Project Report

In vitro penetration studies of Fuse Science Formulations through human skin

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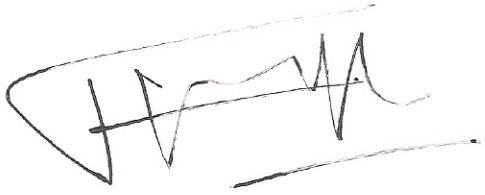
Approval

Study Director



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1. SUMMARY

Nine Fuse Science formulations were tested in an *in vitro* penetration study through human epidermis. Eight different compounds were incorporated into a proprietary encapsulation technology, whereas one of them was also incorporated into a second proprietary encapsulation formulation. The compounds were added as their radioactive label forms, either using [^{14}C] or [^{3}H], in each formulation prior to the application and their radioacitivity was used to analyze the samples. The penetration profile was assessed by collecting the receptor fluid samples at various time-points from the chamber below the epidermis. The selected time-points were 3 minutes, 1 hour, 2, 3.5, 5, 8, and 24 hours after the application of the formulations on the surface of the epidermal membrane. The results showed that Fuse Science's proprietary encapsulation formulas delivered all of the compounds tested, with different physiochemical characteristics, across the epidermis at distinctive rates with unique penetration profiles.

2. INTRODUCTION

Pre-clinical selection of topical formulations was performed using an *in-vitro* penetration study through human epidermal membrane, which assessed the percutaneous absorption profiles of the applied drugs. The method is based on the use of excised human skin as a membrane in a diffusion system that simulates *in-vivo* skin conditions. By analyzing the amount of the drug reaching the receptor solution, penetration profile of the drug in the skin was assessed and used as a tool to determine the feasibility of formulations for subsequent development.

Fuse Science proprietary encapsulation formulations containing eight different compounds were tested in an *in vitro* penetration study through human epidermis. One of the compounds was also formulated in another proprietary encapsulation formulation.
The *in vitro* skin penetration assay was utilized to effectively screen and investigate the formulations with a good correlation to the *in vivo* conditions.[1] In particular, excised human skin or its portion, such as epidermis, is the most selected as the membrane to simulate *in vivo* topical drug delivery.

[1] Franz TJ (1978) The finite dose technique as a valid in vitro model for the study of percutaneous absorption in man. Curr. Probl. Dermatol., vol. 7, Karger, Basel. pp. 58-68.

3. OBJECTIVE

The project aims to assess the penetration profiles of various active ingredients from Fuse Science proprietary encapsulation formulations, using an *in-vitro* penetration study through human epidermis.

4. MATERIALS

4.1 Test Articles

The test articles were received from the Sponsor as follows:
- Radioactive material:

- 250 µCi [8-^{14}C]-caffeine in ethanol solution under argon (Catalog# MC-499, Lot No. 195-132-0521-A-20100630-MW, Specific activity: 52.1 mCi/mmol; concentration 0.1 mCi/mL; 375.9 µg/ml) 2 units
- 250 µCi Nicotinic acid, [carboxy-^{14}C]- (Catalog# MC1324, Lot No. 229-055-0583-A-20120808-NTO, Specific activity: 58.3 mCi/mmol; solid) 1 unit
- 250 µCi Folic acid, diammonium salt, [3', 5', 7', 9-^{3}H]- (Catalog# MT783, Lot No. 250-001-0203-A-20110518-NT, Specific activity: 20.3 Ci/mmol; concentration 0.1 mCi/mL; 23.5 µg/ml in ethanol:water (4:6) solution) 1 unit
- 250 µCi Estradiol, [2,4-^{3}H]- (Catalog# MT524, Lot No. 229-058-0556-A-20101130-TN, Specific activity: 55.6 Ci/mmol; concentration 0.1 mCi/mL; 4.97 µg/ml in ethanol solution) 1 unit
- 50 µCi Paclitaxel, [Benzoyloxy ring-^{14}C (U)]- (Catalog# MC1446, Lot No. 642-079-0756-B-20091009-SB, Specific activity: 75.6 Ci/mmol; concentration 0.1 mCi/mL; 1.1 mg/ml in ethyl acetate solution) 5 units

was received on August 14, 2012 from Moravek Biochemicals Inc. 577 Mercury Lane, Brea, CA 92821; stored in a -20°C refrigerator upon arrival.

- 250 µCi Polyethylene Glycol, [1,2-^{3}H]- (Catalog# ART 0502, Lot No. 120812, Specific activity: 15 Ci/mmol; concentration 1 mCi/mL in ethanol:water (1:1) solution) 1 unit
- 250 µCi Insulin [methyl-^{14}C] (human recombinant; Catalog# ARC 3146, Lot No. 120814, Specific activity: 8.5 µCi/mg; concentration 0.05 mCi/mL in 0.01M potassium phosphate buffer (pH 7.2) solution) 1 unit
- 250 µCi (+)-a-Tocopherol acetate [acetyl-1-^{14}C] (Vitamin E acetate; Catalog# ARC 1323, Lot No. 120813, Specific activity: 55 mCi/mmol; concentration 0.1 mCi/mL in ethanol solution) 1 unit

was received on August 15, 2012 from American Radiolabeled Chemicals Inc. 101 ARC Dr., St. Louis, MO 63146; stored in a -20°C refrigerator upon arrival.

- Non radiolabeled formulations

Two type of formulations without radiolabel:

- Fuse Science proprietary encapsulation formula I formulations, containing different active ingredients
- Fuse Science proprietary encapsulation formula II

were delivered on August 16, 2012 from CURE Pharmaceutical, 1620 Beacon Place, Oxnard, CA 93033. The formulations were used as delivered, without any modification or analysis prior to the study, except for storage and acclimatization.

- Radiolabeled formulations:

Each of the formula I formulations was mixed with the corresponding radioactive label, that was dried overnight. The formulation II was mixed with [8-^{14}C]-caffeine only.
The formulations were mixed independently in Genepharm's facility by a representative of the Sponsor. Each formulation eventually contained a radioactive label of 50 µCi/mL. The mixture were stored at a 4°C refrigerator after preparation.

4.2 Excipients and Reagents

All excipients and reagents were obtained from vendors with noted quality and analytical reports.

4.3 Skin Donor

The skin used in the study was obtained from abdominal surgery on a single human donor, who gave written consent. The excised skin was obtained fresh (within 24 hour after harvest). The donor criteria was not younger than 16 years and not older than 70 years old and do not have diseases affecting the normal appearance of skin. During transport the harvested skin was placed in Eagle's Minimum Essential Media.

5. EXPERIMENTAL PROCEDURES

5.1 Study Design

A comparison study of several topical formulations were performed. The formulations were tested on epidermal membrane using a finite dose application. The receptor solution was continuously stirred, bathing the lower surface of the membrane. At certain time-points, receptor fluid samples were collected by draining the receptor chamber. The chamber was fully replenished with fresh receptor fluid. The amount of radioactive label was analyzed from the receptor fluid samples.

5.2 Skin preparation

Excised human skin without obvious signs of damage or disease was used in this study. After the removal of subcutaneous fat, the surface of the skin is wiped clean with tissue

paper soaked with purified water. The skin was placed, dermal side down, on hot plate set at 60°C for approximately 2 minutes. Using tweezer, the epidermis was separated from dermis. The epidermis sheet is washed twice in purified water, then air-dried and stored at ambient condition (room temperature) in a plastic vessel prior to use.

5.3 Topical Application

Each formulation was applied to the surface of the epidermal membranes at a target dose of 15.6 µL/cm^2 (= 10 µL/cell or 10 µL/0.64cm^2), without knowing the concentration of the non-radiolabeled material. Each test article/condition was tested on six replicates of epidermal membranes from one human donor.

5.4 Transmembrane Diffusion Study

The *in-vitro* delivery study was performed using Franz-type diffusion cells. The diffusion cells were mounted on a holder with magnetic stirrer. The donor chamber of the cell is left open to ambient laboratory environment. The water jacket compartment surrounding the receptor chamber of each cell was connected to a circulating water-bath. The temperature of the cells was maintained by flowing water from the water-bath controlled at 32.0 ± 0.2°C.

The human epidermal membrane sheet from a single donor was cut into multiple smaller membrane sections to fit on the diffusion cells. The membrane was mounted between the donor chamber (where the formulation is applied) and the receptor chamber. The receptor chamber was filled with phosphate buffered saline (pH 7.4; 1 mM) as receptor liquid, free from any air bubbles and continuously bathing the inner surface of the membrane.
Each formulation was applied at time zero on the surface of the epidermal membranes at a target dose of 10 µL/cell (= 10 µL/0.64cm^2 or 15.6 µL/cm^2). The formulation was applied and distributed to the skin using a positive displacement pipetter. The delivery through human epidermis was assessed for 24 hours after the application of the formulations. The receptor fluid was collected in a vial from the receptor chamber of the diffusion cell at 7 time-points: 3 minutes, 1 hour, 2, 3.5, 5, 8 and 24 hours. Fresh receptor fluid refills the receptor chamber. The vial was weighed and saved for sample analysis. The skin membranes were stored.

5.5 Sample Analysis

All samples collected throughout the study period were analyzed for radioactive label content by radioactive assay using Liquid Scintillation Counter for [H-3] or [C-14] isotope, after adding the appropriate liquid scintillation cocktails to them. The amount of applied radioactive materials in each formulation is listed in ***Table 1***. From the results of the analysis, the amount of radiolabels penetrating through human epidermis was measured and the percent of penetration was determined. The total amount of active in-

gredient collected in the receptor fluid for each cell at every time point was calculated. A mean and standard deviation were calculated per formulation for all parameters based on the replicate data obtained from each donor. Subsequently, a grand mean and standard error were calculated per formulation across all donors.

***Table 1**: Dose of radioactive materials applied dose in each formulation*

Formulation	*Applied radioactive material*
Proprietary encapsulation I caffeine	2.94 µg/cm^2
Proprietary encapsulation II caffeine	2.94 µg/cm^2
Proprietary encapsulation I nicotinic acid	1.67 µg/cm^2
Proprietary encapsulation I estradiol	3.88 ng/cm^2
Proprietary encapsulation I polyethylene glycol (PEG)	20.83 ng/cm^2
Proprietary encapsulation I folic acid	18.35 ng/cm^2
Proprietary encapsulation I tocopherol acetate	6.72 µg/cm^2
Proprietary encapsulation I insulin	91.91 µg/cm^2
Proprietary encapsulation I paclitaxel	8.85 ng/cm^2

Once the study was complete, the Sponsor provided the amount of the non-radiolabeled active materials in each formulation as per ***Table 2*** and the amount of active material penetrated was calculated.

***Table 2**: Dose of non-radioactive materials applied in each formulation*

Active	**Supplier**	**Concentration in formulation** (mg/mL)	**Amount applied** (µg/cm^2)
Caffeine	Spectrum	50	781.25
Folic acid	Hawkins	50	781.25
Nicotinic acid	Hawkins	50	781.25
Paclitaxel	AK Scientific	50	781.25
Tocopherol acetate	Hawkins	50	781.25
Estradiol	AK Scientific	50	781.25
PEG 400	CRODA Inc	50	781.25
Insulin	-	0	(91.91)*

**Insulin was only applied in radioactive form; this amount is copied from Table 1*

The density of the individual formulations was assumed to be 1 g/mL based on the density of the base formulation. The Sponsor was responsible for any necessary evaluations related to identity, strength, purity, composition, stability and method of synthesis of the test material.

6. RESULTS

The data is presented in two parts: (i) per time-point and (ii) as cumulative amounts. Samples are named for the applied test articles and abbreviated as follows

caffeine1	Proprietary encapsulation I caffeine formulation
caffeine2	Proprietary encapsulation II caffeine formulation
nicotinic1	Proprietary encapsulation I nicotinic acid formulation
estradiol1	Proprietary encapsulation I estradiol formulation
PEG1	Proprietary encapsulation I polyethylene glycol (PEG) formulation
folic1	Proprietary encapsulation I folic acid formulation
tocopherol1	Proprietary encapsulation I tocopherol acetate formulation
insulin1	Proprietary encapsulation I insulin formulation
paclitaxel1	Proprietary encapsulation I paclitaxel formulation

6.1 Time-point data

Table 3: **Amount of compounds collected in the receptor fluid per time-point.** Calculated as percentage of the applied dose

Test Samples	Amount at each time interval (% applied dose)						
	3 min	1 h	2 h	3.5 h	5 h	8 h	24 h
caffeine1	0.050%	0.374%	1.144%	1.623%	1.351%	1.271%	1.223%
caffeine2	0.005%	0.236%	0.752%	0.852%	0.811%	0.699%	0.749%
nicotinic1	0.008%	0.138%	0.263%	0.273%	0.225%	0.251%	0.314%
estradiol1	0.000%	0.056%	0.061%	0.341%	0.414%	0.358%	0.176%
PEG1	0.000%	0.040%	0.035%	0.093%	0.291%	0.057%	0.038%
folic1	0.000%	0.071%	0.189%	0.238%	0.356%	0.356%	0.317%
tocopherol1	0.000%	0.027%	0.018%	0.020%	0.012%	0.009%	0.018%
insulin1	0.000%	0.006%	0.014%	0.014%	0.023%	0.024%	0.028%
paclitaxel1	0.000%	0.022%	0.043%	0.050%	0.049%	0.051%	0.063%

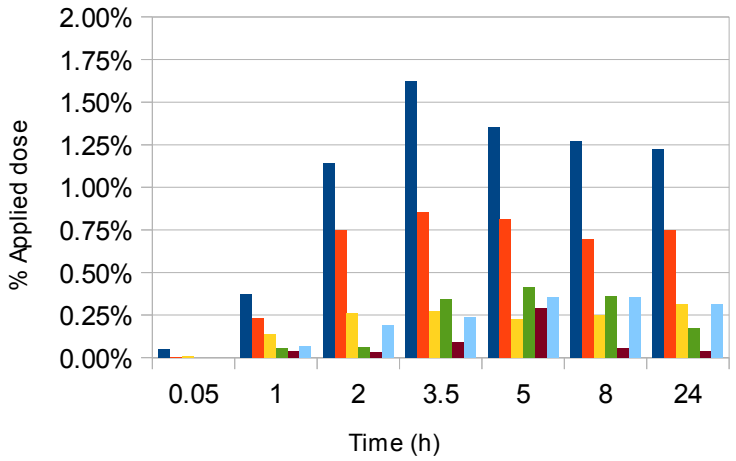

Figure 1: Amount of compounds collected in the receptor fluid per time-point (caffeine, nicotinic acid, estradiol, polyethylene glycol (PEG), and folic acid)

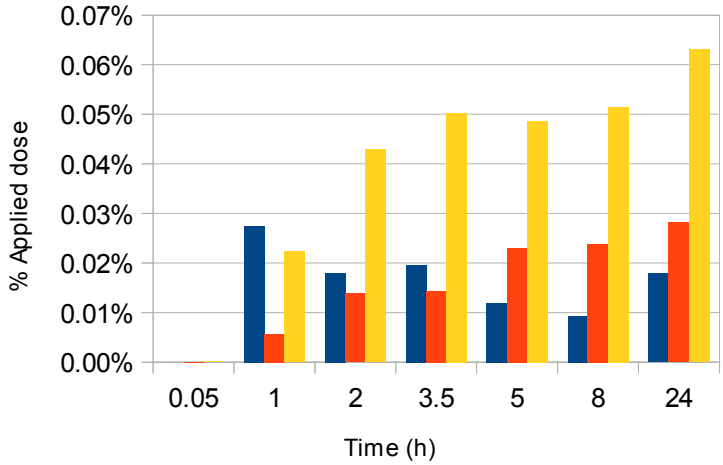

Figure 2: Amount of compounds collected in the receptor fluid per time-point (tocopherol acetate, insulin, and paclitaxel)

Table 4: **Estimate amount of compounds* collected in the receptor fluid per time-point.**

Calculated as the total amount of material penetrating the skin (µg/cm²)

Test Samples	Dosage at each time interval (µg/cm²)						
	3 min	1 h	2 h	3.5 h	5 h	8 h	24 h
caffeine1	0.39	2.91	9.33	15.60	19.88	25.53	29.44
nicotinic1	0.06	1.08	2.12	3.22	3.88	5.18	6.33
estradiol1	0.00	0.44	0.48	3.10	3.71	5.91	5.08
PEG1	0.00	0.31	0.27	1.04	2.55	1.48	2.84
folic1	0.00	0.55	1.48	2.42	4.26	5.20	6.73
tocopherol1	0.00	0.21	0.14	0.37	0.23	0.44	0.38
insulin1**	0.00	0.05	0.11	0.16	0.29	0.34	0.51
paclitaxel1	0.00	0.17	0.34	0.57	0.71	0.98	1.20

Note:

* The data presented is only from the formulations using the proprietary encapsulation I.
** Insulin was applied at 0.588% topical dose. The calculation above was an extrapolation to 5%, based on the radiolabel assessment.

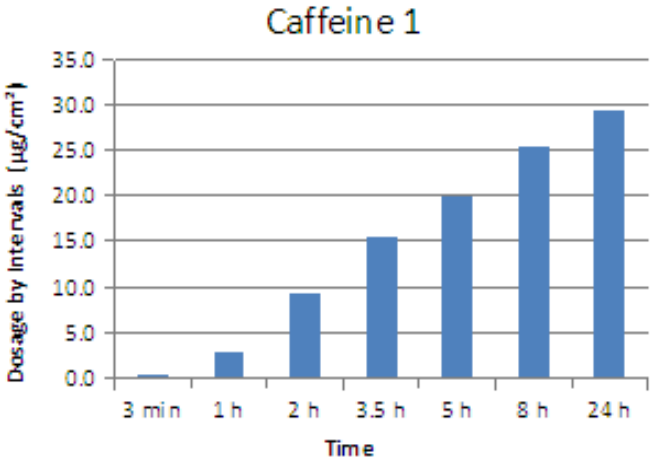

Figure 3: Calculated amount of caffeine from formulation I collected in the receptor fluid per time-point.

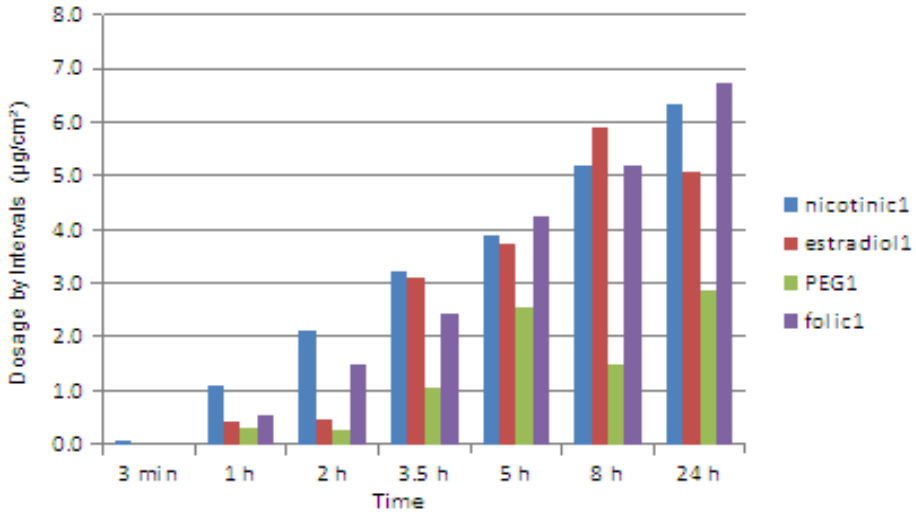

Figure 4: Calculated amount of compounds collected in the receptor fluid per time-point (nicotinic acid, estradiol, polyethylene glycol-400 (PEG-400), and folic acid)

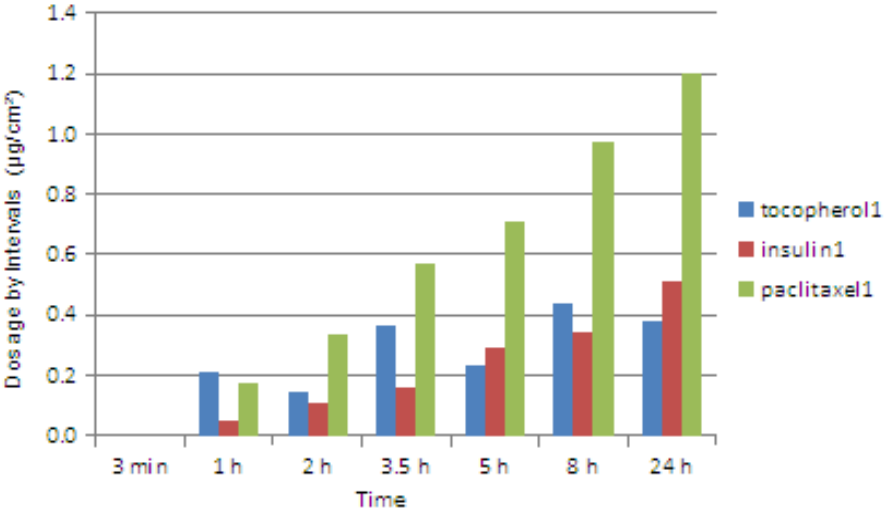

Figure 5: Calculated amount of compounds collected in the receptor fluid per time-point (tocopherol acetate, insulin, and paclitaxel)

6.2 Cumulative data

***Table 5*: Cumulative amount of compounds collected in the receptor fluid at each time-point.**

Calculated as percentage of the applied dose

Test Samples	Cumulative amount at each time interval (% applied dose)						
	3 min	1 h	2 h	3.5 h	5 h	8 h	24 h
caffeine1	0.050%	0.423%	1.567%	3.191%	4.542%	5.813%	7.036%
caffeine2	0.005%	0.241%	0.992%	1.844%	2.655%	3.354%	4.102%
nicotinic1	0.008%	0.146%	0.409%	0.683%	0.908%	1.159%	1.473%
estradiol1	0.000%	0.056%	0.117%	0.458%	0.872%	1.231%	1.406%
PEG1	0.000%	0.040%	0.074%	0.167%	0.459%	0.515%	0.553%
folic1	0.000%	0.071%	0.260%	0.499%	0.855%	1.211%	1.528%
tocopherol1	0.000%	0.027%	0.045%	0.065%	0.077%	0.086%	0.104%
insulin1	0.000%	0.006%	0.020%	0.034%	0.057%	0.081%	0.109%
paclitaxel1	0.000%	0.022%	0.065%	0.116%	0.164%	0.216%	0.279%

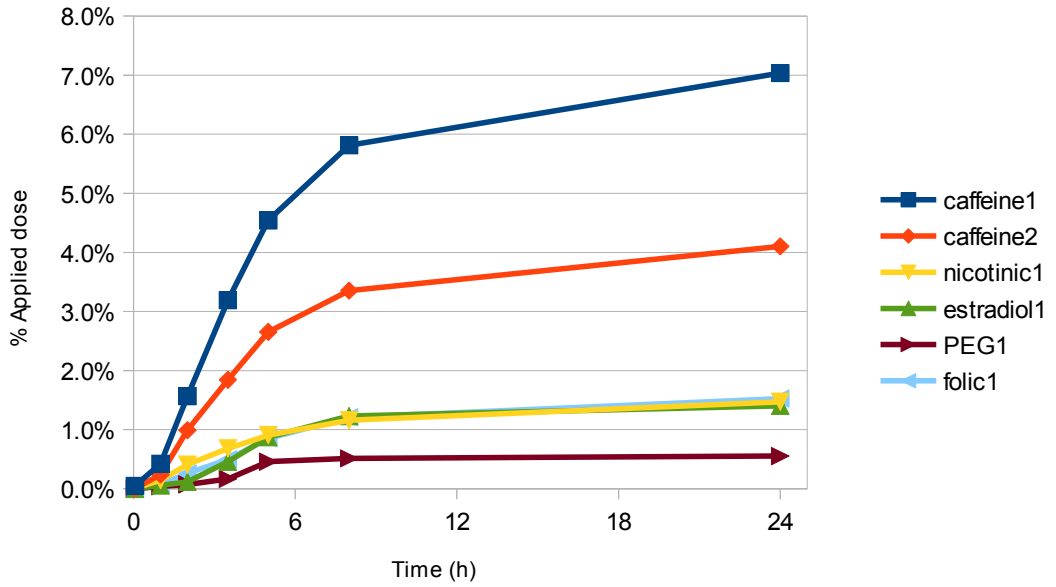

Figure 6: Cumulative amount of compounds collected in the receptor fluid per time-point (caffeine, nicotinic acid, estradiol, polyethylene glycol (PEG), and folic acid)

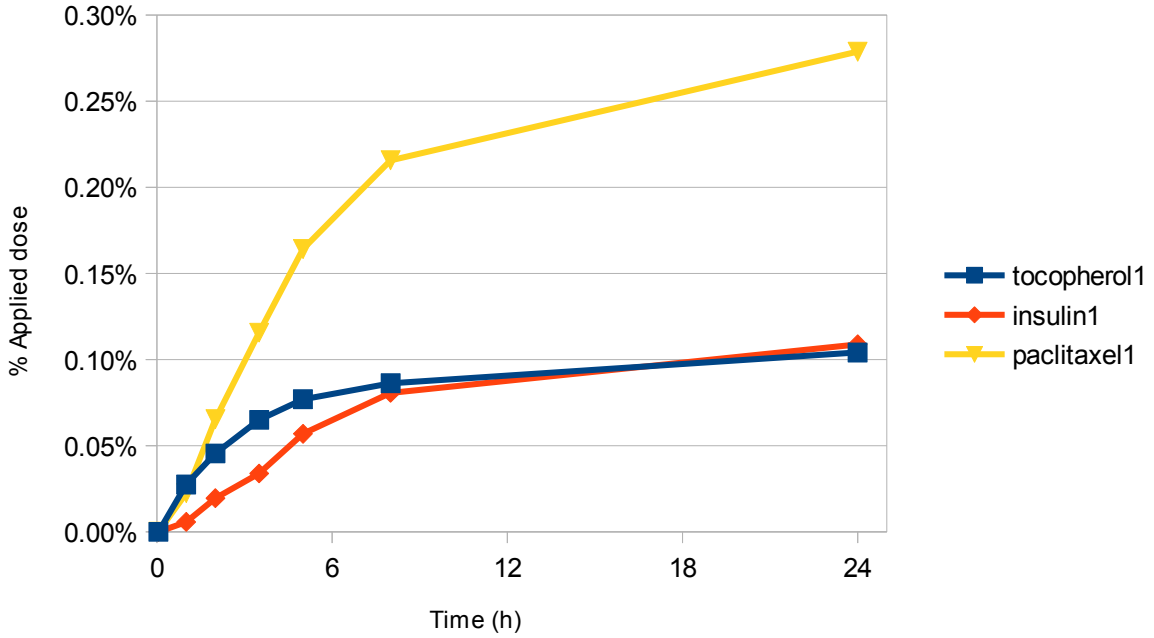

Figure 7: Cumulative amount of compounds collected in the receptor fluid per time-point (tocopherol acetate, insulin, and paclitaxel)

***Table 6*: Estimate cumulative amount of compounds* collected in the receptor fluid at each time-point.**

Calculated as the total amount of material penetrating the skin (µg/cm²)

Test Samples	Cumulative dosage at each time interval (µg/cm²)						
	3 min	1 h	2 h	3.5 h	5 h	8 h	24 h
caffeine1	0.39	3.30	12.24	24.93	35.48	45.41	54.97
nicotinic1	0.06	1.14	3.20	5.34	7.09	9.05	11.51
estradiol1	0.00	0.44	0.91	3.58	6.81	9.62	10.98
PEG1	0.00	0.31	0.58	1.30	3.59	4.02	4.32
folic1	0.00	0.55	2.03	3.90	6.68	9.46	11.94
tocopherol1	0.00	0.21	0.35	0.51	0.60	0.67	0.81
insulin1**	0.00	0.05	0.16	0.27	0.45	0.63	0.85
paclitaxel1	0.00	0.17	0.51	0.91	1.28	1.69	2.18

Note:
* The data presented is only from the formulations using the proprietary encapsulation I.
** Insulin was applied at 0.588% topical dose. The calculation above was an extrapolation to 5%, based on the radiolabel assessment.

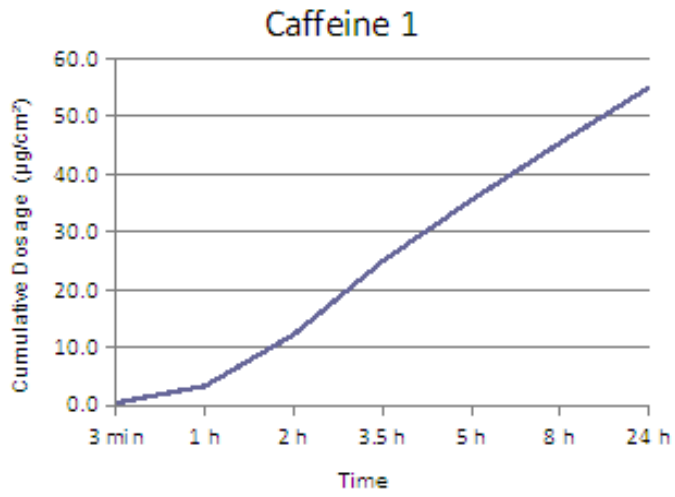

Figure 8: Calculated cumulative amount of caffeine from formulation I collected in the receptor fluid per time-point

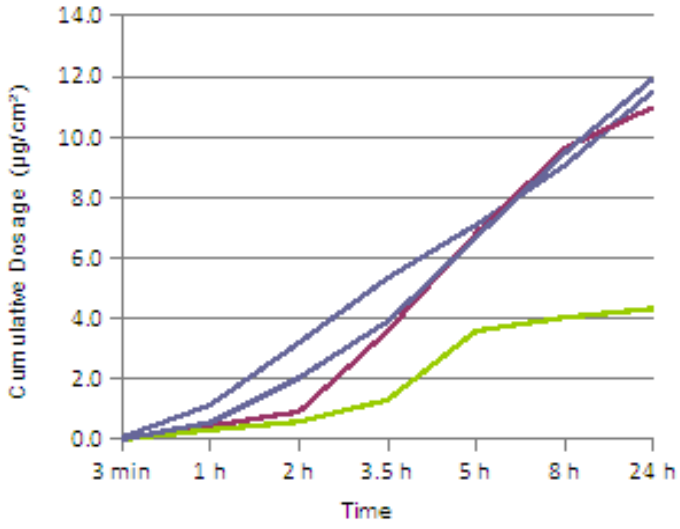

Figure 9 Calculated cumulative amount of compounds collected in the receptor fluid per time-point (nicotinic acid, estradiol, polyethylene glycol (PEG), and folic acid)

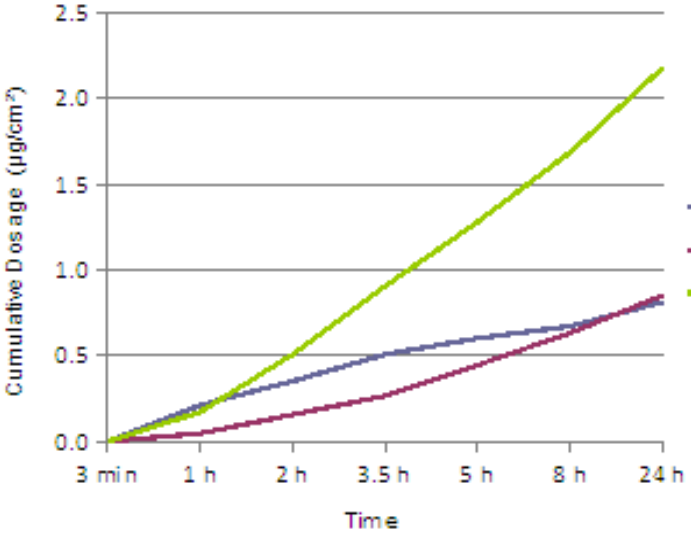

Figure 10: Calculated cumulative amount of compounds collected in the receptor fluid per time-point (tocopherol acetate, insulin, and paclitaxel)

- The encapsulated formulation delivered various compounds at a different rate depending on each physicochemical property.
- Among the tested compounds, caffeine was delivered at the highest rate from the formulation I and to a lesser extent from formulation II. It was delivered the most in 24 hours, from both proprietary formulations, with the formulation I delivered the highest amount.
- Smaller molecules, such as nicotinic acid and folic acid, were delivered in at a higher rate than larger molecules.
- Estradiol, a lipophilic compound, was delivered at a peak rate at 5-hour time-point after the application.
- Insulin and paclitaxel maintained a steady delivery through the 24-hour time-point.
- The penetration profile of most of the compounds followed the sigmoidal pattern with a steady state ended at around 8-hour time-point.

7. CONCLUSION

- Fuse Science possesses proprietary patchless encapsulation technology, which can deliver a variety of compounds with different physicochemical characteristics across the epidermis at distinctive rates and unique penetration profiles in a simple roll-on application.
- The patchless encapsulation formula can deliver some amounts of large, rigid, lipophilic to small, flexible, hydrophilic molecules across the epidermis.
- The patchless encapsulation formula delivers caffeine at a higher rate in comparison to other molecules.
- Smaller molecules, such as nicotinic acid and folic acid, were delivered in at a higher rate than larger molecules.
- Estradiol, a lipophilic compound, was delivered at a peak rate at 5-hour time-point after the application.
- Insulin and paclitaxel maintained a steady delivery through the 24-hour time-point.

End of report.

APPENDIX: Raw Data

1. Fuse Science proprietary encapsulation I caffeine formulation

Radioactivity count per cell per time-point *(in cpm)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
G	176.75	456.75	1874.25	2479.75	2395.75	2010.75	1863.75
H	68.25	341.25	2168.25	2122.75	1891.75	1758.75	1797.25
I	19.25	257.25	2423.75	2532.25	2381.75	2147.25	1681.75
K	71.75	967.75	1048.25	1373.75	1153.25	1128.75	1037.75
B	0.00	67.03	206.89	190.12	107.10	206.48	463.30
E	0.00	442.86	17.95	1780.95	383.97	359.43	493.57
H	0.00	0.00	10.59	518.10	841.58	999.85	945.46

Standard (100%): 96785.0 cpm

Timepoint Amount *(% applied dose)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
G	0.183%	0.472%	1.937%	2.562%	2.475%	2.078%	1.926%
H	0.071%	0.353%	2.240%	2.193%	1.955%	1.817%	1.857%
I	0.020%	0.266%	2.504%	2.616%	2.461%	2.219%	1.738%
K	0.074%	1.000%	1.083%	1.419%	1.192%	1.166%	1.072%
B	0.000%	0.069%	0.214%	0.196%	0.111%	0.213%	0.479%
E	0.000%	0.458%	0.019%	1.840%	0.397%	0.371%	0.510%
H	0.000%	0.000%	0.011%	0.535%	0.870%	1.033%	0.977%
Average	0.050%	0.374%	1.144%	1.623%	1.351%	1.271%	1.223%
S.E.M	0.025%	0.125%	0.411%	0.362%	0.364%	0.302%	0.234%
n	7	7	7	7	7	7	7

APPENDIX (continued)

***Cumulative Amount** (% applied dose)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
G	0.183%	0.655%	2.591%	5.153%	7.629%	9.706%	11.632%
H	0.071%	0.423%	2.663%	4.857%	6.811%	8.628%	10.485%
I	0.020%	0.286%	2.790%	5.406%	7.867%	10.086%	11.823%
K	0.074%	1.074%	2.157%	3.576%	4.768%	5.934%	7.007%
B	0.000%	0.069%	0.283%	0.479%	0.590%	0.803%	1.282%
E	0.000%	0.458%	0.476%	2.316%	2.713%	3.084%	3.594%
H	0.000%	0.000%	0.011%	0.546%	1.416%	2.449%	3.426%
Average	0.050%	0.423%	1.567%	3.191%	4.542%	5.813%	7.036%
S.E.M	0.025%	0.138%	0.472%	0.799%	1.139%	1.424%	1.647%
n	7	7	7	7	7	7	7

APPENDIX (continued)

2. Fuse Science proprietary encapsulation II caffeine formulation

Radioactivity count per cell per time-point *(in cpm)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
A	8.75	267.75	1702.75	1783.25	1520.75	1072.75	915.25
C	12.25	715.75	1849.75	1933.75	2210.25	1832.25	1597.75
E	8.75	659.75	1716.75	1947.75	1692.25	1706.25	1678.25
C	0.49	40.47	176.10	226.35	236.08	217.71	246.35
I	4.81	33.99	98.29	245.81	250.13	227.98	547.87
L	0.49	92.89	224.19	398.19	314.43	304.17	758.60

Standard (100%): 127883.2 cpm

Timepoint Amount *(% applied dose)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
A	0.007%	0.209%	1.331%	1.394%	1.189%	0.839%	0.716%
C	0.010%	0.560%	1.446%	1.512%	1.728%	1.433%	1.249%
E	0.007%	0.516%	1.342%	1.523%	1.323%	1.334%	1.312%
C	0.000%	0.032%	0.138%	0.177%	0.185%	0.170%	0.193%
I	0.004%	0.027%	0.077%	0.192%	0.196%	0.178%	0.428%
L	0.000%	0.073%	0.175%	0.311%	0.246%	0.238%	0.593%
Average	0.005%	0.236%	0.752%	0.852%	0.811%	0.699%	0.749%
S.E.M	0.002%	0.099%	0.279%	0.281%	0.279%	0.240%	0.183%
n	6	6	6	6	6	6	6

APPENDIX (continued)

***Cumulative Amount** (% applied dose)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
A	0.007%	0.216%	1.548%	2.942%	4.131%	4.970%	5.686%
C	0.010%	0.569%	2.016%	3.528%	5.256%	6.689%	7.938%
E	0.007%	0.523%	1.865%	3.388%	4.712%	6.046%	7.358%
C	0.000%	0.032%	0.170%	0.347%	0.531%	0.702%	0.894%
I	0.004%	0.030%	0.107%	0.299%	0.495%	0.673%	1.102%
L	0.000%	0.073%	0.248%	0.560%	0.806%	1.043%	1.637%
Average	0.005%	0.241%	0.992%	1.844%	2.655%	3.354%	4.102%
S.E.M	0.002%	0.101%	0.371%	0.651%	0.927%	1.162%	1.332%
n	6	6	6	6	6	6	6

APPENDIX (continued)

3. Fuse Science proprietary encapsulation I nicotinic acid formulation

Radioactivity count per cell per time-point *(in cpm)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
B	12.25	148.75	327.25	274.75	365.75	369.25	229.25
D	0.00	222.25	782.25	862.75	561.75	593.25	348.25
F	64.75	225.75	201.25	341.25	201.25	446.25	376.25
A	0.00	0.00	0.00	55.45	19.86	83.91	338.72
D	0.64	5.62	0.00	4.20	5.62	60.43	721.64
J	0.00	784.27	1326.62	1198.51	1102.42	960.79	1135.16

Standard (100%): 166995.2 cpm

Timepoint Amount *(% applied dose)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
B	0.007%	0.089%	0.196%	0.165%	0.219%	0.221%	0.137%
D	0.000%	0.133%	0.468%	0.517%	0.336%	0.355%	0.209%
F	0.039%	0.135%	0.121%	0.204%	0.121%	0.267%	0.225%
A	0.000%	0.000%	0.000%	0.033%	0.012%	0.050%	0.203%
D	0.000%	0.003%	0.000%	0.003%	0.003%	0.036%	0.432%
J	0.000%	0.470%	0.794%	0.718%	0.660%	0.575%	0.680%
Average	0.008%	0.138%	0.263%	0.273%	0.225%	0.251%	0.314%
S.E.M	0.006%	0.071%	0.128%	0.116%	0.101%	0.082%	0.084%
n	6	6	6	6	6	6	6

APPENDIX (continued)

***Cumulative Amount** (% applied dose)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
B	0.007%	0.096%	0.292%	0.457%	0.676%	0.897%	1.034%
D	0.000%	0.133%	0.602%	1.118%	1.455%	1.810%	2.018%
F	0.039%	0.174%	0.294%	0.499%	0.619%	0.887%	1.112%
A	0.000%	0.000%	0.000%	0.033%	0.045%	0.095%	0.298%
D	0.000%	0.004%	0.004%	0.006%	0.010%	0.046%	0.478%
J	0.000%	0.470%	1.264%	1.982%	2.642%	3.217%	3.897%
Average	0.008%	0.146%	0.409%	0.683%	0.908%	1.159%	1.473%
S.E.M	0.006%	0.071%	0.194%	0.308%	0.408%	0.489%	0.544%
n	6	6	6	6	6	6	6

APPENDIX (continued)

4. Fuse Science proprietary encapsulation I estradiol formulation

Radioactivity count per cell per time-point *(in cpm)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
A	0.00	5.69	9.19	51.19	51.19	110.69	37.19
B	0.00	9.19	5.69	23.19	82.69	103.69	23.19
A	0.00	0.00	14.00	52.50	45.50	14.00	35.00
D	0.00	14.00	0.00	70.00	63.00	0.00	3.50
G	0.00	0.00	21.00	42.00	38.50	3.50	14.00
J	0.00	17.50	0.00	42.00	59.50	63.00	31.50

Standard (100%): 13709.7 cpm

Timepoint Amount *(% applied dose)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
A	0.000%	0.041%	0.067%	0.373%	0.373%	0.807%	0.271%
B	0.000%	0.067%	0.041%	0.169%	0.603%	0.756%	0.169%
A	0.000%	0.000%	0.102%	0.383%	0.332%	0.102%	0.255%
D	0.000%	0.102%	0.000%	0.511%	0.460%	0.000%	0.026%
G	0.000%	0.000%	0.153%	0.306%	0.281%	0.026%	0.102%
J	0.000%	0.128%	0.000%	0.306%	0.434%	0.460%	0.230%
Average	0.000%	0.056%	0.061%	0.341%	0.414%	0.358%	0.176%
S.E.M	0.000%	0.021%	0.025%	0.046%	0.046%	0.150%	0.039%
n	6	6	6	6	6	6	6

APPENDIX (continued)

***Cumulative Amount** (% applied dose)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
A	0.000%	0.041%	0.109%	0.482%	0.855%	1.663%	1.934%
B	0.000%	0.067%	0.109%	0.278%	0.881%	1.637%	1.806%
A	0.000%	0.000%	0.102%	0.485%	0.817%	0.919%	1.174%
D	0.000%	0.102%	0.102%	0.613%	1.072%	1.072%	1.098%
G	0.000%	0.000%	0.153%	0.460%	0.740%	0.766%	0.868%
J	0.000%	0.128%	0.128%	0.434%	0.868%	1.328%	1.557%
Average	0.000%	0.056%	0.117%	0.458%	0.872%	1.231%	1.406%
S.E.M	0.000%	0.021%	0.008%	0.044%	0.045%	0.153%	0.173%
n	6	6	6	6	6	6	6

APPENDIX (continued)

5. Fuse Science proprietary encapsulation I polyethylene glycol (PEG) formulation

Radioactivity count per cell per time-point *(in cpm)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
C	0.00	10.17	5.04	7.61	6.44	16.94	19.27
D	0.00	18.10	26.50	19.04	16.94	38.63	20.44
B	0.00	10.50	17.50	3.50	0.00	14.00	0.00
E	0.00	0.00	0.00	14.00	77.00	0.00	0.00
H	0.00	17.50	0.00	80.50	196.00	10.50	14.00
K	0.00	0.00	0.00	7.00	115.50	0.00	0.00

Standard (100%): 23581.3 cpm

Timepoint Amount *(% applied dose)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
C	0.000%	0.043%	0.021%	0.032%	0.027%	0.072%	0.082%
D	0.000%	0.077%	0.112%	0.081%	0.072%	0.164%	0.087%
B	0.000%	0.045%	0.074%	0.015%	0.000%	0.059%	0.000%
E	0.000%	0.000%	0.000%	0.059%	0.327%	0.000%	0.000%
H	0.000%	0.074%	0.000%	0.341%	0.831%	0.045%	0.059%
K	0.000%	0.000%	0.000%	0.030%	0.490%	0.000%	0.000%
Average	0.000%	0.040%	0.035%	0.093%	0.291%	0.057%	0.038%
S.E.M	0.000%	0.014%	0.019%	0.051%	0.134%	0.025%	0.017%
n	6	6	6	6	6	6	6

APPENDIX (continued)

***Cumulative Amount** (% applied dose)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
C	0.000%	0.043%	0.065%	0.097%	0.124%	0.196%	0.278%
D	0.000%	0.077%	0.189%	0.270%	0.342%	0.506%	0.592%
B	0.000%	0.045%	0.119%	0.134%	0.134%	0.193%	0.193%
E	0.000%	0.000%	0.000%	0.059%	0.386%	0.386%	0.386%
H	0.000%	0.074%	0.074%	0.416%	1.247%	1.291%	1.351%
K	0.000%	0.000%	0.000%	0.030%	0.519%	0.519%	0.519%
Average	0.000%	0.040%	0.074%	0.167%	0.459%	0.515%	0.553%
S.E.M	0.000%	0.014%	0.030%	0.060%	0.169%	0.166%	0.171%
n	6	6	6	6	6	6	6

APPENDIX (continued)

6. Fuse Science proprietary encapsulation I folic acid formulation

Radioactivity count per cell per time-point *(in cpm)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
E	0.00	9.19	23.19	19.69	23.19	37.19	26.69
F	0.00	5.69	19.69	12.69	9.19	30.19	33.69
C	0.00	0.00	7.00	10.50	24.50	17.50	21.00
F	0.00	10.50	17.50	21.00	17.50	14.00	14.00
I	0.00	0.00	0.00	21.00	31.50	28.00	10.50
L	0.00	0.00	0.00	0.00	21.00	0.00	7.00

Standard (100%): 5938.0 cpm

Timepoint Amount *(% applied dose)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
E	0.000%	0.155%	0.390%	0.332%	0.390%	0.626%	0.449%
F	0.000%	0.096%	0.332%	0.214%	0.155%	0.508%	0.567%
C	0.000%	0.000%	0.118%	0.177%	0.413%	0.295%	0.354%
F	0.000%	0.177%	0.295%	0.354%	0.295%	0.236%	0.236%
I	0.000%	0.000%	0.000%	0.354%	0.530%	0.472%	0.177%
L	0.000%	0.000%	0.000%	0.000%	0.354%	0.000%	0.118%
Average	0.000%	0.071%	0.189%	0.238%	0.356%	0.356%	0.317%
S.E.M	0.000%	0.034%	0.070%	0.057%	0.051%	0.092%	0.070%
n	6	6	6	6	6	6	6

APPENDIX (continued)

***Cumulative Amount** (% applied dose)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
E	0.000%	0.155%	0.545%	0.877%	1.267%	1.894%	2.343%
F	0.000%	0.096%	0.427%	0.641%	0.796%	1.304%	1.871%
C	0.000%	0.000%	0.118%	0.295%	0.707%	1.002%	1.356%
F	0.000%	0.177%	0.472%	0.825%	1.120%	1.356%	1.591%
I	0.000%	0.000%	0.000%	0.354%	0.884%	1.356%	1.533%
L	0.000%	0.000%	0.000%	0.000%	0.354%	0.354%	0.472%
Average	0.000%	0.071%	0.260%	0.499%	0.855%	1.211%	1.528%
S.E.M	0.000%	0.034%	0.102%	0.139%	0.131%	0.208%	0.254%
n	6	6	6	6	6	6	6

APPENDIX (continued)

7. Fuse Science proprietary encapsulation I tocopherol acetate formulation

Radioactivity count per cell per time-point *(in cpm)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
G	0.00	45.50	0.00	45.50	0.00	11.16	100.45
H	0.00	59.24	100.45	237.82	141.66	93.58	127.93
A	0.00	42.88	14.88	25.38	21.88	7.88	28.88
D	0.00	28.88	4.38	28.88	42.88	14.88	18.38
G	0.00	0.00	18.38	0.00	0.00	11.38	11.38
J	0.00	298.38	172.38	0.00	0.00	21.88	21.88

Standard (100%): 287855.2 cpm

Timepoint Amount *(% applied dose)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
G	0.000%	0.016%	0.000%	0.016%	0.000%	0.004%	0.035%
H	0.000%	0.021%	0.035%	0.083%	0.049%	0.033%	0.044%
A	0.000%	0.015%	0.005%	0.009%	0.008%	0.003%	0.010%
D	0.000%	0.010%	0.002%	0.010%	0.015%	0.005%	0.006%
G	0.000%	0.000%	0.006%	0.000%	0.000%	0.004%	0.004%
J	0.000%	0.104%	0.060%	0.000%	0.000%	0.008%	0.008%
Average	0.000%	0.027%	0.018%	0.020%	0.012%	0.009%	0.018%
S.E.M	0.000%	0.015%	0.010%	0.013%	0.008%	0.005%	0.007%
n	6	6	6	6	6	6	6

APPENDIX (continued)

***Cumulative Amount** (% applied dose)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
G	0.000%	0.016%	0.016%	0.032%	0.032%	0.035%	0.070%
H	0.000%	0.021%	0.055%	0.138%	0.187%	0.220%	0.264%
A	0.000%	0.015%	0.020%	0.029%	0.04%	0.04%	0.05%
D	0.000%	0.010%	0.012%	0.022%	0.04%	0.04%	0.05%
G	0.000%	0.000%	0.006%	0.006%	0.006%	0.010%	0.014%
J	0.000%	0.104%	0.164%	0.164%	0.164%	0.171%	0.179%
Average	0.000%	0.027%	0.045%	0.065%	0.077%	0.086%	0.104%
S.E.M	0.000%	0.015%	0.025%	0.028%	0.032%	0.035%	0.039%
n	6	6	6	6	6	6	6

APPENDIX (continued)

8. Fuse Science proprietary encapsulation I insulin formulation

Radioactivity count per cell per time-point *(in cpm)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
I	0.00	27.45	79.75	111.12	132.04	184.33	184.33
J	0.00	37.91	121.58	132.04	173.88	205.25	236.63
B	0.88	18.38	32.38	21.88	56.88	56.88	137.38
E	0.00	28.88	42.88	77.88	42.88	56.88	60.38
H	0.00	11.38	11.38	4.38	49.88	25.38	32.38
K	0.00	18.38	56.88	11.38	119.88	67.38	53.38

Standard (100%): 416819.5 cpm

Timepoint Amount *(% applied dose)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
I	0.000%	0.007%	0.019%	0.027%	0.032%	0.044%	0.044%
J	0.000%	0.009%	0.029%	0.032%	0.042%	0.049%	0.057%
B	0.000%	0.004%	0.008%	0.005%	0.014%	0.014%	0.033%
E	0.000%	0.007%	0.010%	0.019%	0.010%	0.014%	0.014%
H	0.000%	0.003%	0.003%	0.001%	0.012%	0.006%	0.008%
K	0.000%	0.004%	0.014%	0.003%	0.029%	0.016%	0.013%
Average	0.000%	0.006%	0.014%	0.014%	0.023%	0.024%	0.028%
S.E.M	0.000%	0.001%	0.004%	0.005%	0.005%	0.007%	0.008%
n	6	6	6	6	6	6	6

APPENDIX (continued)

***Cumulative Amount** (% applied dose)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
I	0.000%	0.007%	0.026%	0.052%	0.084%	0.128%	0.173%
J	0.000%	0.009%	0.038%	0.070%	0.112%	0.161%	0.218%
B	0.000%	0.005%	0.012%	0.018%	0.031%	0.045%	0.078%
E	0.000%	0.007%	0.017%	0.036%	0.046%	0.060%	0.074%
H	0.000%	0.003%	0.005%	0.007%	0.018%	0.025%	0.032%
K	0.000%	0.004%	0.018%	0.021%	0.050%	0.066%	0.079%
Average	0.000%	0.006%	0.020%	0.034%	0.057%	0.081%	0.109%
S.E.M	0.000%	0.001%	0.005%	0.010%	0.014%	0.021%	0.029%
n	6	6	6	6	6	6	6

APPENDIX (continued)

9. Fuse Science proprietary encapsulation I paclitaxel formulation

Radioactivity count per cell per time-point *(in cpm)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
K	0.00	50.56	41.57	0.00	5.62	59.55	41.57
L	0.00	23.59	131.45	0.00	59.55	77.52	41.57
J	4.49	49.43	193.25	148.30	220.21	0.00	408.96
L	0.00	31.46	534.79	1334.74	1307.78	1172.95	1577.42
C	0.00	49.88	490.88	378.88	270.38	585.38	252.88
F	0.00	193.38	0.88	287.88	193.38	217.88	399.88
I	0.00	298.38	578.38	315.88	347.38	392.88	399.88
L	0.00	410.38	151.38	21.88	0.00	39.38	0.00

Standard (100%): 618512.3 cpm

Timepoint Amount *(% applied dose)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
K	0.000%	0.008%	0.007%	0.000%	0.001%	0.010%	0.007%
L	0.000%	0.004%	0.021%	0.000%	0.010%	0.013%	0.007%
J	0.001%	0.008%	0.031%	0.024%	0.036%	0.000%	0.066%
L	0.000%	0.005%	0.086%	0.216%	0.211%	0.190%	0.255%
C	0.000%	0.008%	0.079%	0.061%	0.044%	0.095%	0.041%
F	0.000%	0.031%	0.000%	0.047%	0.031%	0.035%	0.065%
I	0.000%	0.048%	0.094%	0.051%	0.056%	0.064%	0.065%
L	0.000%	0.066%	0.024%	0.004%	0.000%	0.006%	0.000%
Average	0.000%	0.022%	0.043%	0.050%	0.049%	0.051%	0.063%
S.E.M	0.000%	0.008%	0.013%	0.025%	0.024%	0.023%	0.029%
n	8	8	8	8	8	8	8

APPENDIX (continued)

***Cumulative Amount** (% applied dose)*

Sample	Time (h)						
	0.05	1	2	3.5	5	8	24
K	0.000%	0.008%	0.015%	0.015%	0.016%	0.025%	0.032%
L	0.000%	0.004%	0.025%	0.025%	0.035%	0.047%	0.054%
J	0.001%	0.009%	0.040%	0.064%	0.100%	0.100%	0.166%
L	0.000%	0.005%	0.092%	0.307%	0.519%	0.708%	0.963%
C	0.000%	0.008%	0.087%	0.149%	0.192%	0.287%	0.328%
F	0.000%	0.031%	0.031%	0.078%	0.109%	0.144%	0.209%
I	0.000%	0.048%	0.142%	0.193%	0.249%	0.313%	0.377%
L	0.000%	0.066%	0.091%	0.094%	0.094%	0.101%	0.101%
Average	0.000%	0.022%	0.065%	0.116%	0.164%	0.216%	0.279%
S.E.M	0.000%	0.008%	0.016%	0.035%	0.057%	0.079%	0.107%
n	8	8	8	8	8	8	8