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Research paper

Effects of liquisolid formulations on dissolution of naproxen

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ABSTRACT

The aim of this study was to investigate the use of liquisolid technique in improving the dissolution profiles of naproxen in a solid dosage form. This study was designed to evaluate the effects of different formulation variables, i.e. type of non-volatile liquid vehicles and drug concentrations, on drug dissolution rates. The liquisolid tablets were formulated with three different liquid vehicles, namely Cremophor® EL (polyoxyl 35 castor oil), Synperonic® PE/L61 (poloxamer 181, polyoxyethylene–polyoxypropylene copolymer) and poly ethylene glycol 400 (PEG400) at two drug concentrations, 20%w/w and 40%w/w. Avicel® PH102 was used as a carrier material, Cab-o-sil® M-5 as a coating material and maize starch as a disintegrant. The empirical method as introduced by Spireas and Bolton (1999) [1] was applied strictly to calculate the amounts of coating and carrier materials required to prepare naproxen liquisolid tablets. Quality control tests, i.e. uniformity of tablet weight, uniformity of drug content, tablet hardness, friability test, disintegration and dissolution tests were performed to evaluate each batch of prepared tablets. *In vitro* drug dissolution profiles of the liquisolid formulations were studied and compared with conventional formulation, in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.2) without enzyme. Stability studies were carried out to evaluate the stability of the tablets under humid conditions. Differential scanning calorimetry and Fourier transform infrared were used to investigate physicochemical interaction between naproxen and the excipients. It was found that liquisolid tablets formulated with Cremophor® EL at drug concentration of 20%w/w produced high dissolution profile with acceptable tablet properties. The stability studies showed that the dissolution profiles of liquisolid tablets prepared with Cremophor® EL were not affected by ageing significantly. Furthermore, DSC revealed that drug particles in liquisolid formulations were completely solubilised.

1. Introduction

About 40% of the drug candidates identified via combinatorial screening programmes are poorly water soluble [2]. The aqueous solubility for poorly water-soluble drugs is usually less than 100 μg/ml [3]. The dissolution rate is the rate-limiting factor in drug absorption for class II (low solubility and high permeability) and class IV (low solubility and low permeability) drugs as defined in the Biopharmaceutics Classification System, BCS [4]. Poorly water-soluble drugs are difficult to formulate using conventional techniques. Different techniques have been reported in the literature to achieve better drug dissolution rates. For example, (a) reduce the particle size via micronisation or nanonisation to increase the surface area; (b) use of surfactants; (c) inclusion with cyclodextrins; (d) use of pro-drug and drug derivatisation; (e) formation of solid solutions or amorphous solids and (f) microencapsulation and inclusion of drug solutions or liquid drugs into soft gelatin capsules or specially sealed hard shell capsules.

Among various techniques to overcome the solubility issue, several researchers reported that the formulation of liquisolid tablets is one of the most promising techniques for promoting drug dissolution [6–11]. It is established that soft gelatin capsule preparations containing a solubilised liquid drug show higher and more consistent bioavailability than the conventional oral dosage forms because the active ingredient(s) is already in solution. In fact, liquisolid tablets deliver active ingredient(s) in a similar mechanism as soft gelatin capsule preparation which contains liquid [1,10] because in liquisolid tablets, non-volatile liquid vehicle was used to dissolve the solid drug, and the preparation does not involve drying and evaporation process; therefore, the drug is held in the solution even though it is in a tabletted or encapsulated dosage form. Consequently, drug dissolution properties and oral bioavailability will be improved. The concept of "liquisolid tablets" was evolved from "powdered solution technology" that can be used to formulate "liquid medication". The term "liquid medication" refers to solid drugs dispersed in suitable non-volatile liquid vehicles. By simple mixing of such "liquid medication" with selected carriers

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and coating materials, dry-looking, non-adherent, free-flowing and readily compactible powder admixtures can be produced [5,7–9,11–13].

Spireas and Bolton [1] suggested that particles possess porous surface with high absorption properties may be used as the carrier material such as cellulose, starch and lactose. Increasing moisture content of carriers results in decreased powder flowability [14]. Coating material is required to cover the surface and so maintain the powder flowability. Accordingly, coating material should be a very fine and highly adsorptive silica powders.

The appropriate amounts of carrier and coating materials to produce acceptable flowing and compactible powders are calculated using Eqs. (1)–(3), based on the physical properties of powders termed "flowable liquid-retention potential" (Φ-value) [1]. The ratio (R) of the amount of carrier (Q) and coating (q) materials is closely related to the amount of liquid medication (W). The maximum amount of liquid loads on the carrier material, termed "load factor" (L_f). The coating/carrier ratio (R) is important for determining the "optimum flowable load factor" (L_f) which gives acceptable flowing powders and is characterised by the ratio between (W) and (Q), as shown in Eqs. 1 and 2.

$$L_f = \Phi_{CA} + \Phi_{CO}\,(1/R) \tag{1}$$

where Φ_{CA} is the flowable liquid-retention potential of the carrier and Φ_{CO} is the flowable liquid-retention potential of the coating material.

$$L_f = W/Q \tag{2}$$

From Eq. (2), the amount of Q can be determined and applied to the Eq. (3) to calculate the required amount of the coating (q) material. Then, the amounts of Q and q can be used to prepare liquisolid formulations. It had been proposed that R value of 20 (used with different carriers and coating materials) produces powder admixture with good flow and compactible properties [5,9–16]. Therefore, this ratio will be used in this research.

$$R = Q/q \tag{3}$$

The liquisolid tablets that containing water-insoluble drug are expected to enhance drug dissolution because of increased wetting properties of the drug particles and the large surface area available for dissolution. The liquisolid tablets are suitable to formulate low dose water-insoluble drugs. Recently, a sustained release oral dosage form using liquisolid technology had been formulated successfully [8]. This proved that liquisolid technology can be developed either to improve or to reduce drug dissolution rates depending on the excipients added.

The goal of this study was to improve dissolution of a model hydrophobic drug, naproxen, using liquisolid tablets containing different non-volatile liquid vehicles. Naproxen, non-steroidal anti-inflammatory drug, is a weak acid ($pK_a = 4.15$) which is practically insoluble in water [17]. Various approaches have been tried to enhance the dissolution properties of naproxen, such as formation of naproxen sodium, solid dispersion, complexation with cyclodextrins [18], drug particle size reduction [19] and formation of naproxen disintegrant agglomerates using a crystallo-co-agglomeration technique [20]. However, one strategy that has not been investigated to improve dissolution of naproxen is liquisolid tablet formulations. To the best of our knowledge, there are currently no liquisolid dosage forms available on the market. However, commercial products using liquisolid technology may be available, in the future, on the market based on this research and similar studies.

Propylene glycol, polyethylene glycol 400 (PEG400) and polysorbate 80 (Tween® 80) had been used as non-volatile liquid vehicles in the preparation of immediate release liquisolid tablets with different drugs [1,5–7,9–13,16]. El-Gizawy [12] claimed that polysorbate 80 shows better dissolution rate than propylene glycol and PEG400 when formulated with meloxicam. On the contrary, Nokhodchi et al. [9] reported that indomethacin liquisolid tablets containing propylene glycol demonstrate higher dissolution rate than those containing PEG400 or polysorbate 80 with the same concentration. Accordingly, there is no single non-volatile liquid vehicle which is suitable for a wide range of hydrophobic drugs in formulating liquisolid tablets. In the present study, Cremophor® EL and Synperonic® PE/L61, which have never, to the best of our knowledge, been studied before in liquisolid tablets, were used as non-volatile liquid vehicles in the liqui-solid systems containing naproxen.

2. Materials and methods

2.1. Materials

Naproxen was obtained from Roche-Syntex, S.A. de C.V., Mexico. Microcrystalline cellulose (Avicel® PH102) (FMC Corp., Philadelphia, USA), maize starch (National Starch & Chemical Ltd., Manchester, UK), colloidal silicon dioxide (Cab-o-sil® M-5, particle size of 0.2–0.3 μm) (Cabot Corporation, Rheinfelden, Germany), polyethylene glycol 400 (Sigma–Aldrich, Poole, UK), polyoxyl 35 castor oil (Cremophor® EL) (BASF Aktiengesellschaft, Ludwigshafen, Germany), poloxamer 181 (Synperonic® PE/L61) (ICI surfactants, Everberg, Belgium) were used. All materials were of either pharmacological grade or analytical grade.

2.2. Determination of the optimal flowable liquid-retention potential (Phi, Φ-value) for Avicel® PH102 and Cab-o-sil® M-5

"Angle of slide" measurement was used to evaluate the flow property of powder excipients (Avicel® PH102 and Cab-o-sil® M-5) with liquid vehicles. Several uniform liquid vehicle/powder admixtures which contain 10 g of the carrier or coating materials with increasing amounts of liquid vehicle (Cremophor® EL, Synperonic® PE/L61) were prepared. To measure the angle of slide, the prepared liquid/powder admixtures were placed on polished metal plates, the plate was then tilted gradually until the liquid/powder admixture was about to slide. The angle formed between the plate and the horizontal surface was defined as the angle of slide (θ). The flow properties of excipients will be changed due to adsorption of the liquid vehicle. The flowable liquid-retention potential (Φ-value) of each liquid/powder admixture was calculated using the following equation [13].

$$\Phi - \text{value} = \text{weight of liquid/weight of solid} \tag{4}$$

The Φ-values were plotted against the corresponding θ (Figs. 1 and 2). An angle of slide (for optimal flow properties) corresponding to 33° of a liquid/powder admixture represented the flowable liquid-retention potential, Φ-value, of its powder [13] which is required for preparation of liquisolid tablets. All measurements were carried out in triplicate.

The Φ-values for Avicel® PH102 and Cab-o-sil® M-5 with PEG400 were available from literature as 0.005 and 3.26, respectively [1].

2.3. Preparation of liquisolid powders and compaction into tablets

Naproxen liquisolid formulations, denoted as LS-1 to LS-6 (Table 1), were prepared using Cremophor® EL, Synperonic® PE/L61 and PEG400 as liquid vehicles with two different drug concentrations, 20%w/w and 40%w/w. Naproxen (25 mg/tablet) was dispersed in the liquid vehicle with continuous mixing using pestle and mortar to produce the liquid medication. All liquisolid formu-

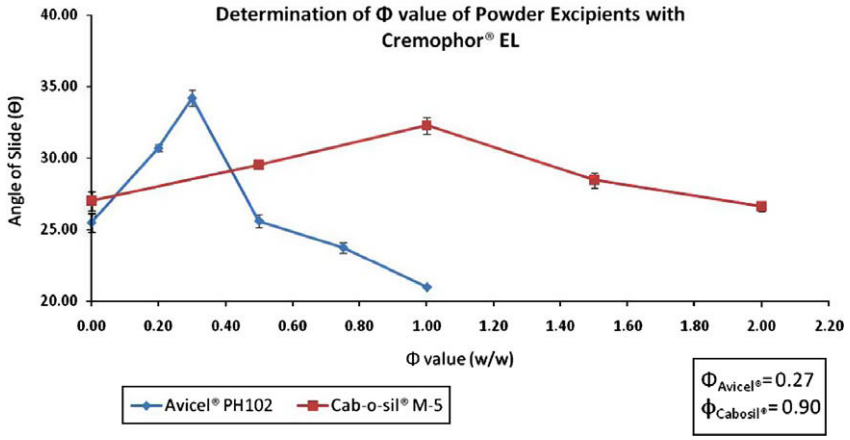

Fig. 1. The angle of slide of various mixtures of powder excipients (i.e. Avicel® PH102 and Cab-o-sil® M-5) with Cremophor® EL. The intersection of each curve with horizontal dashed line at 33° represents the Φ-value of the respective powder excipients.

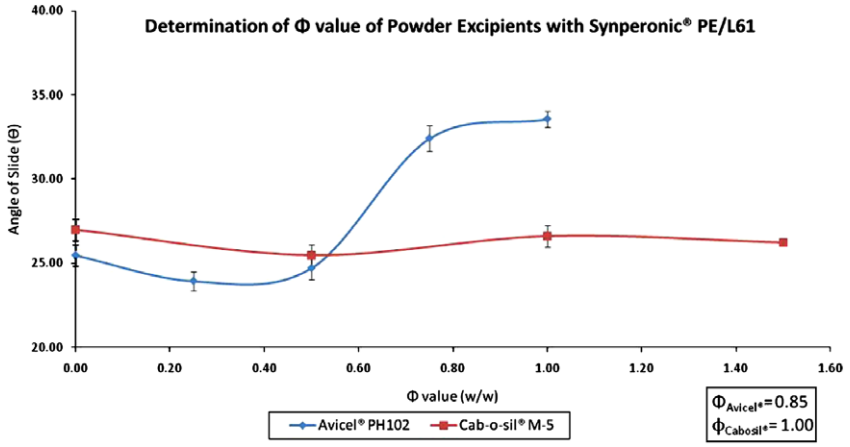

Fig. 2. The angle of slide of various mixtures of powder excipients (i.e. Avicel® PH102 and Cab-o-sil® M-5) with Synperonic® PE/L61. The intersection of each curve with horizontal dashed line at 33° represents the Φ-value of the respective powder excipients.

lations contained Avicel® PH102 as the carrier powder and Cab-o-sil® M-5 as the coating material at a fixed powder ratio (R) of 20. The appropriate amounts of the carrier and coating materials used in the liquisolid formulation were derived from their Φ-value (Figs. 1 and 2) and liquid load factors (L_f), as shown in Eqs. (1)–(3). L_f can be calculated by substitute the flowable liquid-retention potential of the carrier (Φ_{CA}-value) and flowable liquid-retention potential of the coating material (Φ_{CO}-value) into Eq. (1). By knowing liquid load factors (L_f) and amount of liquid medication (W), appropriate amounts of carrier material (Q) and coating material (q) (Table 1) can be calculated using Eqs. (2) and (3). The appropriate amount of carrier Avicel® PH102 was mixed with the drug-vehicle suspension. Cab-o-sil® M-5 was then added to convert the wet mixture into dry powder under continuous mixing. Finally, a 5%w/w of maize starch as a disintegrant was added into the mixture and mixed for 10 min. The final mixture (if compactible, depending on its flow properties, see Section 2.4) was compacted on a 10-mm flat-faced punch and die set using a single punch tabletting machine (Type 3, Manesty Machines Ltd., Liverpool, UK); each batch consisted of 60 tablets. The applied compression force was different from one formulation to another depending on the tablet weight and the preparation; however, sufficient compression force (38 ± 5 kN) was used to attain acceptable tablet hardness. LS-3 and LS-4 (with Synperonic® PE/L61 as a liquid vehicle) were the only liquisolid formulations which were not compactible.

Additionally, a batch of 60 naproxen conventional tablets (DCT) was prepared; each tablet contains 25 mg of naproxen, 100 mg Avicel® PH102, 5 mg of Cab-o-sil® M-5 and 5 mg of maize starch. Such excipients were accurately weighed and mixed in a turbula mixer (Glen Creston Ltd., UK) at a rotation speed of 60 rpm for 15 min. The mixture was compacted using the previously mentioned single punch tabletting machine.

Table 1 depicts the amounts of carrier (Q), coating material (q), drug concentration (w/w) and liquid load factor (L_f) used to prepare different liquisolid formulations LS-1–LS-6.

Physical mixtures, without following the empirical method proposed by Spireas and Bolton [1], have been prepared by dispersing the drug (20 and 40%w/w) in the liquid vehicles followed by addition and mixing of (i) the carrier and coating materials in a ratio of 20:1 and (ii) the disintegrant (5%w/w) to produce 700 mg tablet weight. But this physical mixing produced agglomerated, non-compactible and poorly flowable powders; therefore, physical mixtures efficiency could not be compared with that of liquisolid formulations.

2.4. Determination of flow and packing properties of the prepared liquisolid powders

The flow and packing properties of the prepared liquisolid formulations were determined using tap volumeter (J. Engelsmann

Table 1
Formulation of liqui-solid systems.

Liqui-solid system	Non-volatile liquid vehicle	Drug concentration in liquid medication (%w/w)	Carrier, Avicel® PH102: Coating, Cab-o-sil® M-5 (R)	Liquid load factor (L_f)	Liquid vehicle (mg)	Active ingredient (mg)	Carrier, Q (mg)	Coating, q (mg)	Disintegrant (maize starch) (mg)	Unit dose (mg)	Molecular fraction (F_M)
LS-1	Cremophor® EL	20	20	0.315	100.0	25	396.83	19.84	28.51	570.18	0.52
LS-2	Cremophor® EL	40	20	0.315	37.5	25	198.41	9.92	14.25	285.09	0.26
LS-3	Synperonic® PE/L61	20	20	0.900	100.0	25	138.89	6.94	14.25	285.09	0.24
LS-4	Synperonic® PE/L61	40	20	0.900	37.5	25	69.44	3.47	7.13	142.54	0.12
LS-5	PEG400	20	20	0.168	100.0	25	744.05	37.20	47.70	953.95	0.60
LS-6	PEG400	40	20	0.168	37.5	25	372.02	18.60	23.85	476.97	0.30

AG, Ludwigschafen, Germany). The prepared liquisolid formulations were weighed and poured into a 100 mL cylinder. The poured bulk volume (V_b) and the tapped volume (V_t) after sufficient taps, which recorded to give a constant volume, on a tap volumeter were used to calculate the poured bulk density (P_b) and the tapped density (P_t) in g/mL. Then, the Carr's compressibility index (CI%) was calculated to investigate the flowability of the powders, as follows [21]:

$$\mathrm{CI}\% = (P_t - P_b)/P_t \times 100 \quad (5)$$

According to the British Pharmacopoeia [22], Carr's compressibility index below 25 represent passable flow properties.

2.5. Characterisation of liquisolid formulations

2.5.1. Solubility studies

Solubility studies of naproxen were performed in Cremophor® EL, Synperonic® PE/L61, PEG 400 and distilled water. Saturated solutions were prepared by adding excess amount of naproxen in a small vial containing 10 mL of vehicles. The vials were sealed and rotated (Stuart Rotator, UK) for 72 h at ambient temperature under constant shaking. Then, the supernatant was filtered through a 0.2 μm cellulose nitrate membrane filter (Whatman International Ltd., Maidstone, UK). The drug concentration was determined using UV/vis spectrophotometer (Model M501, Camspec Ltd., Cambridge, UK) at 271 nm after appropriate dilution with distilled water. Fig. 3 shows the data for the calibration curve used to calculate naproxen concentration.

2.5.2. Quality control tests of the prepared tablets

The liquisolid compacts and conventional tablets were evaluated via quality tests which were conducted in accordance to the British Pharmacopoeia [22] specifications.

2.5.2.1. In vitro dissolution studies. *In vitro* dissolution studies were performed using USP dissolution apparatus II (Caleva Ltd., Dorset, UK). Both simulated gastric fluid, SGF (pH 1.2) and simulated intestinal fluid, SIF (pH 7.2) without enzyme were used as dissolution media. The volume of dissolution medium was 1000 mL, and it was maintained at 37 ± 1 °C and stirred at a paddle speed of 50 rpm. Ten millilitres samples were collected at time intervals of 5, 10, 15, 20, 30, 40, 50 and 60 min. The withdrawal samples were replaced by equal amounts of the dissolution medium to maintain a constant volume. The samples extracted at the time intervals were analysed spectrophotometrically at 271 nm for determination of the naproxen content using the calibration curve illustrated in Fig. 3. The dissolution experiment was exploited to compare the dissolution data of liquisolid formulations in tablets and powder forms.

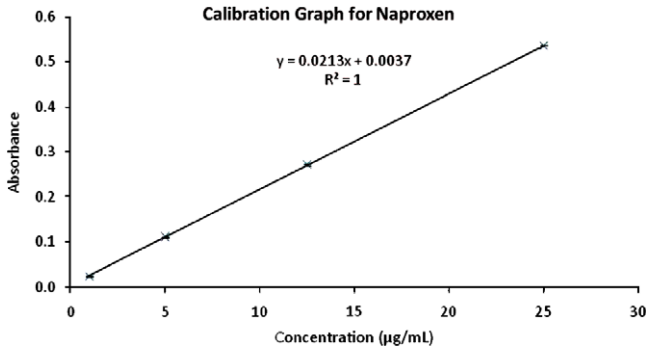

Fig. 3. Calibration curve of naproxen.

2.5.2.2. Uniformity of tablet weight, drug content uniformity, tablet hardness, friability and disintegration tests. For uniformity of tablet weight, 20 tablets were taken randomly from each tablet formulation and weighed individually. The average weight of all tablets and percentage deviation from the mean for each tablet were determined.

In uniformity of drug content, 10 tablets from each batch were taken randomly to examine its content uniformity. Each tablet was weighed and crushed individually. The crushed tablet powders were dissolved in methanol. The solution was filtered using glass microfiber filters (Whatman International Ltd., Maidstone, UK). The drug content was measured using UV/vis spectrophotometer (Model M501, Camspec Ltd., Cambridge, UK) at 271 nm. The percentages of individual drug content were calculated against the average drug content, according to the British Pharmacopoeia [22].

For tablet hardness, the force in Newton required to crush the tablets was examined using hardness tester (Model 2E/205, Schleuniger & Co., Switzerland).

The friability of the prepared tablets was measured using a friability tester (FRV1000, Copley Scientific, UK). The drum was rotated for 4 min at 25 rpm. The losses of mass of 10 tablets were determined, and percentages of friability were calculated using the following equation:

$$\%\mathrm{Friability} = (\text{loss of mass}/\text{initial mass}) \times 100 \quad (6)$$

The disintegration test was performed at 37 ± 1 °C in distilled water for six tablets from each formulation using tablet disintegration unit (Manesty Machines Ltd., Liverpool, UK). The tablets were considered completely disintegrated when there is no residue remains on the screen or a residue consists of a soft mass with no palpably firm or unmoistened core.

2.5.3. Determination of tablet porosity

The porosity of tablets, ε, was calculated using the following equation [23]:

$$\varepsilon = 1 - (\rho_{tablet}/\rho_{true})$$
$$\rho_{tablet} = \text{Weight of tablet}/\pi r^2 h \quad (7)$$

where ε is the tablet porosity; ρ_{tablet} is the tablet density (g/cm^3); ρ_{true} is the true density (g/cm^3) of powder admixtures as determined by helium pycnometry (see next paragraph); r is the radius of tablet (cm); h is the thickness of tablet (cm).

The true density of powders (used for preparations of liquisolid and conventional tablets) was evaluated by a helium pycnometer (AccuPyc 1330, Micrometitics Instrument Inc., Norcross, GA, USA). In this method, the difference in helium pressure before and after sample loading is measured to determine the volume of the sample. Approximately, 1–1.5 g of each powder was used, and the results were the mean and standard deviation of five replicates. The helium pressure was set to be 10 psi.

2.5.4. Stability studies

The tablets were stored at 20 °C and 76% relative humidity condition for up to 4 weeks. The stored tablets were evaluated using dissolution test. The dissolution data (in SGF and SIF) of aged tablets were compared with those of freshly prepared tablets.

2.5.5. Differential scanning calorimetry (DSC)

DSC thermograms of naproxen, Avicel® PH102, Cab-o-sil® M-5, maize starch, conventional and liquisolid formulations were obtained with DSC Refrigerated Cooling System (Model Q1000, TA Instruments, UK). Samples (0.8–6.3 mg) were weighed and transferred into the equipment for analysis in sealed hermetically aluminium pans. The instrument was calibrated with sapphire and indium before running the samples. Thermal behaviour of the samples was investigated at a scanning rate of 10 °C/min, from 0 °C to 180 °C.

2.5.6. Fourier transform infrared (FT-IR) spectroscopy

Infrared spectra of the samples (naproxen, Avicel® PH102, Cab-o-sil® M-5, maize starch, Cremophor® EL, PEG400, Synperonic® PE/L61, conventional and liquisolid formulations) were obtained, using Perkin Elmer FT-IR system Spectrum BX series (Beaconsfield, Buckinghamshire, UK), in the frequency range of 4000–550 cm^{-1} at 4 cm^{-1} resolution. The technique used very small amount of each sample which directly loaded into the system. Spectrum BX series software version 2.19 was used to determine peak positions.

2.5.7. Statistical analysis

Levene's test was applied to test the homogeneity of variances. One-way ANOVA and independent-samples *T*-test were applied if the variances in the groups are equal. If the variances are significantly different, Mann–Whitney test was applied. Results are quoted as statistically significant when $P < 0.05$.

3. Results and discussion

3.1. Flowable liquid-retention potential (Φ-value) and liquid load factor (L_f)

Angle of slide was used to determine flowable liquid-retention potentials (which are needed for calculation of the L_f), as explained in Sections 1 and 2.2. Spireas et al. [15] claimed that angle of slide is the preferred method to determine the flowablity of powders with particle size less than 150 μm. Avicel® PH102 and Cab-o-sil® M-5 have particle size of 113.8 μm [24] and 0.2–0.3 μm (as stated by the manufacturer), respectively. Therefore, angle of slide had been preferred over the other methods, e.g. angle of repose, to determine the flow properties of powder excipients and liquid/powder admixtures. The validity of angle of slide has been proven to be effective [13]. The flow properties of powders are affected by their particle size, shape, porosity, density, moisture content, and surface roughness [25].

Figs. 1 and 2 show the relationship between the angle of slide and the corresponding Φ_{CA}-value and Φ_{CO}-value of Cremophor® EL and Synperonic® PE/L61, respectively. The Φ_{CA}-value and Φ_{CO}-value decide the amount of carrier and coating materials required to produce dry-looking, non-adherent, free-flowing and readily compactible liquisolid formulations (Table 1). Hence, determination of the flow properties of powder excipients and liquid/powder admixtures is an important step to produce a successful liquisolid formulation.

As clearly shown in Table 1, liquisolid formulations with lower drug concentration required more liquid vehicles as well as the carrier and coating materials, and hence larger tablets produced compared to those contained higher drug concentrations. The viscosity of PEG400, Cremophor® EL and Synperonic® PE/L61 are 105–130, 650–800 and 1000 mPa s, respectively [26]. It can be seen from Table 1 that the liquid load factor (L_f) increased with increasing viscosity of the liquid vehicle. Thus, the viscosity of the liquid vehicle is inversely proportional to the amount of carrier and coating materials required in a liquisolid formulation [12].

3.2. Powder flow and packing properties

Powder flow properties are crucial in handling and processing operations such as flow from hoppers, mixing and compression. One of the major problems in handling poor flowing powders in pharmaceutical industry is obtaining reliable and uniform flow out of the hoppers. 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.

The powder flowability of liquisolid formulations was determined using Carr's index (compressibility index) as shown in Table 2. Carr's index is a useful parameter in reflecting interparticle friction. LS-1, LS-2, LS-5 and LS-6 have good flow properties because their CI% were below 25. Additionally, those formulations were compactible into tablets with uniform weight. Regarding LS-5 and LS-6 formulations, excess Cab-o-sil® M-5 was added into LS-5 and LS-6. In this case, Cab-o-sil® M-5 was used as coating to adsorb excessive liquid, whereas excess Cab-o-sil® M-5 may act as a glidant (concentration of 0.1–0.5%) to improve powder flowability. Consequently, the flowability of liquisolid formulation formulated with PEG400 was better than liquisolid formulations formulated with Cremophor® EL (LS-1 and LS-2).

For prepared powder admixtures with Synperonic® PE/L61 (LS-3 and LS-4), the powder flow was poor, and those formulations were not compactible. This may be due to the high viscosity of the liquid vehicle, and hence high liquid load factor (L_f of Synperonic® PE/L61 was 3-fold and 5-fold higher than Cremophor® EL

Table 2
Carr's index (CI%) of prepared liquisolid powders.

Formula[a]	Carr's index (CI%)	Type of flow
LS-1	21.74	Passable
LS-2	22.00	Passable
LS-3	31.58	Very poor
LS-4	28.00	Poor
LS-5	20.00	Fair
LS-6	20.00	Fair

[a] For the composition of each formula refer to Table 1.

and PEG400, respectively) and less carrier and coating materials compared to the other formulations (refer to Table 1). As a result, insufficient amount of Cab-o-sil® M-5 added into the formulation, excess liquid was not completely absorbed by the Cab-o-sil® M-5. As a result, LS-3 and LS-4 have a high liquid content, and so the powder particles bond together easily and form agglomerates. Microcrystalline cellulose (Avicel® PH102) is one of the most commonly use pharmaceutical excipients in tabletting because of its good compactibility properties. The good compactibility can be explained by the nature of microcrystalline particles themselves, which are held together by hydrogen bonds. The strength and cohesiveness of a tablet are attributed to the hydrogen bonds between hydrogen groups on adjacent cellulose molecules. When compacted, the microcrystalline cellulose particles are deformed plastically, and a strong compact is formed due to extremely large surfaces brought in contact during the plastic deformation and the strength of hydrogen bonds formed [27]. The amount of microcrystalline cellulose for LS-3 and LS-4 is less than the other formulations. This can explain the compactibility problem encountered in LS-3 and LS-4 formulations.

3.3. Evaluation of liquisolid (LS-1, LS-2, LS-5 and LS-6) and conventional (DCT) tablets

3.3.1. Tablet weight uniformity and drug content uniformity

All liquisolid and conventional tablets complied with the British Pharmacopoeia (BP) weight uniformity test. Also, all tablets had met BP content uniformity criteria, in which each individual content was between 85% and 115% of the average content. Fahmy and Kassem [6] claimed that usually the process involved adsorption of liquid formulation onto carriers gives uniform drug distribution; therefore, promote good content uniformity. However, there is no distinct difference in drug content uniformity observed between liquisolid and conventional tablets in this study.

3.3.2. Tablet hardness, friability and disintegration

Liquisolid and conventional tablets complied with BP friability test as friability was less than 1%, and there were no cracked, split or broken tablets. Therefore, they are expected to withstand fracturing and attrition during normal handling, packaging and transporting processes. Table 3 shows the results from hardness, friability and disintegration tests.

The compression force applied for LS-1, LS-2, LS-5, LS-6 and DCT is 38 ± 5 kN. Generally, ideal tablet hardness should be produced without applying excessive compression force where rapid tablet disintegration and drug dissolution are maintained at the same time [27]. The tablet hardness depends on a number of factors such as particle size, compression force, interparticle force. The most important of which is compression force. Usually, increase in compression force, tablet hardness and fracture resistance increased as well [25]. Tablets with a high hardness are normally associated with long disintegration time. Also, the disintegration time can be affected by other physical properties such as tablet porosity and pore structure. Tablets with increased hardness or prepared under large compression forces will have smaller pores and will require more time for the absorption of water into the tablet, which in turn resulting in prolonged disintegration time [28–29]. Accordingly, appropriate compression force applied will produce tablet hardness that is hard enough to avoid breakage during normal handling and soft enough to be disintegrated and release the active drug ingredient(s).

Table 4 shows the results of the true density of powder admixtures and porosity of liquisolid and conventional tablets. From Tables 3 and 4, when there was increase in tablet hardness (Table 3), there was decrease in tablet porosity (Table 4); thus, a longer disintegration time is expected. For example, LS-6 was harder than LS-2, and also LS-6 showed significant ($P < 0.05$) longer disintegration time and lower percentage of porosity compared to LS-2 (Tables 3 and 4). For LS-1 and LS-2 tablets, although LS-1 was harder than LS-2 but this increase in hardness was not significant ($P > 0.05$), additionally there was no significant difference ($P > 0.05$) in disintegration time of both formulations (Table 3). The poor disintegration probably can be overcome by reducing the compression force. For a drug in a tablet become fully available for absorption, the tablet must first disintegrate and release the drug to the body fluids for dissolution. Hence, tablet disintegration has a huge influence on the dissolution of the drug from tablets.

3.3.3. In vitro dissolution studies

The solubility results of naproxen in Cremophor® EL, Synperonic® PE/L61, PEG400 and distilled water are shown in Table 5. Naproxen was soluble in Synperonic® PE/L61 and more soluble in PEG400 and Cremophor® EL. In liquisolid formulations, the drug solubility in the solvents is important, as the higher the solubility, the more the drug particles dissolved in the liquid vehicles prior to the adsorption onto the carrier materials.

The solubility of a drug in the solvents is affected by different physicochemical properties of the solvents, such as hydrophilicity, polarity, viscosity, chemical structure and molecular weight, to different extents [10]. Cremophor® EL, Synperonic® PE/L61 and PEG400 possess hydrophilic–lipophilic balance (HLB) values of 13, 3 and 12, respectively [30–31]. The higher HLB values indicate hydrophilic or polar properties, whereas low HLB values suggest lipophilic or non-polar characteristics [32]. The factors that can affect the dissolution rate of a dosage form can be categorised into three categories [33]. The first factor is the physicochemical properties of the drug, including solubility, particle size and crystalline state such as polymorphism, state of hydration, solvation and complexation. Secondly, the dosage form, and the third factor is the dissolution apparatus and the test parameters.

The dissolution profiles of naproxen liquisolid tablets and conventional tablets in SGF and SIF are shown in Figs. 4 and 5, respectively. The dissolution profiles of naproxen from liquisolid tablets with either Cremophor® EL (LS-1 and LS-2) or PEG400 (LS-5 and LS-6) produced higher drug dissolution rate ($P < 0.05$) in comparison with the conventional tablets (DCT) in both dissolution media.

Table 3
Hardness, friability and disintegration of liquisolid and conventional tablets.

Formula[a]	Hardness (N) ± SD[b]	Friability test %Friability	Disintegration time (min) ± SD[b]
LS-1	39.24 ± 7.85	0.04	16.19 ± 2.15
LS-2	18.97 ± 2.27	0.11	21.07 ± 3.11
LS-5	178.54 ± 4.50	0.10	26.44 ± 5.64
LS-6	194.57 ± 1.50	0.18	36.59 ± 8.89
DCT	100.06 ± 3.92	0.24	14.69 ± 6.57

[a] For the composition of each formula refer to Table 1.
[b] SD, standard deviation from the mean.

Table 4
True density of powder admixtures, and porosity of liquisolid and conventional tablets.

Formula[a]	True density (g/cm^3) ± SD[b]	Tablet porosity (%)
LS-1	1.5186 ± 0.0009	26.48
LS-2	1.6579 ± 0.0011	34.45
LS-5	1.6130 ± 0.0035	23.54
LS-6	1.6883 ± 0.0010	18.34
DCT	1.7128 ± 0.0020	18.25

[a] For the composition of each formula refer to Table 1.
[b] SD, standard deviation from the mean.

Table 5
Solubility of naproxen in various liquid vehicles.

Liquid vehicle	Naproxen solubility ± SD[a] (%w/w)
Cremophor® EL	10.48 ± 0.15
Synperonic® PE/L61	4.86 ± 0.10
PEG400	12.09 ± 0.03
Distilled water	0.0017 ± 0.0001

[a] SD, standard deviation from the mean.

The percentages of naproxen released from LS-1, LS-2, LS-5 and LS-6 in SGF at 60 min are 62.15%, 55.06%, 17.57% and 6.80%, respectively, while DCT had a maximum drug released of 2.13% at 60 min. In SIF, LS-1, LS-2, LS-5 and LS-6 reached 102.31%, 98.48%, 86.77% and 53.12% drug released at 60 min, respectively, whereas only 38.37% drug released from DCT.

The Noyes–Whitney equation, in the next paragraph, can be used to explain the dissolution results as follow:

$$dC/dt = DS(C_S - C)/h \quad (8)$$

where dC/dt is the dissolution rate of the drug particles, D is the diffusion coefficient of the dissolved drug particles, which affected by the viscosity of the dissolution medium; S is the surface area exposed to dissolution; h is the thickness of the diffusion layer, and it is affected by agitation; C_s is the saturation solubility of the drug in solution in the diffusion layer, and C is the concentration of the drug in the dissolution medium. All the dissolution tests were stirred under the same paddle speed (50 rpm) and dissolution media with same viscosity; therefore, h and D were assumed to be constant. Therefore, this leaves S and $(C_s - C)$ as the factors affecting dissolution rates of liquisolid formulations.

The drug particles in liquisolid formulations were dispersed in selected hydrophilic liquid vehicle, which means the wetting properties of the drug particles were increased; hence, the surface area of drug particles available for dissolution increased tremendously.

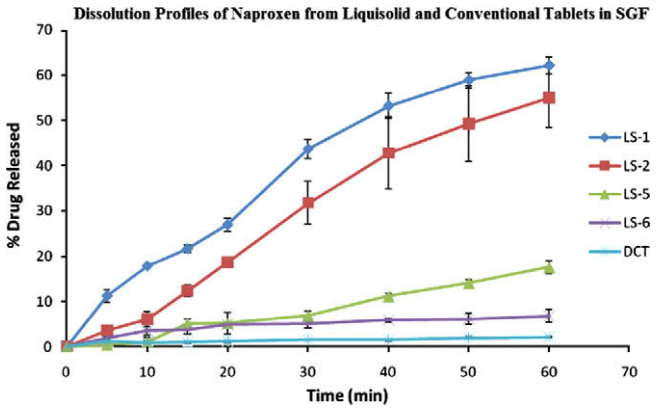

Fig. 4. Percentages of drug released (±SD) from the liquisolid tablets and conventional tablets in simulated gastric fluid (SGF).

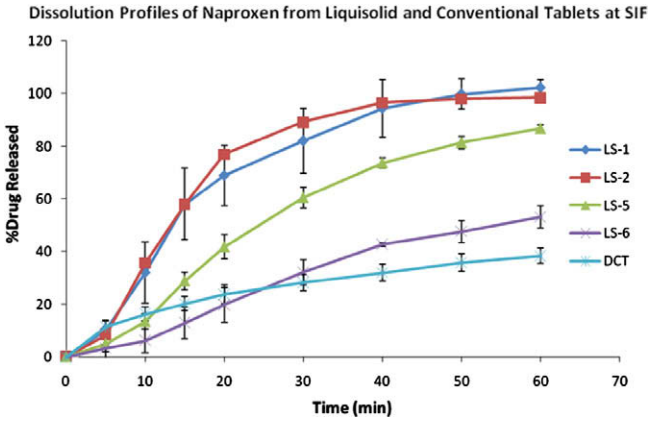

Fig. 5. Percentages of drug released (±SD) from the liquisolid tablets and conventional tablets in simulated intestinal fluid (SIF), SD removed for dissolution profile of LS-2 for clarity of the Figure.

After liquisolid tablet was disintegrated, the primary particles of liquisolid suspended in the dissolution medium contained drug particles in a state of molecular dispersion. For conventional tablet, the surface exposed for dissolution is very limited, due to the hydrophobicity of the drug particles. Accordingly, the higher dissolution rates observed in liquisolid formulations may be attributed to significantly larger surface area of the molecularly dispersed drug particles.

Since the drug particles in liquisolid formulations are in a state of molecular dispersion, its saturation solubility (C_s) might be increased. The small amount of liquid vehicle in a liquisolid tablet might not be adequate to increase the overall saturation solubility of drug particles in the dissolution medium. Nevertheless, in the diffusion layer (the solid/liquid interface between primary liquisolid particles and dissolution medium), in such a micro-environment, it is highly possible that infinite amounts of liquid vehicle diffuse with the drug particles away from the primary liquisolid particles. In this case, small amount of liquid vehicle might be sufficient to improve the solubility of drug particles by acting as a co-solvent with the dissolution medium of the diffusion layer. As a consequence of increase in C_s, the concentration gradient $(C_s - C)$ of the drug will be increased, and hence, the drug dissolution rate will be increased [6,7,9–11,16].

As shown in Table 5, naproxen has a slightly higher solubility in PEG400 compared to Cremophor® EL. Therefore, theoretically, the liquisolid tablets formulated with PEG400 (LS-5 and LS-6) should have a better dissolution rate than those formulated with Cremophor® EL (LS-1 and LS-2) [7,9,10]. However, it has been clearly shown in Fig. 5 that first 10 min naproxen dissolution from LS-1, LS-2, LS-5 and LS-6 in SIF were 31.99, 35.56, 13.42 and 6.18%, respectively. Similar sequence was shown in SGF, meaning that liquisolid tablets which are formulated with Cremophor® EL show higher dissolution rates than those formulated with PEG400. This can be explained by the tablet hardness and tablet porosity that cause longer disintegration time (Table 3) for LS-5 and LS-6. To further study if tablet hardness and disintegration have the prominent effects on the dissolution of naproxen liquisolid formulations, comparison between the dissolutions of uncompacted LS-1, LS-2, LS-5 and LS-6 liquisolid formulations (powders) were performed and will be discussed later.

Figs. 4 and 5 show that formulations with smaller drug concentration (20%w/w) have a higher dissolution than higher drug concentration (40%w/w) in either liquisolid tablets formulated with Cremophor® EL or PEG400 in both dissolution media. This can be explained by the dissolved drug in the liquid medication as follows:

$$F_M = C_L/C_d \quad (9)$$

where F_M is the fraction of molecularly dispersed or dissolved drug in liquid medication of the prepared liquisolid formulation, C_L is the saturation solubility of naproxen in the liquid vehicle and C_d is the drug concentration in the liquid medication. According to Spireas et al. [11], F_M value can not exceed unity.

The saturation solubility of naproxen in Cremophor® EL is 10.48%w/w (see Table 5), by applying Eq. (9), it can be calculated that 52.4% of the drug was solubilised in LS-1 and 26.2% of naproxen was solubilised in LS-2. The higher the drug concentration in a liquisolid formulation, the smaller the amount of liquid vehicle was added, thereby reduced the amount of drug solubilised in the liquid vehicle. Apparently, LS-1 which has 52.4% of drug available in solubilised form promote higher dissolution rate than LS-2. It was proven that F_M is directly proportional to the drug dissolution rate [9–11]. The F_M values of such liquisolid formulations were listed in Table 1. Another explanation for this phenomenon is that high concentration of the drug could precipitate within the silica (Cab-o-sil® M-5) pores; thus, drug dissolution rate would be reduced [13]. The potential of naproxen to precipitate within the silica pores is depending on the solubility of the drug in the solvent, the degree of saturation of the drug solution or the interactions between drug and excipients [34].

Comparing the dissolution of naproxen in SGF and SIF dissolution media, it was found that the drug exhibited higher dissolution rate in SIF as a dissolution medium compared to that in SGF. This can be explained on the basis that naproxen is a weak acid ($pK_a = 4.15$) which displays pH-dependent solubility and dissolution. The weak acids react with bases in SIF and then exist as ions that are ordinarily soluble in water. In the other words, the concentration of the drug is high when the drug is mostly ionised. Therefore, its dissolution rate increased markedly with increasing the pH. The percentage of a weak acid drug being ionised at a certain pH can be calculated using the following equation [35].

$$\%\text{Ionised} = 100/(1 + \text{antilog}(pKa - pH)) \quad (10)$$

The pH of the stomach ranges from 1.0 to 3.0 and that of the small intestine ranges from 6.0 to 8.0. Accordingly, the percentage of drug ionised will be different in different parts of the gastrointestinal tract. Based on the above equation (Eq. (10)), when naproxen is in SGF (pH 1.2), 11.21% of naproxen is ionised, whereas 99.91% of drug is ionised in SIF (pH 7.2). Figs. 4 and 5 proved that pH influenced naproxen dissolution profiles. LS-2, LS-5, LS-6 and DCT show statistically significant difference ($P < 0.05$) dissolution profile in SGF and SIF. Whereas the dissolution profiles of LS-1 are not statistically significant ($P = 0.078$) in SGF and SIF. The non-statistically significant of LS-1 in SGF and SIF implied that the dissolutions of LS-1 are equally good in the stomach and small intestine. Therefore, it is expected that naproxen will not precipitate on the gastric mucosa and cause local irritation, but it is ready to dissolve in the gastric fluid and available for absorption. In order to understand the original properties of the uncompacted liquisolid (powder) formulations, dissolution studies were performed on all uncompacted liquisolid and conventional formulations in SGF and SIF, as shown in Figs. 6 and 7. The percentage drug release of LS-1, LS-2, LS-3, LS-4, LS-5, LS-6 and DCT powders at 10 min were (i) 64.46%, 62.65%, 2.20%, 10.03%, 73.26%, 67.88% and 16.49%, respectively, in SGF and (ii) 101.56%, 106.49%, 46.24%, 85.27%, 107.85%, 96.74% and 83.50%, respectively, in SIF.

There is direct relationship between the surface area of powder particle and its dissolution rate. The surface area increases with decreasing particle size. Powders have relatively large surface area in comparison with the tablet form. Therefore, as expected, liquisolid powders demonstrated higher dissolution compared to the

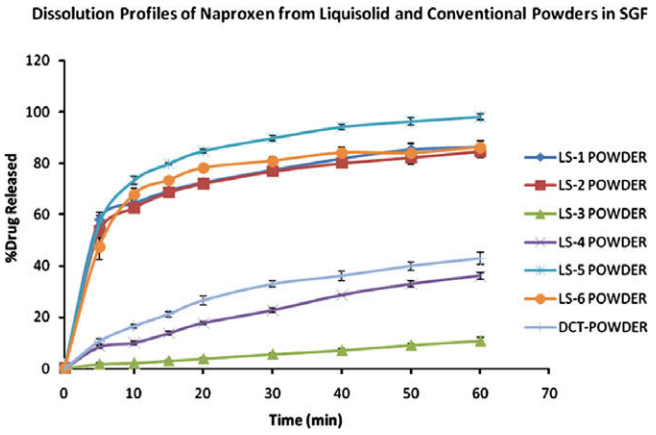

Fig. 6. Percentages of drug released (±SD) from the liquisolid powders and conventional powders in simulated gastric fluid (SGF).

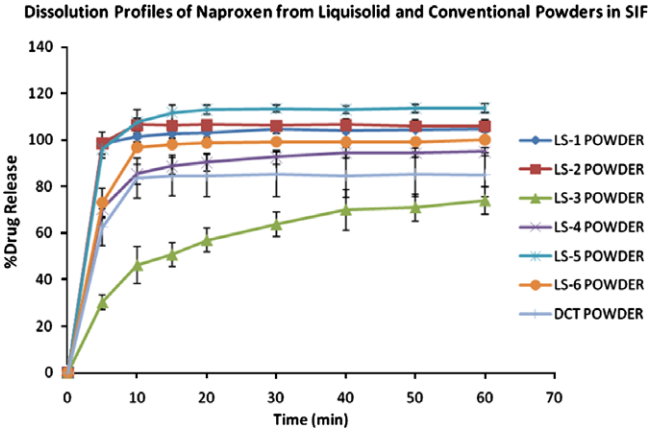

Fig. 7. Percentages of drug released (±SD) from the liquisolid powders and conventional powders in simulated intestinal fluid (SIF).

liquisolid tablets. It was also observed that liquisolid powders have a higher initial dissolution rate compared to the tablet form. This is because tablets have to disintegrate first before releasing drug particles.

In contrary to the liquisolid in tablets form, the dissolution rates of LS-5 and LS-6 powders appeared to be slightly higher than LS-1 and LS-2 powders, as shown in Figs. 6 and 7. This proved that tablet hardness and porosity will affect the dissolution rates but to lesser extent as the higher dissolution rates of LS-5 and LS-6 powders than the LS-1 and LS-2 powders that were not statistically significant ($P > 0.05$). These data confirmed that the formulation properties and composition played the major role in enhancing the drug dissolution.

LS-3 and LS-4, which were formulated with Synperonic® PE/L61, were not compactible, and the powders were agglomerated and exhibited a poor flowability. Agglomerated particles have small surface area and hence LS-3 and LS-4 powders exhibited low dissolution rates compared to DCT powder (Figs. 6 and 7). Also, the solubility of naproxen in Synperonic® PE/L61 was not as high as in PEG400 and Cremophor® EL. Therefore, it was expected that LS-3 and LS-4 have lower dissolution rates than the other liquisolid formulations (Figs. 6 and 7). As a result, Synperonic® PE/L61 is not an ideal liquid vehicle in formulating naproxen liquisolid formulations.

3.3.4. Stability studies

The stability studies of liquisolid tablets were performed to investigate whether the dissolution of liquisolid tablets in SGF

(Figs. 8A and 9A), and SIF (Figs. 8B and 9B) is affected by storage under a stressed condition of humidity. The results revealed that the dissolution rates of liquisolid tablets were not affected by the humid condition, as there was no significant difference ($P > 0.05$) in dissolution rates of aged liquisoid tablets compared to the fresh liquisolid tablets. Therefore, the liquisolid tablets were not affected by ageing. On comparing the dissolution of liquisolid tablets containing Cremophor® EL with that of liquisolid tablets formulated with PEG400 after ageing, the results of dissolution in both media (SGF and SIF) revealed that the dissolution rate of liquisolid tablets formulated with Cremophor® EL (Fig. 8) was significantly higher ($P < 0.05$) compared with tablets formulated with PEG400 (Fig. 9). Accordingly, Cremophor® EL containing tablets showed better drug dissolution before and after storage compared with PEG400 containing compacts.

3.4. Differential scanning calorimetry (DSC)

The DSC of pure naproxen is shown in (Fig. 10), while the DSC profiles of Avicel® PH102, Cab-o-sil® M-5, maize starch and powders of all liquisolid and DCT formulations are presented in Fig. 11. DSC is one of the most common applications to determine and predict the physicochemical interaction between components in a formulation. The thermogram of pure naproxen (Fig. 10) showed a sharp endothermic peak (T_{onset} = 156.21 °C, T_m = 157.49 °C, ΔH_{fusion} = 139.8 J/g) due to drug melting. The sharp endothermic peak indicated that the naproxen was in crystalline anhydrous state. Both thermogram of Avicel® PH102 and maize starch (Fig. 11) displayed very broad peaks. The thermogram of Avicel® PH102 displayed a broad peak at 70.36 °C, and a very weak peak at 117.93 °C. Those peaks might correspond to the evaporation of water associated with Avicel® PH102 particles. The thermogram of Cab-o-sil® M-5 showed a small

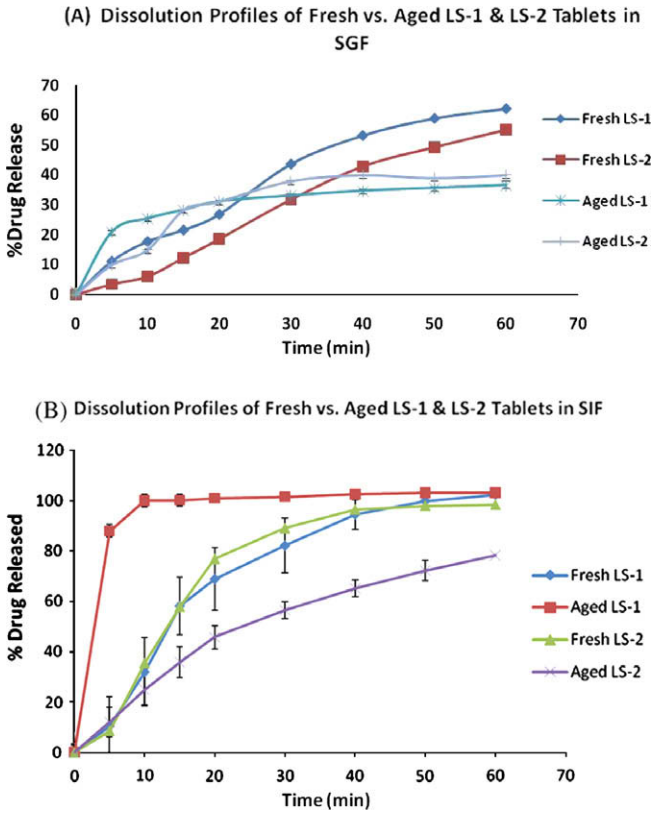

Fig. 8. Percentages of drug released (±SD) from fresh vs. aged LS-1 and LS-2 tablets in: (A) simulated gastric fluid (SGF) and (B) simulated intestinal fluid (SIF).

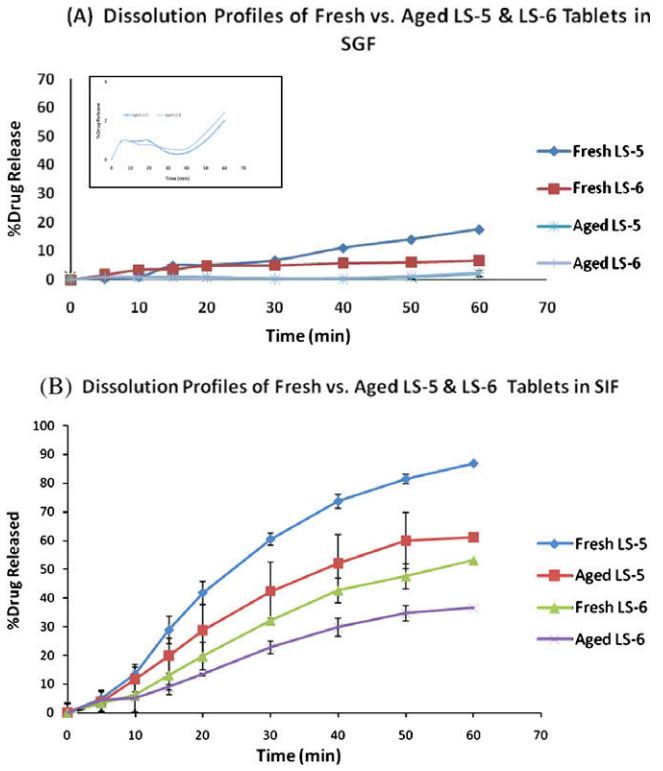

Fig. 9. Percentages of drug released (±SD) from fresh vs. aged LS-5 and LS-6 tablets in: (A) simulated gastric fluid (SGF) and (B) simulated intestinal fluid (SIF). The insert shows the dissolution profiles of the aged LS-5 and LS-6 (overlapped in the main Figure).

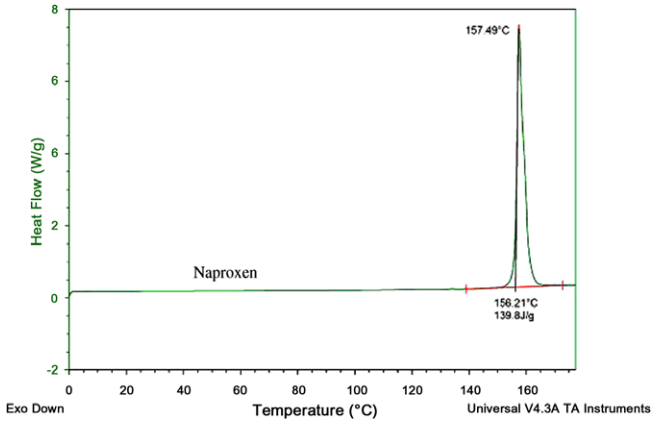

Fig. 10. DSC thermogram of pure naproxen.

peak at 117.77 °C which implied that the Cab-o-sil® M-5 was nearly in an amorphous state [6].

DSC thermograms of liquisolid formulations (Fig. 11) revealed a peak at about 74–90 °C which was markedly broadened, the intensity was reduced and the characteristic melting peak of naproxen was completely disappeared. This is an indicative of complete solubilisation of naproxen and/or interactions between the naproxen and the excipients [18,36]. The broad peak in the DSC profiles of liquisolid formulations might be corresponded to the melting and decomposition of the whole liqui-solid system [6]. From the thermogram of DCT formulation (Fig. 11), the characteristic melting peak of naproxen was presented at 156.56 °C, indicating that there are no changes in crystallinity or interaction between drug and excipients in the conventional formulation. The melting point of

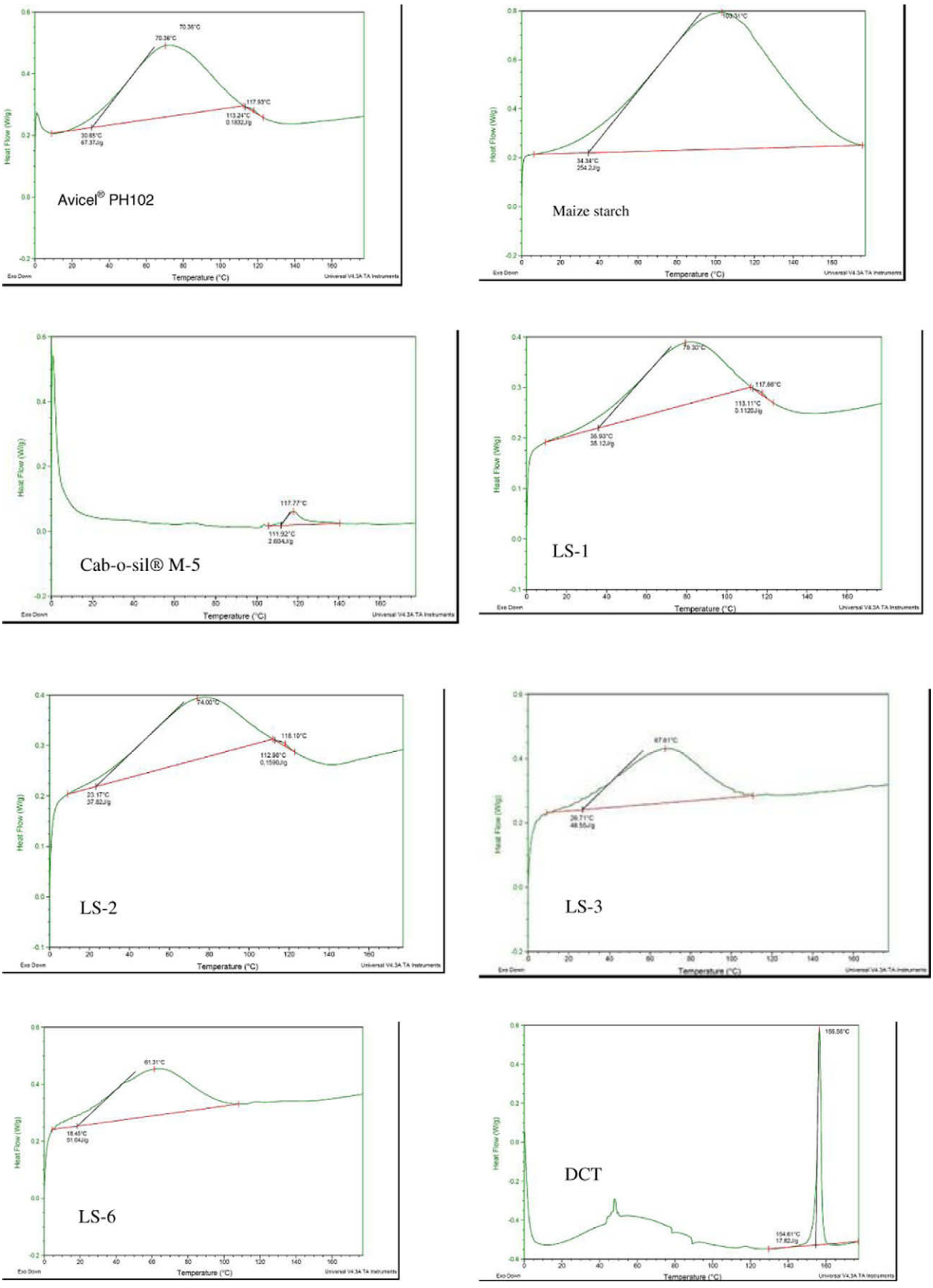

Fig. 11. DSC thermograms of pure excipients and naproxen within liquisolid formulations. For compositions refer to Table 1.

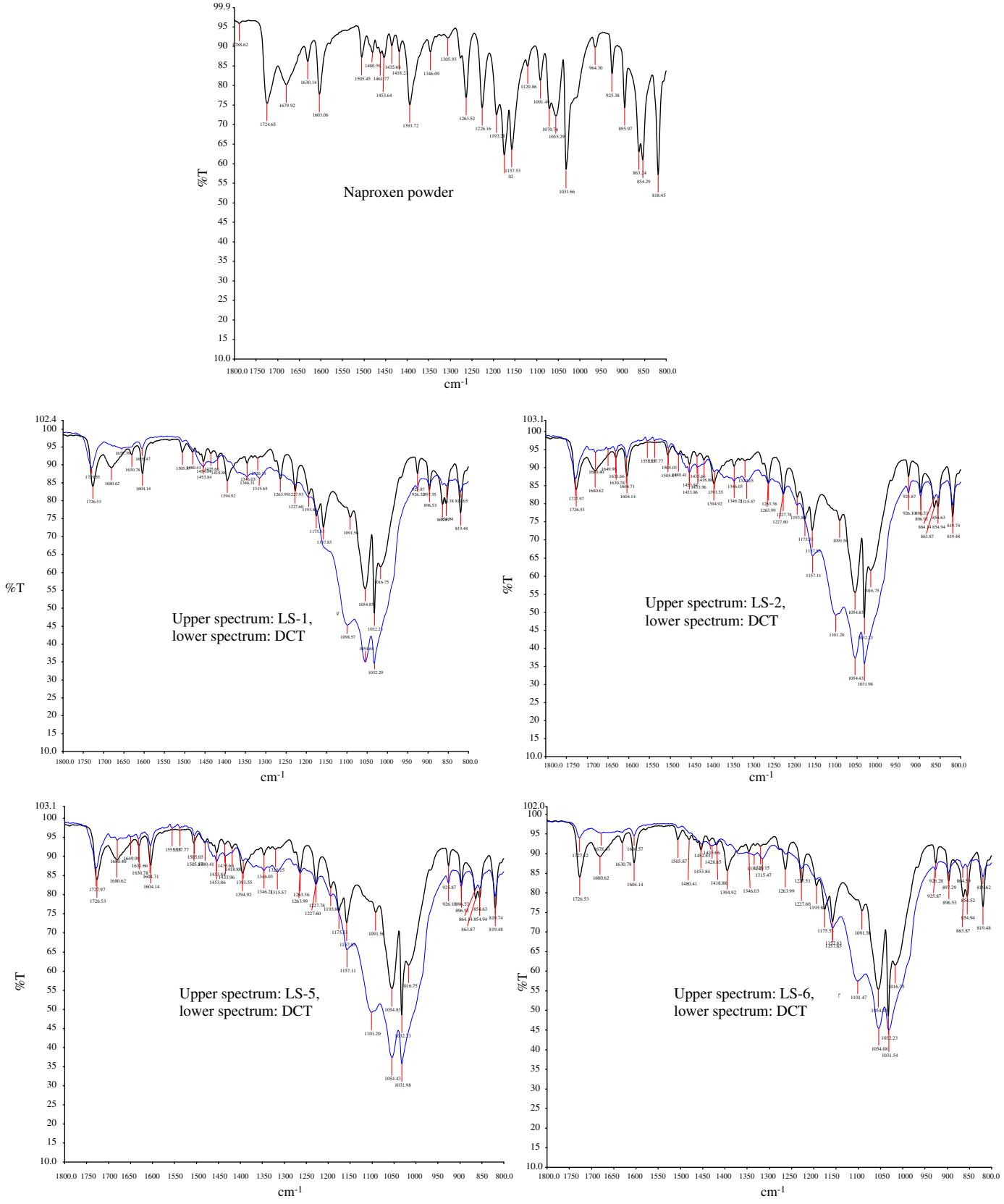

Fig. 12. FT-IR spectra of naproxen, liquisolid: LS-1, LS-2, LS-5 LS-6 and conventional DCT powders. For compositions refer to Table 1.

a substance is closely related to its solubility via latent heat of fusion, which is the amount of heat generated during melting or fusion. Generally, crystal with weak bonds has a low-melting point and low heat of fusion. On the contrary, crystal with strong bonds gives high melting point and high heat of fusion. The structure of the drug crystal has to be disrupted in order to disperse or solubi-

lise in a solvent. Accordingly, high melting point usually reflects low solubility [37].

3.5. Fourier transform infrared (FT-IR)

Samples of pure naproxen, liquisolid (LS-1, LS-2, LS-5 and LS-6) and conventional (DCT) powders were subjected to FT-IR spectroscopic analysis, and their spectra at 800–1800 cm^{-1} are shown in (Fig. 12). The characteristic absorption bands of naproxen are the C=O stretching region, which are between 1600 and 1800 cm^{-1}. A reduction in intensity of the characteristic absorption bands of naproxen were observed in liquisolid formulations, which might be attributed to the hydrogen bonding interaction between the carboxylic group of naproxen and the hydroxyl group of the liquid vehicles; this resulted in drug dissolution enhancement as shown by dissolution data.

4. Conclusions

In conclusion, this study showed that liquisolid technique could be a promising strategy in improving dissolution of poorly water-soluble drugs and formulating immediate release solid dosage forms. The results generated in this study described the relationship between formulation variables and dissolution profiles.

The liquisolid tablets formulated with Cremophor® EL at drug concentration of 20%w/w is the best formulation among the six batches of liquisolid tablets prepared, in terms of faster disintegration time, superior dissolution profile and acceptable tablet properties. Cremophor® EL is a promising new liquid vehicle in formulating liquisolid formulations. Liquisolid technique changes the properties of naproxen particles by simply dispersed the drug particles in a non-volatile hydrophilic liquid vehicle, which in turn increase the wetting properties and surface area of drug particles, and hence improve the dissolution profiles and might be oral bioavailability of the drug. At present, naproxen is available commercially in high dose tablets between 250 and 500 mg; the liquisolid formulations may help in reduction in this dose. The stability studies showed that the dissolution of liquisolid tablets was not affected by ageing significantly. Furthermore, DSC revealed that drug particles in liquisolid formulations were completely solubilised in the liquid vehicle.

The liquid vehicle plays a contribution role in improving dissolution profiles of a poorly water-soluble drug in liquisolid formulations, besides choosing a suitable liquid vehicle according to its viscosity and HLB value. The key step in formulating a successful liquisolid tablets is determination of optimal flowable liquid-retention potential (Φ-value).

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