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Preparation and in vitro evaluation of solid dispersions of halofantrine

Ahmad M. Abdul-Fattah [1], Hridaya N. Bhargava *

Department of Pharmaceutical Sciences, Massachusetts College of Pharmacy and Health Sciences, Boston, MA 02115, USA

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Abstract

The low aqueous solubility of halofantrine (HF) and its low bioavailability from commercially available tablets (Halfan®) suggested the formulation of solid dispersions (SDs) of HF to reduce its particle size and improve its wettability and aqueous solubility. Preformulation studies involved the development of a high performance liquid chromatography (HPLC) method for the analysis of HF. In addition, solubility studies were conducted on HF in aqueous solutions containing different concentrations of various carriers. Formulation studies included the preparation of SDs and physical mixtures (PMs) of HF with different carriers and their physicochemical characterization using differential scanning calorimetry (DSC), Fourier-Transform infra-red (FT-IR) spectroscopy and dissolution studies. A 3-month stability study at elevated temperatures was conducted on representative SDs of HF with selected carriers.

Keywords: Halofantrine; Solid dispersion; PEG 8000; PVP K30; Gelucire® 44/14; Sodium taurocholate; Dissolution rate

1. Introduction

Halofantrine (HF) (Fig. 1), a member of the phenanthrene methanols, is clinically used as an alternative to treat acute malarial attacks caused by chloroquine resistant and multidrug resistant strains of plasmodium falciparum (Tracy and Webster, 1996). HF is marketed as the hydrochloride salt and is available as suspension, tablets and capsules (USP DI, 1999; Flaharty et al., 1998). Mean oral bioavailability of HF is reported to be about 4.7% (Ajayi and Fleckenstein, 1994). The poor aqueous solubility of the drug ($< 0.01\%$) is responsible for the poor absorption of HF after oral administration with wide intra- and intersubject variability.

Abbreviations: AUC, area under the curve; C_{max}, concentration maximum (in plasma); DSC, differential scanning calorimetry; FT-IR, Fourier transform-infra red; HCl, hydrochloride; HF, halofantrine; HPLC, high performance liquid chromatography; NaTC, sodium taurocholate; P., plasmodium; PC, phosphatidyl choline; PEG 8000, polyethylene glycol 8000; PVP K30, polyvinyl pyrrolidone; %R.S.D., percent relative standard deviation.

* Corresponding author. Tel.: +1-617-732-2913; fax: +1-617-732-2244.

E-mail address: bhargava@mcp.edu (H.N. Bhargava).

[1] Present address: School of Pharmacy, University of Connecticut, Storrs, CT 06269, USA.

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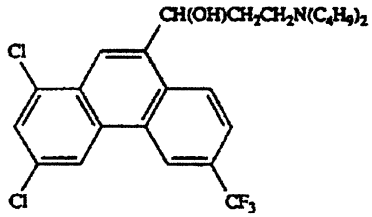


Fig. 1. HF base.

Table 2
PMs of HF with PVP K30; quantities and proportions of HF and PVP K30 used

Sample	PVP K30 (g)	HF (g)	Ratio (carrier:HF)
PM1	0.75	0.5	60:40
PM2	2	0.5	80:20
PM3	4.5	0.5	90:10

The resulting erratic plasma profiles limit the therapeutic effectiveness and potentially stimulate the development of resistance (Charman, 1997).

Many studies have used the free base of HF to formulate in lipid formulations to improve its bioavailability (Porter et al., 1996; Pouton, 1997; Khoo et al., 1998) due to its high solubility in long chain triglycerides (>70 mg/g of lipid). Furthermore, the high solubility of HF base in long chain triglycerides was consistent with the possibility of intestinal lymphatic transport being a significant contributor for the bioavailability of HF (Porter et al., 1996). In a study conducted by Khoo et al., the oral bioavailability of HF base was found to increase when formulated in lipidic self emulsifying drug delivery systems (SEDDS) and self microemulsifying drug delivery systems (SMEDDS) (Khoo et al., 1998).

Several techniques have been used to improve the oral bioavailability of poorly soluble drugs. No attempt has been made to improve the bioavailability of HF by improving its dissolution rate using the SD technique with a water-soluble carrier (Chiou and Riegelman, 1971). The increase in dissolution rate from SDs can be attributed to one or a combination of the following factors (Swarbrick, 1990; Shargel, 1993): a reduction of particle size of the drug, a solubilizing effect on the drug by the water soluble carrier, enhancement of the wettability and dispersibility of the drug by the carrier material, and the possible formation of a metastable dispersion that has a greater solubility resulting in a faster dissolution rate.

Among the popular carriers used in the formation of SDs are polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP). Both polymers are freely soluble in water and are available in various molecular weights. The molecular size of both polymers favors the formation of interstitial solid solutions (van den Mooter et al., 1998). Gelucire®

Table 1
Preparation of SDs of HF with different carriers; quantities and proportions of HF and excipient(s) used

Sample	PEG 8000 (g)	PVP K30 (g)	Gelucire® 44/14 (g)	Phospha-tidyl choline (g)	HF (g)	Ratio (carrier:HF)
SD1	0.75	–	–	–	0.5	60:40
SD2	–	0.75	–	–	0.5	60:40
SD3	–	–	0.75	–	0.5	60:40
SD4	–	0.7425	–	0.0125 (1%)	0.495	60:40
SD5	–	0.5	–	–	0.5	50:50
SD6	–	2	–	–	0.5	80:20
SD7	–	4.5	–	–	0.5	90:10
SD8 (lyophilized)	–	0.75	–	–	0.5	60:40

Table 3
Total solubility of HF in aqueous solutions of PEG 8000, PVP K30 and Gelucire® 44/14 at 37 °C

PEG 8000 (% w/v)	Total HF at saturation (μg/ml)	PVP K30 (% w/v)	Total HF at saturation (μg/ml)	Gelucire® 44/14 (% w/v)	Total HF at saturation (μg/ml)
0	0.590 ± 0.02	0	0.590 ± 0.02	0	0.590 ± 0.02
–	–	–	–	1	128.662 ± 0.12
–	–	5	35.738 ± 0.04	5	291.019 ± 0.14
10	0.856 ± 0.03	10	59.317 ± 0.05	10	389.139 ± 0.13
20	1.197 ± 0.05	20	148.988 ± 0.17	20	495.421 ± 0.19
30	1.169 ± 0.03	30	262.677 ± 0.12	30	556.397 ± 0.16

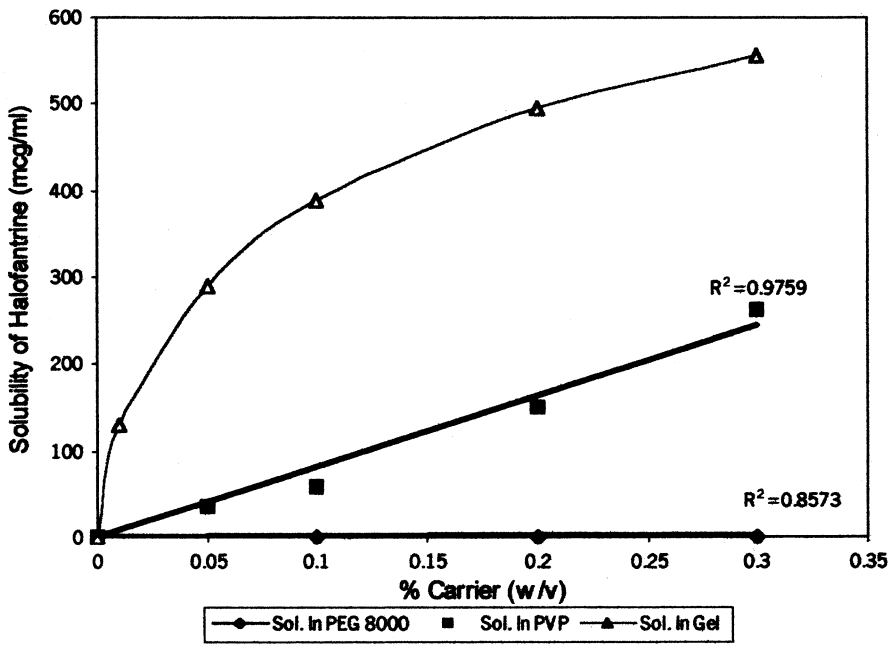


Fig. 2. Solubility curves for HF in presence of increasing concentrations of different carriers in DI-distilled water.

44/14[2] has also been investigated as a novel water-soluble carrier for SDs (Serajuddin et al., 1988).

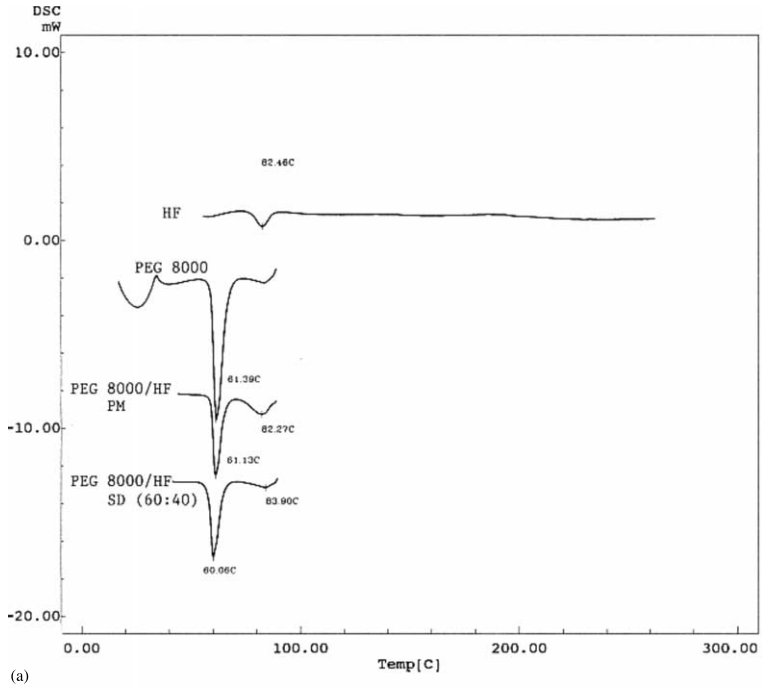
The purpose of our study was to formulate the free base of HF in SDs with different water-soluble carriers, the free base being more favorable in physicochemical profile relative to the hydro- and lipophobic characters of the hydrochloride salt (Charman, 1997), and to evaluate the effect of the SDs on the dissolution rate, as well as stability of the drug.

2. Materials and methods

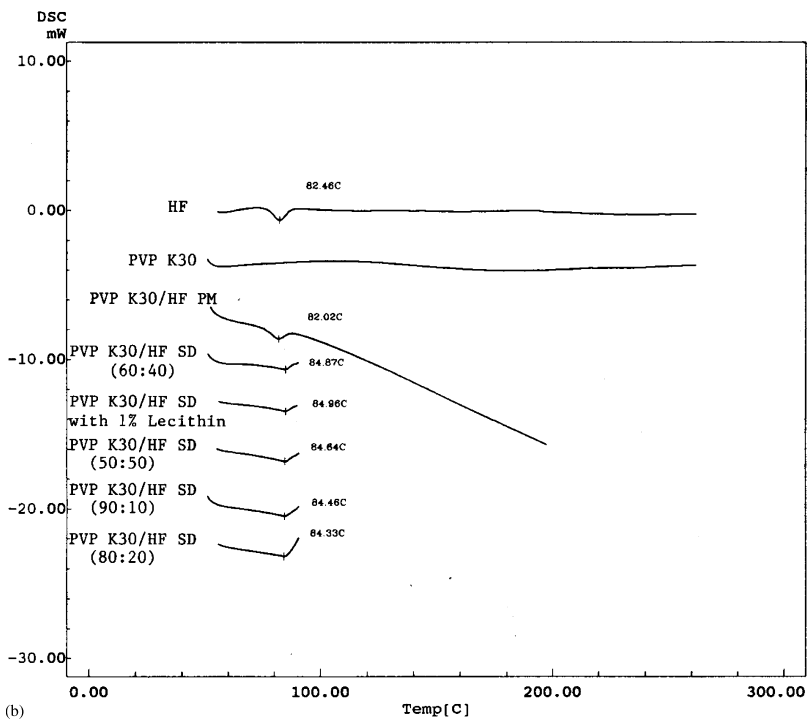
2.1. Chemicals and reagents

HF was a generous gift of SmithKline Beecham Pharmaceuticals (Essex, UK). Halfan® (Smithkline Beecham Laboratoires Pharmaceutiques, Nanterre cedex, France) 250 mg tablets, were purchased locally. Kollidone (PVP K30) was purchased from Amend drug & chemical Co., Inc.

[2] Gelucire® 44/14is an inert semi-solid waxy material which is amphiphilic in character. It has a melting point of 44 °C and an HLB value of 14. It is derived from the reaction of hydrogenated palm kernel oil with PEG 1500 (Product Literature, Gattefosse Bulletin, 1999).



(a)



(b)

Fig. 3. (a) A comparison for different thermograms of PEG 8000–HF systems. (b) A comparison for different thermograms of PVP K30–HF systems. (c) A comparison for different thermograms of Gelucire 44/14®–HF systems.

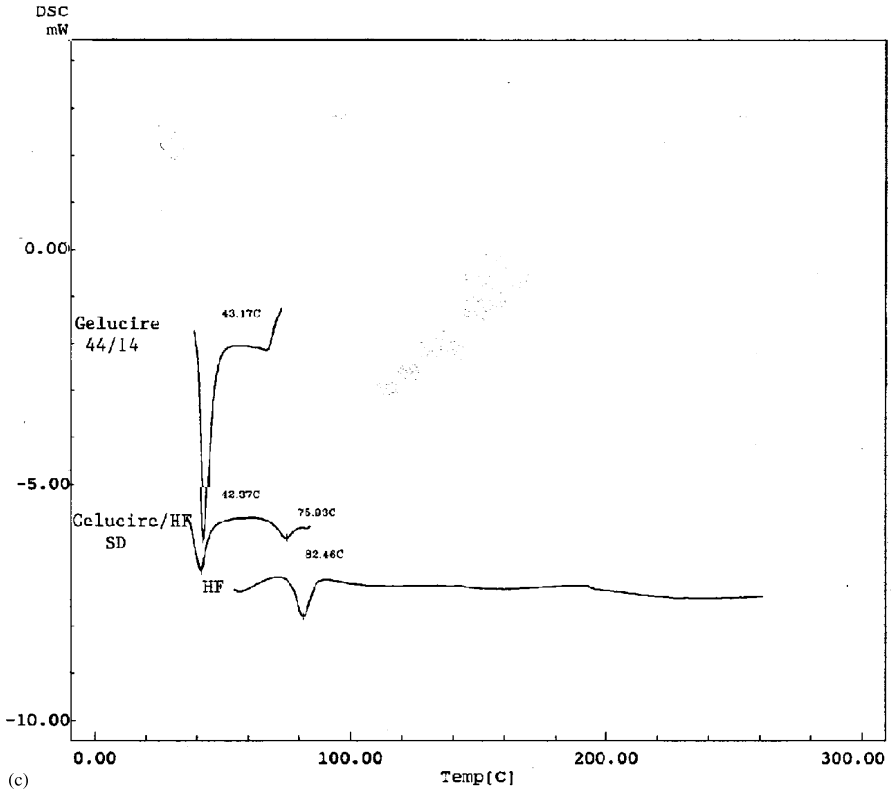


Fig. 3. (*Continued*)

(Irvington, NJ) and PEG 8000 and Type XVI-E L-α-phosphatidyl choline (L-α-Lecithin) from fresh egg yolk were purchased from Sigma chemi-cal Co. (St. Louis, MO). Gelucire® 44/14 was kindly supplied by Gattefosse (Cedex, France). All other chemicals used were of analytical or HPLC grade.

2.2. Methods

HF has a tendency to adsorb onto glass (Keeratithakul et al., 1991), hence all glassware was silanized prior to their use in the experiments with AquaSil™ fluid, Pierce (Rockford, IL).

2.2.1. Preparation of solid dispersions and physical mixtures

2.2.1.1. Solid dispersions by solvent method. The required amount of HF and excipient (PEG 8000, HF-PVP K30 or HF- Gelucire® 44/14) were weighed and dissolved in alcohol, USP, in a round bottom flask with the aid of heating at 60 °C and ultrasonication. The alcohol was evaporated at 50 °C under reduced pressure in a rotavapor for 2 h and further drying was done in a vacuum desiccator for 12 h. The dispersions were stored in a glass desiccator. The dried mass was ground in a mortar and sieved. The powder fraction corresponding to mesh size less than 60 was collected for further investigation.

2.2.1.2. HF-PVP K30-PC solid dispersion by solvent method. A SD of HF-PVP K30 with phosphatidyl choline was prepared by the solvent method, as described in Section 2.2.1.1.

2.2.1.3. HF-PVP K30 solid dispersion by freeze drying. A SD of HF-PVP K30 was prepared by a modified solvent method in which alcohol was removed by lyophilization. The required amount of

HF and PVP K30 were weighed and dissolved in alcohol, USP, in a round bottom flask with the aid of heating at 60 °C and ultrasonication. The solution was transferred to glass vials, frozen (-50 °C) and lyophilized (VirTis® type lyophilizer, model 10-800). The lyophilized mass was ground in a mortar and sieved. The powder fraction corresponding to mesh size less than 60 was collected for further investigation.

Table 1 summarizes the ingredients used in each solid dispersion (SD) and their quantities.

2.2.1.4. Physical mixtures of HF-PVP K30. Three physical mixtures (PMs) of different proportions of HF with PVP K30 were prepared. The required amounts of PVP K30 and HF were weighed and mixed thoroughly by light trituration for 3 min in a mortar. The mixture was sieved and the powder fraction corresponding to mesh size less than 60 was collected for further investigation. Table 2 summarizes the quantity of each ingredient used in the PMs.

2.2.2. Analysis of HF

HF was analyzed using isocratic reverse-phase HPLC. The system consisted of a Hewlett Packard Series 1100 (HP 1100) system equipped with a multiple wavelength UV detector and an HP 3395 integrator. The stationary phase was a Zorbax® SB-CN (Cyano) column (5 μm, 150×4.6 mm internal diameter, Mac Mod Analytical Inc.). The mobile phase consisted of 80:20 (v/v) Acetonitrile-0.025 M potassium phosphate monobasic aqueous buffer (pH 5.0 adjusted with 0.1 N sodium hydroxide solution). The flow rate was 1 ml/min. The wavelength of detection was 259 nm, the chart speed was 0.5 cm/min., the column temperature was ambient and the injection volume was 100 μl. The retention time of the HPLC peak of HF was 7.1 min and the limit of detection was 1 ng/ml. The percent relative standard deviation (%R.S.D.) of the intraday and the interday variability was not more than 0.6 ($n = 3$) and 1.23 ($n = 5$), respectively.

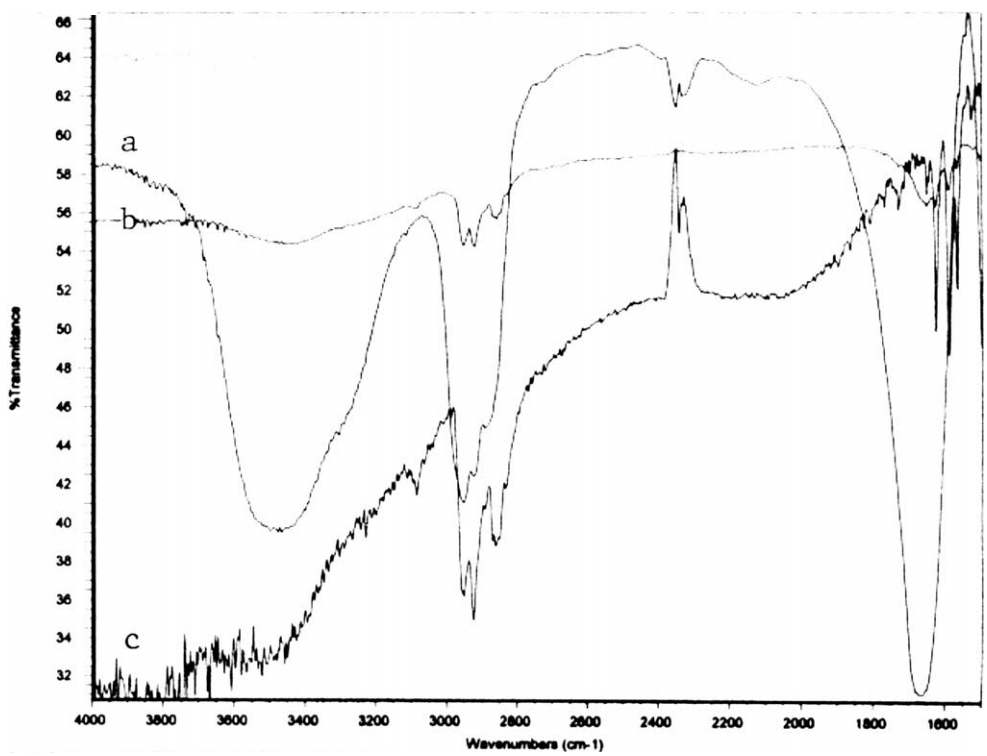


Fig. 4. IR spectrum of (a) PVP K30, (b) PM of PVP K30-HF and (c) HF.

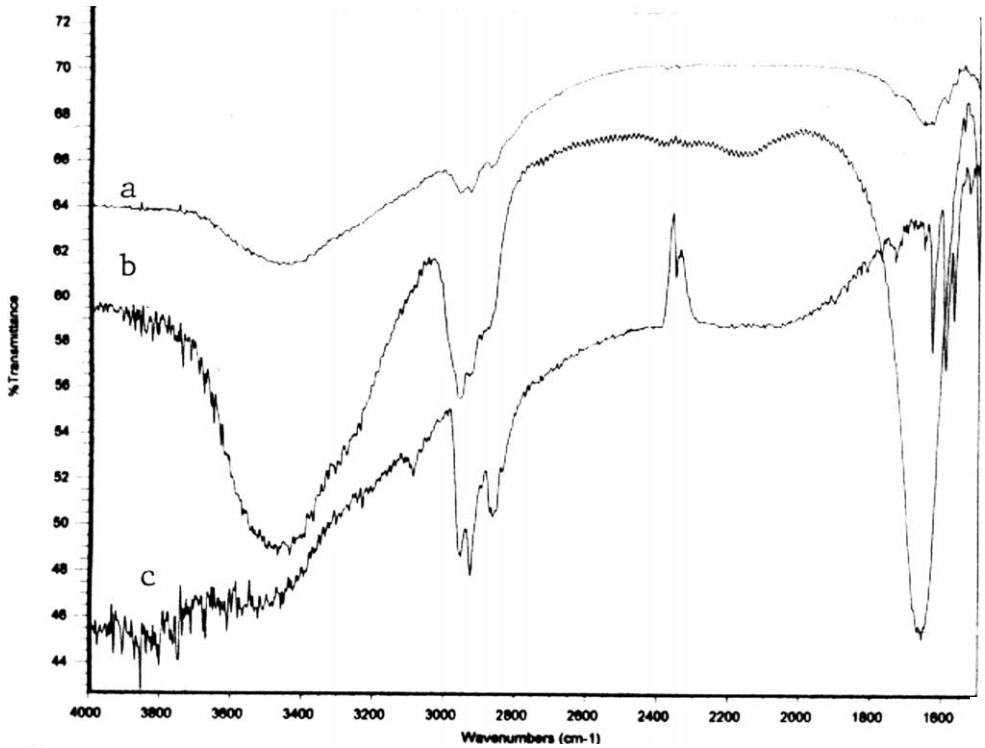


Fig. 5. IR spectrum of (a) S.D. of PVP K30-HF (60:40), (b) PVP K30 and (c) HF.

2.2.3. Solubility measurements of HF

An excess amount of HF (10 mg) was added to 10 ml of distilled water, as well as distilled water containing increasing concentrations of Gelucire® 44/14 (0, 1, 5, 10, 20 and 30% w/v), PVP K30 (0, 5, 10, 20 and 30% w/v) and PEG 8000 (10, 20 and 30% w/v) in 50 ml glass tubes. The tubes were screw capped, kept at 37 ± 0.5 °C for 72 h and shaken vigorously every 6 h to attain equilibrium. Before analysis, solutions were brought to room temperature, aliquots of the supernatant liquid were withdrawn, filtered through 0.45 μm syringe filters, diluted appropriately with water and the filtrate analyzed for HF by HPLC.

2.2.4. Thermal analysis

Thermal analysis was carried out with a differential scanning calorimeter (DSC), model DSC-50 Schimadzu equipped with a TA-50 WSI Schimadzu Thermal Analyzer (Kyoto, Japan). All samples were prepared by placing 8 mg of the powder into an aluminum pan, which was covered and crimped for analysis. The thermograms were obtained by heating the samples at a rate of 10–15 °C per min. Plots of heat flow versus temperature were recorded. An additional PM of PEG 8000 and HF (60:40) was prepared to compare its DSC thermogram and FT-IR spectrum to that of the PEG 8000-HF (60:40) SD.

2.2.5. Infrared spectroscopy

Fourier-transform infrared (FT-IR) spectra were obtained by an Impact 410 FT-IR, Nicolet Instrument Corp. (Madison, WI) using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 4000–400 per cm and the resolution was 1 per cm.

2.2.6. Dissolution studies

Dissolution studies were performed using USP XXIV Apparatus 2 (paddle) method. Samples of ground Halfan® tablets, PMs and SDs equivalent

to 50 mg of HF were added to the dissolution medium (200 ml of 20 mM acetate buffer with 1 mM sodium taurocholate pH 5.5 at a temperature of 37 °C). The latter was stirred with a rotating paddle at 100 rpm. Three microliter samples were withdrawn at predetermined time intervals from each vessel, filtered (0.45 μm), appropriately diluted and analyzed for HF spectrophotometrically at 259 nm (UV spectrophotometry was chosen for convenience and efficiency, and since no degradation of HF base was observed by HPLC when stored at 37 °C for 24 h). The same volume of fresh medium was replaced and correction for cumulative dilution was calculated. The percent of HF dissolved for each formula ($n = 6$) was plotted versus time.

2.2.7. Solid state stability studies

An accelerated 3-month stability study was conducted only on a SD of PVP K30 with HF (80:20) (SD6) and Gelucire® 44/14 with HF (60:40) (SD3). The samples were stored at 4, 25 and 45 °C and analyzed initially and after 1–3 months for HF content by HPLC.

Ten milligrams of the SD was dissolved in 50 ml of the mobile phase. 0.2 ml of the solution was further diluted with 20 ml of the mobile phase and injected into the LC in triplicate for the analysis of HF content.

3. Results and discussion

3.1. Solubility studies

The effect of different carriers on the aqueous solubility of HF is shown in Fig. 2 and Table 3. The aqueous solubility of HF was found to be 0.59 μg/ml.

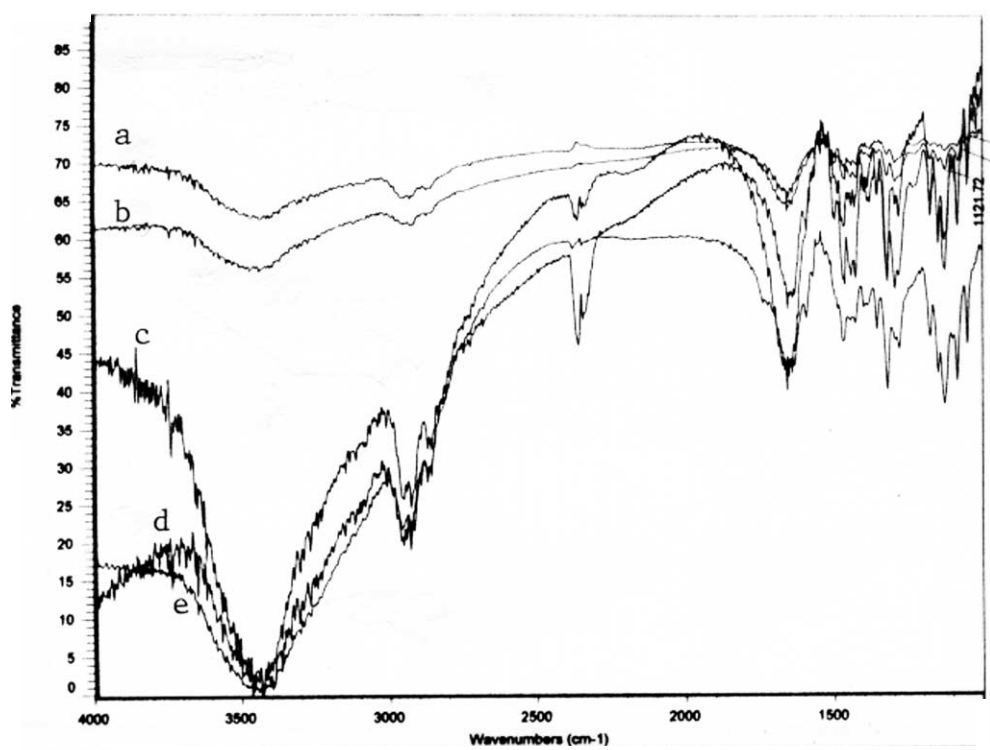


Fig. 6. IR spectrum of (a) lyophilized SD of PVP K30-HF, (b) SD of PVP K30-HF (50:50), (c) SD of PVP K30-HF (90:10), (d) SD of PVP K30-HF (80:20) and (e) SD of PVP K30-HF (60:40).

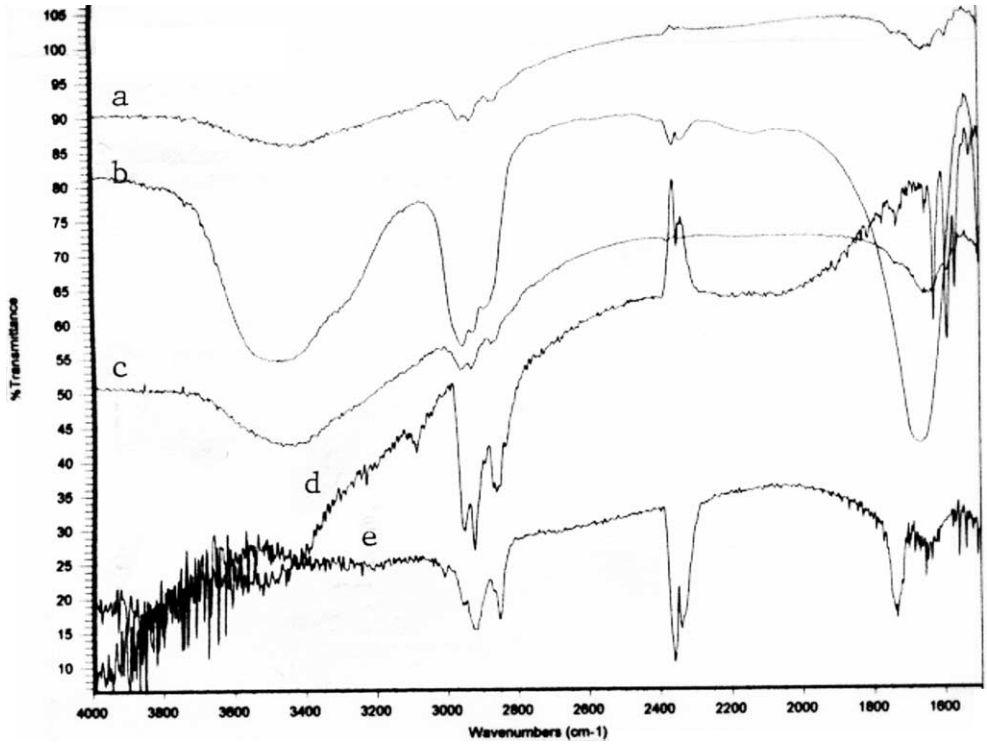


Fig. 7. IR spectrum of (a) lecithin, (b) PVP K30, (c) SD of PVP K30-HF with 1% Lecithin, (d) HF and (e) SD of PVP K30-HF (60:40).

PEG 8000 did not alter the aqueous solubility of HF. The solubility curve had a slope of 0.023. In the presence of PVP K30 the aqueous solubility of HF increased significantly with increasing concentration of PVP K30. This may be attributed to the improved wetting of HF in the presence of PVP K30 probably due to the formation of intermolecular hydrogen bonding between the carbonyl group of PVP K30 and the hydrogen atom in the hydroxyl group of HF. The relationship appears to be linear ($R^2 = 0.9759$). The solubility curve had a slope of 8.1359 indicating approximately a 354-fold increase in the solubility of HF in the presence of PVP K30 than in the presence of PEG 8000.

The aqueous solubility of HF was highest in the presence of Gelucire® 44/14. The aqueous solubility of HF increased with increasing concentration of Gelucire® 44/14. However unlike with PVP K30, the solubility relationship was not linear. The slope of the linear portion of the solubility curve for HF in Gelucire® 44/14 was determined to be 53.087. This signifies approximately a 6.5-fold higher solubility of HF in the presence of Gelucire® 44/14 than in the presence of PVP K30. As a non ionic surfactant with a hydrophilic-lipophilic balance (HLB) of 14, Gelucire® 44/14 reduces the interfacial tension between HF particles and water, decreases the contact angle and hence promotes the wetting of HF particles and decreases their flocculation (Boylan, 1986).

3.2. Thermal analysis

Interactions between HF and the different excipients used to prepare the SDs were studied by observing the DSC scans of pure HF, PVP K30, PEG 8000, Gelucire® 44/14 and lecithin, as well as the DSC scans of PMs and SDs.

As evident from the thermograms in Fig. 3a, there was no interaction between HF and PEG 8000 in the PM since there was no shift in the

melting peak of HF and PEG 8000, or a change in the value of ΔH. In the SD of PEG 8000 and HF, only a small shift was observed in the melting peak of HF (within range of experimental error). However, there was an appreciable reduction in ΔH of HF from 35.19 to 5.45 mJ that indicates the formation of a SD.

Thermograms in Fig. 3b show that there was no appreciable shift in the melting peak of HF in a PM with PVP K30. However, there was an observable change in ΔH (21.56 mJ) that signifies some interaction between HF and PVP K30 even in the PM. In the case of the SDs of PVP K30 with HF, there was an observable shift in the melting peak for HF that seemed to be almost consistent in all SDs (84.65 ± 0.266 °C, %R.S.D. = 0.31) even in the presence of lecithin. This signifies some form of interaction between the drug and the carrier that is more prominent in a SD than in a PM. In addition, there was an appreciable decrease in ΔH of HF indicating the formation of a SD.

The DSC thermogram for a SD of HF and Gelucire® 44/14 compared with the DSC thermogram of pure HF and pure Gelucire® 44/14 (Fig. 3c) indicates an observable decrease in the melting point of both substances in the SD. This indicates some form of interaction between both the substances. An appreciable decrease in ΔH from 35.19 to 10.43 mJ was observed indicating the formation of a SD.

3.3. Fourier-transform infrared spectroscopy (FT-IR)

In compounds with a secondary hydroxyl (OH) group, the OH group shows a stretching vibration as a broad band around 3635–3620 per cm. However, this was not the case with HF. No broad bands or even sharp peaks appeared around this region (Fig. 4c). The most probable reason is the involvement of the OH group in an intra-molecular hydrogen bond with the lone pair of electrons

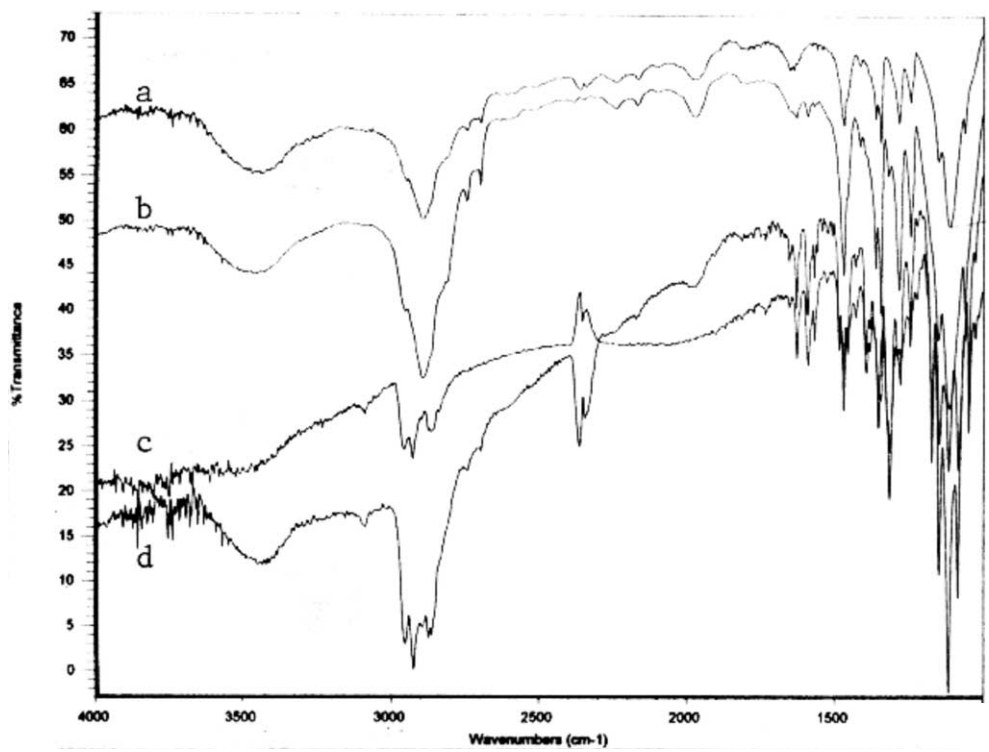


Fig. 8. IR spectrum of (a) PEG 8000, (b) SD of PEG 8000-HF, (c) HF and (d) PM of PEG 8000-HF.

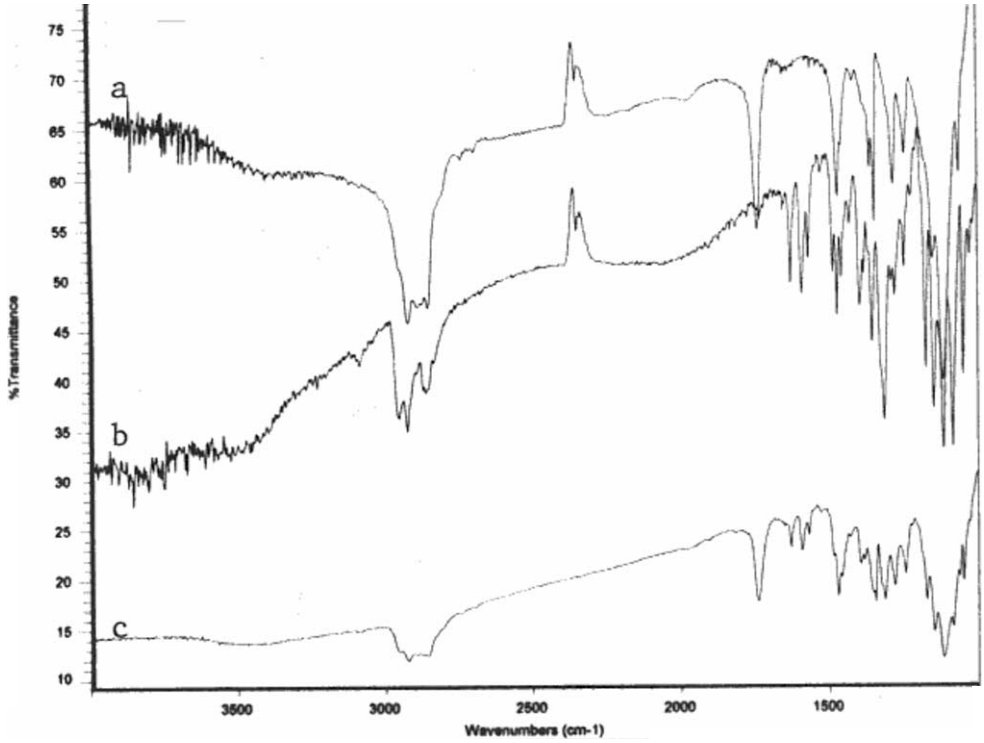


Fig. 9. IR spectrum of (a) Gelucire 44/14®, (b) HF and (c) SD of Gelucire 44/14®–HF.

of the tertiary nitrogen atom (the distance between the hydrogen atom and the nitrogen atom is 5 bonds). In return, this prevents the appearance of the characteristic band for the OH stretching vibration. The presence of this band would have been a strong indication of specific interactions between HF and other molecules e.g. intermolecular hydrogen bonding. Owing to its absence, difficulty is expected in evaluating intermolecular hydrogen bonding by FT-IR. The stretching vibration for C–N group of a tertiary amine is usually not diagnostic since it lies in the fingerprint region of the IR spectrum. The bands in the region of 2954–2852 per cm of the spectrum of HF represent asymmetric CH_3 and CH_2 stretching vibrations. They are not very valuable bands for evaluating intermolecular hydrogen bonding.

The most distinct peak in the IR spectrum of PVP K30 (Fig. 4a) was the stretching vibration of the carbonyl group that would typically appear around 1715 per cm. Since the carbonyl group is part of a five-membered heterocyclic ring with a tertiary amide, the peak for carbonyl stretching appeared around 1655 per cm. This band is especially sharp, because of the dipolar nature of the N–C–O group. Tertiary amides tend to be hygroscopic, hence absorb moisture resulting in another broad band around 3467 per cm that appeared in the IR spectrum of pure PVP K30.

Although intermolecular hydrogen bonding was suspected between the hydroxyl group of HF and the carbonyl group of PVP K30, it could not be confirmed by FT-IR. A decrease in the intensity of the band for the carbonyl stretching alone, that appeared in all spectra PVP K30 with HF (PM and SDs) was not conclusive evidence to support intermolecular hydrogen bonding. A decrease in the intensity of the band for the carbonyl stretching in PVP K30 is also a marker for the amount of PVP K30. Careful examination of the IR spectra of the PM (Fig. 4b) and SDs of HF with PVP K30 (Figs. 5 and 6), whether prepared by solvent method or by lyophilization, revealed insignificant

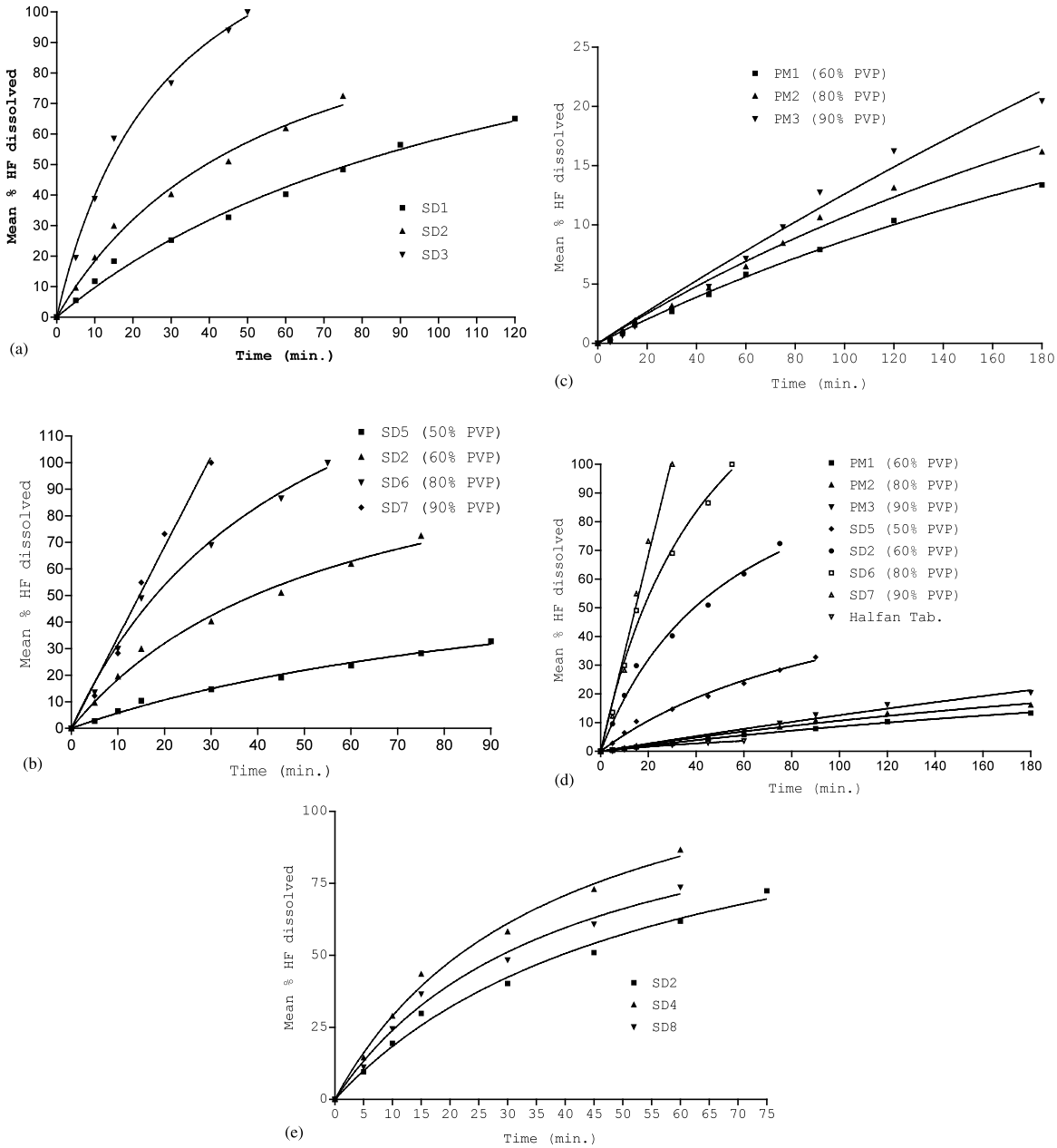


Fig. 10. (a) Comparative plots of mean% HF dissolved against time for SD1, SD2 and SD3 in acetate buffer pH 5.5 with 1 mM NaTC. (b) Comparative plots of mean% HF dissolved against time for SD2, SD5, SD6 and SD7 in acetate buffer pH 5.5 with 1 mM NaTC. (c) Comparative plots of mean% HF dissolved against time for PM1, PM2 and PM3 in acetate buffer pH 5.5 with 1 mM NaTC. (d) A comparative plot of mean% HF dissolved against time for Halfan®, PM1, PM2, PM3, SD2, SD5 SD6 and SD7 in acetate buffer pH 5.5 with 1 mM NaTC. (e) A comparative plot of mean% HF dissolved against time for SD2, SD4 and SD8 in acetate buffer pH 5.5 with 1 mM NaTC.

Table 4
Dissolution data

Time (min)	SD1	SD2	SD3	
(*a*) *For SD1, SD2 and SD3 in acetate buffer pH 5.5 with 1 mM NaTC* (*mean% HF dissolved* ± S.D.*)				
0	0	0	19.51 ± 2.61	
5	5.51 ± 1.04	9.56 ± 2.46	38.83 ± 3.78	
10	11.79 ± 1.94	19.46 ± 4.99	58.56 ± 4.05	
15	18.34 ± 2.56	29.88 ± 7.65	76.77 ± 4.21	
30	25.28 ± 3.12	40.28 ± 9.11	93.96 ± 4.62	
45	32.73 ± 3.59	50.97 ± 10.69	100	
50	–	–	–	
60	40.33 ± 4.03	61.88 ± 12.29	–	
75	48.35 ± 4.14	72.41 ± 13.23	–	
120	56.55 ± 4.37	–	–	
180	65.07 ± 4.75	–		
	SD5	SD2	SD6	SD7
(*b*) *For SD2, SD5, SD6 and SD7 in acetate buffer pH 5.5 with 1 mM NaTC* (*Mean% HF dissolved* ± S.D.*)				
0	0	0	0	0
5	2.8 ± 0.46	9.56 ± 2.46	13.58 ± 2.33	12.25 ± 1.50
10	6.47 ± 0.52	19.46 ± 4.99	29.98 ± 6.52	28.27 ± 3.37
15	10.43 ± 0.42	29.88 ± 7.65	49.06 ± 5.32	54.93 ± 5.23
20	–	–	–	73.19 ± 5.51
30	14.72 ± 0.55	40.28 ± 9.11	69.05 ± 6.76	100
40	–	–	–	–
45	19.17 ± 1.11	50.97 ± 10.69	86.56 ± 5.37	–
50	–	–	–	–
55	–	–	100	–
60	23.70 ± 1.80	61.88 ± 12.29	–	–
75	28.30 ± 2.49	72.41 ± 13.23	–	–
90	32.81 ± 3.05	–	–	–
	PM1 (60:40 PVP K30-HF)	PM2 (80:20 PVP K30-HF)	PM3 (90:10 PVP K30-HF)	Halfan® tablets
(*c*) *For PM1, PM2, PM3 in acetate buffer pH 5.5 with 1 mM NaTC* (*mean% HF dissolved* ± S.D.*)				
0	0	0	0	0
5	0.28 ± 0.10	0.45 ± 0.12	0.13 ± 0.10	0.51 ± 0.07
10	0.84 ± 0.22	1.12 ± 0.20	0.68 ± 0.22	0.87 ± 0.02
15	1.55 ± 0.38	1.94 ± 0.32	1.44 ± 0.39	1.20 ± 0.07
30	2.70 ± 0.62	3.16 ± 0.47	2.87 ± 0.61	2.27 ± 0.06
45	4.13 ± 0.92	4.68 ± 0.64	4.80 ± 0.84	2.99 ± 0.10
60	5.82 ± 1.23	6.47 ± 0.78	7.15 ± 1.11	3.63 ± 0.11
75	–	8.45 ± 1.067	9.82 ± 1.47	–
90	7.93 ± 1.59	10.62 ± 1.39	12.77 ± 1.91	–
120	10.37 ± 1.97	13.12 ± 1.76	16.24 ± 2.47	–
	SD2	SD4	SD8	
(*d*) *For SD2, SD4 & SD8 in acetate buffer pH 5.5 with 1 mM NaTC* (*mean% HF dissolved* ± S.D.*)				
0	0	0	0	
5	9.56 ± 2.46	14.49 ± 1.67	11.23 ± 1.04	
10	19.46 ± 4.99	28.91 ± 2.92	24.55 ± 1.83	
15	29.88 ± 7.65	43.47 ± 4.31	36.58 ± 2.84	
30	40.28 ± 9.11	58.20 ± 5.42	48.42 ± 3.67	
45	50.97 ± 10.69	72.92 ± 6.31	60.84 ± 4.36	
60	61.88 ± 12.29	86.56 ± 4.57	73.69 ± 5.06	
75	72.41 ± 13.23	–	–	

shifts in peaks in the IR spectra for the two compounds. It was concluded, with some reservation, the absence of interaction between the two compounds by FT-IR.

The IR spectrum for lecithin (L-α-phosphatidylcholine) is shown in Fig. 7a. Two distinct bands appeared in this spectrum; a band around 1730 per cm representing stretching vibration of the carbonyl group, and another band around 1242 per cm representing C–O stretching vibration. Examination of the IR spectrum of a SD of PVP K30 and HF with 1% lecithin (Fig. 7c) showed insignificant shifts in peaks in the IR spectra for all three compounds.

The IR spectrum of PEG 8000 is shown in Fig. 8a. A very distinctive peak for PEG 8000 was a broad band around 3432 per cm that represents the stretching vibration for the OH groups. Examination of the IR spectrum of the PM (Fig. 8d) as well as the SD (Fig. 8b) of PEG 8000 with HF showed insignificant shifts in peaks in the IR spectra for the two compounds indicating the absence of interaction between the two compounds.

The IR spectrum of Gelucire® 44/14 is shown in Fig. 9a. A very characteristic peak for Gelucire® 44/14 is a small broad band around 3467 per cm that represents the stretching vibration for the OH group of free PEG 1500. Examination of the IR spectrum of the SD of Gelucire® 44/14 with HF (Fig. 9c) showed insignificant shifts in peaks in the IR spectra for the two compounds suggesting the absence of interaction between the two compounds.

Table 5
%HF for stability studies

Time (weeks)	4 °C	25 °C	45 °C
(a) %HF remaining in PVP K30-HF SD (SD6) for stability studies			
Initial	100	100	100
1 month	89.44	100.7	92.98
2 months	89.82	88.12	83
3 months	91.28	93.36	87.1
(b) %HF remaining in Gelucire® 44/14-HF SD (SD3) for stability studies			
Initial	100	100	100
1 month	93.22	95.34	83.04
2 months	90.36	89.92	75.08
3 months	77.42	77.35	72.84

3.4. Dissolution studies

Review of literature did not reveal any compendial method for the dissolution testing of HF. However, Humberstone et al. used the rotating disc method to determine the intrinsic dissolution rates of HF HCl in 20 mM sodium acetate buffer pH 5.5 with different concentrations of sodium taurocholate (NaTC). Two hundred milliliters of the dissolution medium maintained at 37 °C was used (Humberstone et al., 1996).

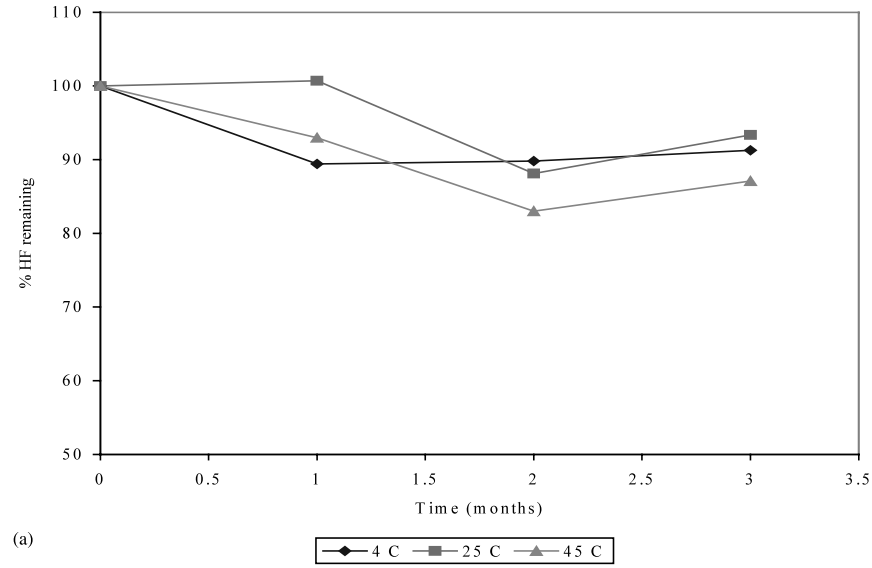
3.4.1. Effect of different carriers on the dissolution of HF from solid dispersions

Fig. 10a compares the mean% HF dissolved from three SDs (SD1, SD2, SD3) containing the same proportion (60% w/w) of three different carriers (namely PEG 8000, PVP K30 and Gelucire® 44/14, respectively) in acetate buffer pH 5.5 with 1 mM NaTC. Dissolution was the highest from the SD containing Gelucire® 44/14 as a carrier followed by the SD containing PVP K30 as a carrier and was the least with the SD containing PEG 8000.

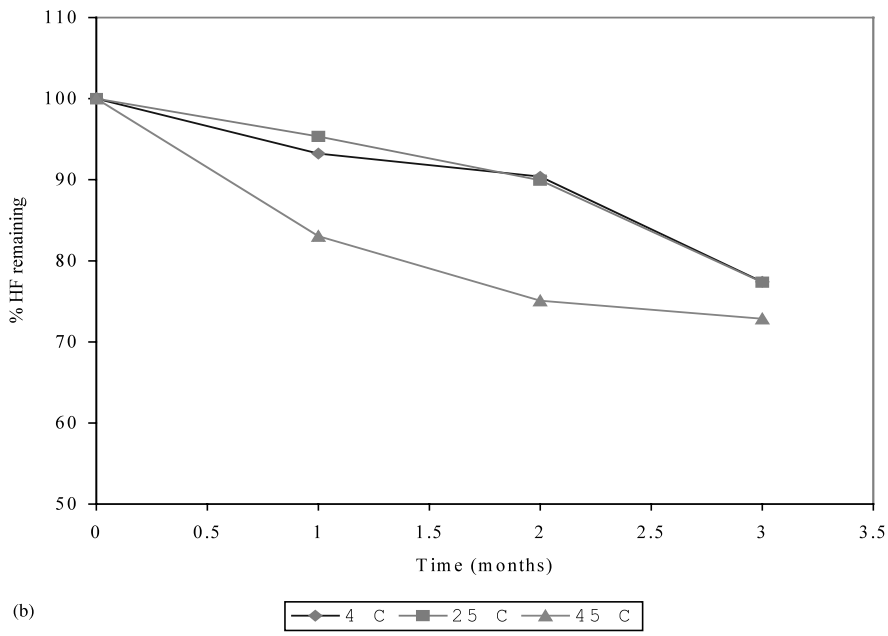
Increase in the dissolution of HF from the SD containing PEG 8000 as a carrier could be attributed to the reduction in particle size of HF that occurred during preparation of the dispersion. A greater increase in the dissolution of HF was observed in case of the SDs containing PVP K30 and Gelucire® 44/14 as carriers. This can be attributed to a reduction in the particle size of HF and an increase in solubility of HF by both carriers. In case of the SD utilizing Gelucire® 44/14 as a carrier, the highest dissolution was observed owing to micellar solubilization of HF (as shown by solubility studies).

3.4.2. Effect of carrier concentration (PVP K30) on the dissolution rate of HF from solid dispersions

Fig. 10b compares the mean% HF dissolved from four SDs (SD2, SD5, SD6 and SD7) containing different proportions (60, 50, 80 and 90% w/w, respectively) of PVP K30 as a carrier in acetate buffer pH 5.5 with 1 mM NaTC versus time. Dissolution of HF increased with increasing proportion of PVP K30. Dissolution of HF was highest with the highest concentration of PVP K30 used and was least with the lowest concentration of PVP K30 used.



(a)



(b)

Fig. 11. (a) %HF remaining in SD6 stability studies vs. time. (b) %HF remaining in SD3 stability studies vs. time.

3.4.3. Effect of concentration of carrier (PVP K30) on the dissolution rate of HF from physical mixtures

Fig. 10c compares the mean% HF dissolved from three PMs (PM1, PM2 and PM3) containing different proportions of PVP K30 (60, 80 and 90% w/w, respectively) as a carrier in acetate buffer pH 5.5 with 1 mM NaTC versus time. Dissolution was highest from the PM containing 90% by weight PVP K30 (PM3). No significant

difference, however, was observed between the dissolution of HF from PM1 and PM2.

The dissolution of HF from PMs was significantly higher than Halfan® containing an equivalent amount of HF (50 mg). This demonstrates the solubilizing effects of PVP K30. Dissolution of HF from all SDs prepared by the solvent method (SD2, SD5, SD6, SD7) was significantly higher than from the PMs (PM1, PM2, PM3) and from Halfan®. The increase in dissolution from SDs can be attributed to a reduction in the particle size of HF as well as the solubilizing effect of PVP K30. Fig. 10d is a comparative plot of the dissolution profiles for HF from Halfan®, PMs and SDs prepared by the solvent method in acetate buffer pH 5.5 with 1 mM NaTC

Additionally, the dissolution of HF from the three SDs employing different carriers was significantly higher than from Halfan®.

3.4.4. Effect of additives and the method of preparation on the dissolution rate of HF from solid dispersions using the same carrier

Fig. 10e compares the mean% HF dissolved from three SDs (SD2, SD4 and SD8) containing the same proportion (60% w/w) of PVP K30 as a carrier, but prepared by different methods. SD2 and SD4 were prepared by the solvent method but SD4 also had 1% w/w lecithin incorporated into the formula. SD8 was prepared by lyophilization.

The addition of 1% w/w lecithin (in SD4) had the greatest impact on the dissolution rate of HF from SDs compared with a SD without lecithin (SD2). Lecithin molecules can form vesicles that entrap some dissociated HF molecules; also, the lipid-soluble HF base molecules could be accommodated in the bilayer structure of the lecithin molecules. The increase in dissolution of HF from HF-lecithin-PVP K30 SD could be due to the formation of lipid vesicles that entrapped a certain concentration of HF. Moreover, the enhancement of the dissolution behavior of HF from the SD in the presence of lecithin may be due to the extraction of HF in solution by the lipid vesicles formed from the dissolution of lecithin, leading to an increase in the apparent solubility of HF (Venkataram and Rogers, 1988). Additionally, lecithin (a surfactant) improves the wetting properties of HF by a reduction in the interfacial tension and contact angle between HF and the dissolution medium.

The dissolution of HF from a SD prepared by lyophilization (SD8) was more than from a SD prepared by the regular solvent method (SD2). These results are in agreement with the findings of Betageri et al. who justify the behavior as a change in the crystal properties of the drug from crystalline to amorphous form in a lyophilized SD. This, in turn, causes a higher surface free energy for the drug in a lyophilized SD resulting in a higher dissolution rate (Betageri and Makarla, 1995). The initial rapid dissolution of HF from a lyophilized SD compared with a SD prepared by the solvent method could be due to finely divided particles of HF in the lyophilized SD surrounded intimately in the matrix by the PVP K30 particles.

The dissolution of HF from SD4 was higher than from SD8 suggesting that the addition of 1% w/w lecithin had a more significant effect on the dissolution of HF.

Table 4a–d summarize the dissolution data (mean ± standard deviation (S.D.)) obtained for all PMs and SDs.

3.5. Solid state stability studies

Results for the stability studies on SD3 are reported in Table 5a and Fig. 11a. Results for the stability studies on SD6 are reported in Table 5b and Fig. 11b. A more prominent decrease in the concentration of HF in the SD employing Gelucire® 44/14 as a carrier than from the SD employing PVP K30 as a carrier was observed. HPLC chromatograms were free from any peaks but the peak of HF. This suggested that the loss of HF was most probably due to a physical rather than chemical instability. Most likely, physical loss may be due to precipitation of HF from the SDs. However, no further studies were pursued to confirm and investigate this phenomenon.

4. Conclusions

The dissolution of HF from the PMs was higher than from Halfan®. The formulation of HF in SDs

significantly improved its dissolution rate compared with Halfan® tablets. SDs of HF with the same proportion of Gelucire® 44/14 and PVP K30 as carriers were superior in dissolving HF compared with with PEG 8000. The dissolution of HF from PVP K30-HF SDs depended on the concentration of the carrier. Dissolution of HF increased with an increase in carrier content (PVP K30). The dissolution of HF from SDs employing the same concentration of PVP K30 as a carrier showed greatest dissolution of HF from a SD containing 1% w/w lecithin as a carrier, followed by a SD prepared by lyophilization, followed by a SD prepared by the regular solvent method. Three-month stability studies at elevated temperature showed that HF exhibited poor stability in a Gelucire® 44/14 based SD, while it showed excellent stability in a PVP K30 based SD.

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