Solubility and Stability of Delta-9-Tetrahydrocannabinol in Lipid Excipients

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INTRODUCTION

Delta-9-Tetrahydrocannabinol (THC) is one of the most effective antinociceptive agents used in the treatment of peripheral neuropathy. THC is highly lipophilic and susceptible to thermal and oxidative degradation. Identifying appropriate solvents in which THC is stable as well as adequately solubilized is crucial in developing various dosage forms. Lipid solvent systems are of utmost utility and relevance for formulating highly lipophilic drugs.

OBJECTIVES

- To identify appropriate solid and liquid lipid excipients for development of THC dosage forms based on their solubilizing property.
- To study the stability of THC in lipid excipients at different storage conditions.
- To evaluate the effect of butylated hydroxytoluene and ascorbyl palmitate on stability of THC in lipid excipients at different storage conditions.

MATERIAL AND METHODS

- Lipid vehicles listed in Table 1 and 2 were obtained from Gattefossé USA (Paramus, NJ). THC used for solubility studies were procured from Cayman Chemicals.
- The solubility of THC in 9 different solid lipid excipients was qualitatively determined using a differential scanning calorimeter (DSC).
- Different quantities (0, 250, 500, and 750 mg) of THC were taken into glass vials, and to these vials, excipients were added to make up the weight of the mixture to 1000 mg.
- Vials placed on hot plate-maintained at temperature slightly above the melting point of individual excipients for 15 to 20 min with constant stirring. Molten mixture transferred to DSC pans, sealed hermitically and placed for equilibration at room temperature for 24 h.
- DSC analysis of samples was performed over the temperature range of 20 to 200 °C at 20 °C/min heating rate.
- The solubility of THC in 19 different liquid lipid excipients was evaluated by the addition of excipients to tubes containing THC and vortexed for 15 min at room temperature.
- The samples were filtered and analyzed for THC content using HPLC.
- The stability of THC with and without antioxidants (butylated hydroxytoluene and ascorbyl palmitate) in the excipients were studied at 25 ± 2 °C and 4 ± 3 °C for 3 months.

RESULTS

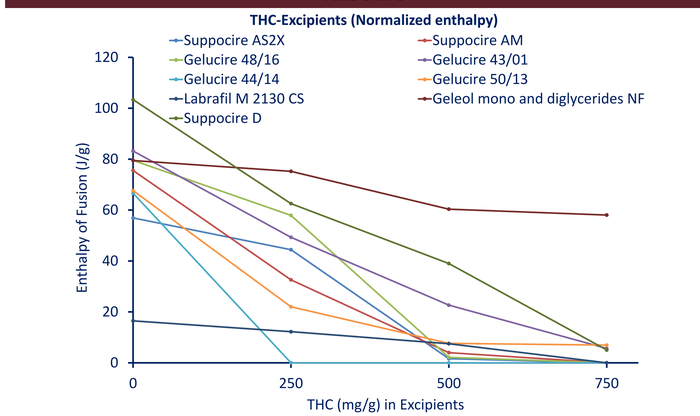

Figure 1. The Change in Enthalpy of Fusion (measured by DSC) with increasing THC concentrations in solid excipients.

Results

Table 1. The solubility of THC in solid lipid excipients

Excipients	THC Solubility in excipients (mg/g)
Suppocire® AS2X	>500
Suppocire®AM	>500
Suppocire® D	>750
Gelucire® 48-16	>500
Gelucire®43-01	>750
Gelucire® 44-14	>250
Gelucire® 50-13	>500
Labrafil®M 2130 CS	>750
Geleol™mono and diglycerides NF	>500

Table 2. The solubility of THC in liquid lipid excipients

Excipients	THC Solubility (mg/g) Mean ± SD (n=3)	THC Solubility (%) Mean ± SD (n=3)
Transcutol®HP	434 ± 1.96	43.4 ± 0.20
Refined Soybean Oil IV	>500	>50
Refined Sesame Oil IV	489 ± 6.95	48.9 ± 0.70
Refined Olive Oil IV	479 ± 4.29	47.9 ± 0.43
Plurol® Oleique CC 497	>500	>50
Plurol® Diisostearique	>500	>50
Peceol™	487 ± 2.96	48.7 ± 0.30
Maisine® CC	>500	>50
Lauroglycol™ FCC	477 ± 12.0	47.7 ± 1.20
Lauroglycol™ 90	470 ± 5.08	47.0 ± 0.51
Labrasol® ALF	422 ± 2.23	42.2 ± 0.22
Labrafil® M2125 CS	419 ± 2.76	41.9 ± 0.28
Labrafil® M1944 CS	454 ± 3.07	45.4 ± 0.31
Labrafac™ PG	>500	>50
Labrafac™ Lipophile WL	421 ± 3.38	42.1 ± 0.34
Capryol™ PGMC	485 ± 14.7	48.5 ± 1.47
Capryol™90	496 ± 5.21	49.6 ± 0.52
Labrafac™ MC 60	496 ± 5.09	49.6 ± 0.51

Table 3. The stability data of THC in lipid excipient at 25 °C ± 2 °C / 60% RH and 5 °C ± 3 °C with and without antioxidants for three-month (mean ± SD) n=3.

Lipid excipients	3 Month THC assay (%)			
	25 °C ± 2 °C / 60% RH		5 °C ± 3 °C	
	Without antioxidants	With antioxidants	Without antioxidants	With antioxidants
THC	69.7 ± 2.13	68.8 ± 1.57	80.8 ± 1.93	78.0 ± 0.23
Labrasol®	96.0 ± 2.10	97.2 ± 0.73	99.7 ± 1.37	99.4 ± 1.19
Capryol™ 90	94.9 ± 0.92	101 ± 2.27	96.8 ± 1.69	99.8 ± 1.62
Transcutol®HP	96.9 ± 2.66	99.5 ± 0.73	96.2 ± 1.67	99.5 ± 1.31
Labrafac™ Lipophile WL 1349	95.9 ± 0.31	98.9 ± 0.93	97.4 ± 1.06	96.7 ± 0.63
Labrafac™ MC 60	96.2 ± 3.32	97.7 ± 2.59	96.5 ± 2.25	98.0 ± 0.70
Maisine® CC	98.0 ± 1.23	98.4 ± 0.63	99.4 ± 0.75	99.6 ± 0.52
Peceol™	88.0 ± 1.94	95.5 ± 1.49	92.4 ± 1.58	88.3 ± 1.94
Refined sesame oil	81.6 ± 4.56	83.4 ± 0.73	98.9 ± 0.92	98.1 ± 1.34
Gelucire ®44/14	93.7 ± 1.79	97.6 ± 0.37	94.4 ± 1.06	98.7 ± 2.10
Geleol™ mono & diglycerides	88.1 ± 2.43	91.0 ± 0.73	87.6 ± 1.33	99.5 ± 2.04
Labrafil® M 2125 CS	96.3 ± 0.40	98.4 ± 0.50	96.9 ± 0.89	99.0 ± 0.65
Suppocire® CM	87.9 ± 4.64	91.0 ± 1.47	89.3 ± 0.76	99.3 ± 0.57

RESULTS AND CONCLUSION

- The results demonstrated that the liquid and solid lipid excipients used in the study could solubilize THC freely and mitigate the degradation of THC significantly.
- THC in its neat form was poorly stable but when dissolved in lipid-based excipients its stability improved significantly.
- THC in lipid excipients was more stable at 5 ± 3 °C compared to samples stored at 25 ± 2 °C.
- The antioxidants used in the excipients, further improved the stability of THC in excipients.
- These excipients offer safe options for further oral and topical formulation development of THC

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GATTEFOSSÉ

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