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## **APPENDICES**



## APPENDIX I

Spectra of UV, FT-IR and  $^1\text{H-NMR}$

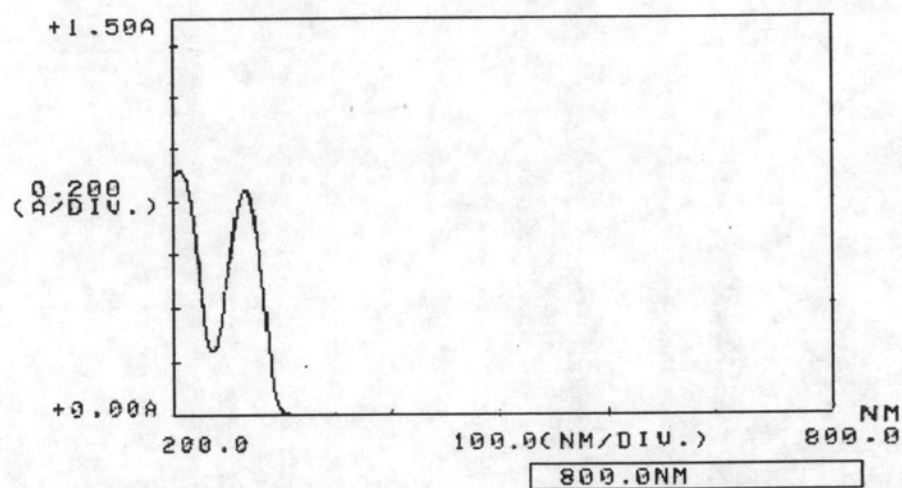


Figure 54 UV spectrum of zidovudine in water with  $\lambda_{\max}$  of 266 nm.

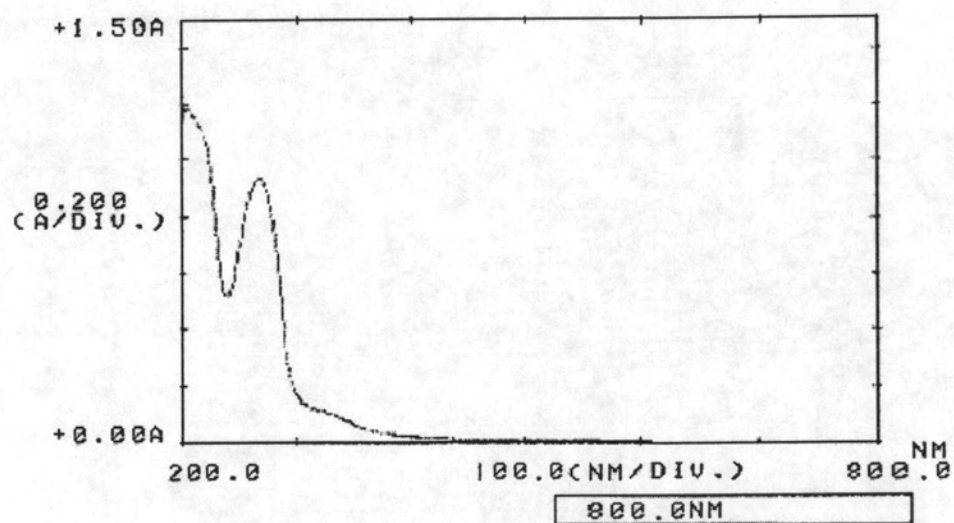


Figure 55 UV spectrum of dextrin-zidovudine conjugate in water with  $\lambda_{\max}$  of 267 nm.

Figure 56 FT-IR spectrum of zidovudine (KBr disc).

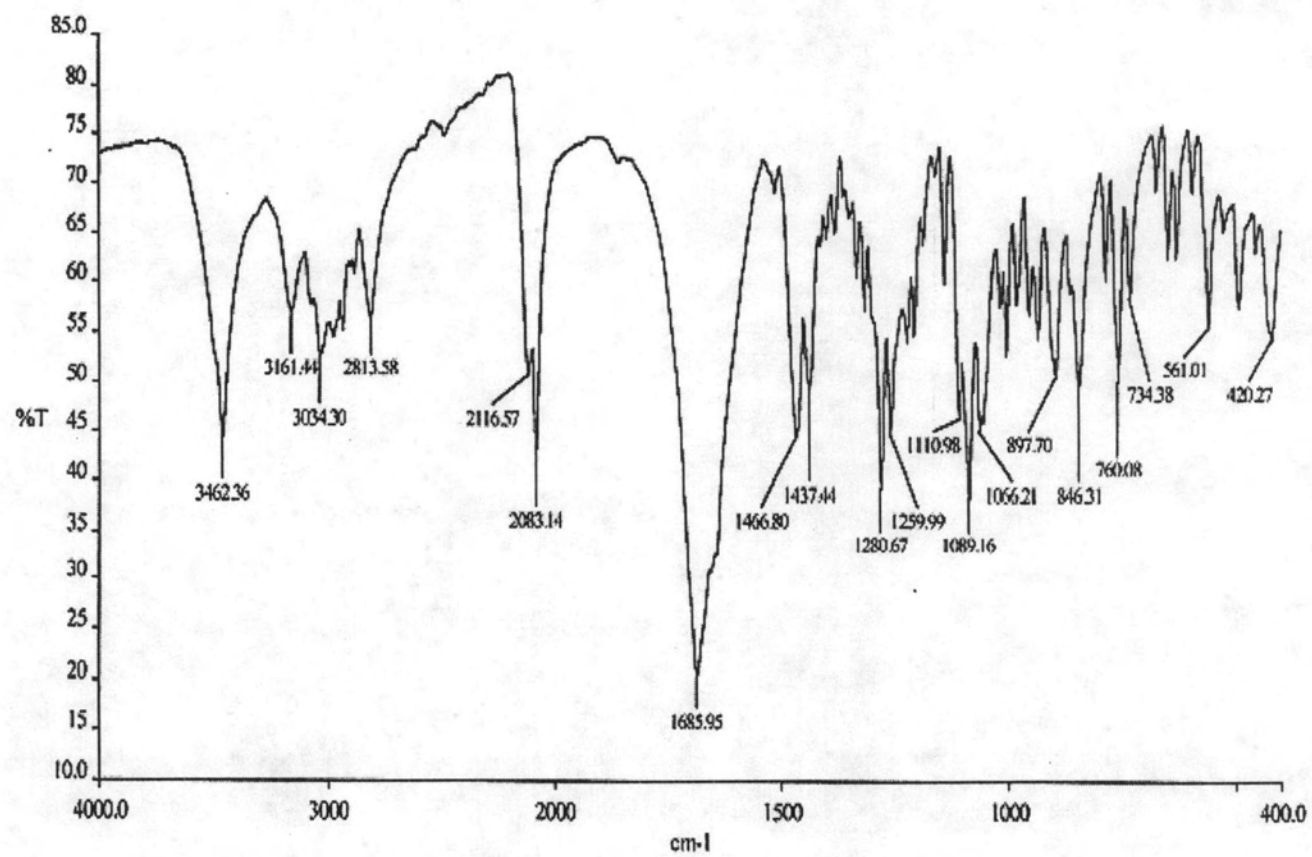


Figure 57 FT-IR spectrum of succinylated zidovudine (KBr disc).

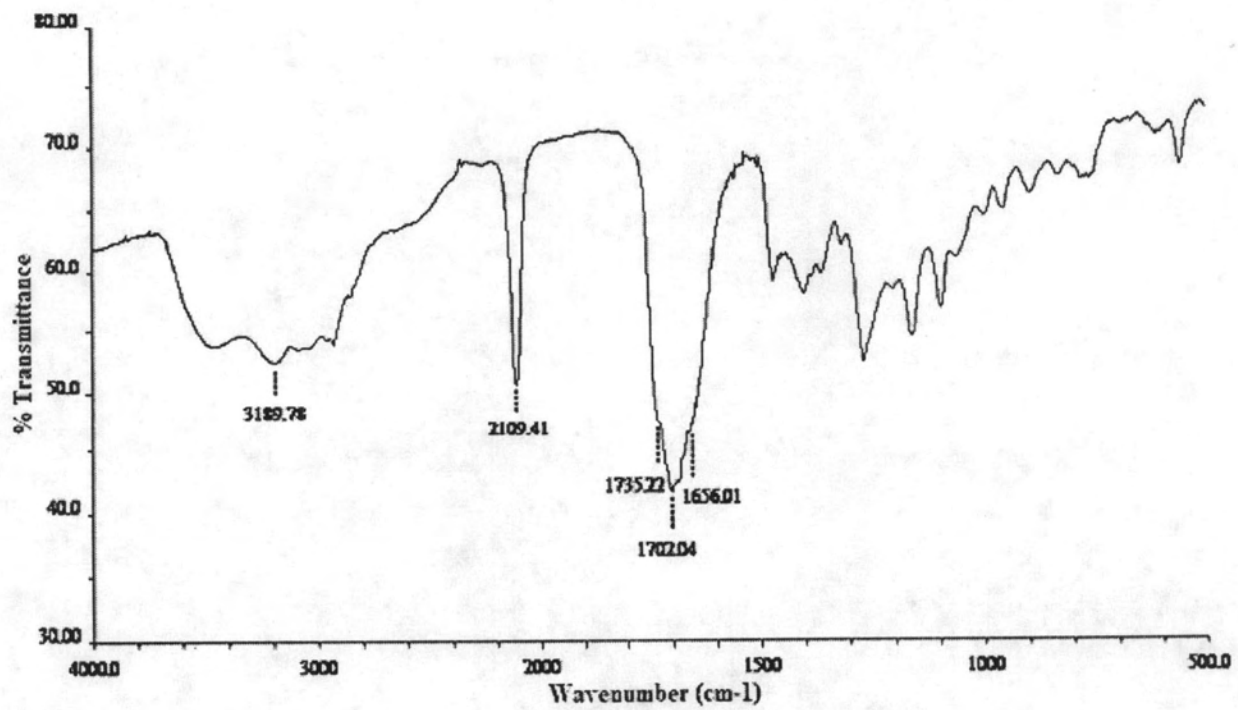


Figure 58 FT-IR spectrum of dextrin (KBr disc).

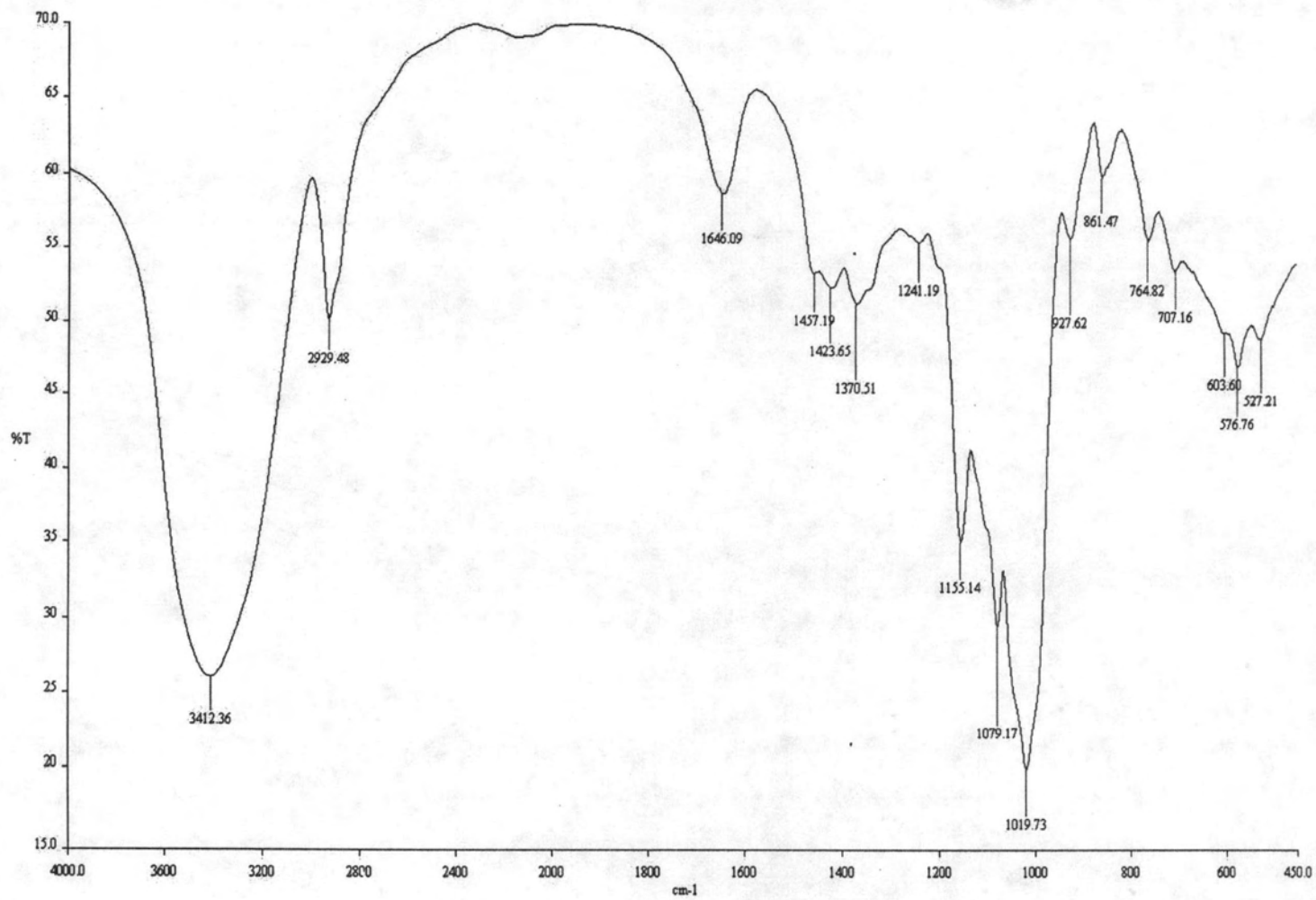
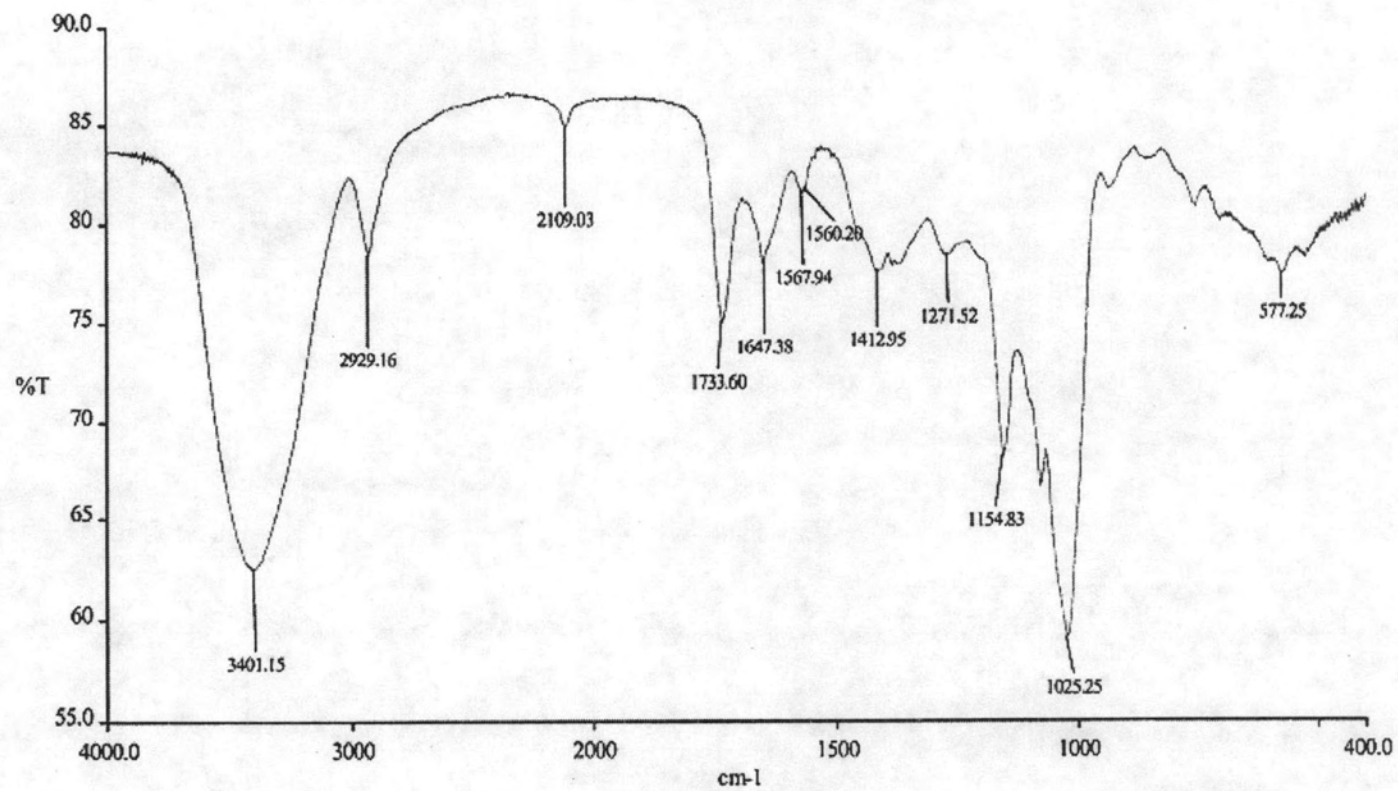


Figure 59 FT-IR spectrum of dextrin-zidovudine conjugate (KBr disc).



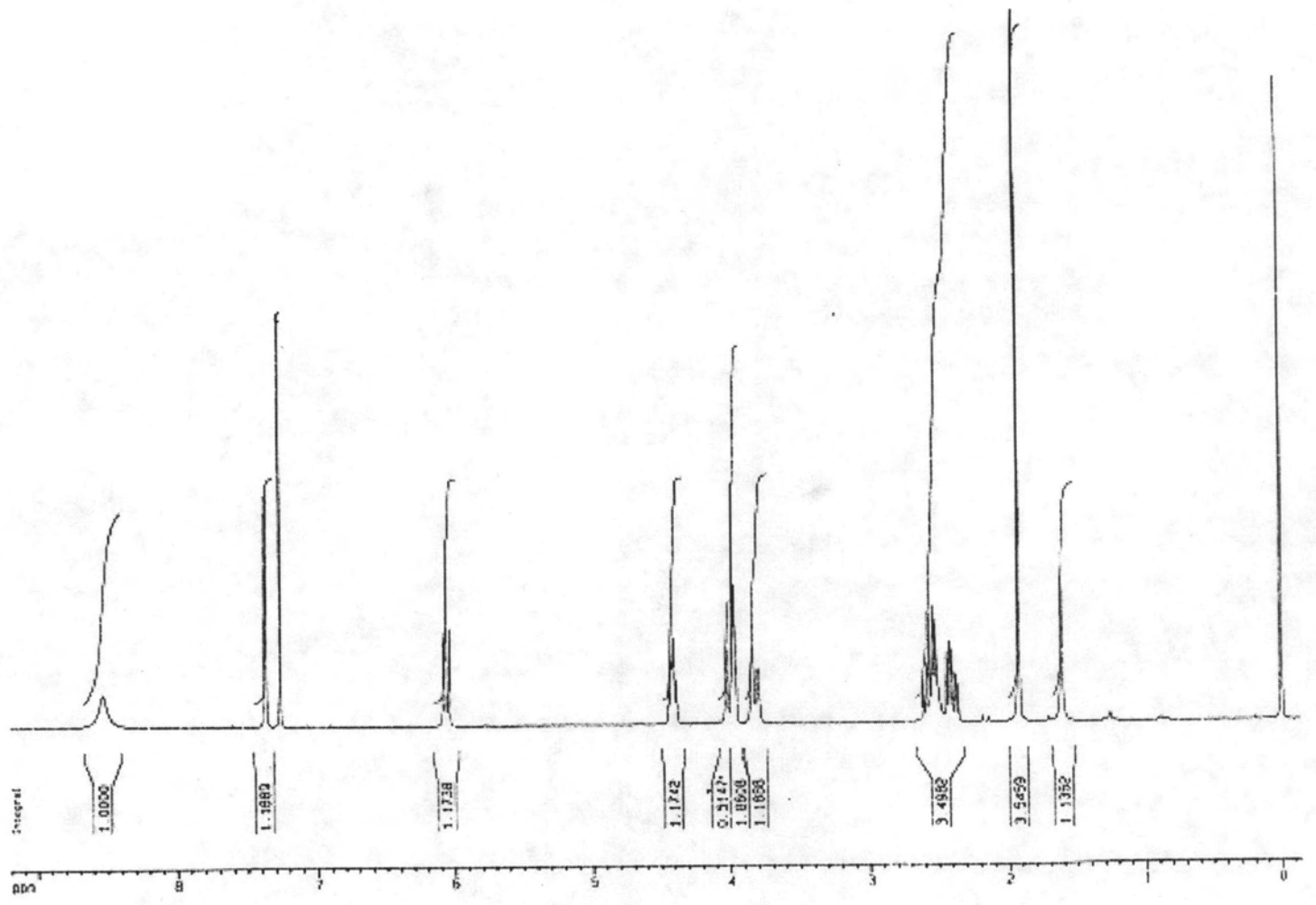


Figure 60 <sup>1</sup>H-NMR spectrum of zidovudine (CDCl<sub>3</sub>, 300 MHz).

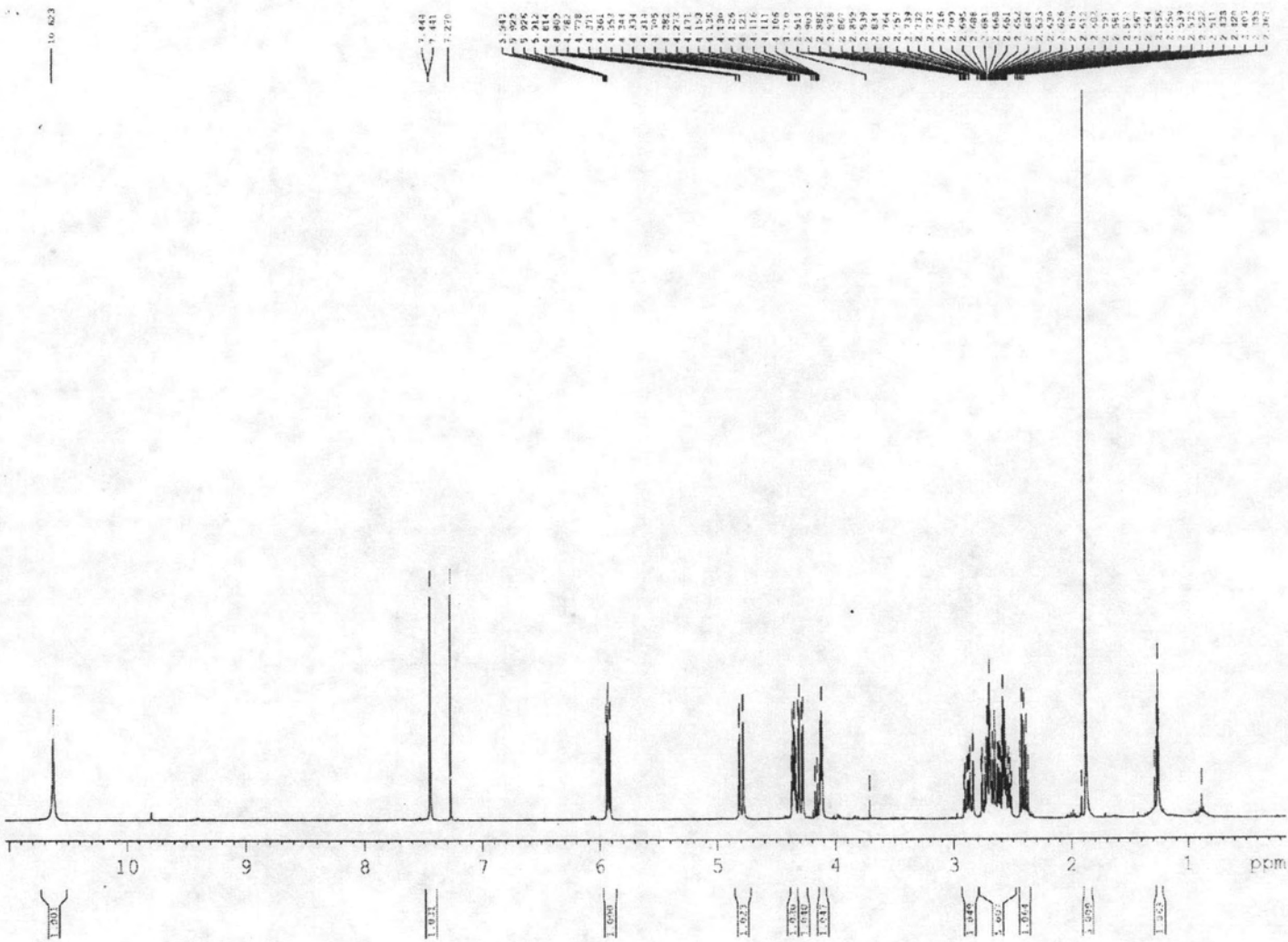


Figure 61  $^1\text{H}$ -NMR spectrum of succinylated zidovudine ( $\text{CDCl}_3$ , 400 MHz).



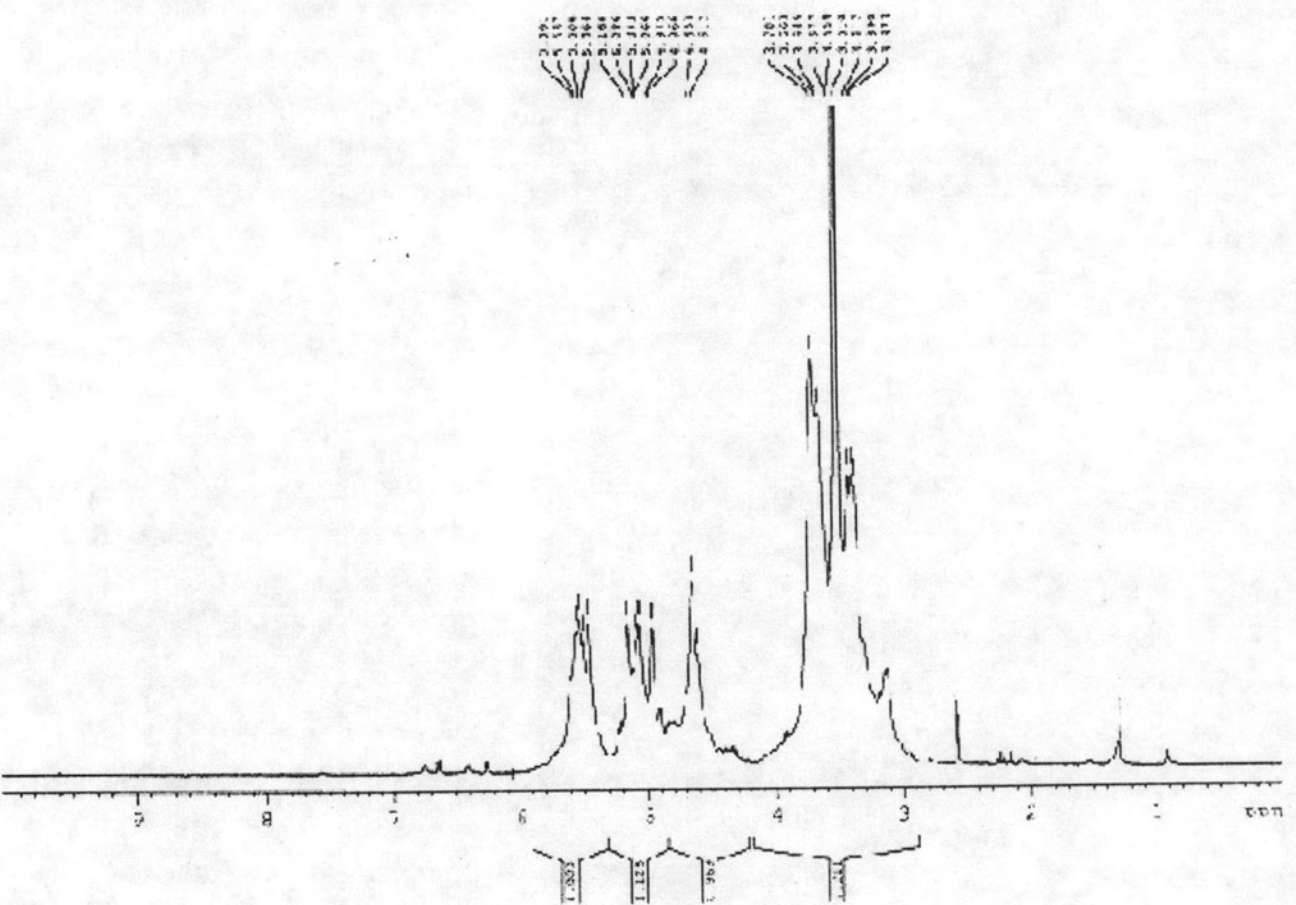


Figure 62  ${}^1\text{H-NMR}$  spectrum of dextrin ( $\text{D}_2\text{O}$ , 400 MHz).

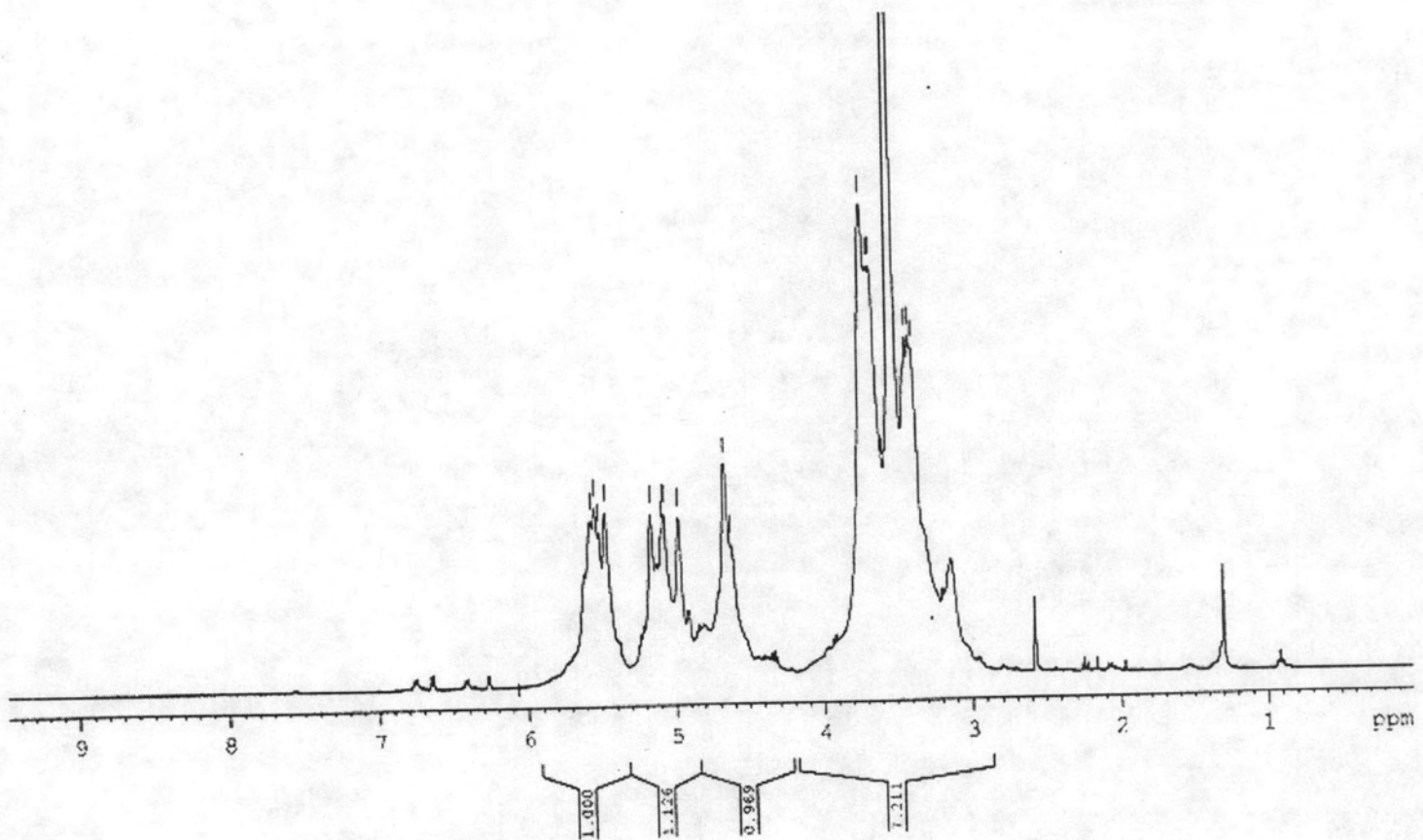


Figure 63  $^1\text{H-NMR}$  spectrum of dextrin, expanded ( $\text{D}_2\text{O}$ , 400 MHz).

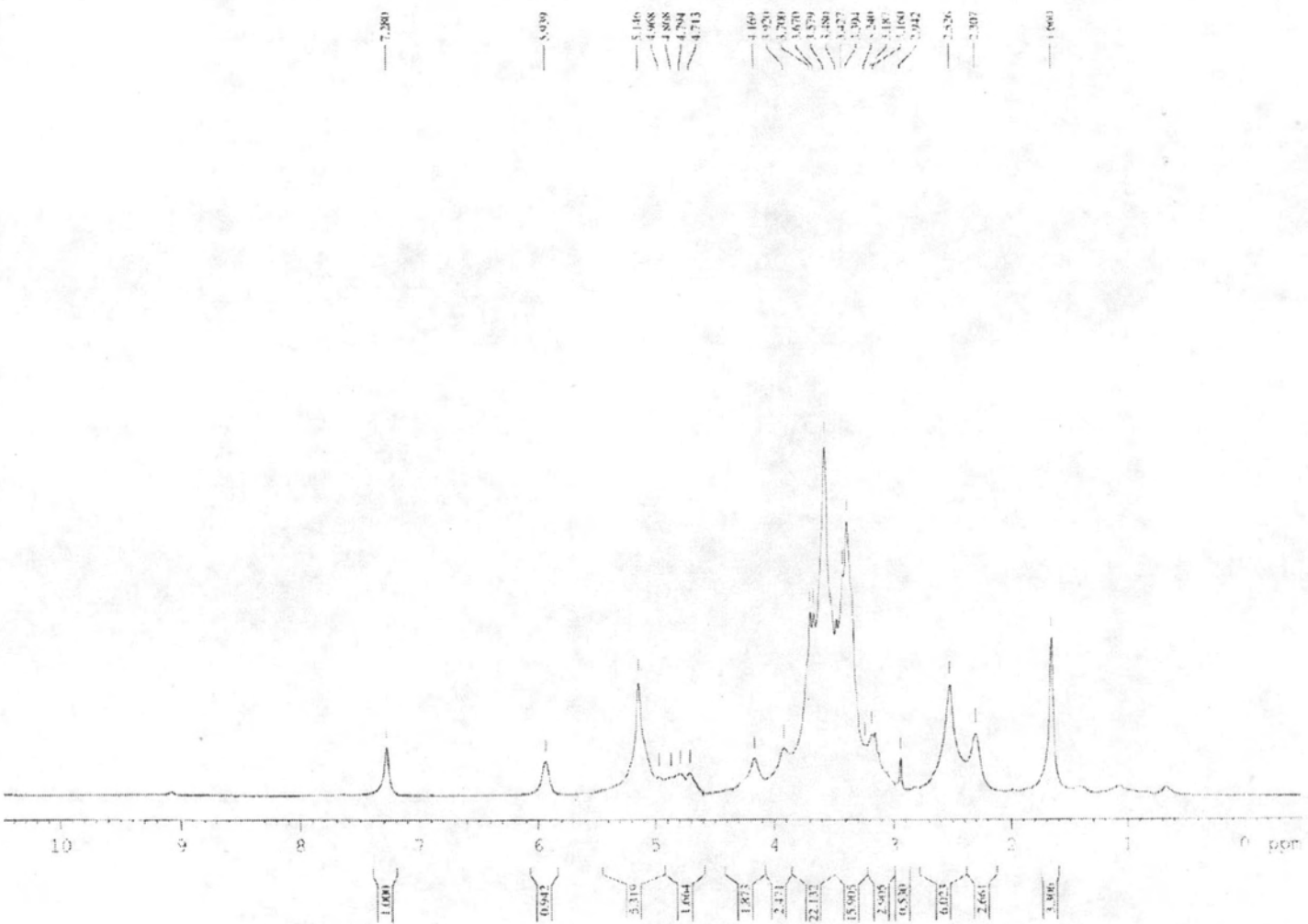


Figure 64  $^1\text{H-NMR}$  spectrum of dextrin-zidovudine conjugate ( $\text{D}_2\text{O}$ , 400 MHz).

## APPENDIX II

The data of *in vitro* and *in vivo* studies

**Table 31** Release of zidovudine from the dextrin-zidovudine conjugate in buffer solutions at pH 5.5.

Time	% Zidovudine released (mole)			Average $\pm$ S.D.
	n1	n2	n3	
0	0.04	0.03	0.04	0.04 $\pm$ 0.01
0.25	0.06	0.07	0.08	0.07 $\pm$ 0.01
0.5	0.07	0.08	0.09	0.08 $\pm$ 0.01
1	0.08	0.09	0.09	0.09 $\pm$ 0.01
2	0.10	0.11	0.10	0.10 $\pm$ 0.01
4	0.13	0.15	0.15	0.14 $\pm$ 0.01
8	0.26	0.22	0.25	0.25 $\pm$ 0.02
12	0.35	0.33	0.36	0.35 $\pm$ 0.02
16	0.47	0.42	0.47	0.45 $\pm$ 0.03
20	0.59	0.63	0.55	0.59 $\pm$ 0.04
24	0.68	0.75	0.69	0.71 $\pm$ 0.04
48	1.32	1.56	1.36	1.41 $\pm$ 0.13

**Table 32** Release of succinylated zidovudine from the dextrin-zidovudine conjugate in buffer solutions at pH 5.5.

Time	% Succinylated zidovudine released (mole)			Average $\pm$ S.D.
	n1	n2	n3	
0	0.05	0.06	0.07	0.06 $\pm$ 0.01
0.25	0.08	0.11	0.08	0.09 $\pm$ 0.02
0.5	0.10	0.14	0.11	0.12 $\pm$ 0.02
1	0.12	0.14	0.14	0.13 $\pm$ 0.01
2	0.14	0.19	0.15	0.16 $\pm$ 0.23
4	0.19	0.21	0.21	0.20 $\pm$ 0.01
8	0.21	0.26	0.22	0.23 $\pm$ 0.02
12	0.22	0.28	0.24	0.24 $\pm$ 0.03
16	0.40	0.36	0.41	0.39 $\pm$ 0.02
20	0.55	0.57	0.57	0.56 $\pm$ 0.01
24	0.65	0.63	0.67	0.65 $\pm$ 0.02
48	1.60	1.88	1.60	1.69 $\pm$ 0.16

**Table 33** Release of zidovudine from the dextrin-zidovudine conjugate in buffer solutions at pH 7.4.

Time	% Zidovudine released (mole)			Average $\pm$ S.D.
	n1	n2	n3	
0	0.04	0.05	0.05	0.05 $\pm$ 0.01
0.25	0.29	0.17	0.22	0.23 $\pm$ 0.06
0.5	0.85	0.66	0.76	0.76 $\pm$ 0.09
1	1.13	0.90	1.20	1.07 $\pm$ 0.16
2	1.86	1.44	1.70	1.66 $\pm$ 0.21
4	3.41	3.04	2.94	3.13 $\pm$ 0.25
8	6.54	5.61	6.06	6.07 $\pm$ 0.46
12	8.82	6.79	8.33	7.98 $\pm$ 1.06
16	10.99	8.67	11.61	10.42 $\pm$ 1.55
20	13.50	11.56	11.22	12.09 $\pm$ 1.23
24	15.90	14.86	13.25	14.67 $\pm$ 1.34
48	28.96	25.36	20.88	25.07 $\pm$ 4.05

**Table 34** Release of succinylated zidovudine from the dextrin-zidovudine conjugate in buffer solutions at pH 7.4.

Time	% Succinylated zidovudine released (mole)			Average $\pm$ S.D.
	n1	n2	n3	
0	0.08	0.09	0.11	0.09 $\pm$ 0.01
0.25	0.73	0.27	0.66	0.55 $\pm$ 0.25
0.5	1.34	0.97	1.10	1.14 $\pm$ 0.19
1	2.26	1.51	1.98	1.92 $\pm$ 0.38
2	3.98	2.89	3.59	3.49 $\pm$ 0.55
4	7.18	5.55	6.35	6.36 $\pm$ 0.81
8	12.97	10.86	12.20	12.01 $\pm$ 1.07
12	17.07	14.94	16.42	16.14 $\pm$ 1.09
16	20.31	18.50	19.28	19.36 $\pm$ 0.91
20	24.45	21.21	24.07	23.25 $\pm$ 1.77
24	28.35	25.06	27.69	27.03 $\pm$ 1.74
48	46.58	40.25	43.42	43.42 $\pm$ 3.16

**Table 35** Release of zidovudine from the dextrin-zidovudine conjugate in plasma.

Time	% Zidovudine released (mole)			Average $\pm$ S.D.
	n1	n2	n3	
0	0.07	0.05	0.05	0.06 $\pm$ 0.01
0.25	1.28	0.46	1.03	0.92 $\pm$ 0.42
0.5	1.23	0.97	1.53	1.24 $\pm$ 0.28
1	1.95	1.81	2.40	2.06 $\pm$ 0.31
2	4.71	4.10	5.83	4.88 $\pm$ 0.88
4	9.57	8.12	10.32	9.34 $\pm$ 1.12
8	18.05	16.20	20.26	18.17 $\pm$ 2.04
12	25.33	24.31	26.51	25.38 $\pm$ 1.10
16	31.13	27.71	33.86	30.92 $\pm$ 3.09
20	36.89	34.51	38.81	36.74 $\pm$ 2.16
24	43.00	40.57	43.31	42.29 $\pm$ 1.50
48	77.21	74.69	73.74	75.21 $\pm$ 1.79

**Table 36** Release of succinylated zidovudine from the dextrin-zidovudine conjugate in plasma.

Time	% Succinylated zidovudine released (mole)			Average $\pm$ S.D.
	n1	n2	n3	
0	0.11	0.08	0.10	0.10 $\pm$ 0.02
0.25	0.97	0.79	1.02	0.93 $\pm$ 0.12
0.5	1.64	1.37	1.76	1.59 $\pm$ 0.20
1	3.27	2.91	3.88	3.35 $\pm$ 0.49
2	6.75	6.37	7.43	6.85 $\pm$ 0.54
4	14.15	13.15	14.82	14.04 $\pm$ 0.84
8	23.33	18.84	21.48	21.22 $\pm$ 2.26
12	29.70	24.04	28.17	27.30 $\pm$ 2.93
16	33.58	30.61	32.18	32.12 $\pm$ 1.48
20	36.17	33.26	35.15	34.86 $\pm$ 1.48
24	36.97	35.07	36.14	36.06 $\pm$ 0.95
48	31.97	30.00	32.55	31.50 $\pm$ 1.34

**Table 37** Hemolytic effect of dextrin, dextran, the dextrin-zidovudine conjugate, PEI, zidovudine, and combination of zidovudine and dextrin.

Type	Conc (mg/mL)	% Hemolysis			Average $\pm$ S.D.
		n1	n2	n3	
Dextrin	0.5	11.83	12.40	13.56	12.59 $\pm$ 0.88
	1.0	10.38	12.69	12.40	11.83 $\pm$ 1.26
	1.5	12.11	12.40	11.25	11.92 $\pm$ 0.60
	2.0	10.96	12.40	11.54	11.63 $\pm$ 0.73
	2.5	12.40	12.69	12.40	12.50 $\pm$ 0.17
Dextran	0.5	11.83	13.84	13.56	13.08 $\pm$ 1.09
	1.0	12.40	12.11	10.96	11.83 $\pm$ 0.76
	1.5	11.83	11.25	12.11	11.73 $\pm$ 0.44
	2.0	11.25	13.56	13.27	12.69 $\pm$ 1.26
	2.5	12.69	13.84	14.42	13.65 $\pm$ 0.88
Conjugate	0.5	14.71	12.69	14.13	13.84 $\pm$ 1.04
	1.0	14.42	14.13	12.69	13.75 $\pm$ 0.93
	1.5	12.98	12.11	12.11	12.40 $\pm$ 0.50
	2.0	13.27	11.54	14.42	13.08 $\pm$ 1.45
	2.5	12.69	13.84	13.84	13.46 $\pm$ 0.67
PEI	0.5	22.50	21.92	21.92	22.11 $\pm$ 0.33
	1.0	27.69	27.98	27.40	27.69 $\pm$ 0.29
	1.5	36.34	52.78	60.57	49.90 $\pm$ 12.37
	2.0	100.95	87.68	114.50	101.04 $\pm$ 13.41
	2.5	68.36	127.48	76.43	90.76 $\pm$ 32.06
AZT*	0.09	14.42	12.98	13.27	13.56 $\pm$ 0.76
	0.19	12.40	13.84	11.83	12.69 $\pm$ 1.04
	0.28	13.84	13.84	11.83	13.17 $\pm$ 1.17
	0.38	11.54	12.13	13.84	13.17 $\pm$ 1.42
	0.47	12.11	15.29	14.42	13.94 $\pm$ 1.64
AZT + dextrin**	0.5	12.11	12.98	13.27	12.79 $\pm$ 0.60
	1.0	10.10	11.25	11.54	10.96 $\pm$ 0.76
	1.5	10.38	12.69	11.25	11.44 $\pm$ 1.17
	2.0	11.54	10.38	10.67	10.86 $\pm$ 0.60
	2.5	11.83	13.27	12.69	12.59 $\pm$ 0.73

\* Zidovudine concentration as equivalent as zidovudine loading in the dextrin-zidovudine conjugate

\*\* shown as total concentration of combination of zidovudine and dextrin that contained zidovudine amount equivalent as zidovudine loading in the dextrin-zidovudine conjugate



**Table 38** Cytotoxicity towards lung epithelial BEAS-2B cells after incubation with dextrin, dextran, the dextrin-zidovudine conjugate, PEI, zidovudine, and the combination of dextrin and zidovudine.

Type	Conc ( $\mu\text{g/mL}$ )	% Apoptosis			Average $\pm$ S.D.
		n1	n2	n3	
Dextrin	1	4.15	5.20	3.70	4.35 $\pm$ 0.77
	50	7.45	4.67	2.76	4.96 $\pm$ 2.36
	100	5.53	7.21	4.19	5.64 $\pm$ 1.52
	500	6.25	5.65	4.33	5.41 $\pm$ 0.98
Dextran	1	5.86	6.25	7.73	6.61 $\pm$ 0.99
	50	5.71	9.09	3.31	6.04 $\pm$ 2.90
	100	6.76	5.77	6.28	6.27 $\pm$ 0.49
	500	9.02	6.37	4.17	6.52 $\pm$ 2.43
Conjugate	1	4.19	3.05	5.13	4.12 $\pm$ 1.04
	50	10.31	8.75	6.43	8.50 $\pm$ 1.95
	100	8.22	13.04	11.93	11.06 $\pm$ 2.53
	500	8.56	8.76	6.38	7.90 $\pm$ 1.32
PEI	1	4.29	2.48	5.19	3.99 $\pm$ 1.38
	50	17.53	18.07	21.51	19.03 $\pm$ 2.16
	100	23.66	22.55	25.22	23.81 $\pm$ 1.34
	500	22.95	25.53	24.67	24.38 $\pm$ 1.31
AZT*	0.19	12.58	14.77	9.21	12.19 $\pm$ 2.80
	9.46	12.43	23.93	17.22	17.86 $\pm$ 5.78
	18.92	18.33	16.31	16.15	16.93 $\pm$ 1.22
	94.60	20.11	21.28	18.44	19.94 $\pm$ 1.43
AZT + dextrin**	1	18.52	19.11	16.67	18.10 $\pm$ 1.27
	50	34.62	28.67	33.53	32.27 $\pm$ 3.17
	100	27.95	25.23	31.09	28.09 $\pm$ 2.94
	500	32.80	24.68	24.63	27.37 $\pm$ 4.71

\* Zidovudine concentration as equivalent as zidovudine loading in the dextrin-zidovudine conjugate

\*\* shown as total concentration of combination of zidovudine and dextrin that contained zidovudine amount equivalent as zidovudine loading in the dextrin-zidovudine conjugate

**Table 39** Zidovudine plasma concentrations at various time intervals following intravenous administration of free zidovudine in rats.

Time	Zidovudine conc ( $\mu\text{g/mL}$ )			Average $\pm$ S.D.
	n1	n2	n3	
0.02	21.71	26.01	23.34	23.68 $\pm$ 2.17
0.25	2.75	3.17	2.41	2.78 $\pm$ 0.38
0.5	1.30	1.62	1.19	1.37 $\pm$ 0.23
0.75	1.24	1.40	1.05	1.23 $\pm$ 0.18
1	0.68	0.81	0.59	0.69 $\pm$ 0.11
1.5	0.22	0.24	0.26	0.24 $\pm$ 0.02
2	0.11	0.09	0.08	0.09 $\pm$ 0.01
3	0.06	0.05	0.04	0.05 $\pm$ 0.01
4	0.03	0.04	0.03	0.03 $\pm$ 0.01
5	0.02	0.02	0.02	0.02 $\pm$ 0.00

**Table 40** Zidovudine plasma concentrations at various time intervals following intravenous administration of the dextrin-zidovudine conjugate in rats.

Time	Zidovudine conc ( $\mu\text{g/mL}$ )			Average $\pm$ S.D.
	n1	n2	n3	
0.02	4.91	3.90	4.41	4.41 $\pm$ 0.50
0.25	1.61	1.16	1.57	1.45 $\pm$ 0.25
0.5	0.64	0.60	0.57	0.60 $\pm$ 0.03
0.75	0.40	0.43	0.36	0.40 $\pm$ 0.04
1	0.23	0.19	0.20	0.21 $\pm$ 0.02
1.5	0.08	0.13	0.11	0.11 $\pm$ 0.02
2	0.08	0.10	0.08	0.09 $\pm$ 0.01
3	0.11	0.09	0.08	0.10 $\pm$ 0.02
4	0.12	0.13	0.11	0.12 $\pm$ 0.01
6	0.18	0.15	0.17	0.17 $\pm$ 0.01
8	0.18	0.09	0.14	0.14 $\pm$ 0.04
12	0.13	0.13	0.10	0.12 $\pm$ 0.02
20	0.09	0.11	0.09	0.10 $\pm$ 0.02
24	0.06	0.10	0.07	0.08 $\pm$ 0.02
30	0.07	0.05	0.07	0.06 $\pm$ 0.01

## VITA

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