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Liquisolid technique to enhance and to sustain griseofulvin dissolution: Effect of choice of non-volatile liquid vehicles

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ABSTRACT

Liquisolid systems were originally designed to enhance dissolution of hydrophobic drugs. Recently, the same technique was explored to control drug release via hydrophobic carriers. This work aimed to study the effects of different liquid vehicles on release characteristics of griseofulvin as a model hydrophobic drug. Fast dissolution tablets were prepared using three different non-ionic surfactants namely Cremophor®EL, Synperonic®PE/L61 and Capryol™ 90, on the contrary Kollicoat®SR 30D was used for production of grieseofulvin sustained release formulations. Avicel® PH102 and Cab-O-Sil® M5 were used as carrier and coat materials, respectively. The effect of formulation parameters, such as drug concentration and carrier to coat ratio, on enhancing drug dissolution was explored. Drug concentrations of 20% and 40% (w/w), and *R*-values (carrier to coat ratio) of 10 and 20 were used. The mathematical model was utilized to formulate liquisolid powder systems. All fast release liquisolid formulations showed higher percentage drug dissolution efficiency (%DE) than conventional directly compacted tablets. Cremophor®EL showed the best dissolution enhancement with %DE of about 90%, compared to only 23% for conventional tablets; DSC data suggested loss of griseofulvin crystallinity and thermal behavior. Kollicoat® SR 30D retarded the drug release even in the presence of hydrophilic carrier; DSC data suggested that only small fraction of the drug was present in the molecular state within the system. The used liquisolid vehicles showed promise to enhance and to control (depend on the choice of the liquid vehicle) the release of griseofulvin from liquisolid compacts.

1. Introduction

Recent advances in drug discovery are continuously increasing the number of lipophilic molecules which are difficult to deliver due to bioavailability issues. These drugs are a challenging concern for industry due to poor and irregular solubility, resulting in poor bioavailability. One of the techniques used to improve drug solubility is the preparation of liquisolid compacts. From the historical point of view, liquisolid compacts were evolved from 'powdered solutions' which depended on preparing a true solution of the drug in a high boiling point, water-miscible solvent, which was carried out on the extensive surface of an inert carrier such as silica. Since dissolution of a non-polar drug is often the rate limiting step in gastrointestinal absorption, better bioavailability of an orally administered water-insoluble drug is achieved when the drug is already in solution, thereby displaying enhanced dissolution rates (Kulkarni et al., 2010).

A liquisolid system refers to formulations formed by converting liquid drugs (oil), drug suspensions or drug solution in non-volatile liquid vehicle into dry, non-adherent, free-flowing and compactible powder mixtures. This is usually obtained by mixing the liquid medication (drug and liquid vehicle) with a carrier excipient that forms a thin layer around the drug particles. The obtained liquid medication-carrier system is blended with an adsorbing agent (commonly known as coating agent) so as to get an apparently dry looking, free flowing powder mix that can be easily compacted into tablets. Various grades of cellulose, starch, lactose are used as the carriers, whereas very fine silica powder is used as the coating material. The good flow and compression properties of liquisolid system may be accredited to the large surface area of silica and fine particle size of carriers (Spireas et al., 1992).

Spireas and Sadu (1998) and Spireas et al. (1998) were pioneers in formulating liquisolid tablets, where the dissolutions of pridinsolone and hydrocortisone were improved by using the liquisolid technique. Since then, many research articles were performed using the same approach to improve dissolution of many drugs (for example see Nokhodchi et al., 2005; Javadzadeh et al., 2005; Fahmy and Kassem, 2008; Tiong and Elkordy, 2009; Yadav and Yadav, 2009;

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Akinlade et al., 2010; Hentzschel et al., 2012). The enhanced drug dissolution by liquisolid method could be attributed to increased surface area, increased aqueous solubility, and improved wettability of drug particles (Javadzadeh et al., 2007a). By the proper design of the liquisolid formulation, a powder mix of good flow and compaction properties could be obtained. Therefore, this technique is industrially applicable due to simplicity and comparable low cost (Hentzschel et al., 2012). Moreover, stability issues are of no major concern as it was reported that these compacts are not greatly affected by different storage conditions (Javadzadeh et al., 2009, 2007a; Sheth and Jarowski, 1990; Tiong and Elkordy, 2009).

Liquisolid systems were initially designed to improve drug dissolution. Recently, it was investigated as a possible means to sustain the drug release by proper selection of carrier excepients. Sustained release dosage forms are designed to release the drug at a predetermined rate by maintaining a constant drug release for specific period of time with minimum side effects in terms of efficacy, safety and patient compliance. So far, only few drugs, to the best of our knowledge, have been formulated as liquisolid systems with prolonged drug release (Gonjari et al., 2009; Javadzadeh et al., 2008; Nokhodchi et al., 2010, 2007). The reported sustained drug release liquisolid formulations based mainly on using hydrophobic carriers such as Eudragit® RL or RS instead of hydrophilic carriers, or hydrophilic carrier with the incorporation of retarding agent as HPMC (Gonjari et al., 2009). Hydrophobic carriers may lead to poor wetting properties of the compacts resulting in slow disintegration and thus, prolonged drug release. In the present study, a different approach (choice of liquid vehicles) will be applied to sustain drug release from liquisolid formulations.

The aim of this work was to utilize the liquisolid technique to modify the drug release rate, using griseofulvin as a model drug. Both fast and sustained release formulations were prepared, based only on the selection of a proper vehicle for the intended purpose. As there is no single non-volatile liquid vehicle which is suitable for a variety of hydrophobic drugs in preparing liquisolid tablets, in this study three different non-ionic surfactants were used (Cremophor® EL, Synperonic® PE/L61 and Capryol™ 90) as the liquid vehicles for fast release griseofulvin formulations. The work also explored the effect of some critical formulation parameters, such as drug concentration, carrier to coat ratio, on the drug release. Kollicoat® SR 30 D, a polyvinyl acetate dispersion used mainly for the production of sustained-release formulations and taste masking purposes due to its water insolubility characters (Zezhi et al., 2002) was used as a vehicle for sustained release griseofulvin formulations. The theoretical model of liquisolid systems (Spireas and Bolton, 1999) was applied to calculate the appropriate quantities of carrier and coating excipients for each liquid vehicle required to produce acceptable flowing and compactible powders. The selected powders were then compacted into tablets and the physicomechanical and physicochemical characterizations were performed. The in vitro drug dissolution of liquisolid formulations were compared to that of conventional directly compacted tablets.

2. Materials and methods

2.1. Materials

Griseofulvin was purchased from Sigma–Aldrich, Poole, UK. Microcrystalline cellulose (Avicel® PH102) from FMC Corporation, Philadelphia, USA; colloidal silicon dioxide (Cab-O-Sil® M5, particle size of 0.2–0.3 μm) from Cabot Corporation, Rheinfelden, Germany; polyvinyl acetate (Kollicoat® SR 30D) and Polyoxyl 35 castor oil (Cremophor® EL) from BASF Aktiengesellschaft, Ludwigshafen, Germany were used. Propylene glycol monocaprylate (Capryol™ 90) was obtained from Gattefosse, France and Poloxamer 181 (Synperonic® PE/L61) was obtained from ICI surfactants, Everberg, Belgium. Other ingredients were of analytical grade.

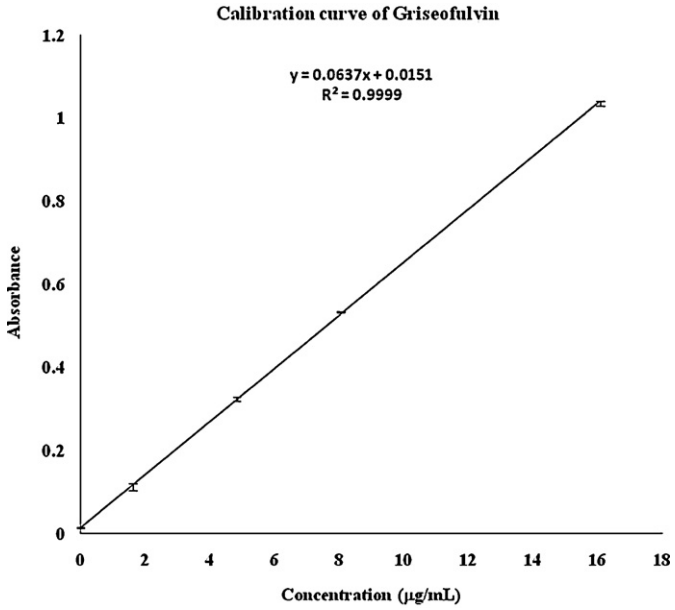

Fig. 1. Griseofulvin calibration curve.

2.2. Solubility studies

The solubility studies of griseofulvin were performed as explained by Spireas and Sadu (1998). The solubility of griseofulvin was determined in Cremophor® EL, Synperonic® PE/L61, Capryol™ 90, Kollicoat® SR 30D, and in distilled water. Saturated solutions in respective solvents were prepared by adding an excess amount of griseofulvin and rotated for 72 h to reach equilibrium at 25 °C using a mechanical shaker (Stuart Rotator, UK). The filtered supernatants were further diluted with ethanol and analyzed spectrophotometrically using a UV/visible spectrophotometer (Model M501, Camspec Ltd., Cambridge, UK) at 291 nm for their griseofulvin content. The solubility of griseofulvin in the respective liquid vehicle was calculated (after the suitable dilution with ethanol which was used as a blank) using griseofulvin calibration curve (Fig. 1).

2.3. Measuring angle of slide

This experiment was designed to measure the flowable liquid retention potential (Φ-value) for Avicel® PH102 (carrier material, Φ_{Ca}) and Cab-O-Sil® M5 (coating material, Φ_{Co}), and the optimum liquid load factor (L_f). The Φ-value of a powder is the maximum amount of a given non-volatile liquid that can be retained inside powder bulk (w/w) while maintaining acceptable flowability. Whereas, L_f is the mass ratio (w/w) of the liquid medication to the carrier powder in the liquisolid formulation. Powder admixtures containing 5 g of either carrier or coating with increasing quantity of non-volatile liquid vehicle (Cremophor® EL, Synperonic® PE/L61, Capryol™ 90, Kollicoat® SR 30D) were mixed using a mortar and pestle. Each admixture was then placed on a shiny metal plate; the plate was then tilted till the admixture slides. The angle formed between the plate and the horizontal surface, at which admixture slides were measured as angle of slide (θ). The flowable liquid retention potential was calculated using the following Eq. (1)

$$\Phi \text{ value} = \frac{\text{Weight of non-volatile liquid}}{\text{Weight of carrier or coat}} \quad (1)$$

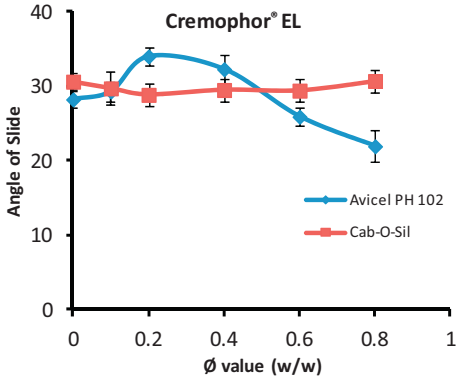

Fig. 2. Angle of slide for different mixtures of Avicel® PH102 and Cab-O-Sil® M5 with Cremophor® EL.

Each admixture has specific Φ-values (Φ_{Ca} and Φ_{Co} were used for carrier Φ-values and coating Φ-value, respectively) which were determined and plotted against respective measured angle of slide for all non-volatile liquid vehicles (see Fig. 2 for Cremophor® EL, as an example). The Φ-value which corresponded to an angle of slide of 33° was reported to represent the flowable liquid retention potentials of powder admixture (Akinlade et al., 2010).

2.4. Preparation of powders for liquisolid and conventional tablets

Several griseofulvin liquisolid formulations were prepared in batches of 50 tablets, at two different drug concentrations of 20 and 40% (w/w) in liquid vehicles. Each formulation contains Avicel® PH102 as carrier and Cab-O-Sil® M5 as coating material, at carrier/coat ratio (R-value) of 10 and 20 for fast dissolving formulations, while it was kept at 10 for sustained release ones. The appropriate amounts of carrier and coating materials used for each formulation depend upon L_f of that formulation. The Φ_{Ca} and Φ_{Co} values for each particular liquid vehicle were used to calculate L_f (Eq. (2)) of that respective liquid vehicle. Once the liquid load factor (L_f) and amount of liquid medication (W) were determined, amount of carrier (Q) and coating (q) can be calculated by rearranging Eqs. (3) and (4). Table 1 summarizes the liquisolid formulations, where LS1-LS12 represents fast release formulations and LS13-LS14 represents sustained release griseofulvin formulations.

$$L_f = \Phi_{Ca} + \Phi_{Co} \times \frac{1}{R} \quad (2)$$

$$L_f = \frac{W}{Q} \quad (3)$$

$$R = \frac{Q}{q} \quad (4)$$

The drug-vehicle liquid system was produced by mixing griseofulvin (20 mg/tablet) in non-volatile liquid vehicle using a mortar and pestle. To this liquid medication, the calculated amount of the carrier (Avicel® PH102) was added by continuous mixing in the mortar. Then, coating material (Cab-O-Sil® M5) was carefully added and mixed until mortar contents start to look like dry powder. In the last stage of the preparation, a 5% (w/w) maize starch as a disintegrant and 0.75% (w/w) of magnesium stearate as a lubricant were added and mixed. To ensure proper mixing of excipients, all formulations were rotated in turbula mixer (System Schatz, Basel, Switzerland) for 5 min. All liquisolid preparations were compacted into tablets using a single punch tablet machine (Type 3, Manesty Machines Ltd., Liverpool, UK) having flat-faced punch with a compression force that provide acceptable tablet hardness. Two of the formulations (LS2 and LS8) were not compactible, accordingly

Table 1
Key formulation characteristics of prepared formulations.

Formula	Non-volatile liquid vehicle	Drug conc. in liquid vehicle (%, w/w)	Carrier: coating (R)	Liquid vehicle (mg)	Active ingredient (mg)	Carrier (Q) (mg)	Coating (q) (mg)	Liquid load factor (L_f)	Disintegrant (mg)	Lubricant (0.75%) (mg)	Unit dose (mg)
LS1	Cremophor® EL	20	10	80	20	384.61	38.46	0.26	26.15	4.11	549.2
LS2		40	10	30	20	192.30	19.23		13.07	2.05	274.6
LS3	Synperonic® PE/L61	20	10	80	20	1000	100	0.10	60	9.45	1260
LS4		40	10	30	20	500	50		30	4.72	630
LS5	Capryol™ 90	20	10	80	20	500	50	0.20	32.5	5.11	682.5
LS6		40	10	30	20	250	25		16.25	2.55	341.25
LS7	Cremophor® EL	20	20	80	20	454.5	22.7	0.26	28.86	4.54	610.7
LS8		40		30	20	227.3	11.4		14.43	2.27	305.4
LS9	Synperonic® PE/L61	20	20	80	20	1111.1	55.55	0.10	63.33	9.97	1340
LS10		40		30	20	555.5	27.77		31.67	4.98	669.9
LS11	Capryol™ 90	20	20	80	20	555.55	27.77	0.20	34.17	5.38	723
LS12		40		30	20	277.77	13.88		17.08	2.69	361.5
LS13	Kollicoat® SR 30D	20	10	80	20	200	20.0	0.5	16.0	2.52	336
LS14		40	10	30	20	100	10.0		8.00	1.26	168
CT	Conventional tablets	–	–	–	20	250	50	–	16.25	2.5	338.8

no tablets were produced for LS2 and LS8. For comparison, conventional griseofulvin (20 mg/tablet) tablets (CT) were prepared by mixing all tablet excipients, except non-volatile liquid vehicle (Table 1), using turbula mixer for 10 min, followed by compression.

2.5. Pre-compression studies

2.5.1. Determination of flow property

Flowability of liquisolid admixture is important in formulation of tablet dosage form on industrial scale. Therefore, it was essential to study the flowability of these liquisolid powder admixtures prior to compression. Flowability can be evaluated using parameters such as Carr's index or angle of repose (Banker, 1987). Therefore, flowability was determined using Carr's compressibility index (CI %), which depends upon tapped and poured bulk densities of the admixture. Tap volumeter (J. Engelmann AG, Ludwigshafen, Germany) was used to determine tapped and poured densities of the admixtures. A weighed quantity of the prepared admixture was poured into 100 mL cylinder. Then, poured bulk volume (V_b) and tapped volume (V_t) were obtained after sufficient taps. By knowing V_b and V_t values, poured bulk density (P_b) and tapped density (P_t) were calculated. As per British Pharmacopoeia (2011), powders with CI% below 25 shows better flow properties. The CI% of each powder mix was calculated using Eq. (5) (Carr, 1965).

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

2.5.2. Differential scanning calorimetry (DSC)

DSC is used to detect any physicochemical interaction between drug and excipients. The DSC thermograms of carrier material, coating material, and powder mix for conventional and liquisolid preparations were obtained using DSC refrigerated cooling system (Model Q1000, TA Instruments, UK). All samples (2–4 mg) were weighed and hermetically sealed in aluminum pans. After calibration of instrument with sapphire and indium, thermal behaviors of samples were examined from 20 °C to 280 °C, at a scanning rate of 10 °C/min.

2.5.3. Fourier transform infrared spectroscopy (FTIR)

FTIR spectroscopy helps to determine any chemical interaction between drug and excipients used in formulation. The FTIR spectra for griseofulvin, carrier, coating, powder mix for liquisolid and conventional preparations were obtained using PerkinElmer FTIR system spectrum BX series (Beaconsfield, Buckinghamshire, UK), in the frequency range of 4000–500 cm^{-1} and resolution of 4 cm^{-1}. 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.

2.6. Quality control studies

Formulated liquisolid and conventional tablets were evaluated by quality control tests as described in British Pharmacopoeia (2011).

2.6.1. Physical characterization tests

All tablets were evaluated regarding weight variation, content uniformity, hardness, disintegration time and friability.

2.6.2. In vitro dissolution studies

The in vitro drug release studies were performed according to the British Pharmacopoeia (2011) conditions for griseofulvin dissolution. The USP dissolution apparatus II (Caleva Ltd., Dorset, UK) was used at 100 rpm and the test was run for pure drug, conventional tablets and liquisolid compacts (LS1-LS14). The distilled water (1000 mL) was used as a dissolution medium at 37 ± 1 °C. Samples (10 mL) of dissolution medium were collected at specified time intervals (5, 10, 15, 20, 25, 30, 45, 60, 90 and 150 min) and the collected samples were analyzed for drug content, using UV/visible spectrophotometer at 291 nm and the constructed calibration curve (Fig. 1). The dissolution time was conducted for 90 and 150 min for fast release and sustained release formulations, respectively.

2.7. Dissolution data analysis

To analyze the in vitro release data of all liquisolid compacts and to predict the time required for the release of 50% and 90% of the initial drug dose from Kollicoat® SR 30D containing formulations, various kinetic models were used to describe the release kinetics. The following plots were made: amount of drug released versus time (zero order kinetic model); amount of drug released versus time (first order kinetic model); amount of drug released versus cube root of time (Hixson–Crowell cube root law), and amount of drug released versus square root of time (Higuchi model).

2.8. Stability studies

Selected immediate release liquisolid tablets (LS1, LS3, LS4, LS5 and LS10) were stored at 23 °C and 63% relative humidity (RH) conditions for 4 weeks. Dissolution study of stored tablets was performed to test for any aging effect after storage at high RH.

2.9. Statistical analysis

Student *t*-test was used to analyze all the data. Results were quoted as significant where $P < 0.05$.

3. Results and discussion

3.1. Solubility study of griseofulvin

The solubility of griseofulvin in the nonionic surfactants Cremophor® EL, Synperonic® PE/L61 and Capryol™ 90 was 4.961 ± 0.54, 1.469 ± 0.32 and 3.726 ± 0.41 mg/mL, respectively. For Kollicoat® SR 30D, liquid vehicle for sustained release formulations, the solubility was limited to 0.415 mg/mL. The drug was practically insoluble in distilled water. From the results, the liquid vehicle in which the drug has the highest solubility is supposed to enhance rate of drug dissolution the most and the liquid vehicle with minimum drug solubility in (least drug solubility) retards the rate of drug release (Javadzadeh et al., 2008). The solubility of a drug in the solvent is affected by physicochemical properties of the solvents such as hydrophilicity and polarity (Tiong and Elkordy, 2009), Cremophor® EL has the highest hydrophilicity and polarity, as indicated by its high hydrophilic lipophilic balance (HLB) value (Section 3.4.2), compared to other solvents and accordingly the drug has the highest solubility in Cremophor® EL.

3.2. Measuring angle of slide for determination of flowable liquid retention potential (Φ-value) for Avicel® PH102 and Cab-O-Sil® M5 and optimum liquid load factor (L_f)

Angle of slide determination is an important step in the formulation of liquisolid tablets. The relationship of angle of slide with corresponding Φ_{Ca} and Φ_{Co} for Cremophor® EL liquid vehicle can be seen in Fig. 2. The Φ_{Ca} and Φ_{Co} values are listed in Table 2. The Φ_{Ca} and Φ_{Co} values for respective non-volatile liquids were used to calculate L_f (refer to Eqs. (2) and (3)). The L_f was then used to decide the optimum amount of carrier and coating

Table 2
Liquid-retention potentials (Φ value) for carrier (Φ_{Ca}) and coating material (Φ_{Co}) for each liquid vehicle, with the corresponding liquid load factor (L_f).

Liquid vehicle	Cremophor® EL	Synperonic® PE/L61	Capryol™ 90	Kollicoat® SR 30 D
Φ_{Ca}	0.18	0.08	0.16	0.4
Φ_{Co}	0.80	0.20	0.40	1.0
L_f	0.26	0.10	0.20	0.5

materials required to ensure dry looking, free flowing and compactible powdered systems (Spireas et al., 1992; Tiong and Elkordy, 2009). In this study, the dry looking, free flowing and compactible properties of the prepared griseofulvin powder admixtures were evaluated depending on powder Carr's compressibility index (Sections 2.5.1 and 3.3.1). The lowest liquid load factor was shown for formulations containing Synperonic® PE/L61 and accordingly the amount of carrier and coating materials was higher compared to other formulations (Table 2). This is may be due to higher viscosity of Synperonic® PE/L61 (1.0 Pa s, Tiong and Elkordy, 2009) compared to those of Cremophor® EL (0.65–0.80 Pa s, Tiong and Elkordy, 2009) and Capryol™ 90 (0.069 Pa s, as determined for this research using Haake VT 500 viscometer (Thermo Fischer Scientific, UK)).

3.3. Pre-compression studies (characterization of powder admixtures)

3.3.1. Determination of flow property

Powder flowability is crucial in the industrial production of tablet dosage forms, as uniform powder stream through hopper confirms uniformity of both tablet weight and drug content. Determination of Carr's compressibility index, the ratio of bulk and tap density, was used to measure the flowability of all liquisolid formulations. The results are shown in Table 3, where powders having CI% below 25 represent better flow properties (British Pharmacopoeia, 2011). The obtained results indicate that all formulations have CI% values which were less than 25. However, formulation containing 40% (w/w) drug in Cremophor® EL (LS8) showed poor flow with CI% of 24.52% and it was not compactible into tablets.

3.3.2. Differential scanning calorimetry (DSC)

DSC was used for the investigation of any interaction between the drug and its excipients. Fig. 3 shows the thermograms for griseofulvin conventional powder admixture; LS1, LS4, LS5 (as examples for Cremophor® EL, Synperonic® PE/L61 and Capryol™ 90 containing liquisolid formulations, respectively); LS13 and LS14 liquisolid powders. *R*-value (either 10 or 20) has no effect on formulation

Table 3
Flow properties of liquisolid powder mixtures.

Formulation[a]	Carr's Index (CI%)	Type of flow
LS1	18.78 ± 1.3	Fair
LS2	17.42 ± 1.2	Fair
LS3	15.10 ± 2.1	Good
LS4	22.05 ± 1.9	Passable
LS5	22.65 ± 1.5	Passable
LS6	22.31 ± 2.3	Passable
LS7	23.62 ± 1.3	Passable
LS8	24.52 ± 2.4	Poor
LS9	19.41 ± 1.0	Fair
LS10	11.92 ± 0.8	Excellent
LS11	13.64 ± 1.1	Excellent
LS12	16.66 ± 2.0	Good
LS13	22.34 ± 1.1	Passable
LS14	17.61 ± 1.7	Fair

[a] Details of each formulation are listed in Table 1.

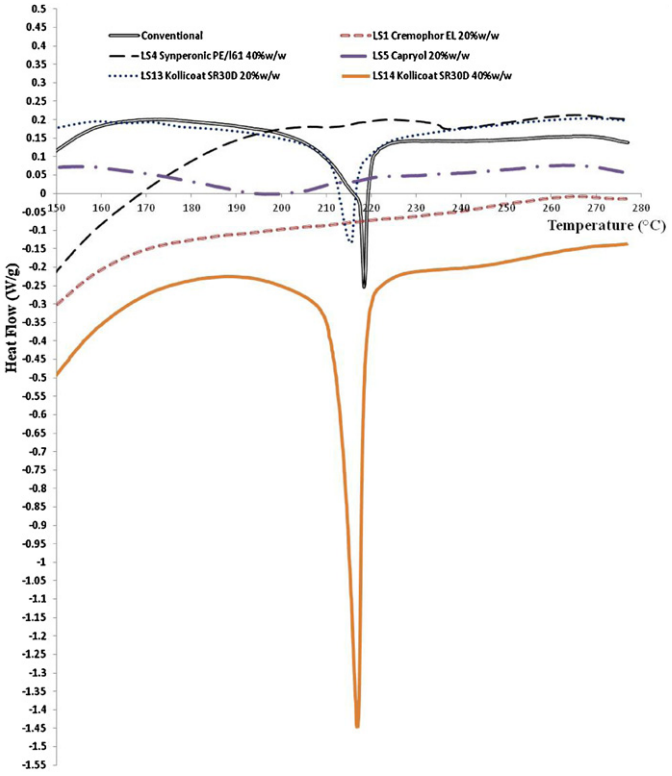

Fig. 3. Differential scanning calorimetery for griseofulvin conventional and liquisolid formulations (endothermic down).

DSC thermograms. The thermogram of griseofulvin, as indicated by Jarmer et al. (2005), showed a sharp endothermic peak at T_m of 219.6 °C, corresponding to its melting point, and high enthalpy of 112 J/g, indicating the drug crystallinity. Disappearance of this characteristic peak or shiftening to a lower T_m would indicate change in the crystalline nature of the drug.

The thermogram for conventional preparation shows griseofulvin peak at slightly lower T_m of 218.3 °C with reduction in the peak intensity, indicating a very slight change in drug crystallinity in conventional formulation (Fig. 3). For LS1 and LS4, the drug endothermic peak completely disappeared indicating that the drug is completely solubilized and molecularly dispersed with excipients within the liquisolid system. This would explain the improved drug dissolution from Cremophor® EL and Synperonic® PE/L61 formulations with burst effect (refer to Fig. 6) compared to griseofulvin conventional preparation. For Capryol™ 90 containing drug liquisolid formulations, the DSC scan revealed, as shown with LS5, a small broad endothermic peak at 196.3 °C with very small enthalpy (3.55 J/g), indicating reduction of both griseofulvin melting point and crystallinity (and not complete solubilization of the drug in the liquid vehicle as in the case of the above two mentioned liquid vehicles (LS1 and LS4)). The reduction of drug crystallinity had a positive effect in enhancing the drug release from Capryol™ 90 containing liquisolid formulations (refer to Fig. 6). With sustained release formulations (LS13 and LS14), the thermograms show a clear sharp endothermic peak at T_m of 217 °C and reduction in the enthalpy. This indicates that the drug retain its crystalline nature when mixed with Kollicoat® SR 30D. The slight reduction in T_m may be due to the presence of a small fraction of the drug in the molecular state within the system. Such findings could explain the slow release characteristics of the drug from LS13 and LS14 (Fig. 9) as the drug is present mainly in suspension form, in addition to its slow diffusion through the liquid coat surrounding each individual drug particle.

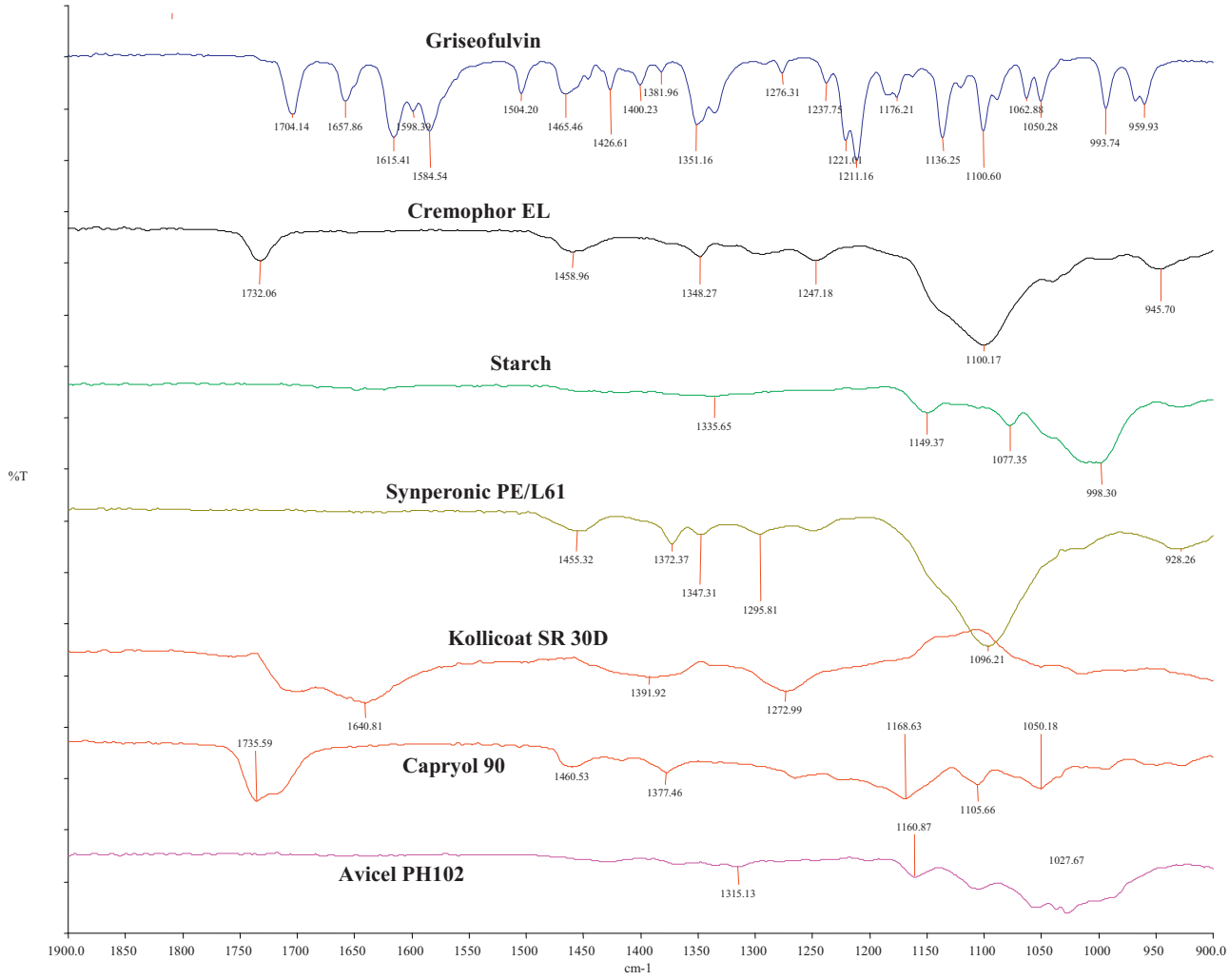

Fig. 4. Fourier transform infra red (FTIR) spectra of pure griseofulvin and pure excipients.

3.3.3. Fourier transfrom infra red spectroscopy (FTIR)

If the drug and the liquid vehicle or excipients interact, the peaks corresponding to the functional groups in the drug FTIR will shift to different wavenumbers compared to spectra of the pure drug and pure excipients (Silverstein et al., 1991). Fig. 4 exhibited the FTIR spectra of pure drug and pure excipients used in the liquisolid formulations. The spectrum of pure griseofulvin shows characteristic peaks at between 1750 and 1500 cm^{-1} due to the C=O stretch of the benzofuranone ring, cyclohexanone carbonyl and C=C stretch of the cyclic ring (Townley, 1979).

FTIR spectra of liquisolid admixture (with both *R*-values, 10 and 20) prepared with low drug concentration (20%, w/w) showed decrease intensity of all peaks compared to admixture prepared with high drug concentration (40%, w/w) (Fig. 5). There were: (i) a small shift for the griseofulvin peak from 1704 to 1706 cm^{-1}; (ii) appearance of new peak at about 1540 cm^{-1}; (iii) splitting of the drug peak at 1659 cm^{-1} into two peaks in FTIR spectra for griseofulvin with Cremophor® EL, indicating drug–liquid vehicle interaction. Same changes were noticed in FTIR spectra of drug liquisolid formulations containing Synperonic® PE/L61; this interaction can explain the enhanced drug release from those formulations compared to drug alone (see Fig. 6).

For FTIR spectra of Capryol™ 90 containing formulations (Fig. 5), there were shifts of the characteristic drug bands to higher wavenumbers (for example shift of drug peak from 1615 to 1618 cm^{-1}). Also, there were disappearance of the peak at 1585 cm^{-1} and appearance of a new peak at about 1540 cm^{-1}, suggesting hydrogen bonding between the hydroxyl group of the liquid vehicle and the carboxylic group of griseofulvin (which was favorable for drug dissolution improvement, Fig. 6).

For FTIR spectra of Kollicoat® SR 30D containing formulations (Fig. 5), there were only minor shifts of the characteristic drug bands to higher wavenumbers (for example shifts of drug peak from 1704 to 1707 cm^{-1} and from 1615 to 1616 cm^{-1}). These small shifts indicate a lack of interaction between this vehicle and the drug (accordingly, the drug dissolution behavior from those formulations was different compared to Cremophor® EL, Synperonic® PE/L61 and Capryol™ 90 liquisolid drug formulations, See below). The FTIR data confirmed DSC results.

3.4. Quality control studies

3.4.1. Weight uniformity, content uniformity, hardness, friability and disintegration time tests

All prepared tablets complied with the pharmacopeial required specifications for the weight variation and content uniformity tests. Results of hardness, friability, disintegration time are represented in Table 4. Hardness test showed an average hardness of liquisolid tablets ranging from 2.3 ± 0.73 to 9.2 ± 1.1 Kg/cm^2, compared to 10.6 ± 2.5 Kg/cm^2 for conventional tablets. Generally, formulations with higher *R*-value showed more hardness, higher compactness of this group of tablets may be due to the

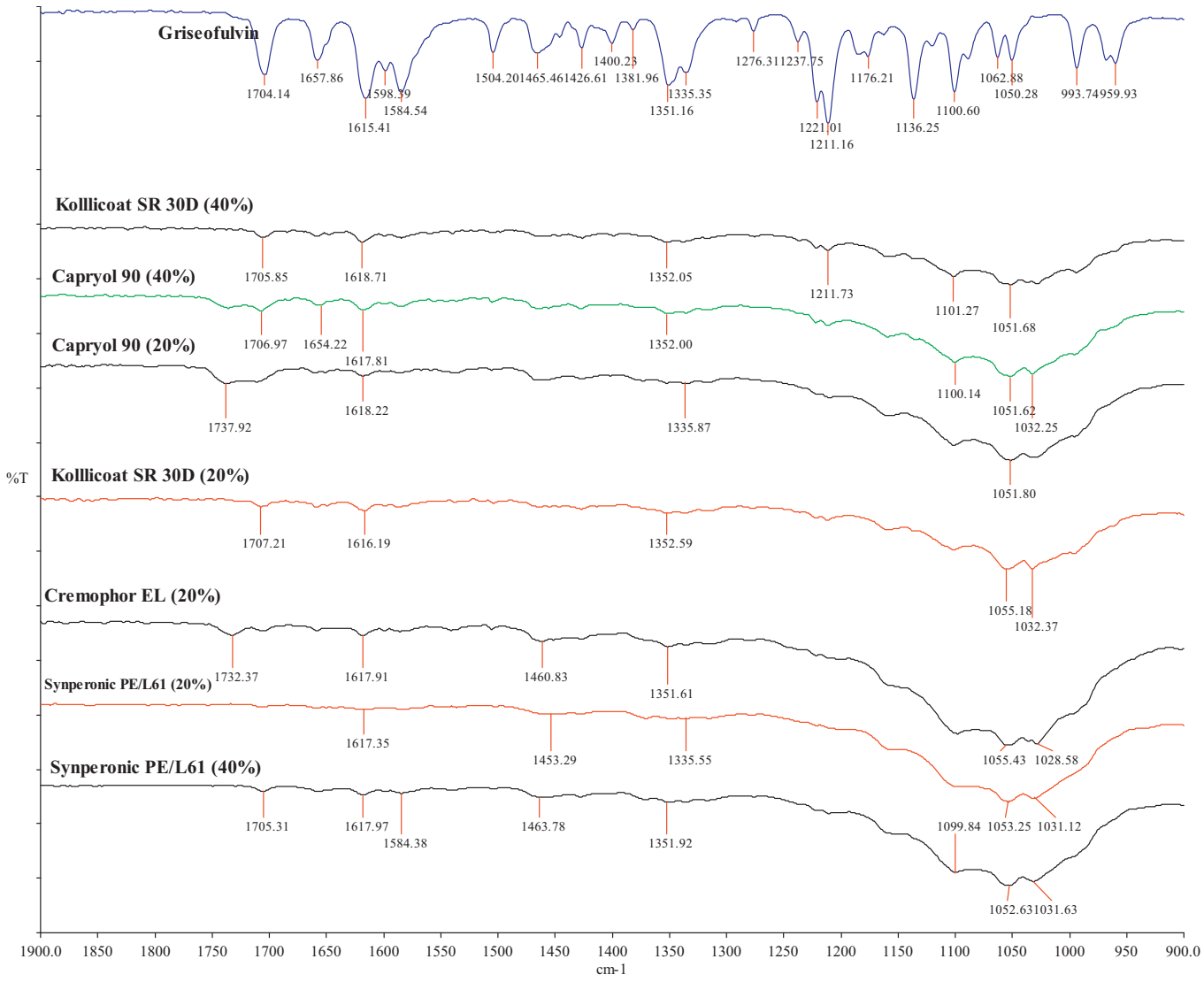

Fig. 5. Fourier transform infra red (FTIR) spectra of griseofulvin liquisolid formulations.

higher concentration of Avicel® PH 102, leading to plastic deformation of powder admixtures and formation of more hydrogen bonding between its molecules (Shangraw, 1989). Friability studies of liquisolid tablets are in the range of 0.15–1.33%. This indicates acceptable resistance is shown by liquisolid tablets to withstand handling. Regarding disintegration time, it was found to be in the range of 0.83 ± 0.21 to 6.46 ± 0.27 min for liquisolid preparations intended for immediate drug release characteristics (Table 4), accordingly the results of disintegration time comply with the British Pharmacopoeia (2011) specification. Those tablets prepared using kolloicoat® SR 30D showed a longer disintegration time (Table 4), this may be due to the effect of the water

Table 4
Quality control results and dissolution parameters for liquisolid formulations and conventional tablets.

Formulation	Hardness (Kg/cm^2)	%Friability	Disintegration time (min)	Q_{5min} (%)[a]	$t_{50\%}$ (min)[b]	%Dissolution efficiency
LS1	2.8 ± 0.40	0.15	6.46 ± 0.27	39.5 ± 1.31	15 ± 1.1	56.53 ± 1.4
LS3	6.7 ± 1.20	1.15	1.57 ± 0.20	28.2 ± 2.62	45 ± 3.1	64.96 ± 4.6
LS4	5.4 ± 0.92	0.28	1.18 ± 0.09	30.2 ± 0.93	25 ± 2.5	52.22 ± 2.9
LS5	3.6 ± 0.44	1.06	3.22 ± 0.41	36.6 ± 2.80	25 ± 1.4	49.11 ± 5.1
LS6	2.3 ± 0.73	0.88	1.18 ± 0.13	28.6 ± 1.32	25 ± 2.3	39.42 ± 3.7
LS7	4.2 ± 0.27	0.29	4.86 ± 0.92	57.3 ± 2.70	<5	89.52 ± 2.6
LS9	6.2 ± 1.30	0.33	0.93 ± 0.11	32.7 ± 0.96	45 ± 1.8	68.32 ± 1.5
LS10	7.8 ± 2.01	0.62	0.84 ± 0.21	26.0 ± 1.14	30 ± 2.1	51.44 ± 1.1
LS11	8.7 ± 1.6	0.77	1.31 ± 0.37	26.0 ± 3.40	60 ± 2.5	52.39 ± 2.8
LS12	6.9 ± 0.33	1.33	0.83 ± 0.21	28.2 ± 2.71	25 ± 0.6	48.03 ± 5.1
LS13	7.3 ± 1.02	0.34	17.22 ± 2.6	0.94 ± 0.13	>90	12.25 ± 2.1
LS14	9.2 ± 1.1	0.62	11.35 ± 1.9	0.44 ± 0.06	>90	10.25 ± 1.4
Conventional	10.6 ± 2.5	0.16	0.70 ± 0.11	3.42 ± 0.71	>90	23.25 ± 3.6

[a] The percentage drug released after 5 min.
[b] The time required for the dissolution of 50% of the drug dose.

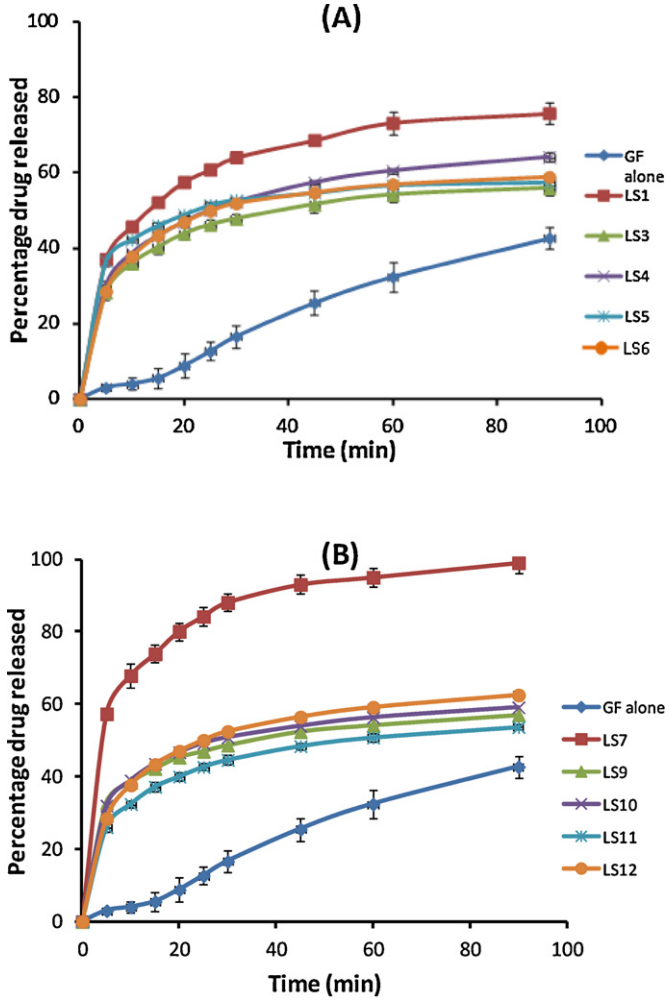

Fig. 6. Dissolution profiles of griseofulvin from conventional (GF alone) and immediate release liquisolid tablets (LS1-LS12) at carrier/coat ratio of 10 (A) and 20 (B).

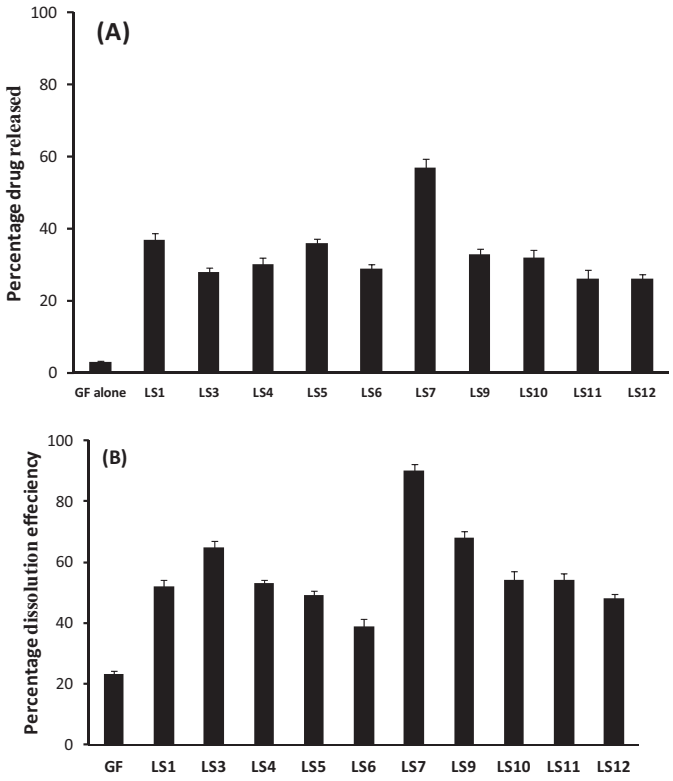

Fig. 7. Percentage griseofulvin released after 5 min (A), and percentage dissolution efficiency (B) from different liquisolid formulations.

immiscible vehicle that may retard tablet wetting which is a prerequisite for tablet disintegration. Faster disintegration time indicate rapid release rates. These are in accordance with dissolution rates (see below Figs. 6 and 9).

3.4.2. *In vitro dissolution results for immediate release formulations*

For immediate releasing tablets, three formulation parameters that would affect the drug dissolution rate were investigated. These parameters included the effect of vehicle type, effect of drug concentration in the liquid medication and effect of carrier/coat ratio (*R*-value).

The dissolution profiles of the liquisolid tablets for fast release formulations and conventional control griseofulvin tablets are shown in Fig. 6. The percentage drug released after 5 min (Q_5) and the time required for the release of 50% of the drug (t_{50}) were determined and are shown in Table 4. Additionally, percentage dissolution efficiency (%DE) was calculated from the area under each dissolution curve at time "*t*", and measured using the trapezoidal rule and expressed as a percentage of the area of the rectangle described by 100% dissolution at the same time (Khan, 1975) were also calculated (Table 4). Both Q_5 and %DE are presented as histograms (to show better comparison between the prepared formulations) in Fig. 7.

From the dissolution profiles, it can be seen that all liquisolid formulations significantly ($P < 0.05$) improved drug dissolution compared to conventional tablets. Concerning the dissolution parameters, all fast release formulations (LS1- LS12) showed a significant ($P < 0.05$) improvement in %DE, Q_5 and t_{50} with compared to conventional tablets.

In the liquisolid systems, liquid medications containing drug were adsorbed on the surface of carrier materials. The drug might be in a solid form or soluble form where it will be held within the powder substrate in solution, or in a solubilized, almost molecularly dispersed state based on the degree of the drug solubility in the liquid vehicle. Due to significantly increased wetting properties and surface area of the drug particles available for dissolution, liquisolid tablets were expected to enhance drug release characteristics and, consequently, improved oral bioavailability (Fahmy and Kassem, 2008). When a liquisolid tablet is exposed to the dissolution medium, drug located onto the surface of compact dissolves fast and diffuses into dissolution medium. This can be assumed to be the cause of the burst release effect observed, compared to control Fig. 6.

Among the tested vehicles, Cremophor® EL, signified by LS1 and LS7, presented the best dissolution performance with the highest drug release. LS7 showed a prompt drug release with a Q_5 value of 57%, compared to only 3.0% for conventional tablets (Fig. 6A). Regarding t_{50}, LS7 and LS1 displayed a release of more than 50% of the drug in about 5 and 15 min, respectively. The remaining formulations had t_{50} ranging from 25 to 45 min (Table 4). Regarding the percentage dissolution efficiency there was about 4-fold enhancement in %DE from LS7 compared to control (Fig. 6B). The superiority of formulations prepared using Cremophor® EL as liquid vehicle could be explained by the higher drug solubility in the vehicle, as reflected from the solubility studies (Section 3.1). This would suggest that the amount of drug available in the molecular dispersion form was higher, confirmed by DSC data (Fig. 3). In the meantime, being hydrophilic surfactant with HLB value of 12–14 (compared to HLB values of 5 and 3 of Capryol™ 90 and Synperonic® PE/L61,

respectively), Cremophor® EL improved the wettability of the drug particles, which is a crucial step preceding drug dissolution. This result is in agreement with a previous study where Cremophor® EL was superior to PEG400 in improving the dissolution of Naproxen (Tiong and Elkordy, 2009). Also in the present study, the release kinetic models showed that the mechanism of griseofulvin release from Cremophor® EL (LS1and LS7) followed Hixson–Crowell model which explains that the rate of drug release from a formulation is limited by the drug particle area (Hixson and Crowell, 1931), while the mechanism of griseofulvin release from both Capryol™ 90 (LS5) and Synperonic® PE/L61 (LS3 and LS9) was in accordance with Higuchi model which demonstrates drug dissolution based on diffusion process (Higuchi, 1963).

Preparing liquisolid tablets containing Cremophor® EL would add an advantage to the formulation in enhancing drug bioavailability due to its physiological effect; it was reported that Cremophor® EL can inhibit P-glycoprotein (Benoit and Lanprecht, 2004; Elkordy et al., 2012; Rege et al., 2002). This P-glycoprotein reduces intestinal absorption of many drugs by efflux transportation, so reduces plasma drug concentration (Srirangam and Vidya, 2010). Consequently, any increase in bioavailability of poorly water soluble drugs when formulated in liquisolid tablets using Cremophor® EL as vehicle would be due to the dual improved effect of both solubility/dissolution and intestinal absorption.

Regarding the effect of drug concentration on the %DE (Fig. 7B), it was found that the %DE is always (with both *R*-values and all liquid vehicles used) higher from liquisolid tablets with the lower drug concentration. The less drug concentration in the liquid vehicle means more fraction of the drug is liable to be in a solution form (i.e. molecularly dispersed), which is a prerequisite for fast drug dissolution. Drug in the higher concentration will exceed the solubility limits far more than the lower concentration and thus decreasing fraction of dissolved drug in the liquid vehicle (Hentzschel et al., 2012). Moreover, the more vehicle available means even distribution of the vehicle over the remaining un-dissolved drug particles that will help in good wetting of the drug during the dissolution step.

Microcrystalline cellulose and colloidal silica were used as carrier and coating materials, respectively. It was found that the higher the specific surface area of an excipient, the higher the liquid load factor, and consequently the lower the tablet weight (Spireas et al., 1992). For instance, the liquid adsorption capacity of microcrystalline cellulose (specific surface area of 1.18 m^2/g) is higher than that of lactose (0.35 m^2/g), starch (0.6 m^2/g), and sorbitol (0.37 m^2/g). Meantime, it was reported that microcrystalline cellulose had more liquid retention potential in comparison with lactose, and the formulations containing microcrystalline cellulose as carrier, showed higher dissolution rate (Javadzadeh et al., 2007b). Therefore, microcrystalline cellulose was selected as the carrier in this study. As the carrier type and amount play a major role in obtaining the dry form of powder from the liquid medication, the effect of carrier to coating material ratio (*R*-value) on the drug dissolution was investigated. Two *R*-values of 10 and 20 were studied. Generally, the higher *R*-value showed higher drug dissolution as reflected from the %DE shown in Fig. 7B and Table 4. Now to estimate the effect of *R*-value, the behaviors of LS1 and LS7 will be discussed in details as they showed the highest drug release. Both LS1 and LS7 are prepared using the same non-volatile liquid (Cremophor® EL), the same drug concentration in the liquid medication (20%, w/w), but have two *R*-values of 10 and 20, respectively. Keeping all formulation variables constant, the results indicated that the higher *R*-value showed a significant ($P < 0.05$) higher %DE. Liquisolid tablets with high *R*-value would contain high amount of microcrystalline cellulose, low amount of colloidal silica, and a low liquid load factor (ratio of liquid medication to carrier). Microcrystalline cellulose is known to act as disintegrant due to wicking

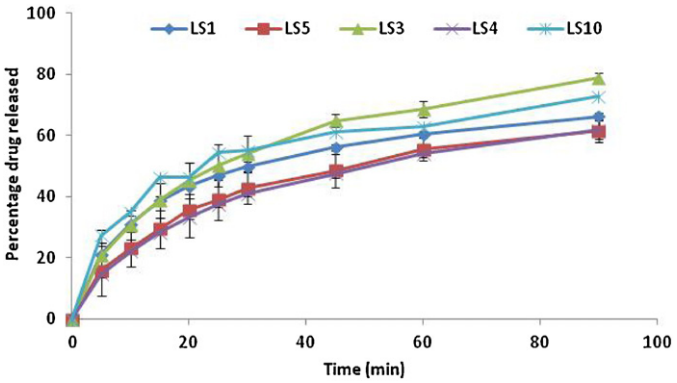

Fig. 8. Dissolution profiles of griseofulvin from immediate release liquisolid tablets at carrier/coat ratio of 10 and 20 after 4 week storage at 23 °C/63%RH. For details composition, refer to Table 1.

effect that allows water to enter the tablet matrix by means of capillary pores, which break the hydrogen bonding between adjacent bundles of cellulose microcrystals. Colloidal silica is known to be hydrophobic in nature that would retard the drug release. Higher microcrystalline cellulose concentration would overcome, to a certain extent, the effect of colloidal silica. On the contrary, if low *R*-value is used, the amount of colloidal silica is high, relative to carrier. In this condition, liquid load factor will be high and the liquisolid compact will be overloaded with the liquid medication (Javadzadeh et al., 2007b; Spireas et al., 1999).

The overall results indicated that to prepare fast disintegrating/immediate release liquisolid tablets, Cremophor® EL, Synperonic® PE/L61 and Capryol™ 90 are good choice of vehicles to prepare the liquid medication of griseofulvin with superiority of Cremophor®EL. Those liquid vehicles result in liquid load factors which allow preparation of griseofulvin tablets with more acceptable and manageable drug load and tablet weights (Table 1) compared to griseofulvin compacts prepared in a study by Hentzschel et al. (2012). In general, the lower the drug concentration and the higher carrier/coat ratio are, the better the improvement in dissolution behavior of the drug.

The stability studies of liquisolid tablets (LS1, LS3, LS4, LS5 and LS10) were performed to investigate whether the dissolution of liquisolid compacts (Fig. 8) is affected by storage under a stressed condition of RH. The results showed that the dissolution rates of liquisolid tablets were not affected by the humid condition (there was no significant difference ($P > 0.05$) in dissolution rates of aged liquisoid tablets compared to the fresh liquisolid tablets). Therefore, the liquisolid of griseofulvin tablets containing Cremophor® EL, Synperonic® PE/L61 and Capryol™ 90 were stable and not affected by storage.

3.4.3. *In vitro dissolution results for sustained release formulations*

Many techniques have been described to produce sustained release formulations, among which the liquisolid technology is a quite new and promising in achieving a sustained release pattern. This part of the present work investigated the role of liquid vehicle (which has not been tried before to the best of our knowledge) in sustaining the drug release, while using a hydrophilic carrier. The selected non-volatile liquid, that showed the least drug solubility was Kollicoat® SR 30 D, was investigated for the possibility of relying on the liquid vehicle alone to sustain the drug release from liquisolid tablets. Kollicoat® SR 30 D is a polyvinyl acetate dispersion stabilized with povidone and sodium lauryl sulfate, applied mainly for the production of pH-independent sustained-release

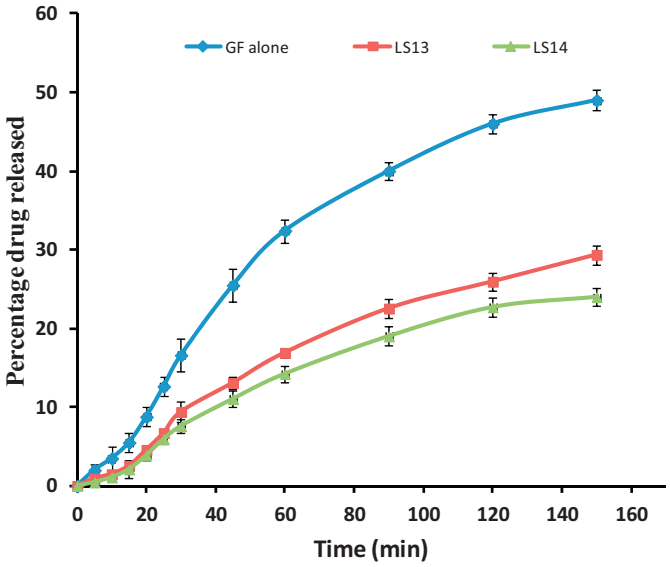

Fig. 9. Dissolution profiles of griseofulvin from conventional (GF alone) and sustained release liquisolid formulations (LS13, LS14).

formulations and taste masking purposes due to its water insolubility characters (Zezhi et al., 2002).

In designing the griseofulvin sustained release formulations in this study, the *R*-value was kept at the low value of 10, which means that the amount of hydrophobic colloidal silica was high so as to aid in retarding the drug release. Two liquisolid formulations, namely LS13 and LS14, were prepared with a drug concentration of 20 and 40% (w/w), respectively. The dissolution profiles are shown in Fig. 9, together with conventional directly compacted tablets as control. Dissolution parameters listed are in Table 4.

The dissolution profiles show that the drug release from liquisolid tablets were lower than the control, with a Q_{5min} of only $0.94 \pm 0.13\%$ and $0.44 \pm 0.065\%$ and %DE of only 12.2% and 10.2% for LS13 and LS14, respectively, compared to 3.42 ± 0.71 (Q_{5min}) and 23.0% (%DE) for the conventional tablets. Since, the drug is dissolved in the liquid vehicle within the powder matrix, the drug release will be governed mainly by disintegration of tablets and miscibility of liquid vehicles with the dissolution medium (Hentzschel et al., 2012), LS13 and LS14 have longer disintegration time compared to other liquisolid griseofulvin compacts (Table 4). This would indicate that the non-volatile liquid vehicle Kollicoat® SR 30D has the potential to sustain the drug release, even in the presence of hydrophilic carrier. The water insoluble polymer is expected to form a coat around each drug particles during the preparation of the liquid medication suspension, thus reducing drug wettability and dissolution. Meantime, keeping the *R*-value low indicates that the amount of colloidal silica is high relative to the carrier. Being hydrophobic, colloidal silica would additionally reduce the wettability of the drug particles augmenting the effect of the polymeric liquid vehicle. It was also stated that with low *R*-value the liquisolid tablets are overloaded with liquid formulation due to a high liquid load factor (in agreement with our results, $L_f = 0.5$, Table 1), resulting in oversaturation and local precipitation of the drug that would decrease the release rates (Zezhi et al., 2002).

Accordingly, the two formulations seam to reduce drug release (Fig. 9), there is no significant difference ($P < 0.05$) between LS13 and LS14. There was no statistical difference for LS13 and control ($P > 0.05$) but the results were statistically significant ($P < 0.05$) for LS14 and control. Hence, LS14 was more effective in promoting a sustaining effect on the drug release. This could be explained on the basis that in LS13 with the high vehicle concentration (23.8%, w/w), the fraction of the molecularly dispersed drug was higher relative to LS14 (which contains 17.9% (w/w) Kollicoat® SR 30D). At the same time, LS14 contained a large percentage of the drug; this would increase the amount of the undissolved drug in the liquid medication. Comparing the drug release from immediate (LS1-LS12) and sustained (LS13, LS14) release formulations statistically, the drug release was significantly ($P < 0.05$) different.

With respect to the drug release kinetics from Kollicoat® SR 30D containing liquisolid formulations, the best linearity was found in Higuchi's equation plot with R^2 values of 0.989 and 0.995 for LS13 and LS14, respectively. This implies that drug release from tablets as a square root of time dependent process based on Fickian diffusion. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. The release mechanism of the drug by this process could be explained by the fact that Kollicoat® SR 30D is an aqueous dispersion composed of 27% polyvinylacetate, 2.5% povidone and 0.3% sodium lauryl sulfate. Polyvinyl acetate is a water insoluble polymer, so passage of aqueous dissolution medium through this polymeric coat or film around each drug particle to reach the core drug was controlled by presence of povidone and sodium lauryl sulfate in the Kollicoat® SR 30D coating. These soluble components dissolved and leached out of the film forming a porous membrane, i.e. acting as channeling agent (Sultana et al., 2010). Through this porous membrane water entered into the core and drug was released slowly through diffusion process. The best model describes the release of the drug from LS13 and LS14, i.e. Hugchi model was used to predict the time required for 50% and 90% drug release from the formulations. The results were: (i) 7.15 and 9 h for 50% of griseofulvin to be released from LS13 and LS14, respectively and (ii) 20.7 and 26.15 h for 90% of griseofulvin to be released from LS13 and LS14, respectively. This demonstrates that those formulations are effective to sustain the release of the drug over extended period of time.

4. Conclusion

This study provides evidence of the possible control of drug release from liquisolid tablets by proper choice of the liquid vehicle. For immediate release formulations, Cremophor® EL provided the best dissolution profile with additional benefit of being a P-glycoprotein inhibitor that would improve the bioavailability of some drugs suffering from intestinal efflux transportation. The results showed that dissolution rate was affected by changing the ratio of the carrier (microcrystalline cellulose) to coating material (Cab-O-Sil® M5) and drug concentration. On the contrary, the use of Kollicoat® SR 30D as a vehicle reduced the drug dissolution rate at high drug concentration. Drug release from this system was diffusion through the matrix. At present, griseofulvin is commercially available in this high dose tablets between 125 and 500 mg; the liquisolid formulations may not only help in reduction in this dose but also may help in production of sustained release griseofulvin formulations by choosing a suitable liquid vehicle to control the drug release.

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