RESEARCH ARTICLE

Pharmacokinetic Studies and Evaluation of Nanoparticulate Drug Delivery System in the Treatment of Cancer

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ABSTRACT

Cancer is a leading cause of mortality globally. The rising incidence of cancer worldwide has presented a significant challenge to healthcare practitioners. The primary forms of cancer are associated with elevated mortality rates. Cancer therapies encompass surgery, chemotherapy, radiation, and immunotherapy; chemotherapy remains the primary modality. For many decades, the predominant method of chemotherapy has been intravenous drug delivery, which presents disadvantages such as safety concerns, discomfort, and suboptimal patient compliance. Conversely, oral medication has numerous advantages, including ease of administration, enhanced safety, and greater patient acceptance. In this study, we have developed a unique lipid-based drug delivery system for methotrexate and paclitaxel to enhance their bioavailability and efficacy. Methotrexate and Paclitaxel had the highest accumulation in the spleen, liver, and kidney, which may facilitate enhanced drug delivery in small cell carcinoma, hence improving efficacy. Methotrexate and Paclitaxel had the highest accumulation in the spleen, liver, and kidneys, which may facilitate improved drug delivery in small cell cancer.

Keywords: cancer, methotrexate and Paclitaxel, Stability

Keywords: Pomegranate peel extract, phytosomes, acute oral toxicity study, In vivo antidiabetic study

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INTRODUCTION

The human body, with its 30 trillion cells, is a complex system where errors in cellular processes can lead to cancer. Cancer cells exhibit uncontrolled growth and can migrate from their original site to distant organs, highlighting their aggressive and invasive nature.[1,2] Malignant malignancies spread through a process called metastasis, where cancer cells bypass the body's defenses, travel via the circulatory system, and invade other organs. These cells consume nutrients from neighboring cells, forming secondary tumors in vital organs. Metastasis remains a risk even after treatment or recurrence, as surgery cannot prevent it, just as it cannot fully address localized tumors. Malignant cells may already circulate in the bloodstream before cancer is clinically detected, making metastasis a persistent challenge despite advanced treatment options.[3,4,5] Certain organs, such as the liver, lungs, bone marrow, and lymph nodes, are particularly prone to developing secondary cancers during metastasis.[6,7] Chemotherapy employs specific drugs to destroy tumor cells and can serve as either a primary or adjuvant therapy. As a primary treatment, it may delay radiation in young children, while as an adjuvant, it is used before or after other treatments. Chemotherapy is also effective in treating recurrent tumors, helping to manage and reduce their progression.[8,9,10]

METHODOLOGY

Animal selections

Animals were randomly grouped and housed in polypropylene cages with controlled lighting, temperature, and humidity. Rats received pelletized food daily and water via inverted 100ml bottles. Six animals per cage were marked on specific body parts for identification, with one left unmarked. Housing arrangements were based on the treatment method.

Dosage and drug administration

The dosage of methotrexate and paclitaxel for adults is 12 mg/m², equating to 20.76 mg for a 70 kg adult. For a 200 g rat, the calculated dose is 0.3737 mg (1.50 mg/kg body weight). The bioequivalent SLN formulations, containing methotrexate and paclitaxel at 0.25 mg/ml and 0.20 mg/ml respectively, required 1.50 ml per 200 g rat to deliver the intended dose. Due to the large solution volume, direct intravenous injection was impractical. Instead, a butterfly needle facilitated a slow, continuous infusion into the tail vein over 20–30 minutes per rat. Both oral tablets and intravenous methotrexate formulations were tested in the study. A commercial 20 mg/ml methotrexate formulation was purchased for comparison with PTX-SLN and MTX-SLN batches. For intravenous administration, SLN formulations were infused via the tail vein over 20–30 minutes using a butterfly needle to ensure controlled dosing.

Treatment groups

The animals were divided into 32 groups of three rats each. Each rat was weighed and administered a single dose of

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Table 2: Plasma and tissue concentrations of market formulation

Time(h)	Concentration in µg±SE						
	Plasma	Liver	Spleen	Brain	Ovary	Heart	Kidneys
0.5	4	1.25	0.36	0.54	0.00	0.79	9.48
1	1.85	0.08	0.03	0.00	0.10	0.45	1.85
2	1.64	0.52	1.48	0.075	0.00	0.74	1.52
4	0.88	0.19	0.08	0.25	0.00	0.018	1.69
8	0.41	0.68	0.19	0.17	0.00	0.055	1.10
12	0.04	0.16	0.08	0.02	0.00	0.020	0.15
18	0.21	0.55	0.11	0.43	0.00	0.000	0.26
24	0.18	0.08	0.07	0.05	0.00	0.000	0.07

Table 3: Plasma and tissue concentrations of PTX-SLN

Time(h)	Concentration in µg±SE						
	Plasma	Liver	Spleen	Brain	Ovary	Heart	Kidneys
0.5	0.12	0.57	0.04	0.27	0.00	0.000	0.27
1	0.18	0.08	0.07	0.05	0.00	0.36	0.07
2	0.12	0.57	0.04	0.27	0.00	0.71	0.27
4	0.04	0.05	0.02	0.02	0.00	0.08	0.09
8	0.29	0.54	0.03	0.43	0.00	0.63	0.21
12	0.18	0.06	0.01	0.09	0.00	0.10	0.07
18	0.12	0.42	0.02	0.33	0.00	0.51	0.43
24	0.01	0.01	0.02	0.05	0.00	0.08	0.02

Table 1: Plasma and tissue concentrations of MTX-SLN

Time(h)	Concentration in µg±SE						
	Plasma	Liver	Spleen	Brain	Ovary	Heart	Kidneys
0.5	3.18	0.84	0.40	0.006	0.00	0.57	2.54
1	1.12	0.19	0.06	0.010	0.00	0.28	0.14
2	2.84	0.27	0.44	0.127	0.00	0.43	0.87
4	0.34	0.11	0.14	0.015	0.00	0.06	0.30
8	1.14	0.17	0.32	0.015	0.38	0.51	0.45
12	0.18	0.03	0.03	0.006	0.09	0.23	0.15
18	0.76	0.17	0.15	0.041	0.18	0.59	0.57
24	0.04	0.02	0.03	0.008	0.02	0.09	0.31

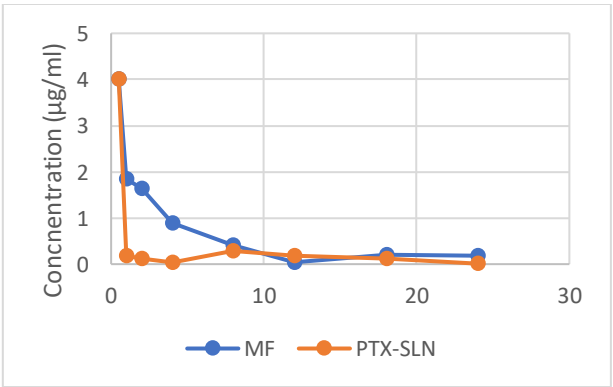

Figure 1: Plasma

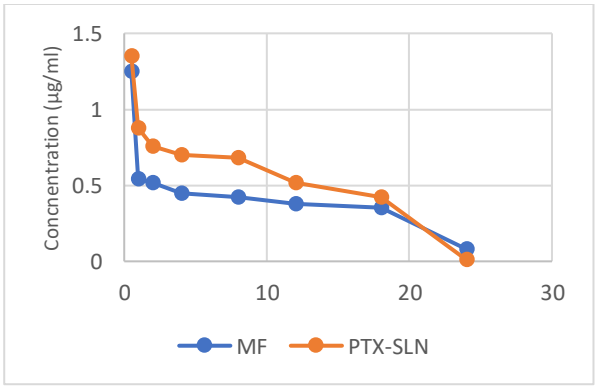

Figure 2: liver

1.55 mg/kg of the drug, either intravenously via the tail vein or orally. Blood samples were collected at predetermined intervals under ether anesthesia via retroorbital puncture using fine glass capillaries. Blood was collected in small glass tubes containing 0.3% sodium citrate solution. Dissection followed, during which tissues were separated, weighed, labeled, sealed, and stored in a deep freezer at -23°C for further processing.

Extraction of drug

Extraction of drug from plasma

The HPLC method was employed to quantify methotrexate and paclitaxel concentrations. Blood samples were centrifuged at 3000 rpm for 15 minutes using a Remi centrifuge, and the supernatant plasma was collected in clean glass test tubes. To 0.45 ml of plasma, 0.05 ml of

Table 4: PTX-SLN and MTX-SLN after IV administration.

Organ/Tissue	C_{max} (ug/ml) ± SE			Mean AUC (0-24h) (ug.h/ml) ± SE			Mean MRT (h) ± SE		
	MF	PTX-SLN	MTX-SLN	MF	PTX-SLN	MTX-SLN	MF	PTX-SLN	MTX-SLN
Plasma	4.00 ±11.12	3.18 ±0.65	17.56 ±1.36	9.53 ± 1.44	11.80 ±0.84	19.65 ±1.24	12.26 ± 1.17	4.18 ±0.45	19.35± 1.36
Liver	1.01 ±0.09	1.42 ±0.26	20.66 ± 0.52	13.63 ±0.47	22.29 ± 0.46	21.24± 0.65	20.34± 0.19	1.65 ±0.45	21.36 ± 0.52
Spleen	4.23 ± 0.55	0.84 ±0.11	2.08 ± 0.24	5.08 ± 0.51	14.42 ± 1.05	3.65 ± 0.45	5.46 ± 0.94	0.79± 0.11	3.64 ± 0.24
Brain	1.17 ±0.11	0.44 ± 0.08	5.29 ± 0.08	9.36 ± 0.37	21.30 ± 1.11	6.58 ± 1.25	21.44 ±0.64	0.66 ± 0.08	6.85 ± 0.08
Ovary	0.07 ± 0.01	0.13 ± 0.01	0.30 ± 0.01	0.28 ± 0.02	3.76 ±0.18	0.56± 0.02	3.11 ±0.17	0.23 ± 0.01	0.74 ± 0.01
Heart	0.46 ± 0.05	0.38 ± 0.05	1.22 ±0.09	0.11 ±0.01	3.47 ±0.11	1.65 ±0.10	0.50 ± 0.001	0.45 ± 0.05	1.64 ± 0.09
Kidneys	0.71 ± 0.04	0.84 ± 0.08	11.12 ±0.19	15.20 ±0.63	17.49 ±0.15	13.25 ±0.21	21.40 ±0.69	0.95 ± 0.08	14.25 ±0.19

Table 5: Dunnett's multiple comparison test on PTX-SLN.

Organ/Tissue	C_{max}	Mean AUC (0-24h)	Mean MRT (h)
Plasma	3.18	6.35	10.26
Liver	5.64	8.67	17.65
Spleen	0.348	5.66	1.32
Brain	1.302	15.34	20.19
Ovary	0.895	15.37	24.36
Heart	0.456	2.94	1.62
Kidneys	11.25	4.88	6.79

Table 6: Dunnett's multiple comparison test on MTX-SLN

Organ/Tissue	C_{max}	Mean AUC (0-24h)	Mean MRT (h)
Plasma	4.18	5.35	10.26
Liver	2.64	25.67	8.65
Spleen	2.67	21.66	0.32
Brain	3.697	27.34	18.19
Ovary	2.895	28.37	19.36
Heart	1.456	13.94	5.62
Kidneys	4.567	19.88	13.79

internal standard solution (100 ppm) and 0.5 ml of 10% perchloric acid (1:1 ratio) were added. The mixture was vortexed for three minutes on a cyclo mixer, and precipitated proteins were separated by centrifuging the sample again at 3000 rpm for 15 minutes. The supernatant was filtered using a 0.22 µm nylon membrane, and 100 µl of the filtrate was injected into the HPLC system. Chromatograms were recorded, and the drug concentrations were calculated in µg/ml.

Extraction of drug from tissues

Tissue samples were homogenized using a Remi tissue homogenizer with varying saline volumes based on tissue size: liver (5 ml), brain, kidneys, lungs, spleen (4 ml), and heart, ovaries (3 ml, 2 ml). To 0.45 ml of homogenized tissue, 0.05 ml of internal standard (100 ppm) and 0.5 ml of 10% perchloric acid (1:1) were added. Samples were processed as per the plasma protocol, and methotrexate content was quantified in µg/ml.

Pharmacokinetic analysis

Non-compartmental analysis was performed to determine pharmacokinetic parameters, using the drug concentration-time profile obtained from plasma and tissues. The elimination rate constant was also calculated after oral and intravenous administration.

RESULTS

IV routes of administration

Drug levels in plasma and organs are presented in Tables 1–6, while Figures 1–7 and 8–14 illustrate comparative drug concentration-time profiles for market formulations, PTX-SLN, and MTX-SLN after IV administration. The table summarizes Cmax, AUC (0–24h), and MRT values. An unpaired t-test compared PTX-SLN and MTX-SLN's AUC (0–24h), MRT, and Cmax against market formulations. Results of one-way ANOVA with Dunnett's test evaluated differences among formulations and controls.

CONCLUSION

The tissue distribution and in vivo pharmacokinetics of solid lipid nanoparticulate (SLN) formulations of paclitaxel (PTX) and methotrexate (MTX) were investigated. Bonferroni post-test assessed differences between and within groups for Cmax, AUC (0–24h), and MRT across intravenous (IV) and oral routes. MTX-SLN's pharmacokinetics and tissue distribution were compared to commercially available injection (IV) and tablet (oral). MTX-SLN exhibited a higher AUC (0–24h) and lower plasma concentrations than the marketed formulation (MF), indicating enhanced plasma bioavailability. While plasma levels for MF dropped within 4 hours, MTX-SLN maintained stable levels longer. For MTX-SLN, the Cmax in cancer cells (1.42 µg/ml) surpassed that of MF (1.01 µg/ml). MTX-SLN displayed significantly higher AUC (0–24) and MRT ($p<0.05$) compared to MF. One-way ANOVA and Dunnett's post-test revealed significant differences: for MTX-INJ, Cmax in kidneys, liver, and plasma was notably

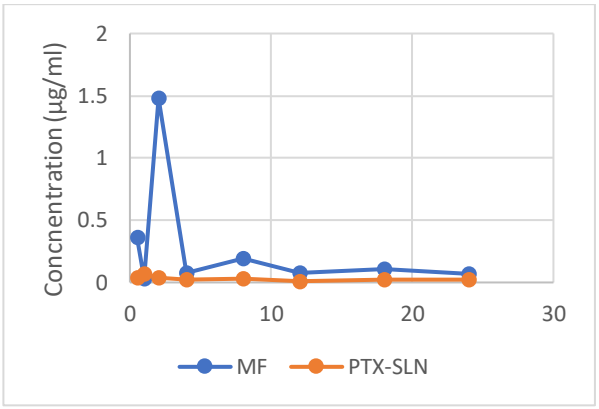

Figure 3: Spleen

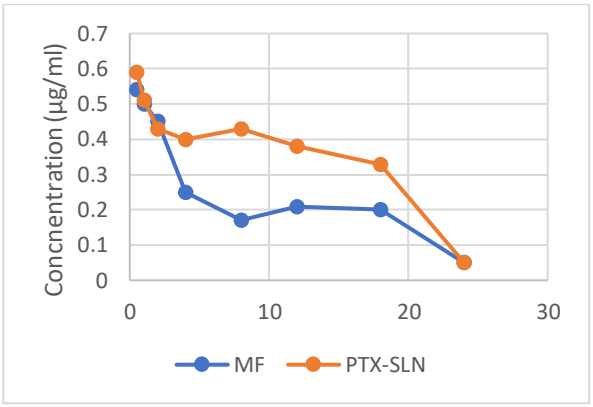

Figure 4: Brain

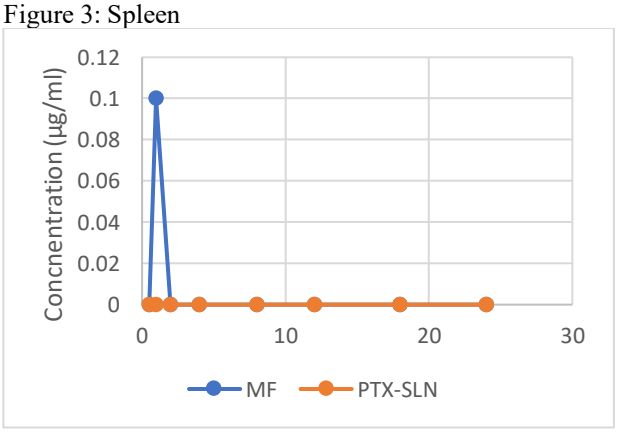

Figure 5: Ovary

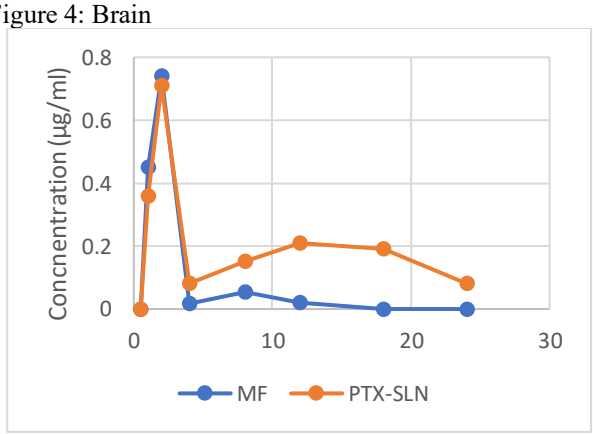

Figure 6: Heart

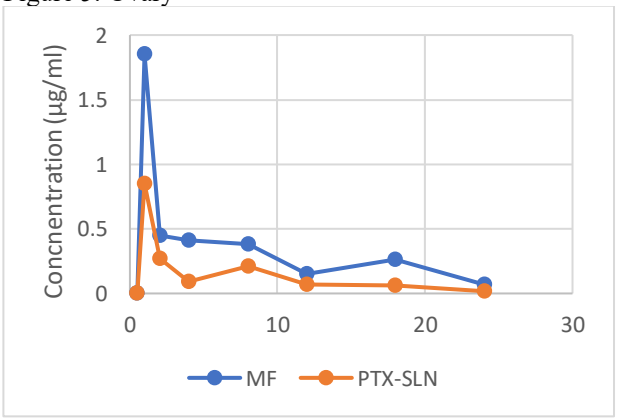

Figure 7: kidney

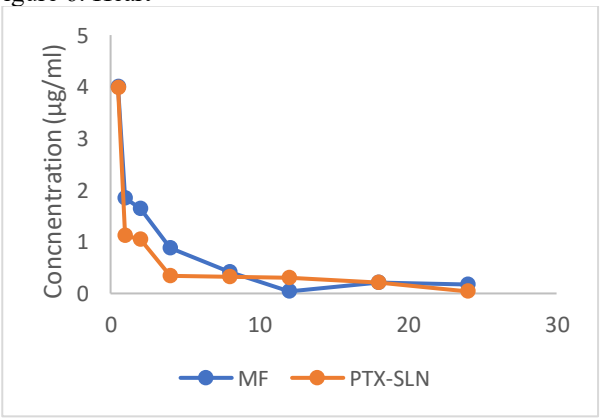

Figure 8: Plasma

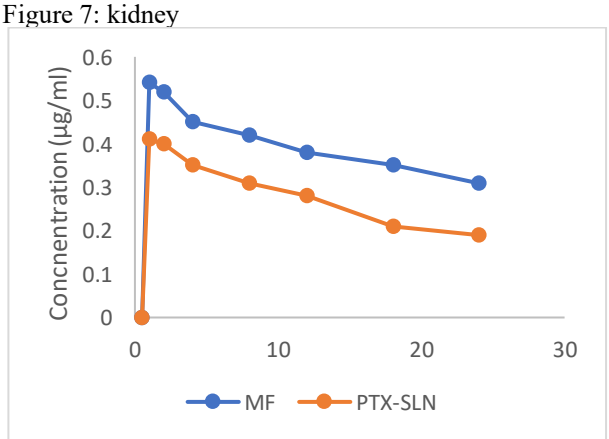

Figure 9: Liver

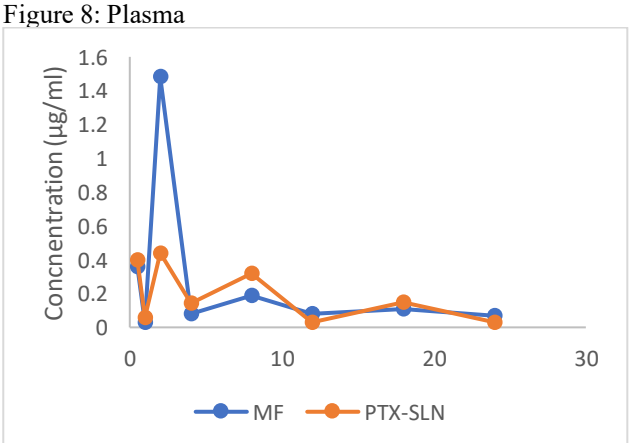

Figure 10: Spleen

higher ($p<0.01$) than in lungs, while for MTX-SLN, Cmax in kidneys, brain, and plasma differed significantly ($p<0.05$). MTX-INJ showed a lung Cmax nearly four times that in liver and plasma and eight times that in kidneys. In

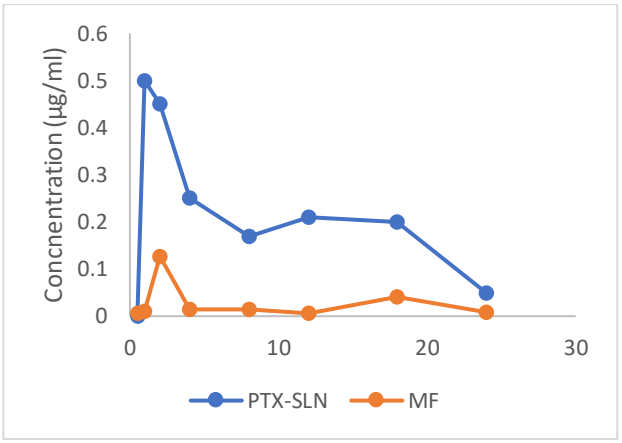

Figure 11: Barin

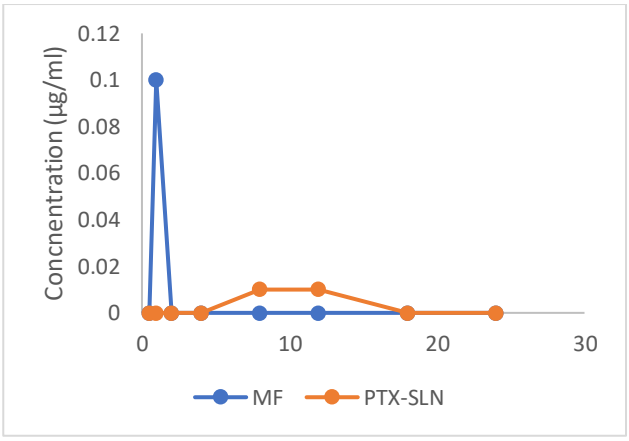

Figure 12: Ovary

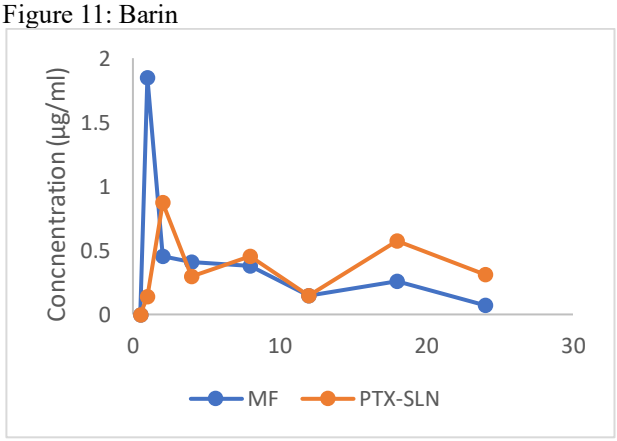

Figure 13: Heart

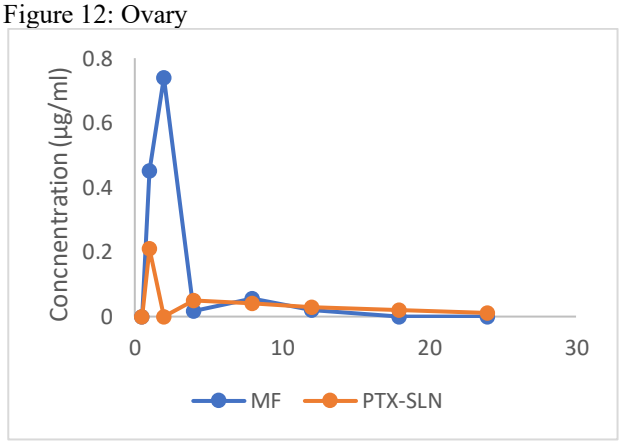

Figure 14: Kidneys

MTX-SLN, kidney Cmax was less than twice lung Cmax, and plasma Cmax was approximately double. Brain Cmax remained lower than lung Cmax. Unlike the marketed injectable, which distributed more to kidneys, plasma, and liver, MTX-SLN concentrated the drug more in the lungs.

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