Chapter 6
Radiolabelling and In vivo Biodistribution of Saquinavir formulations

Radiolabelling and In vivo biodistribution of Saquinavir formulations

6.1 Introduction:

The purpose of the present study was to examine the pharmacokinetics and biodistribution of ^{99m}Tc labeled Saquinavir formulations after oral administration to mice. We have compared pharmacokinetic & biodistribution of two formulations in nanometer size range (Solid Lipid Nanoparticle and Nanosuspension) with conventional suspension after oral administration. Intravenous administration of conventional suspension was also carried out to determine the relative bioavailability values of Saquinavir following oral administration in different formulations. Quality control test such as labelling efficiency (radiochemical purity) and stability of labeled complex in buffer, serum , Cysteine Histidine and DTPA were carried out prior to pharmacokinetic and biodistribution study. Another purpose of the present investigation was to compare the efficiency of SLN versus drug nanocrystals to enhance oral drug absorption of Saquinavir.

Technetium Chemistry:

^{99m}Tc belongs to group VIIB of the periodic table and has atomic number 43. ^{99m}Tc can exist in eight oxidation namely 1^- to 7+ among the 7+ and 4+ are the most stable state and are represented in oxides, sulphides, halides and pertechnetate. The chemical form of ^{99m}Tc from Molybdenum generator is available as sodium pertechnetate (^{99m}Tc-$NaTCO_4$). The pertechnetate ion, $^{99m}TcO_4$- has the oxidation state 7+ from ^{99m}Tc, resembeles the permanganate ions Mn O_4-. Pertechnetate is nonreactive and does not label any compound by direct addition, so prior to labeling any compound reduction of ^{99m}Tc from 7+ state to lower oxidation is required (Saha, 1993). Among the various reducing agent stannous chloride is used commonly in acidic medium in most preparation of ^{99m}Tc labeled compounds. The reduced ^{99m}Tc species are chemically reactive and combine with wide variety of compounds bearing chemical groups like –COOH, -OH, $-NH_2$, and –SH.

6.2 Materials:

Diethylene triamine penta acetic acid (DTPA), cysteine, histidine, rabbit serum and stannous chloride dehydrate ($SnCl_2$. H_2O) were purchased from Sigma-Aldrich, Germany, Sodium pertechnetate from BARC (Bhabha Atomic Research Center,

Mumbai, India), Instant thin layer chromatography ITLC-SG was purchased from Gelman science. Inc., Ann Arbor, MI.

6.3 Method:

Labeling Efficiency:

The radiochemical purity of 99mTc with Saquinavir loaded Solid Lipid Nanoparticles (SQSLN), Saquinavir Nanosuspension (SNS) and Saquinavir Microsuspension (SMS) were estimated by Paper Chromatography (PC) and Ascending Instant Thin Layer chromatography (ITLC) using silica gel coated fiber sheets (Theobald AE., 1990). Paper chromatography was performed using 0.9% saline as the mobile phase to determine the percentage of ^{99m}Tc pertechnetate in the radiolabelled preparation. The amount of reduced technetium was determined by ITLC-SG using pyridine: acetic acid: water (3:5:1.5 v/v) as mobile phase. The strip was cut and the radioactivity in each segment was determined in a well type gamma ray counter (Sodium iodide [Thalidium (Tl)] scintillation counter, Electronics Corporation of India Ltd., Mumbai). The reduced/hydrolysed (R/H) technetium along with the labeled complex remained at the point of application while both the free pertechnetate and the labeled complex moved away with the solvent front. By subtracting the radioactivity moved with the solvent front using saline from that using pyridine/acetic acid/water as a mixture, the net amount of 99mTc- formulation (SLN/NS/MS) was calculated.

6.4 Optimization of radiolabeling of Saquinavir loaded SLN, NS and MS by direct labeling procedure:

The radiolabeling of formulations (SQSLN, SNS , SMS) were carried out using direct labeling procedure with ^{99m}Tc by simple reduction method using stannous chloride **(Arulsudar N., et al., 2003)**. Briefly, 1.0 ml of ^{99m}Tc in saline (2 mCi/ml) was added along with 0.1 ml of 0.5M bicarbonate buffer pH 9.0 followed by 0.1 ml of stannous chloride ($SnCl_2$) solution (1mg/ml) to the respective formulation. The labeling was carried out by mixing the reagents at ambient temperature for 10 to 15 minutes. The radiochemical purity of the labeled complex was estimated by ascending ITLC using 0.9% saline as developing solvent. Labeling procedure was standardized with respect to reagent concentrations and reaction parameters to achieve stable labeling in higher yields.

6.5 Stability Study of 99mTc-labeled Complexes:

Stability studies of radiolabelled complexes were carried out by incubating 0.1 ml of labeled preparation at different conditions as mentioned below:

(a) Buffer:

Stability of the complexes was studied in 0.05M phosphate buffer containing 0.9 % saline at room temperature. Samples were taken at different time intervals (1, 4 and 24 hrs) and studied for PC & ITLC.

(b)Serum:

Complexes (50μL) were incubated with 0.5 mL of rabbit serum at 37°C for different time interval. Samples were taken at different time intervals (1, 4 and 24 hrs) and studied for PC & ITLC.

(c) Challenge with cysteine and histidine:

The complexes were tested for instability towards exchange with cysteine and histidine. 0.1 mL of complex was reacted with 10μL of cysteine and histidine solution corresponding to final concentration of 0.1M (in aqueous medium), and incubated for 1hrs at 37°C. After incubation, the purity of the ^{99m}Tc-labelled complexes was estimated by PC and ITLC as mentioned above.

(d) Challenge studies with DTPA:

The binding affinity of labeled complexes was confirmed by transchelation using DTPA. The stability of the complexes was performed using 0.1 ml of complex incubated with 50 and 100 mM of DTPA for 2 hrs at 37°C.

After incubation, the purity of the ^{99m}Tc-labelled complexes was estimated by PC and ITLC as mentioned above.

6.6 Pharmacokinetic and Biodistribution study:

Swiss albino mice of either sex weighing about 20 -30 gm were selected for the study. Biodistribution studies of ^{99m}Tc-labeled complexes were carried out according to approved method by local Animal Ethical Committee of Baba Atomic Research center (BARC), Mumbai, India. The animals were kept on fasting overnight before experiment but had free access to water. They were then randomly divided into three groups of 12 animals in each group, to receive ^{99m}Tc-labeled complexes. Each animal was administered with 0.5 mL of the ^{99m}Tc-labeled SQSLN, SNS and SMS (200 μg of Saquinavir or 8mg/kg) by oral gavage. Blood was withdrawn by cardiac puncture after different time intervals (1, 4, 8 and 24 hrs) and the mice were sacrificed by

chloroform inhalation at each interval. Blood was weighed and the radioactivity present in the whole blood was calculated by keeping 7.3% of the body weight as the total blood weight (Wu et al., 1981). Major organs (heart, liver, spleen, stomach, kidney, lungs, and intestine with gall bladder) were isolated, weighed and the radioactivity was measured in a well type gamma ray counter (Gamma ray spectrophotometer, Type GRS23C, Electronics Corporation of India Ltd., Mumbai). The radioactivity was interpreted as percentage of injected dose per gram of organ/tissue. It was then converted to value of µg per gram.

In a separate series of experiments, the ^{99m}Tc-labeled SQ in microsuspension (SMS) was administered intravenously (i.v.) via the tail vein in mice. For these studies, mice were injected with ^{99m}Tc labeled SMS (0.1 mL per animal) by tail vein. At specific time points (1, 4, 8 and 24 hrs), blood was withdrawn by cardiac puncture and the radioactivity present in the whole blood was calculated as mentioned above.

6.7 Pharmacokinetic analysis:

The noncompartmental pharmacokinetic analysis was performed (Shin et al, 2000). Trapezoidal method was employed to calculate the AUC of plasma concentration (Cp) as a function of time (t). Mean residence time (MRT) was calculated as area under the first moment curve (AUMC) divided by area under the curve (AUC). AUMC was determined using a plot of plasma concentration multiplied by time (C x t) versus time and calculation of its area under the curve by the Trapezoidal method. All the pharmacokinetic parameters were calculated in MS-Excel software. The maximum plasma concentration (C_{max}) and time to reach maximum plasma concentration (t_{max}) were determined by visual inspection of the experimental data as well as the plasma concentration curve using MS –Excel software. The elimination rate constant (K_{el}) was calculated by the regression analysis from the slope of the line and the half-life ($t_{1/2}$) of the drug was obtained by $0.693/K_{el}$. The relative bioavailability of SQ was calculated using following equation (Venkateswarlu et al., 2005).

$Fr = AUC_{SQSLN} / AUC_{SMS}$

and

$Fr = AUC_{SNS} / AUC_{SMS}$

6.7.1 Data analysis:

The statistical significance of the differences between the formulations was tested by the one way ANOVA followed by Dunnets comparison test. All the values were reported as mean ± standard error of mean (S.E.M.) of three determinations.

6.8 Results and Discussion:

6.8.1 Stability of the ^{99m}Tc labeled complexes:

The radiolabeling of formulations (SQSLN, SNS, SMS) were carried out using direct labeling procedure with ^{99m}Tc by simple reduction method using stannous chloride. Radiochemical purity and stability data of the labeled formulations were obtained by ITLC using 0.9% saline. These labeled complexes were tested for stability in saline and serum for 24 hrs. Table 6.1 shows the radiolabelling efficiency of ^{99m}Tc labeled Saquinavir loaded formulations. The data demonstrates that the labeled complexes remained stable in- vitro in saline as well as serum upto 24 hrs. Formulations were labeled with high efficiency of more than 80 %. All the three formulations could be labeled in good yields and stability. The serum stability of these labeled complexes indicates their use as suitable markers for biodistribution study.

6.8.2 Cysteine, Histidine and DTPA challenge tests:

In vitro stability of radiolabeled complexes was determined by Cysteine, Histidine and DTPA challenge studies. High binding affinity of the labeled complexes was ascertained by incubating the labeled formulations with cysteine (0.1 M), histidine (0.1 M) and DTPA (50 and 100mM) (Table 6.2 and 6.3). Challenge test performed with DTPA in 50 mM and 100 mM concentration did not exhibit significant transchelation which was about 6-10 %. This may be due to higher strength and binding affinity of ^{99}Tc with formulation.

Table 6.1: Stability of radiolabeled SQSLN, SQNS and SQMS formulation in saline (room temperature) and serum (37°C).

	% Radiolabeling Efficiency					
	Saline			Serum		
Time	1 hrs	4 hrs	24 hrs	1 hrs	4 hrs	24 hrs
SQSLN	89.66	87.39	84.33	83.77	81.26	80.66
SQNS	87.4	85.83	83.20	84.38	85.13	82.55
SQMS	88.26	85.33	83.69	83.18	81.99	80.45

Table 6.2: Cysteine and Histidine challenge test of radiolabeled SQSLN, SQNS and SQMS formulation after 1 hr at 37°C.

	% Transchelation	
	0.1 M Cysteine	0.1 M Histidine
SQ	6.43	7.77
SQSLN	7.21	7.62
SQNS	6.12	6.98
SQMS	8.13	8.95

Table 6.3: DTPA challenge test of radiolabeled SQSLN, SQNS and SQMS formulation for 2 hrs at 37°C

	% Transchelation	
Conc. Of DTPA	50 mM	100 mM
SQ	7.99	9.46
SQSLN	6.33	8.92
SQNS	7.08	9.03
SQMS	6.99	9.29

6.8.3 Pharmacokinetic and Biodistribution study:

Pharmacokinetic and Biodistribution study of ^{99m}Tc labeled Saquinavir formulations i.e. SQSLN, SNS and SMS were investigated in healthy Swiss albino mice. . Blood was obtained by cardiac puncture, weighed and the radioactivity present in the whole blood was calculated by keeping 7.3% of the body weight as total blood weight. Percentage radioactivity of injected dose per gram of organ was obtained which was converted to microgram per gram of organ.

The plasma concentration- time curve after oral and I.V. administration of Saquinavir Microsuspension (SMS) is shown in Fig. 1 while Fig 2 depicts plasma concentration–time profile of oral administration of three formulations SMS, SNS and SQSLN. Table 6.4 gives Mean plasma concentration (µg/gm) after oral administration of SMS, SNS and SQSLN and Intravenous administration of SMS. The Pharmacokinetic parameters after oral administration of SMS, SNS and SQSLN and Intravenous administration of SMS are summarized in Table 6.5.

Table 6.4 Mean plasma concentration (µg/gm) after oral administration of SMS, SNS and SQSLN and Intravenous administration of SMS.

Time(Hours)	Mean Plasma Concentration ± S.E.M. (µg/gm)			
	SMS		SNS	SQSLN
	I.V.	Oral		
1	17.70 ± 1.51	0.56± 0.31	5.72± 0.99	1.83± 0.03
4	11.10 ± 1.27	2.72 ± 0.82	3.91± 0.91	6.43± 0.83
8	6.74 ± 0.99	1.30 ± 0.65	2.44 ± 0.77	4.78± 0.59
24	1.91 ± 0.71	0.54± 0.3	0.97± 0.022	2.39± 0.29

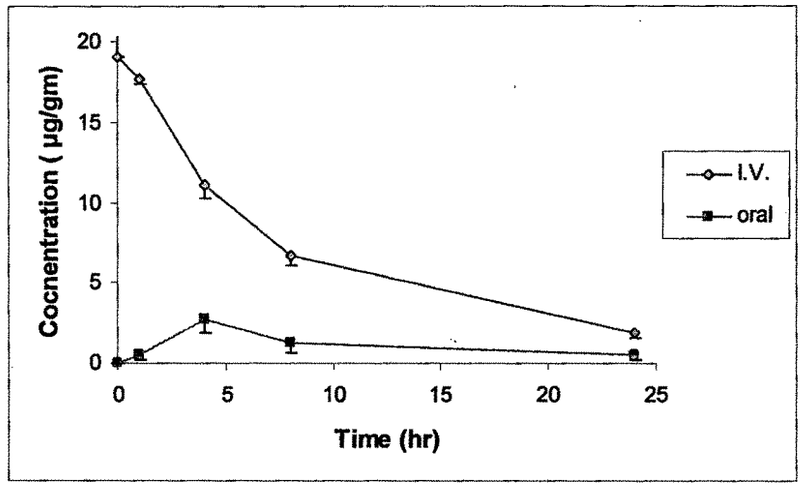


Fig. 6.1 Plasma concentration- time curve after oral and I.V. administration of Saquinavir Microsuspension (SMS).

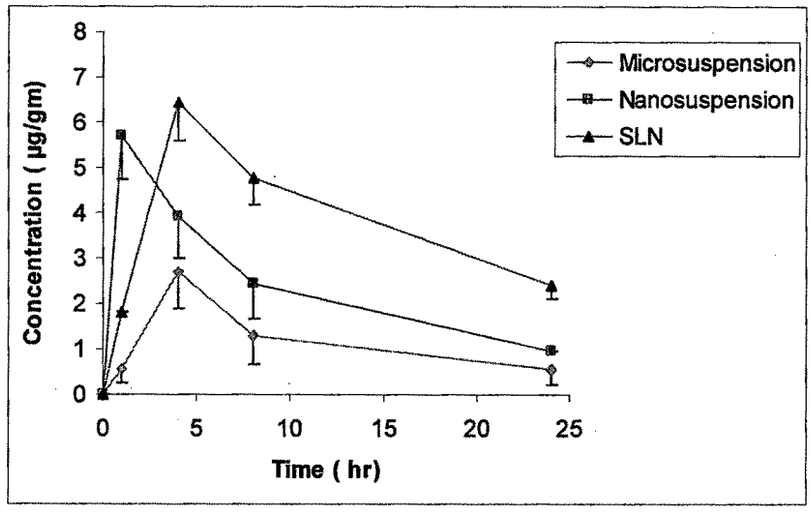


Fig 6.2 Plasma concentration time profile of SMS, SNS and SQSLN after oral administration.

Table 6.5 Pharmacokinetic parameters after oral administration of SMS, SNS and SQSLN and Intravenous administration of SMS.

Parameters	Formulation			
	SMS (control)		SNS	SQSLN
	I.V.	Oral	Oral	Oral
Cmax (µg/gm)	---	2.72 ± 0.67	5.72 ± 0.57 *	6.43 ± 0.47 **
$t_{1/2}$ (h)	8.793 ± 0.56	12.62 ± 0.43	12.02 ± 0.76 ^{NS}	15.99 ± 0.63 *
AUC (0 → t) (µg.h/L)	156.93 ± 12.18	27.64 ± 2.59	57.28 ± 2.48 **	93.08, ± 3.84 **
AUC (0 →inf) (µg.h/L)	226.13 ± 20.21	42.68 ± 3.78	84.56 ± 3.93 **	150.44 ± 5.31**
MRT (h)	10.41 ± 0.62	17.51 ± 0.76	15.42 ± 0.57 ^{NS}	23.82 ± 0.90 **
Kel (hr^{-1})	0.096 ± 0.002	0.053 ± 0.002	0.067 ± 0.002 **	0.04 ± 0.003 **
Vss (L)	8.87 ± 0.34	82.05 ± 0.912	36.47 ± 0.98 **	31.67 ± 0.698 **
Fr (%)	100	18.87	37.39	66.53

Each value represents the mean ± SEM of three determinations (n=3).

- Comparisons of SNS and SQSLN were made to SMS (control).
- * $P < 0.05$
- ** $P < 0.01$
- Ns – non significant - $P > 0.05$

After oral administration, nanoparticulate formulations i.e. SQSLN and SNS exhibited higher plasma level concentration compared to SMS. The AUC $_{(0\rightarrow inf)}$ for the

intravenous administration and oral suspension were about 226.13 ± 35.02 and 42.68 ± 6.55 μg.h/L respectively which was significantly different ($p<0.01$; ANOVA followed by Dunnett's multiple comparison test). Following oral administration of Saquinavir nanosuspension (SNS) and Saquinavir SLN (SQSLN) formulations to mice, the AUC $_{(0\rightarrow inf)}$ values were 84.56 ± 3.93 and 150.44 ± 5.31 μg/gm respectively which were significantly different ($p<0.001$) from AUC obtained on oral administration of SMS.

The relative bioavailability for SNS and SQSLN were 37.39% and 66.53 % respectively compared to 18.87 % bioavailability obtained after administration of SMS. It indicates improvement in bioavailability of Saquinavir from nanoparticulate formulation than Microsuspension. Highest C_{max} (6.43± 0.47 μg/gm) amongst all tested formulations was observed with SQSLN followed by SNS (5.72 ± 0.57) and SMS (2.72 ± 0.67) . The statastical difference was more significant with SQSLN (P< 0.001) than SNS (P<0.05).

The average $T_{1/2}$ values were 12.02 ± 0.76, 15.99 ± 0.63 h for SNS and SQSLN formulations, respectively, as compared to 8.793 ± 0.56 and 12.62 ± 0.43 h following administration of I.V.injection and oral administration of SMS. The $T_{1/2}$ value was not stastically significant in case of SNS (P> 0.05) when compared with control (SMS).

The average K_{el} was 0.0096 ± 0.002 h^{-1} after intravenous administration of SMS and 0.053 ± 0.002 h^{-1} after oral SMS while nanoparticulate formulations exhibited values 0.067 ± 0.002 and 0.04 ± 0.003 h^{-1} for SNS and SQSLN, respectively.

The sustained-release characteristic of the SQSLN was reflected in the MRT in the body. MRT was considerably increased following administration of the SQSLN as compared to SNS. The average MRT after oral administration of SQSLN, SNS and SMS were 23.82 ± 0.90, 15.42 ± 0.57 and 17.51 ± 0.76 h, respectively, as compared to 10.41 ± 0.62 after I.V. administration and they were significantly different ($p<0.001$, ANOVA followed by Dunnett's multiple comparison test). This may be due to prolonged release of SQ from SQSLN as observed in *in vitro* release compared to SNS. Also the bioadhesive property of SLN helps to improve **MRT** in gut in turn improving absorption of SLN over a period of time (Irache et al 1998). However,

when one way ANOVA was applied amongst oral formulations (SMS as control), it was found that MRT of SNS was not significant (P> 0.05).

6.8.4 Biodistribution Study:

In case of ^{99m}Tc labeled SMS, SNS and SQSLN, Liver, Intestine and Stomach accumulated major portion of the administered radioactivity. Liver is one of the major organs of reticuloendothelial system (RES) which are known to accumulate and metabolize nanoparticles (Arien A. et al 2006). The biodistribution data (Table 6.6) reveals higher initial rapid uptake by liver, which was 43.88 ± 6.23 and 29.63 ± 1.81 and 26.99 ± 2.01μg/gm for SMS, SNS and SQSLN respectively after 1 hour of oral administration. It can be observed that uptake was faster for SMS than nanoparticles. After 24 hours, 9.04 ±1.17, 14.71 ± 1.58 and 13.33 ± 1.4 μg/gm SMS, SNS and SQSLN, was observed, indicating rapid metabolism of SMS compared to SNS and SQSLN. These results suggest that SNS and SQSLN were cleared much more slowly than SMS.

Spleen also showed higher uptake of labeled complexes compared to other organs. After 1 hour of administration, 5.56 ± 0.99μg/gm of SMS was observed while significantly higher levels i.e. 17.09 ± 0.99 and 13.01 ± 1.67 μg/gm were observed after administration of SNS and SQSLN respectively. Although, there was no statistically significant difference between SMS (1.66 ± 0.21 μg /gm) and SNS (2.21 ± 0.27 μg/gm) after 24 hours of administration (p>0.05 ANOVA followed by Dunnett's multiple comparison test), significantly higher levels observed for SQSLN formulation (9.04 ± 0.89 μg/gm) (P<0.05). The higher uptake of radiolabeled complexes by reticuloendothelial cell (RES) containing organs such as liver and spleen may be due to an enhanced lymphatic uptake as reported by Maincent et al and Jani et al. (Maincent et al 1992 and Jani et al 1989). Similar higher uptake was observed after administration of [^{14}C] AZT bound to nanoparticles after oral administration to rats. (Krueter J. et al 1997).

Table 6.6. Biodistribution of ^{99m}Tc labeled SMS, SNS and SQSLN after oral administration in mice

Organs	µg /gram of organ ± S.D.											
	1 Hrs			4 Hrs			8 Hrs			24 Hrs		
	SMS	SNS	SQSLN	SMS	SNS	SQSLN	SMS	SNS	SQSLN	SMS	SNS	SQSLN
Blood	0.56 ± 0.31	5.72 ± 0.99	1.83 ± 0.03	2.72 ± 0.82	3.91 ± 0.91	6.43 ± 0.83	1.3 ± 0.65	2.44 ± 0.77	4.78 ± 0.59	0.54 ± 0.3	0.97 ± 0.022	2.39± 0.29
Liver	43.88 ± 6.23	29.63 ± 1.81	26.99 ± 2.01	49.81 ± 5.76	35.41 ± 2.79	30.11 ± 2.45	29.11 ± 4.44	28.74 ± 3.99	19.2 ± 2.12	9.04 ± 1.17	14.71 ± 1.58	13.33 ± 1.4
Ints +GB	25.36 ± 1.91	21.21 ± 1.56	18.68 ± 1.44	37.98 ± 3.01	49 ± 3.56	42.22 ± 2.15	21.11 ± 2.26	32.07 ± 3.16	37.77 ± 2.78	9.78 ± 1.55	18.18 ± 2.19	26.66 ± 2.96
Kidney	7.62 ± 1.87	6.9 ± 1.12	6.4 ± 1.04	17.88 ± 2.11	16.99 ± 1.68	11.11 ± 0.99	11.24 ± 1.61	23.76 ± 1.89	15.88 ± 1.65	3.11 ± 0.43	8.15 ± 0..87	5.06 ± 0.32
Stomach	46.66 ± 5.32	54.7 ± 3.88	61.99 ± 4.25	37.78 ± 4.99	41.9 ± 3.21	48.75 ± 3.89	27.21 ± 2.42	28.5± 1.87	33.78 ± 1.99	16.64 ± 0.96	18.5 ± 1.23	10.6± 1.11
Heart	2.01 ± 0.09	5.56 ± 0.85	7.01 ± 1.01	3.99 ± 0.95	7.99 ± 1.45	8.77 ± 1.58	2.89 ± 0.75	3.45 ± 0.85	3.66 ± 0.98	0.56 ± 0.1	1.03 ± 0.04	1.06 ± 0.02
Lungs	3.33 ± 0.84	8.91 ± 1.55	6.56 ± 1.13	5.01 ± 1.03	12.25 ± 1.01	8.88 ± 0.98	4.66 ± 0.81	9.87 ± 1.98	6.65 ± 0.68	1.09 ± 0.04	4.13 ± 0.5	2.98 ± 0.3
Spleen	5.56 ± 0.99	17.09 ± 2.04	13.01 ± 1.67	7.77 ± 1.02	14.03 ± 1.11	19.9 ± 1.98	4.12 ± 0.98	9.56 ± 1.3	15.55 ± 1.49	1.66 ± 0.21	2.21 ± 0.27	9.04 ± 0.89

The values represented here are the mean of three values with Standard Deviation (S.D.). Radioactivity is expressed as nanogram of administered dose per gram of tissue or organ.

There was increased radioactivity in intestine at 4 hrs when compared to 1 hrs in all formulations, which was 25.36 ± 1.91 to 37.98 ± 3.01 μg/gm in case of SMS, 21.21 ± 1.56 to 49 μg/gm in case of SNS and 18.68 ± 1.44 to 42.22 ± 2.15μg/gm for SQSLN. After 24 hours, highest radioactivity was observed for SQSLN (26.66 μg/gm) followed by SNS (18.18 μg/gm). The possible explanation is that nanoparticles would allow a more intimate contact with the absorptive cells in the GIT due to their bioadhesive properties (Irache et al 1998).

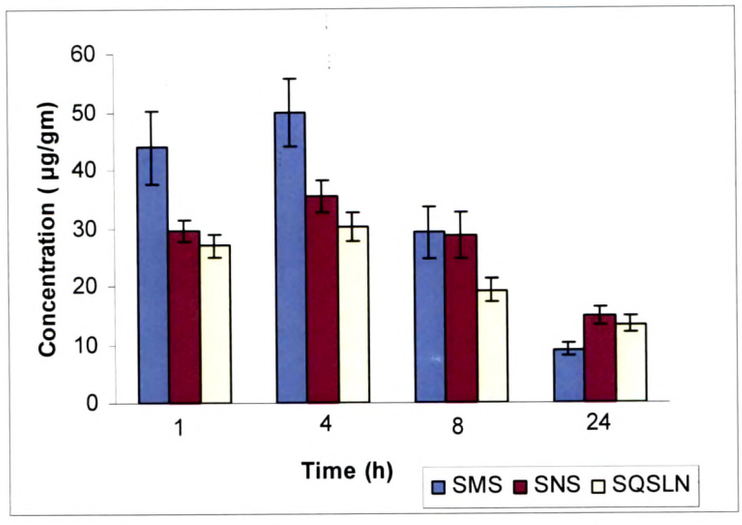
The radioactivity in stomach was found to decrease over a period of time of 24 hrs. The decrease was more pronounced for SQSLN (from 61.99 ± 4.25 to 10.6 ± 1.11μg/gm) and SNS (54.7 ± 3.88 to 18.5 ± 1.23 μg/gm) than SMS (46.66 ± 5.32 to 16.64 ± 0.96 μg/gm). This suggests rapid transport of SQSLN and SNS from stomach than SMS. The statistical difference was not significant when comparing SMS with SNS and SQSLN ($P>0.05$ ANOVA followed by Dunnett's multiple comparison test). It is important to note that the stomach and intestines of the rats are cleaned of all food or waste material and thus the levels measured for these organs correspond to the levels of the actual tissue. The radioactivity in stomach also pointed to the fact that there is no in vivo leaching of radioactivity as free Technetium.

No significant radioactivity was found in heart and lungs. Radioactivity was seen in kidney, which might be because of free ^{99m}Tc formed after metabolism of the radiolabeled complexes in liver and this water soluble complex might have excreted in urine. Maximum radioactivity was observed for SNS (23.76 ± 1.89μg/gm) and SQSLN (15.88 ± 1.65μg/gm) after 8 hours while in case of SMS higher radioactivity was observed after 4 hours (17.88 ± 2.11 μg/gm). It indicates rapid elimination of SMS compared to SNS and SQSLN.

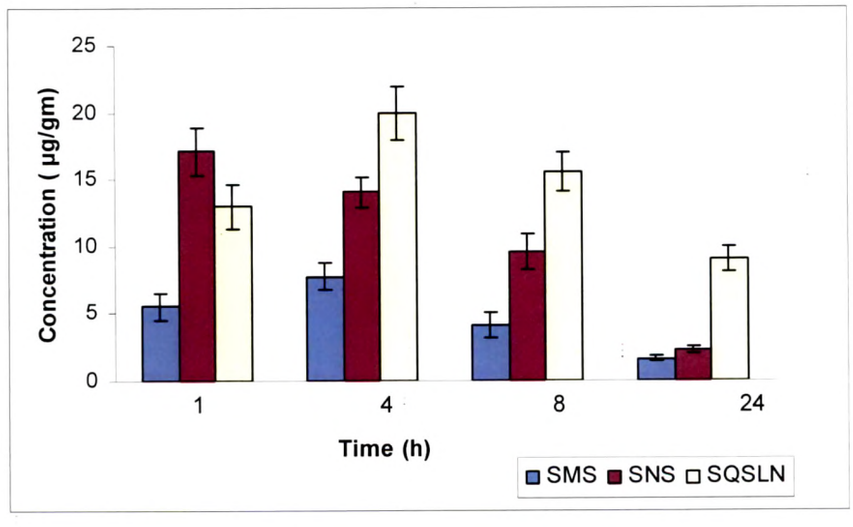
Three formulations were tested: a nanosuspension (SNS), one solid lipid nanoparticle preparation (SQSLN) and one suspension in micron size (SMS). Both colloidal drug delivery systems (SNS and SQSLN) showed more than two fold increase in bioavailability compared to conventional microsuspension (SMS). SLN showed prolonged residence time in blood (MRT = 23.82 ± 0.90) compared to SNS (MRT=15.42 ± 0.57). Significant difference was observed in Cmax and AUC (0 → inf) between SNS, SQSLN compared to SMS.

Fig 6.3 Concentration (µg/gm) time profile of ^{99m}Tc labeled SMS, SNS and SQSLN in different organs

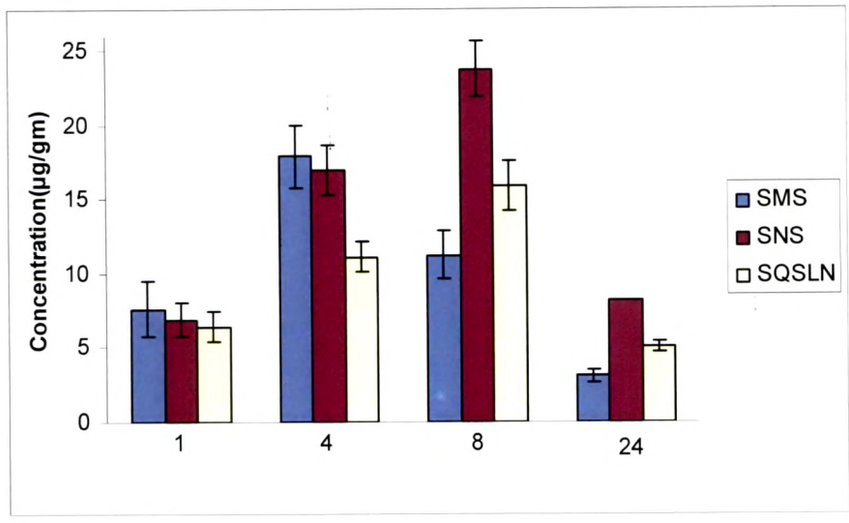
(a) Liver



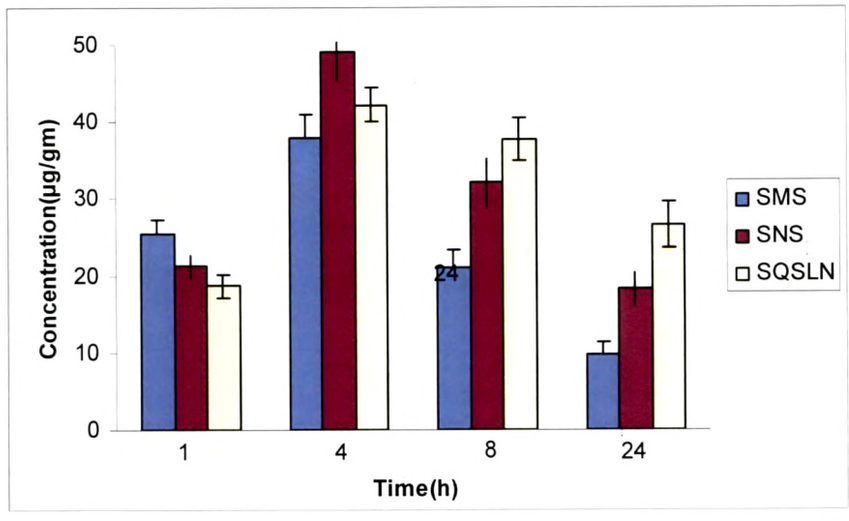
(b) Spleen



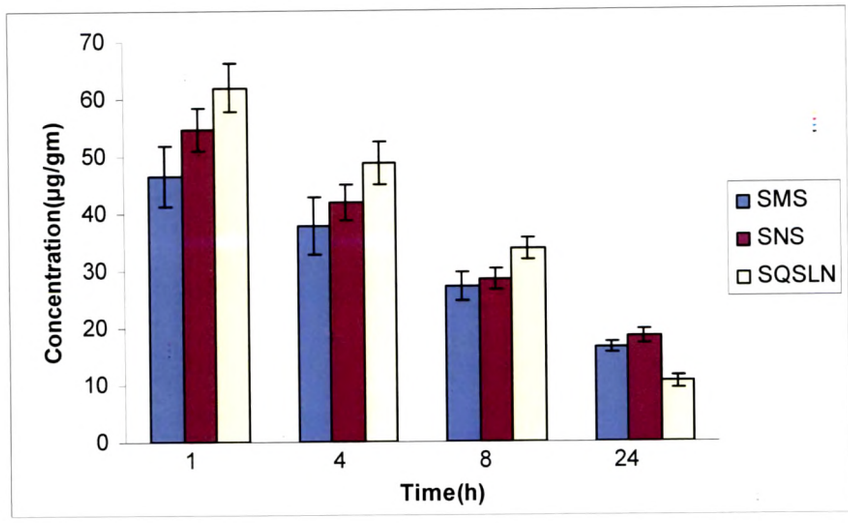
(c) Kidney



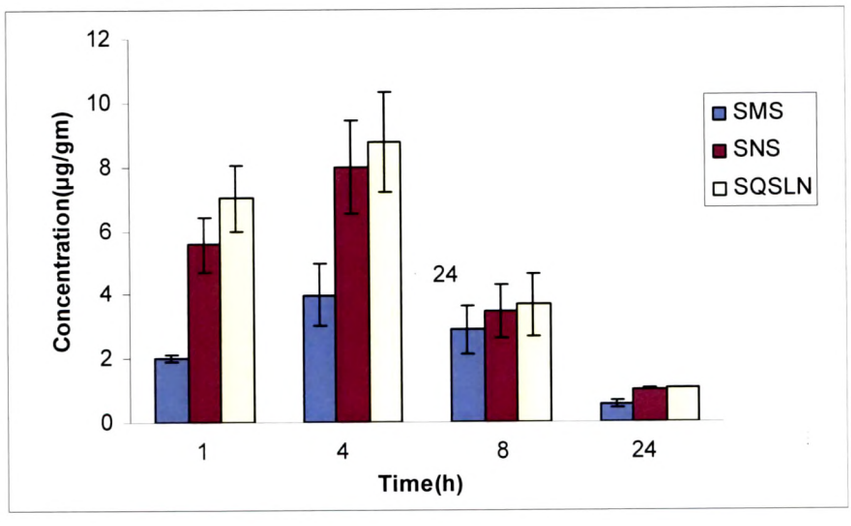
(d) Intestine



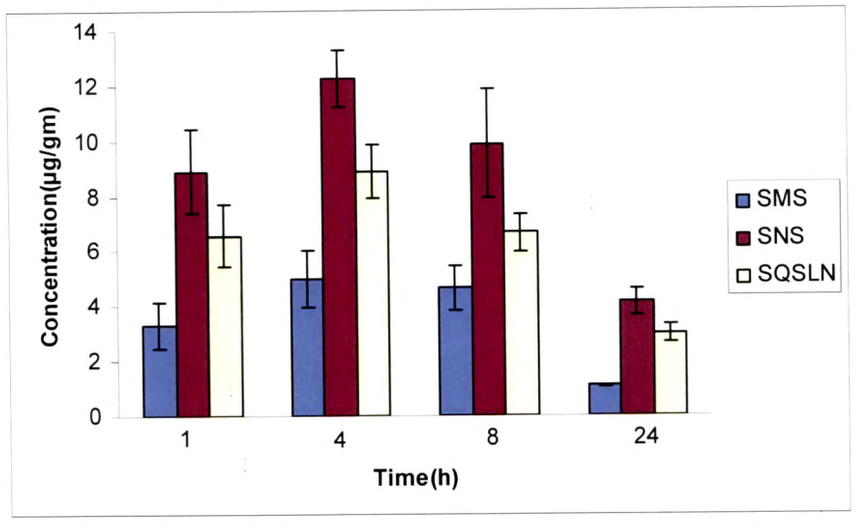
(e) Stomach



(f) Heart



(g) Lung



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