SD Rats 50 BALB/c MICE (Female)** under this proposal for a duration of 12 months

Prof. Vikash Kumar Dubey	Dr. Vinod Tiwari	Dr. Shesh Narayan Mishra
Name & Signature	**Name & Signature**	**Name & Signature**
Chairman	**Member Secretary**	**Main Nominee of CPCSEA**

Note: The CPCSEA Guideline should be followed strictly while handling the animals.

Chapter 8

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