**RESEARCH ARTICLE**

**Rapidly absorbed orodispersible tablet containing molecularly dispersed felodipine for management of hypertensive crisis: Development, optimization and in vitro/in vivo studies**

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**Abstract**
A liquisolid orodispersible tablet of felodipine, a BCS Class II drug, was developed to improve drug dissolution and absorption through the buccal mucosa for management of hypertensive crisis. A 24 full-factorial design was applied to optimize felodipine liquisolid systems (FLSS) having acceptable flow properties and possessing enhanced drug dissolution rates. Four formulation variables; The liquid type, X1 (PG or PEG), drug concentration, X2 (10% and 20%), type of coat, X3 (Aerosil® and Aeroperl®) and excipients ratio, X4 (10 and 20) were included in the design. The systems were assessed for dissolution and flow properties. Following optimization, the formulation components (X1, X2, X3, and X4) were PEG, 10%, Aerosil® and 20, respectively. The optimized FLS was compressed into felodipine liquisolid orodispersible tablet using Prosolv® as carrier material (FLDT-2). The in vitro and in vivo disintegration times of FLDT-2 were 9 and 7 s, respectively. The in vivo pharmacokinetic study using human volunteers showed a significant increase in dissolution and absorption rates of the formulation of FLDT-2 compared to soft gelatin capsules filled with felodipine solution in PEG under the same conditions. Our results proposed that the optimized FLDT formulation could be promising to manage hypertensive crisis.

**Keywords:** Felodipine, optimization, orodispersible tablet, full-factorial design, liquisolid

**Introduction**
Felodipine is a calcium channel blocker from the class of dihydropyridines. It is widely used due to its selective vasodilator effect in cardiovascular disorders primarily arterial hypertension and it dilates vessels without effects on cardiac contractility.[1–3] It provides smooth plasma concentrations and stable blood pressure reduction with little or no effects on heart rate.[3] There was no indication that felodipine treatment increases the total mortality or the incidence of cardiovascular events. Thus felodipine is generally safe for treatment of hypertension and maintains the quality of life in the treated hypertensive patients.[4] Felodipine was proposed as a candidate drug in emergency and treatment of hypertensive crisis.[5] It was found that intravenous felodipine infusion was equally effective as nifedipine infusion in cases of emergency and hypertensive crisis where they lowered the blood pressure in more than 90% of the patients. Felodipine is superior to nifedipine since it does not suffer from light sensitivity. Therefore, orodispersible tablets (ODTs) of felodipine may provide the rapid onset of action required for emergency. However, Felodipine is a model drug of the Biopharmaceutical Classification System (BCS) class II, Which features poor solubility, high permeability. The rate of absorption of class II drugs such as felodipine is often controlled by its solubility and dissolution rate in the fluid present at the absorption site. Various techniques have been employed to enhance the dissolution rate and absorption efficiency of water-insoluble drug such as micronization, co-grinding, formulation of inclusion complexes, solubilization by surfactants, solid dispersions, solid solutions, hydrotrophy and cosolvency.[6–8]

The most promising technique for promoting dissolution is the formation of liquisolid compact that promotes dissolution rate of water-insoluble drugs to a greater extent and also enhances the drug flow property.

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*Received 08 November 2011; accepted 10 January 2012*
Liquisolid compacts of poorly soluble drugs containing a drug molecularly dispersed in a solubilizing vehicle show enhanced drug dissolution due to an increased surface area of drug, an increased aqueous solubility of the drug, and an improved wettability of the drug particles. Accordingly, this improved drug dissolution may result in higher drug absorption and thus, an improved oral bioavailability.[9–13]

The concept of liquisolid compacts can be used to formulate liquid medications such as liquid drugs and suspensions or suspensions of water-insoluble solid drugs carried in suitable nonvolatile solvent systems into acceptably flowing and compressible powders. Simple blending of such liquid medications with selected powder excipients referred as the carrier (cellulose) and coating materials (silicates), can yield dry-looking, non-adherent, free-flowing, and readily compressible powders.[14–17]

Literature lacks any data about the application of liquisolid technique for development of felodipine liquisolid orodispersible tablet (FLODT) useful for management of hypertension crisis. The developed FLODT with enhanced solubility and dissolution hastens the absorption of felodipine and avoids its hepatic first pass metabolism through the partial absorption from buccal mucosa and esophagus. Thus, the aim of this study was the formulation and optimization of liquisolid systems that contain molecularly dispersed felodipine and possess enhanced dissolution and absorption rates. The liquisolid systems that showed acceptable flowability were then compressed into FLODT. Furthermore felodipine pharmacokinetics was studied after buccal administration of the optimized FLODT to human volunteers compared to a felodipine solution in PEG filled in soft capsule (felodipine soft capsule).

Materials

Felodipine was kindly obtained from Alkan Pharmaceutical Industries (Cairo, Egypt). Propylene glycol, polyethylene glycol 400, Polysorbate 80 were obtained from El-Nasr pharmaceutical chemicals company (Cairo, Egypt). Prosolv® SMCC 90 and Vivapur® PH 102 (MCC PH 102) were kindly provided by RJS (Rosenberg, Germany). Aerosil® 200 pharma (granulated silicon dioxide) and Aeroperl® 300 pharma (granulated silicon dioxide) were obtained from Degussa (Hanau-Wolfgang, Germany). Crospovidone and Aspartame were purchased from Sigma, (St. Louis, USA). Lemon flavor was kindly supplied by chemical industry development (CID), (Egypt). The internal standard Solifenacin succinate was kindly supplied by DELTA Pharma (Egypt). Acetonitrile and methanol were from Sigma Aldrich (St. Louis, USA). All other chemicals were of analytical grade.

Methods

Preliminary screening of liquid vehicle and liquid load factor range appropriate for formulating felodipine liquisolid systems

5 mg felodipine was dispersed in the liquid vehicles (propylene glycol (PG), polyethylene glycol 400 (PEG) and polysorbate 80) in glass vial. The mixture was heated to 60°C with constant stirring. The dispersion was then sonicated for 15 min until a homogenous mixture was formed. The liquid medication was then mixed with the calculated amount of the carrier material (MCC® PH 102) in a mortar using pestle. The coating material (Aeroperl®) was then added to the mixture with gentle mixing. The mixture of carrier and coating material (excipient ratio) was set at a ratio of 20:1. Finally, each liquisolid powder was blended with 10% w/w of a disintegrating agent (Crospovidone®). Depending on the concentration of drug dispersion and the amount of carrier material, different liquid load factors (ranged from 0.125 to 0.23) were employed in the liquisolid systems. The composition of these liquisolid systems is shown in Table 1. The flow properties of the liquisolid systems were estimated by determining Carr’s index, and Hausner’s ratio. The Bulk density and Tap densities were determined for the calculation of Hausner’s ratio and Carr’s Index.[18,19]

Formulation optimization of felodipine liquisolid systems (FLSs)

In order to produce dry-looking, non-adherent, free-flowing and readily compressible liquisolid powders possessing optimum drug dissolution, a 24 full-factorial design was employed to evaluate the individual and combined effects of four formulation variables on felodipine dissolution rate. In this design, four factors are evaluated, each at two levels, and experimental trials were performed at all sixteen possible combinations. The liquid type, X1 (PG or PEG), drug concentration, X2 (10%
In vitro dissolution of felodipine from the prepared liquisolid systems in distilled water
In vitro dissolution of FLSs in distilled water were performed to study the extent of drug dissolution enhancement. The dissolution of felodipine from its liquisolid systems was performed in 500 mL distilled water maintained at 37 ± 0.5°C using the USP Dissolution Tester Apparatus II (VK 700, Vankel, USA), at a rotation speed of 50 rpm. Aliquots from the dissolution medium were withdrawn at 5, 10, 15, 20, 30, 45 and 60 min time intervals. The withdrawn samples were then centrifuged at 5000 rpm for 10 min and analyzed for felodipine content by measuring the absorbance at λ_{max} 363.6 nm using distilled water as blank. A similar volume of distilled water was added to the dissolution medium in order to maintain a constant volume in the dissolution vessel. The cumulative amount of felodipine dissolved from each liquisolid system after 30 min (Q_{30}) was used for assessment of drug dissolution.

Compression of the optimized FLSs into orodispersible tablets
The optimized FLSs were mixed with 6 mg lemon flavour and 3 mg aspartame and then compressed into 11 mm ODTs using a single punch machine. Batches of 200 biconvex tablets (310 mg each), containing 5 mg of felodipine per tablet, were prepared and exposed to further investigation.

Evaluation of the optimized felodipine liquisolid orodispersible tablets (FLODTs)
Physical characterization
FLODTs were evaluated by carrying out tests for weight variation, friability, hardness, disintegration, dissolution, and content uniformity. All the tests were carried out in triplicate and according to the compendial specifications. The in vitro disintegration test was carried out on six tablets in distilled water at 37 ± 2°C using the USP disintegration apparatus (Logan instruments incorporation, NJ, USA).

Determination of wetting time and water absorption ratio
Wetting time and water absorption ratio of FLODTs was determined by placing five circular tissue papers in a
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The in vivo recorded disintegration time (felt that the tablet had disappeared in their mouths was until the volunteers was noted as the wetting time. These measurements were carried out in replicates of three. Wetting time was recorded using a stopwatch.

The weight of the tablet prior to placement in the petri dish was noted utilizing a Shimadzu digital balance (Japan). The wetted tablet was removed and reweighed. Water absorption ratio, , was then determined according to the following equation.

\[ R = 100 \times \frac{W_a - W_b}{W_b} \]

Where and were tablet weights before and after water absorption, respectively.

**In vitro dissolution**

The in vitro dissolution of felodipine from FLODTs was performed in 500 mL 0.5% SLS solution maintained at 37 ± 0.5°C using the USP Dissolution Tester Apparatus II, at a rotation speed of 50 rpm as previously mentioned.

**In vivo disintegration time**

In vivo disintegration time of FLODTs was determined by placing ODT into the mouth of two healthy males adult volunteers without water. The time until the volunteers felt that the tablet had disappeared in their mouths was recorded as in vivo disintegration time (n = 3).

**Pharmacokinetic study in healthy human volunteers**

**Study design and subjects**

The study was carried out to compare the pharmacokinetics of felodipine from the optimized FLODT-2 to a soft capsule filled with felodipine solution in PEG. A singledose, two-period randomized cross-over design was adopted under fasting condition. Four healthy adult male volunteers participated in this comparative study (weight 65–80 kg, age between 25 and 35 years, and height from 167 to 185 cm), and all are nonsmokers. The biochemical examination of the volunteers revealed normal kidney and liver functions. The nature and the purpose of the study were fully explained to them. None of the volunteers were on any drug treatment one week before the participation in the study. An informed written consent was obtained from each volunteer. The in vivo study protocol was reviewed and approved by the research ethics committee at the Faculty of Pharmacy, Cairo University, Egypt. The protocol complies with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for humans.

The study was performed on two periods. Period I, half the number of volunteers (group 1) received the optimized FLODT-2 in their buccal cavities (treatment A) and the other half (group 2) swallowed one felodipine soft capsule (treatment B). Both treatments were administered after 12-h overnight fasting. Food and drink (other than water, which was allowed after 2 h) were not allowed until 4 h after dosing, and then a standard breakfast and lunch were given to all volunteers according to a time schedule. A washout period of 1 week separated the periods. In period II, group 1 received treatment B and group 2 received treatment A.

**Sample collection**

The study was supervised by a physician who was also responsible for the volunteers’ safety and collection of samples during the study. Blood samples (~5 mL), for felodipine analysis were drawn into evacuated heparinized glass tubes through an indwelling cannula at the following sampling times: 0 min (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 5, 8 and 24 h after administration of each treatment. Blood samples were centrifuged at 3500 rpm for 10 min at 4°C; plasma was transferred directly into 5 mL plastic tubes and stored frozen at −20°C pending drug analysis.

**Sample preparation**

All frozen human plasma samples were thawed at ambient temperature. Human plasma samples (1 mL) were placed in 7 mL glass tubes, and 50 μL of IS solution was added to each and vortexed for 30 s. Two mL Methyl-t-butyl-ether was then added, and samples were then vortexed for 1 min. The tubes were then centrifuged for 15 min at 3000 rpm. The upper organic phases were then transferred to clean glass tubes, filtered through 0.45 μm Millipore filter and evaporated to dryness using centrifugal vacuum concentrator (Eppendorf, Germany) at 40°C. Dry residues were then reconstituted with 100 μL of mobile phase and 20 μL was injected using the autosampler.

**LC–MS/MS assay of felodipine**

The quantitative determination of felodipine in human plasma was performed by a sensitive and selective liquid chromatographic method coupled with electrospray ionization tandem mass spectrometry (LC–MS/MS) procedure described by Kim et al. The mobile phase was composed of a mixture of acetonitrile and ammonium acetate (80:20, v/v). Solifenacin succinate was used as internal standard (IS).

**Pharmacokinetic and statistical analysis**

Plasma concentration-time data of felodipine was analyzed for each subject by non-compartmental pharmacokinetic models using computer program, Kinetics® (version 5, Thermo Fisher Scientific, NY, USA). The was calculated as 0.693/K. The maximum drug concentration (ng/mL) and the time to reach (h) were obtained from the individual plasma concentration-time curves. The area under the curve (ng h/mL) was determined as the area under the plasma concentration-time curve up to the last measured sampling
time and calculated by the linear trapezoidal rule. The area under the curve from zero to infinity \( \text{AUC}_{0-\infty} \) (ng h/mL) was calculated as \( \text{AUC}_{0-\infty} = \text{AUC}_{0-24} + C_t/K \) where \( C_t \) is the last measured concentration at the time \( t \).

The pharmacokinetic parameters, \( C_{max} \), \( t_{1/2} \), \( \text{AUC}_{0-24} \), and \( \text{AUC}_{0-\infty} \) were compared between treatments A and B with ANOVA test for the untransformed data. The non-parametric Signed Rank Test (Mann–Whitney’s test) was used to compare the medians of \( t_{max} \) for treatments A and B using the software Minitab®. The level of significance was \( \alpha = 0.05 \). A \( p \) value of \( \leq 0.05 \) was considered statistically significant.

**Results and discussions**

**Preliminary screening of liquid vehicle and liquid load factor range appropriate for formulating felodipine liquisolid systems**

Several liquisolid systems were preliminary prepared to select the type of liquid vehicle, drug concentration and the range of load factors (L\(_f\)) to be used in optimization of liquisolid systems. These preliminary liquisolid systems were evaluated by determination of their flow properties through measurement of Carr’s index and Hausner’s ratio (Table 1). Liquisolid systems prepared by polysorbate 80 were characterized by poor flow as indicated by the higher values of HR and CI (1.43 and 30.2, respectively) (Table 1). Thus, it was excluded from further studies. An acceptably flowing and compressible liquisolid system can be prepared only if a maximum liquid load on the carrier material is not exceeded; such a characteristic amount of liquid is termed the liquid load factor (L\(_f\)) and defined as the ratio of the weight of liquid medication (W) over the weight of the carrier powder (Q) in the system.\(^{24}\) It is obvious that decreasing the liquid load factors (L\(_f\)), enhances the powder flow. A reasonable flow was achieved within the whole range of liquid load factors (L\(_f\)) between 0.125 and 0.23, this is in agreement with what was stated in literature that it is hard to prepare formulation with good flowability and compactability when loading factor is above 0.25.\(^{14,15,25}\) Therefore, PEG and PG were used as liquid vehicles with a load factor less than 0.25.

**Formulation optimization of felodipine liquisolid systems (FLSs)**

Based on the results of preliminary screenings, the appropriate liquid vehicles (PG and PEG) and liquid load factor (L\(_f\)) lower than 0.25 were selected to formulate FLSs having optimum flow as well as dissolution properties. In order to rapidly obtain the optimal FLSs, a 2\(^4\) factorial design was applied in this study. The liquid type (PG and PEG) (X\(_1\)), drug concentration in liquid vehicle (10% and 20%) (X\(_2\)), type of coat (Aerosil and Aeroperl) (X\(_3\)) and excipient ratio (10 and 20) (X\(_4\)) were chosen as formulation variables. The cumulative amount of felodipine dissolved in water in 30 min (Q\(_{30}\)) was selected as response variable. The flow properties and Q\(_{30}\) of FLSs are summarized in Table 2. Constant weight of MCC PH 102 (210 mg) was used as a carrier giving L\(_f\) 0.119 or 0.238 (lower than 0.25), based on weight of liquid medication. Two felodipine concentrations in liquid vehicles were used. The lower concentration (10%, w/w) gave a molecular solution of felodipine while a molecular suspension was obtained by the higher felodipine concentration (20%, w/w). Aeroperl® is a granulated highly pure colloidal silicon dioxide prepared to be used in pharmaceutical products. Aeroperl® is advantageous over Aerosil® as it has higher specific surface area and tapped density. It can serve as a good candidate for liquisolid tablets.

The optimum liquisolid system of this study is selected to have optimum flow properties and the maximum felodipine dissolution (Q\(_{30}\)). Powder flow properties are crucial in handling and processing operations such as flow from hoppers, mixing and compression. A uniform flow from the hoppers into the die cavity ensures uniform tablet weight and drug content. Poor flowing powders present many difficulties to the pharmaceutical industry.\(^{17}\)

The powder flowability of FLSs was determined using Hausner’s ratio and Carr’s index (compressibility index, CI). Hausner’s ratio (HR) was related to the inter particle friction; powders with a low interparticle friction had a ratio of approximately 1.25 indicating a good flow. All FLSs showed acceptable Hausner’s ratio except FLS-8 whose Hausner’s ratio was 1.27 i.e. above 1.25.\(^{20}\) Generally powders with Carr’s index (CI) below 25% have acceptable flowability,\(^{17}\) while powders with CI below 18% are considered very flowing. The sixteen liquisolid systems had CI between 13.5% (FLS-9) to 21.3% (FLS-8) which means that all liquisolid systems have acceptable flow.

The *in vitro* dissolution results (Q\(_{30}\)) of felodipine from FLSs are shown in Figure 1 and Table 2. It is obvious that FLS-6, FLS -2, FLS -10 and FLS -14 give the highest values of Q\(_{30}\), 36.72%, 32.50%, 18.91% and 18.765%, respectively. These liquisolid systems composed of 10% drug concentration in PEG as a liquid vehicle. The higher Q\(_{30}\) values could be due to the lower concentration of drug thus the majority of drug was found in a molecularly solubilized form. The Q\(_{30}\) values of FLS-10 and FLS -14 are approximately half that of FLS -6, FLS -2. It is worthy to note that increasing the excipient ratio from 10 (in FLS -10 and FLS -14) to 20 (in FLS -6 and FLS -2) approximately doubled the values of Q\(_{30}\). Other FLSs, containing 10% and 20% drug concentration in PG had significantly lower Q\(_{30}\) values. The limited increase of felodipine dissolution by these systems was probably due to the lower solubility of felodipine in PG.

**Analysis of full-factorial experimental design**

2\(^4\) full-factorial experimental design was designed to evaluate main effects and interactions of the four chosen variables that may affect the dissolution rate of FLSs. The
standardized effect of the independent variables and their interaction on the dependent variable was investigated by preparing Pareto charts (Figure 2). The chart includes a vertical reference line at the critical p value of 0.05. An effect that exceeds the vertical line is considered to be statistically significant.[27,28]

The fact that the bars for the variables X₁, X₂ and X₄ extend after the reference line indicates that using PEG as a liquid vehicle, maximum value of excipient ratio[20] and lowest value of drug concentration (10%) significantly increased the values of Q₃₀ and consequently felodipine dissolution rate. These observations conform to what was previously stated in literature that liquisolid systems with higher excipient ratio (contain high amount of cellulose and low amount of silica) show enhanced disintegration and de-aggregation properties and the consequent enhancement of felodipine dissolution.[14] Liquisolid systems with lower drug concentration in the liquid vehicle contain higher fraction of drug that is solubilized and molecularly dispersed in the liquid vehicle leading to better dissolution.[9,12,15] The type of coat had a non significant effect on drug dissolution (Figure 2).

As shown in Figure 2, the extension of the bars of the interactions (X₁X₂) and (X₁X₄) and (X₂X₄) after the reference line in the Pareto chart indicates that there were significant interactions (liquid type/drug concentration, liquid type/excipient ratio and drug concentration/ excipient ratio) on the mean Q₃₀ values of FLSs. It is obvious that the dissolution rate of FLSs containing PEG were positively affected by excipient ratio and negatively affected by drug concentration with greater extent than that of FLSs containing PG. Figure 3 shows the contour plots of Q₃₀ for FLSs containing a) PG/Aerosil®, b) PG/Aeroperl®, c) PEG/Aerosil®, and d) PEG/Aeroperl®. Rapid dissolution of felodipine from FLSs containing PG could be obtained by using high excipient ratio with low drug concentration or low excipient ratio with high drug concentration (Figure 3a and 3b). However, in case of FLSs containing PEG, the maximum dissolution rate could be obtained only by using the highest excipient ratio[20] with the smallest drug concentration (10%) with Aerosil® or Aeroperl® as coat material (Figure 3c and 3d). The enhancement of dissolution rate from FLSs...
containing PEG was higher than that obtained from FLSs containing PG. This observation could be due to the higher solubility of felodipine in PEG.

**The effect of different carriers on dissolution properties of the optimized FLSs**

The relatively low Q30 values (36.7% or 32.5%) of the optimized FLSs, containing MCC PH 102, PEG, 10% drug concentration, an excipient ratio of 20 and Aerosil® or Aeroperl®, encouraged us to use other carrier materials to enhance dissolution rate and flow properties. Other FLSs were prepared using the same formulation variables of the optimized system except the carrier type. Prosolv® and a mixture of mannitol and MCC in a ratio of 1:1 were used instead of MCC PH 102. The composition of these optimized liquisolid systems are shown in Table 3.

The flow and dissolution properties of the prepared FLSs were compared with that obtained from FLS containing MCC PH 102 (FLS-2 and FLS-6). As shown in Table 3, all the optimized FLSs show acceptable flow as indicated by the values of HR (below 1.25) and CI (below 25%).

It is obvious that the optimized FLSs containing Aerosil® gave higher dissolution rate than those FLSs containing Aeroperl®. Moreover, the optimized FLSs containing Mannitol/MCC and Prosolv® as carriers (58.5% and 41.1%, respectively) gave higher dissolution rate than that of the original one containing MCC PH 102 (36.72%).

**Evaluation of the optimized FLODTs**

The optimized FLSs were compressed into Liquisolid ODTs of felodipine using Prosolv® and MCC PH 102 as carriers.
Table 3. Composition of the optimized FLSs using different carrier materials and their flow and dissolution properties.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Carrier type</th>
<th>Liquid vehicle</th>
<th>Type of coat</th>
<th>Drug concentration %</th>
<th>Excipients ratio (carrier:coat)</th>
<th>H.R.</th>
<th>C.I.</th>
<th>Qn (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLS-2</td>
<td>MCC PH 102</td>
<td>PEG</td>
<td>Aeroperl®</td>
<td>10</td>
<td>20</td>
<td>1.19</td>
<td>20</td>
<td>32.5 ± 1.9</td>
</tr>
<tr>
<td>FLS-6</td>
<td>MCC PH 102</td>
<td>PEG</td>
<td>Aerosil®</td>
<td>10</td>
<td>20</td>
<td>1.18</td>
<td>15.50</td>
<td>36.7 ± 2.4</td>
</tr>
<tr>
<td>FLS--17</td>
<td>Mannitol:MCC</td>
<td>PEG</td>
<td>Aeroperl®</td>
<td>10</td>
<td>20</td>
<td>1.19</td>
<td>16.48</td>
<td>51.6 ± 5.0</td>
</tr>
<tr>
<td>FLS--18</td>
<td>Mannitol:MCC</td>
<td>PEG</td>
<td>Aerosil®</td>
<td>10</td>
<td>20</td>
<td>1.16</td>
<td>14.13</td>
<td>58.5 ± 1.5</td>
</tr>
<tr>
<td>FLS--19</td>
<td>Prosolv®</td>
<td>PEG</td>
<td>Aeroperl®</td>
<td>10</td>
<td>20</td>
<td>1.14</td>
<td>12.70</td>
<td>40.3 ± 4.6</td>
</tr>
<tr>
<td>FLS--20</td>
<td>Prosolv®</td>
<td>PEG</td>
<td>Aerosil®</td>
<td>10</td>
<td>20</td>
<td>1.16</td>
<td>13.70</td>
<td>41.1 ± 2.7</td>
</tr>
</tbody>
</table>

Table 4. Characterization of FLODTs.

<table>
<thead>
<tr>
<th>Test</th>
<th>FLODT-1 (MCC PH 102)</th>
<th>FLODT-2 (Prosolv®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (mg)</td>
<td>312.12 ± 2.04</td>
<td>314.13 ± 0.94</td>
</tr>
<tr>
<td>Drug content</td>
<td>98.23 ± 0.65</td>
<td>99.18 ± 0.27</td>
</tr>
<tr>
<td>Friability</td>
<td>0.07%</td>
<td>0.02%</td>
</tr>
<tr>
<td>Hardness (Kg)</td>
<td>3.5 ± 0.01</td>
<td>4 ± 0.12</td>
</tr>
<tr>
<td>In vitro Disintegration time</td>
<td>11 ± 0.42 s</td>
<td>9 ± 0.25 s</td>
</tr>
<tr>
<td>In vivo Disintegration time</td>
<td>8 ± 0.14 s</td>
<td>7 ± 0.19 s</td>
</tr>
<tr>
<td>Wetting Time</td>
<td>6.5 ± 0.12 s</td>
<td>6 ± 0.08 s</td>
</tr>
<tr>
<td>Water absorption percent</td>
<td>127% ± 3.14</td>
<td>145% ± 4.08</td>
</tr>
</tbody>
</table>

Each FLODT contains 210 mg carrier, 10.5 mg Aerosil, 5 mg felodipine, 30 mg Crospovidone, 3 mg aspiratam and 6 mg lemon flavor.

carrier materials. However, MCC: Mannitol carrier produced friable tablets so that it was excluded. The composition of FLODTs is shown in Table 4.

Table 4 shows the results of the tests performed to evaluate FLODTs. It is clear that they conformed to the requirements that should be present in tablets as uniformity of weight and drug content. FLODTs also possessed acceptable hardness and friability. The in vitro disintegration times of FLODT-1 and FLODT-2 were 11 sec and 9 sec, respectively. The in vivo disintegration times of FLODT-1 and FLODT-2 were 8 sec and 7 sec, respectively. The rapid disintegration of FLODT-2 could be explained by its rapid wetting (wetting time 6 sec.) and its high water absorption capacity (147%).

Figure 4 demonstrates comparison of drug dissolution from FLODT-1 and FLODT-2 to that from conventional felodipine tablet (5 mg felodipine with 10.5 mg Aerosil, 30 mg Crospovidone and 264 mg MCC PH 102) and felodipine soft capsule (soft gelatin capsule filled with 5 mg felodipine dissolved in 0.5 gm PEG) in 500 mL 0.5% sodium lauryl sulphate solution. Dissolution profiles reveal that felodipine was rapidly dissolved from FLODT-2 and felodipine soft capsule where 80.4% and 62.3% were dissolved after 10 min. dissolution, respectively, followed by FLODT-1 (59.7%) and finally conventional felodipine tablet (29.4%).

FLODT-1, FLODT-2 and felodipine soft capsule showed enhanced dissolution as the drug particles in these formulations were molecularly solubilized in PEG. After these systems are disintegrated in dissolution medium, drug particles are in a state of molecular dispersion. Thus, the higher dissolution rates observed in these systems may be attributed to significantly larger surface area of the molecularly dispersed drug particles.[15] The conventional felodipine tablet has a limited surface exposed for dissolution due to the hydrophobicity of the drug particles.

Complete felodipine dissolution was obtained from FLODT-2 and felodipine soft capsules (approximately 100% dissolved after 1 h). Therefore, they were selected for the in vivo pharmacokinetic study.

**Pharmacokinetic Study in Healthy Human Volunteers**

The mean plasma concentration-time profiles of felodipine following administration of single buccal dose of FLODT-2 and a single oral dose of felodipine soft capsule to four healthy human volunteers are shown in Figure 5. The mean pharmacokinetic characteristics are summarized in Table 5. After buccal administration of FLODT-2, felodipine was rapidly absorbed and reached a Cmax of 15.69 ± 4.08 ng/mL at a Tmax of 1 ± 0.25. After the oral administration of felodipine soft capsule, felodipine reached a Cmax of 13.44 ± 3.75 ng/mL at a Tmax of 1.25 ± 0.29. Statistically insignificant differences (p > 0.05) were found between the pharmacokinetic parameters AUC0–24, AUC0–∞, Cmax and t1/2 determined for both the optimized FLODT-2 and felodipine soft capsule which satisfied the bioequivalence criteria. The mean Tmax estimated from the optimized FLODT-2 was smaller and statistically significantly different (p = 0.0218) relative to the mean Tmax of felodipine soft capsule. This faster rate of
Felodipine absorption obtained from FLODT-2 could be attributed to the partial absorption of drug through the membrane of buccal cavity and esophagus. Moreover, the rapid absorption of drug from FLODT correlates well with the results of in vitro dissolution which showed that felodipine was rapidly dissolved from FLODT-2 than that from the soft capsule.

Based on these findings, it could be concluded that a promising rapidly absorbed orodispersible tablet of felodipine was successfully designed for management of hypertensive crisis. However, because of the small number of volunteers recruited in the study, the results can only be considered preliminary, and the efficacy of the optimized FLODT in emergency cases should be clinically studied with a larger number of volunteers to prove its clinical usability.

### Conclusion

In this study, FLs were prepared and in vitro evaluated. A 2^4 full-factorial experimental design was applied in order to rapidly obtain the optimal FLS having acceptable flow and enhanced dissolution properties. The optimized FLODT formulation showed a significant increase in dissolution rate compared to felodipine solution in PEG filled in soft gelatin capsule in 0.5% SLS solution. The in vivo pharmacokinetic study suggests that the optimized FLODT developed in this work may be useful for management of hypertensive crisis due to the enhanced dissolution and rapid absorption of felodipine through the buccal mucosa. Further clinical studies with a larger number of subjects should be performed to prove the clinical usability of the optimized FLODT in emergency cases.

### Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

### References


