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Intestinal lymphatic transport of three retinoids in the rat after oral administration: effect of lipophilicity and lipid vehicle

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Abstract

The retinoids are highly lipophilic molecules and are known to be transported in the intestinal lymph after oral administration. Three retinoids, isotretinoin, etretinate and temarotene were used to study the effects of solubility and lipophilicity on lymphatic uptake in the rat after oral administration in each of three oily vehicles, cottonseed oil, Miglyol 812 and linoleic acid. Lipid solubility showed a general increase with increasing log P of the retinoid. The most lipophilic retinoid, temarotene, showed solubilities between 109.5 mg/ml (linoleic acid) and 170.6 mg/ml (Miglyol 812), whereas the least lipophilic retinoid, isotretinoin showed much lower solubilities between 5.1 (cottonseed oil) and 30.5 mg/ml (linoleic acid). Lymphatic uptake of temarotene was 4000-times and from etretinate 1000-times greater than that for isotretinoin after administration in linoleic acid. The lymphatic uptake of temarotene and etretinate from cottonseed oil were 27- and 26-times greater than that for isotretinoin and from Miglyol 812, 22- and 10-times greater than isotretinoin. These decreases in absorption via the lymphatic route reflect a decrease in log P value from temarotene (log $P \approx 8.7$) to etretinate (log $P \approx 7.8$) to isotretinoin (log $P \approx 6.8$). The rank order of increasing lymphatic uptake from each of the three oils shows an inverse relationship with solubility of the retinoid in each of the oils

Keywords: Retinoid; Isotretinoin; Etretinate; Temarotene; Lymphatic Uptake; Lipophilicity; Solubility; Oil Vehicle

1. Introduction

The lipophilicity of a molecule is known to be a major factor which determines the degree of lymphatic absorption of the molecule after oral administration (Sieber et al., 1974; Kamp and Neumann, 1975; Sieber, 1976; Palin, 1985). Lipophilic drugs which are transported in significant quantities in the intestinal lymph reside in the chylomicron fraction of the lymph (Sieber, 1976; Kamp and Neumann, 1975; Vost and MacLean, 1984). Log P and oil solubility may be used as indicators of the lipophilicity of a molecule where log P is the logarithm to base 10

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of the partition coefficient of a compound between two phases, usually octan-1-ol and water. The solubility of a compound is an absolute measurement of the equilibrium of the solute between the solvent and its pure phase (Szuts and Harosi, 1991). It is possible for one compound to have a large log P value but not necessarily a high solubility in an oil whilst another compound may be very soluble in an oil but have a relatively low log P value (Charman and Stella, 1986). In addition, a high solubility of a compound in a solvent such as octanol will not always relate to a high solubility in a poorly solvating, largely hydrocarbon vehicle such as a long chain fatty acid triglyceride (Charman and Stella, 1986).

The lymphatic transport of the three retinoids in the rat, their log P (octanol-water), and their solubility in an oil from each of three classes of lipid vehicles, cottonseed oil (a mixed long chain triglyceride), Miglyol 812 (a mixed medium chain triglyceride) and linoleic acid (a long chain, C_{18} fatty acid) were investigated and the relationships between these properties examined.

2. Materials and methods

It has been well established that retinoids are sensitive to light, especially ultraviolet light. Consequently all samples were protected using aluminium foil wrapping and all procedures involving the use of retinoids (e.g., weighing) were undertaken in conditions of red/amber illumination.

2.1. Chemicals and reagents

Isotretinoin, etretinate and temarotene were supplied by Roche Products Ltd. Pentobarbitone was purchased from Evans, UK, Slough, UK, and Miglyol 812 from Dynamit Nobel, Slough, UK. All other chemicals were from Sigma, Poole, UK and were of analytical grade or better.

2.2. Measurement of retinoid solubility in oils and determination of log P

The solubility of each retinoid, isotretinoin, etretinate and temarotene, was determined in each of the three oils used for oral dosing studies, cottonseed, Miglyol 812 and linoleic acid. Duplicate measured volumes of each oil (1.0 ml) were transferred by positive displacement pipette into microcentrifuge tubes (1.5 ml). Small additions (5–10 mg) of the retinoid were accurately weighed into each tube, to give a known concentration in the oil. Oil samples were placed in an ultrasonic water bath for 30 min (during which time the temperature of the samples increased from 24 to 55–60°C). Samples were allowed to equilibrate at 24°C and each oil sample was visually examined for signs of precipitation. After centrifugation (3000 × g, 10 min), a small sample of oil (ca. 20 mg) was removed from each tube for analysis. In oil samples where no visible signs of precipitation was observed, further additions of retinoid followed by sonication were made until visible precipitation was observed. Quantitative analysis of the retinoid in each sample of oil was carried out using the hplc method described below.

The simplest and most frequently used technique for the experimental determination of P is to allow a compound to distribute between an aqueous and an organic phase in a glass vessel. Once equilibrium has been reached the concentration of the solute in one or both phases is measured. This is known as the shake flask method (Lyman, 1982). The range of possible values for P covers several orders of magnitude, therefore it is most convenient to express the partition coefficient in terms of its logarithm to base 10 (log P). The shake flask method is normally restricted to compounds with log P values of less than 4 units because of the difficulties in measuring very low concentrations of molecule in one of the phases (Lyman, 1982; Brookes et al., 1986). In our studies log P was estimated using the method of Rekker (Rekker, 1977; Rekker and de Kort, 1979). The method is based on the addition of various functional groups or fragmental constants to the overall properties of a molecule and log P values may be calculated from the equation.

$$\log P = \sum f_n . a_n$$

where f_n = fragmental constant for a molecular fragment n and a_n = number of times this fragment appears in the molecule.

2.3. In vivo studies

Male Wistar rats weighing 200–250 g were used for the studies. They were fed standard rat chow with water ad libitum and maintained on a 12-h cycle of day and night. Animals were fasted for 16 h prior to the experimental procedure.

2.4. Oral dosing and sample collection

Oily solutions (3 mg/ml) of each retinoid, isotretinoin, etretinate and temarotene, were prepared in each of the three oily vehicles, cottonseed, Miglyol 812 and linoleic acid. Each oily vehicle-retinoid combination was administered by gavage (0.5 ml) over a period not exceeding 30 s to a group of twelve animals. Anaesthesia was induced with pentobarbitone (72 mg/kg) administered intraperitoneally. Additional pentobarbitone was administered as and when required to maintain anaesthesia. Six animals in each group underwent tracheostomy and jugular vein cannulation for collection of blood samples ($\approx$0.2 ml). The remaining animals underwent intestinal lymphatic duct cannulation based on the method of Bollman et al. (1948), the cannula being glued into position using a drop of cyanoacrylate cement. The cannula was exteriorised, cut short (ca. 3 cm) and immobilised using 'blu-tack'. A further length of saline filled cannula (ca. 50 cm) and containing a small air space (5 μl), was attached to the lymphatic cannula using a snapped off hypodermic syringe needle. The second cannula was allowed to hang vertically to provide a slight negative pressure on the lymph duct and assist the flow of lymph. The air space in the cannula was used to monitor the flow of lymph. The second cannula and was replaced periodically and lymph was drained into pre-weighed micro-centrifuge tubes (1.5 ml) and stored at -20°C. The time of collection of each lymph sample and its size (mass) were recorded.

2.5. Analysis of samples

The HPLC system consisted of a pump and variable-wavelength UV detector (LKB Models 2150 and 2151, respectively, LKB-Produkter, Bromma, Sweden), a Gilson auto sampling-injector (Model 231-401, Gilson International, Villiers-le-Bel, France) and a Spectra-Physics data integrator (Model SP4290, Spectra-Physics, San José, CA, USA). Plasma and lymph samples containing isotretinoin were analysed under the following conditions: the HPLC column was a Spherisorb (Phase Separations, Queensferry, UK) ODS2 (15 cm $\times$ 4.6 mm int. diam.) with a 5-μm particle size; the mobile phase consisted of acetonitrile (70% v/v) and 0.1 M ammonium acetate adjusted to pH 6.0 (30% v/v). The flow rate was 1.0 ml/min, the injection volume was 20 μl and the compounds were detected by their UV absorbance at 350 nm. Plasma and lymph samples containing isotretinoin were extracted using a direct protein precipitation method involving the addition of acetonitrile (200 μl) and acetonitrile (100 μl), containing the internal standard (Ro 11-5036, 7.5 ng), to plasma or lymph (100 μl). The mixture was, after thorough mixing, centrifuged (13 000 $\times$ g, 10 min) and the supernatant removed by aspiration.

Blood and lymph samples containing temarotene were analysed by hplc under the following conditions: the column was a Spherisorb ODS2 (15 cm $\times$ x 4.6 mm int. diam.) with a 5-μm particle size; the mobile phase consisted of acetonitrile (90% v/v) and 0.1 M ammonium acetate adjusted to pH 6.0 (10% v/v). The flow rate was 1 ml/min, the injection volume was 20 μl and the compounds were detected by their UV absorbance at 280 nm. Blood and lymph samples containing temarotene were extracted using the direct protein precipitation method described above for isotretinoin but using Ro 15-1570 (200 ng) as the internal standard.

Blood and lymph samples containing etretinate were analysed by normal phase hplc under the following conditions: the column was a Spherisorb CN (15 cm $\times$ 4.6 mm int. diam.) with a 3-μm particle size; the mobile phase consisted of hexane (99.15% v/v), methyl benzoate (0.6% v/v)

and propionic acid (0.25% v/v). The flow rate was 1 ml/min, the injection volume was 20 μl and the compounds were detected by their UV absorbance at 360 nm. Blood and lymph samples containing temarotene were extracted using the direct protein precipitation method described above for isotretinoin but using isotretinoin (200 ng) as the internal standard.

Analysis of the retinoid concentration in the oil samples was carried out using the appropriate hplc method described above.

An aliquot (ca. 150 μl) of each oil sample was transferred by positive displacement pipette into a Millipore Ultrafree filter unit (0.1 μm pore size) and centrifuged (10 000 $\times$ g, 20 min) to remove undissolved retinoid. A small accurately weighed sample (10–50 mg) of the filtered oil was dispensed into a volumetric flask (10 ml) and adjusted to volume using THF. THF was found to disperse and solubilise the oil samples completely and was miscible with the HPLC mobile phase.

A sample (25 μl) of the retinoid in THF was injected onto the HPLC system using a fixed volume loop injection system. Peak areas were calculated using a computing integrator and retinoid concentrations were calculated by comparison of the peak areas of the oil samples with the appropriate standard retinoid solution.

All assay methods were linear over the range used in these studies ($r^2 > 0.995$) and demonstrated good recovery, precision (variability < 10%) and accuracy.

Table 1
Log P, melting point, calculated water solubility and oil solubility data for isotretinoin, etretinate and temarotene

	Isotretinoin	Etretinate	Temarotene
Log P (Rekker)[a]	6.76	7.82	8.66
Melting point	174–175	104-105	81-82
Log S_w	−7.005	−8.364	−8.975
Oil solubility (mg/ml)			
Cottonseed	5.10	21.3	165.5
Miglyol 812	12.0	44.5	170.6
Linoleic acid	30.5	25.1	109.5

[a]Log P data from Nankervis (1992).

2.6. Analysis of data

The plasma and lymph concentration data from each group of rats were treated as follows. The concentration of retinoid determined in each sample was corrected for sample volume and administered dose (mg/kg) to give a dose adjusted plasma or lymph concentration (ng/ml/kg). The mean intestinal lymph flow rate (ml/min) for each dose group was calculated from the volume of each lymph sample and the time over which the sample was collected, for each dose group. This product of the lymph flow rate and the mean lymphatic retinoid concentration gave a figure for the mean lymphatic uptake rate (ng/h/kg). An estimate of plasma retinoid uptake was made by subtracting the lymphatic uptake rate from the total retinoid uptake rate. Total retinoid uptake was estimated from the product of the volume of distribution at steady state (V_{ss}) (Liu et al., 1990; Nankervis et al., 1994) and the mean plasma isotretinoin con-

Table 2
Lymphatic and plasma uptake data for isotretinoin, etretinate and temarotene in the rat (6 mg/kg) after oral administration in each of three oils (0.5 ml)

	Isotretinoin		Etretinate		Temarotene	
	Lymph uptake (ng/h/kg)	Plasma uptake (ng/h/kg)	Lymph uptake (ng/h/kg)	Plasma uptake (ng/h/kg)	Lymph uptake (ng/h/kg)	Plasma uptake (ng/h/kg)
Cottonseed	151	7 530	3 980	11 500	4 060	4 830
Miglyol 812	55	10 700	514	25 300	1 230	8 290
Linoleic acid	1.1	104	1030	310	4 110	13 500

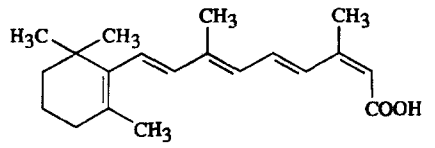
centration. The solubility of isotretinoin, etretinate and temarotene in each of the three oily vehicles are displayed in Table 1. Lymph and plasma uptake data are displayed in Table 2.

3. Results and discussion

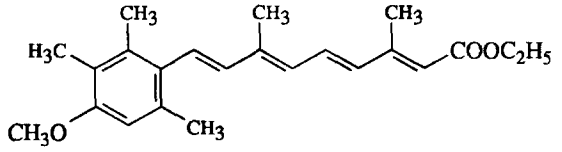
The most polar retinoid, isotretinoin, which has a dissociable carboxyl terminal group, was found to have the lowest estimated log P value (log P = 6.76) and appears to be least lipophilic retinoid of those studied here. Etretinate has an esterified terminal carboxyl group together with a conjugated ring system and is more lipophilic (log P = 7.82) in nature than isotretinoin. Temarotene has a cyclised terminal group with no polar groups and was found to the most lipophilic retinoid (log P = 8.66). The log P data for the three retinoids, isotretinoin, etretinate and temarotene are in agreement with expected values after considering the structural properties of the molecules (Fig. 1).

The solubility of temarotene in each of the three oils was greater than in either of the other retinoids (Table 1). The greatest solubility was measured in Miglyol 812 (170.6 mg/ml) followed by cottonseed oil (165.5 mg/ml) and linoleic acid (109.5 mg/ml). The corresponding figures for isotretinoin were 12.0, 5.1 and 30.5 mg/ml, and for etretinate, 44.5, 21.3 and 25.1 mg/ml. The solubility of each retinoid, isotretinoin, etretinate and temarotene in each of the three oils, cottonseed, Miglyol 812 and linoleic acid follows an increasing trend with an increase in log P of the retinoid (Fig. 2). These differences in relative solubility of the retinoids in the three oils may reflect differences in the polarity of oils and the effect these changes have on the solubility of a retinoid as it becomes more lipophilic. The differences may also be explained by differences in the physical associations of the retinoid with an oil, such as hydrophobic interactions (Van der Waals forces) and hydrogen bonding.

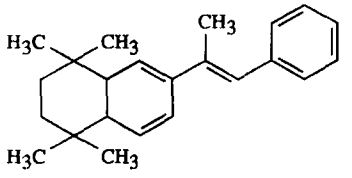
The lymphatic and plasma uptake rates for the three retinoids after oral administration in each oily vehicle are shown in Table 2. The lymphatic uptake rate of each retinoid, isotretinoin, etretinate and temarotene in each of the three oils,



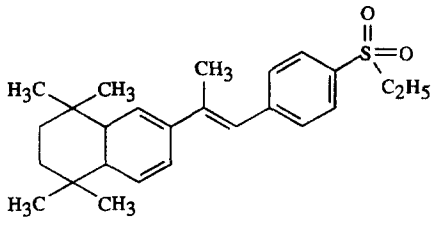
13-*cis*-retinoic acid (Isotretinoin, Ro 04-3780)



Etretinate (Ro 10-9359)



Temarotene (Ro 15-0778)



Internal standard 2 (Ro 15-1570)

Fig. 1. Chemical structures of the retinoids.

cottonseed, Miglyol 812 and linoleic acid follows an increasing trend with an increase in lymphatic uptake of the retinoid after oral administration in that oil (Fig. 3). However, the rank order for lymphatic uptake from the three oily vehicles changes with each retinoid. Isotretinoin showed the lowest lymphatic uptake from the long chain

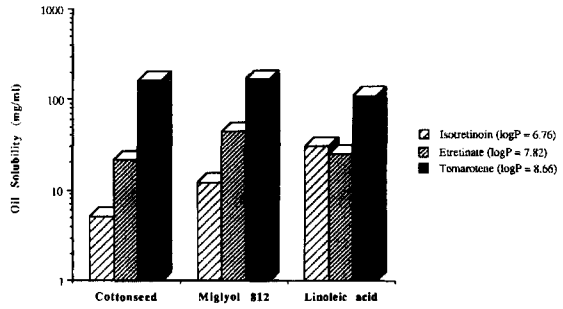


Fig. 2. Solubility of the three retinoids in three oil vehicles.

fatty acid, linoleic acid (1.1 ng/h/kg), with approximately fifty-fold greater uptake from the mixed medium chain triglyceride oil, Miglyol 812 (55 ng/h/kg) and one hundred and fifty-fold greater from the mixed long chain triglyceride oil, cottonseed (155 ng/h/kg). The more lipophilic retinoid, etretinate, showed the lowest lymphatic uptake rate from Miglyol 812 (514 ng/h/kg), approximately two-fold greater uptake from linoleic acid (1030 ng/h/kg) and eight-fold greater from cottonseed oil (3980 ng/h/kg). The most lipophilic retinoid, temarotene, showed the lowest lymphatic uptake from Miglyol 812 (1230 ng/h/kg) with almost three-fold greater uptake from cottonseed oil (4060 ng/h/kg) and linoleic acid (4110 ng/h/kg). The rank order of increasing lymphatic uptake appears to follow an inverse relationship with solubility of the retinoid in each of the three oils (Fig. 4).

The solubility of a substance is defined as the amount of dissolved solute in equilibrium with its

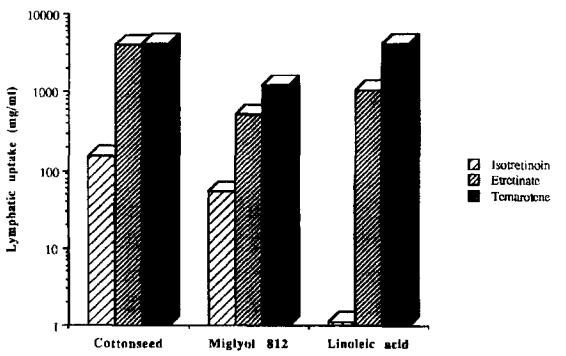


Fig. 3. Lymphatic uptake of the three retinoids when closed in three oil vehicles.

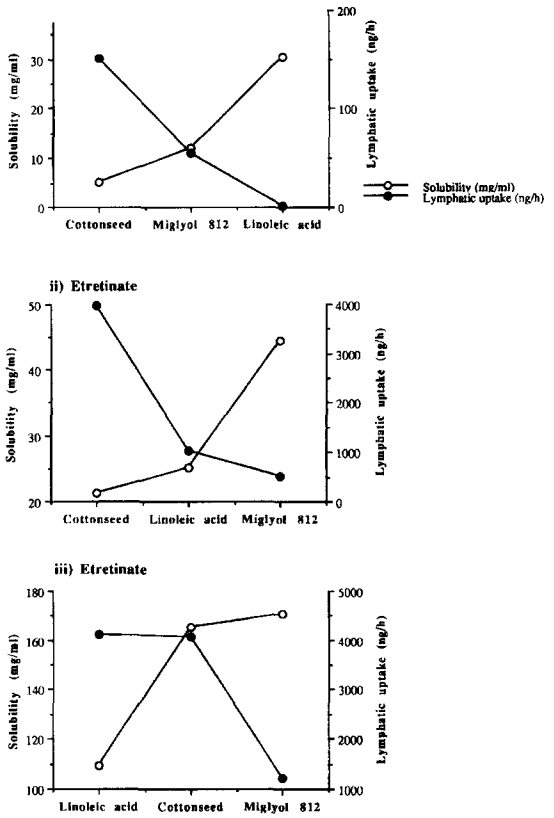


Fig. 4. Lymphatic uptake against oil solubility for the three retinoids.

pure state (Szuts and Harosi, 1991). The solubility of a non-electrolyte in water may be determined from the following relationship (Yalkowsky and Morozowich, 1980):

$$\log S_w = -\log P - 0.01\text{M.P.} + 0.5 + A$$

where S_w = solubility in water of a non-electrolyte compound, M.P = melting point of the compound, A = variable to allow for the presence ($A = 1.0$) or absence ($A = 0$) of an acidic proton in the compound.

Using this relationship, together with the calculated log P data for the retinoids (Table 1) and their melting points (Table 1), the solubility of the retinoids has been calculated (Table 1). As expected, the most polar retinoid, isotretinoin, shows the greatest solubility (log $S_w = -7.0$), dependent upon the degree of ionisation of the terminal carboxy group (Fig. 1). The more

lipophilic retinoid, etretinate, shows a lower solubility (log $S_w = -8.4$) and the most lipophilic retinoid, temarotene, shows a very low solubility (log $S_w = -9.0$). These calculated solubility data would suggest that the least lipophilic retinoid, isotretinoin, would be more readily absorbed from the gastrointestinal tract (de Blaey and Polderman, 1980), but this was not confirmed by the in vivo studies reported here.

We have observed here an inverse relationship between lymphatic absorption after oral administration in the oil and the solubility of the retinoid in the oil. These results may be somewhat surprising, since it has been reported that lipophilic drugs are preferentially absorbed via the lymphatic route (Sieber, 1976; Noguchi et al., 1985a; Noguchi et al., 1985b). Therefore, an increase in the solubility of compound in the oil may have been expected to increase the lymphatic uptake of that compound. However, the absorption of a retinoid from the gastrointestinal tract may involve the release of retinoid from the oily vehicle into the fluid milieu of the gut. Therefore, a higher solubility of retinoid in water together with with a lower solubility in the oily vehicle may be postulated to enhance absorption (de Blaey and Polderman, 1980).

A possible hypothesis which may explain the inverse oil solubility/lymphatic uptake is proposed as follows. The retinoid is likely to escape from the oil dosing vehicle before passing across the diffusional barrier of the unstirred water layer in the gut. Such a process must clearly be related to the solubility (affinity) of the retinoid in an oil (Armstrong and James, 1980). The more readily the process occurs (the lower the solubility of the retinoid in the oil), the more thermodynamically favourable it will be for the retinoid to partition out of the oil and subsequently to diffuse across the unstirred water layer. After this stage of the absorption process, the oil is likely to then play a secondary role in facilitating the incorporation of drug into lymph and its subsequent lymphatic transport, potentially by stimulating the lymph flow and chylomicron formation.

The extent of lymphatic uptake has been demonstrated here to be related to the type of oil. In the present studies. the retinoid concentration in oil system was kept constant (3 mg/ml) and the same volume of oil (0.5 ml) was administered to each animal. The percentage saturation of retinoid in the oil may be determined by calculating the ratio of the concentration of retinoid in the oil dosed to the animal divided by the saturation solubility of the retinoid in the oil (Table 1). The percentage saturation of isotretinoin (3 mg/ml) was 58% in cottonseed oil, 25% in Miglyol 812 and 10% in linoleic acid. This decrease in percentage saturation parallels the downward trend in lymphatic uptake from 150 to 1 ng/h found in the studies reported here. It may be postulated therefore that either an increase in the percentage retinoid saturation in the oil or a decrease in the solubility of the retinoid in the oil may be important in increasing lymphatic uptake. However, in other studies (Nankervis et al., 1995) when isotretinoin was presented in linoleic acid (0.5 ml) at an oral dose of 75 mg/kg (percentage saturation, 93%), the dose-adjusted lymphatic uptake was 150-times smaller than when isotretinoin was administered in cottonseed oil (0.5 ml) at an oral dose of 6 mg/kg (58% saturation). This observation would therefore add merit to the hypothesis that solubility in oily vehicle is a key determinant in the lymphatic uptake of the retinoids.

It is also noteworthy to consider the role of the individual oils in the lymphatic uptake process. Previously, it has been shown (Palin et al., 1982; Palin and Wilson, 1984) that Miglyol 812 (a mixed medium chain triglyceride) is transported mainly via the portal circulation. It would would therefore be expected that Miglyol 812, when used as an oily vehicle, would enhance the portal transport of drugs. Our studies show that Miglyol 812 produces the highest plasma uptake for two of the three retinoids. Linoleic acid (long chain fatty acid) and cottonseed oil would be expected to promote lymphatic transport (Cheema et al., 1987). The results of the lymphatic uptake studies reported here are not clear cut in this regard and do not unequivocally confirm these previous investigations.

In summary, we are of the opinion that the principal factor controlling lymphatic uptake in the three retinoids studied here is that of solubility of the retinoid in the oily vehicle.

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