Limonene GP1/PG organogel as a vehicle in transdermal delivery of haloperidol

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Abstract
Penetration enhancers are a classical means for improving transdermal drug delivery (TDD). Enhancers permeate into the skin and reversibly decrease the barrier resistance. Basically, our aim is to formulate a transdermal gel containing an appropriate enhancer for a controlled drug release. Terpenes, namely limonene, linalool and cineole, in propylene glycol (PG) were first investigated in vitro for their capacity to enhance the percutaneous release of an anti-psychotic drug, haloperidol (HP). Relative to oxygenated linalool and cineole, hydrocarbon limonene was more effective as a skin enhancer; it increased human skin permeability and decreased lag time. Limonene was thus incorporated in an organogel comprised of gelator GP1 and PG. This skin-friendly gel in a transdermal patch could act as a long-acting formulation that delivers HP at a sustained percutaneous rate. The microscopic framework of the organogel is a branched network of interlocking fibres. Varying the gelator content modulates the fibre density and gel stiffness, and presents different degrees of resistance to drug diffusion on the vehicle side. Rheological and permeation studies demonstrated that an increase in gelator concentration increased gel moduli and decreased drug flux simultaneously. The rheology of the gel matrix influenced drug release rate in a manner described by several experimentally-derived correlations.

Keywords: Penetration enhancers; Transdermal; Terpenes; Haloperidol; Organogel; Rheology

1. Introduction
Transdermal drug delivery (TDD), the delivery of drugs across the skin, is gaining wide acceptance among patients (Finnin and Morgan, 1999). It is a viable administration route for potent, low molecular weight therapeutic agents susceptible to first-pass metabolism (Kalia and Guy, 2001). Advantages of TDD include non-invasiveness, prolonged drug levels in the blood stream, reduced side effects, improved bioavailability, better patient compliance and easy termination of drug administration (Barry, 2004; Gupta and Garg, 2002).

The skin is the most accessible organ of the human body and continues to be preferred site for the application of topical dosage forms (Gupta and Garg, 2002). Stratum corneum (SC), the outermost layer of the skin, is a remarkable transport barrier which effectively retards the diffusion of exogenous and endogenous moieties into and out of the host (Johnson et al., 1996). The continuous SC has been the usual target in TDD. Incorporation of chemical penetration enhancers into topical applications has been used since the sixties (Barry, 2004) to temporarily disrupt its elegant molecular structure (Johnson et al., 1996). Chemical enhancers intensify TDD via increased drug solubility in the donor formulation, increased partitioning into the SC, or disruptions of the intracellular proteins and intercellular lipids (Barry, 1991; Walker and Smith, 1996).

Terpenes were reported to promote percutaneous drug absorption (Yamane et al., 1995; Almirall et al., 1996; Cornwell and Barry, 1993). Terpenes are grouped according to the number of isoprene units and are further sub-divided into chemical classes of hydrocarbons, alcohols, oxides and ketones (Hashida and Yamashita, 1995). We will be assessing...
Fig. 1. Chemical structures of (a) linalool, (b) cineole, (c) limonene, (d) haloperidol and (e) dibutyllauroylglutamide (GP1).

terpenes—linalool, cineole and limonene (Fig. 1)—as potential penetration enhancers for a lipophilic drug.

Haloperidol (HP) (Fig. 1d) is the model drug in our study. HP is widely prescribed to treat acute and chronic psychosis. HP can be given up to a maximum oral dose of 200 mg/day in acute psychosis (Vaddi et al., 2002a). A transdermal organogel as a long-acting formulation would be appropriate for maintenance therapy. Also, the physiochemical properties of HP satisfy the general TDD design requirements (Samanta et al., 2003); HP has a low molar mass (375.9 Da) and is sufficiently lipophilic \( \log P = 3.36 \) to partition into the SC (Kalia and Guy, 2001).

With penetration enhancers, systemic TDD has established major footing (Barry, 2004). These chemicals dispersed in a suitable semisol vehicle enhance the amount of drug penetration (Gupta and Garg, 2002). A terpene in a viscoelastic organogel (Abdallah and Weiss, 2000) forms a simple transdermal system. Our organogel is composed primarily of gelator, dibutyllauroylglutamate commonly known as GP1 (Fig. 1e), and organic solvent, propylene glycol (PG). Both constituents are common ingredients in cosmetics and thus biocompatible with the skin (Schreiber, 2001; Vaddi et al., 2002b). The organogel accommodates hydrophobic HP, adheres better to the skin and may overcome poor patient compliance. Other features of this biomaterial are thermostressibility, a high degree of stability to moisture and temperature, and the capability of controlling drug release (Anand et al., 2001). Our objectives are to establish the role of a gel vehicle in TDD, the effect of terpene on gel rheology, and the correlation between drug permeation and gel rheology.

2. Materials and methods

2.1. Materials

Cineole, \((\pm)\)-limonene, \((\pm)\)-linalool, haloperidol, droperidol, propylene glycol, sodium dihydrogen phosphate monohydrate, phosphoric acid, \( \text{dl} \)-lactic acid and antibiotic antimycotic solution were obtained from Sigma-Aldrich. GP1, and HPLC grade methanol and acetonitrile were obtained from Kishimoto Sangyo, FisherChemicals and Tedia, respectively. Chemicals were of at least reagent grade. Milli-Q water (18 MΩ cm; Millipore, USA) was used in the preparation of aqueous solutions. All materials were used as received.

2.2. Drug assay

Haloperidol (HP) concentration was determined with a reversed phase high performance liquid chromatograph (HPLC) from Shimadzu, Japan. The stationary phase was SymmetryShield C18 column (3.5 μm, 3 mm × 100 mm; Waters, USA). The mobile phase was a 70:30 volume ratio of 0.05 M phosphate buffer (adjusted to pH 3 with phosphoric acid) and acetonitrile. Mobile phase flowrate was set at 0.7 mL/min. A 100-μL sample was injected and detected at a wavelength of 254 nm. Droperidol (DP) was used as an internal standard. Under these conditions, retention times of HP and DP were 3.1 and 1.7 min, respectively. Standard solutions of HP (0.05–2 g/mL) with DP (0.2 g/mL) were prepared in 0.03% \( \text{v/v} \) lactic acid (Vaddi et al., 2001). As HP is slightly basic \( (pK_a = 8.3) \), the presence of lactic acid prevents drug precipitation. The internal calibration curve of HP concentration against HP to DP peak area ratio was linear \( (r^2 = 0.999) \). Limits of detection and quantitation of this drug
assay were 0.0067 and 0.0224 µg/mL, respectively. Coefficients of variation of intra- and inter-day measurements were < 5%.

2.3. Preparation of human epidermal membrane

Abdominal skins of 45-year-old Eurasian female and 40-year-old Chinese female were obtained with patients’ consent from the Singapore General Hospital, Singapore. Full-thickness skin with epidermis facing downwards was immersed in water of 60°C for 2 min (Vaddi et al., 2002a). After which, the epidermis was carefully peeled off and stored at −80°C. Prior to permeation studies, the epidermis was thawed and hydrated in an aqueous 0.9% w/v sodium chloride and 1% v/v antibiotic antimycotic solution under room conditions for 12 h.

2.4. Gel preparation

Organogels containing 2–10% w/v GP1, 5% v/v limonene and 2.5 mg/mL HP in PG were prepared. Measured amounts of GP1, limonene and PG were mixed and placed in an oven at 120°C for fast dissolution (Sawant and Liu, 2002; Liu and Sawant, 2002). The oven temperature was subsequently lowered to 90°C. HP was then added into the liquid mixture and this was kept at 90°C for another 30 min. The resulting drug-gel solution was cooled naturally to room temperature, and a white gel was formed. As for the drug-free gel, the intermediate temperature-lowering step was omitted. The saturation solubility of HP in the donor compartment of the diffusion cell. One millilitre of drug solution (HP in PG with or without terpene) was placed in a heater/stirrer block (PermeGear, USA) and maintained isothermally at 37°C. The entire receptor solution was replaced with an equivalent volume.

2.5. Permeation studies

Amber-glassed Franz diffusion cells (PermeGear, USA) were used in the permeation studies. Epidermis of 1.5 cm × 1.5 cm, with stratum corneum (SC) side up, was mounted between the donor and receptor compartments of the diffusion cell. One millilitre of drug solution (HP in PG with or without terpene) or 1 g of drug-loaded gel was placed into the donor cell. 0.03% v/v lactic acid and 1% v/v antimycotic solution constituted the receptor fluid (Vaddi et al., 2002a). To minimize evaporation, the donor compartment and sampling port were covered with paraffin and aluminum foil. Assembled diffusion cells in triplicate were placed in a heater/stirrer block (PermeGear, USA) and maintained isothermally at 37°C. The entire receptor solution was drawn periodically from the sampling port for HPLC analysis and was replaced with an equivalent volume.

2.6. Permeation parameters

Permeation of drug molecules across the epidermis can be described by Fick’s 2nd law of diffusion, Eq. (2.1) (Crank, 1975).

\[ Q = \frac{A}{L^2} \left[ \frac{D}{6t} \sum_{n=1}^{\infty} \frac{(-1)^n}{n^2} e^{-D(n^2/4L^2)t} \right] \]  

The plasma concentration \( \frac{Q}{L} \) over time \( t \) plot. The gradient and x-intercept of the linear portion of the plot yield steady-state flux \( J_{ss} \) and lag time \( \tau_l \) accordingly. \( J_{ss} \), over drug concentration \( C_o \), in the donor solution gives permeability \( \frac{KD}{L} \) (Vaddi et al., 2001; Wang et al., 2008).

\[ KD = \frac{J_{ss}}{C_o} \]  

Diffusion parameter \( D/L^2 \) reflects the mobility of the drug solute in the skin, and partition parameter \( KL \) reflects the distribution of the drug between the skin and the donor solution. Enhancement index \( EI \), a ratio of permeabilities in the presence and absence of terpenes, measures the enhancement in drug penetration (Vaddi et al., 2002b).

\[ D = \frac{1}{6n} \]  

\[ KL = \frac{KD/L}{D/L^2} \]  

\[ EI = \frac{(KD/L)_{\text{amine/PG}}}{(KD/L)_{\text{PG}}} \]  

The plasma concentration \( P_e \) of HP delivered via a transdermal patch is estimated from Eq. (2.6). Patch area \( T_a \) of 16 cm² and HP plasma clearance \( C_L \) of 36.5 L/h are assumed (Almirall et al., 1996; Vaddi et al., 2002b).

\[ P_e = \frac{J_{ss} \times T_a}{C_L} \]  

2.7. Gel rheology

Rheology of organogel was characterized on advanced rheometric expansion system (ARES) from Rheometric Scientific, USA. A gel sample placed between an upper plate fixture of 25 mm dia. and a Peltier surface was subjected to sinusoidal oscillations. A gap of 1 mm was maintained between the plate and the Peltier surface. In a dynamic strain sweep test conducted at 1 Hz and 32°C, elastic modulus \( G’ \) and viscous modulus \( G’’ \) versus strain \( \gamma \) profiles were generated as \( \gamma \) increased from 0.01 to 10% in a log sweep mode. \( G’ \) and \( G’’ \) are obtained from the initial linear viscoelastic region. The strain level where \( G’ \) begins to drop is defined as critical strain \( \gamma_c \), which is the onset of gel fibre rupture.

2.8. Statistical analysis

Statistical analysis was performed using Minitab 13.32. One-way analysis of variance (ANOVA) with Tukey’s comparison ascertainment the effects of terpene type and gelator concentration on the permeation and rheological parameters. Two-sample t-test compared two groups of data, for example, a treated group versus a control. Changes were significant if \( P < 0.05 \).
3. Results and discussion

3.1. Human skin permeation of HP in terpene/PG

Fig. 2 and Table 1 show the cumulative permeation plots and permeation parameters of haloperidol (HP) in PG with and without terpenes. Terpene concentration C_{Terp} and HP concentration C_{HP} in the donor vehicle were fixed at 5% w/v and 2.5 mg/mL, respectively. In order to elucidate the action of terpenes on drug permeation, abdominal skin from a single donor (45-year-old Eurasian female) was used so as to eliminate inter- and intra-individual differences. With respect to the control, hydrocarbon limonene greatly improved permeability KD/L×cm/h from 14.1 to 9.2 h (P < 0.05). On the other hand, oxygenated linalool and cineole produced a moderate enhancement and extended t_{L}. The latter may be due to the conditioning of the epidermis in the early stage of diffusion (Vaddi et al., 2003). On the whole, the three terpenes facilitated percutaneous drug penetration by increasing partition parameter KL, i.e. a higher drug solubility in the skin.

Vaddi et al. (2002b, 2003) had reported the enhancing effect of several oxygenated terpenes (alcohols and oxides) on the permeation of HP through human skin. Here, we have shown hydrocarbon limonene to be a potential chemical enhancer and a more effective one for HP in comparison to oxygenated linalool and cineole. The effectiveness of hydrocarbon limonene had also been demonstrated for other lipophilic drugs such as ketoprofen, indomethacin and estradiol (Gupta and Garg, 2002; Williams and Barry, 2004). In addition, limonene has a low skin irritancy and when administered with a pretreatment method, it allows a reversible change in the skin structure (Hashida and Yamashita, 1995).

The great enhancement by limonene suggests that there are possibly multiple mechanisms that could have resulted in a more permeable intercellular pathway for HP. They include an increased HP solubility within the skin, partial extraction of SC lipids (Krishnaiah et al., 2002), phase separation within the SC lipid lamellae (Moghi et al., 1997) and limonene–PG synergy (Barry, 1991).

The therapeutic HP plasma concentration ranges from 0.8 to 5.15 ng/mL (Almirall et al., 1996; Vaddi et al., 2002b). Only limonene was able to elicit an in vitro HP flux J_{ss} that corresponded to a predicted plasma level P_{ss} within the therapeutic window. We would expect P_{ss} to approximate the in vivo plasma level, as good in vitro–in vivo correlation was found for hydrophobic permeants (Valiveti et al., 2004).

3.2. Human skin permeation of HP in limonene GP1/PG organogel

We have shown limonene to be a suitable chemical enhancer and therefore it was incorporated into GP1/PG organogel. Limonene concentration C_{limo} and HP were fixed at 5% w/v and 2.5 mg/mL, respectively. Gelator concentration C_{GP1} was varied from 2 to 10% w/v so as to determine the effect of C_{GP1} on HP permeation. Fig. 3 illustrates the permeation profiles and Table 2 lists the permeation parameters of HP in the prepared gels. In this permeation study, abdominal skin was obtained from a 40-year-old Chinese female, unlike the previous one. Interestingly, we have shown HP = 2.5 mg/mL, C_{HP} = 5% v/v. Data was expressed as mean ± S.D. (n = 3).

Table 1

<table>
<thead>
<tr>
<th>Terpene/PG</th>
<th>Δt (h)</th>
<th>D_{ss} (x10^{-6} cm/h)</th>
<th>KL (x10^{-4} cm/h)</th>
<th>KD/L (x10^{-4} cm/h)</th>
<th>J_{ss} (x10^{-6} mg/cm²/h)</th>
<th>EII</th>
<th>P_{ss} (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PG (control)</td>
<td>14.08 ± 0.09</td>
<td>1.19 ± 0.07</td>
<td>0.74 ± 0.34</td>
<td>0.99 ± 0.43</td>
<td>0.20 ± 0.10</td>
<td>–</td>
<td>0.009</td>
</tr>
<tr>
<td>Linalool/PG</td>
<td>23.82 ± 4.48</td>
<td>0.72 ± 0.15</td>
<td>10.15 ± 5.18</td>
<td>7.20 ± 3.36</td>
<td>1.66 ± 0.78</td>
<td>8.05</td>
<td>0.729</td>
</tr>
<tr>
<td>Limonene/PG</td>
<td>9.23 ± 1.52</td>
<td>1.84 ± 0.33</td>
<td>13.41 ± 4.75</td>
<td>23.72 ± 5.24</td>
<td>6.35 ± 1.45</td>
<td>26.52</td>
<td>2.869</td>
</tr>
<tr>
<td>Cineole/PG</td>
<td>21.11 ± 2.09</td>
<td>0.79 ± 0.08</td>
<td>7.66 ± 5.15</td>
<td>6.15 ± 4.57</td>
<td>1.62 ± 1.15</td>
<td>6.88</td>
<td>0.708</td>
</tr>
</tbody>
</table>

C_{HP} = 2.5 mg/mL, C_{Terp} = 5% v/v. Data was expressed as mean ± S.D. (n = 3).
Table 2

<table>
<thead>
<tr>
<th>C_{GP1} (% w/v)</th>
<th>t_L (h)</th>
<th>DL (×10^{-3} h⁻¹)</th>
<th>KL (×10^{-3} cm/h)</th>
<th>KD/L (×10^{-4} cm/h)</th>
<th>J_{ss} (×10^{-3} mg/cm² h)</th>
<th>P_{ss} (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (control)</td>
<td>9.04 ± 1.70</td>
<td>1.89 ± 0.35</td>
<td>14.13 ± 1.40</td>
<td>26.37 ± 2.71</td>
<td>6.59 ± 0.68</td>
<td>2.889</td>
</tr>
<tr>
<td>2</td>
<td>12.80 ± 1.17</td>
<td>1.31 ± 0.12</td>
<td>15.39 ± 2.16</td>
<td>20.00 ± 1.40</td>
<td>5.00 ± 0.35</td>
<td>2.192</td>
</tr>
<tr>
<td>4</td>
<td>9.75 ± 1.06</td>
<td>1.72 ± 0.18</td>
<td>9.60 ± 1.79</td>
<td>16.52 ± 2.33</td>
<td>4.13 ± 0.58</td>
<td>1.811</td>
</tr>
<tr>
<td>6</td>
<td>10.18 ± 1.60</td>
<td>1.66 ± 0.24</td>
<td>7.01 ± 0.81</td>
<td>11.72 ± 2.64</td>
<td>2.93 ± 0.66</td>
<td>1.285</td>
</tr>
<tr>
<td>8</td>
<td>11.92 ± 2.15</td>
<td>1.43 ± 0.29</td>
<td>7.43 ± 2.74</td>
<td>10.12 ± 2.27</td>
<td>2.53 ± 0.57</td>
<td>1.109</td>
</tr>
<tr>
<td>10</td>
<td>10.75 ± 2.36</td>
<td>1.60 ± 0.31</td>
<td>7.45 ± 1.16</td>
<td>11.76 ± 2.17</td>
<td>2.94 ± 0.54</td>
<td>1.284</td>
</tr>
</tbody>
</table>

C_{HP} = 2.5 mg/mL, C_{Limo} = 5% v/v, C_{GP1} = 0–10% w/v. Data was expressed as mean ± S.D. (n = 3).

there were no significant inter-individual differences (P > 0.05) between the permeation parameters of “control” in Table 2 and “Limonene/PG” in Table 1.

Over the tested C_{GP1} range, t_L and diffusion parameter D/L² were essentially constant (P > 0.05) whereas KL, KD/L, and J_{ss} were significantly reduced (P < 0.05). The near constant t_L and reduced KL with C_{GP1} indicate that GP1 does not interfere with the action of limonene, and that the gel mesh-like structure (Fig. 4) effectively retards HP diffusion on the vehicle side which decreases HP concentration at the gel–skin interface. The other consequence of an increasing C_{GP1} was that P_{ss} approached the lower therapeutic limit of 0.8 ng/mL. Nevertheless, the gel formulation would still be appropriate for maintenance therapy.

3.3. Rheology of organogel

Fig. 5a and b illustrate the elastic G′ and viscous G″ moduli of plain, limonene and HP–limonene gels against gelator concentration C_{GP1}. Plain gel (control) was composed of GP1 and PG. Limonene gel contained 5% v/v limonene in plain gel and HP–limonene gel contained 2.5 mg/mL HP in limonene gel. Rheology was conducted at 32 °C to mimic the normal skin surface temperature. G′ and G″ of plain gel increased in a monotonic manner with C_{GP1}, while the moduli of limonene gel increased rapidly before reaching a plateau. Enhanced gel rigidity was due to the presence of HP.
to a more compact fibrous network (Sawant and Liu, 2002; Liu and Sawant, 2001). At each GP1, G′ and G″ of limonene were greater than those of plain gel (P<0.05), except at 10% w/v GP1. The marked increases in gel moduli induced by limonene imply an enhanced gel physical stability. The presence of limonene could achieve a greater stability at the same GP1, or maintain a comparable stability (to the control) at a lower GP1.

As shown in Fig. 5c, there was an inverse relationship between critical strain γo and CGP1. γo can be taken as a measure of gel brittleness; a lower γo indicates a more brittle gel. γo of the organogels generally decreased with CGP1 (P<0.05). At the same CGP1, γo of limonene gel was lower relative to the control (P<0.05, except at 10% w/v GP1). There was a trade-off in mechanical properties where greater G′ and G″ were accompanied by a lower γo. The further addition of HP into limonene gel produced no appreciable changes in G′, G″ and γo.

We have tried to correlate gel rheology and gel microstructure, and to observe the effects of CGP1 and Cgw on the latter visually. The gel microstructure was examined with scanning electron microscopy (SEM). Prior to SEM, the gel sample was pretreated with supercritical CO2 fluid extraction (SFE) and the resulting residue was coated with a layer of platinum (Sawant and Liu, 2002). Micrographs (not included here) of an intact gel network were not readily obtained. The analysis was further complicated by the presence of several morphologies in a single sample—fibrous mesh, sintered masses and axially-aligned fibres. The high operating pressure of SFE (100 bar) and the high solvating power of supercritical CO2 could have destabilized the porous scaffold, resulting in a poor rheology-microstructure correlation. Nevertheless, SEM identified characteristic structural features of GP1-based organogels such as nano-sized fibrils, and a branched, three-dimensional network (Fig. 4).

### 3.4. Permeability–rheology correlation of HP–limonene organogel

Fig. 6a and b show the permeability and rheology of HP-limonene organogel. The direct influence of gel rheology on HP permeation was well illustrated. At CGP1 ≤ 6% w/v, a higher G′ or G″ and a lower γo decreased permeability KD/L. At CGP1 > 6% w/v, a constant rheology (P>0.05) led to no further reduction in KD/L. These rheological descriptors are possible predictors of the percutaneous delivery of HP dispersed in the organogel. Gallagher et al. also obtained a similar decreasing permeation of ketoprofen across nylon membrane with Cabosil content. Apparently, the decrease was in part due to a higher gel viscosity at a higher Cabosil content (Gallagher et al., 2003).

Fig. 6 would not be applicable for other skin samples. To circumvent inconsistencies associated with different skin models (Bond and Barry, 1988) and skin obtained from different anatomical sites (Barel and Clarys, 1995), a gel resistance–rheology relationship was hypothesized. In TDD with organogel as a drug vehicle, the total resistance Rf to drug transport (reciprocal of KD/L) is contributed by two components in series, the skin and the gel matrix. At CGP1 = 0% w/v, resistance is dictated by the skin and resistance due to limonene/PG solution is assumed to be negligible. A gel introduces an added resistance in addition to that offered by the skin (Fig. 7). As such, Rf is taken to be the sum of skin resistance Rskin and gel resistance Rgel.

Table 3 shows a substantial contribution of Rgel towards Rf, and the former seems to vary in some defined ways with G′, G″ and γo. Through regression analyses and mathematical manipulations, Rgel can be expressed as functions of gel rheology, independent of the skin. Eqs. (3.1) and (3.2) are linear relationships between the logarithm of Rgel and gel moduli (G′, G″). Eq. (3.3) is a multiple regressed correlation which encompasses

![Fig. 7. A hypothesized resistance model in the transdermal delivery of HP in limonene GP1/PG organogel.](image)
the three rheological descriptors and qualitatively summarizes their general influences on $R_g\text{gel}$. These empirical correlations, together with experimentally-obtained skin resistance and gel rheology, provide an estimate of HP flux at a specific $C_{GP1}$ or conversely, an estimate of $C_{GP1}$ that will deliver a specific HP flux. This iterative scheme reduces the number of permeation experiments to be performed and avoids a rigorous process of trial and error. Hence, the organogel could function both as a drug reservoir and a rate-controlling matrix in a transdermal patch.

\[
\log R_g\text{gel} = 2.06 + 1.25 \times 10^{-6} \log G', \quad r^2 = 0.953
\]  

4. Conclusion

Limonene was the selected chemical enhancer as it increased skin permeability, shortened lag time and facilitated therapeutic HP delivery in vitro. The addition of limonene into GP1/PG organogel increased gel moduli and this could indicate an enhanced gel physical stability. Organogel as a drug vehicle organogel increased gel moduli and this could indicate an enhanced gel physical stability. Organogel as a drug vehicle.

References


